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(54) Title: TREATMENT OF OBESITY WITH G-PROTEIN COUPLED RECEPTOR 75 (GPR75) INHIBITORS

(57) Abstract: The present disclosure provides methods of treating subjects having obesity, methods of identifying subjects having an increased risk of developing obesity, methods of detecting human G-protein coupled receptor 75 variant nucleic acid molecules and variant polypeptides, and GPR75 variant nucleic acid molecules and variant polypeptides.

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Treatment Of Obesity With G-Protein Coupled Receptor 75 (GPR75) Inhibitors

Reference To Sequence Listing

This application includes a Sequence Listing submitted electronically as a text file named 18923804802SEQ, created on June 20, 2021, with a size of 533 kilobytes. The Sequence Listing is incorporated herein by reference.

Field

The present disclosure relates generally to the treatment of subjects having obesity with G-Protein Coupled Receptor 75 (GPR75) inhibitors, methods of identifying subjects having an increased risk of developing obesity, methods of detecting GPR75 variant nucleic acid molecules and variant polypeptides, and GPR75 variant nucleic acid molecules and GPR75 variant polypeptides.

Background

Obesity and its cardio-metabolic complications, in particular type 2 diabetes and coronary artery disease, account for significant morbidity and mortality globally. There is a substantial unmet medical need for safe and effective weight loss approaches.

Lifestyle interventions on diet and physical activity are the first option for the management of obesity and overweight, but efficacy can be limited, and weight regain is common. Bariatric surgery can be highly effective for weight loss in severely obese or high-risk patients, but its use is limited by its invasive nature, cost, risk of perioperative adverse events including perioperative death. While a few drugs have demonstrated efficacy in weight-reduction, pharmacotherapy for the treatment of obesity is limited by the modest weight loss induced by most drugs, side effect profile of some agents, contraindications, low compliance, and barriers to treatment including underprescription.

GPR75 is a member of the G protein-coupled receptor family. GPRs are cell surface receptors that activate guanine-nucleotide binding proteins upon the binding of a ligand. GPR75 is activated by the chemokine CCL5/RANTES. GPR75 is likely coupled to heterotrimeric Gq proteins, and stimulates inositol trisphosphate production and calcium mobilization upon activation. Together with CCL5/RANTES, GPR75 may play a role in neuron survival through activation of a downstream signaling pathway involving the PI3, Akt and MAP kinases.

CCL5/RANTES may also regulate insulin secretion by pancreatic islet cells through activation of this receptor.

Summary

The present disclosure provides methods of treating a subject having obesity, the method comprising administering a G-Protein Coupled Receptor 75 (GPR75) inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having excessive weight, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having elevated BMI, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having elevated body fat mass, percentage, or volume, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having excessive food intake, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject to prevent weight gain or to maintain weight loss, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject with a therapeutic agent that treats or inhibits obesity, wherein the subject is obese, the method comprising the steps of: determining whether the subject has a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide by: obtaining or having obtained a biological sample from the subject; and performing or having performed a sequence analysis on the biological sample to determine if the subject has a genotype comprising the GPR75 missense variant nucleic acid molecule; and administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount to a subject that is GPR75 reference; and administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount to a subject that is heterozygous for a GPR75 missense variant nucleic acid molecule; wherein the presence of a genotype having the GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide indicates the subject has a reduced risk of developing obesity.

The present disclosure also provides methods of identifying a subject having an increased risk for developing obesity, wherein the method comprises: determining or having determined the presence or absence of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample obtained from the subject; wherein: when the subject is GPR75 reference, then the subject has an increased risk for developing obesity; and when the subject is heterozygous or homozygous for a GPR75 missense variant nucleic acid molecule, then the subject has a decreased risk for developing obesity.

The present disclosure also provides methods of detecting a human GPR75 variant nucleic acid molecule in a subject comprising assaying a sample obtained from the subject to determine whether a nucleic acid molecule in the sample is: a genomic nucleic acid molecule comprising a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411

according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830

according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at

a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

The present disclosure also provides methods of detecting the presence of a human GPR75 Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs variant polypeptide, comprising performing an assay on a sample obtained from a subject to determine whether a GPR75 protein in the sample comprises SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, or SEQ ID NO:108.

The present disclosure also provides isolated alteration-specific probes or alteration-specific primers comprising at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; or positions 600-606 according to SEQ ID NO:50, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; position 980-983 according to SEQ ID NO:29, or the complement thereof; position 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; or position 980-983 according to SEQ ID NO:53, or the complement

thereof; or position 6,411 according to SEQ ID NO:6, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof; position 5,831 according to SEQ ID NO:61, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; position 891 according to SEQ ID NO:103, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof.

The present disclosure also provides molecular complexes comprising an alteration-specific primer or an alteration-specific probe hybridized to a genomic nucleic acid molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to: nucleotides at positions corresponding to positions 5,539-5,540 according to SEQ ID NO:2, or the complement thereof; an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; nucleotides at positions corresponding to positions 5,919-5,920 according to SEQ ID NO:5, or the complement thereof; a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

The present disclosure also provides molecular complexes comprising an alteration-specific primer or an alteration-specific probe hybridized to an mRNA molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to: nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:11, or the complement thereof; nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:16, or the complement

thereof; nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:21, or the complement thereof; nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:26, or the complement thereof; an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:14, or the complement thereof; nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:19, or the complement thereof; nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:24, or the complement thereof; nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:29, or the complement thereof; a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

The present disclosure also provides molecular complexes comprising an alteration-specific primer or an alteration-specific probe hybridized to a cDNA molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to: nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:35, or the complement thereof; nucleotides at

positions corresponding to positions 439-440 according to SEQ ID NO:40, or the complement thereof; nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:45, or the complement thereof; nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:50, or the complement thereof; an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:38, or the complement thereof; nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:43, or the complement thereof; nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:48, or the complement thereof; nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:53, or the complement thereof; a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, or the complement thereof, wherein the polypeptide comprises: a frameshift beginning at a position corresponding to

position 110 according to SEQ ID NO:56, a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59, or a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60.

The present disclosure also provides isolated genomic nucleic acid molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof.

The present disclosure also provides isolated mRNA molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof.

The present disclosure also provides isolated cDNA molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a

CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

The present disclosure also provides isolated human GPR75 polypeptides having an amino acid sequence at least about 90% identical to: SEQ ID NO:56, wherein the polypeptide lacks amino acids at positions corresponding to positions 110 to 540 according to SEQ ID NO:55; SEQ ID NO:59, wherein the polypeptide lacks amino acids at positions corresponding to positions 236 to 540 according to SEQ ID NO:55; or SEQ ID NO:60, wherein the polypeptide lacks amino acids at positions corresponding to positions 400 to 540 according to SEQ ID NO:55.

The present disclosure also provides therapeutic agents that treat or inhibit obesity for use in the treatment of obesity in a subject having: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions

5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof;

comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement

thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

The present disclosure also provides GPR75 inhibitors for use in the treatment of obesity in a subject having: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position

corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement

thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Brief Description Of The Drawings

The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several features of the present disclosure.

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Figure 1 shows baseline characteristics of individuals included in the exome-wide association study. Abbreviations: UKB, UK Biobank; GHS, Geisinger Health System; MCPS, Mexico City Prospective Study; SD, standard deviation; N, number of participants; WHO, World Health Organization; IQR, interquartile range; kg/m^2, kilograms per square meter; mg/dL, milligrams per deciliter; mmHg, millimeters of mercury.

Figure 2 shows association results for GPR75 with body mass index in the UKB, GHS and MCPS cohorts. Abbreviations: CI, confidence intervals; SD, standard deviation; BMI, body mass index; AAF, alternative allele frequency; RR, reference-reference genotype; RA, reference-alternative heterozygous genotype; AA, alternative-alternative homozygous genotype; pLOF, predicted loss of function; UKB, UK Biobank; GHS, Geisinger Health System MyCode study; MCPS, Mexico City Prospective Study.

Figure 3 shows association of GPR75 with body mass index in the exome-wide gene-burden analysis. The Table reports association statistics for the GPR75 gene for which the gene burden of rare pLOF variants was associated with body mass index at the exome-wide level of statistical significance ($p<3.6\times10^{-7}$). Analyses were performed in 645,626 participants from the UKB, GHS and MCPS studies. Genomic coordinates reflect chromosome and physical position in base pairs according to Genome Reference Consortium Human Build 38. Abbreviations: CI, confidence interval; SD, standard deviation; BMI, body mass index; AAF, alternative allele frequency; RR, reference-reference genotype; RA, reference-alternative heterozygous genotype; AA, alternative-alternative homozygous genotype; pLOF, predicted loss of function; Missense (1/5), missense variant predicted to be deleterious by at least 1 out of 5 in silico prediction algorithms; Missense (5/5), missense variant predicted to be deleterious by 5 out of 5 in silico prediction algorithms.

Figure 4 shows protein-truncating variants in GPR75 associated with lower body mass index in humans. Panel A shows a linear model of the GPR75 protein and its domains (top; intra- and extra-cellular domains in yellow, transmembrane domains in orange), the distribution on the GPR75 protein of 46 predicted loss of function variants found by exome sequencing (middle) and the distribution of BMI in standardized units among heterozygous carriers of each variant (bottom). In the bottom sub-panel, horizontal blue bars show the mean

BMI in non-carriers, while horizontal red bars show the overall covariates-adjusted mean BMI in carriers of any predicted loss-of-function genetic variant in GPR75. Panel B shows meta-analysis of the association with BMI of predicted loss-of-function variants in GPR75 in discovery and additional cohorts. Abbreviations: CI, confidence interval; RR, reference-reference genotype; RA, reference-alternative heterozygous genotype; AA, alternative-alternative homozygous genotype; DHS, Dallas Heart Study; SINAI, Mount Sinai BioMe cohort; DUKE, Duke Catheterization Genetics cohort; TAICHI, Taiwanese Chinese persons from the Taiwan Metabochip Consortium; PMBB, University of Pennsylvania Medicine BioBank; MALMO, Malmö Diet and Cancer Study; AFR, African ancestry; AMR; American ancestry; EAS, East Asian ancestry; EUR, European ancestry; SAS, South Asian ancestry. MCPS included individuals of Admixed American ancestry.

Figure 5 shows association with body mass index of GPR75 pLOF variants within age and sex subgroups. Abbreviations: Confidence interval, CI; standard deviation, SD; body mass index, BMI; alternative allele frequency, AAF; P-value, p; reference-reference genotype, RR; reference-alternative genotype, RA; alternative-alternative genotype, AA; kilograms per square meter, kg/m^2; predicted loss of function, pLOF.

Figure 6 shows association with risk of obesity for GPR75 pLOF variants. Abbreviations: OR, odds ratio; CI, confidence intervals; P-value, p; AAF, alternative allele frequency; reference-reference genotype, RR; reference-alternative genotype, RA; alternative-alternative genotype, AA; pLOF, predicted loss of function. Results are from a meta-analysis of the UKB, GHS and MCPS studies.

Figure 7 shows distribution in body mass index categories for carriers and non-carriers of predicted loss-of-function variants in GPR75 or MC4R. Distribution of heterozygous carriers of predicted loss of function genetic variants in GPR75 (top), non-carriers (middle) and heterozygous carriers of predicted loss of function genetic variants in MC4R (bottom) in body mass index categories according to the World Health Organization's classification in the UKB, GHS and MCPS cohorts.

Figure 8 shows association of GPR75 pLOF variants with self-reported thinner than average comparative body size at age 10 in UKB. Abbreviations: predicted loss of function, pLOF; UK Biobank, UKB; alternative allele frequency, AAF; confidence interval, CI; odds ratio, OR; P-value, p; reference-reference genotype, RR; reference-alternative genotype, RA; alternative-alternative genotype, AA.

Figure 9 shows association of pLOF variants in GPR75 and MC4R with body fat and lean mass indices estimated by bioelectrical impedance. Association analyses were performed in 423,418 participants of the UK Biobank study who underwent whole exome sequencing and bioelectrical impedance measurements. Abbreviations: pLOF, predicted loss of function; kg, kilograms; CI, confidence interval.

Figure 10 shows association of pLOF genetic variants in GPR75 with cardio-metabolic phenotypes in the UKB, GHS and MCPS studies. Abbreviations: P-value, p; SD, standard deviations; CI, confidence intervals; pLOF, predicted loss of function; AAF, alternative allele frequency; RR, reference-reference genotype; RA, reference-alternative heterozygous genotype; AA, alternative-alternative homozygous genotype; Hemoglobin A1C, HbA1c; Aspartate transaminase, AST; Alanine transaminase, ALT; High-density lipoprotein cholesterol, HDL-C; Low-density lipoprotein cholesterol, LDL-C; milligrams per deciliter, mg/dL; millimetre of mercury, mmHg; units per liter, U/L.

Figure 11 shows GPR75, ASB3 and GPR75-ASB3 genes. The figure shows the gene model and chromosomal locations for the GPR75, GPR75-ASB3 and ASB3 genes. GPR75 shares exon 1, containing non-coding sequence, with the GPR75-ASB3 readthrough gene. Exon 2 of GPR75, containing its entire coding sequence, is exclusive to the GPR75 gene and is not shared with any other gene. ASB3 and GPR75-ASB3 share several exons with each other but not with GPR75. The underlying representation is from Ensembl region plot (Version 85).

Figure 12 shows GPR75 predicted loss of function variants identified by exome-sequencing. The Table lists the predicted loss of function (pLOF) variants in the GPR75 gene found by exome sequencing which contributed to the gene burden analysis. Imputation INFO score values below 0.3 are typically considered to be of very low quality. Abbreviations: chromosome, position, reference, alternative, CPRA; alternative allele frequency, AAF; complementary DNA, cDNA; human genome variation society, HGVS.

Figure 13 shows no association with BMI for the burden of rare nonsynonymous variants in ASB3 or GPR75-ASB3. Abbreviations: alternative allele frequency, AAF; confidence intervals, CI; standard deviation, SD; body mass index, BMI; kilograms per square meter, kg/m^2; P-value, p; reference-reference genotype, RR; reference-alternative genotype, RA; alternative-alternative genotype, AA; predicted loss of function, pLOF.

Figure 14 shows association with BMI of the burden of pLOF variants in GPR75 after adjusting for ASB3, GPR75-ASB3 and common variants genotypes in the region. Abbreviations:

Confidence interval, CI; standard deviation, SD; body mass index, BMI; kilograms per square meter, kg/m^2; P-value, p; alternative allele frequency, AAF; reference-reference genotype, RR; reference-alternative genotype, RA; alternative-alternative genotype, AA; predicted loss of function, pLOF. * standard covariates included all fine-mapped common variants from the GWAS analysis including rs59428052 near ASB3.

Figure 15 shows common variants associated with BMI at the GPR75 locus. The Table reports a list of 26 common variants which were associated with BMI at the genome-wide threshold of statistical significance ($p<5\times10^{-8}$) within 500 kb either side of GPR75 in Europeans. The variants are annotated to the nearest gene, and whether they are in LD (R^2 > 0.8) with an eQTL sentinel or nonsynonymous coding variant. At the GPR75 locus, no common variants were associated with BMI at genome-wide significance in admixed Americans. Abbreviations: chromosome, position, reference, alternative, CPRA; alternative allele frequency, AAF; posterior probability of causal association, PPA; linkage disequilibrium, LD; expression quantitative trait loci, eQTL.

Figure 16 shows associations with BMI for common variants at the GPR75 locus. Results from GWAS analyses of common imputed variants in European ancestry individuals from UKB and GHS are shown in the left panel and those from GWAS analyses in admixed Americans from the MCPS cohort in the right panel. The sentinel variant in the GWAS of European individuals (rs59428052) is highlighted in the left panel. There were no genome-wide significant associations in Admixed Americans ($p<5x10^{-8}$).

Figure 17 shows association of pLOF genetic variants in GPR75 with body mass index in sensitivity analyses. The Table reports leave-one-out analyses excluding one genetic variant at a time as well as an analysis excluding variants associated with lower BMI in individual-variant analyses (bottom row). Abbreviations: CI, confidence intervals; SD, standard deviation; BMI, body mass index; p, P-value; pLOF, predicted loss of function.

Figure 18 shows predicted loss of function variants in GPR75 associated with BMI in individual variant analyses. This Table reports association statistics for GPR75 pLOF variants which were included in the gene burden analysis and were also individually associated with BMI at an inverse-variance weighted meta-analysis $p<0.05$. Abbreviations: AAF, alternative allele frequency; CI, confidence intervals; SD, standard deviation; BMI, body mass index; P-value, p; frame shift, fs; pLOF, predicted loss of function.

Figure 19 shows *in vitro* expression studies of two predicted loss-of-function genetic variants in GPR75. Panel A shows results of quantitative reverse transcription polymerase chain reaction experiments which measured GPR75 mRNA levels. Expression of GPR75 was calculated relative to the beta-actin gene. Values represent the mean and standard deviation of 3 technical replicates representative of 1 of 3 biological replicate experiments performed for each condition. Panel B shows Western blotting analysis of GPR75 protein levels. GPR75 Ala110fs and Gln234* protein products correspond to the predicted molecular weight of 14 and 25 kDa, respectively. The results are representative of 3 biological replicates. Panel C shows immunofluorescence staining experiments describing the cellular localization of GPR75. The top images show intracellular staining achieved by membrane permeabilization, while the bottom images show plasma membrane localization (non-permeabilized cellular membrane). Panel D shows flow cytometry analysis of the cell surface expression of GPR75. Identified cell populations are presented in percent (%) of live HA-TAG GPR75 positive cells. Values represent the mean of 4 biological replicates per condition and their standard deviation. All experiments were performed in HEK293 cells that were transfected with green fluorescent protein control plasmids (Control), GPR75-wildtype (GPR75), GPR75-Ala110fs or GPR75-Gln234* plasmids. Abbreviations: SSC, side scatter; HA, hemagglutinin tag.

Figure 20 shows association with BMI of N- vs C-terminal truncating genetic variants in GPR75. Abbreviations: CI, confidence intervals; SD, standard deviation; BMI, body mass index; p, p-value; AAF, alternative allele frequency; RR, reference-reference genotype; RA, reference-alternative heterozygous genotype; AA, alternative-alternative homozygous genotype; kg/m^2, kilograms per square meter.

Figure 21 shows average body weights in GPR75 WT (designated with HIST and WT) and homozygote knockouts (designated with KO) male (top panel) and female (bottom panel) mice.

Figure 22 shows percentage difference of body composition of male homozygote knockouts (designated with KO) compared to wild type. BMC, bone mineral content; BMD, bone mineral density; P, p-value.

Figure 23 shows average fat volume and percent fat volume of GPR75 WT (HIST and WT) and homozygote knockouts (designated with KO) male mice.

Figure 24 shows weight-gain during high-fat diet and metabolic phenotype in mice with a genetic deletion of Gpr75. Panel A shows weekly body weight gain during a 14-weeks

high-fat diet challenge; Panel B shows changes in fasting blood glucose before and after the high-fat diet challenge; Panel C shows results of a glucose tolerance test at the end of the 14-week high-fat diet challenge; Panel D shows plasma insulin at the end of the 14-week high-fat diet challenge. Each panel shows results in $Gpr75^{+/+}$ (WT), $Gpr75^{+/-}$ (HET), and $Gpr75^{-/-}$ (KO) mice. Number of mice included in each group and analysis are in parenthesis. Results are presented as mean ± standard error. Abbreviations: ns, not statistically-significant; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 by two-way ANOVA with Tukey's multiple comparisons test.

Figure 25 shows plasma leptin, adiponectin and leptin-adiponectin ratio in mouse experiments. Panel A shows plasma leptin levels in $Gpr75^{+/+}$ (WT), $Gpr75^{+/-}$ (HET), and $Gpr75^{-/-}$ (KO) mice after the high-fat diet challenge expressed as fold difference compared to wild-type (set as 1). Absolute levels (mean ± standard deviation) for wild-type mice were 208±42 pg/mL. Panel B shows plasma adiponectin levels in $Gpr75^{+/+}$ (WT), $Gpr75^{+/-}$ (HET), and $Gpr75^{-/-}$ (KO) mice after the high-fat diet challenge expressed as fold difference compared to wild-type (set as 1). Absolute levels (mean ± standard deviation) for wild-type mice were 3,911±1,656 ng/mL. Panel C shows ratio of leptin to adiponectin in $Gpr75^{+/+}$ (WT), $Gpr75^{+/-}$ (HET), and $Gpr75^{-/-}$ (KO) expressed in ratio units. Number of mice included in each group and analysis are in parenthesis in the x-axis labels. Results are presented as mean ± standard deviation. ns, not statistically-significant; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 by two-way ANOVA with Tukey's multiple comparisons test.

Figure 26 shows body weight, fat mass, lean mass, bone mass, and blood glucose levels measured in high-fat diet mouse experiments. Body weight (Panel A), fat mass (Panel B, top), lean mass (Panel B, middle), bone mass (Panel B, bottom) and blood glucose levels (Panel C) for $Gpr75^{+/+}$, $Gpr75^{+/-}$ and $Gpr75^{-/-}$ mice (black circles, red squares and blue triangles, respectively) maintained on chow diet (week 0 or -1) and during 9 weeks of high fat diet feeding (HFD). *, P<0.05 for $Gpr75^{-/-}$ vs $Gpr75^{+/+}$ mice. #, P<0.05 for $Gpr75^{+/-}$ vs $Gpr75^{+/+}$ mice. $, P<0.05 for the last high fat diet data point vs the first data point obtained on chow diet prior to high fat diet feeding, for the respective genotype.

Figure 27 shows chow-fed female Gpr75 knockout mice are not insulin resistant and exhibit improved glucose tolerance.

Description

Various terms relating to aspects of the present disclosure are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art, unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any respect. This holds for any possible non-expressed basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

As used herein, the term "about" means that the recited numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical value is used, unless indicated otherwise by the context, the term "about" means the numerical value can vary by ±10% and remain within the scope of the disclosed embodiments.

As used herein, the term "comprising" may be replaced with "consisting" or "consisting essentially of" in particular embodiments as desired.

As used herein, the term "isolated", in regard to a nucleic acid molecule or a polypeptide, means that the nucleic acid molecule or polypeptide is in a condition other than its native environment, such as apart from blood and/or animal tissue. In some embodiments, an isolated nucleic acid molecule or polypeptide is substantially free of other nucleic acid molecules or other polypeptides, particularly other nucleic acid molecules or polypeptides of animal origin. In some embodiments, the nucleic acid molecule or polypeptide can be in a highly purified form, i.e., greater than 95% pure or greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same nucleic acid molecule or polypeptide in alternative physical forms, such as dimers or alternatively phosphorylated or derivatized forms.

As used herein, the terms "nucleic acid", "nucleic acid molecule", "nucleic acid sequence", "polynucleotide", or "oligonucleotide" can comprise a polymeric form of nucleotides of any length, can comprise DNA and/or RNA, and can be single-stranded, double-stranded, or multiple stranded. One strand of a nucleic acid also refers to its complement.

As used herein, the term "subject" includes any animal, including mammals. Mammals include, but are not limited to, farm animals (such as, for example, horse, cow, pig), companion animals (such as, for example, dog, cat), laboratory animals (such as, for example, mouse, rat, rabbits), and non-human primates (such as, for example, apes and monkeys). In some embodiments, the subject is a human. In some embodiments, the subject is a patient under the care of a physician.

Variants in the GPR75 gene associated with a decreased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake, in subjects has been identified in accordance with the present disclosure. For example, a genetic alteration that deletes the CCAGTAG heptanucleotide of positions 5,540-5,546 in the human GPR75 reference (see, SEQ ID NO:1), or changes the guanine nucleotide of position 5,557 in the human GPR75 reference (see, SEQ ID NO:1) to adenine, or the cytosine nucleotide of position 5,911 in the human GPR75 reference (see, SEQ ID NO:1) to thymine, or deletes the AAAG tetranucleotide at positions 5,920-5,923 in the human GPR75 reference (see, SEQ ID NO:1), or inserts the thymine nucleotide at position 6,411 in the human GPR75 reference (see, SEQ ID NO:1) has been observed to indicate that the human having such an alteration may have a decreased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake. It is believed that no variants of the GPR75 gene or protein have any known association with obesity, body weight, BMI, body fat mass, percentage, or volume, and/or body lean mass, percentage, or volume. Altogether, the genetic analyses described herein surprisingly indicate that the GPR75 gene and, in particular, variants in the GPR75 gene, associate with a decreased risk of developing obesity, associate with lower weight, lower BMI, lower body fat mass, percentage, or volume, and/or lower lean body mass, percentage, or volume. Therefore, subjects that are GPR75 reference that have an increased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake may be treated such that obesity is prevented, the symptoms thereof are reduced, and/or development of symptoms is repressed. Accordingly, the present disclosure provides methods

of leveraging the identification of such variants in subjects to identify or stratify risk in such subjects of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake, or to diagnose subjects as having an increased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake, such that subjects at risk or subjects with active disease may be treated accordingly. Additionally, the present disclosure provides isolated GPR75 variant genomic nucleic acid molecules, variant mRNA molecules, and variant cDNA molecules. Also provided herein are GPR75 loss-of-function variant nucleic acid molecules discovered to be associated with decreased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake.

Additional missense variants in the GPR75 gene that may be associated with a decreased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake comprise (according to GRCh38/hg38 (Dec. 2013) human genome assembly) (and, hence, can be included in any of the embodiments described herein): a substitution of thymine with cytosine at the chromosome 2 position 53,854,656 resulting in replacement of glutamine with arginine at a position corresponding to position 34 according to SEQ ID NO:55; a substitution of guanine with alanine at the chromosome 2 position 53,854,330 resulting in replacement of arginine with tryptophan at a position corresponding to position 143 according to SEQ ID NO:55; a substitution of thymine with cytosine at the chromosome 2 position 53,854,321 resulting in replacement of methionine with valine at a position corresponding to position 146 according to SEQ ID NO:55; a substitution of cytosine with guanine at the chromosome 2 position 53,854,191 resulting in replacement of cysteine with serine at a position corresponding to position 189 according to SEQ ID NO:55; a substitution of alanine with guanine at the chromosome 2 position 53,853,780 resulting in replacement of isoleucine with threonine at a position corresponding to position 326 according to SEQ ID NO:55; a substitution of thymine with adenine at the chromosome 2 position 53,853,634 resulting in replacement of isoleucine with leucine at a position corresponding to position 375 according to SEQ ID NO:55; and a substitution of cytosine with thymine at the chromosome 2 position 53,853,181 resulting in replacement of glutamic acid with lysine at a position corresponding to position 526 according to SEQ ID NO:55.

Additional variants in the GPR75 gene may be associated with an increased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or

volume, and/or excessive food intake, in subjects, and they may be considered gain-of-function (GOF) variants. Such GOF may include (according to GRCh38/hg38 (Dec. 2013) human genome assembly): a substitution of adenine with thymine at the chromosome 2 position 53,854,437 resulting in replacement of phenylalanine with tyrosine at position corresponding to position 107 according to SEQ ID NO:55; and a substitution of guanine with adenine at the chromosome 2 position 53,853,697 resulting in replacement of leucine with phenylalanine at position corresponding to position 354 according to SEQ ID NO:55. Thus, subjects having either variant may be treated with a GPR75 inhibitor. Such subjects can be assessed for the risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake by detecting the presence of a GOF variant.

For purposes of the present disclosure, any particular human can be categorized as having one of three GPR75 genotypes: i) GPR75 reference; ii) heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide; or iii) homozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide. A human is GPR75 reference when the human does not have a copy of a GPR75 missense variant nucleic acid molecule. A human is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide when the human has a single copy of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide. As used herein, a GPR75 missense variant nucleic acid molecule is any GPR75 nucleic acid molecule (such as, a genomic nucleic acid molecule, an mRNA molecule, or a cDNA molecule) encoding a GPR75 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. A human who has a GPR75 polypeptide having a partial loss-of-function (or predicted partial loss-of-function) is hypomorphic for GPR75. The GPR75 predicted loss-of-function variant nucleic acid molecule can be any nucleic acid molecule encoding GPR75 Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs. The GPR75 missense variant nucleic acid molecule can also be any nucleic acid molecule encoding Lys404* and Ser219fs, or can be c.-110+1G>A. A human is homozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide when the human has two copies of a GPR75 missense variant nucleic acid molecule.

For subjects that are genotyped or determined to be GPR75 reference, such subjects have an increased risk of developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake. For subjects that are genotyped or determined to be either GPR75 reference or heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide, such subjects can be treated with a GPR75 inhibitor.

In any of the embodiments described herein, the GPR75 missense variant nucleic acid molecule can be any GPR75 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding a GPR75 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. For example, the GPR75 missense variant nucleic acid molecule can be any nucleic acid molecule encoding GPR75 Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs. The GPR75 missense variant nucleic acid molecule can also be any nucleic acid molecule encoding Lys404* and Ser219fs, or can be c.-110+1G>A.

GPR75 missense variant nucleic acid molecules also include, but are not limited to, 2:53853134:T:G, 2:53853135:T:G, 2:53853136:A:C, 2:53853200:GGT:G, 2:53853245:GT:G, 2:53853256:G:A, 2:53853352:G:A, 2:53853354:CCA:C, 2:53853382:TG:T, 2:53853502:T:A, 2:53853535:G:A, 2:53853547:T:A, 2:53853560:G:GA, 2:53853641:GTT:G, 2:53853680:CAATTCAAACTGGT:C, 2:53853692:G:T, 2:53853730:G:A, 2:53853771:G:C, 2:53853853:G:A, 2:53853877:G:A, 2:53853926:G:T, 2:53853927:T:TA, 2:53853946:G:GT, 2:53853967:TGG:T, 2:53854009:G:A, 2:53854037:A:AG, 2:53854045:ACTTT:A, 2:53854051:T:A, 2:53854057:G:A, 2:53854078:G:A, 2:53854099:CAG:C, 2:53854135:CAT:C, 2:53854137:TAGAG:T, 2:53854306:G:A, 2:53854380:G:C, 2:53854409:A:AG, 2:53854421:ACTACTGG:A, 2:53854474:C:A, 2:53854476:C:CA, 2:53854485:AG:A, 2:53854644:TG:T, 2:53854685:TC:T, 2:53854695:G:T, 2:53854740:TG:T, 2:53854755:A:G, and 2:53859827:C:T (according to GRCh38/hg38 (Dec. 2013) human genome assembly).

In any of the embodiments described herein, the GPR75 predicted loss-of-function polypeptide can be any GPR75 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function. In any of the embodiments described herein, the GPR75 predicted loss-of-function polypeptide can be any of the GPR75 polypeptides described herein including, for example, GPR75 Ala110fs,

Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs. The GPR75 predicted loss-of-function polypeptide can also be Lys404* or Ser219fs.

In any of the embodiments described herein, the subject can be obese, or have excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake. In any of the embodiments described herein, the subject can be obese. In any of the embodiments described herein, the subject can have excessive weight. In any of the embodiments described herein, the subject can have elevated BMI. In any of the embodiments described herein, the subject can have elevated body fat mass, percentage, or volume. In any of the embodiments described herein, the subject can have excessive food intake.

Symptoms of obesity include, but are not limited to, excess body fat accumulation (particularly around the waist), breathlessness, increased sweating, snoring, inability to cope with sudden physical activity, feeling very tired every day, back and joint pains, skin problems (from moisture accumulating in the folds of skin).

The present disclosure provides methods of treating a subject having obesity, the methods comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having excessive weight, the methods comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having elevated BMI, the methods comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having elevated body fat mass, percentage, or volume, the methods comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject having excessive

food intake, the methods comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

The present disclosure also provides methods of treating a subject to prevent weight gain or to maintain weight loss, the method comprising administering a GPR75 inhibitor to the subject. In some embodiments, the subject is GPR75 reference or is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

In any of the embodiments described herein in which a subject is treated with a GPR75 inhibitor, the subject can be GPR75 reference (i.e., the subject does not have a copy of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide). In any of the embodiments described herein in which a subject is treated with a GPR75 inhibitor, the subject can be heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide (i.e., the subject only has a single copy a reference GPR75 nucleic acid molecule). The subject's genotype need not be determined at the time of the administration of the GPR75 inhibitor.

In some embodiments, the GPR75 inhibitor comprises an inhibitory nucleic acid molecule. Examples of inhibitory nucleic acid molecules include, but are not limited to, antisense nucleic acid molecules, small interfering RNAs (siRNAs), and short hairpin RNAs (shRNAs). Such inhibitory nucleic acid molecules can be designed to target any region of a GPR75 nucleic acid molecule, such as an mRNA molecule. In some embodiments, the antisense RNA, siRNA, or shRNA hybridizes to a sequence within a GPR75 genomic nucleic acid molecule or mRNA molecule and decreases expression of the GPR75 polypeptide in a cell in the subject. In some embodiments, the GPR75 inhibitor comprises an antisense RNA that hybridizes to a GPR75 genomic nucleic acid molecule or mRNA molecule and decreases expression of the GPR75 polypeptide in a cell in the subject. In some embodiments, the antisense nucleic acid molecules comprise or consist of the nucleotide sequences set forth in SEQ ID NOs:109-529. In some embodiments, the GPR75 inhibitor comprises an siRNA that hybridizes to a GPR75 genomic nucleic acid molecule or mRNA molecule and decreases expression of the GPR75 polypeptide in a cell in the subject. In some embodiments, the siRNA molecules comprise or consist of the nucleotide sequences (sense and antisense strand pairs) set forth in SEQ ID NOs:530-1457 (i.e., SEQ ID NO:530 and SEQ ID NO:531, for example, form the sense and

antisense strands, respectively, of an siRNA molecule; likewise with the sense and antisense strands of the remaining siRNA molecules set forth in SEQ ID NOs:530-1457). In some embodiments, the GPR75 inhibitor comprises an shRNA that hybridizes to a GPR75 genomic nucleic acid molecule or mRNA molecule and decreases expression of the GPR75 polypeptide in a cell in the subject. Suitable GPR75-specific siRNAs and shRNAs are disclosed in, for example, Garcia et al., Circ. Res., 2017, 120, 1776-1788.

The inhibitory nucleic acid molecules disclosed herein can comprise RNA, DNA, or both RNA and DNA. The inhibitory nucleic acid molecules can also be linked or fused to a heterologous nucleic acid sequence, such as in a vector, or a heterologous label. For example, the inhibitory nucleic acid molecules disclosed herein can be within a vector or as an exogenous donor sequence comprising the inhibitory nucleic acid molecule and a heterologous nucleic acid sequence. The inhibitory nucleic acid molecules can also be linked or fused to a heterologous label. The label can be directly detectable (such as, for example, fluorophore) or indirectly detectable (such as, for example, hapten, enzyme, or fluorophore quencher). Such labels can be detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. Such labels include, for example, radiolabels, pigments, dyes, chromogens, spin labels, and fluorescent labels. The label can also be, for example, a chemiluminescent substance; a metal-containing substance; or an enzyme, where there occurs an enzyme-dependent secondary generation of signal. The term “label” can also refer to a “tag” or hapten that can bind selectively to a conjugated molecule such that the conjugated molecule, when added subsequently along with a substrate, is used to generate a detectable signal. For example, biotin can be used as a tag along with an avidin or streptavidin conjugate of horseradish peroxidate (HRP) to bind to the tag, and examined using a calorimetric substrate (such as, for example, tetramethylbenzidine (TMB)) or a fluorogenic substrate to detect the presence of HRP. Exemplary labels that can be used as tags to facilitate purification include, but are not limited to, myc, HA, FLAG or 3XFLAG, 6XHis or polyhistidine, glutathione-S-transferase (GST), maltose binding protein, an epitope tag, or the Fc portion of immunoglobulin. Numerous labels include, for example, particles, fluorophores, haptens, enzymes and their calorimetric, fluorogenic and chemiluminescent substrates and other labels.

The disclosed inhibitory nucleic acid molecules can comprise, for example, nucleotides or non-natural or modified nucleotides, such as nucleotide analogs or nucleotide substitutes. Such nucleotides include a nucleotide that contains a modified base, sugar, or phosphate

group, or that incorporates a non-natural moiety in its structure. Examples of non-natural nucleotides include, but are not limited to, dideoxynucleotides, biotinylated, aminated, deaminated, alkylated, benzylated, and fluorophor-labeled nucleotides.

The inhibitory nucleic acid molecules disclosed herein can also comprise one or more nucleotide analogs or substitutions. A nucleotide analog is a nucleotide which contains a modification to either the base, sugar, or phosphate moieties. Modifications to the base moiety include, but are not limited to, natural and synthetic modifications of A, C, G, and T/U, as well as different purine or pyrimidine bases such as, for example, pseudouridine, uracil-5-yl, hypoxanthin-9-yl (I), and 2-aminoadenin-9-yl. Modified bases include, but are not limited to, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (such as, for example, 5-bromo), 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

Nucleotide analogs can also include modifications of the sugar moiety. Modifications to the sugar moiety include, but are not limited to, natural modifications of the ribose and deoxy ribose as well as synthetic modifications. Sugar modifications include, but are not limited to, the following modifications at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl, and alkynyl may be substituted or unsubstituted $C_{1\text{-}10}$alkyl or $C_{2\text{-}10}$alkenyl, and $C_{2\text{-}10}$alkynyl. Exemplary 2' sugar modifications also include, but are not limited to, $-O[(CH_2)_nO]_mCH_3$, $-O(CH_2)_nOCH_3$, $-O(CH_2)_nNH_2$, $-O(CH_2)_nCH_3$, $-O(CH_2)_n$-ONH_2, and $-O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m, independently, are from 1 to about 10. Other modifications at the 2' position include, but are not limited to, $C_{1\text{-}10}$alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other

substituents having similar properties. Similar modifications may also be made at other positions on the sugar, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Modified sugars can also include those that contain modifications at the bridging ring oxygen, such as CH_2 and S. Nucleotide sugar analogs can also have sugar mimetics, such as cyclobutyl moieties in place of the pentofuranosyl sugar.

Nucleotide analogs can also be modified at the phosphate moiety. Modified phosphate moieties include, but are not limited to, those that can be modified so that the linkage between two nucleotides contains a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl and other alkyl phosphonates including 3'-alkylene phosphonate and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. These phosphate or modified phosphate linkage between two nucleotides can be through a 3'-5' linkage or a 2'-5' linkage, and the linkage can contain inverted polarity such as 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts, and free acid forms are also included. Nucleotide substitutes also include peptide nucleic acids (PNAs).

In some embodiments, the antisense nucleic acid molecules are gapmers, whereby the first one to seven nucleotides at the 5' and 3' ends each have 2'-methoxyethyl (2'-MOE) modifications. In some embodiments, the first five nucleotides at the 5' and 3' ends each have 2'-MOE modifications. In some embodiments, the first one to seven nucleotides at the 5' and 3' ends are RNA nucleotides. In some embodiments, the first five nucleotides at the 5' and 3' ends are RNA nucleotides. In some embodiments, each of the backbone linkages between the nucleotides is a phosphorothioate linkage.

In some embodiments, the siRNA molecules have termini modifications. In some embodiments, the 5' end of the antisense strand is phosphorylated. In some embodiments, 5'-phosphate analogs that cannot be hydrolyzed, such as 5'-(E)-vinyl-phosphonate are used.

In some embodiments, the siRNA molecules have backbone modifications. In some embodiments, the modified phosphodiester groups that link consecutive ribose nucleosides have been shown to enhance the stability and *in vivo* bioavailability of siRNAs The non-ester groups (-OH, =O) of the phosphodiester linkage can be replaced with sulfur, boron, or acetate to give phosphorothioate, boranophosphate, and phosphonoacetate linkages. In addition,

substituting the phosphodiester group with a phosphotriester can facilitate cellular uptake of siRNAs and retention on serum components by eliminating their negative charge. In some embodiments, the siRNA molecules have sugar modifications. In some embodiments, the sugars are deprotonated (reaction catalyzed by exo- and endonucleases) whereby the 2'-hydroxyl can act as a nucleophile and attack the adjacent phosphorous in the phosphodiester bond. Such alternatives include 2'-O-methyl, 2'-O-methoxyethyl, and 2'-fluoro modifications.

In some embodiments, the siRNA molecules have base modifications. In some embodiments, the bases can be substituted with modified bases such as pseudouridine, 5'-methylcytidine, N6-methyladenosine, inosine, and N7-methylguanosine.

In some embodiments, the siRNA molecules are conjugated to lipids. Lipids can be conjugated to the 5' or 3' termini of siRNA to improve their *in vivo* bioavailability by allowing them to associate with serum lipoproteins. Representative lipids include, but are not limited to, cholesterol and vitamin E, and fatty acids, such as palmitate and tocopherol.

In some embodiments, a representative siRNA has the following formula:

Sense: mN*mN*/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/*mN*/32FN/

Antisense: /52FN/*/i2FN/*mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN/i2FN/mN*N*N

wherein: "N" is the base; "2F" is a 2'-F modification; "m" is a 2'-O-methyl modification, "I" is an internal base; and "*" is a phosphorothioate backbone linkage.

The present disclosure also provides vectors comprising any one or more of the inhibitory nucleic acid molecules disclosed herein. In some embodiments, the vectors comprise any one or more of the inhibitory nucleic acid molecules disclosed herein and a heterologous nucleic acid. The vectors can be viral or nonviral vectors capable of transporting a nucleic acid molecule. In some embodiments, the vector is a plasmid or cosmid (such as, for example, a circular double-stranded DNA into which additional DNA segments can be ligated). In some embodiments, the vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Expression vectors include, but are not limited to, plasmids, cosmids, retroviruses, adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus and tobacco mosaic virus, yeast artificial chromosomes (YACs), Epstein-Barr (EBV)-derived episomes, and other expression vectors known in the art.

The present disclosure also provides compositions comprising any one or more of the inhibitory nucleic acid molecules disclosed herein. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the compositions comprise a carrier and/or excipient. Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules. A carrier may comprise a buffered salt solution such as PBS, HBSS, etc.

In some embodiments, the GPR75 inhibitor comprises a nuclease agent that induces one or more nicks or double-strand breaks at a recognition sequence(s) or a DNA-binding protein that binds to a recognition sequence within a GPR75 genomic nucleic acid molecule. The recognition sequence can be located within a coding region of the GPR75 gene, or within regulatory regions that influence the expression of the gene. A recognition sequence of the DNA-binding protein or nuclease agent can be located in an intron, an exon, a promoter, an enhancer, a regulatory region, or any non-protein coding region. The recognition sequence can include or be proximate to the start codon of the GPR75 gene. For example, the recognition sequence can be located about 10, about 20, about 30, about 40, about 50, about 100, about 200, about 300, about 400, about 500, or about 1,000 nucleotides from the start codon. As another example, two or more nuclease agents can be used, each targeting a nuclease recognition sequence including or proximate to the start codon. As another example, two nuclease agents can be used, one targeting a nuclease recognition sequence including or proximate to the start codon, and one targeting a nuclease recognition sequence including or proximate to the stop codon, wherein cleavage by the nuclease agents can result in deletion of the coding region between the two nuclease recognition sequences. Any nuclease agent that induces a nick or double-strand break into a desired recognition sequence can be used in the methods and compositions disclosed herein. Any DNA-binding protein that binds to a desired recognition sequence can be used in the methods and compositions disclosed herein.

Suitable nuclease agents and DNA-binding proteins for use herein include, but are not limited to, zinc finger protein or zinc finger nuclease (ZFN) pair, Transcription Activator-Like Effector (TALE) protein or Transcription Activator-Like Effector Nuclease (TALEN), or Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) systems. The length of the recognition sequence can vary, and includes, for example, recognition sequences that are about 30-36 bp for a zinc finger protein or ZFN pair, about 15-18 bp for each

ZFN, about 36 bp for a TALE protein or TALEN, and about 20 bp for a CRISPR/Cas guide RNA.

In some embodiments, CRISPR/Cas systems can be used to modify a GPR75 genomic nucleic acid molecule within a cell. The methods and compositions disclosed herein can employ CRISPR-Cas systems by utilizing CRISPR complexes (comprising a guide RNA (gRNA) complexed with a Cas protein) for site-directed cleavage of GPR75 nucleic acid molecules.

Cas proteins generally comprise at least one RNA recognition or binding domain that can interact with gRNAs. Cas proteins can also comprise nuclease domains (such as, for example, DNase or RNase domains), DNA binding domains, helicase domains, protein-protein interaction domains, dimerization domains, and other domains. Suitable Cas proteins include, for example, a wild type Cas9 protein and a wild type Cpf1 protein (such as, for example, FnCpf1). A Cas protein can have full cleavage activity to create a double-strand break in a GPR75 genomic nucleic acid molecule or it can be a nickase that creates a single-strand break in a GPR75 genomic nucleic acid molecule. Additional examples of Cas proteins include, but are not limited to, Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5e (CasD), Cas6, Cas6e, Cas6f, Cas7, Cas8a1, Cas8a2, Cas8b, Cas8c, Cas9 (Csn1 or Csx12), Cas10, Cas10d, CasF, CasG, CasH, Csy1, Csy2, Csy3, Cse1 (CasA), Cse2 (CasB), Cse3 (CasE), Cse4 (CasC), Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, and Cu1966, and homologs or modified versions thereof. Cas proteins can also be operably linked to heterologous polypeptides as fusion proteins. For example, a Cas protein can be fused to a cleavage domain, an epigenetic modification domain, a transcriptional activation domain, or a transcriptional repressor domain. Cas proteins can be provided in any form. For example, a Cas protein can be provided in the form of a protein, such as a Cas protein complexed with a gRNA. Alternately, a Cas protein can be provided in the form of a nucleic acid molecule encoding the Cas protein, such as an RNA or DNA.

In some embodiments, targeted genetic modifications of GPR75 genomic nucleic acid molecules can be generated by contacting a cell with a Cas protein and one or more gRNAs that hybridize to one or more gRNA recognition sequences within a target genomic locus in the GPR75 genomic nucleic acid molecule. For example, a gRNA recognition sequence can be located within a region of SEQ ID NO:1. The gRNA recognition sequence can also include or be proximate to a position corresponding to: position 5,540-5,546, 5,557, 5,911, 5,920-5,923, or 6,411 according to SEQ ID NO:1. For example, the gRNA recognition sequence can be located

from about 1000, from about 500, from about 400, from about 300, from about 200, from about 100, from about 50, from about 45, from about 40, from about 35, from about 30, from about 25, from about 20, from about 15, from about 10, or from about 5 nucleotides of a position corresponding to: position 5,540-5,546, 5,557, 5,911, 5,920-5,923, or 6,411 according to SEQ ID NO:1. The gRNA recognition sequence can include or be proximate to the start codon of a GPR75 genomic nucleic acid molecule or the stop codon of a GPR75 genomic nucleic acid molecule. For example, the gRNA recognition sequence can be located from about 10, from about 20, from about 30, from about 40, from about 50, from about 100, from about 200, from about 300, from about 400, from about 500, or from about 1,000 nucleotides of the start codon or the stop codon.

The gRNA recognition sequences within a target genomic locus in a GPR75 genomic nucleic acid molecule are located near a Protospacer Adjacent Motif (PAM) sequence, which is a 2-6 base pair DNA sequence immediately following the DNA sequence targeted by the Cas9 nuclease. The canonical PAM is the sequence 5'-NGG-3' where "N" is any nucleobase followed by two guanine ("G") nucleobases. gRNAs can transport Cas9 to anywhere in the genome for gene editing, but no editing can occur at any site other than one at which Cas9 recognizes PAM. In addition, 5'-NGA-3' can be a highly efficient non-canonical PAM for human cells. Generally, the PAM is about 2-6 nucleotides downstream of the DNA sequence targeted by the gRNA. The PAM can flank the gRNA recognition sequence. In some embodiments, the gRNA recognition sequence can be flanked on the 3' end by the PAM. In some embodiments, the gRNA recognition sequence can be flanked on the 5' end by the PAM. For example, the cleavage site of Cas proteins can be about 1 to about 10, about 2 to about 5 base pairs, or three base pairs upstream or downstream of the PAM sequence. In some embodiments (such as when Cas9 from *S. pyogenes* or a closely related Cas9 is used), the PAM sequence of the non-complementary strand can be 5'-NGG-3', where N is any DNA nucleotide and is immediately 3' of the gRNA recognition sequence of the non-complementary strand of the target DNA. As such, the PAM sequence of the complementary strand would be 5'-CCN-3', where N is any DNA nucleotide and is immediately 5' of the gRNA recognition sequence of the complementary strand of the target DNA.

A gRNA is an RNA molecule that binds to a Cas protein and targets the Cas protein to a specific location within a GPR75 genomic nucleic acid molecule. An exemplary gRNA is a gRNA effective to direct a Cas enzyme to bind to cleave a GPR75 genomic nucleic acid molecule,

wherein the gRNA comprises a DNA-targeting segment that hybridizes to a gRNA recognition sequence within the GPR75 genomic nucleic acid molecule that includes or is proximate to a position corresponding to: position 5,540-5,546, 5,557, 5,911, 5,920-5,923, or 6,411 according to SEQ ID NO:1. For example, a gRNA can be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, from about 10, from about 15, from about 20, from about 25, from about 30, from about 35, from about 40, from about 45, from about 50, from about 100, from about 200, from about 300, from about 400, from about 500, or from about 1,000 nucleotides of a position corresponding to: position 5,540-5,546, 5,557, 5,911, 5,920-5,923, or 6,411 according to SEQ ID NO:1. Other exemplary gRNAs comprise a DNA-targeting segment that hybridizes to a gRNA recognition sequence present within a GPR75 genomic nucleic acid molecule that includes or is proximate to the start codon or the stop codon. For example, a gRNA can be selected such that it hybridizes to a gRNA recognition sequence that is located from about 5, from about 10, from about 15, from about 20, from about 25, from about 30, from about 35, from about 40, from about 45, from about 50, from about 100, from about 200, from about 300, from about 400, from about 500, or from about 1,000 nucleotides of the start codon or located from about 5, from about 10, from about 15, from about 20, from about 25, from about 30, from about 35, from about 40, from about 45, from about 50, from about 100, from about 200, from about 300, from about 400, from about 500, or from about 1,000 nucleotides of the stop codon. Suitable gRNAs can comprise from about 17 to about 25 nucleotides, from about 17 to about 23 nucleotides, from about 18 to about 22 nucleotides, or from about 19 to about 21 nucleotides. In some embodiments, the gRNAs can comprise 20 nucleotides.

Examples of suitable gRNA recognition sequences located within the human GPR75 reference gene are set forth in Table 1 as SEQ ID NOS:61-98.

Table 1: Guide RNA Recognition Sequences Near GPR75 Variation(s)

Strand	gRNA Recognition Sequence	SEQ ID NO:
-	ACACCATCCGGAGCCGGTGCAGG	61
-	GAAAGCATCCGGGATACTACTGG	62
+	TGATCGCCCTGCACCGGCTCCGG	63
+	GCACCGGCTCCGGATGGTGTTGG	64
+	ACCGGCTCCGGATGGTGTTGGGG	65

+	CACCGGCTCCGGATGGTGTTGGG	66
-	GGAAAGGAGGCCGTGCGATTAGG	67
+	GGGGAAACAGCCTAATCGCACGG	68
-	CACCATCCGGAGCCGGTGCAGGG	69
+	TGGCAGTGATCGCCCTGCACCGG	70
-	CATGATGATGAAGCCTGAACTGG	71
+	CGCCCTGCACCGGCTCCGGATGG	72
-	TCCCCAACACCATCCGGAGCCGG	73
-	CTGTCACTCCACAAATGAAGAGG	74
-	GACTTGAGCGTTCTTCCGCAGGG	75
-	GCATCGACTGTGATTACAGGGGG	76
-	GCCGGCATGGCACACTGGATGGG	77
-	GAAGCATCGACTGTGATTACAGG	78
-	AGCATCGACTGTGATTACAGGGG	79
-	TGACTTGAGCGTTCTTCCGCAGG	80
+	TCATGATTGCTCAGACCCTGCGG	81
-	CATCGACTGTGATTACAGGGGGG	82
-	AAGCATCGACTGTGATTACAGGG	83
+	TCCAGACCACAGCCTTTCATGGG	84
+	CCCATGTCCAGTCTGATTGCTGG	85
-	ACAGAGCCGGCATGGCACACTGG	86
+	CAGACCACAGCCTTTCATGGGGG	87
+	TTCATGGGGGTCCCTGTGCAGGG	88
+	AAGACTCGACTTCGAGCCATGGG	89
+	AAAGACTCGACTTCGAGCCATGG	90
+	CGACTTCGAGCCATGGGAAAAGG	91
+	TATATTCTCGGAACAGTGCAGGG	92
+	CTCTGGTGCCTCCAATACATAGG	93
+	ATATATTCTCGGAACAGTGCAGG	94
+	TGCCTCCAATACATAGGCCTGGG	95
-	AACCCAGGCCTATGTATTGGAGG	96

-	AAAAACCCAGGCCTATGTATTGG	97
-	TTCGAGGTTCCCTTTTCCCATGG	98

The Cas protein and the gRNA form a complex, and the Cas protein cleaves the target GPR75 genomic nucleic acid molecule. The Cas protein can cleave the nucleic acid molecule at a site within or outside of the nucleic acid sequence present in the target GPR75 genomic nucleic acid molecule to which the DNA-targeting segment of a gRNA will bind. For example, formation of a CRISPR complex (comprising a gRNA hybridized to a gRNA recognition sequence and complexed with a Cas protein) can result in cleavage of one or both strands in or near (such as, for example, within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, or more base pairs from) the nucleic acid sequence present in the GPR75 genomic nucleic acid molecule to which a DNA-targeting segment of a gRNA will bind.

Such methods can result, for example, in a GPR75 genomic nucleic acid molecule in which a region of SEQ ID NO:1 is disrupted, the start codon is disrupted, the stop codon is disrupted, or the coding sequence is disrupted or deleted. Optionally, the cell can be further contacted with one or more additional gRNAs that hybridize to additional gRNA recognition sequences within the target genomic locus in the GPR75 genomic nucleic acid molecule. By contacting the cell with one or more additional gRNAs (such as, for example, a second gRNA that hybridizes to a second gRNA recognition sequence), cleavage by the Cas protein can create two or more double-strand breaks or two or more single-strand breaks.

In some embodiments, the GPR75 inhibitor comprises a small molecule. In some embodiments, the GPR75 inhibitor is an inhibitor of CCL5 (RANTES) including, but not limited to, [^{44}AANA^{47}]-RANTES and Met-CCL$_5$ (see, Braunersreuther et al., Arteriosclerosis, Thrombosis, and Vasc. Biol., 2008, 28, 1090-1096; Proudfoot et al., J. Biol. Chem., 1999, 274, 32478-32485; and Matsui et al., J. Neroimmunol., 2002, 128, 16-22). In some embodiments, the GPR75 inhibitor is an inhibitor of the interaction between GPR75 and 20-Hydroxyeicosatetraenoic acid (20-HETE), including, but not limited to, fatty acid analogs, terminal acetylenic fatty acids, terminal di-bromo fatty acids, sulfonated fatty acids, TS-011, Het0016, 5,14,20-HEDE, 5,14,20-HEDGE, 6,15,20-HEDE, 17-ODYA, DDMS, DDBB, 2,5,8,11,14,17-hexaoxanonadecan-19-yl-20-hydroxyeicosa 6(z), 15(z)-dienote (20-sola), and 6(z),15(z)hyroxyeicosa-6,15-dienamido-diencoic acid (aaa) (see, Miyata et al., Br. J. Pharmacol., 2001, 133, 325-329; Miyata et al., J. Pharmacol. Exp. Ther., 2005, 314, 77-85; Pandey et al., J.

Pharmacol. Exp. Ther., 2017, 363, 412-418; and Savas et al., J. Biol. Chem., 2016, 291, 16904-16919). In some embodiments, the GPR75 inhibitor is any of the antagonists described in PCT Publication WO 2017/156164. In some embodiments, the GPR75 inhibitor is an inhibitor of the interaction between GPR75 and 20-HETE is a blocking antibody.

In some embodiments, the methods of treatment further comprise detecting the absence of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample from the subject. As used throughout the present disclosure, a "GPR75 missense variant nucleic acid molecule" is any GPR75 nucleic acid molecule (such as, for example, genomic nucleic acid molecule, mRNA molecule, or cDNA molecule) encoding a GPR75 polypeptide having a partial loss-of-function, a complete loss-of-function, a predicted partial loss-of-function, or a predicted complete loss-of-function.

The present disclosure also provides methods of treating a subject with a therapeutic agent that treats or inhibits obesity, wherein the subject is obese. In some embodiments, the methods comprise determining whether the subject has a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide by obtaining or having obtained a biological sample from the subject, and performing or having performed a sequence analysis on the biological sample to determine if the subject has a genotype comprising the GPR75 missense variant nucleic acid molecule. When the subject is GPR75 reference, the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor is administered or continued to be administered to the subject in a standard dosage amount. When the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor is administered or continued to be administered to the subject in an amount that is the same as or lower than a standard dosage amount. The presence of a genotype having the GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide indicates the subject has a reduced risk of developing obesity. In some embodiments, the subject is GPR75 reference. In some embodiments, the subject is heterozygous for a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide.

For subjects that are genotyped or determined to be either GPR75 reference or heterozygous for a GPR75 missense variant nucleic acid molecule, such subjects can be treated with a GPR75 inhibitor, as described herein.

Detecting the presence or absence of a GPR75 missense variant nucleic acid molecule in a biological sample from a subject and/or determining whether a subject has a GPR75 missense variant nucleic acid molecule can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*. In any of these embodiments, the nucleic acid molecule can be present within a cell obtained from the subject.

In some embodiments, when the subject is GPR75 reference, the subject is also administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount. In some embodiments, when the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, the subject is also administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a dosage amount that is the same as or lower than a standard dosage amount.

In some embodiments, the treatment methods further comprise detecting the absence of a GPR75 predicted loss-of-function polypeptide in a biological sample from the subject. In some embodiments, when the subject does not have a GPR75 predicted loss-of-function polypeptide, the subject is also administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount. In some embodiments, when the subject has a GPR75 predicted loss-of-function polypeptide, the subject is also administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a dosage amount that is the same as or lower than a standard dosage amount.

The present disclosure also provides methods of treating a subject with a therapeutic agent that treats or inhibits obesity, wherein the subject is obese. In some embodiments, the method comprises determining whether the subject has a GPR75 predicted loss-of-function polypeptide by obtaining or having obtained a biological sample from the subject, and performing or having performed an assay on the biological sample to determine if the subject has a GPR75 predicted loss-of-function polypeptide. When the subject does not have a GPR75 predicted loss-of-function polypeptide, the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor is administered or continued to be administered to the subject in a standard dosage amount. When the subject has a GPR75 predicted loss-of-function polypeptide, the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor is administered or continued to be administered to the subject in an amount that is the same as

or lower than a standard dosage amount. The presence of a GPR75 predicted loss-of-function polypeptide indicates the subject has a reduced risk of developing obesity. In some embodiments, the subject has a GPR75 predicted loss-of-function polypeptide. In some embodiments, the subject does not have a GPR75 predicted loss-of-function polypeptide.

Detecting the presence or absence of a GPR75 predicted loss-of-function polypeptide in a biological sample from a subject and/or determining whether a subject has a GPR75 predicted loss-of-function polypeptide can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*. In any of these embodiments, the polypeptide can be present within a cell obtained from the subject.

Examples of therapeutic agents that treat or inhibit obesity and/or increased BMI include, but are not limited to, sibutramine, orlistat, phentermine, lorcaserin, naltrexone, liraglutide, diethylpropion, bupropion, metformin, pramlintide, topiramate, and zonisamide, or any combination thereof. Examples of therapeutic agents that treat or inhibit obesity and/or increased BMI also include, but are not limited to, sibutramine, orlistat, phentermine and topiramate, lorcaserin, bupropion and naltrexone, liraglutide, phentermine and diethylpropion, bupropion, metformin, pramlintide, topiramate, and zonisamide, or any combination thereof.

In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is a GLP1R agonist including, but not limited to, BYETTA® or BYDUREON® (exenatide), VICTOZA® or SAXENDA® (liraglutide), LYXUMIA® or ADLYXIN® (lixisenatide), TANZEUM® (albiglutide), TRULICITY® (dulaglutide), and OZEMPIC® (semaglutide), or any combination thereof. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is BYETTA® (exenatide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is BYETTA® (exenatide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is VICTOZA® (liraglutide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is SAXENDA® (liraglutide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is LYXUMIA® (lixisenatide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is ADLYXIN® (lixisenatide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is TANZEUM® (albiglutide). In some embodiments, the

therapeutic agent that treats or inhibits obesity and/or increased BMI is TRULICITY® (dulaglutide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is OZEMPIC® (semaglutide). In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is chosen from exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide, or any combination thereof. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is exenatide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI liraglutide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is lixisenatide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is albiglutide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is dulaglutide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or increased BMI is semaglutide.

In some embodiments, the therapeutic agent that treats or inhibits obesity and/or reduces BMI is a melanocortin 4 receptor (MC4R) agonist. In some embodiments, the MC4R agonist comprises a protein, a peptide, a nucleic acid molecule, or a small molecule. In some embodiments, the protein is a peptide analog of MC4R. In some embodiments, the peptide is setmelanotide. In some embodiments, the therapeutic agent that treats or inhibits obesity and/or reduces BMI is a combination of setmelanotide and one or more of sibutramine, orlistat, phentermine, lorcaserin, naltrexone, liraglutide, diethylpropion, bupropion, metformin, pramlintide, topiramate, and zonisamide. In some embodiments, the MC4R agonist is a peptide comprising the amino acid sequence His-Phe-Arg-Trp. In some embodiments, the small molecule is 1,2,3R,4-tetrahydroisoquinoline-3-carboxylic acid. In some embodiments, the MC4R agonist is ALB-127158(a).

In some embodiments, the dose of the therapeutic agents that treat or inhibit obesity and/or a GPR75 inhibitor can be reduced by about 10%, by about 20%, by about 30%, by about 40%, by about 50%, by about 60%, by about 70%, by about 80%, or by about 90% for subjects that are heterozygous for a GPR75 missense variant nucleic acid molecule (i.e., a lower than the standard dosage amount) compared to subjects that are GPR75 reference (who may receive a standard dosage amount). In some embodiments, the dose of the therapeutic agents that treat or inhibit obesity and/or a GPR75 inhibitor can be reduced by about 10%, by about 20%, by about 30%, by about 40%, or by about 50%. In addition, the dose of therapeutic agents that

treat or inhibit obesity and/or a GPR75 inhibitor in subjects that are heterozygous for a GPR75 missense variant nucleic acid molecule can be administered less frequently compared to subjects that are GPR75 reference.

Administration of the therapeutic agents that treat or inhibit obesity and/or GPR75 inhibitors can be repeated, for example, after one day, two days, three days, five days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, eight weeks, two months, or three months. The repeated administration can be at the same dose or at a different dose. The administration can be repeated once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more. For example, according to certain dosage regimens a subject can receive therapy for a prolonged period of time such as, for example, 6 months, 1 year, or more.

Administration of the therapeutic agents that treat or inhibit obesity and/or GPR75 inhibitors can occur by any suitable route including, but not limited to, parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, intraperitoneal, topical, intranasal, or intramuscular. Pharmaceutical compositions for administration are desirably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically and pharmaceutically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. The term “pharmaceutically acceptable” means that the carrier, diluent, excipient, or auxiliary is compatible with the other ingredients of the formulation and not substantially deleterious to the recipient thereof.

In some embodiments, the therapeutic agents that treat or inhibit obesity and/or GPR75 inhibitors (such as any of the inhibitory nucleic acid molecules disclosed herein) are administered intrathecally (i.e., introduction into the subarachnoid space of the spinal cord or into the spinal canal so that the therapeutic agent can reach the cerebrospinal fluid of a subject, or introduction into the anatomic space or potential space inside a sheath, including, by way of non-limiting examples, the arachnoid membrane of the brain or spinal cord). In some embodiments, intrathecal administration results in the therapeutic agent acting on, without limitation, the cortex, the cerebellum, the striatum, the cervical spine, the lumbar spine, or the thoracic spine. Therapeutic agents administered intrathecally may ultimately act on targets throughout the entire central nervous system. In some embodiments, the intrathecal

administration is into the cisterna magna or by the lumbar area or region. In some embodiments, the intrathecal administration into the lumbar area or region results in delivery of the therapeutic agent to the distal spinal canal. Exemplary methods for intrathecal administration are described in, for example, Lazorthes et al., Advances in Drug Delivery Systems and Applications in Neurosurgery, 143-192. In some embodiments, the intrathecal administration is by injection, by bolus injection, by a catheter, or by a pump. In some embodiments, the intrathecal administration is by lumber puncture. In some embodiments, the pump is an osmotic pump. In some embodiments, the pump is implanted into subarachnoid space of the spinal canal, below the skin of the abdomen, or behind the chest wall. In some embodiments, the intrathecal administration is by an intrathecal delivery system for a therapeutic substance including a reservoir containing a volume of the therapeutic agent and a pump configured to deliver at least a portion of the therapeutic substance contained in the reservoir. In some embodiments, intrathecal administration is through intermittent or continuous access to an implanted intrathecal drug delivery device (IDDD). In some embodiments, the therapeutic substance is an inhibitory nucleic acid molecule. In some embodiments, the amount of the nucleic acid molecule administered intrathecally ranges from about 10 μg to about 2 mg, from about 50 μg to about 1500 μg, or from about 100 μg to about 1000 μg. In some embodiments, the therapeutic agent is disposed within a pharmaceutical composition. In some embodiments, the pharmaceutical composition does not comprise a preservative.

The terms “treat”, “treating”, and “treatment” and “prevent”, “preventing”, and “prevention” as used herein, refer to eliciting the desired biological response, such as a therapeutic and prophylactic effect, respectively. In some embodiments, a therapeutic effect comprises one or more of a decrease/reduction in obesity, a decrease/reduction in the severity of obesity (such as, for example, a reduction or inhibition of development or obesity), a decrease/reduction in symptoms and obesity-related effects, delaying the onset of symptoms and obesity-related effects, reducing the severity of symptoms of obesity-related effects, reducing the severity of an acute episode, reducing the number of symptoms and obesity-related effects, reducing the latency of symptoms and obesity-related effects, an amelioration of symptoms and obesity-related effects, reducing secondary symptoms, reducing secondary infections, preventing relapse to obesity, decreasing the number or frequency of relapse episodes, increasing latency between symptomatic episodes, increasing time to sustained

progression, expediting remission, inducing remission, augmenting remission, speeding recovery, or increasing efficacy of or decreasing resistance to alternative therapeutics, and/or an increased survival time of the affected host animal, following administration of the agent or composition comprising the agent. A prophylactic effect may comprise a complete or partial avoidance/inhibition or a delay of obesity development/progression (such as, for example, a complete or partial avoidance/inhibition or a delay), or an increased survival time of the affected host animal, following administration of a therapeutic protocol. Treatment of obesity encompasses the treatment of subjects already diagnosed as having any form of obesity at any clinical stage or manifestation, the delay of the onset or evolution or aggravation or deterioration of the symptoms or signs of obesity, and/or preventing and/or reducing the severity of obesity.

The present disclosure also provides methods of identifying a subject having an increased risk for developing obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, and/or excessive food intake. In some embodiments, the method comprises determining or having determined in a biological sample obtained from the subject the presence or absence of a GPR75 missense variant nucleic acid molecule (such as a genomic nucleic acid molecule, mRNA molecule, and/or cDNA molecule) encoding a predicted loss-of-function GPR75 polypeptide. When the subject lacks a GPR75 missense variant nucleic acid molecule (i.e., the subject is genotypically categorized as a GPR75 reference), then the subject has an increased risk for developing obesity. When the subject has a GPR75 missense variant nucleic acid molecule (i.e., the subject is heterozygous or homozygous for a GPR75 missense variant nucleic acid molecule), then the subject has a decreased risk for developing obesity.

Having a single copy of a GPR75 missense variant nucleic acid molecule is more protective of a subject from developing obesity than having no copies of a GPR75 missense variant nucleic acid molecule. Without intending to be limited to any particular theory or mechanism of action, it is believed that a single copy of a GPR75 missense variant nucleic acid molecule (i.e., heterozygous for a GPR75 missense variant nucleic acid molecule) is protective of a subject from developing obesity, and it is also believed that having two copies of a GPR75 missense variant nucleic acid molecule (i.e., homozygous for a GPR75 missense variant nucleic acid molecule) may be more protective of a subject from developing obesity, relative to a subject with a single copy. Thus, in some embodiments, a single copy of a GPR75 missense variant nucleic acid molecule may not be completely protective, but instead, may be partially or

incompletely protective of a subject from developing obesity. While not desiring to be bound by any particular theory, there may be additional factors or molecules involved in the development of obesity that are still present in a subject having a single copy of a GPR75 missense variant nucleic acid molecule, thus resulting in less than complete protection from the development of obesity.

Determining whether a subject has a GPR75 missense variant nucleic acid molecule in a biological sample from a subject and/or determining whether a subject has a GPR75 missense variant nucleic acid molecule can be carried out by any of the methods described herein. In some embodiments, these methods can be carried out *in vitro*. In some embodiments, these methods can be carried out *in situ*. In some embodiments, these methods can be carried out *in vivo*. In any of these embodiments, the nucleic acid molecule can be present within a cell obtained from the subject.

In some embodiments, when a subject is identified as having an increased risk of developing obesity, the subject is further treated with a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor, as described herein. For example, when the subject is GPR75 reference, and therefore has an increased risk for developing obesity, the subject is administered a GPR75 inhibitor. In some embodiments, such a subject is also administered a therapeutic agent that treats or inhibits obesity. In some embodiments, when the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, the subject is administered the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a dosage amount that is the same as or lower than a standard dosage amount. In some embodiments, the subject is GPR75 reference. In some embodiments, the subject is heterozygous for a GPR75 missense variant nucleic acid molecule.

The present disclosure also provides methods of detecting the presence or absence of a GPR75 missense genomic variant nucleic acid molecule in a biological sample from a subject, and/or a GPR75 missense variant mRNA molecule in a biological sample from a subject, and/or a GPR75 missense variant cDNA molecule produced from an mRNA molecule in a biological sample from a subject. It is understood that gene sequences within a population and mRNA molecules encoded by such genes can vary due to polymorphisms such as single-nucleotide polymorphisms. The sequences provided herein for the GPR75 variant genomic nucleic acid molecule, GPR75 variant mRNA molecule, and GPR75 variant cDNA molecule are only

exemplary sequences. Other sequences for the GPR75 variant genomic nucleic acid molecule, variant mRNA molecule, and variant cDNA molecule are also possible.

The biological sample can be derived from any cell, tissue, or biological fluid from the subject. The biological sample may comprise any clinically relevant tissue, such as a bone marrow sample, a tumor biopsy, a fine needle aspirate, or a sample of bodily fluid, such as blood, gingival crevicular fluid, plasma, serum, lymph, ascitic fluid, cystic fluid, or urine. In some cases, the sample comprises a buccal swab. The biological sample used in the methods disclosed herein can vary based on the assay format, nature of the detection method, and the tissues, cells, or extracts that are used as the sample. A biological sample can be processed differently depending on the assay being employed. For example, when detecting any GPR75 variant nucleic acid molecule, preliminary processing designed to isolate or enrich the biological sample for the genomic DNA can be employed. A variety of techniques may be used for this purpose. When detecting the level of any GPR75 variant mRNA molecule, different techniques can be used enrich the biological sample with mRNA molecules. Various methods to detect the presence or level of an mRNA molecule or the presence of a particular variant genomic DNA locus can be used.

In some embodiments, detecting a human GPR75 missense variant nucleic acid molecule in a subject comprises assaying or genotyping a biological sample obtained from the subject to determine whether a GPR75 genomic nucleic acid molecule in the biological sample, and/or a GPR75 mRNA molecule in the biological sample, and/or a GPR75 cDNA molecule produced from an mRNA molecule in the biological sample, comprises one or more variations that cause a loss-of-function (partial or complete) or are predicted to cause a loss-of-function (partial or complete).

In some embodiments, the methods of detecting the presence or absence of a GPR75 missense variant nucleic acid molecule (such as, for example, a genomic nucleic acid molecule, an mRNA molecule, and/or a cDNA molecule produced from an mRNA molecule) in a subject, comprise performing an assay on a biological sample obtained from the subject. The assay determines whether a nucleic acid molecule in the biological sample comprises a particular nucleotide sequence.

In some embodiments, the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1 (for genomic nucleic acid molecules); lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-

545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10 (for mRNA molecules); lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34 (for cDNA molecules).

In some embodiments, the nucleotide sequence comprises: an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3 (for genomic nucleic acid molecules); an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or an adenine at a position corresponding to position 617 according to SEQ ID NO:27 (for mRNA molecules); an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51 (for cDNA molecules).

In some embodiments, the nucleotide sequence comprises: a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4 (for genomic nucleic acid molecules); a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or a uracil at a position corresponding to position 971 according to SEQ ID NO:28 (for mRNA molecules); a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52 (for cDNA molecules).

In some embodiments, the nucleotide sequence: lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1 (for genomic nucleic

acid molecules); lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10 (for mRNA molecules); lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34 (for cDNA molecules).

In some embodiments, the nucleotide sequence comprises: an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6 (for genomic nucleic acid molecules); an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30 (for mRNA molecules); an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54 (for cDNA molecules).

In some embodiments, the nucleotide sequence comprises: a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof (for genomic nucleic acid molecules); a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof (for mRNA molecules); a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position

corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof (for cDNA molecules).

In some embodiments, the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

In some embodiments, the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to

SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

In some embodiments, the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position

corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

In some embodiments, the biological sample comprises a cell or cell lysate. Such methods can further comprise, for example, obtaining a biological sample from the subject comprising a GPR75 genomic nucleic acid molecule or mRNA molecule, and if mRNA, optionally reverse transcribing the mRNA into cDNA. Such assays can comprise, for example determining the identity of these positions of the particular GPR75 nucleic acid molecule. In some embodiments, the method is an *in vitro* method.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule, the GPR75 mRNA molecule, or the GPR75 cDNA molecule in the biological sample, wherein the sequenced portion comprises one or more variations that cause a loss-of-function (partial or complete) or are predicted to cause a loss-of-function (partial or complete).

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; or positions 600-606 according to SEQ ID NO:26, or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; or positions 600-606 according to SEQ ID NO:50, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1; ii) a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; or iii) a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a

position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; or position 617 according to SEQ ID NO:27, or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; or position 617 according to SEQ ID NO:51, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3; ii) an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or an adenine at a position corresponding to position 617 according to SEQ ID NO:27; or iii) an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; or position 971 according to SEQ ID NO:28, or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample,

wherein the sequenced portion comprises a position corresponding to: position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; or position 971 according to SEQ ID NO:52, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4; ii) a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or a uracil at a position corresponding to position 971 according to SEQ ID NO:28; or iii) a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; or positions 980-983 according to SEQ ID NO:29, or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; or positions 980-983 according to SEQ ID NO:53, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1; ii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID

NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; or iii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; or position 1,471 according to SEQ ID NO:30 or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6; ii) an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; or iii) an insertion of a thymine at a position corresponding to

position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of: i) the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; or position 891 according to SEQ ID NO:103, or the complement thereof; and/or iii) the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA in the biological sample, wherein the sequenced portion comprises a position corresponding to: position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: i) a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99; ii) a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or iii) a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 genomic

nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; position 5,557 according to SEQ ID NO:3, or the complement thereof; position 5,911 according to SEQ ID NO:4, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 6,411 according to SEQ ID NO:6, or the complement thereof; or position 5,831 according to SEQ ID NO:99, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample comprises: a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; position 617 according to SEQ ID NO:27, or the complement thereof; position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; position 971 according to SEQ ID NO:28, or the complement thereof; positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; positions 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the

complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; position 891 according to SEQ ID NO:103, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102; or comprises a guanine at a

position corresponding to position 891 according to SEQ ID NO:103, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 cDNA molecule produced from the mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to SEQ ID NO:50, or the complement thereof; position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; position 617 according to SEQ ID NO:51, or the complement thereof; position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; position 971 according to SEQ ID NO:52, or the complement thereof; positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; positions 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, the complement thereof; position 1,471 according to SEQ ID NO:54, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof. When the sequenced portion of the GPR75 nucleic acid molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36; comprises an adenine at a position corresponding to position 457 according to

SEQ ID NO:41; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42; a comprises thymine at a position corresponding to position 732 according to SEQ ID NO:47; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, then the GPR75 nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to positions 5,540-5,546 according to SEQ ID NO:2; ii) mRNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, or positions 600-606 according to SEQ ID NO:26; and/or iii) cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, or positions 600-606 according to SEQ ID NO:50; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule corresponding to positions

5,540-5,546 according to SEQ ID NO:2; ii) mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, or positions 600-606 according to SEQ ID NO:26; and/or iii) cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, or positions 600-606 according to SEQ ID NO:50; and c) determining whether the extension product of the primer comprises: i) a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1; ii) a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; or iii) a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to position 5,557 according to SEQ ID NO:3; ii) mRNA molecule that is proximate to a position corresponding to: position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27 and/or iii) cDNA molecule that is proximate to a position corresponding to: position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, or position 617 according to SEQ ID NO:51; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule corresponding to position 5,557 according to SEQ ID NO:3; ii) mRNA molecule corresponding to: position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, or position 617 according to SEQ ID NO:27; and/or iii) cDNA molecule corresponding to: position 556 according to SEQ ID NO:36, position

457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, or position 617 according to SEQ ID NO:51; and c) determining whether the extension product of the primer comprises: i) an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3; ii) an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or an adenine at a position corresponding to position 617 according to SEQ ID NO:27; or iii) an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to position 5,911 according to SEQ ID NO:4; ii) mRNA molecule that is proximate to a position corresponding to: position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, or position 971 according to SEQ ID NO:28; and/or iii) cDNA molecule that is proximate to a position corresponding to: position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, or position 971 according to SEQ ID NO:52; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule corresponding to position 5,911 according to SEQ ID NO:4; ii) mRNA molecule corresponding to: position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, or position 971 according to SEQ ID NO:28; and/or iii) cDNA molecule corresponding to: position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, or position 971 according to SEQ ID NO:52; and c) determining whether the extension product of the primer comprises: i) a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4; ii) a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or a uracil at a position corresponding to position 971 according to SEQ ID NO:28; or iii) a thymine at a position

corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to positions 5,920-5,923 according to SEQ ID NO:5; ii) mRNA molecule that is proximate to a position corresponding to: positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, or positions 980-983 according to SEQ ID NO:29; and/or iii) cDNA molecule that is proximate to a position corresponding to: positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, or positions 980-983 according to SEQ ID NO:53; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule corresponding to positions 5,920-5,923 according to SEQ ID NO:5; ii) mRNA molecule corresponding to: positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, or positions 980-983 according to SEQ ID NO:29; and/or iii) cDNA molecule corresponding to: positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, or positions 980-983 according to SEQ ID NO:53; and c) determining whether the extension product of the primer comprises: i) a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1; ii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; or iii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according

to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to position 6,411 according to SEQ ID NO:6; ii) mRNA molecule that is proximate to a position corresponding to: position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, or position 1,471 according to SEQ ID NO:30; and/or iii) cDNA molecule that is proximate to a position corresponding to: position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, or position 1,471 according to SEQ ID NO:54; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule corresponding to position 6,411 according to SEQ ID NO:6; ii) mRNA molecule corresponding to: position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, or position 1,471 according to SEQ ID NO:30; and/or iii) cDNA molecule corresponding to: position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, or position 1,471 according to SEQ ID NO:54; and c) determining whether the extension product of the primer comprises: i) an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6; ii) an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; or iii) an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a

position corresponding to position 5,831 according to SEQ ID NO:99; ii) mRNA molecule that is proximate to a position corresponding to: position 830 according to SEQ ID NO:100; position 731 according to SEQ ID NO:101; position 652 according to SEQ ID NO:102; or position 891 according to SEQ ID NO:103; and/or iii) cDNA molecule that is proximate to a position corresponding to: position 830 according to SEQ ID NO:104; position 731 according to SEQ ID NO:105; position 652 according to SEQ ID NO:106; or position 891 according to SEQ ID NO:107; b) extending the primer at least through the position of the nucleotide sequence of the GPR75: i) genomic nucleic acid molecule that is proximate to a position corresponding to position 5,831 according to SEQ ID NO:99; ii) mRNA molecule that is proximate to a position corresponding to: position 830 according to SEQ ID NO:100; position 731 according to SEQ ID NO:101; position 652 according to SEQ ID NO:102; or position 891 according to SEQ ID NO:103; and/or iii) cDNA molecule that is proximate to a position corresponding to: position 830 according to SEQ ID NO:104; position 731 according to SEQ ID NO:105; position 652 according to SEQ ID NO:106; or position 891 according to SEQ ID NO:107; and c) determining whether the extension product of the primer comprises: i) a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or iii) a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106; or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule that is proximate to a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according

to SEQ ID NO:99; b) extending the primer at least through the position of the nucleotide sequence of the GPR75 genomic nucleic acid molecule corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99; and c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 mRNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30; position 830 according to SEQ ID NO:100; position 731 according to SEQ ID NO:101; position 652 according to SEQ ID NO:102; or position 891 according to SEQ ID NO:103; b) extending the primer at least through the position of the nucleotide sequence of the GPR75 mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to

SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103; and c) determining whether the extension product of the primer: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprises a guanine at a position

corresponding to position 731 according to SEQ ID NO:101, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107; b) extending the primer at least through the position of the nucleotide sequence of the GPR75 cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107; and c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG

heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

In some embodiments, the assay comprises sequencing the entire nucleic acid molecule. In some embodiments, only a GPR75 genomic nucleic acid molecule is analyzed. In some embodiments, only a GPR75 mRNA is analyzed. In some embodiments, only a GPR75 cDNA obtained from GPR75 mRNA is analyzed.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion comprises: i) a deletion of a CCAGTAG

heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; ii) a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; or a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; and/or iii) a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: i) lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; ii) lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; or lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; and/or iii) lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; or lacking a

CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion comprises: i) an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; ii) an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; and/or iii) an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: i) an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; ii) an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; and/or iii) an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion comprises: i) a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; or a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; and/or iii) a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: i) a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; or a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; and/or iii) a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human

GPR75 polypeptide, wherein the amplified portion comprises: i) a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; ii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; and/or iii) a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: i) lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; ii) lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; or lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; and/or iii) lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; or lacking an AAAG

tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion comprises: i) an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; and/or iii) an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: i) an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; and/or iii) an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the

complement thereof; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion comprises: i) a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and/or iii) a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule comprising: i) a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and/or iii) a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof or; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606

according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid

molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652

according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the amplified portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at

a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; b) labeling the amplified nucleic acid molecule with a detectable label; c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG

tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and d) detecting the detectable label.

In some embodiments, the nucleic acid molecule is mRNA and the determining step further comprises reverse-transcribing the mRNA into a cDNA prior to the amplifying step.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: i) lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; ii) lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; or lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; and/or iii) lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to

positions 361-367 according to SEQ ID NO:33, or the complement thereof; or lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: i) an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; ii) an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; and/or iii) an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: i) a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; a or uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; and/or iii) a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a

thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof;. and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: i) lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; ii) lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; or lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; and/or iii) lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; or lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: i) an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or an

insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; and/or iii) an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule comprising: : i) a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and/or iii) a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3,

or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to

positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and detecting the detectable label.

In some embodiments, the determining step, detecting step, or sequence analysis comprises: contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or

the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and detecting the detectable label.

Alteration-specific polymerase chain reaction techniques can be used to detect mutations such as SNPs in a nucleic acid sequence. Alteration-specific primers can be used because the DNA polymerase will not extend when a mismatch with the template is present.

In some embodiments, the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into a cDNA prior to the amplifying step. In some embodiments, the nucleic acid molecule is present within a cell obtained from the subject.

In some embodiments, the assay comprises contacting the biological sample with a primer or probe, such as an alteration-specific primer or alteration-specific probe, that specifically hybridizes to a GPR75 variant genomic sequence, variant mRNA sequence, or

variant cDNA sequence and not the corresponding GPR75 reference sequence under stringent conditions, and determining whether hybridization has occurred.

In some embodiments, the assay comprises RNA sequencing (RNA-Seq). In some embodiments, the assays also comprise reverse transcribing mRNA into cDNA, such as by the reverse transcriptase polymerase chain reaction (RT-PCR).

In some embodiments, the methods utilize probes and primers of sufficient nucleotide length to bind to the target nucleotide sequence and specifically detect and/or identify a polynucleotide comprising a GPR75 variant genomic nucleic acid molecule, variant mRNA molecule, or variant cDNA molecule. The hybridization conditions or reaction conditions can be determined by the operator to achieve this result. The nucleotide length may be any length that is sufficient for use in a detection method of choice, including any assay described or exemplified herein. Such probes and primers can hybridize specifically to a target nucleotide sequence under high stringency hybridization conditions. Probes and primers may have complete nucleotide sequence identity of contiguous nucleotides within the target nucleotide sequence, although probes differing from the target nucleotide sequence and that retain the ability to specifically detect and/or identify a target nucleotide sequence may be designed by conventional methods. Probes and primers can have about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% sequence identity or complementarity with the nucleotide sequence of the target nucleic acid molecule.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1 (genomic nucleic acid molecule), a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8; a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; or a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10 (for mRNA molecules); a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446

according to SEQ ID NO:32; a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, and a second primer derived from the 3' flanking sequence adjacent to a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, to produce an amplicon that is indicative of the presence of a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, a deletion of a CCAGUAG heptanucleotide at positions corresponding

to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, a deletion of a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, a deletion of a CCAGUAG

heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or a deletion of a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3 (genomic nucleic acid molecule), an adenine at a position corresponding to position 556 according to SEQ ID NO:12; an adenine at a position corresponding to position 457 according to SEQ ID NO:17; an adenine at a position corresponding to position 378 according to SEQ ID NO:22; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27 (for mRNA molecules); an adenine at a position corresponding to position 556 according to SEQ ID NO:36; an adenine at a position corresponding to position 457 according to SEQ ID NO:41; an adenine at a position corresponding to position 378 according to SEQ ID NO:46; or an adenine at a position corresponding to position 617 according to SEQ ID NO:51 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, an adenine at a position corresponding to position 617 according to SEQ ID NO:27, an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, and a second primer derived from the 3' flanking sequence adjacent to an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, an adenine at a position corresponding to position 556 according to

SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, an adenine at a position corresponding to position 617 according to SEQ ID NO:27, an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51 to produce an amplicon that is indicative of the presence of the SNP at positions encoding an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, an adenine at a position corresponding to position 617 according to SEQ ID NO:27, an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, an adenine at a position corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, an adenine at a position corresponding to position 617 according to SEQ ID NO:27, an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, an adenine at a position

corresponding to position 556 according to SEQ ID NO:12, an adenine at a position corresponding to position 457 according to SEQ ID NO:17, an adenine at a position corresponding to position 378 according to SEQ ID NO:22, an adenine at a position corresponding to position 617 according to SEQ ID NO:27, an adenine at a position corresponding to position 556 according to SEQ ID NO:36, an adenine at a position corresponding to position 457 according to SEQ ID NO:41, an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or an adenine at a position corresponding to position 617 according to SEQ ID NO:51.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4 (genomic nucleic acid molecule), a uracil at a position corresponding to position 910 according to SEQ ID NO:13; a uracil at a position corresponding to position 811 according to SEQ ID NO:18; a uracil at a position corresponding to position 732 according to SEQ ID NO:23; or a uracil at a position corresponding to position 971 according to SEQ ID NO:28 (for mRNA molecules); a thymine at a position corresponding to position 910 according to SEQ ID NO:37; a thymine at a position corresponding to position 811 according to SEQ ID NO:42; a thymine at a position corresponding to position 732 according to SEQ ID NO:47; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, a uracil at a position corresponding to position 971 according to SEQ ID NO:28, a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, and a second primer derived from the 3' flanking sequence adjacent to a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a uracil at a position corresponding to position 910 according to SEQ

ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, a uracil at a position corresponding to position 971 according to SEQ ID NO:28, a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52 to produce an amplicon that is indicative of the presence of the SNP at positions encoding a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, a uracil at a position corresponding to position 971 according to SEQ ID NO:28, a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding to position 732 according to SEQ ID NO:23, a uracil at a position corresponding to position 971 according to SEQ ID NO:28, a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, a uracil at a position corresponding to position 910 according to SEQ ID NO:13, a uracil at a position corresponding to position 811 according to SEQ ID NO:18, a uracil at a position corresponding

to position 732 according to SEQ ID NO:23, a uracil at a position corresponding to position 971 according to SEQ ID NO:28, a thymine at a position corresponding to position 910 according to SEQ ID NO:37, a thymine at a position corresponding to position 811 according to SEQ ID NO:42, a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or a thymine at a position corresponding to position 971 according to SEQ ID NO:52.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1 (genomic nucleic acid molecule), a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10 (for mRNA molecules); a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32; a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions

corresponding to positions 980-983 according to SEQ ID NO:34, and a second primer derived from the 3' flanking sequence adjacent to a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34 to produce an amplicon that is indicative of the presence of a deletion of an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions

corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, a deletion of an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, a deletion of an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, a deletion of an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or a deletion of an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6 (genomic nucleic acid molecule), an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30 (for mRNA molecules); an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; an insertion of a thymine at a position

corresponding to position 1,232 according to SEQ ID NO:49; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, and a second primer derived from the 3' flanking sequence adjacent to an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54 to produce an amplicon that is indicative of the presence of an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an

insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54.

In some embodiments, to determine whether a GPR75 nucleic acid molecule (genomic nucleic acid molecule, mRNA molecule, or cDNA molecule), or complement thereof, within a biological sample comprises a nucleotide sequence comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99 (genomic nucleic acid molecule), a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position

corresponding to position 652 according to SEQ ID NO:102, or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, (for mRNA molecules); a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107 (for cDNA molecules), the biological sample can be subjected to an amplification method using a primer pair that includes a first primer derived from the 5' flanking sequence adjacent to guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, a guanine at a position corresponding to position 891 according to SEQ ID NO:103, a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, and a second primer derived from the 3' flanking sequence adjacent to guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, a guanine at a position corresponding to position 891 according to SEQ ID NO:103, a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, to produce an amplicon that is indicative of the presence of an insertion of guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, a guanine at a position corresponding to position 891 according to SEQ ID NO:103, a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position

corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107. In some embodiments, the amplicon may range in length from the combined length of the primer pairs plus one nucleotide base pair to any length of amplicon producible by a DNA amplification protocol. This distance can range from one nucleotide base pair up to the limits of the amplification reaction, or about twenty thousand nucleotide base pairs. Optionally, the primer pair flanks a region including positions comprising an insertion of guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, a guanine at a position corresponding to position 891 according to SEQ ID NO:103, a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides on each side of positions comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, a guanine at a position corresponding to position 830 according to SEQ ID NO:100, a guanine at a position corresponding to position 731 according to SEQ ID NO:101, a guanine at a position corresponding to position 652 according to SEQ ID NO:102, a guanine at a position corresponding to position 891 according to SEQ ID NO:103, a guanine at a position corresponding to position 830 according to SEQ ID NO:104, a guanine at a position corresponding to position 731 according to SEQ ID NO:105, a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Similar amplicons can be generated from the mRNA and/or cDNA sequences. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose, such as the PCR primer analysis tool in Vector NTI version 10 (Informax Inc., Bethesda Md.); PrimerSelect (DNASTAR Inc., Madison, Wis.); and Primer3 (Version 0.4.0.COPYRGT., 1991, Whitehead Institute for Biomedical Research, Cambridge, Mass.). Additionally, the sequence can be visually scanned and primers manually identified using known guidelines.

Illustrative examples of nucleic acid sequencing techniques include, but are not limited to, chain terminator (Sanger) sequencing and dye terminator sequencing. Other methods involve nucleic acid hybridization methods other than sequencing, including using labeled primers or probes directed against purified DNA, amplified DNA, and fixed cell preparations (fluorescence in situ hybridization (FISH)). In some methods, a target nucleic acid molecule may be amplified prior to simultaneous with detection. Illustrative examples of nucleic acid amplification techniques include, but are not limited to, polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), and nucleic acid sequence based amplification (NASBA). Other methods include, but are not limited to, ligase chain reaction, strand displacement amplification, and thermophilic SDA (tSDA).

In hybridization techniques, stringent conditions can be employed such that a probe or primer will specifically hybridize to its target. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target sequence to a detectably greater degree than to other non-target sequences, such as, at least 2-fold, at least 3-fold, at least 4-fold, or more over background, including over 10-fold over background. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 2-fold. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 3-fold. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by at least 4-fold. In some embodiments, a polynucleotide primer or probe under stringent conditions will hybridize to its target nucleotide sequence to a detectably greater degree than to other nucleotide sequences by over 10-fold over background. Stringent conditions are sequence-dependent and will be different in different circumstances.

Appropriate stringency conditions which promote DNA hybridization, for example, 6X sodium chloride/sodium citrate (SSC) at about 45°C., followed by a wash of 2X SSC at 50°C, are known or can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Typically, stringent conditions for hybridization and detection will be those in which the salt concentration is less than about 1.5 M Na^+ ion, typically about 0.01 to 1.0 M Na^+ ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about

30°C for short probes (such as, for example, 10 to 50 nucleotides) and at least about 60°C for longer probes (such as, for example, greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Optionally, wash buffers may comprise about 0.1% to about 1% SDS. Duration of hybridization is generally less than about 24 hours, usually about 4 to about 12 hours. The duration of the wash time will be at least a length of time sufficient to reach equilibrium.

The present disclosure also provides methods of detecting the presence of a human GPR75 predicted loss-of-function polypeptide comprising performing an assay on a biological sample obtained from a subject to determine whether a GPR75 polypeptide in the subject contains one or more variations that causes the polypeptide to have a loss-of-function (partial or complete) or predicted loss-of-function (partial or complete). The GPR75 predicted loss-of-function polypeptide can be any of the GPR75 variant polypeptides described herein. In some embodiments, the methods detect the presence of GPR75 Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs. In some embodiments, the methods detect the presence of Lys404*, Ser219fs, or c.-110+1G>A.

In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample comprises amino acids 110-130 according to SEQ ID NO:56. In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample comprises amino acids 236-239 according to SEQ ID NO:59. In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample comprises amino acids 400-425 according to SEQ ID NO:60. In some embodiments, the methods comprise performing an assay on a sample obtained from a subject to determine whether a GPR75 polypeptide in the sample comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108.

In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to any one or more of positions 110-130 according to SEQ ID NO:56 or SEQ ID NO:55. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 116 according to SEQ ID NO:57 or SEQ ID NO:55. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to any of positions 234-540 according to SEQ ID NO:55. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to any one or more of positions 236-239 according to SEQ ID NO:59 or SEQ ID NO:55. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to any one or more of positions 400-425 according to SEQ ID NO:60 or SEQ ID NO:55. In some embodiments, the detecting step comprises sequencing at least a portion of the polypeptide that comprises a position corresponding to position 207 according to SEQ ID NO:108.

In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to any one or more of positions 110-130 according to SEQ ID NO:56 or SEQ ID NO:55. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 116 according to SEQ ID NO:57 or SEQ ID NO:55. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to any of positions 234-540 according to SEQ ID NO:55. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to any one or more of positions 236-239 according to SEQ ID NO:59 or SEQ ID NO:55. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to any one or more of positions 400-425 according to SEQ ID NO:60 or SEQ ID NO:55. In some embodiments, the detecting step comprises an immunoassay for detecting the presence of a polypeptide that comprises a position corresponding to position 207 according to SEQ ID NO:108 or SEQ ID NO:55.

In some embodiments, when the subject does not have a GPR75 predicted loss-of-function polypeptide, the subject has an increased risk for developing obesity or any of excessive weight, an elevated BMI, an elevated body fat mass, percentage, or volume, and/or excessive food intake. In some embodiments, when the subject has a GPR75 predicted loss-of-function polypeptide, the subject has a decreased risk for developing obesity or any of excessive weight, an elevated BMI, an elevated body fat mass, percentage, or volume, and/or excessive food intake.

The present disclosure also provides isolated nucleic acid molecules that hybridize to GPR75 variant genomic nucleic acid molecules, GPR75 variant mRNA molecules, and/or GPR75 variant cDNA molecules (such as any of the genomic variant nucleic acid molecules, mRNA variant molecules, and cDNA variant molecules disclosed herein). In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, or positions 600-606 according to SEQ ID NO:50.

In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: position 5,557 according to SEQ ID NO:3, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, or position 617 according to SEQ ID NO:51.

In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: position 5,911 according to SEQ ID NO:4, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, or position 971 according to SEQ ID NO:52.

In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: positions 5,920-5,923 according to SEQ ID NO:5, positions 919-922 according to SEQ ID NO:14, positions 820-823

according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, or positions 980-983 according to SEQ ID NO:53.

In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: position 6,411 according to SEQ ID NO:6, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, or position 1,471 according to SEQ ID NO:54.

In some embodiments, the isolated nucleic acid molecules hybridize to a portion of the GPR75 nucleic acid molecule that includes a position corresponding to: position 5,831 according to SEQ ID NO:99, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, position 891 according to SEQ ID NO:103, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107.

In some embodiments, such isolated nucleic acid molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, at least about 60, at least about 65, at least about 70, at least about 75, at least about 80, at least about 85, at least about 90, at least about 95, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 2000, at least about 3000, at least about 4000, or at least about 5000 nucleotides. In some embodiments, such isolated nucleic acid molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, or at least about 25 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of at least about 18 nucleotides. In some embodiments, the

isolated nucleic acid molecules comprise or consists of at least about 15 nucleotides. In some embodiments, the isolated nucleic acid molecules consist of or comprise from about 10 to about 35, from about 10 to about 30, from about 10 to about 25, from about 12 to about 30, from about 12 to about 28, from about 12 to about 24, from about 15 to about 30, from about 15 to about 25, from about 18 to about 30, from about 18 to about 25, from about 18 to about 24, or from about 18 to about 22 nucleotides. In some embodiments, the isolated nucleic acid molecules consist of or comprise from about 18 to about 30 nucleotides. In some embodiments, the isolated nucleic acid molecules comprise or consist of at least about 15 nucleotides to at least about 35 nucleotides.

In some embodiments, such isolated nucleic acid molecules hybridize to GPR75 variant nucleic acid molecules (such as genomic nucleic acid molecules, mRNA molecules, and/or cDNA molecules) under stringent conditions. Such nucleic acid molecules can be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein, and can be used in any of the methods described herein.

In some embodiments, the isolated nucleic acid molecules hybridize to at least about 15 contiguous nucleotides of a nucleic acid molecule that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to GPR75 variant genomic nucleic acid molecules, GPR75 variant mRNA molecules, and/or GPR75 variant cDNA molecules. In some embodiments, the isolated nucleic acid molecules consist of or comprise from about 15 to about 100 nucleotides, or from about 15 to about 35 nucleotides. In some embodiments, the isolated nucleic acid molecules consist of or comprise from about 15 to about 100 nucleotides. In some embodiments, the isolated nucleic acid molecules consist of or comprise from about 15 to about 35 nucleotides.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 539-545 according to SEQ ID NO:11, or the complement

thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; or positions 600-606 according to SEQ ID NO:50, or the complement thereof.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: position 5,557 according to SEQ ID NO:3, or the complement thereof; position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; position 617 according to SEQ ID NO:27, or the complement thereof; position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; or position 617 according to SEQ ID NO:51, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to: positions 5,557-5,559 according to SEQ ID NO:3, or the complement thereof; positions 556-558 according to SEQ ID NO:12, or the complement thereof; positions 457-459 according to SEQ ID NO:17, or the complement thereof; positions 378-380 according to SEQ ID NO:22, or the complement thereof; positions 617-619 according to SEQ ID NO:27, or the complement thereof; positions 556-558 according to SEQ ID NO:36, or the complement thereof; positions 457-459 according to SEQ ID NO:41, or the complement thereof; positions 378-380 according to SEQ ID NO:46, or the complement thereof; or positions 617-619 according to SEQ ID NO:51, or the complement thereof.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: position 5,911 according to SEQ ID NO:4, or the

complement thereof; position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; position 971 according to SEQ ID NO:28, or the complement thereof; position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; or position 971 according to SEQ ID NO:52, or the complement thereof. In some embodiments, the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising positions corresponding to: positions 5,911-5,913 according to SEQ ID NO:4, or the complement thereof; positions 910-912 according to SEQ ID NO:13, or the complement thereof; positions 811-813 according to SEQ ID NO:18, or the complement thereof; positions 732-734 according to SEQ ID NO:23, or the complement thereof; positions 971-973 according to SEQ ID NO:28, or the complement thereof; positions 910-912 according to SEQ ID NO:37, or the complement thereof; positions 811-813 according to SEQ ID NO:42, or the complement thereof; positions 732-734 according to SEQ ID NO:47, or the complement thereof; or positions 971-973 according to SEQ ID NO:52, or the complement thereof.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; positions 980-983 according to SEQ ID NO:29, or the complement thereof; positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; or positions 980-983 according to SEQ ID NO:53, or the complement thereof.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion

comprises a position corresponding to: position 6,411 according to SEQ ID NO:6, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof.

In some embodiments, the isolated alteration-specific probes or alteration-specific primers comprise at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the portion comprises a position corresponding to: position 5,831 according to SEQ ID NO:99, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; position 891 according to SEQ ID NO:103, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof.

In some embodiments, the alteration-specific probes and alteration-specific primers comprise DNA. In some embodiments, the alteration-specific probes and alteration-specific primers comprise RNA.

In some embodiments, the probes and primers described herein (including alteration-specific probes and alteration-specific primers) have a nucleotide sequence that specifically hybridizes to any of the nucleic acid molecules disclosed herein, or the complement thereof. In some embodiments, the probes and primers specifically hybridize to any of the nucleic acid molecules disclosed herein under stringent conditions.

In some embodiments, the primers, including alteration-specific primers, can be used in second generation sequencing or high throughput sequencing. In some instances, the primers, including alteration-specific primers, can be modified. In particular, the primers can comprise various modifications that are used at different steps of, for example, Massive Parallel

Signature Sequencing (MPSS), Polony sequencing, and 454 Pyrosequencing. Modified primers can be used at several steps of the process, including biotinylated primers in the cloning step and fluorescently labeled primers used at the bead loading step and detection step. Polony sequencing is generally performed using a paired-end tags library wherein each molecule of DNA template is about 135 bp in length. Biotinylated primers are used at the bead loading step and emulsion PCR. Fluorescently labeled degenerate nonamer oligonucleotides are used at the detection step. An adaptor can contain a 5'-biotin tag for immobilization of the DNA library onto streptavidin-coated beads.

The probes and primers described herein can be used to detect a nucleotide variation within any of the GPR75 variant genomic nucleic acid molecules, GPR75 variant mRNA molecules, and/or GPR75 variant cDNA molecules disclosed herein. The primers described herein can be used to amplify GPR75 variant genomic nucleic acid molecules, GPR75 variant mRNA molecules, or GPR75 variant cDNA molecules, or a fragment thereof.

In the context of the disclosure "specifically hybridizes" means that the probe or primer (such as, for example, the alteration-specific probe or alteration-specific primer) does not hybridize to a nucleic acid sequence encoding a GPR75 reference genomic nucleic acid molecule, a GPR75 reference mRNA molecule, and/or a GPR75 reference cDNA molecule.

In some embodiments, the probes (such as, for example, an alteration-specific probe) comprise a label. In some embodiments, the label is a fluorescent label, a radiolabel, or biotin.

The present disclosure also provides supports comprising a substrate to which any one or more of the probes disclosed herein is attached. Solid supports are solid-state substrates or supports with which molecules, such as any of the probes disclosed herein, can be associated. A form of solid support is an array. Another form of solid support is an array detector. An array detector is a solid support to which multiple different probes have been coupled in an array, grid, or other organized pattern. A form for a solid-state substrate is a microtiter dish, such as a standard 96-well type. In some embodiments, a multiwell glass slide can be employed that normally contains one array per well.

The present disclosure also provides molecular complexes comprising or consisting of any of the G-protein coupled receptor 75 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein and any of the alteration-specific primers or alteration-specific probes described herein. In some embodiments, the GPR75 nucleic acid molecules (genomic nucleic acid molecules, mRNA

molecules, or cDNA molecules), or complement thereof, in the molecular complexes are single-stranded. In some embodiments, the GPR75 nucleic acid molecule is any of the genomic nucleic acid molecules described herein. In some embodiments, the GPR75 nucleic acid molecule is any of the mRNA molecules described herein. In some embodiments, the GPR75 nucleic acid molecule is any of the cDNA molecules described herein. In some embodiments, the molecular complex comprises or consists of any of the GPR75 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein and any of the alteration-specific primers described herein. In some embodiments, the molecular complex comprises or consists of any of the GPR75 nucleic acid molecules (genomic nucleic acid molecules, mRNA molecules, or cDNA molecules), or complement thereof, described herein and any of the alteration-specific probes described herein.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to a genomic nucleic acid molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the genomic nucleic acid molecule: at nucleotides at positions corresponding to positions 5,539-5,540 according to SEQ ID NO:2, or the complement thereof; at an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; at thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; at nucleotides at positions corresponding to positions 5,919-5,920 according to SEQ ID NO:5, or the complement thereof; at a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or at a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe that is hybridized to a genomic nucleic acid molecule at: an ACT codon at positions corresponding to positions 5,557-5,559 according to SEQ ID NO:3, a TAA codon at positions corresponding to positions 5,911-5,913 according to SEQ ID NO:4, or a TGT codon at positions corresponding to positions 5,830-5,832 according to SEQ ID NO:99.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to a genomic nucleic acid molecule

that comprises SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:99.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to an mRNA molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the mRNA molecule: at nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:11, or the complement thereof; at nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:16, or the complement thereof; at nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:21, or the complement thereof; at nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:26, or the complement thereof; at an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; at an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; at an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; at an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; at a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; at a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; at a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; at a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; at nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:14, or the complement thereof; at nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:19, or the complement thereof; at nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:24, or the complement thereof; at nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:29, or the complement thereof; at a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; at a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; at a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, the complement thereof; at of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; at a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement

thereof; at a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; at a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or at a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe that is hybridized to an mRNA molecule at: an ACU codon at positions corresponding to positions 556-558 according to SEQ ID NO:12, an ACU codon at positions corresponding to positions 457-459 according to SEQ ID NO:17, an ACU codon at positions corresponding to positions 378-380 according to SEQ ID NO:22, an ACU codon at positions corresponding to positions 617-619 according to SEQ ID NO:27; a UAA codon at positions corresponding to positions 910-912 according to SEQ ID NO:13, a UAA codon at positions corresponding to positions 811-813 according to SEQ ID NO:18, a UAA codon at positions corresponding to positions 732-734 according to SEQ ID NO:23, a UAA codon at positions corresponding to positions 971-973 according to SEQ ID NO:28, a UGU codon at positions corresponding to positions 829-831 according to SEQ ID NO:100, a UGU codon at positions corresponding to positions 730-732 according to SEQ ID NO:101, a UGU codon at positions corresponding to positions 651-653 according to SEQ ID NO:102, or a UGU codon at positions corresponding to positions 890-892 according to SEQ ID NO:103.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to an mRNA molecule that comprises SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to a cDNA molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to a cDNA molecule: at nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:35, or the complement thereof; at nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:40, or the complement thereof; at nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:45, or the complement thereof; at nucleotides at positions

corresponding to positions 599-600 according to SEQ ID NO:50, or the complement thereof; at an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; at an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; at an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; at an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; at a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; at a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; at a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; at a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; at nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:38, or the complement thereof; at nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:43, or the complement thereof; at nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:48, or the complement thereof; at nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:53, or the complement thereof; at a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; at a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; at a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; at a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; at a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; at a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; at a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or at a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe that is hybridized to a cDNA molecule at: an ACT codon at positions corresponding to positions 556-558 according to SEQ ID NO:36, an ACT codon at positions corresponding to positions 457-459 according to SEQ ID NO:41, an ACT codon at positions corresponding to positions 378-380 according to SEQ ID NO:46, an ACT

codon at positions corresponding to positions 617-619 according to SEQ ID NO:51; a TAA codon at positions corresponding to positions 910-912 according to SEQ ID NO:37, a TAA codon at positions corresponding to positions 811-813 according to SEQ ID NO:42, a TAA codon at positions corresponding to positions 732-734 according to SEQ ID NO:47, a TAA codon at positions corresponding to positions 971-973 according to SEQ ID NO:52, a TGT codon at positions corresponding to positions 829-831 according to SEQ ID NO:104, a TGT codon at positions corresponding to positions 730-732 according to SEQ ID NO:105, a TGT codon at positions corresponding to positions 651-653 according to SEQ ID NO:106, or a TGT codon at positions corresponding to positions 890-892 according to SEQ ID NO:107.

In some embodiments, the molecular complex comprises or consists of an alteration-specific primer or an alteration-specific probe hybridized to a cDNA molecule that comprises SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, or SEQ ID NO:54, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

In some embodiments, the molecular complex comprises an alteration-specific probe or an alteration-specific primer comprising a label. In some embodiments, the label is a fluorescent label, a radiolabel, or biotin. In some embodiments, the molecular complex further comprises a non-human polymerase.

The present disclosure also provides isolated nucleic acid molecules comprising a nucleotide sequence encoding a human GPR75 variant polypeptide. In some embodiments, the GPR75 variant polypeptide comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the isolated nucleic acid molecule encodes a GPR75

variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:56, and comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:56. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of SEQ ID NO:56. Each of these nucleic acid molecules encodes a GPR75 polypeptide that lacks amino acids at positions corresponding to positions 110-540 according to SEQ ID NO:55. In some embodiments, each of these nucleic acid molecules encodes a GPR75 polypeptide that comprises amino acids at positions corresponding to positions 110-130 according to SEQ ID NO:56.

In some embodiments, the GPR75 variant polypeptide comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according

to SEQ ID NO:57. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:57, and comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:57. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of SEQ ID NO:57.

In some embodiments, the GPR75 variant polypeptide terminates at a position corresponding to position 233 according to SEQ ID NO:58, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the

isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:58, and terminates at a position corresponding to position 233 according to SEQ ID NO:58. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:58. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of SEQ ID NO:58.

In some embodiments, the GPR75 variant polypeptide comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:59, and comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:59. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of

SEQ ID NO:59. Each of these nucleic acid molecules encodes a GPR75 polypeptide that lacks amino acids at positions corresponding to positions 236-540 according to SEQ ID NO:55. In some embodiments, each of these nucleic acid molecules encodes a GPR75 polypeptide that comprises amino acids at positions corresponding to positions 236-239 according to SEQ ID NO:59.

In some embodiments, the GPR75 variant polypeptide comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:60, and comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:60. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of SEQ ID NO:60. Each of these nucleic acid molecules encodes a GPR75 polypeptide that lacks

amino acids at positions corresponding to positions 400-540 according to SEQ ID NO:55. In some embodiments, each of these nucleic acid molecules encodes a GPR75 polypeptide that comprises amino acids at positions corresponding to positions 400-425 according to SEQ ID NO:60.

In some embodiments, the GPR75 variant polypeptide comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108, or the complement thereof. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 90% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 92% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 94% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 96% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the isolated nucleic acid molecule encodes a GPR75 variant polypeptide having an amino acid sequence that has at least about 98% sequence identity to SEQ ID NO:108, and comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide comprising SEQ ID NO:108. In some embodiments, the nucleic acid molecule encodes a GPR75 variant polypeptide consisting of SEQ ID NO:108.

The nucleotide sequence of a GPR75 reference genomic nucleic acid molecule is set forth in SEQ ID NO:1. See, also, ENSG00000119737.6, hg38 chr2:53,852,912-53,859,967.

Referring to SEQ ID NO:1, positions 5,540-5,546 are a CCAGTAG heptanucleotide. Referring to SEQ ID NO:1, position 5,557 is a guanine. Referring to SEQ ID NO:1, position 5,911 is a cytosine. Referring to SEQ ID NO:1, positions 5,920-5,923 are an AAAG tetranucleotide. Referring to SEQ ID NO:1, position 6,411 is a cytosine. Referring to SEQ ID NO:1, position 5,831 is an adenine.

A variant genomic nucleic acid molecule of GPR75 exists, wherein the CCAGTAG heptanucleotide at positions 5,540-5,546 (referring to SEQ ID NO:1) is deleted. The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:2.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the guanine at position 5,557 (referring to SEQ ID NO:1) is replaced with adenine. The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:3.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the cytosine at position 5,911 (referring to SEQ ID NO:1) is replaced with thymine. The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:4.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the AAAG tetranucleotide at positions 5,920-5,923 (referring to SEQ ID NO:1) is deleted. The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:5.

Another variant genomic nucleic acid molecule of GPR75 exists, a thymine is inserted at position 6,411 (referring to SEQ ID NO:1). The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:6.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the adenine at position 5,831 (referring to SEQ ID NO:1) is replaced with guanine. The nucleotide sequence of this GPR75 variant genomic nucleic acid molecule is set forth in SEQ ID NO:99.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the thymine at position 53,853,547 on chromosome 2 (according to GRCh38/hg38 (Dec. 2013) human genome assembly) is replaced with adenine, resulting in Lys404*. Referring to SEQ ID NO:1, the variation is AAG to TAG (at the codon at positions 6,421-6,423 on the coding strand). Each of the methods described herein in regard to any of the variants described herein can be carried out with this additional variant (i.e., genomic, mRNA, and cDNA molecules) as well.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the CAG beginning at position 53,854,099 on chromosome 2 (according to GRCh38/hg38 (Dec. 2013) human genome assembly) is replaced with cytosine, resulting in Ser219fs. Referring to SEQ ID NO:1, the variation is GTC (at positions 5,869-5,871 on the coding strand) to G. Each of the

methods described herein in regard to any of the variants described herein can be carried out with this additional variant (i.e., genomic, mRNA, and cDNA molecules) as well.

Another variant genomic nucleic acid molecule of GPR75 exists, wherein the cytosine at position 53,859,827 on chromosome 2 (according to GRCh38/hg38 (Dec. 2013) human genome assembly) is replaced with thymine (with a cDNA designated c.-110+1G>A), which is a splice donor site variation 110 bases upstream of the start codon. Referring to SEQ ID NO:1, the variation is G (at position 141 on the coding strand) to A. Each of the methods described herein in regard to any of the variants described herein can be carried out with this additional variant (i.e., genomic, mRNA, and cDNA molecules) as well.

The present disclosure also provides isolated genomic nucleic acid molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide. In some embodiments, the nucleotide sequence of the genomic nucleic acid molecule lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof. An example is set forth in SEQ ID NO:2.

In some embodiments, the nucleotide sequence of the genomic nucleic acid molecule lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. An example is set forth in SEQ ID NO:5.

In some embodiments, the nucleotide sequence of the genomic nucleic acid molecule comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:1, or the complement thereof. An example is set forth in SEQ ID NO:6.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546

according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules

comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof.

In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules

comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:2. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:2. In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:3. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:3. In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:4. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:4. In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:5. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:5. In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:6. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:6. In some embodiments, the isolated genomic nucleic acid molecules comprise SEQ ID NO:99. In some embodiments, the isolated genomic nucleic acid molecules consist of SEQ ID NO:99.

In some embodiments, the isolated genomic nucleic acid molecules comprise less than the entire genomic DNA sequence. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 2000, at least about 3000, at least about 4000, at least about 5000, at least about 6000, at least about 7000, at least about 8000, at least about 9000, or at least about 10000 contiguous nucleotides of any of the GPR75 genomic nucleic acid molecules disclosed herein. In some embodiments, the isolated genomic nucleic acid molecules comprise or consist of at least about 1000 to at least about 2000 contiguous nucleotides of any of the GPR75 genomic nucleic acid molecules disclosed herein. In some embodiments, these isolated genomic nucleic acid molecules lack a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1. In some embodiments, these isolated genomic nucleic acid molecules lack an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1. In some embodiments, these isolated genomic nucleic acid molecules comprise the insertion of thymine at a position corresponding to position 6,411 according to SEQ ID NO:6.

The nucleotide sequence of a GPR75 reference mRNA molecule is set forth in SEQ ID NO:7. Referring to SEQ ID NO:7, positions 539-545 are a CCAGUAG heptanucleotide. Referring to SEQ ID NO:7, position 566 is a guanine. Referring to SEQ ID NO:7, position 910 is a cytosine. Referring to SEQ ID NO:7, positions 919-922 are an AAAG tetranucleotide. Referring to SEQ ID NO:7, position 1,410 is a cytosine. Referring to SEQ ID NO:7, position 830 is an adenine.

The nucleotide sequence of another GPR75 reference mRNA molecule is set forth in SEQ ID NO:8. Referring to SEQ ID NO:8, positions 440-446 are a CCAGUAG heptanucleotide. Referring to SEQ ID NO:8, position 457 is a guanine. Referring to SEQ ID NO:8, position 811 is a cytosine. Referring to SEQ ID NO:8, positions 820-823 are an AAAG tetranucleotide. Referring to SEQ ID NO:8, position 1,311 is a cytosine. Referring to SEQ ID NO:8, position 731 is an adenine.

The nucleotide sequence of another GPR75 reference mRNA molecule is set forth in SEQ ID NO:9. Referring to SEQ ID NO:9, positions 361-367 are a CCAGUAG heptanucleotide. Referring to SEQ ID NO:9, position 378 is a guanine. Referring to SEQ ID NO:9, position 732 is a

cytosine. Referring to SEQ ID NO:9, positions 741-744 are an AAAG tetranucleotide. Referring to SEQ ID NO:9, position 1,232 is a cytosine. Referring to SEQ ID NO:9, position 652 is an adenine.

The nucleotide sequence of another GPR75 reference mRNA molecule is set forth in SEQ ID NO:10. Referring to SEQ ID NO:10, positions 600-606 are a CCAGUAG heptanucleotide. Referring to SEQ ID NO:10, position 617 is a guanine. Referring to SEQ ID NO:10, position 971 is a cytosine. Referring to SEQ ID NO:10, positions 980-983 are an AAAG tetranucleotide. Referring to SEQ ID NO:10, position 1,471 is a cytosine. Referring to SEQ ID NO:10, position 891 is an adenine.

A variant mRNA molecule of GPR75 exists, wherein the CCAGUAG heptanucleotide at positions 539-545 (referring to SEQ ID NO:7) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:11.

Another variant mRNA molecule of GPR75 exists, wherein the CCAGUAG heptanucleotide at positions 440-446 (referring to SEQ ID NO:8) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:16.

Another variant mRNA molecule of GPR75 exists, wherein the CCAGUAG heptanucleotide at positions 361-367 (referring to SEQ ID NO:9) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:21.

Another variant mRNA molecule of GPR75 exists, wherein the CCAGUAG heptanucleotide at positions 600-606 (referring to SEQ ID NO:10) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:26.

A variant mRNA molecule of GPR75 exists, wherein the guanine at position 556 (referring to SEQ ID NO:7) is replaced with adenine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:12.

Another variant mRNA molecule of GPR75 exists, wherein the guanine at position 457 (referring to SEQ ID NO:8) is replaced with adenine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:17.

Another variant mRNA molecule of GPR75 exists, wherein the guanine at position 378 (referring to SEQ ID NO:9) is replaced with adenine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:22.

Another variant mRNA molecule of GPR75 exists, wherein the guanine at position 617 (referring to SEQ ID NO:10) is replaced with adenine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:27.

A variant mRNA molecule of GPR75 exists, wherein the cytosine at position 910 (referring to SEQ ID NO:7) is replaced with uracil. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:13.

Another variant mRNA molecule of GPR75 exists, wherein the cytosine at position 811 (referring to SEQ ID NO:8) is replaced with uracil. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:18.

Another variant mRNA molecule of GPR75 exists, wherein the cytosine at position 732 (referring to SEQ ID NO:9) is replaced with uracil. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:23.

Another variant mRNA molecule of GPR75 exists, wherein the cytosine at position 971 (referring to SEQ ID NO:10) is replaced with uracil. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:28.

A variant mRNA molecule of GPR75 exists, wherein the AAAG tetranucleotide at positions 919-922 (referring to SEQ ID NO:7) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:14.

Another variant mRNA molecule of GPR75 exists, wherein the AAAG tetranucleotide at positions 820-823 (referring to SEQ ID NO:8) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:19.

Another variant mRNA molecule of GPR75 exists, wherein the AAAG tetranucleotide at positions 741-744 (referring to SEQ ID NO:9) is deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:24.

Another variant mRNA molecule of GPR75 exists, wherein AAAG tetranucleotide at positions 980-983 (referring to SEQ ID NO:10) is replaced with deleted. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:29.

A variant mRNA molecule of GPR75 exists, wherein a uracil is inserted at position 1,410 (referring to SEQ ID NO:7). The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:15.

Another variant mRNA molecule of GPR75 exists, wherein a uracil is inserted at position 1,311 (referring to SEQ ID NO:8). The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:20.

Another variant mRNA molecule of GPR75 exists, wherein a uracil is inserted at position 1,232 (referring to SEQ ID NO:9). The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:25.

Another variant mRNA molecule of GPR75 exists, wherein a uracil is inserted at position 1,471 (referring to SEQ ID NO:10). The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:30.

A variant mRNA molecule of GPR75 exists, wherein the adenine at position 830 (referring to SEQ ID NO:7) is replaced with guanine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:100.

Another variant mRNA molecule of GPR75 exists, wherein the adenine at position 731 (referring to SEQ ID NO:8) is replaced with guanine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:101.

Another variant mRNA molecule of GPR75 exists, wherein the adenine at position 652 (referring to SEQ ID NO:9) is replaced with guanine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:102.

Another variant mRNA molecule of GPR75 exists, wherein the adenine at position 891 (referring to SEQ ID NO:10) is replaced with guanine. The nucleotide sequence of this GPR75 variant mRNA molecule is set forth in SEQ ID NO:103.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. An example is set forth in SEQ ID NO:11.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. An example is set forth in SEQ ID NO:16.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. An example is set forth in SEQ ID NO:21.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide

sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. An example is set forth in SEQ ID NO:26.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. An example is set forth in SEQ ID NO:14.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. An example is set forth in SEQ ID NO:19.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. An example is set forth in SEQ ID NO:24.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. An example is set forth in SEQ ID NO:29.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof.

The present disclosure also provides isolated mRNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules

comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:7, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or

consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:14, and lacks an

AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:19, and lacks an AAAG

tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at

least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof. In

some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof.

In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 92%

sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof. In some embodiments, the isolated mRNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof.

Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:11. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:11. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:16. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:16. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:21. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:21. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:26. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:26

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:14. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:14. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:19. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:19. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:24. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:24. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:29. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:29.

In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:15. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:15. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:20. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:20. In some embodiments, the isolated mRNA molecules

comprise SEQ ID NO:25. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:25. In some embodiments, the isolated mRNA molecules comprise SEQ ID NO:30. In some embodiments, the isolated mRNA molecules consist of SEQ ID NO:30.

The nucleotide sequence of a GPR75 reference cDNA molecule is set forth in SEQ ID NO:31. Referring to SEQ ID NO:31, positions 539-545 are a CCAGTAG heptanucleotide. Referring to SEQ ID NO:31, position 556 is a guanine. Referring to SEQ ID NO:31, position 910 is a cytosine. Referring to SEQ ID NO:31, positions 919-922 are an AAAG tetranucleotide. Referring to SEQ ID NO:31, position 1,410 is a cytosine. Referring to SEQ ID NO:31, position 830 is an adenine.

The nucleotide sequence of another GPR75 reference cDNA molecule is set forth in SEQ ID NO:32. Referring to SEQ ID NO:32, positions 440-446 are a CCAGTAG heptanucleotide. Referring to SEQ ID NO:32, position 457 is a guanine. Referring to SEQ ID NO:32, position 811 is a cytosine. Referring to SEQ ID NO:32, positions 820-823 are an AAAG tetranucleotide. Referring to SEQ ID NO:32, position 1,311 is a cytosine. Referring to SEQ ID NO:32, position 731 is an adenine.

The nucleotide sequence of another GPR75 reference cDNA molecule is set forth in SEQ ID NO:33. Referring to SEQ ID NO:33, positions 361-367 are a CCAGTAG heptanucleotide. Referring to SEQ ID NO:33, position 378 is a guanine. Referring to SEQ ID NO:33, position 732 is a cytosine. Referring to SEQ ID NO:33, positions 741-744 are an AAAG tetranucleotide. Referring to SEQ ID NO:33, position 1,232 is a cytosine. Referring to SEQ ID NO:33, position 652 is an adenine.

The nucleotide sequence of another GPR75 reference cDNA molecule is set forth in SEQ ID NO:34. Referring to SEQ ID NO:34, positions 600-606 are a CCAGTAG heptanucleotide. Referring to SEQ ID NO:34, position 617 is a guanine. Referring to SEQ ID NO:34, position 971 is a cytosine. Referring to SEQ ID NO:34, positions 980-983 are an AAAG tetranucleotide. Referring to SEQ ID NO:34, position 1,471 is a cytosine. Referring to SEQ ID NO:34, position 891 is an adenine.

A variant cDNA molecule of GPR75 exists, wherein the CCAGTAG heptanucleotide at positions 539-545 (referring to SEQ ID NO:31) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:35.

Another variant cDNA molecule of GPR75 exists, wherein the CCAGTAG heptanucleotide at positions 440-446 (referring to SEQ ID NO:32) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:40.

Another variant cDNA molecule of GPR75 exists, wherein the CCAGTAG heptanucleotide at positions 361-367 (referring to SEQ ID NO:33) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:45.

Another variant cDNA molecule of GPR75 exists, wherein the CCAGTAG heptanucleotide at positions 600-606 (referring to SEQ ID NO:34) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:50.

A variant cDNA molecule of GPR75 exists, wherein the guanine at position 556 (referring to SEQ ID NO:31) is replaced with adenine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:36.

Another variant cDNA molecule of GPR75 exists, wherein the guanine at position 457 (referring to SEQ ID NO:32) is replaced with adenine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:41.

Another variant cDNA molecule of GPR75 exists, wherein the guanine at position 378 (referring to SEQ ID NO:33) is replaced with adenine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:46.

Another variant cDNA molecule of GPR75 exists, wherein the guanine at position 617 (referring to SEQ ID NO:34) is replaced with adenine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:51.

A variant cDNA molecule of GPR75 exists, wherein the cytosine at position 910 (referring to SEQ ID NO:31) is replaced with thymine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:37.

Another variant cDNA molecule of GPR75 exists, wherein the cytosine at position 811 (referring to SEQ ID NO:32) is replaced with thymine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:42.

Another variant cDNA molecule of GPR75 exists, wherein the cytosine at position 732 (referring to SEQ ID NO:33) is replaced with thymine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:47.

Another variant cDNA molecule of GPR75 exists, wherein the cytosine at position 971 (referring to SEQ ID NO:34) is replaced with thymine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:52.

A variant cDNA molecule of GPR75 exists, wherein the AGCC tetranucleotide at positions 919-922 (referring to SEQ ID NO:31) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:38.

Another variant cDNA molecule of GPR75 exists, wherein the AGCC tetranucleotide at positions 820-823 (referring to SEQ ID NO:32) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:43.

Another variant cDNA molecule of GPR75 exists, wherein the AGCC tetranucleotide at positions 741-744 (referring to SEQ ID NO:33) is deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:48.

Another variant cDNA molecule of GPR75 exists, wherein the AGCC tetranucleotide at positions 980-983 (referring to SEQ ID NO:34) is replaced with deleted. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:53.

A variant cDNA molecule of GPR75 exists, wherein a thymine is inserted at position 1,410. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:39.

Another variant cDNA molecule of GPR75 exists, wherein a thymine is inserted at position 1,311. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:44.

Another variant cDNA molecule of GPR75 exists, wherein a thymine is inserted at position 1,232. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:49.

Another variant cDNA molecule of GPR75 exists, wherein a thymine is inserted at position 1,471. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:54.

A variant cDNA molecule of GPR75 exists, wherein the adenine at position 830 (referring to SEQ ID NO:31) is replaced with guanine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:104.

Another variant cDNA molecule of GPR75 exists, wherein the adenine at position 731 (referring to SEQ ID NO:32) is replaced with guanine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:105.

Another variant cDNA molecule of GPR75 exists, wherein the adenine at position 652 (referring to SEQ ID NO:33) is replaced with guanine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:106.

Another variant cDNA molecule of GPR75 exists, wherein the adenine at position 891 (referring to SEQ ID NO:34) is replaced with guanine. The nucleotide sequence of this GPR75 variant cDNA molecule is set forth in SEQ ID NO:107.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. An example is set forth in SEQ ID NO:35.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. An example is set forth in SE ID NO:40.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:43, or the complement thereof. An example is set forth in SE ID NO:45.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. An example is set forth in SE ID NO:50.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. An example is set forth in SE ID NO:38.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide

sequence lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. An example is set forth in SE ID NO:43.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. An example is set forth in SE ID NO:48.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. An example is set forth in SE ID NO:53.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof.

The present disclosure also provides isolated cDNA molecules comprising or consisting of a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules

comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or

consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:50, and lacks a

CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:38, and lacks an AAAG

tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at

least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. In

some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92%

sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 98% sequence identity to SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof.

In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 90% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 92% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 94% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence that has at least about 96% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof. In some embodiments, the isolated cDNA molecules comprise or consist of a nucleotide sequence

that has at least about 98% sequence identity to SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:35. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:35. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:40. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:40. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:45. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:45. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:50. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:50.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:38. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:38. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:43. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:43. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:48. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:48. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:53. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:53.

In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:39. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:39. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:44. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:44. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:49. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:49. In some embodiments, the isolated cDNA molecules comprise SEQ ID NO:54. In some embodiments, the isolated cDNA molecules consist of SEQ ID NO:54.

In some embodiments, the isolated mRNA molecules or cDNA molecules comprise less than the entire mRNA or cDNA sequence. In some embodiments, the isolated mRNA molecules or cDNA molecules comprise or consist of at least about 5, at least about 8, at least about 10, at least about 12, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 200, at least about

300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 1100, at least about 1200, at least about 1300, at least about 1400, at least about 1500, at least about 1600, at least about 1700, at least about 1800, at least about 1900, or at least about 2000 contiguous nucleotides of any of the GPR75 mRNA molecules or cDNA molecules disclosed herein. In some embodiments, the isolated mRNA molecules or cDNA molecules comprise or consist of at least about 400 to at least about 500 contiguous nucleotides of any of the GPR75 mRNA molecules or cDNA molecules disclosed herein. In some embodiments, the isolated cDNA molecules comprise or consist of at least about 1000 to at least about 2000 contiguous nucleotides of any of the GPR75 mRNA molecules or cDNA molecules disclosed herein.

In some embodiments, these isolated mRNA molecules comprise a UAUCCCG heptanucleotide at the position corresponding to positions 539-545 according to SEQ ID NO:11, a UAUCCCG heptanucleotide at the position corresponding to positions 440-446 according to SEQ ID NO:16, a UAUCCCG heptanucleotide at the position corresponding to positions 361-367 according to SEQ ID NO:21, or a UAUCCCG heptanucleotide at the position corresponding to positions 600-606 according to SEQ ID NO:26. In some embodiments, these isolated mRNA molecules comprise an adenine at the position corresponding to position 556 according to SEQ ID NO:12, an adenine at the position corresponding to position 457 according to SEQ ID NO:17, an adenine at the position corresponding to position 378 according to SEQ ID NO:22, or an adenine at the position corresponding to position 617 according to SEQ ID NO:27. In some embodiments, these isolated mRNA molecules comprise a uracil at the position corresponding to position 910 according to SEQ ID NO:13, a uracil at the position corresponding to position 811 according to SEQ ID NO:18, a uracil at the position corresponding to position 732 according to SEQ ID NO:23, or a uracil at the position corresponding to position 971 according to SEQ ID NO:28. In some embodiments, these isolated mRNA molecules comprise an AGCC tetranucleotide at the position corresponding to positions 919-922 according to SEQ ID NO:14, an AGCC tetranucleotide at the position corresponding to positions 820-823 according to SEQ ID NO:19, an AGCC tetranucleotide at the position corresponding to positions 741-744 according to SEQ ID NO:24, or an AGCC tetranucleotide at the position corresponding to positions 980-983 according to SEQ ID NO:29. In some embodiments, these isolated mRNA molecules comprise an insertion of a uracil at the position corresponding to position 1,410 according to SEQ ID NO:15, an insertion of a uracil at the position corresponding to position

1,311 according to SEQ ID NO:20, an insertion of a uracil at the position corresponding to position 1,232 according to SEQ ID NO:25, or an insertion of a uracil at the position corresponding to position 1,471 according to SEQ ID NO:30. In some embodiments, these isolated mRNA molecules comprise a guanine at the position corresponding to position 830 according to SEQ ID NO:100, a guanine at the position corresponding to position 731 according to SEQ ID NO:101, a guanine at the position corresponding to position 652 according to SEQ ID NO:102, or a guanine at the position corresponding to position 891 according to SEQ ID NO:103.

In some embodiments, these isolated cDNA molecules comprise a TATCCCG heptanucleotide at the position corresponding to positions 539-545 according to SEQ ID NO:35, a TATCCCG heptanucleotide at the position corresponding to positions 440-446 according to SEQ ID NO:40, a TATCCCG heptanucleotide at the position corresponding to positions 361-367 according to SEQ ID NO:45, or a TATCCCG heptanucleotide at the position corresponding to positions 600-606 according to SEQ ID NO:50. In some embodiments, these isolated cDNA molecules comprise an adenine at the position corresponding to position 556 according to SEQ ID NO:36, an adenine at the position corresponding to position 457 according to SEQ ID NO:41, an adenine at the position corresponding to position 378 according to SEQ ID NO:46, or an adenine at the position corresponding to position 617 according to SEQ ID NO:51. In some embodiments, these isolated cDNA molecules comprise a thymine at the position corresponding to position 910 according to SEQ ID NO:37, a thymine at the position corresponding to position 811 according to SEQ ID NO:42, a thymine at the position corresponding to position 732 according to SEQ ID NO:47, or a thymine at the position corresponding to position 971 according to SEQ ID NO:52. In some embodiments, these isolated cDNA molecules comprise an AGCC tetranucleotide at the position corresponding to positions 919-922 according to SEQ ID NO:38, an AGCC tetranucleotide at the position corresponding to positions 820-823 according to SEQ ID NO:43, an AGCC tetranucleotide at the position corresponding to positions 741-744 according to SEQ ID NO:48, or an AGCC tetranucleotide at the position corresponding to positions 980-983 according to SEQ ID NO:53. In some embodiments, these isolated cDNA molecules comprise an insertion of a thymine at the position corresponding to position 1,410 according to SEQ ID NO:39, an insertion of a thymine at the position corresponding to position 1,311 according to SEQ ID NO:44, an insertion of a thymine at the position corresponding to position 1,232 according to SEQ ID NO:49, or an

insertion of a thymine at the position corresponding to position 1,471 according to SEQ ID NO:54. In some embodiments, these isolated cDNA molecules comprise a guanine at the position corresponding to position 830 according to SEQ ID NO:104, a guanine at the position corresponding to position 731 according to SEQ ID NO:105, a guanine at the position corresponding to position 652 according to SEQ ID NO:106, or a guanine at the position corresponding to position 891 according to SEQ ID NO:107.

The genomic nucleic acid molecules, mRNA molecules, and cDNA molecules can be from any organism. For example, the genomic nucleic acid molecules, mRNA molecules, and cDNA molecules can be human or an ortholog from another organism, such as a non-human mammal, a rodent, a mouse, or a rat. It is understood that gene sequences within a population can vary due to polymorphisms such as single-nucleotide polymorphisms. The examples provided herein are only exemplary sequences. Other sequences are also possible.

The present disclosure also provides fragments of any of the isolated genomic nucleic acid molecules, mRNA molecules, or cDNA molecules disclosed herein. In some embodiments, the fragments comprise or consist of at least about 5, at least about 8, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, at least about 60, at least about 65, at least about 70, at least about 75, at least about 80, at least about 85, at least about 90, at least about 95, or at least about 100 contiguous residues of any of the nucleic acid molecules disclosed herein, or any complement thereof. In some embodiments, the fragments comprise or consist of at least about 20, at least about 25, at least about 30, or at least about 35 contiguous residues of any of the nucleic acid molecules disclosed herein, or any complement thereof. In this regard, the longer fragments are preferred over the shorter ones. Such fragments may be used, for example, as probes, primers, alteration-specific probes, or alteration-specific primers as described or exemplified herein, and include, without limitation primers, probes, antisense RNAs, shRNAs, and siRNAs, each of which is described in more detail elsewhere herein.

Also provided herein are functional polynucleotides that can interact with the disclosed nucleic acid molecules. Examples of functional polynucleotides include, but are not limited to, antisense molecules, aptamers, ribozymes, triplex forming molecules, and external

guide sequences. The functional polynucleotides can act as effectors, inhibitors, modulators, and stimulators of a specific activity possessed by a target molecule, or the functional polynucleotides can possess a *de novo* activity independent of any other molecules.

The isolated nucleic acid molecules disclosed herein can comprise RNA, DNA, or both RNA and DNA. The isolated nucleic acid molecules can also be linked or fused to a heterologous nucleic acid sequence, such as in a vector, or a heterologous label. For example, the isolated nucleic acid molecules disclosed herein can be within a vector or as an exogenous donor sequence comprising the isolated nucleic acid molecule and a heterologous nucleic acid sequence. The isolated nucleic acid molecules can also be linked or fused to a heterologous label. The label can be directly detectable (such as, for example, fluorophore) or indirectly detectable (such as, for example, hapten, enzyme, or fluorophore quencher). Such labels can be detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. Such labels include, for example, radiolabels, pigments, dyes, chromogens, spin labels, and fluorescent labels. The label can also be, for example, a chemiluminescent substance; a metal-containing substance; or an enzyme, where there occurs an enzyme-dependent secondary generation of signal. The term "label" can also refer to a "tag" or hapten that can bind selectively to a conjugated molecule such that the conjugated molecule, when added subsequently along with a substrate, is used to generate a detectable signal. For example, biotin can be used as a tag along with an avidin or streptavidin conjugate of horseradish peroxidate (HRP) to bind to the tag, and examined using a calorimetric substrate (such as, for example, tetramethylbenzidine (TMB)) or a fluorogenic substrate to detect the presence of HRP. Exemplary labels that can be used as tags to facilitate purification include, but are not limited to, myc, HA, FLAG or 3XFLAG, 6XHis or polyhistidine, glutathione-S-transferase (GST), maltose binding protein, an epitope tag, or the Fc portion of immunoglobulin. Numerous labels include, for example, particles, fluorophores, haptens, enzymes and their calorimetric, fluorogenic and chemiluminescent substrates and other labels.

The disclosed nucleic acid molecules can comprise, for example, nucleotides or non-natural or modified nucleotides, such as nucleotide analogs or nucleotide substitutes. Such nucleotides include a nucleotide that contains a modified base, sugar, or phosphate group, or that incorporates a non-natural moiety in its structure. Examples of non-natural nucleotides include, but are not limited to, dideoxynucleotides, biotinylated, aminated, deaminated, alkylated, benzylated, and fluorophor-labeled nucleotides.

The nucleic acid molecules disclosed herein can also comprise one or more nucleotide analogs or substitutions. A nucleotide analog is a nucleotide which contains a modification to either the base, sugar, or phosphate moieties. Modifications to the base moiety include, but are not limited to, natural and synthetic modifications of A, C, G, and T/U, as well as different purine or pyrimidine bases such as, for example, pseudouridine, uracil-5-yl, hypoxanthin-9-yl (I), and 2-aminoadenin-9-yl. Modified bases include, but are not limited to, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (such as, for example, 5-bromo), 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

Nucleotide analogs can also include modifications of the sugar moiety. Modifications to the sugar moiety include, but are not limited to, natural modifications of the ribose and deoxy ribose as well as synthetic modifications. Sugar modifications include, but are not limited to, the following modifications at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl, and alkynyl may be substituted or unsubstituted C_{1-10}alkyl or C_{2-10}alkenyl, and C_{2-10}alkynyl. Exemplary 2' sugar modifications also include, but are not limited to, $-O[(CH_2)_nO]_mCH_3$, $-O(CH_2)_nOCH_3$, $-O(CH_2)_nNH_2$, $-O(CH_2)_nCH_3$, $-O(CH_2)_n$-ONH_2, and $-O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m, independently, are from 1 to about 10. Other modifications at the 2' position include, but are not limited to, C_{1-10}alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. Similar modifications may also be made at other positions on the sugar, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Modified sugars can also include those that contain modifications at the bridging ring oxygen, such as CH_2 and S.

Nucleotide sugar analogs can also have sugar mimetics, such as cyclobutyl moieties in place of the pentofuranosyl sugar.

Nucleotide analogs can also be modified at the phosphate moiety. Modified phosphate moieties include, but are not limited to, those that can be modified so that the linkage between two nucleotides contains a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl and other alkyl phosphonates including 3'-alkylene phosphonate and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates. These phosphate or modified phosphate linkage between two nucleotides can be through a 3'-5' linkage or a 2'-5' linkage, and the linkage can contain inverted polarity such as 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts, and free acid forms are also included. Nucleotide substitutes also include peptide nucleic acids (PNAs).

The present disclosure also provides vectors comprising any one or more of the nucleic acid molecules disclosed herein. In some embodiments, the vectors comprise any one or more of the nucleic acid molecules disclosed herein and a heterologous nucleic acid. The vectors can be viral or nonviral vectors capable of transporting a nucleic acid molecule. In some embodiments, the vector is a plasmid or cosmid (such as, for example, a circular double-stranded DNA into which additional DNA segments can be ligated). In some embodiments, the vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Expression vectors include, but are not limited to, plasmids, cosmids, retroviruses, adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus and tobacco mosaic virus, yeast artificial chromosomes (YACs), Epstein-Barr (EBV)-derived episomes, and other expression vectors known in the art.

Desired regulatory sequences for mammalian host cell expression can include, for example, viral elements that direct high levels of polypeptide expression in mammalian cells, such as promoters and/or enhancers derived from retroviral LTRs, cytomegalovirus (CMV) (such as, for example, CMV promoter/enhancer), Simian Virus 40 (SV40) (such as, for example, SV40 promoter/enhancer), adenovirus, (such as, for example, the adenovirus major late promoter (AdMLP)), polyoma and strong mammalian promoters such as native immunoglobulin and actin promoters. Methods of expressing polypeptides in bacterial cells or fungal cells (such as, for example, yeast cells) are also well known. A promoter can be, for example, a constitutively

active promoter, a conditional promoter, an inducible promoter, a temporally restricted promoter (such as, for example, a developmentally regulated promoter), or a spatially restricted promoter (such as, for example, a cell-specific or tissue-specific promoter).

Percent identity (or percent complementarity) between particular stretches of nucleotide sequences within nucleic acid molecules or amino acid sequences within polypeptides can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs (Altschul et al., J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 7, 649-656) or by using the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482-489). Herein, if reference is made to percent sequence identity, the higher percentages of sequence identity are preferred over the lower ones.

The present disclosure also provides compositions comprising any one or more of the isolated nucleic acid molecules, genomic nucleic acid molecules, mRNA molecules, and/or cDNA molecules disclosed herein. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the compositions comprise a carrier and/or excipient. Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules. A carrier may comprise a buffered salt solution such as PBS, HBSS, etc.

As used herein, the phrase “corresponding to” or grammatical variations thereof when used in the context of the numbering of a particular nucleotide or nucleotide sequence or position refers to the numbering of a specified reference sequence when the particular nucleotide or nucleotide sequence is compared to a reference sequence (such as, for example, SEQ ID NO:1, SEQ ID NO:7, or SEQ ID NO:31). In other words, the residue (such as, for example, nucleotide or amino acid) number or residue (such as, for example, nucleotide or amino acid) position of a particular polymer is designated with respect to the reference sequence rather than by the actual numerical position of the residue within the particular nucleotide or nucleotide sequence. For example, a particular nucleotide sequence can be aligned to a reference sequence by introducing gaps to optimize residue matches between the two sequences. In these cases, although the gaps are present, the numbering of the residue in the

particular nucleotide or nucleotide sequence is made with respect to the reference sequence to which it has been aligned.

For example, a nucleic acid molecule comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1 means that if the nucleotide sequence of the GPR75 genomic nucleic acid molecule is aligned to the sequence of SEQ ID NO:1, the GPR75 sequence has a deletion of a CCAGTAG heptanucleotide residue at the position that corresponds to positions 5,540-5,546 of SEQ ID NO:1. The same applies for mRNA molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, and cDNA molecules comprising a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31. In other words, these phrases refer to a nucleic acid molecule encoding a GPR75 polypeptide, wherein the genomic nucleic acid molecule has a nucleotide sequence that lacks a CCAGTAG heptanucleotide according to SEQ ID NO:1 and, thus, comprises nucleotides that are homologous to the TATCCCG nucleotides at positions 5,540-5,546 of SEQ ID NO:2 (or wherein the mRNA molecule has a nucleotide sequence that lacks a CCAGUAG heptanucleotide according to SEQ ID NO:7 and, thus, comprises nucleotides that are homologous to the UAUCCCG heptanucleotide residue at positions 539-545 of SEQ ID NO:11, or wherein the cDNA molecule has a nucleotide sequence that lacks a CCAGTAG heptanucleotide according to SEQ ID NO:31 and, thus, comprises residues that are homologous to the TATCCCG residues at positions 539-545 of SEQ ID NO:35). Herein, such a sequence is also referred to as “GPR75 sequence with the Ala110fs alteration” or “GPR75 sequence with the Ala110fs variation” referring to genomic nucleic acid molecules. The same can be carried out for all other molecules disclosed herein.

As described herein, a position within a GPR75 genomic nucleic acid molecule that corresponds to positions 5,540-5,546 according to SEQ ID NO:2, for example, can be identified by performing a sequence alignment between the nucleotide sequence of a particular GPR75 nucleic acid molecule and the nucleotide sequence of SEQ ID NO:2. A variety of computational algorithms exist that can be used for performing a sequence alignment to identify a nucleotide position that corresponds to, for example, positions 5,540-5,546 in SEQ ID NO:2. For example, by using the NCBI BLAST algorithm (Altschul et al., Nucleic Acids Res., 1997, 25, 3389-3402) or

CLUSTALW software (Sievers and Higgins, Methods Mol. Biol., 2014, 1079, 105-116) sequence alignments may be performed. However, sequences can also be aligned manually.

The amino acid sequence of a GPR75 reference polypeptide is set forth in SEQ ID NO:55. Referring to SEQ ID NO:55, the GPR75 reference polypeptide is 540 amino acids in length. Referring to SEQ ID NO:55, position 110 is alanine. Referring to SEQ ID NO:55, position 116 is alanine. Referring to SEQ ID NO:55, position 207 is tyrosine. Referring to SEQ ID NO:55, position 234 is glutamine. Referring to SEQ ID NO:55, position 236 is arginine. Referring to SEQ ID NO:55, position 400 is cysteine.

A GPR75 variant polypeptide exists (SEQ ID NO:56; Ala110fs), wherein the alanine at position 110 (referring to SEQ ID NO:55) is altered due to a frameshift mutation in the underlying mRNA molecule, resulting in a truncated 130 amino acid polypeptide. Referring to SEQ ID NO:56, the nucleotides at positions 110-130 are different than the corresponding nucleotides at the same positions of SEQ ID NO:55.

Another GPR75 variant polypeptide exists (SEQ ID NO:57; Ala116Thr), wherein the alanine at position 116 (referring to SEQ ID NO:55) is replaced with a threonine, resulting in a 540 amino acid polypeptide.

Another GPR75 variant polypeptide exists (SEQ ID NO:58; Gln234Stop), wherein the glutamine at position 234 (referring to SEQ ID NO:55) is altered due to a mutation in the underlying mRNA molecule introducing a Stop codon at amino acid position 234, resulting in a truncated 233 amino acid polypeptide.

Another GPR75 variant polypeptide exists (SEQ ID NO:59; Arg236fs), wherein the arginine at position 236 (referring to SEQ ID NO:55) is altered due to a frameshift mutation in the underlying mRNA molecule, resulting in a truncated 239 amino acid polypeptide. Referring to SEQ ID NO:59, the nucleotides at positions 236-239 are different than the corresponding nucleotides at the same positions of SEQ ID NO:55.

Another GPR75 variant polypeptide exists (SEQ ID NO:60; Cys400fs), wherein the cysteine at position 400 (referring to SEQ ID NO:55) is altered due to a frameshift mutation in the underlying mRNA molecule, resulting in a truncated 425 amino acid polypeptide. Referring to SEQ ID NO:60, the nucleotides at positions 400-425 are different than the corresponding nucleotides at the same positions of SEQ ID NO:55.

Another GPR75 variant polypeptide exists (SEQ ID NO:108; Tyr207Cys), wherein the tyrosine at position 207 (referring to SEQ ID NO:55) is replaced with a cysteine, resulting in a 540 amino acid polypeptide.

The present disclosure also provides isolated human GPR75 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 90% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:56, and comprising nucleotides at positions corresponding to positions 110-130 according to SEQ ID NO:56. In some embodiments, these GPR75 polypeptides lack amino acids at positions corresponding to positions 110-540 according to SEQ ID NO:55.

The present disclosure also provides isolated human GPR75 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:59, and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 90% identical to SEQ ID NO:59, and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:59,

and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:59, and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:59, and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:59, and comprising nucleotides at positions corresponding to positions 236-239 according to SEQ ID NO:59. In some embodiments, these GPR75 polypeptides lack amino acids at positions corresponding to positions 236-540 according to SEQ ID NO:55.

The present disclosure also provides isolated human GPR75 polypeptides having an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 90% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 92% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 94% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 96% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, the isolated human GPR75 polypeptides have an amino acid sequence at least about 98% identical to SEQ ID NO:60, and comprising nucleotides at positions corresponding to positions 400-425 according to SEQ ID NO:60. In some embodiments, these GPR75 polypeptides lack amino acids at positions corresponding to positions 400-540 according to SEQ ID NO:55.

In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises or consists of SEQ ID NO:56. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises SEQ ID NO:56. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide consists of SEQ ID NO:56.

In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises or consists of SEQ ID NO:59. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises SEQ ID NO:59. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide consists of SEQ ID NO:59.

In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises or consists of SEQ ID NO:60. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide comprises SEQ ID NO:60. In some embodiments, the amino acid sequence of the isolated human GPR75 polypeptide consists of SEQ ID NO:60.

In some embodiments, the isolated polypeptides comprise or consist of an amino acid sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to at least about 8, at least about 10, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, or at least about 600 contiguous amino acids of any of the GPR75 polypeptides disclosed herein. In some embodiments, the isolated polypeptides comprise or consist of an amino acid sequence at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to at least about 8, at least about 10, at least about 15, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at

least about 350, at least about 400, at least about 450, at least about 500, at least about 550, or at least about 600 contiguous amino acids of any of the GPR75 polypeptides disclosed herein.

The isolated polypeptides disclosed herein can comprise an amino acid sequence of a naturally occurring GPR75 polypeptide, or can comprise a non-naturally occurring sequence. In some embodiments, the naturally occurring sequence can differ from the non-naturally occurring sequence due to conservative amino acid substitutions. For example, the sequence can be identical with the exception of conservative amino acid substitutions.

In some embodiments, the isolated polypeptides comprise non-natural or modified amino acids or peptide analogs. For example, there are numerous D-amino acids or amino acids which have a different functional substituent than the naturally occurring amino acids.

The present disclosure also provides nucleic acid molecules encoding any of the polypeptides disclosed herein. This includes all degenerate sequences related to a specific polypeptide sequence (i.e., all nucleic acids having a sequence that encodes one particular polypeptide sequence as well as all nucleic acids, including degenerate nucleic acids, encoding the disclosed variants and derivatives of the protein sequences). Thus, while each particular nucleic acid sequence may not be written out herein, each and every sequence is in fact disclosed and described herein through the disclosed polypeptide sequences.

The present disclosure also provides compositions comprising any one or more of the nucleic acid molecules and/or any one or more of the polypeptides disclosed herein. In some embodiments, the compositions comprise a carrier. Examples of carriers include, but are not limited to, poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules.

The present disclosure also provides methods of producing any of the GPR75 polypeptides or fragments thereof disclosed herein. Such GPR75 polypeptides or fragments thereof can be produced by any suitable method.

The present disclosure also provides cells comprising any one or more of the nucleic acid molecules and/or any one or more of the polypeptides disclosed herein. The cells can be *in vitro*, *ex vivo*, or *in vivo*. Nucleic acid molecules can be linked to a promoter and other regulatory sequences so they are expressed to produce an encoded protein.

In some embodiments, the cell is a totipotent cell or a pluripotent cell such as, for example, an embryonic stem (ES) cell such as a rodent ES cell, a mouse ES cell, or a rat ES cell. In some embodiments, the cell is a primary somatic cell, or a cell that is not a primary somatic cell.

The cell can be from any source. For example, the cell can be a eukaryotic cell, an animal cell, a plant cell, or a fungal (such as, for example, yeast) cell. Such cells can be fish cells or bird cells, or such cells can be mammalian cells, such as human cells, non-human mammalian cells, rodent cells, mouse cells or rat cells. Mammals include, but are not limited to, humans, non-human primates, monkeys, apes, cats dogs, horses, bulls, deer, bison, sheep, rodents (such as, for example, mice, rats, hamsters, guinea pigs), livestock (such as, for example, bovine species such as cows, steer, etc.; ovine species such as sheep, goats, etc.; and porcine species such as pigs and boars). The term "non-human animal" excludes humans.

The nucleotide and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three-letter code for amino acids. The nucleotide sequences follow the standard convention of beginning at the 5' end of the sequence and proceeding forward (i.e., from left to right in each line) to the 3' end. Only one strand of each nucleotide sequence is shown, but the complementary strand is understood to be included by any reference to the displayed strand. The amino acid sequence follows the standard convention of beginning at the amino terminus of the sequence and proceeding forward (i.e., from left to right in each line) to the carboxy terminus.

The present disclosure also provides therapeutic agents that treat or inhibit obesity for use in the treatment of obesity (or for use in the preparation of a medicament for treating obesity) in a subject, wherein the subject has any of the genomic nucleic acid molecules, mRNA molecules, and/or cDNA molecules encoding a human GPR75 polypeptide described herein. The therapeutic agents that treat or inhibit obesity can be any of the therapeutic agents that treat or inhibit obesity described herein.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; or lacks a CCAGUAG heptanucleotide at positions

corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; or lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at a position corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457

according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; or a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 5,991 according to SEQ ID NO:4, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human

GPR75 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; or a GPR75 polypeptide that comprises a stop codon at a position corresponding to position 234 according to SEQ ID NO:58.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG heptanucleotide at a position corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human

GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; or a GPR75 polypeptide that comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108.

The present disclosure also provides GPR75 inhibitors for use in the treatment of obesity (or for use in the preparation of a medicament for treating obesity) in a subject, wherein the subject has any of the genomic nucleic acid molecules, mRNA molecules, and/or cDNA molecules encoding a human GPR75 polypeptide described herein. The GPR75 inhibitors can be any of the GPR75 inhibitors described herein.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; or lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; or lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at a position corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 5,557 according to SEQ

ID NO:3, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; or an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; or a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; or iii) a cDNA molecule having a

nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; or a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 5,991 according to SEQ ID NO:4, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; or a GPR75 polypeptide that comprises a stop codon at a position corresponding to position 234 according to SEQ ID NO:58.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions

741-744 according to SEQ ID NO:33, or the complement thereof; or lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG heptanucleotide at a position corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; or a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof.

In some embodiments, the subject comprises: i) a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; ii) an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or iii) a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises: a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

In some embodiments, the subject comprises: a genomic nucleic acid molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position

corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; or a GPR75 polypeptide that comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:108.

All patent documents, websites, other publications, accession numbers and the like cited above or below are incorporated by reference in their entirety for all purposes to the same extent as if each individual item were specifically and individually indicated to be so incorporated by reference. If different versions of a sequence are associated with an accession number at different times, the version associated with the accession number at the effective filing date of this application is meant. The effective filing date means the earlier of the actual filing date or filing date of a priority application referring to the accession number if applicable. Likewise, if different versions of a publication, website or the like are published at different times, the version most recently published at the effective filing date of the application is meant unless otherwise indicated. Any feature, step, element, embodiment, or aspect of the present disclosure can be used in combination with any other feature, step, element, embodiment, or aspect unless specifically indicated otherwise. Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

The following representative embodiments are presented:

Embodiment 1. A method of treating a subject having obesity, the method comprising administering a G-Protein Coupled Receptor 75 (GPR75) inhibitor to the subject.

Embodiment 2. A method of treating a subject having excessive weight, the method comprising administering a GPR75 inhibitor to the subject.

Embodiment 3. A method of treating a subject having elevated BMI, the method comprising administering a GPR75 inhibitor to the subject.

Embodiment 4. A method of treating a subject having elevated body fat mass, percentage, or volume, the method comprising administering a GPR75 inhibitor to the subject.

Embodiment 5. A method of treating a subject having excessive food intake, or to prevent weight gain, or to maintain weight loss, the method comprising administering a GPR75 inhibitor to the subject.

Embodiment 6. The method according to any one of embodiments 1 to 5, wherein the GPR75 inhibitor comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

Embodiment 7. The method according to any one of embodiments 1 to 5, wherein the GPR75 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

Embodiment 8. The method according to embodiment 7, wherein the Cas protein is Cas9 or Cpf1.

Embodiment 9. The method according to embodiment 7 or embodiment 8, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

Embodiment 10. The method according to embodiment 7 or embodiment 8, wherein the gRNA recognition sequence is located from about 1000, from about 500, from about 400, from about 300, from about 200, from about 100, from about 50, from about 45, from about 40, from about 35, from about 30, from about 25, from about 20, from about 15, from about 10, or from about 5 nucleotides of a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

Embodiment 11. The method according to embodiment 7 or embodiment 8, wherein a Protospacer Adjacent Motif (PAM) sequence is about 2 to about 6 nucleotides downstream of the gRNA recognition sequence.

Embodiment 12. The method according to any one of embodiments 7 to 11, wherein the gRNA comprises from about 17 to about 23 nucleotides.

Embodiment 13. The method according to any one of embodiments 7 to 11, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOs:61-98.

Embodiment 14. The method according to any one of embodiments 1 to 13, further comprising detecting the absence of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample from the subject.

Embodiment 15. The method according to embodiment 14, further comprising administering a therapeutic agent that treats or inhibits obesity in a standard dosage amount to a subject that is GPR75 reference.

Embodiment 16. The method according to embodiment 14, further comprising administering a therapeutic agent that treats or inhibits obesity in a dosage amount that is the same as or lower than a standard dosage amount to a subject that is heterozygous for a GPR75 missense variant nucleic acid molecule.

Embodiment 17. The method according to any one of embodiments 14 to 16, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

Embodiment 18. The method according to embodiment 17, wherein the GPR75 missense variant nucleic acid molecule is:

a genomic nucleic acid molecule having a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprising a uracil at a position corresponding to

position 732 according to SEQ ID NO:23, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacking an AAAG tetranucleotide at positions

corresponding to positions 741-744 according to SEQ ID NO:33, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 19. The method according to any one of embodiments 14 to 18, wherein the detecting step is carried out *in vitro*.

Embodiment 20. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2 or SEQ ID NO:1, or the complement thereof; position 5,557 according to SEQ ID NO:3, or the complement thereof; position 5,911 according to SEQ ID NO:4, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5 or SEQ ID NO:1, or the complement thereof; position 6,411 according to SEQ ID NO:6, or the complement thereof; or position 5,831 according to SEQ ID NO:99, or the complement thereof;

wherein when the sequenced portion of the GPR75 genomic nucleic acid molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; then the GPR75 genomic nucleic acid molecule in the biological sample is a GPR75 missense variant nucleic acid molecule.

Embodiment 21. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; position 617 according to SEQ ID NO:27, or the complement thereof; position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; position 971 according to SEQ ID NO:28, or the complement thereof; positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; positions 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; position 891 according to SEQ ID NO:103, or the complement thereof;

wherein when the sequenced portion of the GPR75 mRNA molecule in the biological sample: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27;

comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, then the GPR75 mRNA molecule in the biological sample is a GPR75 missense variant mRNA molecule.

Embodiment 22. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 cDNA molecule produced from an mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to SEQ ID NO:50, or the complement thereof; position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; position 617 according to SEQ ID NO:51, or the complement thereof; position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; position 971 according to SEQ ID NO:52, or the complement thereof;

positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; positions 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; position 1,471 according to SEQ ID NO:54, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof;

wherein when the sequenced portion of the GPR75 cDNA molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; comprises an insertion of a thymine at a position corresponding to position 1,232 according to

SEQ ID NO:49; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, then the GPR75 cDNA molecule in the biological sample is a GPR75 missense variant cDNA molecule.

Embodiment 23. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule that is proximate to a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 genomic nucleic acid molecule corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99.

Embodiment 24. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 mRNA molecule that is proximate to a position

corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103; and

c) determining whether the extension product of the primer: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprises an adenine at a position corresponding to

position 457 according to SEQ ID NO:17, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103.

Embodiment 25. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39,

position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide

at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 26. The method according to any one of embodiments 20 to 25, wherein the detecting step comprises sequencing the entire nucleic acid molecule.

Embodiment 27. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an

adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

d) detecting the detectable label.

Embodiment 28. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement

thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position

corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

d) detecting the detectable label.

Embodiment 29. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a

position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding

to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106,

or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

d) detecting the detectable label.

Embodiment 30. The method according to embodiment 29, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into cDNA prior to the amplifying step.

Embodiment 31. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

detecting the detectable label.

Embodiment 32. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according

to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

detecting the detectable label.

Embodiment 33. The method according to any one of embodiments 14 to 19, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54,

or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

detecting the detectable label.

Embodiment 34. A method of treating a subject with a therapeutic agent that treats or inhibits obesity, wherein the subject is obese, the method comprising the steps of:

determining whether the subject has a G-Protein Coupled Receptor 75 (GPR75) missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide by:

obtaining or having obtained a biological sample from the subject; and

performing or having performed a sequence analysis on the biological sample to determine if the subject has a genotype comprising the GPR75 missense variant nucleic acid molecule; and

administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount to a subject that is GPR75 reference; and

administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount to a subject that is heterozygous for a GPR75 missense variant nucleic acid molecule;

wherein the presence of a genotype having the GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide indicates the subject has a reduced risk of developing obesity.

Embodiment 35. The method according to embodiment 34, wherein the subject is GPR75 reference, and the subject is administered or continued to be administered the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount.

Embodiment 36. The method according to embodiment 34, wherein the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, and the subject is administered or continued to be administered the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount.

Embodiment 37. The method according to any one of embodiments 34 to 36, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

Embodiment 38. The method according to embodiment 37, wherein the GPR75 missense variant nucleic acid molecule is:

a genomic nucleic acid molecule having a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacking an AAAG tetranucleotide at positions

corresponding to positions 919-922 according to SEQ ID NO:7, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34;

comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 39. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; position 5,557 according to SEQ ID NO:3, or the complement thereof; position 5,911 according to SEQ ID NO:4, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 6,411 according to SEQ ID NO:6, or the complement thereof; or position 5,831 according to SEQ ID NO:99, or the complement thereof;

wherein when the sequenced portion of the GPR75 genomic nucleic acid molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, then the GPR75 genomic nucleic acid molecule in the biological sample is a GPR75 missense variant genomic nucleic acid molecule.

Embodiment 40. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement

thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; position 617 according to SEQ ID NO:27, or the complement thereof; position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; position 971 according to SEQ ID NO:28, or the complement thereof; positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; positions 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; or position 1,471 according to SEQ ID NO:30, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; or position 891 according to SEQ ID NO:103, or the complement thereof;

wherein when the sequenced portion of the GPR75 mRNA molecule in the biological sample: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacks

an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, then the GPR75 mRNA molecule in the biological sample is a GPR75 missense variant mRNA molecule.

Embodiment 41. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises sequencing at least a portion of the nucleotide sequence of the GPR75 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to SEQ ID NO:50, or the complement thereof; position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; position 617 according to SEQ ID NO:51, or the complement thereof; position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; position 971 according to SEQ ID NO:52, or the complement thereof; positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; positions 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the

complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; position 1,471 according to SEQ ID NO:54, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof;

wherein when the sequenced portion of the GPR75 cDNA molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49; or comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106; or comprises a guanine at a position corresponding to position

891 according to SEQ ID NO:107, then the GPR75 cDNA molecule in the biological sample is a GPR75 missense variant cDNA molecule.

Embodiment 42. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule that is proximate to a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 genomic nucleic acid molecule corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99.

Embodiment 43. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 mRNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to

SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103; and

c) determining whether the extension product of the primer: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprises a uracil at a position corresponding to

position 732 according to SEQ ID NO:23, comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103.

Embodiment 44. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, comprises an insertion of a thymine at a position corresponding to position

1,410 according to SEQ ID NO:39, comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 45. The method according to any one of embodiments 39 to 44, wherein the sequence analysis comprises sequencing the entire nucleic acid molecule.

Embodiment 46. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement

thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99; and

d) detecting the detectable label.

Embodiment 47. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311

according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or

the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

d) detecting the detectable label.

Embodiment 48. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof;

comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according

to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

d) detecting the detectable label.

Embodiment 49. The method according to embodiment 48, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into cDNA prior to the amplifying step.

Embodiment 50. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

detecting the detectable label.

Embodiment 51. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17,

or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

detecting the detectable label.

Embodiment 52. The method according to any one of embodiments 34 to 38, wherein the sequence analysis comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of

the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof;

comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

detecting the detectable label.

Embodiment 53. The method according to any one of embodiments 34 to 52, wherein the nucleic acid molecule is present within a cell obtained from the subject.

Embodiment 54. The method according to any one of embodiments 34 to 53, wherein the GPR75 inhibitor comprises an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

Embodiment 55. The method according to any one of embodiments 34 to 53, wherein the GPR75 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

Embodiment 56. The method according to embodiment 55, wherein the Cas protein is Cas9 or Cpf1.

Embodiment 57. The method according to embodiment 55 or embodiment 56, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1 or position 5,831 according to SEQ ID NO:1.

Embodiment 58. The method according to embodiment 55 or embodiment 56, wherein the gRNA recognition sequence is located from about 1000, from about 500, from about 400, from about 300, from about 200, from about 100, from about 50, from about 45, from about 40, from about 35, from about 30, from about 25, from about 20, from about 15, from about 10, or from about 5 nucleotides of a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

Embodiment 59. The method according to embodiment 55 or embodiment 56, wherein a Protospacer Adjacent Motif (PAM) sequence is about 2 to 6 nucleotides downstream of the gRNA recognition sequence.

Embodiment 60. The method according to any one of embodiments 55 to 59, wherein the gRNA comprises from about 17 to about 23 nucleotides.

Embodiment 61. The method according to any one of embodiments 55 to 60, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOS:61-98.

Embodiment 62. A method of identifying a subject having an increased risk for developing obesity, wherein the method comprises:

determining or having determined the presence or absence of a G-Protein Coupled Receptor 75 (GPR75) missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample obtained from the subject;

wherein:

when the subject is GPR75 reference, then the subject has an increased risk for developing obesity; and

when the subject is heterozygous for a GPR75 missense variant nucleic acid molecule or homozygous for a GPR75 missense variant nucleic acid molecule, then the subject has a decreased risk for developing obesity.

Embodiment 63. The method according to embodiment 62, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

Embodiment 64. The method according to embodiment 63, wherein the GPR75 missense variant nucleic acid molecule is:

a genomic nucleic acid molecule having a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacking a CCAGUAG heptanucleotide at positions corresponding to positions

600-606 according to SEQ ID NO:10; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprising an adenine at a position corresponding to position 617 according

to SEQ ID NO:51; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 65. The method according to any one of embodiments 62 to 64, wherein the determining step is carried out *in vitro*.

Embodiment 66. The method according to any one of embodiments 62 to 64, wherein the determining step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; position 5,557 according to SEQ ID NO:3, or the complement thereof; position 5,911 according to SEQ ID NO:4, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 6,411 according to SEQ ID NO:6, or the complement thereof; or position 5,831 according to SEQ ID NO:99, or the complement thereof;

wherein when the sequenced portion of the GPR75 genomic nucleic acid molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to

position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, then the GPR75 genomic nucleic acid molecule in the biological sample is a GPR75 missense variant genomic nucleic acid molecule.

Embodiment 67. The method according to any one of embodiments 62 to 66, wherein the determining step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 mRNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 556 according to SEQ ID NO:12, or the complement thereof; position 457 according to SEQ ID NO:17, or the complement thereof; position 378 according to SEQ ID NO:22, or the complement thereof; position 617 according to SEQ ID NO:27, or the complement thereof; position 910 according to SEQ ID NO:13, or the complement thereof; position 811 according to SEQ ID NO:18, or the complement thereof; position 732 according to SEQ ID NO:23, or the complement thereof; position 971 according to SEQ ID NO:28, or the complement thereof; positions 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; positions 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 830 according to SEQ ID NO:100, or the complement thereof; position 731 according to SEQ ID NO:101, or the complement thereof; position 652 according to SEQ ID NO:102, or the complement thereof; or position 891 according to SEQ ID NO:103, or the complement thereof;

wherein when the sequenced portion of the GPR75 mRNA molecule in the biological sample: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; lacks a CCAGUAG heptanucleotide at positions corresponding to

positions 440-446 according to SEQ ID NO:8; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103; then the GPR75 mRNA molecule in the biological sample is a GPR75 missense variant genomic nucleic acid molecule.

Embodiment 68. The method according to any one of embodiments 62 to 66, wherein the determining step comprises sequencing at least a portion of the nucleotide sequence of the GPR75 cDNA molecule in the biological sample, wherein the sequenced portion comprises a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to

SEQ ID NO:50, or the complement thereof; position 556 according to SEQ ID NO:36, or the complement thereof; position 457 according to SEQ ID NO:41, or the complement thereof; position 378 according to SEQ ID NO:46, or the complement thereof; position 617 according to SEQ ID NO:51, or the complement thereof; position 910 according to SEQ ID NO:37, or the complement thereof; position 811 according to SEQ ID NO:42, or the complement thereof; position 732 according to SEQ ID NO:47, or the complement thereof; position 971 according to SEQ ID NO:52, or the complement thereof; positions 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; positions 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; position 1,471 according to SEQ ID NO:54, or the complement thereof; position 830 according to SEQ ID NO:104, or the complement thereof; position 731 according to SEQ ID NO:105, or the complement thereof; position 652 according to SEQ ID NO:106, or the complement thereof; or position 891 according to SEQ ID NO:107, or the complement thereof;

wherein when the sequenced portion of the GPR75 cDNA molecule in the biological sample: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823

according to SEQ ID NO:32; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107; then the GPR75 cDNA molecule in the biological sample is a GPR75 missense variant cDNA molecule.

Embodiment 69. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule that is proximate to a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position corresponding to position 5,831 according to SEQ ID NO:99;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 genomic nucleic acid molecule corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position corresponding to position 5,831 according to SEQ ID NO:99; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411

according to SEQ ID NO:6, or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99.

Embodiment 70. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 mRNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103; and

c) determining whether the extension product of the primer: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103.

Embodiment 71. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) contacting the biological sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to

SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107, and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprises an adenine at a position corresponding to

position 378 according to SEQ ID NO:46, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 72. The method according to any one of embodiments 67 to 71, wherein the determining step comprises sequencing the entire nucleic acid molecule.

Embodiment 73. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411

according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

d) detecting the detectable label.

Embodiment 74. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof;

comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position

corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

d) detecting the detectable label.

Embodiment 75. The method according to any one of embodiments 62 to 66, wherein the determining step comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID

NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to

position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

d) detecting the detectable label.

Embodiment 76. The method according to embodiment 75, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into cDNA prior to the amplifying step.

Embodiment 77. The method according to any one of embodiments 62 to 66, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

detecting the detectable label.

Embodiment 78. The method according to any one of embodiments 62 to 66, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the

complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

detecting the detectable label.

Embodiment 79. The method according to any one of embodiments 62 to 66, wherein the detecting step comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or

the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

detecting the detectable label.

Embodiment 80. The method according to any one of embodiments 62 to 79, wherein the subject is GPR75 reference, and the subject is administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount.

Embodiment 81. The method according to any one of embodiments 62 to 79, wherein the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, and the subject is administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount.

Embodiment 82. A method of detecting a human G-Protein Coupled Receptor 75 (GPR75) variant nucleic acid molecule in a subject comprising assaying a sample obtained from the subject to determine whether a nucleic acid molecule in the sample is:

a genomic nucleic acid molecule comprising a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ

ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7 or the complement thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8 or the complement thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9 or the complement thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10 or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12 or the complement thereof, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17 or the complement thereof, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22 or the complement thereof, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27 or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13 or the complement thereof, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18 or the complement thereof, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23 or the complement thereof, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28 or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10 or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15 or the complement thereof, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20 or the complement thereof, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25 or the complement thereof, comprising an insertion of a uracil

at a position corresponding to position 1,471 according to SEQ ID NO:30 or the complement thereof, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34 or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36 or the complement thereof, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41 or the complement thereof, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46 or the complement thereof, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51 or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37 or the complement thereof, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42 or the complement thereof, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47 or the complement thereof, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52 or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34 or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39

or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44 or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49 or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54 or the complement thereof, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104 or the complement thereof, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105 or the complement thereof, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106 or the complement thereof, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 83. The method according to embodiment 82, wherein the method is an *in vitro* method.

Embodiment 84. The method according to embodiment 82 or embodiment 83, wherein the assay comprises sequencing at least a portion of the nucleic acid molecule, wherein the sequenced portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

Embodiment 85. The method according to embodiment 82 or embodiment 83, wherein the assay comprises sequencing at least a portion of the nucleic acid molecule, wherein the sequenced portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or

the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

Embodiment 86. The method according to embodiment 82 or embodiment 83, wherein the assay comprises sequencing at least a portion of the nucleic acid molecule, wherein the sequenced portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG

heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine

at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 87. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) contacting the sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 genomic nucleic acid molecule that is proximate to a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 genomic nucleic acid molecule corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, position 5,557 according to SEQ ID NO:3, position 5,911 according to SEQ ID NO:4, positions 5,920-5,923 according to SEQ ID NO:5, position 6,411 according to SEQ ID NO:6, or position 5,831 according to SEQ ID NO:99; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprises guanine at a position corresponding to position 5,831 according to SEQ ID NO:99.

Embodiment 88. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) contacting the sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 mRNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions

820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 mRNA molecule corresponding to: positions 539-545 according to SEQ ID NO:11, positions 440-446 according to SEQ ID NO:16, positions 361-367 according to SEQ ID NO:21, positions 600-606 according to SEQ ID NO:26, position 556 according to SEQ ID NO:12, position 457 according to SEQ ID NO:17, position 378 according to SEQ ID NO:22, position 617 according to SEQ ID NO:27, position 910 according to SEQ ID NO:13, position 811 according to SEQ ID NO:18, position 732 according to SEQ ID NO:23, position 971 according to SEQ ID NO:28, positions 919-922 according to SEQ ID NO:14, positions 820-823 according to SEQ ID NO:19, positions 741-744 according to SEQ ID NO:24, positions 980-983 according to SEQ ID NO:29, position 1,410 according to SEQ ID NO:15, position 1,311 according to SEQ ID NO:20, position 1,232 according to SEQ ID NO:25, position 1,471 according to SEQ ID NO:30, position 830 according to SEQ ID NO:100, position 731 according to SEQ ID NO:101, position 652 according to SEQ ID NO:102, or position 891 according to SEQ ID NO:103; and

c) determining whether the extension product of the primer: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, lacks an AAAG tetranucleotide at positions

corresponding to positions 919-922 according to SEQ ID NO:7, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103.

Embodiment 89. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) contacting the sample with a primer hybridizing to a portion of the nucleotide sequence of the GPR75 cDNA molecule that is proximate to a position corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position 457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107;

b) extending the primer at least through the position of the nucleotide sequence of the GPR75 cDNA molecule corresponding to: positions 539-545 according to SEQ ID NO:35, positions 440-446 according to SEQ ID NO:40, positions 361-367 according to SEQ ID NO:45, positions 600-606 according to SEQ ID NO:50, position 556 according to SEQ ID NO:36, position

457 according to SEQ ID NO:41, position 378 according to SEQ ID NO:46, position 617 according to SEQ ID NO:51, position 910 according to SEQ ID NO:37, position 811 according to SEQ ID NO:42, position 732 according to SEQ ID NO:47, position 971 according to SEQ ID NO:52, positions 919-922 according to SEQ ID NO:38, positions 820-823 according to SEQ ID NO:43, positions 741-744 according to SEQ ID NO:48, positions 980-983 according to SEQ ID NO:53, position 1,410 according to SEQ ID NO:39, position 1,311 according to SEQ ID NO:44, position 1,232 according to SEQ ID NO:49, or position 1,471 according to SEQ ID NO:54, position 830 according to SEQ ID NO:104, position 731 according to SEQ ID NO:105, position 652 according to SEQ ID NO:106, or position 891 according to SEQ ID NO:107; and

c) determining whether the extension product of the primer: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54,

comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

Embodiment 90. The method according to any one of embodiments 84 to 89, wherein the assay comprises sequencing the entire nucleic acid molecule.

Embodiment 91. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or position 5,831 according to SEQ ID NO:99, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

d) detecting the detectable label.

Embodiment 92. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position

corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or

the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

d) detecting the detectable label.

Embodiment 93. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

a) amplifying at least a portion of the nucleic acid molecule that encodes the human GPR75 polypeptide, wherein the portion: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position

corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof;

b) labeling the amplified nucleic acid molecule with a detectable label;

c) contacting the labeled nucleic acid molecule with a support comprising an alteration-specific probe, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleic acid sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41,

or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

d) detecting the detectable label.

Embodiment 94. The method according to embodiment 93, wherein the nucleic acid molecule in the sample is mRNA and the mRNA is reverse-transcribed into cDNA prior to the amplifying step.

Embodiment 95. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof; and

detecting the detectable label.

Embodiment 96. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811

according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; and

detecting the detectable label.

Embodiment 97. The method according to embodiment 82 or embodiment 83, wherein the assay comprises:

contacting the nucleic acid molecule in the biological sample with an alteration-specific probe comprising a detectable label, wherein the alteration-specific probe comprises a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of the amplified nucleic acid molecule: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof;

lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof; and

detecting the detectable label.

Embodiment 98. The method according to any one of embodiments 82 to 97, wherein the nucleic acid molecule is present within a cell obtained from the subject.

Embodiment 99. A method of detecting the presence of a human G-Protein Coupled Receptor 75 (GPR75) Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs variant polypeptide, comprising performing an assay on a sample obtained from a subject to determine whether a GPR75 protein in the sample comprises SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, or SEQ ID NO:108.

Embodiment 100. The method according to embodiment 99, wherein the assay comprises sequencing the polypeptide.

Embodiment 101. The method according to embodiment 99, wherein the assay is an immunoassay.

Embodiment 102. An isolated alteration-specific probe or alteration-specific primer comprising at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the portion comprises a position corresponding to:

positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; or positions 600-606 according to SEQ ID NO:50, or the complement thereof;

positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; position 980-983 according to SEQ ID NO:29, or the complement thereof; position 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; or position 980-983 according to SEQ ID NO:53, or the complement thereof; or

position 6,411 according to SEQ ID NO:6, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof.

Embodiment 103. The alteration-specific probe or alteration-specific primer according to embodiment 102, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; or position 6,411 according to SEQ ID NO:6, or the complement thereof.

Embodiment 104. The alteration-specific probe or alteration-specific primer according to embodiment 102, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; position 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; or position 1,471 according to SEQ ID NO:30, or the complement thereof.

Embodiment 105. The alteration-specific probe or alteration-specific primer according to embodiment 102, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to SEQ ID NO:50, or the complement thereof; position 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to

SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; position 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof.

Embodiment 106. The alteration-specific probe or alteration-specific primer according to any one of embodiments 102 to 105, wherein the alteration-specific probe or alteration-specific primer comprises DNA.

Embodiment 107. The alteration-specific probe or alteration-specific primer according to any one of embodiments 102 to 105, wherein the alteration-specific probe or alteration-specific primer comprises RNA.

Embodiment 108. The alteration-specific probe or alteration-specific primer according to any one of embodiments 102 to 107, wherein the alteration-specific probe or alteration-specific primer comprises a label.

Embodiment 109. The alteration-specific probe or alteration-specific primer according to embodiment 108, wherein the label is a fluorescent label, a radiolabel, or biotin.

Embodiment 110. A support comprising a substrate to which an alteration-specific probe or alteration-specific primer according to any one of embodiments 102 to 109 is attached.

Embodiment 111. The support according to embodiment 110, wherein the support is a microarray.

Embodiment 112. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to a genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the genomic nucleic acid molecule: at nucleotides at positions corresponding to positions 5,539-5,540 according to SEQ ID NO:2, or the complement thereof; at an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; at a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; at nucleotides at positions corresponding to positions 5,919-5,920 according to SEQ ID NO:5, or the complement thereof; at a thymine at a position corresponding to position 6,411 according

to SEQ ID NO:6, or the complement thereof; or at a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

Embodiment 113. The molecular complex according to embodiment 112, wherein the genomic nucleic acid molecule comprises SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:99.

Embodiment 114. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to an mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the mRNA molecule: at nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:11, or the complement thereof; at nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:16, or the complement thereof; at nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:21, or the complement thereof; at nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:26, or the complement thereof; at an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; at an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; at an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; at an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; at a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; at a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; at a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; at a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; at nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:14, or the complement thereof; at nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:19, or the complement thereof; at nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:24, or the complement thereof; at nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:29, or the complement thereof; at a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; at a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; at a uracil at a position corresponding to position

1,232 according to SEQ ID NO:25, or the complement thereof; at a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; at a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; at a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; at a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or at a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

Embodiment 115. The molecular complex according to embodiment 114, wherein the mRNA molecule comprises SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

Embodiment 116. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to a cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to: nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:35, or the complement thereof; nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:40, or the complement thereof; nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:45, or the complement thereof; nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:50, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; nucleotides at positions corresponding to positions 918-

919 according to SEQ ID NO:38, or the complement thereof; nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:43, or the complement thereof; nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:48, or the complement thereof; nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:53, or the complement thereof; a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 117. The molecular complex according to embodiment 116, wherein the cDNA molecule comprises SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, or SEQ ID NO:54, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

Embodiment 118. The molecular complex according to any one of embodiments 112 to 117, wherein the alteration-specific probe or alteration-specific primer comprises a label.

Embodiment 119. The molecular complex according to embodiment 118, wherein the label is a fluorescent label, a radiolabel, or biotin.

Embodiment 120. The molecular complex according to any one of embodiments 112 to 119, further comprising a non-human polymerase.

Embodiment 121. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, or the complement thereof, wherein the polypeptide comprises: a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56, a frameshift beginning at a position corresponding

to position 236 according to SEQ ID NO:59, or a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60.

Embodiment 122. The isolated nucleic acid molecule, or the complement thereof, according to embodiment 121, wherein the nucleic acid molecule encodes a GPR75 polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:56, wherein the polypeptide comprises a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56; SEQ ID NO:59, wherein the polypeptide comprises a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59; or SEQ ID NO:60, wherein the polypeptide comprises a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60.

Embodiment 123. The nucleic acid molecule, or complement thereof, according to embodiment 121, wherein the polypeptide comprises SEQ ID NO:56, SEQ ID NO:59, or SEQ ID NO:60.

Embodiment 124. A vector comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 121 to 123.

Embodiment 125. The vector according to embodiment 124, wherein the vector is a plasmid.

Embodiment 126. The vector according to embodiment 124, wherein the vector is a virus.

Embodiment 127. A host cell comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 121 to 123.

Embodiment 128. A host cell comprising the vector according to any one of embodiments 124 to 126.

Embodiment 129. The host cell according to embodiment 127 or embodiment 128, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 130. The host cell according to embodiment 129, wherein the promoter is an exogenous promoter.

Embodiment 131. The host cell according to embodiment 129 or embodiment 130, wherein the promoter is an inducible promoter.

Embodiment 132. The host cell according to any one of embodiments 127 to 131, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 133. A composition comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 121 to 123 and a carrier.

Embodiment 134. A composition comprising the vector according to any one of embodiments 124 to 126 and a carrier.

Embodiment 135. An isolated genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; a lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof.

Embodiment 136. The isolated genomic nucleic acid molecule, or the complement thereof, according to embodiment 135, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:2, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1; SEQ ID NO:5, and lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1; or SEQ ID NO:6, and comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6.

Embodiment 137. The isolated genomic nucleic acid molecule, or the complement thereof, according to embodiment 136, wherein the nucleic acid molecule comprises SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6.

Embodiment 138. A vector comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 135 to 137.

Embodiment 139. The vector according to embodiment 138, wherein the vector is a plasmid.

Embodiment 140. The vector according to embodiment 138, wherein the vector is a virus.

Embodiment 141. A host cell comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 135 to 137.

Embodiment 142. A host cell comprising the vector according to any one of embodiments 138 to 140.

Embodiment 143. The host cell according to embodiment 141 or embodiment 142, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 144. The host cell according to embodiment 143, wherein the promoter is an exogenous promoter.

Embodiment 145. The host cell according to embodiment 143 or embodiment 144, wherein the promoter is an inducible promoter.

Embodiment 146. The host cell according to any one of embodiments 141 to 145, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 147. A composition comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 135 to 137 and a carrier.

Embodiment 148. A composition comprising the vector according to any one of embodiments 138 to 140 and a carrier.

Embodiment 149. An isolated mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or comprises an insertion of a uracil at

a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof.

Embodiment 150. The isolated mRNA molecule, or the complement thereof, according to embodiment 149, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:11, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7; SEQ ID NO:16, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8; SEQ ID NO:21, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9; SEQ ID NO:26, and lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; SEQ ID NO:14, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7; SEQ ID NO:19, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8; SEQ ID NO:24, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9; SEQ ID NO:29, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; SEQ ID NO:15, and comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15; SEQ ID NO:20, and comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20; SEQ ID NO:25, and comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25; or SEQ ID NO:30, and comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30.

Embodiment 151. The isolated mRNA molecule, or the complement thereof, according to embodiment 149, wherein the nucleic acid molecule comprises SEQ ID NO:11, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:29, or SEQ ID NO:30.

Embodiment 152. A vector comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 149 to 151.

Embodiment 153. The vector according to embodiment 152, wherein the vector is a plasmid.

Embodiment 154. The vector according to embodiment 152, wherein the vector is a virus.

Embodiment 155. A host cell comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 149 to 151.

Embodiment 156. A host cell comprising the vector according to any one of embodiments 152 to 154.

Embodiment 157. The host cell according to embodiment 155 or embodiment 156, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 158. The host cell according to embodiment 157, wherein the promoter is an exogenous promoter.

Embodiment 159. The host cell according to embodiment 157 or embodiment 158, wherein the promoter is an inducible promoter.

Embodiment 160. The host cell according to any one of embodiments 155 to 159, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 161. A composition comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 149 to 151 and a carrier.

Embodiment 162. A composition comprising the vector according to any one of embodiments 152 to 154 and a carrier.

Embodiment 163. An isolated cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at

a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

Embodiment 164. The isolated cDNA molecule, or the complement thereof, according to embodiment 163, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:35, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31; SEQ ID NO:40, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32; SEQ ID NO:45, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33; SEQ ID NO:50, and lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; SEQ ID NO:38, and lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31; SEQ ID NO:43, and lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32; SEQ ID NO:48, and lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33; SEQ ID NO:53, and lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; SEQ ID NO:39, and comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39; SEQ ID NO:44, and comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44; SEQ ID NO:49, and comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49; or SEQ ID NO:54, and comprises or an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54.

Embodiment 165. The isolated cDNA molecule, or the complement thereof, according to embodiment 163, wherein the nucleic acid molecule comprises SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:53, or SEQ ID NO:54.

Embodiment 166. A vector comprising the cDNA molecule, or the complement thereof, according to any one of embodiments 163 to 165.

Embodiment 167. The vector according to embodiment 166, wherein the vector is a plasmid.

Embodiment 168. The vector according to embodiment 166, wherein the vector is a virus.

Embodiment 169. A host cell comprising the cDNA molecule, or the complement thereof, according to any one of embodiments 163 to 165.

Embodiment 170. A host cell comprising the vector according to any one of embodiments 166 to 168.

Embodiment 171. The host cell according to embodiment 169 or embodiment 170, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 172. The host cell according to embodiment 171, wherein the promoter is an exogenous promoter.

Embodiment 173. The host cell according to embodiment 171 or embodiment 172, wherein the promoter is an inducible promoter.

Embodiment 174. The host cell according to any one of embodiments 169 to 173, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 175. A composition comprising the cDNA molecule, or the complement thereof, according to any one of embodiments 163 to 165 and a carrier.

Embodiment 176. A composition comprising the vector according to any one of embodiments 166 to 168 and a carrier.

Embodiment 177. An isolated human G-Protein Coupled Receptor 75 (GPR75) polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:56, wherein the polypeptide lacks amino acids at positions corresponding to positions 110 to 540 according to SEQ ID NO:55; SEQ ID NO:59, wherein the polypeptide lacks amino acids at positions corresponding to positions 236 to 540 according to SEQ ID NO:55; or SEQ ID NO:60, wherein the polypeptide lacks amino acids at positions corresponding to positions 400 to 540 according to SEQ ID NO:55.

Embodiment 178. The polypeptide according to embodiment 177, wherein the polypeptide comprises SEQ ID NO:56, SEQ ID NO:59, or SEQ ID NO:60.

Embodiment 179. The polypeptide according to embodiment 177 or embodiment 178, wherein the polypeptide is fused to a heterologous molecule.

Embodiment 180. The polypeptide according to embodiment 179, wherein the heterologous molecule comprises an immunoglobulin Fc domain, a peptide purification tag, a fluorescent protein, or a transduction domain.

Embodiment 181. The polypeptide according to any one of embodiments 177 to 180, wherein the polypeptide is linked to a label.

Embodiment 182. The polypeptide according to embodiment 181, wherein the label is a fluorescent label or a radiolabel.

Embodiment 183. The polypeptide according to embodiment 181, wherein the label comprises polyethylene glycol, polysialic acid, or glycolic acid.

Embodiment 184. A composition comprising the polypeptide according to any one of embodiments 177 to 183 and a carrier or excipient.

Embodiment 185. A host cell expressing the polypeptide according to any one of embodiments 177 to 183.

Embodiment 186. A method of producing the polypeptide according to any one of embodiments 177 to 183, comprising culturing a host cell comprising a nucleic acid molecule encoding the polypeptide, whereby the host cell expresses the polypeptide, and recovering the expressed polypeptide.

Embodiment 187. The method according to embodiment 186, wherein the nucleic acid molecule is under control of a heterologous promoter.

Embodiment 188. The method according to embodiment 186 or embodiment 187, wherein the nucleic acid molecule is under control of an inducible promoter.

Embodiment 189. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, or the complement thereof, wherein the polypeptide: comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57, terminates at a position corresponding to position 233 according to SEQ ID NO:58, or comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:99.

Embodiment 190. The isolated nucleic acid molecule, or the complement thereof, according to embodiment 189, wherein the nucleic acid molecule encodes a GPR75 polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:57, wherein the polypeptide comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57; SEQ ID NO:58, wherein the polypeptide terminates at a position corresponding to position 233 according to SEQ ID NO:58; or SEQ ID NO:99, wherein the polypeptide comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:99.

Embodiment 191. The nucleic acid molecule, or complement thereof, according to embodiment 189, wherein the polypeptide comprises SEQ ID NO:57, SEQ ID NO:58, or SEQ ID NO:99.

Embodiment 192. A vector comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 189 to 191.

Embodiment 193. The vector according to embodiment 192, wherein the vector is a plasmid.

Embodiment 194. The vector according to embodiment 192, wherein the vector is a virus.

Embodiment 195. A host cell comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 189 to 191.

Embodiment 196. A host cell comprising the vector according to any one of embodiments 192 to 194.

Embodiment 197. The host cell according to embodiment 195 or embodiment 196, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 198. The host cell according to embodiment 197, wherein the promoter is an exogenous promoter.

Embodiment 199. The host cell according to embodiment 197 or embodiment 198, wherein the promoter is an inducible promoter.

Embodiment 200. The host cell according to any one of embodiments 195 to 199, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 201. A composition comprising the isolated nucleic acid molecule, or the complement thereof, according to any one of embodiments 189 to 191 and a carrier.

Embodiment 202. A composition comprising the vector according to any one of embodiments 192 to 194 and a carrier.

Embodiment 203. An isolated mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617

according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

Embodiment 204. The isolated mRNA molecule, or the complement thereof, according to embodiment 203, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:12 and comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; SEQ ID NO:17 and comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; SEQ ID NO:22 and comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; SEQ ID NO:27 and comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; SEQ ID NO:13 and comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; SEQ ID NO:18 and comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; SEQ ID NO:23 and comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; SEQ ID NO:28 and comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; SEQ ID NO:100 and comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; SEQ ID NO:101 and comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; SEQ ID NO:102 and comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or SEQ ID NO:103 and comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

Embodiment 205. The isolated mRNA molecule, or the complement thereof, according to embodiment 203, wherein the nucleic acid molecule comprises SEQ ID NO:12, SEQ ID NO:17, SEQ ID NO:22, SEQ ID NO:27, SEQ ID NO:13, SEQ ID NO:18, SEQ ID NO:23, SEQ ID NO:28, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

Embodiment 206. A vector comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 203 to 205.

Embodiment 207. The vector according to embodiment 206, wherein the vector is a plasmid.

Embodiment 208. The vector according to embodiment 206, wherein the vector is a virus.

Embodiment 209. A host cell comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 203 to 205.

Embodiment 210. A host cell comprising the vector according to any one of embodiments 206 to 208.

Embodiment 211. The host cell according to embodiment 209 or embodiment 210, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 212. The host cell according to embodiment 211, wherein the promoter is an exogenous promoter.

Embodiment 213. The host cell according to embodiment 211 or embodiment 212, wherein the promoter is an inducible promoter.

Embodiment 214. The host cell according to any one of embodiments 209 to 213, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 215. A composition comprising the isolated mRNA molecule, or the complement thereof, according to any one of embodiments 203 to 205 and a carrier.

Embodiment 216. A composition comprising the vector according to any one of embodiments 206 to 208 and a carrier.

Embodiment 217. An isolated cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46,

or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 218. The isolated cDNA molecule, or the complement thereof, according to embodiment 217, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:36 and comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; SEQ ID NO:41 and comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; SEQ ID NO:46 and comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; SEQ ID NO:51 and comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; SEQ ID NO:37 and comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; SEQ ID NO:42 and comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; SEQ ID NO:47 and comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; SEQ ID NO:52 and comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; SEQ ID NO:104 and comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; SEQ ID NO:105 and comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; SEQ ID NO:106 and comprises a guanine at a position corresponding to position 652 according to SEQ

ID NO:106, or the complement thereof; or SEQ ID NO:107 and comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 219. The isolated cDNA molecule, or the complement thereof, according to embodiment 217, wherein the nucleic acid molecule comprises SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:46, SEQ ID NO:51, SEQ ID NO:37, SEQ ID NO:42, SEQ ID NO:47, SEQ ID NO:52, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

Embodiment 220. A vector comprising the isolated cDNA molecule, or the complement thereof, according to any one of embodiments 217 to 219.

Embodiment 221. The vector according to embodiment 220, wherein the vector is a plasmid.

Embodiment 222. The vector according to embodiment 220, wherein the vector is a virus.

Embodiment 223. A host cell comprising the isolated cDNA molecule, or the complement thereof, according to any one of embodiments 217 to 219.

Embodiment 224. A host cell comprising the vector according to any one of embodiments 220 to 222.

Embodiment 225. The host cell according to embodiment 223 or embodiment 224, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 226. The host cell according to embodiment 225, wherein the promoter is an exogenous promoter.

Embodiment 227. The host cell according to embodiment 225 or embodiment 226, wherein the promoter is an inducible promoter.

Embodiment 228. The host cell according to any one of embodiments 223 to 227, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 229. A composition comprising the isolated cDNA molecule, or the complement thereof, according to any one of embodiments 217 to 219 and a carrier.

Embodiment 230. A composition comprising the vector according to any one of embodiments 220 to 222 and a carrier.

Embodiment 231. An isolated genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; a thymine at a position corresponding to

position 5,911 according to SEQ ID NO:4, or the complement thereof; or a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

Embodiment 232. The isolated genomic nucleic acid molecule, or the complement thereof, according to embodiment 231, wherein the nucleotide sequence has at least 90% sequence identity to: SEQ ID NO:3, and comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3; SEQ ID NO:4, and comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4; or SEQ ID NO:99, and comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99.

Embodiment 233. The isolated genomic nucleic acid molecule, or the complement thereof, according to embodiment 231, wherein the nucleic acid molecule comprises SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:99.

Embodiment 234. A vector comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 231 to 233.

Embodiment 235. The vector according to embodiment 234, wherein the vector is a plasmid.

Embodiment 236. The vector according to embodiment 234, wherein the vector is a virus.

Embodiment 237. A host cell comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 231 to 233.

Embodiment 238. A host cell comprising the vector according to any one of embodiments 234 to 236.

Embodiment 239. The host cell according to embodiment 237 or embodiment 238, wherein the nucleotide sequence is operably linked to a promoter active in the host cell.

Embodiment 240. The host cell according to embodiment 239, wherein the promoter is an exogenous promoter.

Embodiment 241. The host cell according to embodiment 239 or embodiment 240, wherein the promoter is an inducible promoter.

Embodiment 242. The host cell according to any one of embodiments 237 to 241, wherein the host cell is a bacterial cell, a yeast cell, an insect cell, or a mammalian cell.

Embodiment 243. A composition comprising the isolated genomic nucleic acid molecule, or the complement thereof, according to any one of embodiments 231 to 233 and a carrier.

Embodiment 244. A composition comprising the vector according to any one of embodiments 234 to 236 and a carrier.

Embodiment 245. An isolated human G-Protein Coupled Receptor 75 (GPR75) polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:57, wherein the polypeptide comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57; SEQ ID NO:58, wherein the polypeptide terminates at a position corresponding to position 233 according to SEQ ID NO:58; or SEQ ID NO:99, wherein the polypeptide comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:99.

Embodiment 246. The polypeptide according to embodiment 245, wherein the polypeptide comprises SEQ ID NO:57, SEQ ID NO:58, or SEQ ID NO:99.

Embodiment 247. The polypeptide according to embodiment 245 or embodiment 246, wherein the polypeptide is fused to a heterologous molecule.

Embodiment 248. The polypeptide according to embodiment 247, wherein the heterologous molecule comprises an immunoglobulin Fc domain, a peptide purification tag, a fluorescent protein, or a transduction domain.

Embodiment 249. The polypeptide according to any one of embodiments 245 to 248, wherein the polypeptide is linked to a label.

Embodiment 250. The polypeptide according to embodiment 249, wherein the label is a fluorescent label or a radiolabel.

Embodiment 251. The polypeptide according to embodiment 249, wherein the label comprises polyethylene glycol, polysialic acid, or glycolic acid.

Embodiment 252. A composition comprising the polypeptide according to any one of embodiments 245 to 251 and a carrier or excipient.

Embodiment 253. A host cell expressing the polypeptide according to any one of embodiments 245 to 251.

Embodiment 254. A method of producing the polypeptide according to any one of embodiments 245 to 251, comprising culturing a host cell comprising a nucleic acid molecule encoding the polypeptide, whereby the host cell expresses the polypeptide, and recovering the expressed polypeptide.

Embodiment 255. The method according to embodiment 254, wherein the nucleic acid molecule is under control of a heterologous promoter.

Embodiment 256. The method according to embodiment 254 or embodiment 255, wherein the nucleic acid molecule is under control of an inducible promoter.

Embodiment 257. A therapeutic agent that treats or inhibits obesity for use in the treatment of obesity in a subject having:

a genomic nucleic acid molecule having a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to

position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof;

comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 258. A G-Protein Coupled Receptor 75 (GPR75) inhibitor for use in the treatment of obesity in a subject having:

a genomic nucleic acid molecule having a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position

corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471

according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to

position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

Embodiment 259. The GPR75 inhibitor according to embodiment 258, which is an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

Embodiment 260. The GPR75 inhibitor according to embodiment 258, which comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

Embodiment 261. The GPR75 inhibitor according to embodiment 260, wherein the Cas protein is Cas9 or Cpf1.

Embodiment 262. The GPR75 inhibitor according to embodiment 260 or embodiment 261, wherein the gRNA recognition sequence includes or is proximate to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

Embodiment 263. The GPR75 inhibitor according to embodiment 260 or embodiment 261, wherein the gRNA recognition sequence is located from about 1000, from about 500, from about 400, from about 300, from about 200, from about 100, from about 50, from about 45, from about 40, from about 35, from about 30, from about 25, from about 20, from about 15, from about 10, or from about 5 nucleotides of a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

Embodiment 264. The GPR75 inhibitor according to embodiment 260 or embodiment 261, wherein a Protospacer Adjacent Motif (PAM) sequence is about 2 to about 6 nucleotides downstream of the gRNA recognition sequence.

Embodiment 265. The GPR75 inhibitor according to any one of embodiments 260 to 264, wherein the gRNA comprises from about 17 to about 23 nucleotides.

Embodiment 266. The GPR75 inhibitor according to any one of embodiments 260 to 265, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOS:61-98.

The following examples are provided to describe the embodiments in greater detail. They are intended to illustrate, not to limit, the claimed embodiments. The following examples provide those of ordinary skill in the art with a disclosure and description of how the compounds, compositions, articles, devices and/or methods described herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the scope of any claims. Efforts have been made to ensure accuracy with respect to numbers (such as, for example, amounts, temperature, etc.), but some errors and deviations may be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

Examples

Example 1: Materials and Methods

Participating cohorts

Discovery genetic association studies were performed in the United Kingdom (UK) Biobank (UKB) cohort (Sudlow et al., PLoS Med 12, 2015, e1001779), in the MyCode Community Health Initiative cohort from the Geisinger Health System (GHS) (Carey et al., Genet. Med., 2016, 18, 906-913) and in the Mexico City Prospective Study (MCPS) (Tapia-Conyer et al., Int. J. Epidemiol., 2006, 35, 243-249). The UKB is a population-based cohort study of people aged between 40 and 69 years recruited through 22 testing centers in the UK between 2006-2010. A total of 428,719 European ancestry participants with available whole-exome sequencing and clinical phenotype data were included (Figure 1). UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC; 11/NW/0382), which covers the UK. The GHS MyCode study is a health system-based cohort of patients from Central and Eastern Pennsylvania (USA) recruited in 2007-2019. A total of 121,061 European ancestry participants

with available whole-exome sequencing and clinical phenotype data were included (Figure 1). The GHS MyCode study was approved by the Geisinger Institutional Review Board (2006-0258). The MCPS is a cohort study of people aged ≥35 years recruited from two contiguous urban districts in Mexico City in 1998-2004. The study design and clinical characteristics of participants in MCPS have been described in detail in previous publications (Tapia-Conyer et al., Int. J. Epidemiol., 2006, 35, 243-249; and Alegre-Diaz et al., N. Engl. J. Med., 2016, 375, 1961-1971). A total of 95,846 individuals of Admixed American ancestry with available whole-exome sequencing and clinical phenotype data were included (Figure 1). The MCPS study was approved by the Mexican Ministry of Health, the Mexican National Council for Science and Technology, and the University of Oxford.

The association with BMI of *GPR75* predicted loss-of-function (pLOF) variants was further estimated in an additional 91,328 exomes not included in the discovery set. These included participants of non-European ancestries from the UK Biobank (UKB, N=12,321) (Sudlow et al., PLoS Med 12, 2015, e1001779), and participants in the Mount Sinai BioMe cohort (SINAI, N=21,143), the University of Pennsylvania Medicine BioBank (PMBB; N=7,519), the Duke Catheterization Genetics (CATHGEN) cohort (DUKE; N=8,171) (Kraus et al., J. Cardiovasc. Transl. Res., 2015, 8, 449-457), the Taiwanese Chinese from Taiwan Metabochip consortium (TAICHI; N=11,223) (Assimes et al., PLoS One 11, 2016, e0138014), the Dallas Heart Study (DHS; N=2,088) (Victor et al., Am. J. Cardiol., 2004, 93, 1473-1480) and the Malmö Diet and Cancer Study (MALMO; N=28,863) (Berglund et al., J. Intern. Med., 1993, 233, 45-51). All studies were approved by relevant ethics committees and participants provided informed consent for participation in these studies.

Phenotype definitions

Body mass index was calculated as weight in kilograms divided by the square of height in meters on the basis of anthropometric measurements taken at one of the study visits. BMI measured at the baseline visit was the outcome variable in UKB and MCPS, while median BMI from clinical encounters present in the GHS database was the outcome variable for GHS consistent with previous studies (Dewey et al., Science, 2016, 354). BMI categories were defined on the basis of the World Health Organization classification (WHO, Obesity and overweight, 2020). BMI values were transformed by the inverse standard normal function, applied within each ancestry group and separately in men and women. Body weight differences were calculated for a person 170 cm tall. Overall and regional body lean and fat masses,

percentages and body-surface normalized indices were measured by bioelectrical impedance in the UKB cohort. At the baseline visit, UKB also collected self-reported information on comparative body size at age 10 by asking the multiple choice question: "When you were 10 years old, compared to average would you describe yourself as: thinner, plumper, about average, do not know, prefer not to answer?".

Genotype data

High coverage whole exome sequencing was performed as previously described in detail (Dewey et al., Science, 2016, 354; and Van Hout et al., Nature, 2020, 586, 749-756) and as summarized below. NimbleGen probes (VCRome; for part of the GHS cohort) or a modified version of the xGen design available from Integrated DNA Technologies (IDT; for the rest of GHS and other cohorts) were used for target sequence capture of the exome. A unique 6 base pair (bp) barcode (VCRome) or 10 bp barcode (IDT) was added to each DNA fragment during library preparation to facilitate multiplexed exome capture and sequencing. Equal amounts of sample were pooled prior to exome capture. Sequencing was performed using 75 bp paired-end reads on Illumina v4 HiSeq 2500 (for part of the GHS cohort) or NovaSeq (for the rest of GHS and other cohorts) instruments. Sequencing had a coverage depth (i.e., number of sequence-reads covering each nucleotide in the target areas of the genome) sufficient to provide greater than 20x coverage over 85% of targeted bases in 96% of VCRome samples and 20x coverage over 90% of targeted bases in 99% of IDT samples. Data processing steps included sample de-multiplexing using Illumina software, alignment to the GRCh38 Human Genome reference sequence including generation of binary alignment and mapping files (BAM), processing of BAM files (e.g., marking of duplicate reads and other read mapping evaluations). Variant calling and annotation were based on the GRCh38 Human Genome reference sequence and Ensembl v85 gene definitions using the snpEff software. The snpEff predictions that involve protein-coding transcripts with an annotated start and stop were then combined into a single functional impact prediction by selecting the most deleterious functional effect class for each gene. The hierarchy (from most to least deleterious) for these annotations was frameshift, stop-gain, stop-loss, splice acceptor, splice donor, stop-lost, in-frame indel, missense, other annotations. Predicted LOF genetic variants included: a) insertions or deletions resulting in a frameshift, b) insertions, deletions or single nucleotide variants resulting in the introduction of a premature stop codon or in the loss of the transcription start site or stop site, and c) variants in donor or acceptor splice sites. Missense variants were classified for likely functional impact according to

the number of *in silico* prediction algorithms that predicted deleteriousness using SIFT (Kumar et al., Nat. Protoc., 2009, 4, 1073-1081), Polyphen2_HDIV and Polyphen2_HVAR (Adzhubei et al., Nat. Methods, 2010, 7, 248-249), LRT (Chun et al., Genome Res., 2009, 19, 1553-1561) and MutationTaster (Schwarz et al., Nat. Methods, 2010, 7, 575-576). For each gene, the alternative allele frequency (AAF) and functional annotation of each variant determined inclusion into these 7 gene burden exposures: 1) pLOF variants with AAF < 1%; 2) pLOF or missense variants predicted deleterious by 5/5 algorithms with AAF < 1%; 3) pLOF or missense variants predicted deleterious by 5/5 algorithms with AAF < 0.1%; 4) pLOF or missense variants predicted deleterious by at least 1/5 algorithms with AAF < 1%; 5) pLOF or missense variants predicted deleterious by at least 1/5 algorithms with AAF < 0.1%; 6) pLOF or any missense with AAF < 1%; and 7) pLOF or any missense variants with AAF < 0.1%.

SNP array genotyping was performed in the UKB as previously described (Bycroft et al., Nature, 2018, 562, 203-209). In GHS, genotyping was performed using the Human Omni Express Exome array (OMNI) and the Global Screening array (GSA). In MCPS, genotyping was performed using the GSA array.

In vitro studies of *GPR75* variants

In vitro validation studies were performed for two *GPR75* pLOF genetic variants (Ala110fs and Gln234*) that were: a) individually associated with lower BMI ($p<0.05$), and b) had at least 10 heterozygous carriers. Briefly, pcDNA 3.1 plasmids encoding for N-terminally HA-tagged wild-type, Ala110fs and Gln234* *GPR75* were transiently transfected using Fugene 6 (Promega) in HEK293 cells. HEK293 and HEK293T cell lines were purchased from ATCC and maintained in the Regeneron Tissue Culture Core. Their identity was confirmed by STR profiling. *In vitro* assays included mRNA and protein analysis by Taqman and Western Blotting, and protein localization by fluorescence-activated cell sorting and immunofluorescence.

Cell culture, plasmids and cell transfection: HEK293 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, and antibiotics (50 units/mL penicillin and 50 µg/mL streptomycin; Thermo Fisher Scientific). pcDNA 3.1 plasmids encoding for N-terminus HA-tagged GPR75 wild-type, Ala110fs and Gln234* were synthesized by GenScript (USA). Cells at approximately 60-70% confluence were transiently transfected with plasmid containing cDNA encoding HA-tagged *GPR75* wild-type, Ala110fs and Gln234* and green fluorescent protein control plasmid using FuGENE 6 (Promega) according to the manufacturer's protocol (Promega Literature: # TM350), at a ratio of 1 µg DNA:5 µl FuGENE

transfection reagent. After 48 hours, cells were washed with 1x DPBS (Thermo Fisher Scientific) and collected for downstream analysis.

Western blotting: Transfected HEK293 were collected in RIPA buffer for cell lysis and 5-10 μg of protein was loaded per sample. The following primary antibodies were used: HA (mouse monoclonal, Sigma cat. Cat# H3663) and GAPDH 14C10 (Rabbit mAb, Cell Signaling Cat# 2118). The appropriate LI-COR secondary IRDye antibodies (anti-rabbit (926-32211) and anti-mouse (926-32210)) were used to detect and quantify immunoblots using a LI-COR Odyssey Infrared Imaging System (LI-COR, Lincoln, NE).

Flow cytometry: Cells were washed once with 1x DPBS (Cat# 14190144). Cell Dissociation Buffer (Cat# 13150016) was added and cells were incubated at 37°C for 3 minutes. Cells were re-suspended in culture media and centrifuged at 200xg for 5 minutes. Cells were washed twice with DPBS, re-suspended in DPBS, aliquoted and stained with Live/Dead Blue Fixable Viability Dye (Thermo Fisher Scientific) at room temperature for 15 minutes with no light. Cells were washed twice with DPBS - all washes centrifuged at 400xg for 5 minutes and all staining in the dark. Cells were treated with human Fc Block (BD Biosciences) in MACS buffer (Miltenyi Biotec) for 15 minutes at 4°C and stained with alexa fluor anti-HA.11 epitope tag antibody (Cat# 682404) at 1:100 dilution in MACS buffer for 30 minutes at 4°C. Cells were washed with MACS buffer and fixed with CytoFix (BD Biosciences) for 15 minutes at 4°C. Cells were washed twice with MACS buffer, filtered and FACS was performed on a CytoFLEX (Beckman Coulter). Data was analyzed using FlowJo 10.6.2 (Becton Dickinson & Company).

Immunofluorescence assays: For immunofluorescence assays, cells were seeded onto open 8-well μ-Slides (chamber slide) with a glass bottom (Ibidi, cat# 80827) at a density of 14,000 cells/well. At 48 hours post-transfection, cells were fixed in ice-cold 4% PFA for 10 minutes at RT and washed 3x with ice-cold 1x DPBS (all subsequent wash steps were carried out 3 times ice-cold 1x DPBS for 5 minutes per wash). Cells that were not permeabilized were blocked for 1 hour using 10% normal donkey serum (NDS) (Jackson Immunoresearch Laboratories, # 017-000-121), while permeabilized cells were blocked in 10% NDS with 0.1% Triton X-100; these were subsequently used as staining buffers for non-permeabilized and permeabilized cells, respectively. Cells were incubated with 1:500 (non-permeabilized) or 1:3000 (permeabilized) anti-HA antibody (Sigma, Cat# H3663) for 1 hour at RT, washed and then incubated for 1 hour with 1:1000 alexa fluor 594-conjugated anti-mouse secondary antibody (Thermo Fisher Scientific, Cat# A-21203). Wells were then washed, and slides were

mounted with ProLong® Gold Antifade Reagent with DAPI (Cell Signaling, #8961). Slides were imaged using Zeiss confocal LSM880.

Quantitative real-time polymerase chain reaction: RNA was extracted from transfected HEK293 using TRIzol reagent and following the manufacturer's instructions (Thermo Fisher Scientific). Genomic DNA was removed using MagMAX™Turbo™DNase Buffer and TURBO DNase (Ambion by Life Technologies). mRNA (up to 2 μg) was reverse-transcribed into cDNA using SuperScript® VILO™ Master Mix (ThermoFisher Scientific). *GPR75* cDNA was amplified with the PowerUp SYBR Green Master Mix (Thermo Fisher Scientific) using the QuantStudio 6 Flex Real-Time PCR System (Thermo Fisher Scientific). *ACTINB* housekeeping gene was used as the internal control gene to normalize cDNA input differences. Expression of *GPR75* was calculated relative to *ACTINB* housekeeping gene.

Primer sequences were as follows:

GPR75-forward: 5'-GCTTGTGGCCCAAGTCATTC-3' (SEQ ID NO:1458)

GPR75-reverse: 5'-GAGTGTTGATGGGGGTCGAG-3' (SEQ ID NO:1459)

ACTINB-forward: 5'-CACCATTGGCAATGAGCGGTTC-3' (SEQ ID NO:1460)

ACTINB-reverse: 5'-AGGTCTTTGCGGATGTCCACGT-3' (SEQ ID NO:1461)

Mouse models

The genetically engineered *Gpr75*$^{-/-}$ mouse strain was created using Regeneron's VelociGene® technology (Valenzuela et al., Nat. Biotechnol., 2003, 21, 652-659; and Poueymirou et al., Nat. Biotechnol., 2007, 25, 91-99). Briefly, C57Bl/6NTac embryonic stem cells were targeted for ablation of the entire *Gpr75* locus, beginning immediately after the endogenous ATG and ending at the *Gpr75* stop codon. Ablation was achieved using a modified bacterial artificial chromosome (BAC) targeting construct such that BAC *Gpr75* sequence was replaced with a self-deleting, floxed lacZ reporter cassette containing a neomycin resistance gene under the control of the human *UBC* (ubiquitin) promoter. The deletion was engineered such that the *lacZ* reporter was inserted in frame immediately after the endogenous ATG. This construct was electroporated into C57Bl/6NTac embryonic stem cells. Following selection with neomycin, correctly targeted clones were identified by TaqMan analysis and microinjected into 8-cell Swiss Webster embryos (Charles River Laboratories), resulting in F0 VelociMouse® fully derived from the injected modified embryonic stem cells (Poueymirou et al., Nat. Biotechnol., 2007, 25, 91-99).

Heterozygous *Gpr75*$^{-/+}$ mice were bred to generate age-matched wild type *Gpr75*$^{+/+}$, heterozygous *Gpr75*$^{-/+}$ and knock-out *Gpr75*$^{-/-}$ littermates that were used for experimentation. Male and female mice were housed in static cages (4/cage) with free access to food and water and fed either control chow diet or a high-fat diet (HFD; Envigo, #TD.03584, Huntingdon, UK) for 14 weeks. The control diet consisted of the following components in amounts represented by percent kilocalories (kcal): 13.4% fat, 58.0% carbohydrate, and 28.7% protein. HFD consisted of the following components in percent kilocalories: 58.4% fat, 26.6% carbohydrate, and 15.0% protein.

Fasting blood glucose was measured after overnight fasting before and at the end of the diet-feeding period. An intra-peritoneal glucose tolerance test was performed at the end of the experiment. Followed by an overnight fasting period, glucose (2 g/kg) was administered to each mouse by intra-peritoneal injection. The tip of the tail of each mouse was scratched to draw blood. Blood samples were collected at 0, 30, 60, 90, and 120 minutes, and glucose was measured using Contour blood glucose monitoring system (Bayer, Whippany, NJ). After these measurements, blood was collected in capillary tubes and used for insulin measurements. Blood was centrifuged at 2,000 rpm for 15 minutes to separate the plasma. Ultra-Sensitive Mouse Insulin ELISA kit (Crystal Chem. #90080, Elk Grove Village, IL) was used to quantify plasma insulin levels as per manufacturer's instructions. Plasma levels of leptin and adiponectin were measured by ELISA according to the manufacturer's instructions (Abcam, Cambridge, MA; #ab100718 and #ab108785 for leptin and adiponectin, respectively).

Statistics: The Graph Pad Prism version 9 software was used for statistical analysis. Significance of difference in mean values was determined using repeated measures two-way ANOVA followed by Tukey's *post hoc* multiple comparison test. A p-value<*0.05* was considered to be significant.

Additional high-fat and chow diet experiments were conducted in separate cohorts of mice to further characterize body composition and response in a diet induced obesity model.

Statistical analysis

Overview: The association with BMI of genetic variants or their gene burden was estimated by fitting mixed-effects regression models using BOLT-LMM v2.3.4 (Loh et al., Nat. Genet., 2018, 50, 906-908) or REGENIE v1.0 (Mbatchou et al., Nat. Genet., 2021). These approaches account for relatedness and population structure by estimating a polygenic score using genotypes from across the genome. Then, the association of genetic variants or their

burden is estimated conditional upon that polygenic score along with other covariates. To ensure that rare coding variant or gene-burden associations were statistically independent of BMI-associated common genetic variants, exome association analyses were further adjusted for sentinel common variants (AAF≥1%) identified by fine-mapping genome-wide associations of common alleles with BMI as described below. Results across cohorts were pooled using inverse-variance weighted meta-analysis.

Association with BMI of the burden of rare nonsynonymous variants identified by exome-sequencing: In the primary analysis of this study, the association with BMI of the burden of rare nonsynonymous variants in each gene was estimated by fitting mixed-effects regression models adjusted for a polygenic score that approximates a genomic kinship matrix using BOLT-LMM v2.3.4 (Loh et al., Nat. Genet., 2018, 50, 906-908) or REGENIE v1.0 (Mbatchou et al., Nat. Genet., 2021). Analyses were further adjusted for age, age^2, sex, an age-by-sex interaction term, experimental batch-related covariates, and genetic principal components. Ensuring that rare variants associations are independent of nearby trait-associated common alleles is essential for the correct causal variant and gene attribution in studies focused on exome variation (Mahajan et al., Nat. Genet., 2018, 50, 559-571). To ensure that burden associations were statistically independent of BMI-associated common genetic variants, the exome-wide association analyses were adjusted for common variants identified by fine-mapping genome-wide associations of common alleles with BMI (see, *GWAS of common variants and fine-mapping*). In line with previous similar studies (Do et al., Nature, 2015, 518, 102-106; and Flannick et al., Nature, 2019, 570, 71-76), the exome-wide level of statistical significance for the gene burden analysis was defined as $p<3.6\times10^{-07}$, a Bonferroni correction for 20,000 genes and seven variant selection models.

Rare nonsynonymous single variant analysis: In a secondary analysis, the association with BMI of individual rare nonsynonymous variants (minor allele frequency < 1% and minor allele count > 25) identified by exome sequencing was estimated. The same analytical approach was used as with the gene burden analysis, including adjustment for BMI-associated common variants identified by fine-mapping. This step is preferred to confirm the conditionally-independent nature of the association of these rare variants (Mahajan et al., Nat. Genet., 2018, 50, 559-571). In this analysis, a statistical threshold was used for association of $p<5\times10^{-08}$, a Bonferroni correction for ~1,000,000 rare nonsynonymous variants tested in this analysis which

is also the conventional threshold for genome-wide significance used in GWAS (C. Wellcome Trust Case Control, Nature, 2007, 447, 661-678).

GWAS of common variants and fine-mapping: BMI-associated common variants were identified by performing a genome-wide association study including over 12 million common-to-low-frequency genetic variants imputed using the Haplotype Reference Consortium panel (McCarthy et al., Nat. Genet., 2016, 48, 1279-1283) or the TOPMed Imputation Server (see, world wide web at "imputation.biodatacatalyst.nhlbi.nih.gov /#!pages/home; v1.5.7). In the GHS study, imputation was performed separately in samples genotyped with the Illumina Human Omni Express Exome array (OMNI set) and the Global Screening array (GSA set). Dosage data from imputed variants were then merged across the two GHS sets, to obtain a combined dataset for association analysis. Genome-wide association analyses were performed in the GHS, UKB and MCPS cohorts separately by fitting mixed-effects linear regression models using BOLT-LMM v2.3.4 (Loh et al., Nat. Genet., 2018, 50, 906-908) or REGENIE v1.0 (Mbatchou et al., Nat. Genet., 2021). Results from the UKB and GHS analyses were then combined by inverse variance-weighted meta-analysis to obtain a genome-wide meta-analysis in the European subset of the discovery cohorts. To identify conditionally-independent genetic association signals driven by common variants, fine-mapping at genomic regions harboring genetic variants associated with BMI at the genome-wide significance threshold of $p<5\times10^{-08}$ using the FINEMAP software was performed (Benner et al., Bioinformatics, 2016, 32, 1493-1501). Linkage disequilibrium was estimated using genetic data from the exact set of individuals included in the genome-wide association analyses. Fine-mapping was performed separately in the meta-analysis of the European ancestry GHS and UKB cohorts and in the Admixed American ancestry analysis in the MCPS cohort. Fine-mapping identifies independent common variant signals and assigns a posterior probability of causal association (PPA) for variants assigned to a given independent signal. For each locus that was fine-mapped, the 95% credible variant set, i.e., the minimal set of variants that capture the 95% posterior probability of causal association, were identified. The sentinel variant was also defined as the variant with the highest posterior probability of causal association at each given independent signal.

Generation of a genome wide-polygenic score for BMI in the UKB study: A polygenic score capturing predisposition to higher BMI due to over 2.5 million common variants was generated using the LDpred software (Vilhjalmsson et al., Am. J. Hum. Genet., 2015, 97, 576-

592) with a rho parameter value of 1, from the results of a previous large genome-wide association study in an independent dataset (Adzhubei et al., Nat. Methods, 2010, 7, 248-249).

Phenome-wide analysis for GPR75 predicted loss-of-function variants: A phenome-wide analysis of the association of pLOF variants in *GPR75* with hundreds of continuous traits or disease outcomes in the GHS and UKB studies was performed. To increase power, inverse-variance weighted meta-analysis was performed using the METAL software (Willer et al., Bioinformatics, 2010, 26, 2190-2191) to combine association results across GHS and UKB for disease outcomes available in both studies. To minimize the risk of false positive associations due to the small number of variant carriers, outcomes with ≤25 individuals carrying *GPR75* pLOF genetic variants, determined based on individuals with a non-missing phenotype for continuous traits, or based on affected individuals for binary disease outcomes were excluded. After these exclusions, results were available for 2,173 outcomes. To control for the number of statistical tests performed, associations were considered statistically significant if the association p-value met a Bonferroni correction for 2,173 tests, that is $p<2.3\times10^{-5}$ (corresponding to a p-value threshold of 0.05 divided by 2,173 statistical tests).

Continuous traits and disease outcomes were defined as described below. In the UKB study, for continuous traits, the values of biomarker, imaging variables or other continuous traits measured during one of the UKB visits or their averages within a given study visit or across study visits were used as outcomes. For binary disease outcomes, case status definition required one or more of the following criteria to apply: a) self-reported disease status or use of medication at digital questionnaire or interview with a trained nurse, or b) EHR of inpatient encounters from the UK National Health Service Hospital Episode Statistics database coded using the ICD-10 coding system. For each binary outcome, controls were individuals without any of the criteria for case definition. In the GHS study, for binary disease outcomes, case status definition required one or more of the following criteria to apply: 1) a problem-list entry of the ICD-10 diagnosis code, 2) an inpatient hospitalization-discharge ICD-10 diagnosis code, or 3) an encounter ICD-10 diagnosis code entered for 2 separate outpatient visits on separate calendar days. Controls were individuals without any of the criteria for case definition. Individuals were excluded if they had the relevant ICD-10 code associated with only one outpatient encounter. For continuous traits, data cleaning was performed by removing non-physiological lab values, invalid or contaminated specimens, and those that were over 5x upper limit of normal. Then

the minimum, median, and maximum laboratory result values over the duration of follow-up were derived for each patient and used as outcomes.

Example 2: Loss-of-Function in *GPR75* is Associated with Lower BMI, Lower Body Fat and Protection Against Obesity

High-coverage whole exome sequencing was performed in 645,626 individuals (Example 1), including 428,719 European ancestry individuals from the United Kingdom Biobank cohort (UKB; Figure 1), 121,061 European ancestry individuals from the MyCode Community Health Initiative cohort from the USA-based Geisinger Health System (GHS; Figure 1) and 95,846 Admixed American ancestry individuals from the Mexico City Prospective Study (MCPS; Figure 1).

In an exome-wide meta-analysis across these three cohorts, the burden of rare pLOF variants in the *GPR75* gene was associated with lower BMI at the exome-wide level of statistical significance (inverse-variance weighted (IVW) meta-analysis $p<3.6\times10^{-07}$, a Bonferroni correction for 20,000 genes and seven variant selection models (Example 1)).

Predicted loss-of-function variants in *GPR75* were observed in ~4 out of every 10,000 sequenced people, with similar frequency across populations (Figure 2), and carrier status was associated with 0.34 standard deviations lower BMI, corresponding to 1.8 kg/m^2 lower BMI or approximately 5.3 kg or 12 lbs lower body weight (Figure 3 and Figure 4A).

The association with lower BMI was directionally consistent and statistically significant in each of the constituent cohorts of the discovery meta-analysis (Figure 2), as well as within age and sex subgroups (Figure 5). The association of *GPR75* pLOF variants with lower BMI was further corroborated in a combined analysis including an additional 91,328 individuals not included in the discovery set (per-allele beta in standard deviation (SD) units of BMI in the meta-analysis of discovery and additional cohorts, -0.34, 95% confidence interval (CI), -0.45, -0.22, $p=6.9\times10^{-09}$; Figure 4B). This strong association with lower BMI was accompanied by a corresponding association with protection against obesity. Heterozygous carriers of *GPR75* pLOF variants had 54% lower odds of obesity compared to non-carriers in a meta-analysis of the UKB, GHS and MCPS cohorts (Figure 6; per-allele odds ratio, 0.46, 95% confidence interval, 0.31, 0.67, $p=6.9\times10^{-05}$) and their distribution across BMI categories was dramatically shifted towards lower BMI categories (Figure 7). In UKB, *GPR75* pLOF carriers were more likely to self-

report a thinner than average comparative body size at age 10 compared to non-carriers (Figure 8).

Body composition analysis with bioimpedance in UKB showed that the association with lower BMI was driven by an association with lower overall body fat mass and lower body fat percentage (Figure 9). In an agnostic phenome-wide analysis of *GPR75* pLOF variants (Example 1), statistically-significant associations with common diagnoses or measured continuous traits after correction for the number of statistical tests performed (2,173 phenotypes tested; Bonferroni-corrected p-value threshold, $p<2.3\times10^{-05}$), reflecting the rarity of these variants and the stringent multiple test correction, was not observed.

A detailed analysis of metabolic traits revealed a nominally-significant association (IVW meta-analysis $p<0.05$) with higher high-density lipoprotein cholesterol, which is consistent with a favorable metabolic profile (Figure 10). Carriers of pLOF in *GPR75* had lower odds of type 2 diabetes compared to non-carriers (63,492 cases and 549,961 controls; per-allele odds ratio, 0.92; 95% confidence interval, 0.59, 1.45; p=0.73; Figure 10), but the difference was not statistically significant. Exome sequencing association statistics was interrogated from up to 20,791 type 2 diabetes cases and 24,440 controls included in the T2D Knowledge Portal (world wide web at "t2d.hugeamp.org/"; Accessed January 8th, 2021), and similarly observed numerically lower odds of type 2 diabetes in carriers of *GPR75* pLOF variants (odds ratio for type 2 diabetes, 0.52, 95% CI, 0.14 to 1.97; p=0.30; alternative allele frequency, 0.03%). Due to the rarity of pLOF variants in *GPR75* and given the genetic relationship between BMI and type 2 diabetes, it is estimated that millions of people would need to be sequenced to detect an association at $p<0.05$ (Figure 10). An analysis for HbA1c, a continuous biomarker of glycemic levels, led to similar results (Figure 10).

Example 3: The Association with Lower Adiposity for Rare Protein-Truncating Variants can be Confidently Attributed to the *GPR75* Gene

The genomic context of the BMI association for pLOF variants in *GPR75* was examined. The first and smallest exon of *GPR75*, containing untranslated sequence, is included in both *GPR75* and in a putative *GPR75-ASB3* readthrough gene with the nearby Ankyrin Repeat and SOCS Box Containing 3 (*ASB3*; Figure 11). The second and final *GPR75* exon (containing the entire translated region of *GPR75*) is not shared with any other gene or transcript (Figure 11). A number of analyses was conducted to ensure that the association of pLOF variants could be

firmly attributed to the *GPR75* gene. First, 45 of the 46 pLOF variants in *GPR75* that contributed to the association with lower BMI were located in exon 2 (Figure 12), which is exclusive to the *GPR75* gene (Figure 11). Accordingly, the burden genotypes for pLOF variants in *GPR75* had no linkage disequilibrium (LD; R^2<0.0001) with the burden genotype for pLOF variants affecting the *GPR75-ASB3* readthrough gene or the *ASB3* gene. Second, the association with BMI of the burden of rare coding variants in *ASB3* or in the *GPR75-ASB3* readthrough gene in the large exome sequencing meta-analysis was estimated. There was no association with BMI for the burden of rare nonsynonymous variants in *ASB3* or *GPR75-ASB3* across multiple statistical models with different variant annotation and allele frequency inclusion criteria (Figure 13), including a lack of association for pLOF variants in either *ASB3* or *GPR75-ASB3* (Figure 13). Finally, the association with BMI for the burden of rare pLOF variants in *GPR75* conditional upon *ASB3* and *GPR75-ASB3* genotypes was estimated. The association of *GPR75* pLOF variants with lower BMI was unaffected by adjusting for *ASB3* and *GPR75-ASB3* genotypes (Figure 14). Therefore, the association with lower BMI for rare pLOF variants in *GPR75* can be confidently attributed to the *GPR75* gene.

It was also explored whether there were common variant associations in the locus. In the 1Mb window surrounding *GPR75* (500kb either side of the gene), there were 26 common variants associated with BMI at the genome-wide level of statistical significance (IVW meta-analysis, $p<5\times10^{-08}$) in the GWAS of imputed common variants in Europeans (Figure 15 and Figure 16), while there were no genome-wide significant associations in admixed Americans (Figure 16). These 26 variants all fine-mapped to a signal led by rs59428052 (G-allele frequency, 14.7%; posterior probability of causal association, 30.4%; per-allele beta in SD units of BMI, -0.015; 95% confidence interval, -0.020 to -0.010; $p=1.3\times10^{-09}$), which is an intergenic variant nearest to *ASB3* and approximately 200kb downstream of *GPR75*. The rs59428052 variant did not co-localize with any eQTL signal nor were any of the additional 25 variants at the locus in LD (R^2>0.8) with any sentinel eQTLs in GTEx v8 (Figure 14). Two of the 26 variants were in LD with a missense variant in *ASB3* and *GPR75-ASB3* (rs36020289), which does not affect the *GPR75* transcript (Figure 14).

A formal conditional analysis was performed adjusting for the 26 common variants associated with BMI in the region and identified that the association with lower BMI for pLOF variants in *GPR75* remains unchanged (Figure 14). Therefore, the association with lower BMI for

rare pLOF variants in *GPR75* is independent of any of the 26 common variants associated with BMI at the locus in Europeans.

In summary, the human genetic analysis at the locus indicates that: a) rare pLOF variants in *GPR75* are associated with lower BMI with a large effect association, b) the pLOF association is attributed to *GPR75* and not to other nearby transcripts, cc) the signal is independent of BMI-associated common variants in the region, and d) the small-effect intergenic common variant signal found in that region by GWAS fine-mapping in Europeans has no apparent link with *GPR75*.

Example 4: Loss-of-Function Variants in *GPR75* Associated with Lower Body Adiposity Results in Intracellular Retention of a Truncated GPR75 Receptor

The association with lower BMI for pLOF variants in *GPR75* was due to multiple independent rare pLOF variants predicted to truncate GPR75 at different locations (Figure 4A and Figure 12). Due to their rarity, none of the 46 rare pLOF variants found by exome sequencing in the analysis were well ascertained by array-genotyping or imputation (Figure 12). Leave-one-out analyses showed that the burden signal was robust to the exclusion of one pLOF variant at a time (Figure 17). Out of 46 rare pLOF variants in *GPR75*, five were individually associated with lower BMI at a nominal level of statistical significance (IVW meta-analysis $p<0.05$; Ala110fs; Ser219fs; Gln234*; Cys400fs, Lys404*; Figure 18), while none was associated with higher BMI. When excluding all 5 of these variant sites from analysis, the remaining set of pLOF variants was still associated with lower BMI (Figure 17).

The two most frequent (minor allele count ≥10) amongst the pLOF variants individually associated with BMI expressed *in vitro* showed that they result in cellular retention of a truncated receptor likely leading to a complete loss of function (Figure 19).

It is predicted that that the loss of a functional copy (i.e., haploinsufficiency) or production of a truncated protein that disrupts receptor multimers (i.e., dominant negative effects) may explain the association of GPR75 truncation with lower BMI. It is hypothesized that in the case of haploinsufficiency the earlier N-terminal truncation of GPR75 would result in greater phenotypic impact than a C-terminal truncation within the last intracellular domain. Genetic variants resulting in truncation of GPR75 before the final intracellular domain were associated with -2.1 kg/m^2 lower BMI (IVW meta-analysis $p=4.1\times10^{-07}$) as compared with -1.4 kg/m^2 lower BMI (IVW meta-analysis $p=0.012$) for variants resulting in truncation within the

final domain (Figure 20). This difference was even more pronounced for truncations within the last 100 amino-acids of the final C-terminal domain (Figure 20).

Example 5: Gpr75 Deletion in High-Fat Diet Induced Obesity and its Glycemic Consequences in Mice

GPR75-KO male mice displayed 7% lower body weight compared to wild-type (Figure 21). In contrast, no significant difference was observed in female mice (Figure 21). A more detailed body composition analysis of GPR75-KO mice is summarized in Figure 22. Gpr75 KO mice had 24% lower fat volume and percent fat compared to wild-type (Figure 22 and Figure 23), a statistically significant difference.

In a mouse model of high-fat diet (HFD) induced obesity, experimental deletion of *Gpr75* protected against weight gain and its associated abnormalities in glucose and insulin metabolism (Figure 24). When placed on HFD for 14 weeks, $Gpr75^{+/+}$ mice approximately doubled their weight. Body weight changed from an average (standard deviation) of 20.9 (2.1) to 43.3 (6.5) grams (body weight change, +22.4 grams). In contrast, mice with a genetic deletion of *Gpr75* gained less weight in an allele-dose dependent fashion (body weight change +16.9 grams, difference in weight-change with wild-type -5.5 grams or -25% for $Gpr75^{+/-}$ mice; body weight change +12.6 grams, difference in weight-change with wild-type -9.8 grams or -44% for the $Gpr75^{-/-}$ mice; Figure 24A). Increases in fasting blood glucose seen with HFD in $Gpr75^{+/+}$ mice were reduced in an allele-dose dependent manner in $Gpr75^{-/+}$ and $Gpr75^{-/-}$ mice (Figure 24B). Mice with a genetic deletion in *Gpr75* were also resistant to HFD-induced impairments in glucose tolerance and insulin sensitivity (Figure 24C and Figure 24D). At the end of 14 weeks of HFD, plasma leptin levels were lower in $Gpr75^{-/-}$ and $Gpr75^{+/-}$ mice compared to wild-type mice (Figure 25A), whereas adiponectin levels were higher resulting in a 2- and 10-fold lower leptin to adiponectin ratio in $Gpr75^{+/-}$ and $Gpr75^{-/-}$ mice compared to wild-type (Figure 25B and Figure 25C).

Further analyses in a distinct set of experiments studied the effects of genetic deficiency of *Gpr75* on body composition and blood glucose levels in addition to body weight in *Gpr75*+/+, *Gpr75*+/- and *Gpr75*-/- mice maintained on a chow diet or following a switch to a 60% high fat diet starting on week 0 for 9 weeks. Body weight was examined weekly. Blood glucose levels were measured at weeks -1, 4 and 8. Fat mass, lean mass and bone mass were quantified by micro-computed tomography (mCT) on weeks 0, 5 and 9.

Prior to a switch from chow diet to high fat diet feeding, 10- to 15-week-old male *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice did not exhibit differences in body weight (week 0, Figure 26, Panel A), lean mass (week 0, Figure 26, Panel B), bone mass (week 0, Figure 26, Panel B) or blood glucose levels (week -1, Figure 26, Panel C). However, *Gpr75*$^{-/-}$ mice exhibited a significant reduction in fat mass when compared to *Gpr75*$^{+/+}$ and *Gpr75*$^{+/-}$ mice (Figure 26, Panel B). After 9 weeks of high fat diet feeding *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice gained body weight relative to their body weight at week 0 (Figure 26, Panel A). Following the switch to high fat diet feeding, the body weight of *Gpr75*$^{-/-}$ mice was significantly lower than *Gpr75*$^{+/+}$ mice starting at 1 week of high fat diet feeding thru to 9 weeks of high fat diet feeding (Figure 26, Panel A). In addition, the body weight of *Gpr75*$^{+/-}$ mice was significantly lower than *Gpr75*$^{+/+}$ mice starting at 4 weeks of high fat diet feeding thru to 9 weeks mice (Figure 26, Panel A). In summary, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice show reduced body weight gain with high fat diet feeding.

Assessment of body composition by mCT, revealed that after 9 weeks of high fat diet feeding *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice gained fat mass relative to week 0. At 5 and 9 weeks post-high fat diet feeding, *Gpr75*$^{-/-}$ and *Gpr75*$^{+/-}$ mice exhibited less fat mass relative to *Gpr75*$^{+/+}$ mice (Figure 26, Panel B). Lean mass and bone mass (Figure 26, Panel B) were not significantly different amongst *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice after 5 and 9 weeks of high fat diet feeding. In summary, *Gpr75*$^{-/-}$ and *Gpr75*$^{+/-}$ mice show a reduction in fat mass gain with high fat feeding.

After 8 weeks of high fat diet feeding *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice showed significant increases in blood glucose levels relative to their blood glucose levels with chow diet feeding at week -1 (Figure 26, Panel C). After 4 weeks of high fat diet feeding no differences in blood glucose levels were observed between *Gpr75*$^{+/+}$, *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice (Figure 26, Panel C). However, after 8 weeks of high fat diet feeding, *Gpr75*$^{-/-}$ and *Gpr75*$^{+/-}$ mice exhibited significantly lower blood glucose levels than *Gpr75*$^{+/+}$ mice (Figure 26, Panel C). These data suggest that *Gpr75*$^{+/-}$ and *Gpr75*$^{-/-}$ mice show protection from hyperglycemia associated with high fat diet feeding.

Example 6: Chow-fed Female Gpr75 Knockout Mice are Not Insulin Resistant and Exhibit Improved Glucose Tolerance

An oral glucose tolerance test was performed on 13-week old female Gpr75$^{+/+}$, Gpr75$^{+/-}$ and Gpr75$^{-/-}$ mice. Animals were fasted at 7 a.m. for 4 hours, and then were given a 2 g/kg dose

of dextrose (Hospira, Inc, NDC 0409-6658-02)) via oral gavage at 11 a.m. Glucose measurements were taken using an AlphaTRAK2 glucose meter (Zoetis, Cat#71676-01) and test strips (Zoetis, Cat#71681-01) at 0, 15, 30, 60, and 120 minutes post dextrose administration. Results are shown in Figure 27.

Various modifications of the described subject matter, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference (including, but not limited to, journal articles, U.S. and non-U.S. patents, patent application publications, international patent application publications, gene bank accession numbers, and the like) cited in the present application is incorporated herein by reference in its entirety and for all purposes.

What is Claimed is:

1. A method of treating a subject having obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, or excessive food intake, or to prevent weight gain, or to maintain weight loss, the method comprising administering a GPR75 inhibitor to the subject.

2. The method according to claim 1, wherein the GPR75 inhibitor comprises an inhibitory nucleic acid molecule.

3. The method according to claim 2, wherein the inhibitory nucleic acid molecule is an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

4. The method according to claim 1, wherein the GPR75 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

5. The method according to claim 4, wherein the Cas protein is Cas9 or Cpf1.

6. The method according to claim 4 or claim 5, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

7. The method according to any one of claims 4 to 6, wherein the gRNA comprises from about 17 to about 23 nucleotides.

8. The method according to any one of claims 4 to 8, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOs:61-98.

9. The method according to any one of claims 1 to 8, further comprising detecting the absence of a GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample from the subject.

10. The method according to claim 9, further comprising administering a therapeutic agent that treats or inhibits obesity in a standard dosage amount to a subject that is GPR75 reference.

11. The method according to claim 9, further comprising administering a therapeutic agent that treats or inhibits obesity in a dosage amount that is the same as or lower than a standard dosage amount to a subject that is heterozygous for a GPR75 missense variant nucleic acid molecule.

12. The method according to any one of claims 9 to 11, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

13. A method of treating a subject with a therapeutic agent that treats or inhibits obesity, wherein the subject is obese, the method comprising the steps of:

determining whether the subject has a G-Protein Coupled Receptor 75 (GPR75) missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide by:

obtaining or having obtained a biological sample from the subject; and

performing or having performed a sequence analysis on the biological sample to determine if the subject has a genotype comprising the GPR75 missense variant nucleic acid molecule; and

administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount to a subject that is GPR75 reference; and

administering or continuing to administer the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount to a subject that is heterozygous for a GPR75 missense variant nucleic acid molecule;

wherein the presence of a genotype having the GPR75 missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide indicates the subject has a reduced risk of developing obesity.

14. The method according to claim 13, wherein the subject is GPR75 reference, and the subject is administered or continued to be administered the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount.

15. The method according to claim 13, wherein the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, and the subject is administered or continued to be administered the therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount.

16. The method according to any one of claims 13 to 15, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

17. The method according to claim 16, wherein the GPR75 missense variant nucleic acid molecule is:

a genomic nucleic acid molecule having a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprising an insertion of a uracil at a position corresponding to position 1,410

according to SEQ ID NO:15, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprising a

guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

18. The method according to claim 13, wherein the GPR75 inhibitor comprises an inhibitory nucleic acid molecule.

19. The method according to claim 18, wherein the inhibitory nucleic acid molecule is an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

20. The method according to claim 13, wherein the GPR75 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

21. The method according to claim 20, wherein the Cas protein is Cas9 or Cpf1.

22. The method according to claim 20 or claim 21, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1, positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

23. The method according to any one of claims 20 to 22, wherein the gRNA comprises from about 17 to about 23 nucleotides.

24. The method according to any one of claims 20 to 23, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOs:61-98.

25. A method of identifying a subject having an increased risk for developing obesity, wherein the method comprises:

determining or having determined the presence or absence of a G-Protein Coupled Receptor 75 (GPR75) missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample obtained from the subject;

wherein:

when the subject is GPR75 reference, then the subject has an increased risk for developing obesity; and

when the subject is heterozygous for a GPR75 missense variant nucleic acid molecule or homozygous for a GPR75 missense variant nucleic acid molecule, then the subject has a decreased risk for developing obesity.

26. The method according to claim 25, wherein the GPR75 missense variant nucleic acid molecule is a nucleic acid molecule encoding Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs.

27. The method according to claim 26, wherein the GPR75 missense variant nucleic acid molecule is:

a genomic nucleic acid molecule having a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, lacking an AAAG

tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, comprising an insertion of a thymine at a position corresponding to position

1,311 according to SEQ ID NO:44, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107.

28. The method according to any one of claims 25 to 27, wherein the subject is GPR75 reference, and the subject is administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in a standard dosage amount.

29. The method according to any one of claims 25 to 27, wherein the subject is heterozygous for a GPR75 missense variant nucleic acid molecule, and the subject is administered a therapeutic agent that treats or inhibits obesity and/or a GPR75 inhibitor in an amount that is the same as or lower than a standard dosage amount.

30. A method of detecting a human G-Protein Coupled Receptor 75 (GPR75) variant nucleic acid molecule in a subject comprising assaying a sample obtained from the subject to determine whether a nucleic acid molecule in the sample is:

a genomic nucleic acid molecule comprising a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprising an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprising a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprising a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence: lacking a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7 or the complement thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8 or the complement thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9 or the complement

thereof, lacking a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10 or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12 or the complement thereof, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17 or the complement thereof, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22 or the complement thereof, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27 or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13 or the complement thereof, comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18 or the complement thereof, comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23 or the complement thereof, comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28 or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10 or the complement thereof; comprising an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15 or the complement thereof, comprising an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20 or the complement thereof, comprising an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25 or the complement thereof, comprising an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30 or the complement thereof, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof, or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule produced from an mRNA molecule, wherein the cDNA molecule has a nucleotide sequence: lacking a CCAGTAG heptanucleotide at positions corresponding to

positions 539-545 according to SEQ ID NO:31 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33 or the complement thereof, lacking a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34 or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36 or the complement thereof, comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41 or the complement thereof, comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46 or the complement thereof, comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51 or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37 or the complement thereof, comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42 or the complement thereof, comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47 or the complement thereof, comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52 or the complement thereof; lacking an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33 or the complement thereof, lacking an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34 or the complement thereof; comprising an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39 or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44 or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49 or the complement thereof, comprising an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54 or the complement thereof, comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104 or the complement thereof, comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105 or the complement thereof, comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106 or the complement thereof, or comprising a guanine

at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

31. A method of detecting the presence of a human G-Protein Coupled Receptor 75 (GPR75) Ala110fs, Ala116Thr, Tyr207Cys, Gln234Stop, Arg236fs, or Cys400fs variant polypeptide, comprising performing an assay on a sample obtained from a subject to determine whether a GPR75 protein in the sample comprises SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, or SEQ ID NO:108.

32. An isolated alteration-specific probe or alteration-specific primer comprising at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the portion comprises a position corresponding to:

positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; or positions 600-606 according to SEQ ID NO:50, or the complement thereof;

positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; position 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; position 980-983 according to SEQ ID NO:29, or the complement thereof; position 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; or position 980-983 according to SEQ ID NO:53, or the complement thereof; or

position 6,411 according to SEQ ID NO:6, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; position 1,471 according to SEQ ID NO:30, or the complement thereof;

position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof.

33. The alteration-specific probe or alteration-specific primer according to claim 32, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 5,540-5,546 according to SEQ ID NO:2, or the complement thereof; positions 5,920-5,923 according to SEQ ID NO:5, or the complement thereof; or position 6,411 according to SEQ ID NO:6, or the complement thereof.

34. The alteration-specific probe or alteration-specific primer according to claim 32, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 539-545 according to SEQ ID NO:11, or the complement thereof; positions 440-446 according to SEQ ID NO:16, or the complement thereof; positions 361-367 according to SEQ ID NO:21, or the complement thereof; positions 600-606 according to SEQ ID NO:26, or the complement thereof; position 919-922 according to SEQ ID NO:14, or the complement thereof; positions 820-823 according to SEQ ID NO:19, or the complement thereof; positions 741-744 according to SEQ ID NO:24, or the complement thereof; position 980-983 according to SEQ ID NO:29, or the complement thereof; position 1,410 according to SEQ ID NO:15, or the complement thereof; position 1,311 according to SEQ ID NO:20, or the complement thereof; position 1,232 according to SEQ ID NO:25, or the complement thereof; or position 1,471 according to SEQ ID NO:30, or the complement thereof.

35. The alteration-specific probe or alteration-specific primer according to claim 32, comprising a nucleotide sequence which is complementary to a portion of a nucleotide sequence comprising a position corresponding to: positions 539-545 according to SEQ ID NO:35, or the complement thereof; positions 440-446 according to SEQ ID NO:40, or the complement thereof; positions 361-367 according to SEQ ID NO:45, or the complement thereof; positions 600-606 according to SEQ ID NO:50, or the complement thereof; position 919-922 according to SEQ ID NO:38, or the complement thereof; positions 820-823 according to SEQ ID NO:43, or the complement thereof; positions 741-744 according to SEQ ID NO:48, or the complement thereof; position 980-983 according to SEQ ID NO:53, or the complement thereof; position 1,410 according to SEQ ID NO:39, or the complement thereof; position 1,311 according to SEQ ID NO:44, or the complement thereof; position 1,232 according to SEQ ID NO:49, or the complement thereof; or position 1,471 according to SEQ ID NO:54, or the complement thereof.

36. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to a genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the genomic nucleic acid molecule: at nucleotides at positions corresponding to positions 5,539-5,540 according to SEQ ID NO:2, or the complement thereof; at an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; at a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; at nucleotides at positions corresponding to positions 5,919-5,920 according to SEQ ID NO:5, or the complement thereof; at a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or at a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

37. The molecular complex according to claim 36, wherein the genomic nucleic acid molecule comprises SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:99.

38. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to an mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to the mRNA molecule: at nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:11, or the complement thereof; at nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:16, or the complement thereof; at nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:21, or the complement thereof; at nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:26, or the complement thereof; at an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; at an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; at an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; at an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; at a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; at a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; at a uracil at a position corresponding to position 732 according to SEQ ID

NO:23, or the complement thereof; at a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; at nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:14, or the complement thereof; at nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:19, or the complement thereof; at nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:24, or the complement thereof; at nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:29, or the complement thereof; at a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; at a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; at a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; at a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; at a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; at a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; at a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or at a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

39. The molecular complex according to claim 38, wherein the mRNA molecule comprises SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

40. A molecular complex comprising an alteration-specific primer or an alteration-specific probe hybridized to a cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the alteration-specific primer or the alteration-specific probe is hybridized to: nucleotides at positions corresponding to positions 538-539 according to SEQ ID NO:35, or the complement thereof; nucleotides at positions corresponding to positions 439-440 according to SEQ ID NO:40, or the complement thereof; nucleotides at positions corresponding to positions 360-361 according to SEQ ID NO:45, or the complement thereof; nucleotides at positions corresponding to positions 599-600 according to SEQ ID NO:50, or the complement thereof; comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; an adenine at a

position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; nucleotides at positions corresponding to positions 918-919 according to SEQ ID NO:38, or the complement thereof; nucleotides at positions corresponding to positions 819-820 according to SEQ ID NO:43, or the complement thereof; nucleotides at positions corresponding to positions 740-741 according to SEQ ID NO:48, or the complement thereof; nucleotides at positions corresponding to positions 979-980 according to SEQ ID NO:53, or the complement thereof; a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

41. The molecular complex according to claim 40, wherein the cDNA molecule comprises SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, or SEQ ID NO:54, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

42. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, or the complement thereof, wherein the polypeptide comprises: a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56, a frameshift beginning at a position corresponding to position 236

according to SEQ ID NO:59, or a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60.

43. An isolated genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; a lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof.

44. The isolated genomic nucleic acid molecule, or the complement thereof, according to claim 43, wherein the nucleic acid molecule comprises SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6.

45. An isolated mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; or comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof.

46. The isolated mRNA molecule, or the complement thereof, according to claim 45, wherein the nucleic acid molecule comprises SEQ ID NO:11, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:29, or SEQ ID NO:30.

47. An isolated cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; or comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof.

48. The isolated cDNA molecule, or the complement thereof, according to claim 47, wherein the nucleic acid molecule comprises SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:53, or SEQ ID NO:54.

49. An isolated human G-Protein Coupled Receptor 75 (GPR75) polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:56, wherein the polypeptide lacks amino acids at positions corresponding to positions 110 to 540 according to SEQ ID NO:55; SEQ ID NO:59, wherein the polypeptide lacks amino acids at positions corresponding to

positions 236 to 540 according to SEQ ID NO:55; or SEQ ID NO:60, wherein the polypeptide lacks amino acids at positions corresponding to positions 400 to 540 according to SEQ ID NO:55.

50. The polypeptide according to claim 49, wherein the polypeptide comprises SEQ ID NO:56, SEQ ID NO:59, or SEQ ID NO:60.

51. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, or the complement thereof, wherein the polypeptide: comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57, terminates at a position corresponding to position 233 according to SEQ ID NO:58, or comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:99.

52. The nucleic acid molecule, or complement thereof, according to claim 51, wherein the polypeptide comprises SEQ ID NO:57, SEQ ID NO:58, or SEQ ID NO:99.

53. An isolated mRNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprising a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprising a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprising a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprising a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof.

54. The isolated mRNA molecule, or the complement thereof, according to claim 53, wherein the nucleic acid molecule comprises SEQ ID NO:12, SEQ ID NO:17, SEQ ID NO:22, SEQ

ID NO:27, SEQ ID NO:13, SEQ ID NO:18, SEQ ID NO:23, SEQ ID NO:28, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, or SEQ ID NO:103.

55. An isolated cDNA molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: comprising an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprising an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprising an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprising an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprising a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprising a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprising a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprising a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; comprising a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprising a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprising a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprising a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

56. The isolated cDNA molecule, or the complement thereof, according to claim 55, wherein the nucleic acid molecule comprises SEQ ID NO:36, SEQ ID NO:41, SEQ ID NO:46, SEQ ID NO:51, SEQ ID NO:37, SEQ ID NO:42, SEQ ID NO:47, SEQ ID NO:52, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, or SEQ ID NO:107.

57. An isolated genomic nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence comprises: an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; or a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof.

58. The isolated genomic nucleic acid molecule, or the complement thereof, according to claim 57, wherein the nucleic acid molecule comprises SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:99.

59. An isolated human G-Protein Coupled Receptor 75 (GPR75) polypeptide having an amino acid sequence at least about 90% identical to: SEQ ID NO:57, wherein the polypeptide comprises a threonine at a position corresponding to position 116 according to SEQ ID NO:57; SEQ ID NO:58, wherein the polypeptide terminates at a position corresponding to position 233 according to SEQ ID NO:58; or SEQ ID NO:99, wherein the polypeptide comprises a cysteine at a position corresponding to position 207 according to SEQ ID NO:99.

60. The polypeptide according to claim 59, wherein the polypeptide comprises SEQ ID NO:57, SEQ ID NO:58, or SEQ ID NO:99.

61. A therapeutic agent that treats or inhibits obesity for use in the treatment of obesity in a subject having:

a genomic nucleic acid molecule having a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to

position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to

positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732 according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

62. A G-Protein Coupled Receptor 75 (GPR75) inhibitor for use in the treatment of obesity in a subject having:

a genomic nucleic acid molecule having a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 5,540-5,546 according to SEQ ID NO:1, or the complement thereof; comprises an adenine at a position corresponding to position 5,557 according to SEQ ID NO:3, or the complement thereof; comprises a thymine at a position corresponding to position 5,911 according to SEQ ID NO:4, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 5,920-5,923 according to SEQ ID NO:1, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 6,411 according to SEQ ID NO:6, or the complement thereof; or comprises a guanine at a position corresponding to position 5,831 according to SEQ ID NO:99, or the complement thereof;

an mRNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGUAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:7, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:8, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:9, or the complement thereof; lacks a CCAGUAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:10, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:12, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:17, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:22, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:27, or the complement thereof; comprises a uracil at a position corresponding to position 910 according to SEQ ID NO:13, or the complement thereof; comprises a uracil at a position corresponding to position 811 according to SEQ ID NO:18, or the complement thereof; comprises a uracil at a position corresponding to position 732 according to SEQ ID NO:23, or the complement thereof; comprises a uracil at a position corresponding to position 971 according to SEQ ID NO:28, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:7, or

the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:8, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:9, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:10, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,410 according to SEQ ID NO:15, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,311 according to SEQ ID NO:20, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,232 according to SEQ ID NO:25, or the complement thereof; comprises an insertion of a uracil at a position corresponding to position 1,471 according to SEQ ID NO:30, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:100, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:101, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:102, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:103, or the complement thereof; or

a cDNA molecule having a nucleotide sequence encoding a human GPR75 polypeptide, wherein the nucleotide sequence: lacks a CCAGTAG heptanucleotide at positions corresponding to positions 539-545 according to SEQ ID NO:31, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 440-446 according to SEQ ID NO:32, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 361-367 according to SEQ ID NO:33, or the complement thereof; lacks a CCAGTAG heptanucleotide at positions corresponding to positions 600-606 according to SEQ ID NO:34, or the complement thereof; comprises an adenine at a position corresponding to position 556 according to SEQ ID NO:36, or the complement thereof; comprises an adenine at a position corresponding to position 457 according to SEQ ID NO:41, or the complement thereof; comprises an adenine at a position corresponding to position 378 according to SEQ ID NO:46, or the complement thereof; comprises an adenine at a position corresponding to position 617 according to SEQ ID NO:51, or the complement thereof; comprises a thymine at a position corresponding to position 910 according to SEQ ID NO:37, or the complement thereof; comprises a thymine at a position corresponding to position 811 according to SEQ ID NO:42, or the complement thereof; comprises a thymine at a position corresponding to position 732

according to SEQ ID NO:47, or the complement thereof; comprises a thymine at a position corresponding to position 971 according to SEQ ID NO:52, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 919-922 according to SEQ ID NO:31, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 820-823 according to SEQ ID NO:32, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 741-744 according to SEQ ID NO:33, or the complement thereof; lacks an AAAG tetranucleotide at positions corresponding to positions 980-983 according to SEQ ID NO:34, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,410 according to SEQ ID NO:39, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,311 according to SEQ ID NO:44, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,232 according to SEQ ID NO:49, or the complement thereof; comprises an insertion of a thymine at a position corresponding to position 1,471 according to SEQ ID NO:54, or the complement thereof; comprises a guanine at a position corresponding to position 830 according to SEQ ID NO:104, or the complement thereof; comprises a guanine at a position corresponding to position 731 according to SEQ ID NO:105, or the complement thereof; comprises a guanine at a position corresponding to position 652 according to SEQ ID NO:106, or the complement thereof; or comprises a guanine at a position corresponding to position 891 according to SEQ ID NO:107, or the complement thereof.

63. The method according to claim 62, wherein the GPR75 inhibitor comprises an inhibitory nucleic acid molecule.

64. The method according to claim 63, wherein the inhibitory nucleic acid molecule is an antisense nucleic acid molecule, a small interfering RNA (siRNA), or a short hairpin RNA (shRNA) that hybridizes to a GPR75 mRNA.

65. The method according to claim 62, wherein the GPR75 inhibitor comprises a Cas protein and guide RNA (gRNA) that hybridizes to a gRNA recognition sequence within a GPR75 genomic nucleic acid molecule.

66. The method according to claim 65, wherein the Cas protein is Cas9 or Cpf1.

67. The method according to claim 65 or claim 66, wherein the gRNA recognition sequence includes or is proximate to a position corresponding to: position 5,540-5,546 according to SEQ ID NO:1, position 5,557 according to SEQ ID NO:1, position 5,911 according to SEQ ID NO:1,

positions 5,920-5,923 according to SEQ ID NO:1, position 6,411 according to SEQ ID NO:1, or position 5,831 according to SEQ ID NO:1.

68. The method according to any one of claims 65 to 67, wherein the gRNA comprises from about 17 to about 23 nucleotides.

69. The method according to any one of claims 65 to 69, wherein the gRNA recognition sequence comprises a nucleotide sequence according to any one of SEQ ID NOs:61-98.

Variable	UKB study (N=428,719)	GHS study (N=121,061)	MCPS study (N=95,846)
Age, mean (SD) in years	57 (8)	53 (17)	52 (13)
Women, N (%)	232,553 (54)	73,769 (61)	65,330 (68)
Body mass index, mean (SD) in kg/m^2	27.4 (4.8)	31.1 (7.3)	29.1 (5.1)
Body weight, mean (SD) in kg	78 (16)	88 (23)	70 (14)
Body mass index WHO categories, N (%)			
Underweight (< 18.5 kg/m^2)	2,089 (0.49)	994 (0.82)	499 (0.52)
Healthy weight (18.5 to < 25 kg/m^2)	140,175 (32.70)	23,784 (19.65)	18,599 (19.41)
Overweight (25 to < 30 kg/m^2)	182,564 (42.58)	35,787 (29.56)	40,672 (42.43)
Obesity, non-severe (30 to < 40 kg/m^2)	95,928 (22.37)	46,067 (38.05)	33,203 (34.64)
Severe obesity (≤ 40 kg/m^2)	7,963 (1.86)	14,429 (11.92)	2,873 (3.00)
Blood pressure, mean (SD) in mmHg			
Systolic	138 (19)	124 (11)	127 (17)
Diastolic	82 (11)	74 (7)	83 (10)
Low-density lipoprotein cholesterol, mean (SD) in mg/dL	138 (34)	107 (29)	Not measured
Triglycerides, median (IQR) in mg/dL	132 (93, 191)	124 (90, 172)	Not measured

Figure 1

Gene	Genetic exposure, variant type; allele frequency cut-off in %	Study	Beta (95% CI) per allele in SD units of BMI	p	AAF, fraction of 1	Genotype counts, RR|RA|AA genotypes
GPR75	pLOF; AAF < 1%	UKB	-0.34 (-0.49, -0.19)	6.6E-06	0.0002	428,572|147|0
GPR75	pLOF; AAF < 1%	MCPS	-0.48 (-0.82, -0.13)	7.1E-03	0.0002	95,816|30|0
GPR75	pLOF; AAF < 1%	GHS	-0.27 (-0.52, -0.02)	3.6E-02	0.0002	121,010|51|0

Figure 2

Gene	Genomic Coordinates	Genetic exposure, variant type; frequency cut-off in %	Beta (95% CI) per allele in SD units of BMI	p
GPR75	2: 53853133	pLOF; AAF < 1%	-0.34 (-0.46, -0.22)	2.6×10^{-08}

Gene	AAF, fraction of 1	Genotype counts, RR|RA|AA genotypes	Beta (95% CI) per allele in kg/m² units of BMI	Beta (95% CI) per allele in kgs of body weight	Beta (95% CI) per allele in lbs of body weight
GPR75	0.0002	645,398|228|0	-1.8 (-2.5, -1.2)	-5.3 (-7.1, -3.4)	-11.6 (-15.7, -7.5)

Figure 3

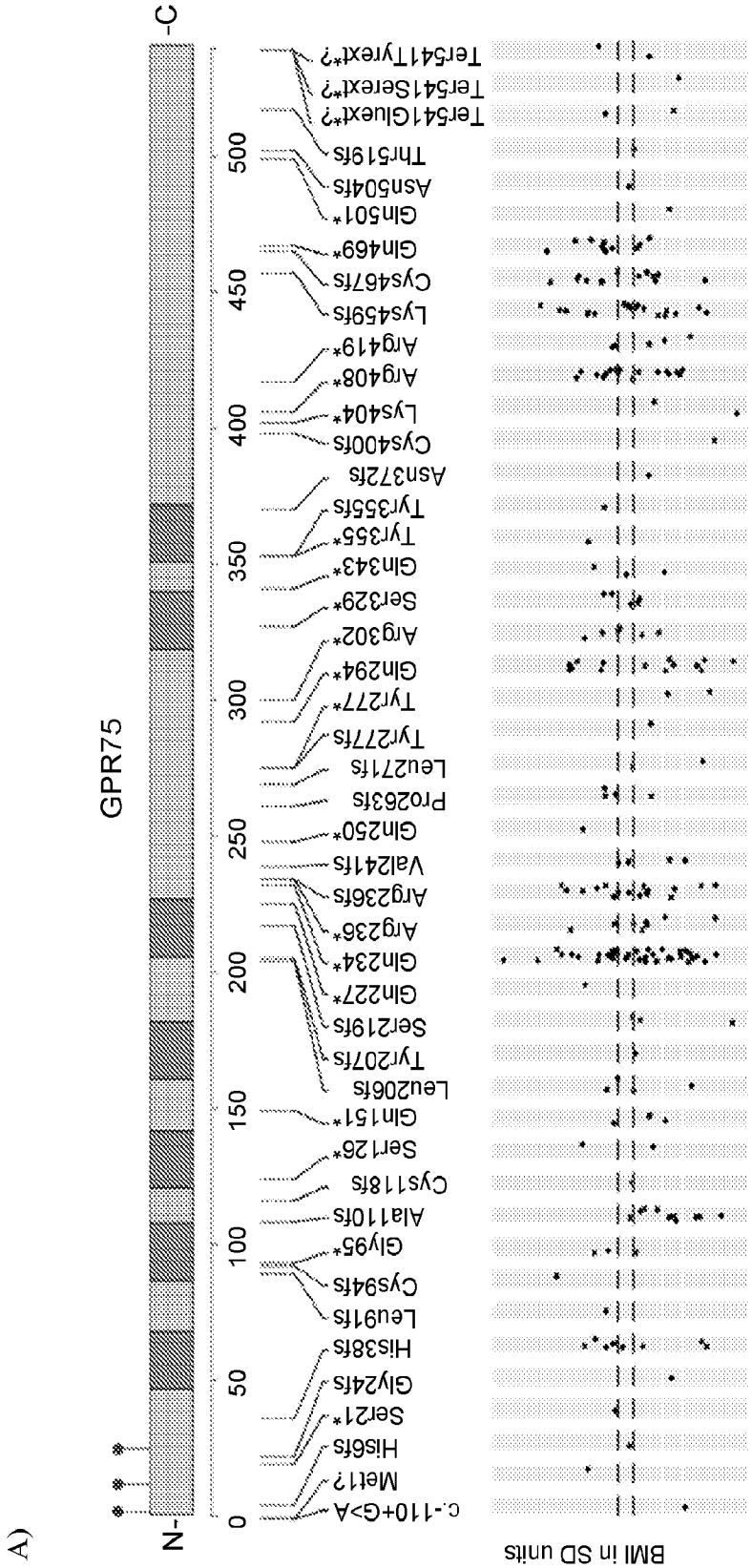

A)
N-
-C
GPR75
0
50
100
150
200
250
300
350
400
450
500
c.-110+G>A
Met1?
His6fs
Ser21*
Gly24fs
His38fs
Leu91fs
Cys94fs
Gly95*
Ala110fs
Cys118fs
Ser126*
Gln151*
Leu206fs
Tyr207fs
Ser219fs
Gln227*
Gln234*
Arg236*
Arg236fs
Val241fs
Gln250*
Pro263fs
Leu271fs
Tyr277fs
Tyr277*
Gln294*
Arg302*
Ser329*
Gln343*
Tyr355*
Tyr355fs
Asn372fs
Cys400fs
Lys404*
Arg408*
Arg419*
Lys459fs
Cys467fs
Gln469*
Gln501*
Asn504fs
Thr519fs
Ter541Glnext*?
Ter541Serext*?
Ter541Tyrext*?
BMI in SD units

Figure 4

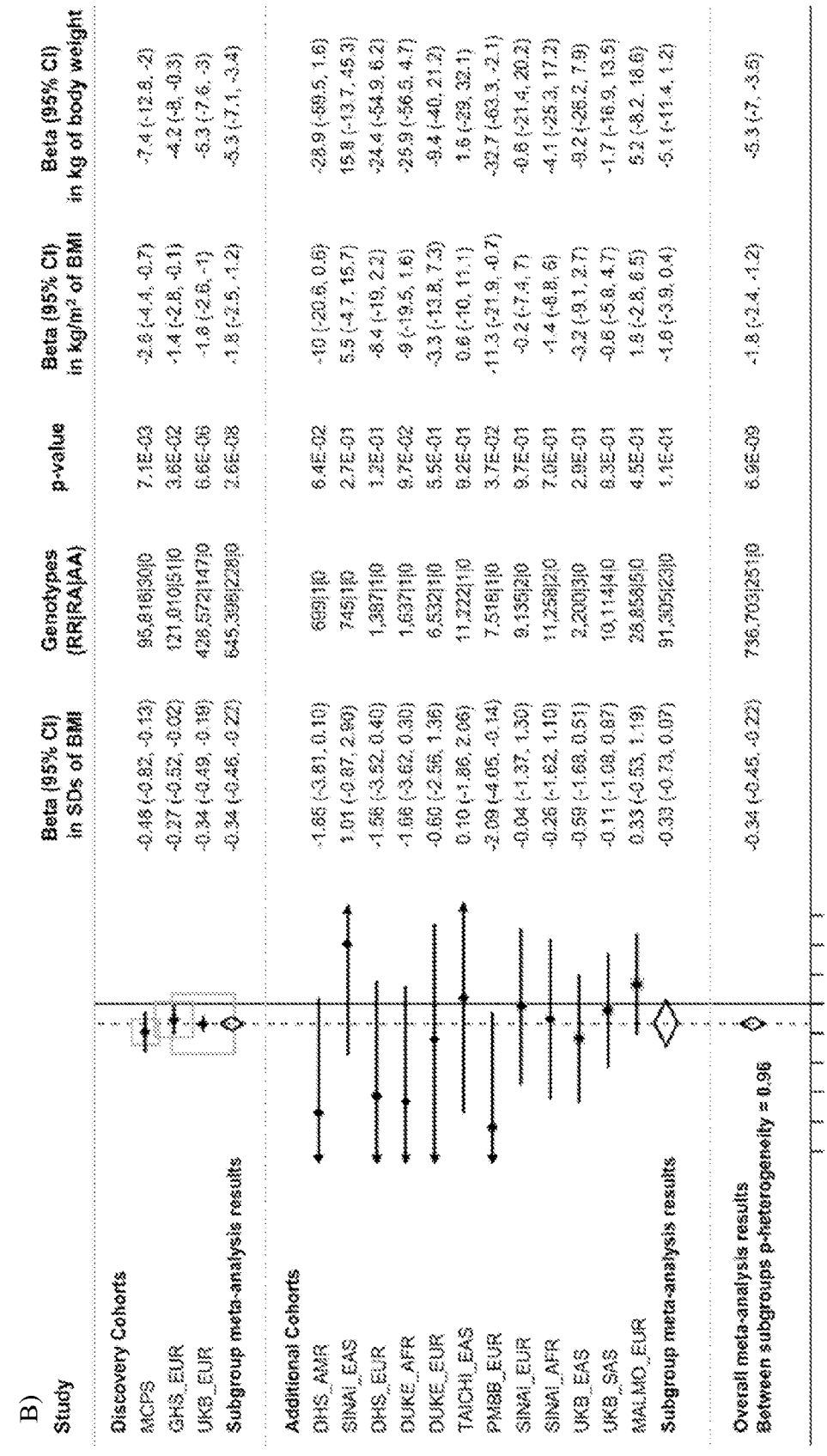


Figure 4 (cont.)

Genetic exposure, variant type; frequency cutoff in %	Group	Beta (95% CI) per allele in SD units of BMI	Beta (95% CI) per allele in kg/m^2 units of BMI	P	AAF, fraction of 1	Genotype counts, RR|RA|AA genotypes	P-value for heterogeneity in effect estimates between groups
GPR75 pLOF; AAF < 1%	Age ≤ median value in cohort	-0.33 (-0.50, -0.17)	-1.80 (-2.70, -0.89)	1.0E-04	0.0002	331,175|117|0	0.93
GPR75 pLOF; AAF < 1%	Age > median value in cohort	-0.35 (-0.52, -0.18)	-1.90 (-2.80, -0.95)	7.8E-05	0.0002	314,223|111|0	
GPR75 pLOF; AAF < 1%	Men	-0.35 (-0.55, -0.16)	-1.90 (-3.00, -0.86)	3.5E-04	0.0002	273,885|89|0	0.91
GPR75 pLOF; AAF < 1%	Women	-0.33 (-0.49, -0.18)	-1.80 (-2.60, -0.97)	2.4E-05	0.0002	371,513|139|0	

Figure 5

Gene	Genetic exposure, variant type; allele frequency cut-off in %	Per-allele OR (95% CI) for obesity	P	AAF, fraction of 1	Genotype counts (cases), RR|RA|AA genotypes	Genotype counts (controls), RR|RA|AA genotypes
GPR75	pLOF; AAF < 1%	0.46 (0.31, 0.67)	6.9E-05	0.0002	200,613|45|0	186,335|94|0

Figure 6

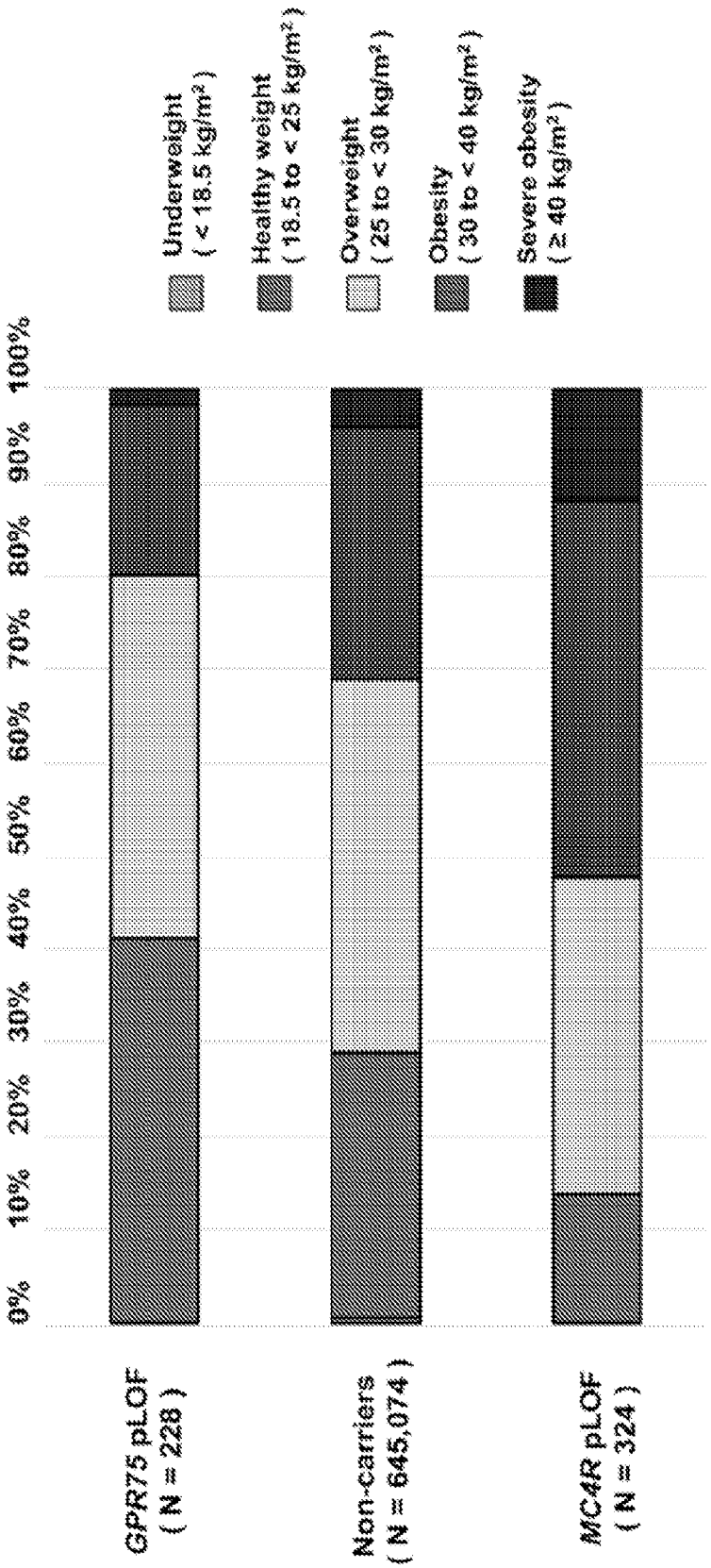

Underweight
(< 18.5 kg/m²)
Healthy weight
(18.5 to < 25 kg/m²)
Overweight
(25 to < 30 kg/m²)
Obesity
(30 to < 40 kg/m²)
Severe obesity
(≥ 40 kg/m²)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
GPR75 pLOF
(N = 228)
Non-carriers
(N = 645,074)
MC4R pLOF
(N = 324)

Figure 7

Genetic exposure, variant type; frequency cutoff in %	Outcome	AAF, fraction of 1	OR (95% CI) per allele	P	Genotype counts (cases), RR|RA|AA genotypes	Genotype counts (controls), RR|RA|AA genotypes
GPR75 pLOF; AAF < 1%	Responded "Thinner" to multiple choice question: "When you were 10 years old, compared to average would you describe yourself as: thinner, plumper, about average, do not know, prefer not to answer?"	1.7E-04	1.66 (1.18, 2.34)	3.9E-03	141,442|62|0	282,026|82|0

Figure 8

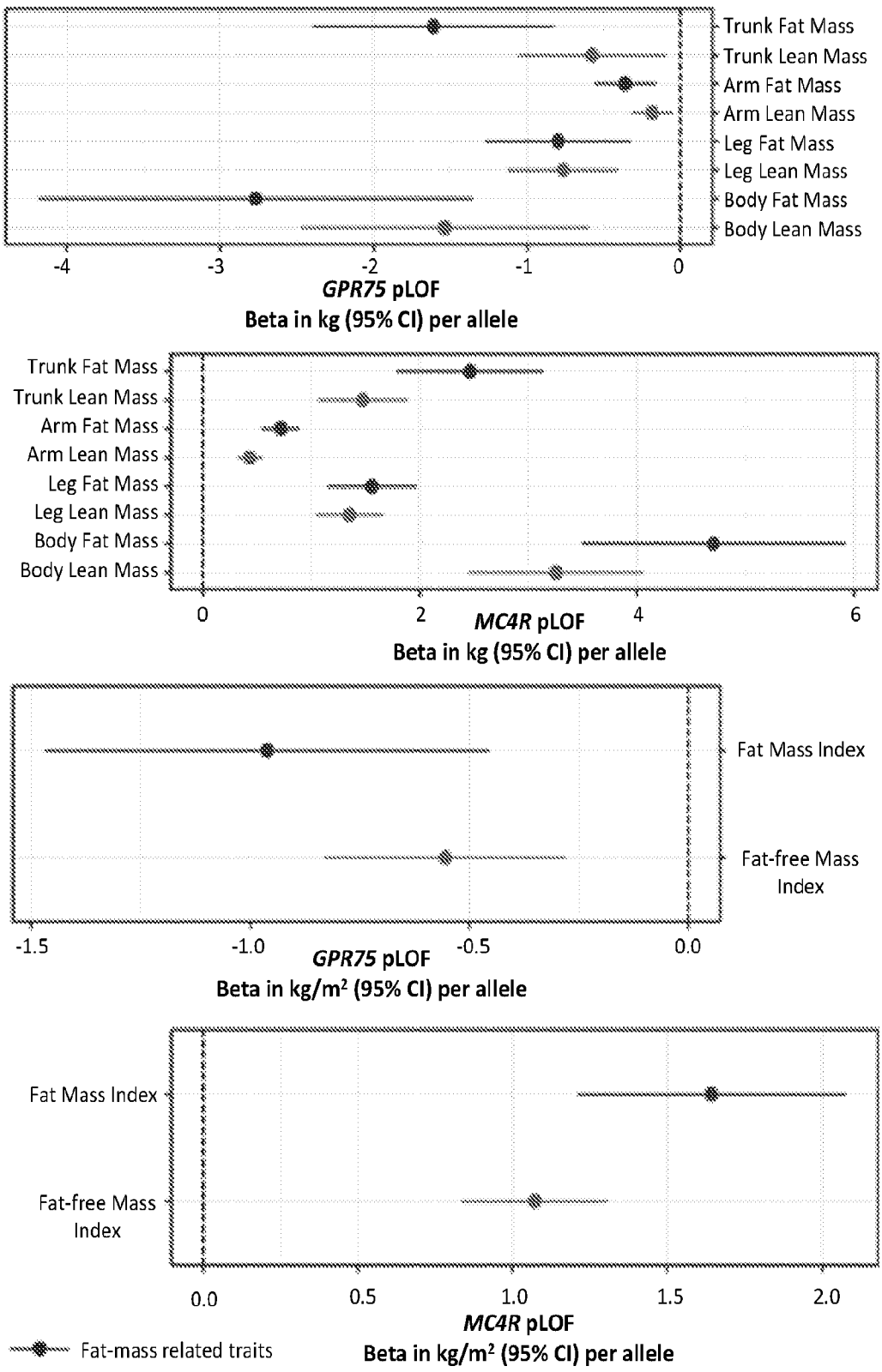

Trunk Fat Mass
Trunk Lean Mass
Arm Fat Mass
Arm Lean Mass
Leg Fat Mass
Leg Lean Mass
Body Fat Mass
Body Lean Mass
-4
-3
-2
-1
0
GPR75 pLOF
Beta in kg (95% CI) per allele
Trunk Fat Mass
Trunk Lean Mass
Arm Fat Mass
Arm Lean Mass
Leg Fat Mass
Leg Lean Mass
Body Fat Mass
Body Lean Mass
0
2
4
6
MC4R pLOF
Beta in kg (95% CI) per allele
Fat Mass Index
Fat-free Mass Index
-1.5
-1.0
-0.5
0.0
GPR75 pLOF
Beta in kg/m² (95% CI) per allele
Fat Mass Index
Fat-free Mass Index
0.0
0.5
1.0
1.5
2.0
MC4R pLOF
Beta in kg/m² (95% CI) per allele
Fat-mass related traits
Lean-mass related traits

Figure 9

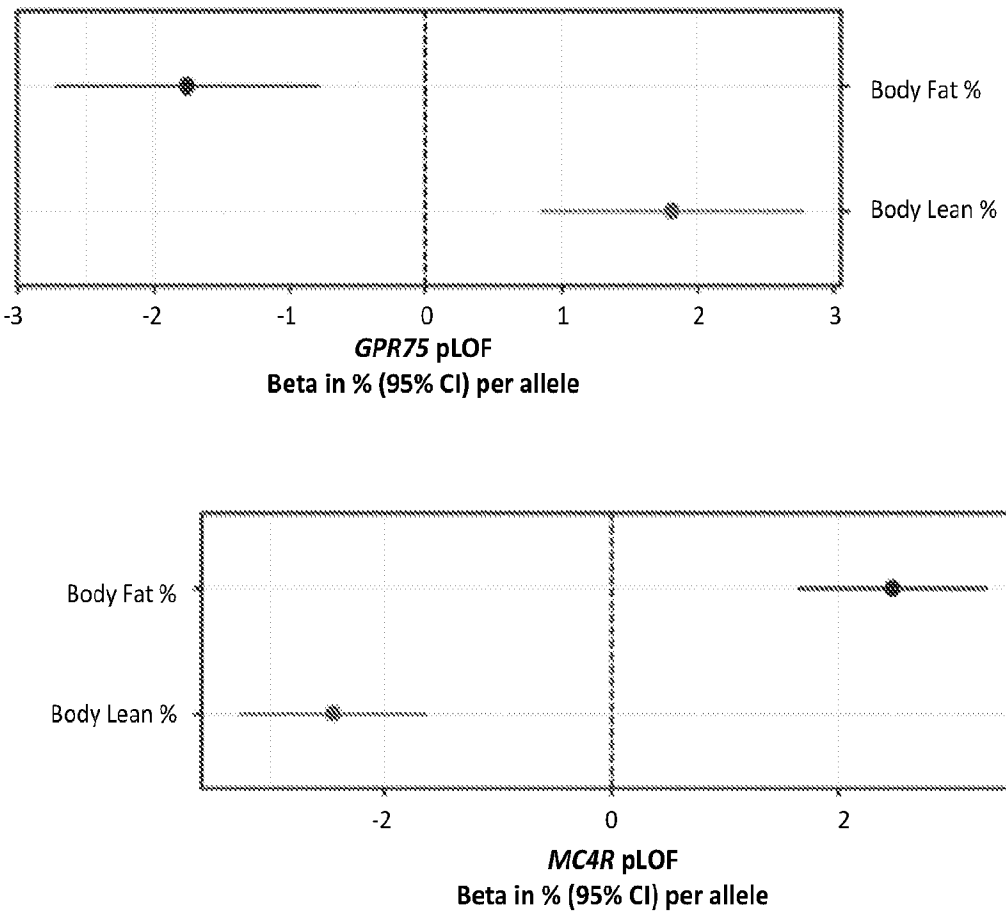


Figure 9 (cont.)

Exposure	Outcome, clinical unit	Beta in SDs or odds ratio (95% CI) per allele	p	Allele counts participants (or disease cases for binary traits), RR|RA|AA	Allele counts controls, RR|RA|AA	Beta in clinical units (95% CI) per allele
GPR75 pLOF genetic variants, AAF < 1%	Glucose[a], mg/dL	-0.04 (-0.19, 0.11)	5.8E-01	461,056|162|0	-	-0.9 (-4.1, 2.3)
	HbA1c, %	-0.06 (-0.19, 0.07)	3.5E-01	574,999|191|0	-	-0.06 (-0.17, 0.06)
	AST[a], U/L	-0.01 (-0.15, 0.13)	9.0E-01	515,532|182|0	-	-0.1 (-1.4, 1.3)
	ALT[a], U/L	-0.11 (-0.25, 0.03)	1.2E-01	518,135|182|0	-	-1.5 (-3.4, 0.4)
	Triglycerides[a], mg/dL	-0.05 (-0.19, 0.08)	4.4E-01	501,508|178|0	-	-4.8 (-16.7, 7.2)
	HDL-C[a], mg/dL	0.19 (0.05, 0.33)	6.3E-03	467,058|167|0	-	2.9 (0.8, 4.9)
	LDL-C[a], mg/dL	-0.02 (-0.15, 0.12)	7.9E-01	500,249|177|0	-	-0.6 (-5.2, 3.9)
	Systolic blood pressure, mmHg	-0.03 (-0.15, 0.08)	5.8E-01	622,080|222|0	-	-0.6 (-2.7, 1.5)
	Diastolic blood pressure, mmHg	-0.03 (-0.15, 0.1)	6.5E-01	618,264|222|0	-	-0.3 (-1.6, 1)
	Waist-to-hip ratio, ratio units	-0.13 (-0.27, 0.01)	8.0E-02	525,809|177|0	-	-0.011 (-0.024, 0.001)
	Type 2 diabetes	0.92 (0.59, 1.45)[b]	7.3E-01	63,468|24|0	549,770|191|0	-

Figure 10

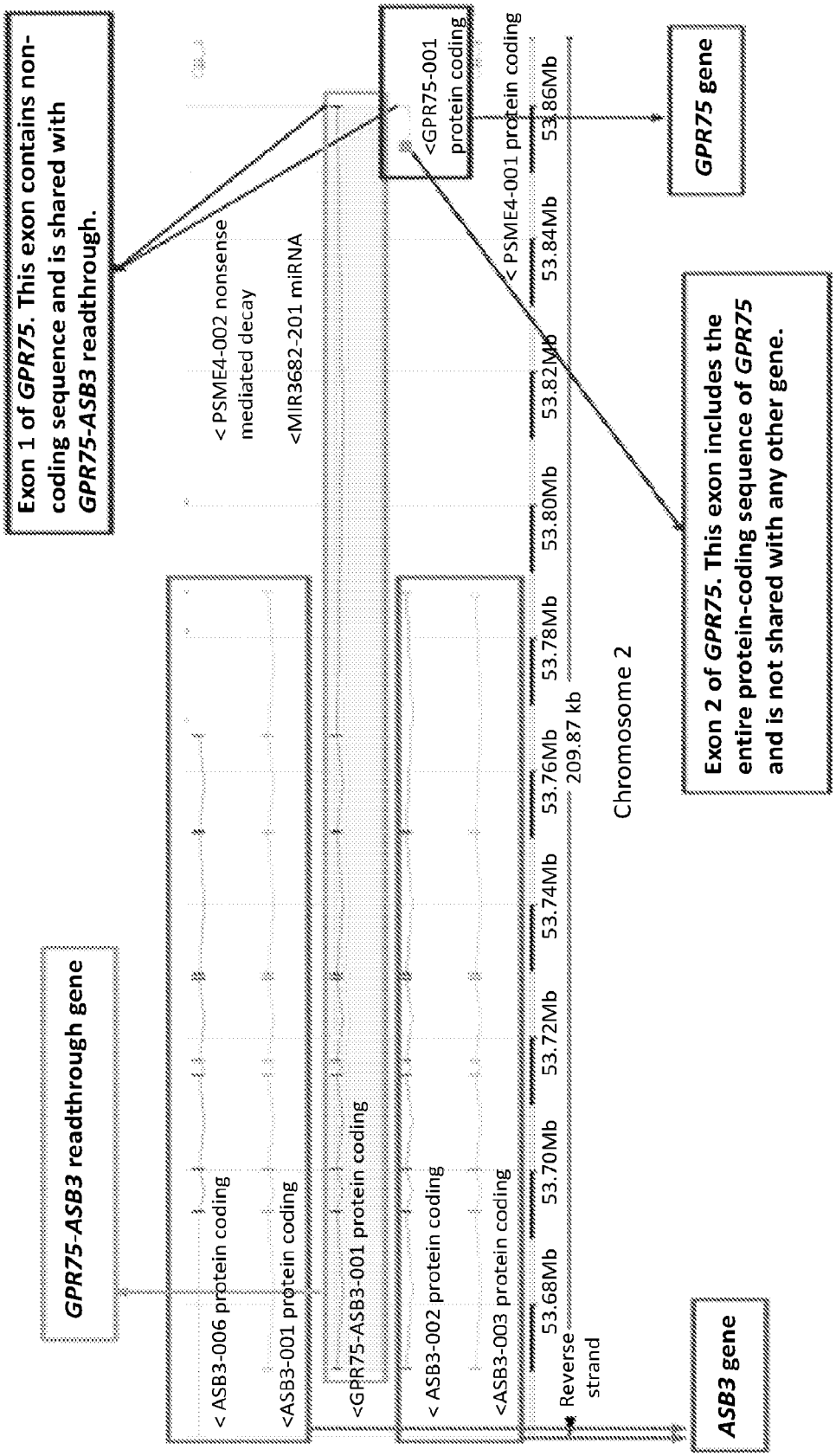

Exon 1 of GPR75. This exon contains non-coding sequence and is shared with GPR75-ASB3 readthrough.
GPR75-ASB3 readthrough gene
< ASB3-006 protein coding
<ASB3-001 protein coding
<GPR75-ASB3-001 protein coding
< ASB3-002 protein coding
<ASB3-003 protein coding
Reverse strand
ASB3 gene
< PSME4-002 nonsense mediated decay
<MIR3682-201 miRNA
<GPR75-001 protein coding
< PSME4-001 protein coding
GPR75 gene
53.68Mb
53.70Mb
53.72Mb
53.74Mb
53.76Mb
53.78Mb
53.80Mb
53.82Mb
53.84Mb
53.86Mb
209.87 kb
Chromosome 2
Exon 2 of GPR75. This exon includes the entire protein-coding sequence of GPR75 and is not shared with any other gene.

Figure 11

Variant (CPRA)	AAF	cDNA change HGVS	Protein change HGVS	Affected exon	In genotyping array	In raw imputed data	Imputation quality INFO score, fraction of 1[a]
2:53853134:T:G	2.3E-06	c.1623A>C	p.Ter541Tyrext*?	Exon 2	No	No	-
2:53853135:T:G	1.2E-06	c.1622A>C	p.Ter541Serext*?	Exon 2	No	No	-
2:53853136:A:C	2.3E-06	c.1621T>G	p.Ter541Gluext*?	Exon 2	No	No	-
2:53853200:GGT:G	7.6E-06	c.1555_1556delAC	p.Thr519fs	Exon 2	No	No	-
2:53853245:GT:G	1.2E-06	c.1511delA	p.Asn504fs	Exon 2	No	No	-
2:53853256:G:A	1.2E-06	c.1501C>T	p.Gln501*	Exon 2	No	No	-
2:53853352:G:A	1.3E-05	c.1405C>T	p.Gln469*	Exon 2	No	No	-
2:53853354:CCA:C	5.4E-05	c.1401_1402delTG	p.Cys467fs	Exon 2	No	No	-
2:53853382:TG:T	1.8E-05	c.1374delC	p.Lys459fs	Exon 2	No	No	-
2:53853502:T:A	5.8E-06	c.1255A>T	p.Arg419*	Exon 2	No	No	-
2:53853535:G:A	1.4E-05	c.1222C>T	p.Arg408*	Exon 2	No	No	-
2:53853547:T:A	1.0E-05	c.1210A>T	p.Lys404*	Exon 2	No	No	-
2:53853560:G:GA	1.2E-06	c.1196dupT	p.Cys400fs	Exon 2	No	No	-
2:53853641:GTT:G	9.0E-06	c.1114_1115delAA	p.Asn372fs	Exon 2	No	No	-
2:53853680:CAATTCAAACTGGT:C	1.2E-06	c.1064_1076delACCAGTTTGAATT	p.Tyr355fs	Exon 2	No	No	-
2:53853692:G:T	1.2E-06	c.1065C>A	p.Tyr355*	Exon 2	No	No	-

Figure 12

Variant (CPRA)	AAF	cDNA change HGVS	Protein change HGVS	Affected exon	In genotyping array	In raw imputed data	Imputation quality INFO score, fraction of 1[a]
2:53853730:G:A	3.5E-06	c.1027C>T	p.Gln343*	Exon 2	No	No	-
2:53853771:G:C	2.1E-05	c.986C>G	p.Ser329*	Exon 2	No	No	-
2:53853853:G:A	5.1E-06	c.904C>T	p.Arg302*	Exon 2	No	No	-
2:53853877:G:A	7.3E-05	c.880C>T	p.Gln294*	Exon 2	No	No	-
2:53853926:G:T	1.8E-05	c.831C>A	p.Tyr277*	Exon 2	No	No	-
2:53853927:T:TA	1.2E-06	c.829dupT	p.Tyr277fs	Exon 2	No	No	-
2:53853946:G:GT	2.3E-06	c.810_811insA	p.Leu271fs	Exon 2	No	No	-
2:53853967:TGG:T	4.7E-06	c.788_789delCC	p.Pro263fs	Exon 2	No	No	-
2:53854009:G:A	1.2E-06	c.748C>T	p.Gln250*	Exon 2	No	No	-
2:53854037:A:AG	4.7E-06	c.719dupC	p.Val241fs	Exon 2	No	No	-
2:53854045:ACTTT:A	1.7E-05	c.708_711delAAAG	p.Arg236fs	Exon 2	No	No	-
2:53854051:T:A	9.3E-06	c.706A>T	p.Arg236*	Exon 2	No	No	-
2:53854057:G:A	2.9E-05	c.700C>T	p.Gln234*	Exon 2	No	Yes, but excluded after QC due to very low imputation quality	0.007
2:53854078:G:A	5.2E-06	c.679C>T	p.Gln227*	Exon 2	No	No	-
2:53854099:CAG:C	3.5E-06	c.656_657delCT	p.Ser219fs	Exon 2	No	No	-

Figure 12 (cont.)

Variant (CPRA)	AAF	cDNA change HGVS	Protein change HGVS	Affected exon	In genotyping array	In raw imputed data	Imputation quality INFO score, fraction of 1[a]
2:53854135:CAT:C	1.2E-06	c.620_621delAT	p.Tyr207fs	Exon 2	No	No	-
2:53854137:TAGAG:T	1.7E-05	c.616_619delCTCT	p.Leu206fs	Exon 2	No	No	-
2:53854306:G:A	1.2E-05	c.451C>T	p.Gln151*	Exon 2	No	No	-
2:53854380:G:C	2.1E-06	c.377C>G	p.Ser126*	Exon 2	No	No	-
2:53854409:A:AG	7.6E-06	c.347dupC	p.Cys118fs	Exon 2	No	No	-
2:53854421:ACTACTGG:A	1.2E-05	c.329_335delCCAGTAG	p.Ala110fs	Exon 2	No	No	-
2:53854474:C:A	1.2E-05	c.283G>T	p.Gly95*	Exon 2	No	No	-
2:53854476:C:CA	1.2E-06	c.280dupT	p.Cys94fs	Exon 2	No	No	-
2:53854485:AG:A	1.2E-06	c.271delC	p.Leu91fs	Exon 2	No	No	-
2:53854644:TG:T	4.2E-05	c.112delC	p.His38fs	Exon 2	No	No	-
2:53854685:TC:T	5.2E-06	c.71delG	p.Gly24fs	Exon 2	No	No	-
2:53854695:G:T	1.2E-06	c.62C>A	p.Ser21*	Exon 2	No	No	-
2:53854740:TG:T	1.2E-06	c.16delC	p.His6fs	Exon 2	No	No	-
2:53854755:A:G	9.0E-06	c.2T>C	p.Met1?	Exon 2	No	No	-
2:53859827:C:T	1.2E-06	c.-110+1G>A	-	Exon 1	No	No	-

Figure 12 (cont.)

SUBSTITUTE SHEET (RULE 26)

Gene	Genetic exposure, variant type; frequency cutoff in %	AAF, fraction of 1	Beta (95% CI) per allele in SD units of BMI	Beta (95% CI) per allele in kg/m2 units of BMI	p	Genotype counts, RR|RA|AA genotypes
ASB3	pLOF; AAF < 1%	0.00015	-0.037 (-0.17, 0.091)	-0.2 (-0.9, 0.49)	0.57	645,432|194|0
ASB3	pLOF plus any missense; AAF < 0.1%	0.00467	-0.0081 (-0.031, 0.015)	-0.044 (-0.17, 0.082)	0.50	639,601|6,023|2
ASB3	pLOF plus any missense; AAF < 1%	0.01375	-0.0069 (-0.021, 0.0068)	-0.037 (-0.11, 0.037)	0.33	627,913|17,677|36
ASB3	pLOF plus deleterious missense (5/5); AAF < 0.1%	0.00015	-0.037 (-0.17, 0.091)	-0.2 (-0.9, 0.49)	0.57	645,432|194|0
ASB3	pLOF plus deleterious missense (5/5); AAF < 1%	0.00015	-0.037 (-0.17, 0.091)	-0.2 (-0.9, 0.49)	0.57	645,432|194|0
ASB3	pLOF plus deleterious missense (1/5); AAF < 0.1%	0.00355	-0.019 (-0.045, 0.0079)	-0.1 (-0.25, 0.042)	0.17	641,041|4,583|2
ASB3	pLOF plus deleterious missense (1/5); AAF < 1%	0.01150	-0.011 (-0.026, 0.0039)	-0.059 (-0.14, 0.021)	0.15	630,803|14,798|25

Figure 13

Gene	Genetic exposure, variant type; frequency cutoff in %	AAF, fraction of 1	Beta (95% CI) per allele in SD units of BMI	Beta (95% CI) per allele in kg/m2 units of BMI	p	Genotype counts, RR|RA|AA genotypes
GPR75-ASB3	pLOF; AAF < 1%	0.00015	-0.039 (-0.17, 0.088)	-0.21 (-0.89, 0.47)	0.55	645,426|200|0
GPR75-ASB3	pLOF plus any missense; AAF < 0.1%	0.00497	-0.0096 (-0.032, 0.013)	-0.052 (-0.17, 0.071)	0.41	639,208|6,416|2
GPR75-ASB3	pLOF plus any missense; AAF < 1%	0.01565	-0.0012 (-0.014, 0.012)	-0.0065 (-0.076, 0.063)	0.85	625,469|20,110|47
GPR75-ASB3	pLOF plus deleterious missense (5/5); AAF < 0.1%	0.00015	-0.039 (-0.17, 0.088)	-0.21 (-0.89, 0.47)	0.55	645,426|200|0
GPR75-ASB3	pLOF plus deleterious missense (5/5); AAF < 1%	0.00015	-0.039 (-0.17, 0.088)	-0.21 (-0.89, 0.47)	0.55	645,426|200|0
GPR75-ASB3	pLOF plus deleterious missense (1/5); AAF < 0.1%	0.00385	-0.02 (-0.046, 0.0056)	-0.11 (-0.25, 0.03)	0.13	640,655|4,969|2
GPR75-ASB3	pLOF plus deleterious missense (1/5); AAF < 1%	0.01319	-0.0045 (-0.019, 0.0096)	-0.024 (-0.1, 0.052)	0.53	628,634|16,956|36

Figure 13 (cont.)

Genetic exposure, variant type; frequency cutoff in %	Additional covariates adjusted for in the analysis in addition to standard covariates*	Beta (95% CI) per allele in SD units of BMI	Beta (95% CI) per allele in kg/m^2 units of BMI	P	AAF, fraction of 1	Genotype counts, RR|RA|AA genotypes
GPR75 pLOF; AAF < 1%	ASB3 pLOF (AAF < 1%); ASB3 pLOF plus any missense (AAF < 0.1%); ASB3 pLOF plus any missense (AAF < 1%); ASB3 pLOF plus deleterious missense (5/5) (AAF < 0.1%); ASB3 pLOF plus deleterious missense (5/5) (AAF < 1%); ASB3 pLOF plus deleterious missense (1/5) (AAF < 0.1%); ASB3 pLOF plus deleterious missense (1/5) (AAF < 1%); GPR75-ASB3 pLOF (AAF < 1%); GPR75-ASB3 pLOF plus any missense (AAF < 0.1%); GPR75-ASB3 pLOF plus any missense (AAF < 1%); GPR75-ASB3 pLOF plus deleterious missense (5/5) (AAF < 0.1%); GPR75-ASB3 pLOF plus deleterious missense (5/5) (AAF < 1%); GPR75-ASB3 pLOF plus deleterious missense (1/5) (AAF < 0.1%); GPR75-ASB3 pLOF plus deleterious missense (1/5) (AAF < 1%)	-0.34 (-0.46, -0.22)	-1.85 (-2.50, -1.19)	3.1E-08	0.00018	645,398|228|0
GPR75 pLOF; AAF < 1%	26 common variants associated with BMI at the locus in Europeans (listed in Table S9)	-0.34 (-0.46, -0.22)	-1.85 (-2.50, -1.19)	3.1E-08	0.00018	645,398|228|0

Figure 14

SUBSTITUTE SHEET (RULE 26)

Variant (CPRA)	dbSNP rsID	AAF	PPA	Sentinel variant in credible set	Nearest gene
2:53634252:A:G	rs59428052	0.147	0.304	Yes	ASB3,GPR75-ASB3
2:53899622:C:A	rs805422	0.431	0.063	No	PSME4
2:53966056:T:C	rs805343	0.524	0.047	No	PSME4
2:53965962:A:G	rs805342	0.523	0.046	No	PSME4
2:53893683:G:A	rs805412	0.415	0.045	No	PSME4
2:53812428:C:G	rs2287347	0.092	0.039	No	ERLEC1,GPR75-ASB3
2:53813267:A:G	rs6545368	0.092	0.026	No	ERLEC1,GPR75-ASB3
2:53965020:G:A	rs805341	0.522	0.024	No	PSME4
2:53921194:C:A	rs805330	0.431	0.022	No	PSME4
2:53807744:G:T	rs6724214	0.092	0.021	No	ERLEC1,GPR75-ASB3
2:53938709:G:T	rs805361	0.438	0.02	No	PSME4
2:53934885:C:T	rs805358	0.439	0.015	No	PSME4
2:53907915:C:T	rs805318	0.44	0.01	No	PSME4
2:54051530:T:C	rs7590846	0.374	0.007	No	ACYP2
2:54051448:C:G	rs1559037	0.373	0.006	No	ACYP2
2:54052186:A:G	rs1833497	0.375	0.005	No	ACYP2
2:54052992:A:C	rs1862122	0.375	0.005	No	ACYP2
2:53899904:C:T	rs805423	0.482	0.005	No	PSME4
2:53995028:C:A	rs7591431	0.361	0.004	No	ACYP2
2:53958004:A:G	rs805335	0.49	0.004	No	PSME4
2:54053847:A:G	rs7558126	0.374	0.004	No	ACYP2
2:53733092:C:T	rs114272138	0.022	0.003	No	ASB3,GPR75-ASB3
2:53822332:G:A	rs3095756	0.412	0.002	No	GPR75-ASB3
2:53720820:C:A	rs77601694	0.022	0.002	No	ASB3,GPR75-ASB3
2:53822111:G:A	rs2542577	0.412	0.002	No	GPR75-ASB3
2:53821221:G:A	rs2542575	0.412	0.002	No	GPR75-ASB3

Figure 15

Variant (CPRA)	Annotation	Nonsynonymous variants in LD (R^2 > 0.8)	R^2 with nonsynonymous variant
2:53634252:A:G	intergenic	None	
2:53899622:C:A	intronic	None	
2:53966056:T:C	intronic	None	
2:53965962:A:G	intronic	None	
2:53893683:G:A	synonymous	None	
2:53812428:C:G	intronic;intronic	None	
2:53813267:A:G	intronic;intronic	None	
2:53965020:G:A	intronic	None	
2:53921194:C:A	intronic	None	
2:53807744:G:T	intronic	None	
2:53938709:G:T	intronic	None	
2:53934885:C:T	intronic	None	
2:53907915:C:T	intronic	None	
2:54051530:T:C	intronic	None	
2:54051448:C:G	intronic	None	
2:54052186:A:G	intronic	None	
2:54052992:A:C	intronic	None	
2:53899904:C:T	synonymous	None	
2:53995028:C:A	intronic	None	
2:53958004:A:G	intronic	None	
2:54053847:A:G	intronic	None	
2:53733092:C:T	intronic	2:53765485:G:C,2:53765485:G:C	0.83,0.83
2:53822332:G:A	intergenic	None	
2:53720820:C:A	intronic;intronic	2:53765485:G:C,2:53765485:G:C	0.83,0.83
2:53822111:G:A	intergenic	None	
2:53821221:G:A	intergenic	None	

Figure 15 (cont.)

Variant (CPRA)	Nonsynonymous variant effect	Gene for nonsynonymous change	Sentinel eQTL in LD (R^2 > 0.8)
2:53634252:A:G			None
2:53899622:C:A			None
2:53966056:T:C			None
2:53965962:A:G			None
2:53893683:G:A			None
2:53812428:C:G			None
2:53813267:A:G			None
2:53965020:G:A			None
2:53921194:C:A			None
2:53807744:G:T			None
2:53938709:G:T			None
2:53934885:C:T			None
2:53907915:C:T			None
2:54051530:T:C			None
2:54051448:C:G			None
2:54052186:A:G			None
2:54052992:A:C			None
2:53899904:C:T			None
2:53995028:C:A			None
2:53958004:A:G			None
2:54053847:A:G			None
2:53733092:C:T	missense,missense	ASB3,GPR75-ASB3	None
2:53822332:G:A			None
2:53720820:C:A	missense,missense	ASB3,GPR75-ASB3	None
2:53822111:G:A			None
2:53821221:G:A			None

Figure 15 (cont.)

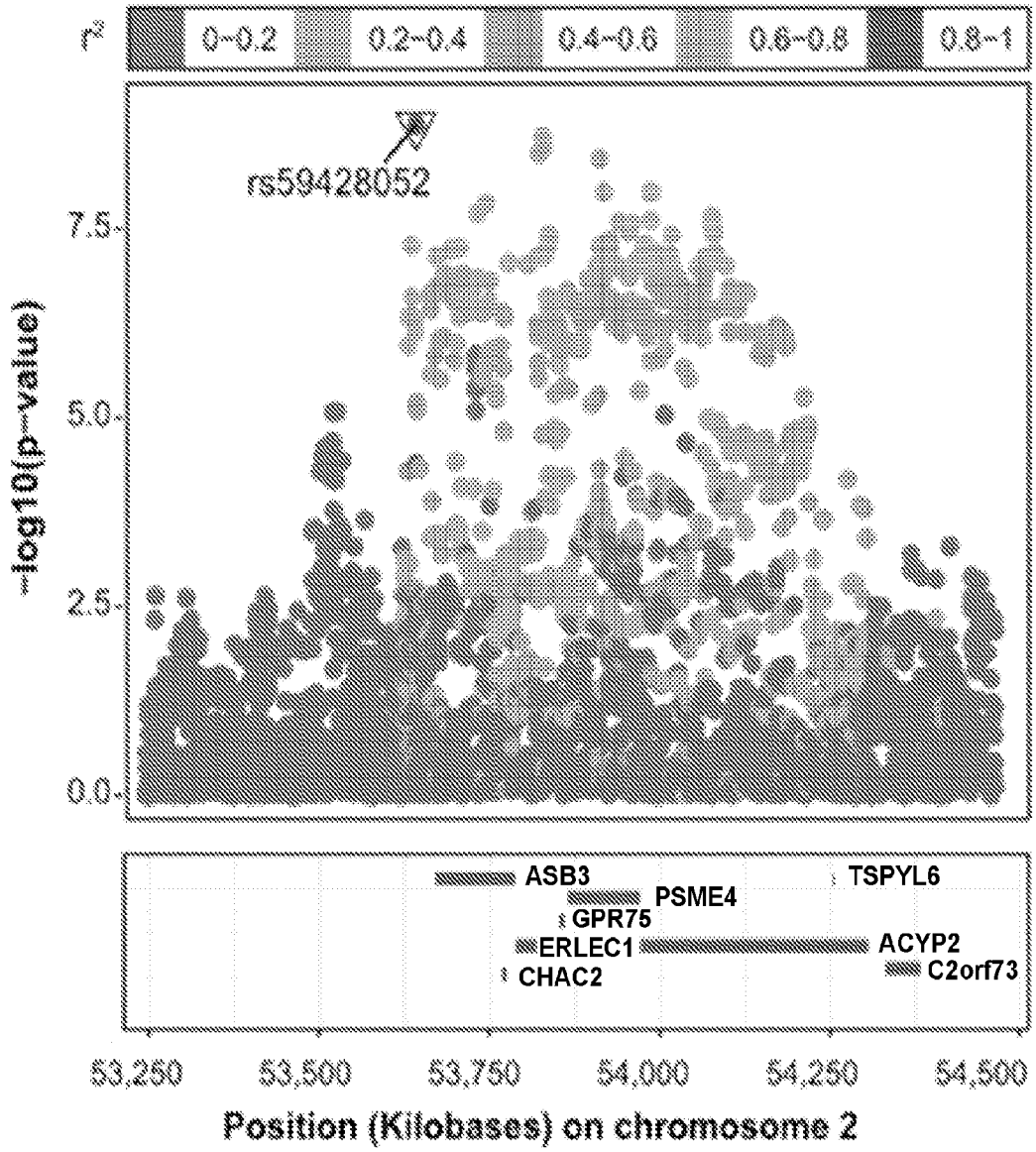

r²
0-0.2
0.2-0.4
0.4-0.6
0.6-0.8
0.8-1
rs59428052
7.5
5.0
2.5
0.0
-log10(p-value)
ASB3
PSME4
GPR75
ERLEC1
CHAC2
TSPYL6
ACYP2
C2orf73
53,250
53,500
53,750
54,000
54,250
54,500
Position (Kilobases) on chromosome 2

Figure 16

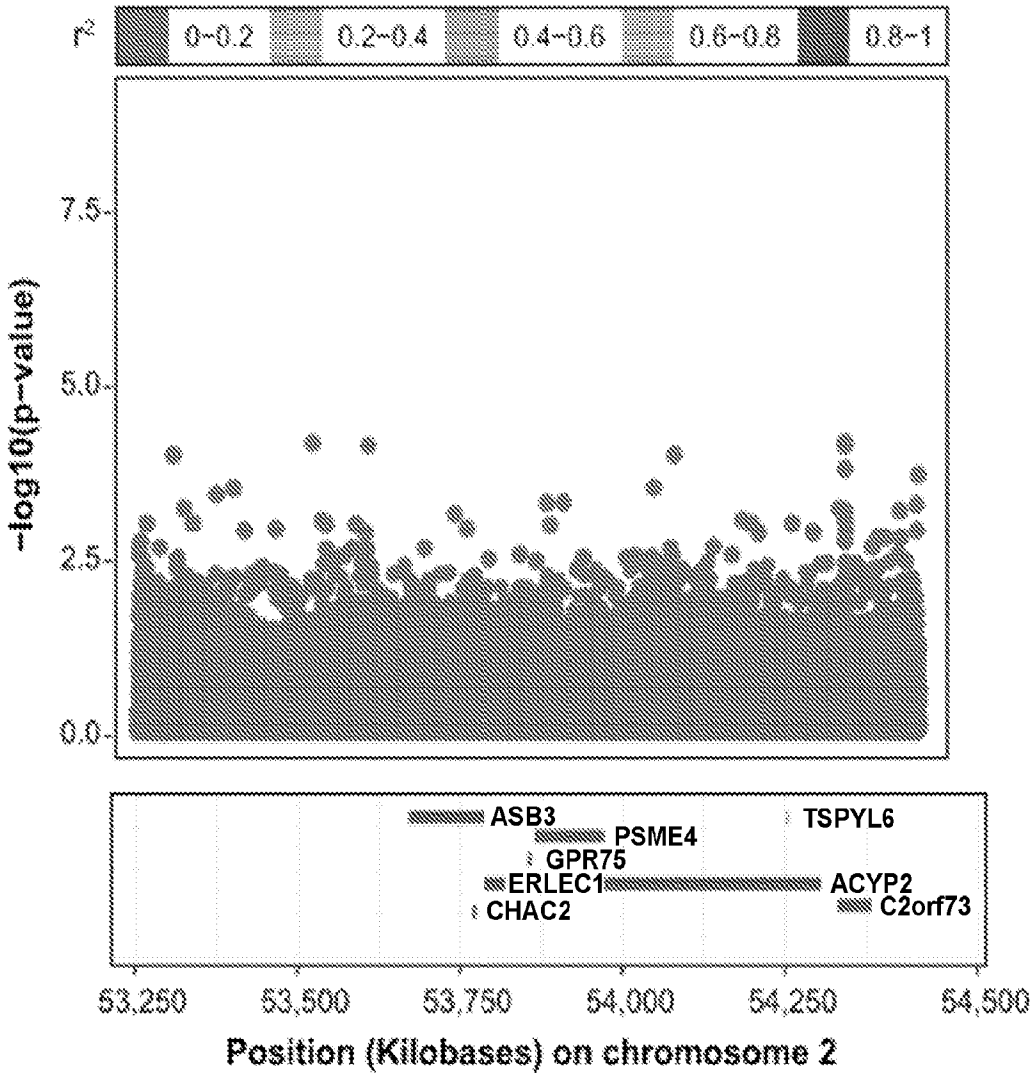


Figure 16 (cont.)

Exposure	Excluded genetic variants	Number of genetic variants left in the analysis	Beta (95% CI) per allele in SD units of BMI	p
GPR75 pLOF genetic variants with AAF < 1%	None (main analysis as reported in Table 1)	46	-0.34 (-0.46, -0.22)	2.6E-08
	2:53853134:T:G	45	-0.34 (-0.46, -0.22)	2.5E-08
	2:53853135:T:G	45	-0.33 (-0.45, -0.22)	3.9E-08
	2:53853136:A:C	45	-0.34 (-0.45, -0.22)	3.9E-08
	2:53853200:GGT:G	45	-0.34 (-0.46, -0.22)	3.0E-08
	2:53853245:GT:G	45	-0.34 (-0.46, -0.22)	2.7E-08
	2:53853256:G:A	45	-0.33 (-0.45, -0.22)	3.9E-08
	2:53853352:G:A	45	-0.36 (-0.49, -0.24)	4.9E-09
	2:53853354:CCA:C	45	-0.36 (-0.48, -0.24)	8.1E-09
	2:53853382:TG:T	45	-0.35 (-0.48, -0.23)	3.6E-08
	2:53853502:T:A	45	-0.33 (-0.45, -0.21)	7.0E-08
	2:53853535:G:A	45	-0.34 (-0.47, -0.22)	5.5E-08
	2:53853547:T:A	45	-0.33 (-0.45, -0.21)	8.4E-08
	2:53853560:G:GA	45	-0.33 (-0.45, -0.21)	6.2E-08

Figure 17

Exposure	Excluded genetic variants	Number of genetic variants left in the analysis	Beta (95% CI) per allele in SD units of BMI	p
GPR75 pLOF genetic variants with AAF < 1%	2:53853641:GTT:G	45	-0.34 (-0.46, -0.22)	2.8E-08
	2:53853680:CAATTCAAACTGGT:C	45	-0.34 (-0.46, -0.22)	2.4E-08
	2:53853692:G:T	45	-0.34 (-0.46, -0.22)	1.9E-08
	2:53853730:G:A	45	-0.34 (-0.46, -0.22)	2.3E-08
	2:53853771:G:C	45	-0.34 (-0.46, -0.22)	2.2E-08
	2:53853853:G:A	45	-0.34 (-0.46, -0.22)	2.2E-08
	2:53853877:G:A	45	-0.33 (-0.45, -0.21)	1.2E-07
	2:53853926:G:T	45	-0.33 (-0.45, -0.21)	5.9E-08
	2:53853927:T:TA	45	-0.34 (-0.46, -0.22)	3.0E-08
	2:53853946:G:GT	45	-0.33 (-0.45, -0.21)	5.4E-08
	2:53853967:TGG:T	45	-0.34 (-0.46, -0.22)	1.9E-08
	2:53854009:G:A	45	-0.34 (-0.46, -0.22)	2.1E-08
	2:53854037:A:AG	45	-0.33 (-0.45, -0.21)	4.6E-08
	2:53854045:ACTTT:A	45	-0.34 (-0.46, -0.21)	1.0E-07

Figure 17 (cont.)

Exposure	Excluded genetic variants	Number of genetic variants left in the analysis	Beta (95% CI) per allele in SD units of BMI	p
GPR75 pLOF genetic variants with AAF < 1%	2:53854051:T:A	45	-0.33 (-0.45, -0.21)	8.5E-08
	2:53854057:G:A	45	-0.34 (-0.47, -0.2)	4.7E-07
	2:53854078:G:A	45	-0.34 (-0.46, -0.22)	1.7E-08
	2:53854099:CAG:C	45	-0.33 (-0.45, -0.21)	8.9E-08
	2:53854135:CAT:C	45	-0.34 (-0.46, -0.22)	3.0E-08
	2:53854137:TAGAG:T	45	-0.34 (-0.46, -0.22)	3.3E-08
	2:53854306:G:A	45	-0.34 (-0.46, -0.22)	3.1E-08
	2:53854380:G:C	45	-0.34 (-0.46, -0.22)	2.3E-08
	2:53854409:A:AG	45	-0.34 (-0.46, -0.22)	2.7E-08
	2:53854421:ACTACTGG:A	45	-0.31 (-0.43, -0.19)	7.2E-07
	2:53854474:C:A	45	-0.34 (-0.46, -0.22)	1.8E-08
	2:53854476:C:CA	45	-0.34 (-0.46, -0.23)	1.4E-08
	2:53854485:AG:A	45	-0.34 (-0.46, -0.22)	2.3E-08
	2:53854644:TG:T	45	-0.34 (-0.46, -0.21)	5.6E-08
	2:53854685:TC:T	45	-0.34 (-0.45, -0.22)	3.5E-08

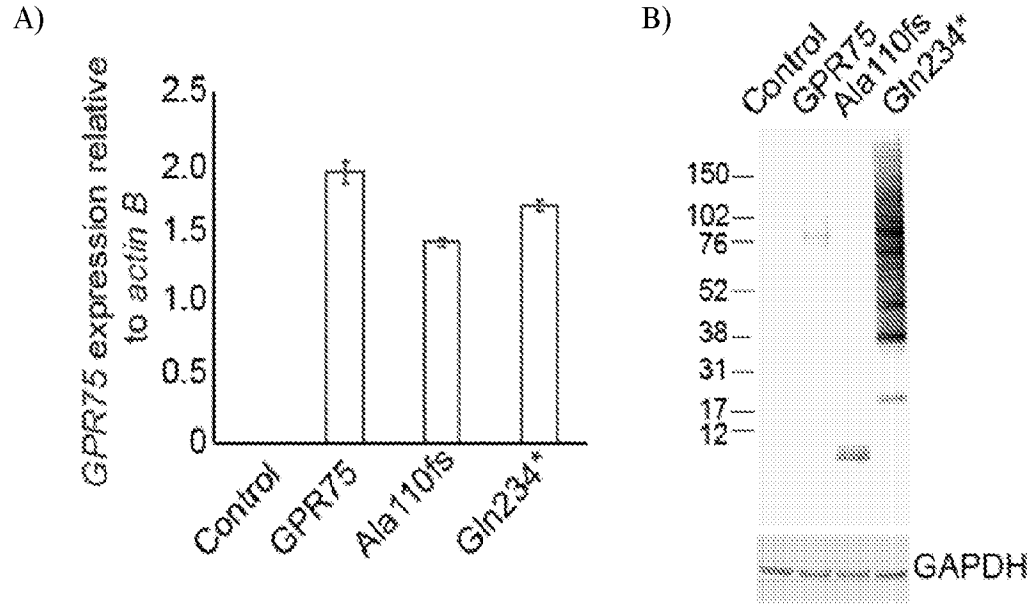
Figure 17 (cont.)

Exposure	Excluded genetic variants	Number of genetic variants left in the analysis	Beta (95% CI) per allele in SD units of BMI	p
GPR75 pLOF genetic variants with AAF < 1%	2:53854695:G:T	45	-0.34 (-0.46, -0.22)	2.3E-08
	2:53854740:TG:T	45	-0.34 (-0.46, -0.22)	2.6E-08
	2:53854755:A:G	45	-0.34 (-0.46, -0.22)	2.1E-08
	2:53859827:C:T	45	-0.33 (-0.45, -0.21)	4.9E-08
	5 variants associated with body mass index (Ala110fs, Ser219fs, Gln234*, Cys400fs, Lys404*)	41	-0.26 (-0.39, -0.12)	2.2E-04

Figure 17 (cont.)

Gene	Genetic exposure, variant type	Description	AAF, fraction of 1	Beta (95% CI) per allele in SD units of BMI	p
2:53853547:T:A; *GPR75* Lys404*	404* allele	Single variant exome analysis (AAF<1%)	1.0E-05	-1.77 (-3.12, -0.43)	9.5E-03
2:53853560:G:GA; *GPR75* Cys400fs	400fs allele	Single variant exome analysis (AAF<1%)	1.2E-06	-2.25 (-4.04, -0.47)	1.3E-02
2:53854057:G:A; *GPR75* Gln234*	234* allele	Single variant exome analysis (AAF<1%)	2.9E-05	-0.35 (-0.64, -0.06)	1.8E-02
2:53854099:CAG:C; *GPR75* Ser219fs	219fs allele	Single variant exome analysis (AAF<1%)	3.5E-06	-1.16 (-2.19, -0.13)	2.8E-02
2:53854421:ACTACTGG:A; *GPR75* Ala110fs	110fs allele	Single variant exome analysis (AAF<1%)	1.2E-05	-099 (-1.55, -0.42)	6.2E-04

Figure 18


A)
GPR75 expression relative to actin B
2.5
2.0
1.5
1.0
0.5
0
Control
GPR75
Ala110fs
Gln234*
B)
Control
GPR75
Ala110fs
Gln234*
150
102
76
52
38
31
17
12
GAPDH

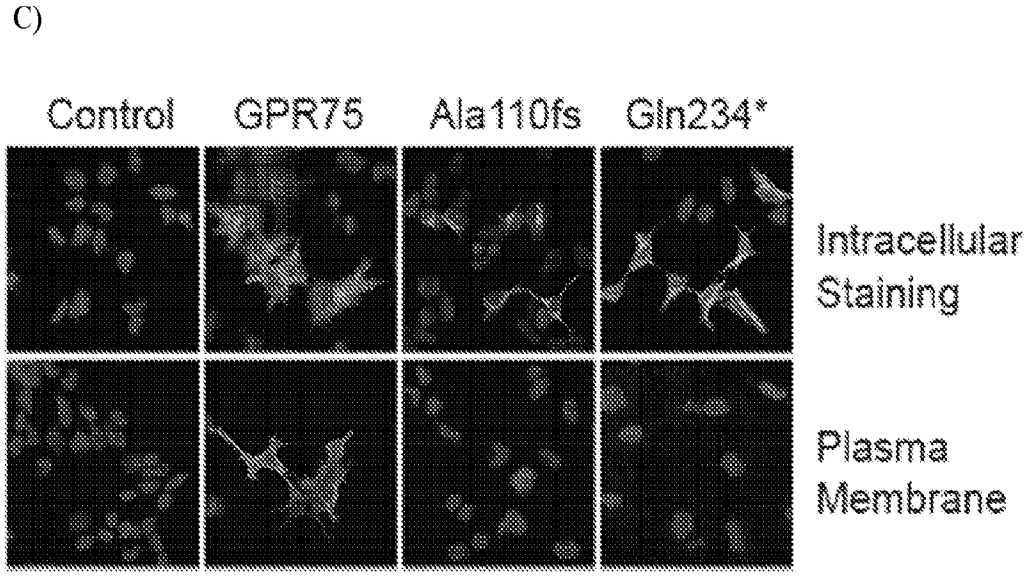

C)
Control
GPR75
Ala110fs
Gln234*
Intracellular Staining
Plasma Membrane

Figure 19

D)

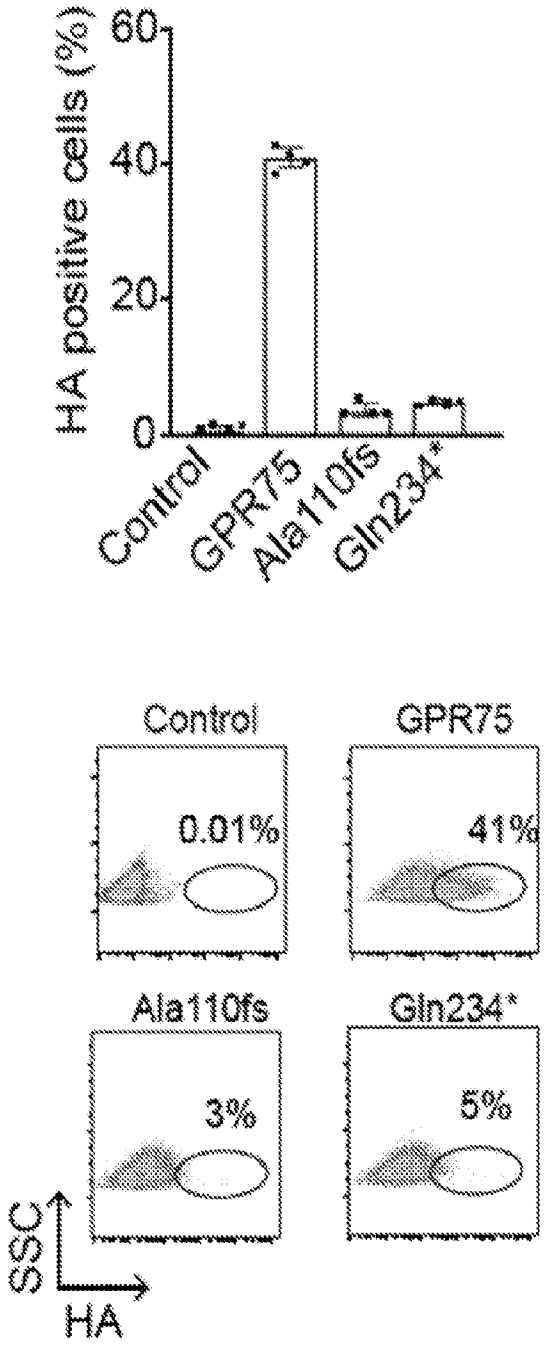
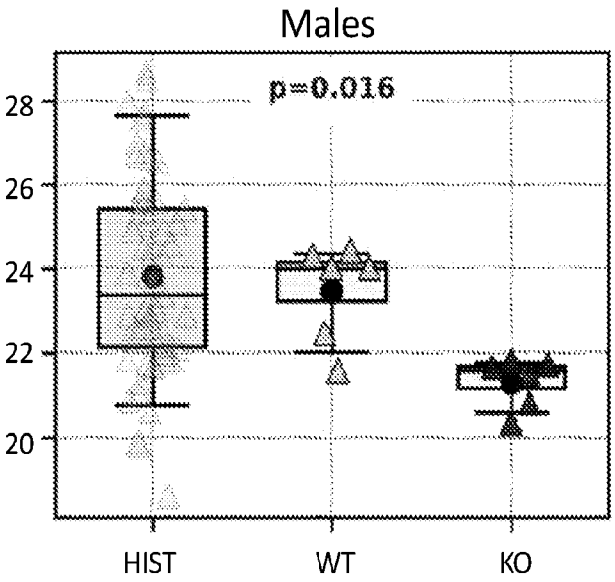


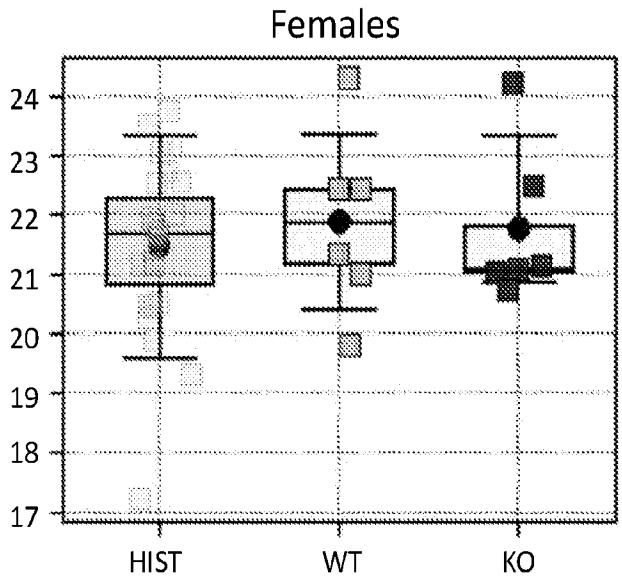
Figure 19 (cont.)

Exposure	Number of variant sites	Beta (95% CI) per allele in SD units of BMI	p	AAF, fraction of 1	Genotype counts, RR|RA|AA genotypes	Beta (95% CI) per allele in kg/m^2 units of BMI
N-terminal variants – truncation *before* last intracellular domain	32	-0.38 (-0.53, -0.23)	4.1E-07	0.00012	645,477|149|0	-2.1 (-2.9, -1.3)
C-terminal variants – truncation *within* last intracellular domain	14	-0.26 (-0.46, -0.06)	0.012	0.00006	645,547|79|0	-1.4 (-2.5, -0.3)
N-terminal variants – truncation *before* last 100 amino acids	37	-0.4 (-0.54, -0.26)	6.4E-09	0.00014	645,450|176|0	-2.2 (-2.9, -1.4)
C-terminal variants – truncation *within* last 100 amino acids	9	-0.13 (-0.38, 0.12)	0.32	0.00004	645,574|52|0	-0.7 (-2.1, 0.7)

Figure 20



p-value	EXP/WT ratio	effect-size (95% CI)
0.016	0.909	-2.33 (-4.07-0.582)



p-value	EXP/WT ratio	effect-size (95% CI)
0.873	0.995	-0.072 (-1.37-1.22)

Figure 21

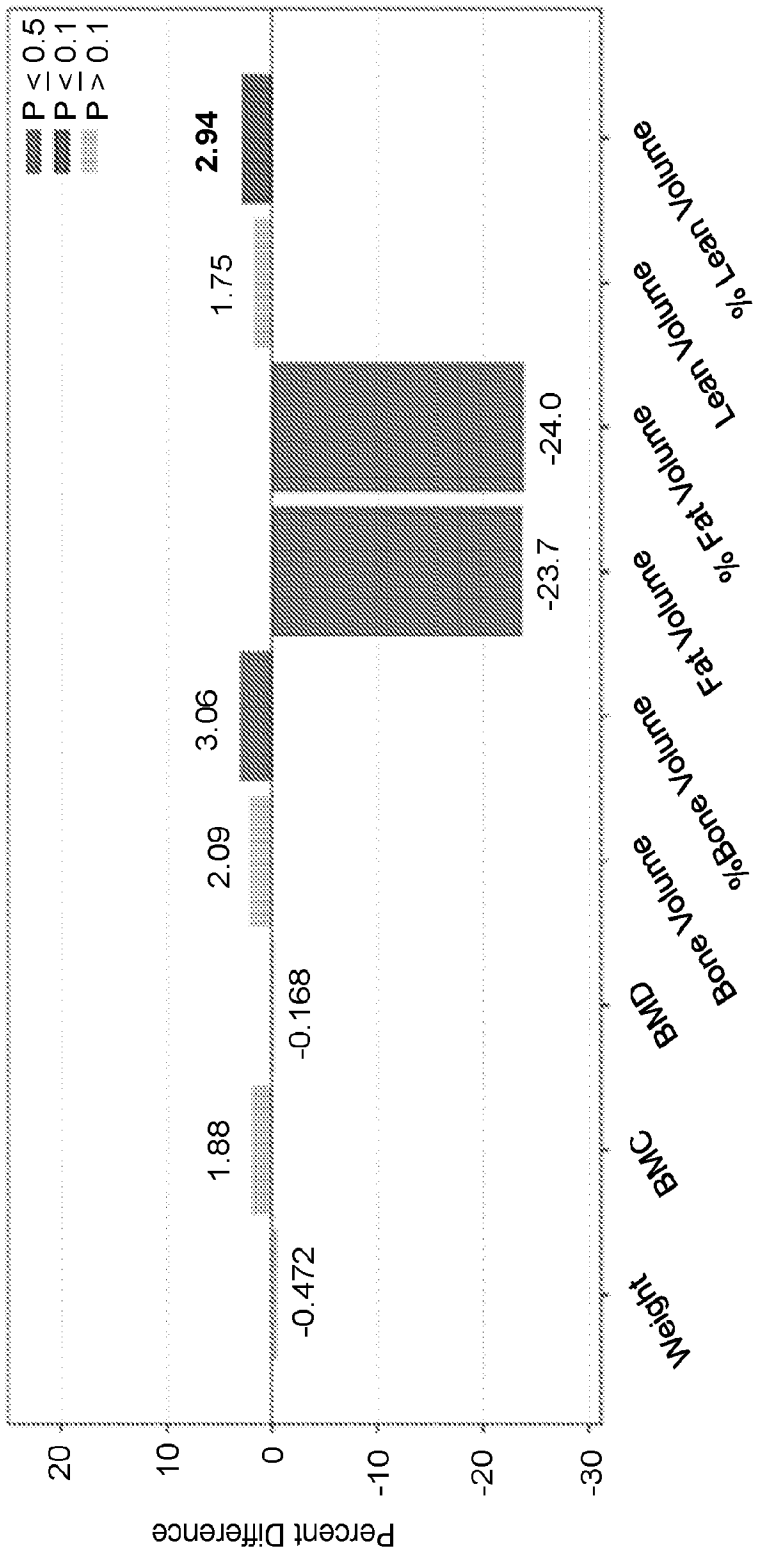

P <= 0.5
P <= 0.1
P > 0.1
Percent Difference
20
10
0
-10
-20
-30
-0.472
1.88
-0.168
2.09
3.06
-23.7
-24.0
1.75
2.94
Weight
BMC
BMD
Bone Volume
%Bone Volume
Fat Volume
% Fat Volume
Lean Volume
% Lean Volume

Figure 22

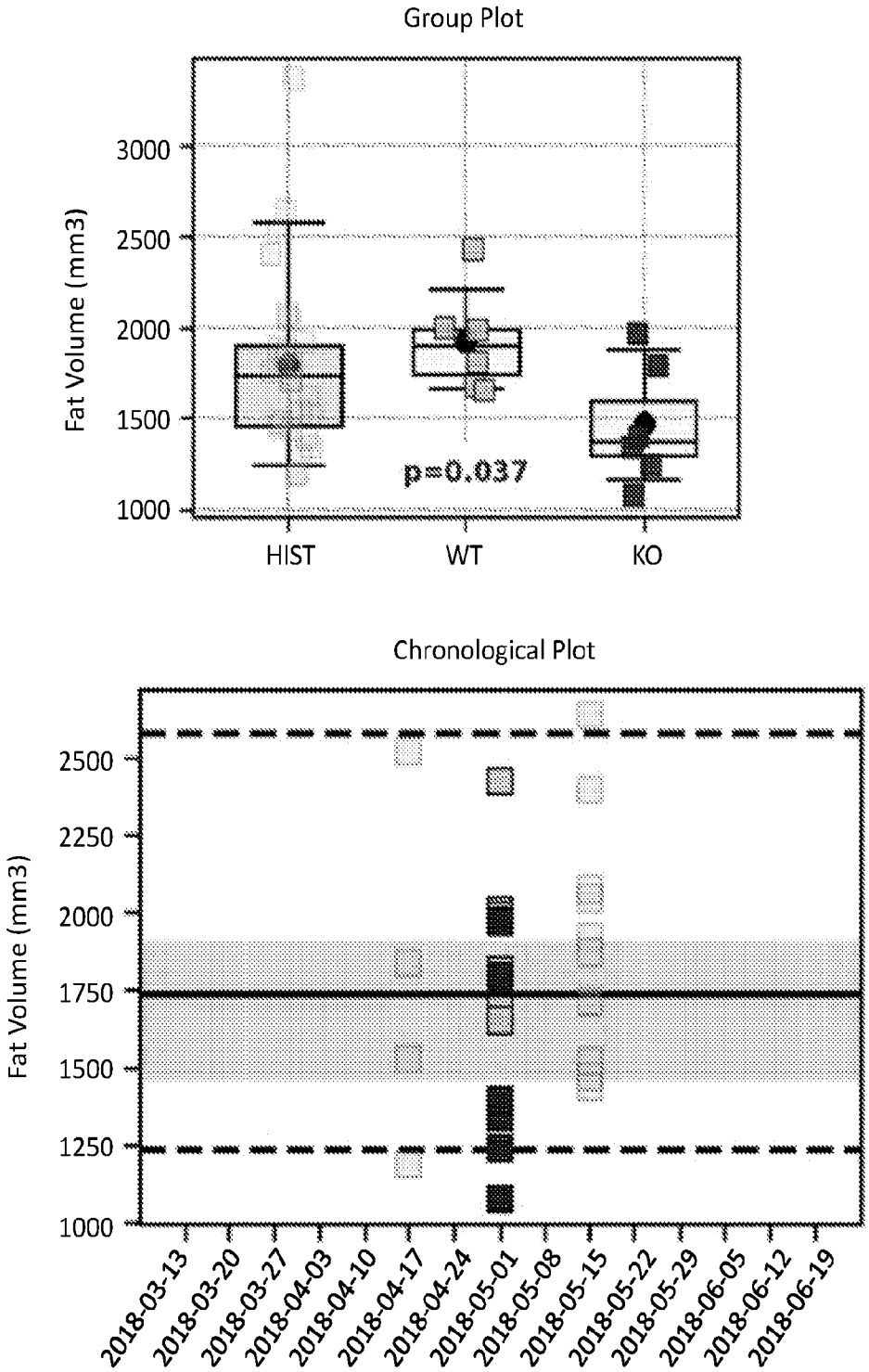

Group Plot
Fat Volume (mm3)
3000
2500
2000
1500
1000
p=0.037
HIST
WT
KO
Chronological Plot
Fat Volume (mm3)
2500
2250
2000
1750
1500
1250
1000
2018-03-13
2018-03-20
2018-03-27
2018-04-03
2018-04-10
2018-04-17
2018-04-24
2018-05-01
2018-05-08
2018-05-15
2018-05-22
2018-05-29
2018-06-05
2018-06-12
2018-06-19

Figure 23

Fat Volume (mm3)

group	n	mean	std	p05	med.	P95
WT	6	1926	285	1666	1900	2212
KO	6	1469	340	1160	1368	1879
HIST	26	1799	496	1239	1736	2578

p-value	EXP/WT ratio	effect-size (95% CI)
0.037	0.763	-1.45 (-2.94-0.032)

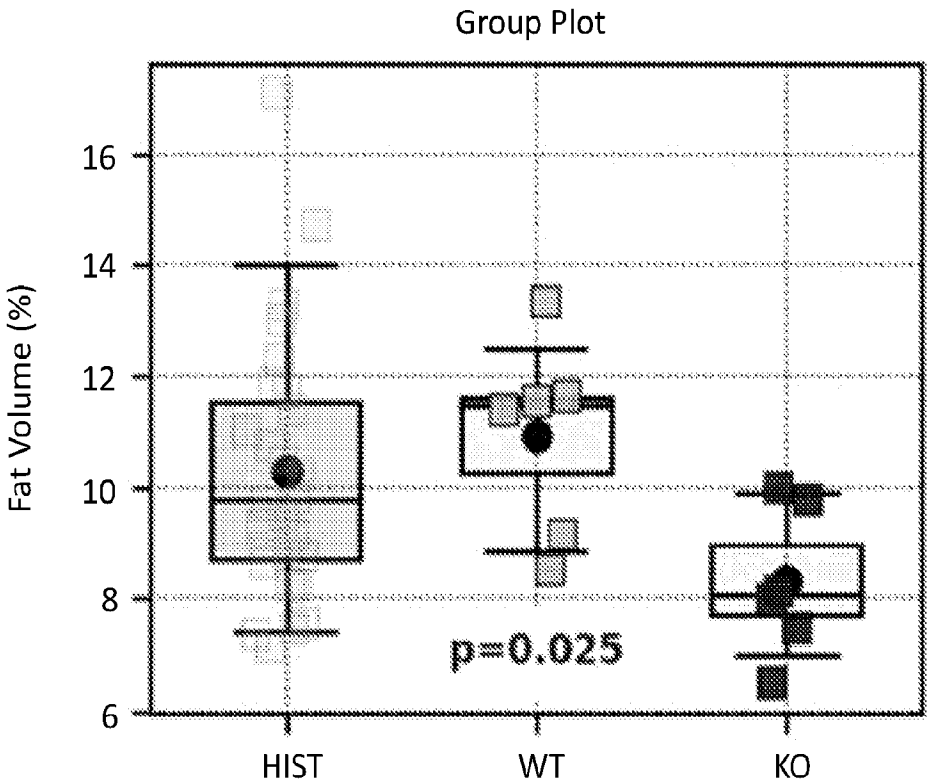
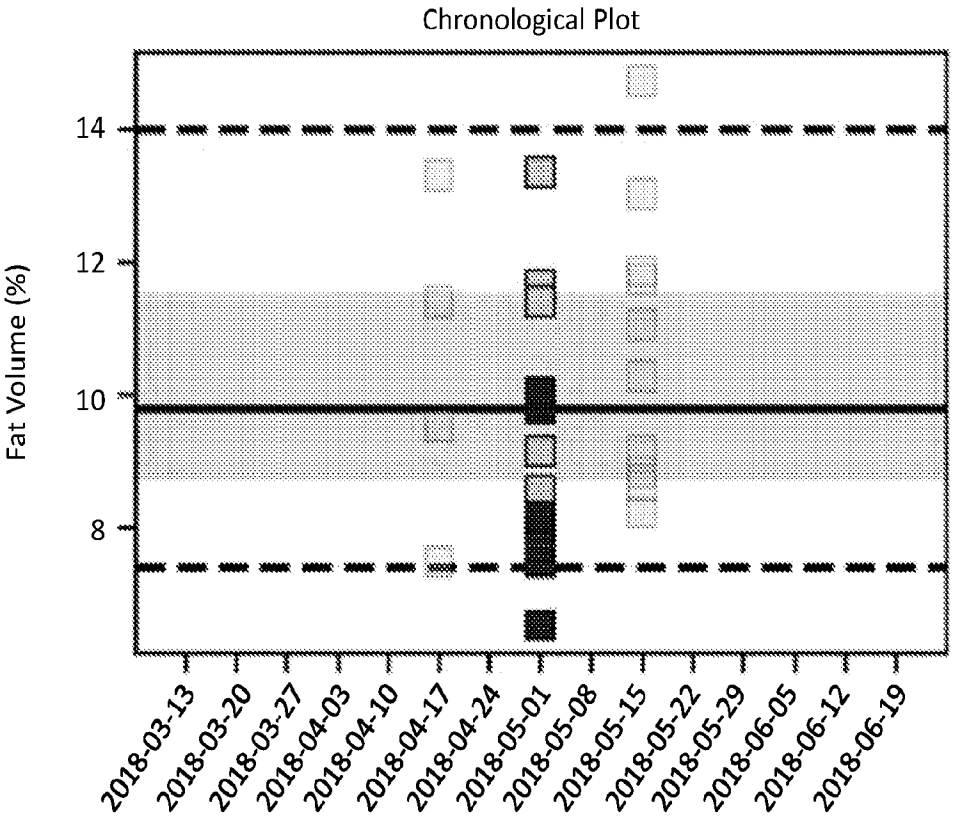


Figure 23 (cont.)



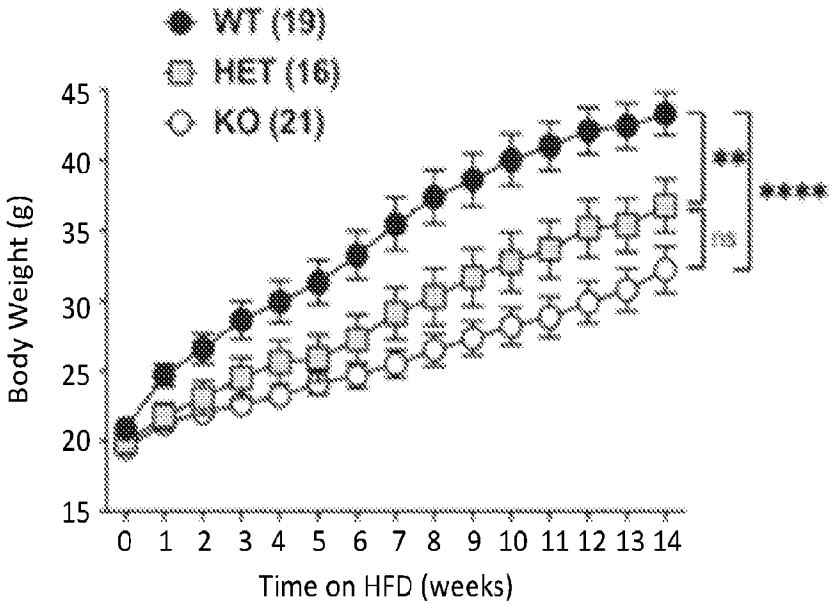
Fat Volume (%)

group	n	mean	std	p05	med.	P95
WT	6	10.9	1.78	8.85	11.5	12.5
KO	6	8.32	1.36	6.98	8.06	9.91
HIST	26	10.3	2.41	7.41	9.79	14.0

p-value	EXP/WT ratio	effect-size (95% CI)
0.025	0.760	-1.66 (-3.20--0.118)

Figure 23 (cont.)

A)


WT (19)
HET (16)
KO (21)
Body Weight (g)
45
40
35
30
25
20
15
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time on HFD (weeks)
**
ns
****

B)

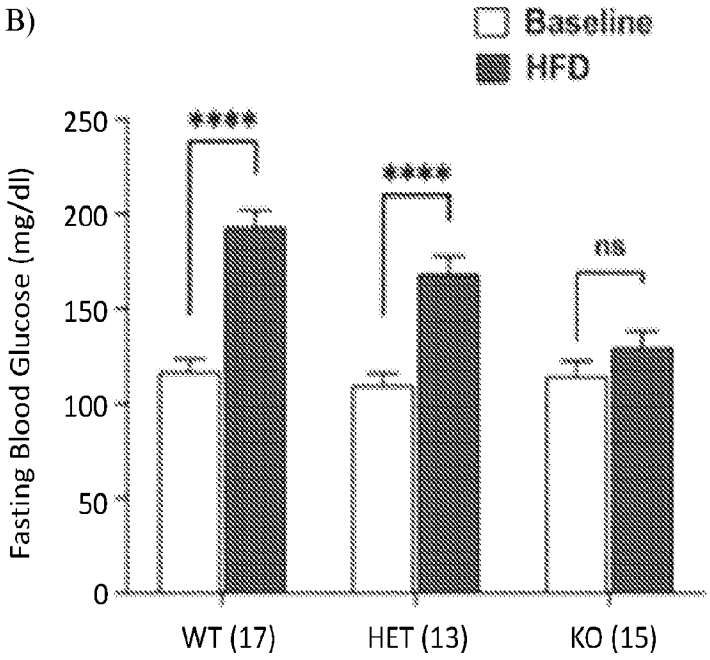
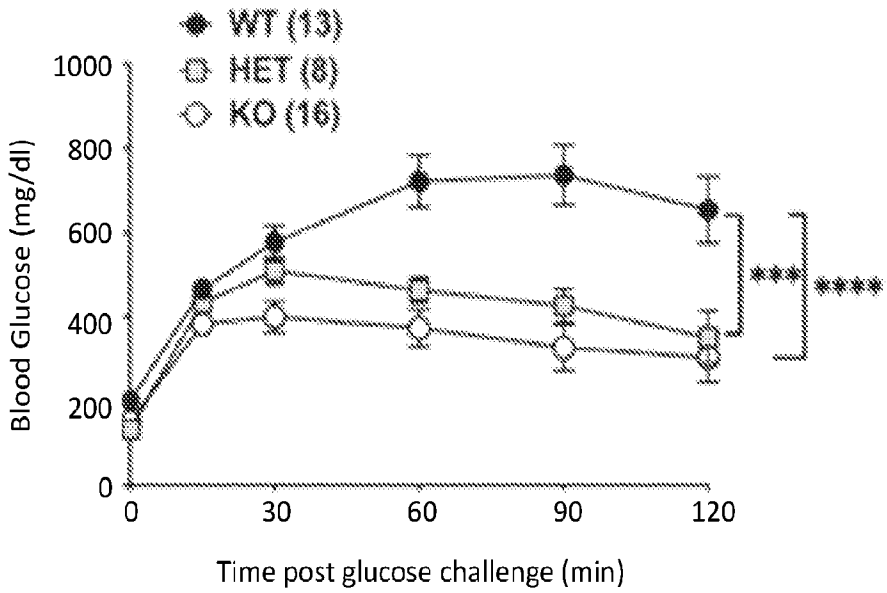

Baseline
HFD
Fasting Blood Glucose (mg/dl)
250
200
150
100
50
0
****
****
ns
WT (17)
HET (13)
KO (15)

Figure 24

C)



D)

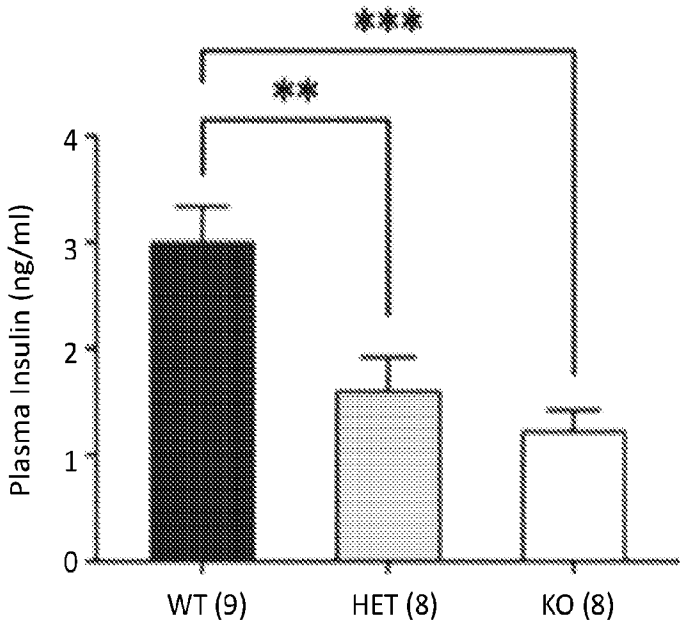
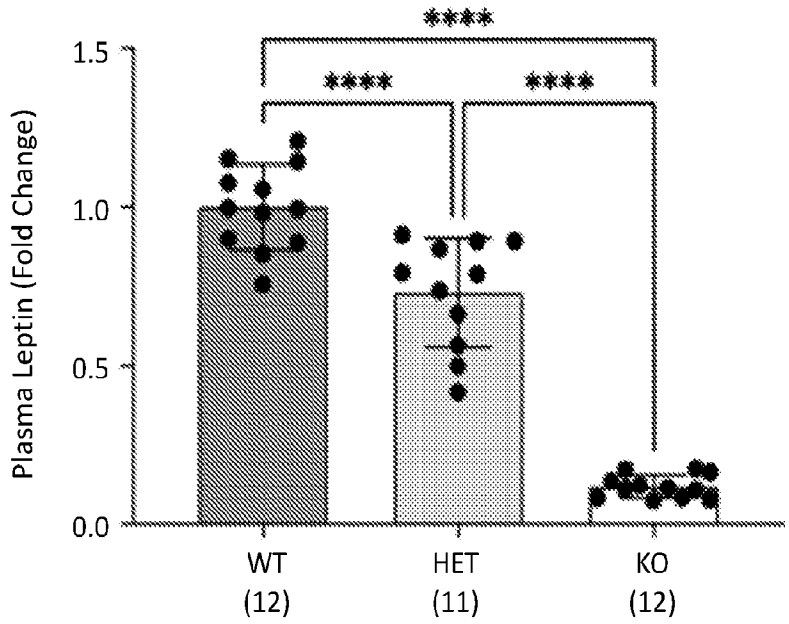


Figure 24 (cont.)

A)


****
****
****
Plasma Leptin (Fold Change)
1.5
1.0
0.5
0.0
WT
(12)
HET
(11)
KO
(12)

B)

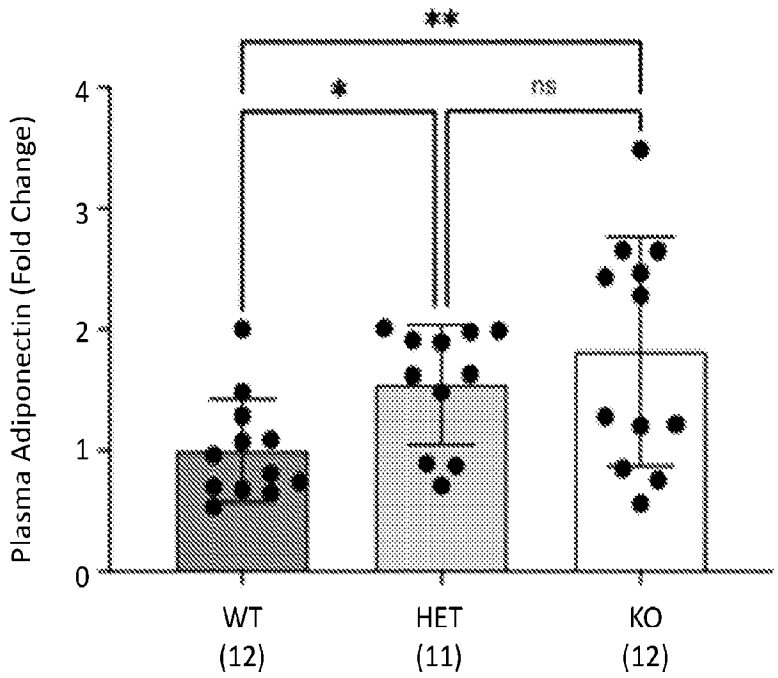

**
*
ns
Plasma Adiponectin (Fold Change)
4
3
2
1
0
WT
(12)
HET
(11)
KO
(12)

Figure 25

C)

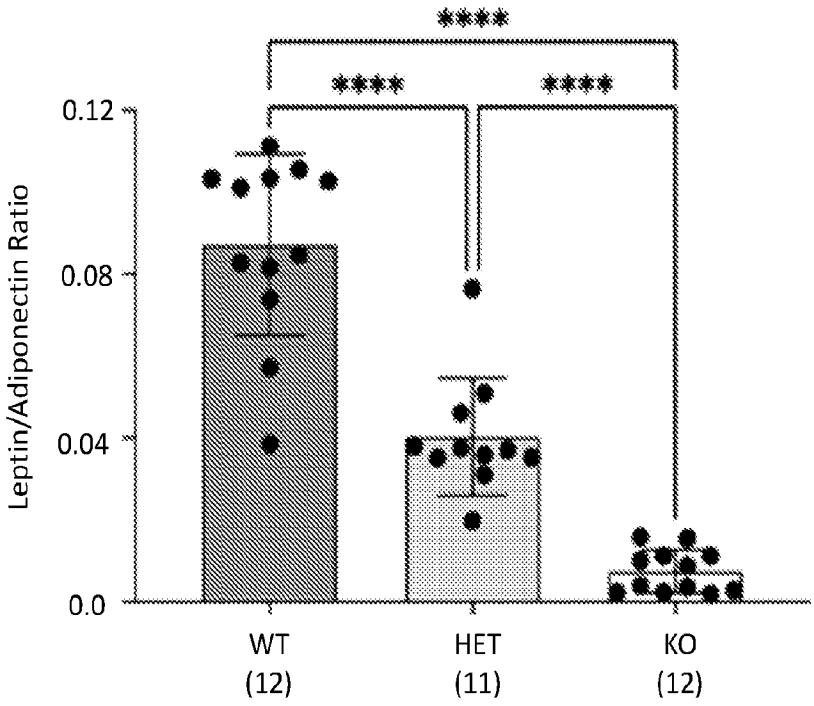


Figure 25 (cont.)

A)

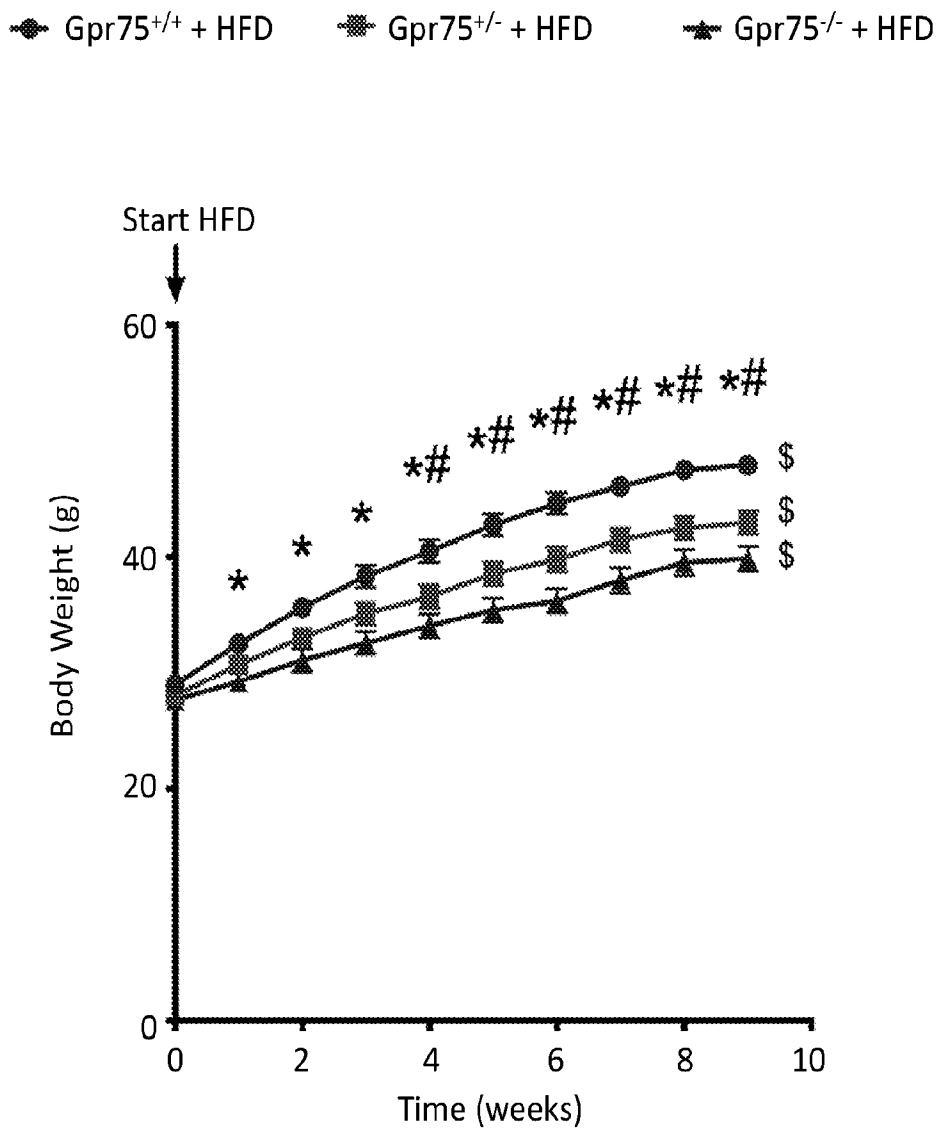

Gpr75+/+ + HFD
Gpr75+/- + HFD
Gpr75-/- + HFD
Start HFD
Body Weight (g)
60
40
20
0
0
2
4
6
8
10
Time (weeks)
*
*
*
*#
*#
*#
*#
*#
*#
$
$
$

Figure 26

B)

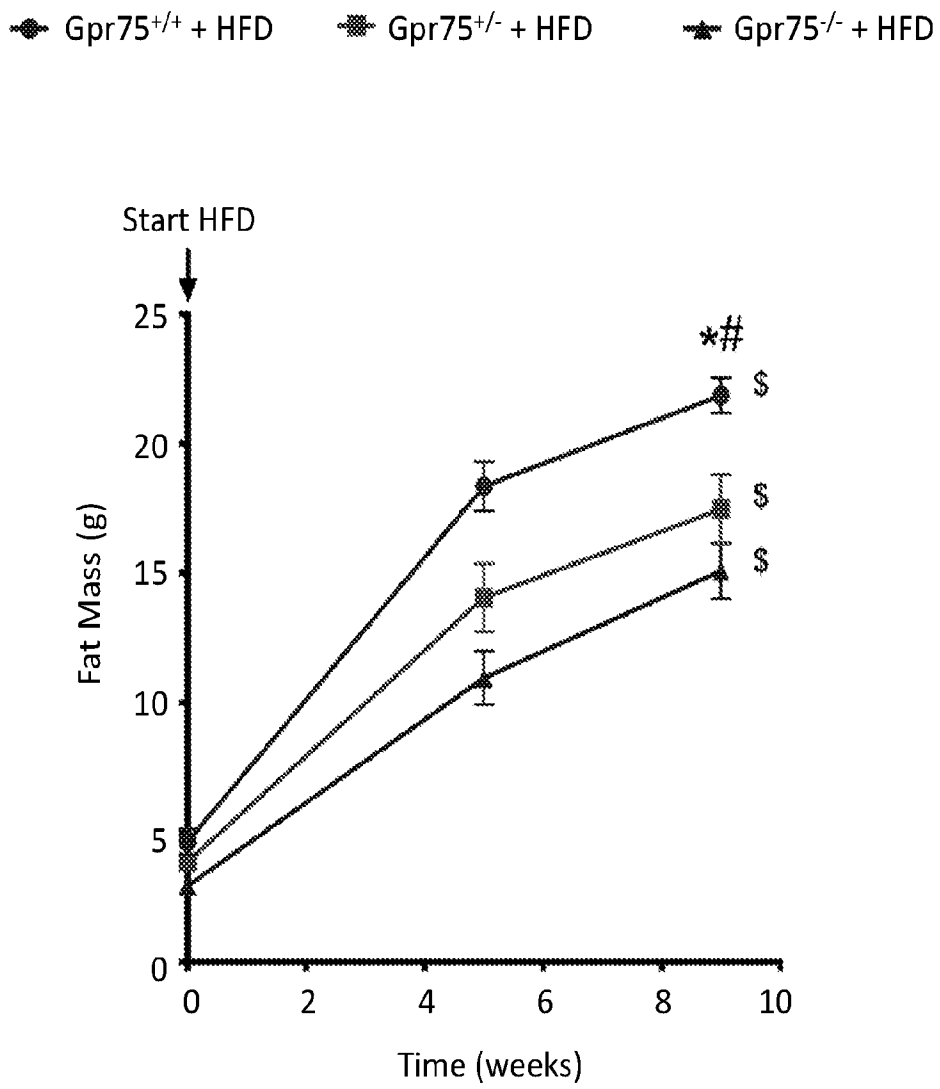


Figure 26 (cont.)

B)

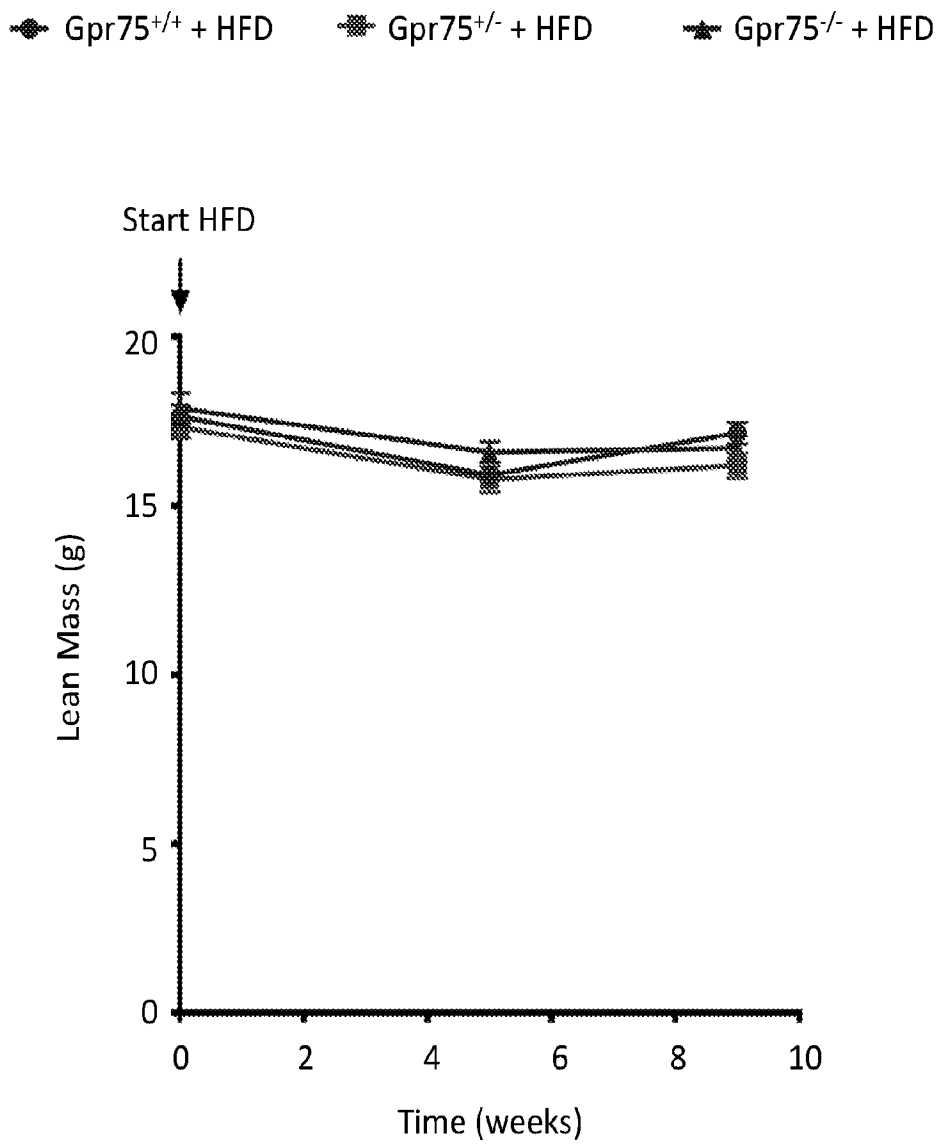


Figure 26 (cont.)

B)

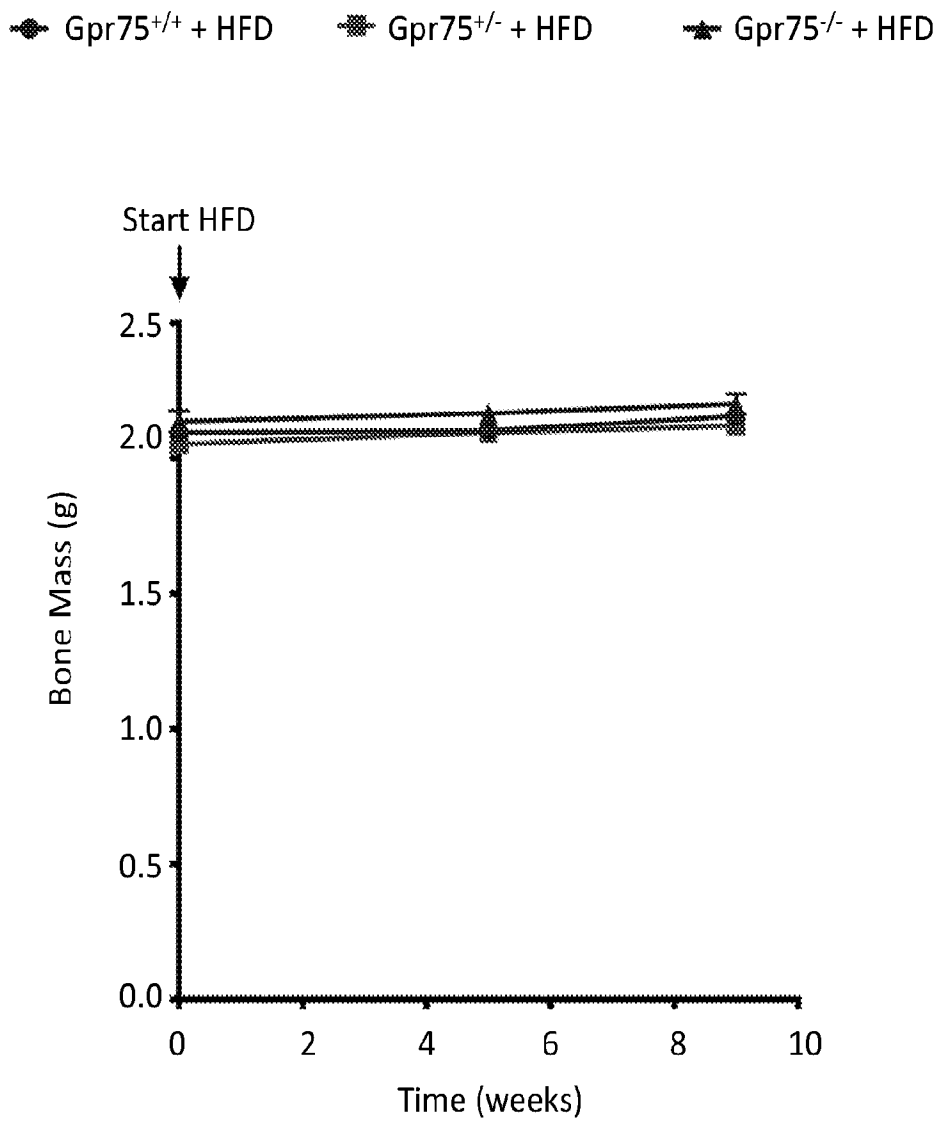


Figure 26 (cont.)

C)

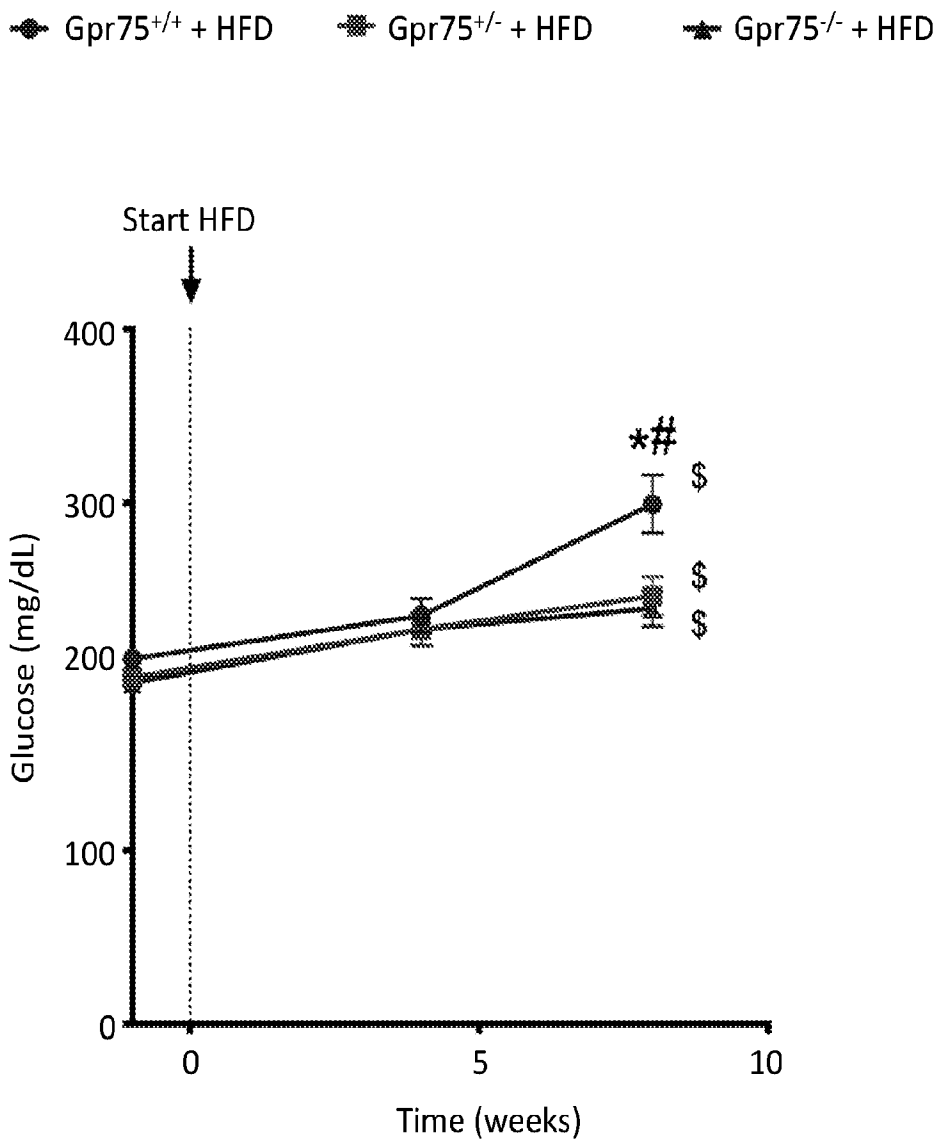


Figure 26 (cont.)

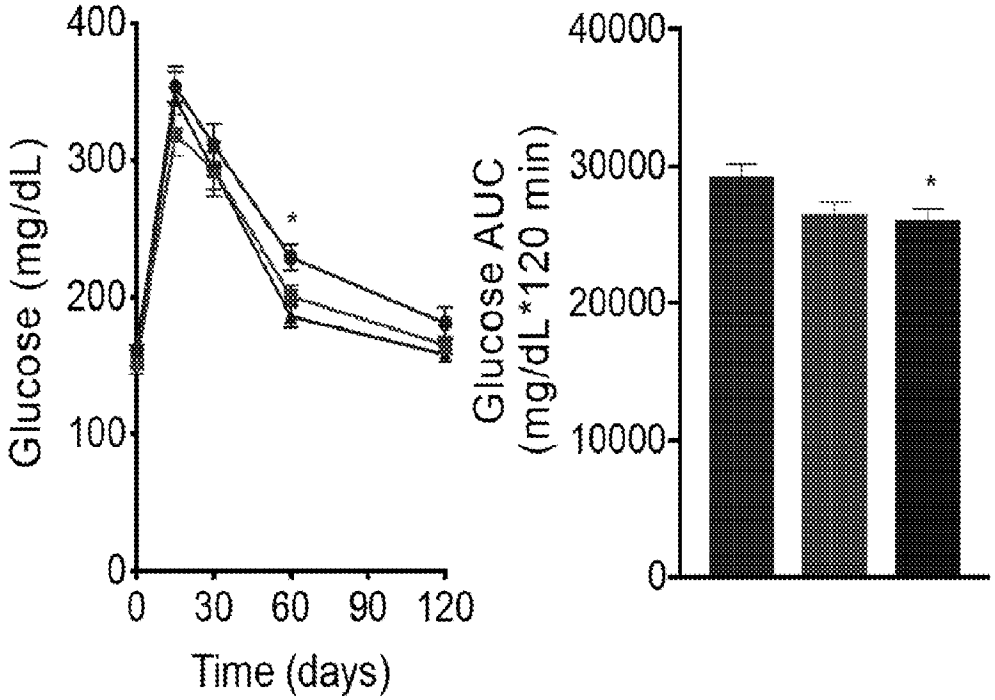

400
300
200
100
0
Glucose (mg/dL)
0
30
60
90
120
Time (days)
*
40000
30000
20000
10000
0
Glucose AUC
(mg/dL*120 min)
*

Figure 27

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/038260

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 C12Q1/6883 A61K31/7088 A61P3/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N C12Q A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, Sequence Search, EMBASE, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/156164 A1 (UNIV TEXAS [US]; NEW YORK MEDICAL COLLEGE [US]) 14 September 2017 (2017-09-14) cited in the application	1-3
Y	paragraphs [0048], [0049], [0250]; claims 1,24,25; figure 4; example 8	4-24, 62-69

Y	US 2008/108080 A1 (CHISSOE STEPHANIE [US]) 8 May 2008 (2008-05-08)	4-24, 62-69
A	paragraphs [0007] - [0009]; claim 1; example 2; tables 5,8	1-3

X	WO 2013/036290 A1 (UNIV YALE [US]; ELINAV ERAN [US] ET AL.) 14 March 2013 (2013-03-14)	1-3
Y	page 7; claims 12-27	4-24, 62-69

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 2021	06/12/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bucka, Alexander

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/040790 A2 (BAYER HEALTHCARE AG [DE]; GOLZ STEFAN [DE] ET AL.) 6 May 2005 (2005-05-06)	1-3
A	page 26 - page 27; claims 1-3,12,18-26; example 3 page 42 - page 43	4-24, 62-69

A	SAUER C G ET AL: "EVALUATION OF THE G PROTEIN COUPLED RECEPTOR-75 (GPR75) IN AGE RELATED MACULAR DEGENERATION", BRITISH JOURNAL OF OPHTHALMOLOGY, BMJ PUBLISHING GROUP, GB, vol. 85, no. 8, August 2001 (2001-08), pages 969-975, XP008042107, ISSN: 0007-1161, DOI: 10.1136/BJO.85.8.969 table 2	1-24, 62-69

A	DEDONI SIMONA ET AL: "The orphan G-protein-coupled receptor 75 signaling is activated by the chemokine CCL5", JOURNAL OF NEUROCHEMISTRY, vol. 146, no. 5, 2 September 2018 (2018-09-02), pages 526-539, XP055845796, GB ISSN: 0022-3042, DOI: 10.1111/jnc.14463 page 529, left-hand column; figures 8,9	1-24, 62-69

A	GARCIA VICTOR ET AL: "20-HETE Signals Through G-Protein-Coupled Receptor GPR75 (Gq) to Affect Vascular Function and Trigger Hypertension", CIRCULATION RESEARCH, vol. 120, no. 11, 26 May 2017 (2017-05-26) , pages 1776-1788, XP055843677, US ISSN: 0009-7330, DOI: 10.1161/CIRCRESAHA.116.310525 figures 2-6	1-24, 62-69

	-/--	

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIU BO ET AL: "The novel chemokine receptor, G-protein-coupled receptor 75, is expressed by islets and is coupled to stimulation of insulin secretion and improved glucose homeostasis", DIABETOLOGIA, vol. 56, no. 11, 27 August 2013 (2013-08-27), pages 2467-2476, XP055843674, BERLIN, DE ISSN: 0012-186X, DOI: 10.1007/s00125-013-3022-x Retrieved from the Internet: URL:https://link.springer.com/content/pdf/10.1007/s00125-013-3022-x.pdf> the whole document -----	1-24, 62-69
A	TANEERA JALAL ET AL: "Orphan G-protein coupled receptor 183 (GPR183) potentiates insulin secretion and prevents glucotoxicity-induced [beta]-cell dysfunction", MOLECULAR AND CELLULAR ENDOCRINOLOGY, ELSEVIER IRELAND LTD, IE, vol. 499, 21 September 2019 (2019-09-21), XP085904198, ISSN: 0303-7207, DOI: 10.1016/J.MCE.2019.110592 [retrieved on 2019-09-21] figure 6 -----	1-24, 62-69
T	AKBARI PARSA ET AL: "Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity", SCIENCE, vol. 373, no. 6550, 2 July 2021 (2021-07-02), page eabf8683, XP055845760, US ISSN: 0036-8075, DOI: 10.1126/science.abf8683 Retrieved from the Internet: URL:https://www.science.org/doi/pdf/10.1126/science.abf8683> the whole document -----	1-24, 62-69

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/038260

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/038260

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12, 19-24, 62-69(completely); 13-18(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12, 19-24, 62-69(completely); 13-18(partially)

A method of treating a subject having obesity, excessive weight, elevated BMI, elevated body fat mass, percentage, or volume, or excessive food intake, or to prevent weight gain, or to maintain weight loss, the method comprising administering a GPR75 inhibitor to the subject.

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2. claims: 25-29

A method of identifying a subject having an increased risk for developing obesity, wherein the method comprises: determining or having determined the presence or absence of a G-Protein Coupled Receptor 75 (GPR75) missense variant nucleic acid molecule encoding a predicted loss-of-function GPR75 polypeptide in a biological sample obtained from the subject;wherein: when the subject is GPR75 reference, then the subject has an increased risk for developing obesity; and when the subject is heterozygous for a GPR75 missense variant nucleic acid molecule or homozygous for a GPR75 missense variant nucleic acid molecule, then the subject has a decreased risk for developing obesity.

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3. claims: 30, 31

A method of detecting a human G-Protein Coupled Receptor 75 (GPR75) variant nucleic acid molecule in a subject comprising assaying a sample obtained from the subject to determine whether a nucleic acid molecule in the sample is: a genomic nucleic acid molecule comprising a nucleotide sequence as defined in claim 30.

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4. claims: 32-41

An isolated alteration-specific probe or alteration-specific primer comprising at least about 15 nucleotides, wherein the alteration-specific probe or alteration-specific primer comprises a nucleotide sequence which is complementary to a portion of a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the portion comprises a position corresponding to the sequences defined in claim 32.

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5. claims: 42-60

An isolated nucleic acid molecule comprising a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, or the complement thereof, wherein the

polypeptide comprises: a frameshift beginning at a position corresponding to position 110 according to SEQ ID NO:56, a frameshift beginning at a position corresponding to position 236 according to SEQ ID NO:59, or a frameshift beginning at a position corresponding to position 400 according to SEQ ID NO:60.

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6. claims: 61(completely); 13-18(partially)

A therapeutic agent that treats or inhibits obesity for use in the treatment of obesity in a subject having: a genomic nucleic acid molecule having a nucleotide sequence encoding a human G-Protein Coupled Receptor 75 (GPR75) polypeptide, wherein the nucleotide sequence is as defined in claim 61.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/038260

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