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(54) Title: GENETIC SUSCEPTIBILITY VARIANTS OF TYPE 2 DIABETES MELLITUS

(57) **Abrégé/Abstract:**

Association analysis has shown that certain genetic variants are susceptibility variants for Type 2 diabetes. The invention relates to diagnostic applications of such susceptibility variants, including methods of determining increased susceptibility to Type 2 diabetes, as well as methods of determining decreased susceptibility to Type 2 diabetes in an individual. The invention further relates to kits for determining a susceptibility to Type 2 diabetes based on the variants described herein.



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(54) Title: GENETIC SUSCEPTIBILITY VARIANTS OF TYPE 2 DIABETES MELLITUS

(57) Abstract: Association analysis has shown that certain genetic variants are susceptibility variants for Type 2 diabetes. The invention relates to diagnostic applications of such susceptibility variants, including methods of determining increased susceptibility to Type 2 diabetes, as well as methods of determining decreased susceptibility to Type 2 diabetes in an individual. The invention further relates to kits for determining a susceptibility to Type 2 diabetes based on the variants described herein.



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GENETIC SUSCEPTIBILITY VARIANTS OF TYPE 2 DIABETES MELLITUS

BACKGROUND OF THE INVENTION

5 Diabetes mellitus, a metabolic disease wherein carbohydrate utilization is reduced and lipid and protein utilization is enhanced, is caused by an absolute or relative deficiency of insulin. In the more severe cases, diabetes is characterized by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis and coma. Long term complications include development of neuropathy, retinopathy, nephropathy, generalized
10 degenerative changes in large and small blood vessels and increased susceptibility to infection. The most common form of diabetes is Type II, non-insulin-dependent diabetes that is characterized by hyperglycemia due to impaired insulin secretion and insulin resistance in target tissues. Both genetic and environmental factors contribute to the disease. For example, obesity plays a major role in the development of the disease.
15 Type 2 diabetes is often a mild form of diabetes mellitus of gradual onset.

The health implications of Type 2 diabetes are enormous. In 1995, there were 135 million adults with diabetes worldwide. It is estimated that close to 300 million will have diabetes in the year 2025. (King, H., *et al.*, *Diabetes Care*, 21(9): 1414-1431
(1998)). The prevalence of Type 2 diabetes in the adult population in Iceland is 2.5%
20 (Vilbergsson, S., *et al.*, *Diabet. Med.*, 14(6): 491-498 (1997)), which comprises approximately 5,000 people over the age of 34 who have the disease.

Type 2 diabetes is characterized by hyperglycemia, which can occur through mechanisms such as impaired insulin secretion, insulin resistance in peripheral tissues and increased glucose output by the liver. Most Type 2 diabetes patients suffer serious
25 complications of chronic hyperglycemia including nephropathy, neuropathy, retinopathy and accelerated development of cardiovascular disease. The prevalence of Type 2 diabetes worldwide is currently 6% but is projected to rise over the next decade (Amos, A. F., McCarty, D. J., Zimmet, P., *Diabet Med* 14 Suppl 5, S1 (1997)). This increase in prevalence of Type 2 diabetes is attributed to increasing age of the population and rise in
30 obesity.

There is evidence for a genetic component to the risk of Type 2 diabetes, including prevalence differences between various racial groups (Zimmet, P. *et al.*, *Am J Epidemiol* 118, 673 (1983), Knowler, W.C., Pettitt, D.J., Saad, M.F., Bennett, P.H., *Diabetes Metab Rev* 6, 1 (1990)), higher concordance rates among monozygotic than dizygotic twins

(Newman, B. *et al.*, *Diabetologia* 30, 763 (1987), Barnett, A.H., Eff, C., Leslie, R.D., Pyke, D.A., *Diabetologia* 20, 87 (1981)) and a sibling relative risk (λ_s) for Type 2 diabetes in European populations of approximately 3.5 (Gloyn, A.L., *Ageing Res Rev* 2, 111 (2003)).

Two approaches have thus far been used to search for genes associated with Type 2 diabetes. Single nucleotide polymorphisms (SNPs) within candidate genes have been tested for association and have, in general, not been replicated or confer only a modest risk of Type 2 diabetes – the most widely reported being a protective Pro12Ala polymorphism in the peroxisome proliferator activated receptor gamma gene (PPARG2) (Altshuler, D. *et al.*, *Nat Genet* 26, 76 (2000)) and an at risk polymorphism in the potassium inwardly-rectifying channel, subfamily J, member 11 gene (KIR6.2) (Gloyn A.L. *et al.*, *Diabetes* 52, 568 (2003)).

Genome-wide linkage scans in families with the common form of Type 2 diabetes have yielded several loci, and the primary focus of international research consortia has been on loci on chromosomes 1, 12 and 20 observed in many populations (Gloyn, A.L., *Ageing Res Rev* 2, 111 (2003)). The genes in these loci have yet to be uncovered. However, in Mexican Americans, the calpain 10 (CAPN10) gene was isolated out of a locus on chromosome 2q (Horikawa, Y. *et al.*, *Nat Genet* 26, 163 (2000)). The rare Mendelian forms of Type 2 diabetes, namely maturity-onset diabetes of the young (MODY), have yielded six genes by positional cloning (Gloyn, A.L., *Ageing Res Rev* 2, 111 (2003)).

Genome-wide significant linkage to chromosome 5q for Type 2 diabetes mellitus in the Icelandic population has been reported (Reynisdottir, I. *et al.*, *Am J Hum Genet* 73, 323 (2003)); in the same study, suggestive evidence of linkage to 10q and 12q was also reported. Linkage to the 10q region has also been observed in Mexican Americans (Duggirala, R. *et al.*, *Am J Hum Genet* 64, 1127 (1999)).

The transcription factor 7-like 2 gene (TCF7L2; formerly TCF4) has been associated with Type 2 diabetes ($P = 2.1 \times 10^{-9}$) (Grant, S.F. *et al.*, *Nat Genet* 38, 320 (2006)). The original finding in an Icelandic cohort of association of the microsatellite marker DG10S478 within intron 3 of the gene ($P = 2.1 \times 10^{-9}$) was replicated in a Danish cohort ($P = 4.8 \times 10^{-3}$) and in a US cohort ($P = 3.3 \times 10^{-9}$). Compared with non-carriers, heterozygous and homozygous carriers of the at-risk alleles (38% and 7% of the population, respectively) have relative risks of 1.45 and 2.41. This corresponds to a population attributable risk of 21%. Association of the TCF7L2 variant has now been replicated in 10 independent studies with similar relative risk found in the different populations studied. The TCF7L2 gene product is a high mobility group box-containing transcription factor previously implicated in blood glucose homeostasis. It is thought to act through regulation of proglucagon gene expression in enteroendocrine cells via the Wnt signaling pathway.

Despite the advances in unravelling the genetics of Type 2 diabetes, the high prevalence of the disease and increasing population affected shows an unmet medical need to define additional genetic factors involved in Type 2 diabetes to more precisely define the associated risk factors. People with impaired fasting glucose or impaired glucose tolerance are asymptomatic but are at a high risk of developing Type 2 diabetes. Currently there is very little information to distinguish those within this high risk group, where lifestyle intervention would be the best choice for disease prevention, from those individuals for whom preventive medication would be more appropriate. Identification of susceptibility genes will allow a better understanding of the pathophysiology of the disease and as a direct benefit for the patient it will facilitate better approaches for diagnosis and treatment. Also needed are therapeutic agents for prevention of Type 2 diabetes.

SUMMARY OF THE INVENTION

The present invention relates to methods of diagnosing an increased susceptibility to Type 2 diabetes, as well as methods of diagnosing a decreased susceptibility to Type 2 diabetes or diagnosing a protection against Type 2 diabetes, by evaluating certain markers or haplotypes that have been found to be associated with increased or decreased susceptibility of Type 2 diabetes.

In a first aspect, the present invention relates to a method of determining a susceptibility to Type 2 diabetes in a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the markers set forth in Tables 10-12, and markers in linkage disequilibrium therewith, and wherein determination of the presence or absence of the at least one allele is indicative of a susceptibility to Type 2 diabetes. In one embodiment, the at least one polymorphic marker is selected from the markers set forth in Tables 10-12 and 14. In an alternative aspect the method of determining a susceptibility to Type 2 diabetes is a method of diagnosing a susceptibility to Type 2 diabetes.

In one embodiment, the at least one polymorphic marker is present within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3. In another embodiment, the at least one polymorphic marker comprises at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID

NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In another embodiment, the at least one polymorphic marker comprises at least one marker in strong linkage disequilibrium, as defined by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2, with one or more markers selected from the group consisting of the markers set forth in Table 22, Table 23 and Table 24. In one preferred embodiment, the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), and markers in linkage disequilibrium therewith. In another preferred embodiment, the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), and rs6931514 (SEQ ID NO:37). In one embodiment, the at least one marker is selected from marker rs7756992 (SEQ ID NO:21), and markers in linkage disequilibrium therewith. In another embodiment, the at least one markers is selected from the markers set forth in Table 22. In another embodiment, the at least one marker is selected from marker rs10882091 (SEQ ID NO:4), and markers in linkage disequilibrium therewith. In another embodiment, the at least one markers is selected from the markers set forth in Table 23. In yet another embodiment, the at least one marker is selected from marker rs2191113 (SEQ ID NO:13), and markers in linkage disequilibrium therewith. In another embodiment, the at least one markers is selected from the markers set forth in Table 24.

In one embodiment, the method of determining a susceptibility, or diagnosing a susceptibility, of Type 2 diabetes, further comprises assessing the frequency of at least one haplotype in the individual. In one such embodiment, the at least one haplotype is selected from the haplotypes that comprise at least one polymorphic marker as set forth in Tables 1-6, and polymorphic markers in linkage disequilibrium therewith. In another embodiment, the at least one haplotype is selected from the haplotypes that comprise at least one polymorphic marker selected from at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In another embodiment, the at least one haplotype is selected from the haplotypes set forth in Tables 1-6 and 14.

In a second aspect, the invention relates to a method of determining a susceptibility to Type 2 diabetes in a human individual, comprising determining whether at least one at-risk allele in at least one polymorphic marker is present in a genotype dataset derived from the individual, wherein the at least one polymorphic marker is
5 selected from the markers set forth in Tables 10-12, and markers in linkage disequilibrium therewith, and wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility to Type 2 diabetes in the individual. The genotype dataset comprises in one embodiment information about marker identity, and the allelic status of the individual, i.e. information about the identity of the two alleles
10 carried by the individual for the marker. The genotype dataset may comprise allelic information about one or more marker, including two or more markers, three or more markers, five or more markers, one hundred or more markers, etc. In some embodiments, the genotype dataset comprises genotype information from a whole-genome assessment of the individual including hundreds of thousands of markers, or even
15 one million or more markers.

In one embodiment, the at least one polymorphic marker is present within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3. In another embodiment, the at least one polymorphic marker comprises at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID
20 NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID
25 NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In another embodiment, the at least one polymorphic marker comprises at least one marker in strong linkage disequilibrium, as defined by numeric values for $|D' |$ of greater than 0.8 and/or r^2 of greater than 0.2, with one or more markers selected from the group consisting of the markers set forth in Table 22, Table 23 and Table 24. In one preferred
30 embodiment, the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), and markers in linkage disequilibrium therewith. In another preferred embodiment, the at least one polymorphic marker is
35 selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), and rs6931514 (SEQ ID NO:37). In one embodiment, the at least one marker is selected from marker rs7756992 (SEQ ID NO:21), and markers in linkage disequilibrium therewith. In another embodiment, the at
40 least one markers is selected from the markers set forth in Table 22. In another

embodiment, the at least one marker is selected from marker rs10882091 (SEQ ID NO: 4), and markers in linkage disequilibrium therewith. In another embodiment, the at least one markers is selected from the markers set forth in Table 23. In yet another embodiment, the at least one marker is selected from marker rs2191113 (SEQ ID NO: 13), and markers in linkage disequilibrium therewith. In another embodiment, the at least one markers is selected from the markers set forth in Table 24. In yet another embodiment, the at least one marker is selected from markers in linkage disequilibrium with the SLC30A gene on chromosome 8, between position 118,032,398 and 118,258,134 (NCBI Build 36 of the Human genome assembly). In one such embodiment, the at least one marker is located within the SLC30A gene.

In one embodiment, the method of determining a susceptibility, or diagnosing a susceptibility, of Type 2 diabetes, further comprises assessing the frequency of at least one haplotype in the individual. In one such embodiment, the at least one haplotype is selected from the haplotypes that comprise at least one polymorphic marker as set forth in Tables 1-6, and polymorphic markers in linkage disequilibrium therewith. In another embodiment, the at least one haplotype is selected from the haplotypes that comprise at least one polymorphic marker selected from at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In another embodiment, the at least one haplotype is selected from the haplotypes set forth in Tables 1-6 and 14.

In certain embodiments of the invention, determination of the presence of at least one at-risk allele of at least one polymorphic marker in a nucleic acid sample from the individual is indicative of an increased susceptibility to Type 2 diabetes. In one embodiment, the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.15. In another embodiment, the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.20.

In some embodiments, the presence of rs2497304 allele A, rs947591 allele A, rs10882091 allele C rs7914814 allele T, rs6583830 allele A, rs2421943 allele G, rs6583826 allele G, rs7752906 allele A, rs1569699 allele C, rs7756992 allele G, rs9350271 allele A, rs9356744 allele C, rs9368222 allele A, rs10440833 allele A, rs6931514 allele G, rs1860316 allele A, rs1981647 allele C, rs1843622 allele T,

rs2191113 allele A, and/or rs9890889 allele A is indicative of increased susceptibility of Type 2 diabetes.

5 In particular embodiments, the presence of at least one protective allele in a nucleic acid sample from the individual is indicative of a decreased susceptibility of Type 2 diabetes. In another embodiment, the absence of at least one at-risk allele in a nucleic acid sample from the individual is indicative of a decreased susceptibility of Type 2 diabetes.

10 Particular embodiments of the methods of the invention relate to the at least one marker or haplotype being further associated with insulin response and/or impaired glucose tolerance in an individual.

In other embodiments, the presence of, or the determination of, at least one allele or haplotype in an at-risk marker is indicative of an increased susceptibility to Type 2 diabetes, and wherein the at least one allele or haplotype is further indicative of decreased insulin response and/or impaired glucose tolerance.

15 In certain embodiments of the invention, linkage disequilibrium is characterized by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2. However, other values for the r^2 and $|D'|$ measures are also possible in other embodiments, and such embodiments are also within the scope of the claimed invention, as described in further detail herein.

20 Another aspect of the invention relates to a method of assessing a susceptibility to Type 2 diabetes in a human individual, comprising screening a nucleic acid from the individual for at least one polymorphic marker or haplotype in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, that correlates with increased occurrence of Type 2 diabetes in a human population, wherein the presence of an at-risk marker allele in the at least one
25 polymorphism or an at-risk haplotype in the nucleic acid identifies the individual as having elevated susceptibility to diabetes, and wherein the absence of the at least one at-risk marker allele or at-risk haplotype in the nucleic acid identifies the individual as not having the elevated susceptibility.

In one embodiment, the polymorphism or haplotype is selected from rs2497304
30 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316
35 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium

therewith, as characterized by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2.

Certain embodiments of the invention further comprise a step of screening the nucleic acid for the presence of at least one at-risk genetic variant for Type 2 diabetes not associated with LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2) and LD Block C17 (SEQ ID NO:3). Such additional genetic variants can in specific embodiments include any variant that has been identified as a susceptibility or risk variant for Type 2 diabetes, including other variants described herein. In one embodiment, the step comprises screening the nucleic acid for the presence or absence of at least one at-risk allele of at least one at-risk variant for Type 2 diabetes in the TCF7L2 gene, wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility of Type 2 diabetes. In another embodiment, the at least one at-risk variant in the TCF7L2 gene is selected from marker DG10S478, rs12255372, rs7895340, rs11196205, rs7901695, rs7903146, rs12243326 and rs4506565, and markers in linkage disequilibrium therewith.

In another aspect of the present invention, the presence of the marker or haplotype found to be associated with Type 2 diabetes, and as such useful for determining a susceptibility to Type 2 diabetes, is indicative of a different response rate of the subject to a particular treatment modality for Type 2 diabetes.

In another aspect, the invention relates to a method of identification of a marker for use in assessing susceptibility to Type 2 diabetes in human individuals, the method comprising:

identifying at least one polymorphic marker within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, or at least one polymorphic marker in linkage disequilibrium therewith;

determining the genotype status of a sample of individuals diagnosed with, or having a susceptibility to, Type 2 diabetes; and

determining the genotype status of a sample of control individuals;

wherein a significant difference in frequency of at least one allele in at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing susceptibility to Type 2 diabetes.

In one embodiment, "significant" is determined by statistical means, e.g. the difference is statistically significant. In one such embodiment, statistical significance is

characterized by a P-value of less than 0.05. In other embodiments, the statistical significance is characterized a P-value of less than 0.01, less than 0.001, less than 0.0001, less than 0.00001, less than 0.000001, less than 0.0000001, less than 0.00000001, or less than 0.000000001.

5 In one embodiment, the at least one polymorphic marker is in linkage disequilibrium, as characterized by numerical values of r^2 of greater than 0.2 and/or $|D'|$ of greater than 0.8 with at least one marker selected from marker rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19),
10 rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31).

15 In one embodiment, an increase in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of the at least one allele in the control sample, is indicative of the at least one polymorphism being useful for assessing increased susceptibility to Type 2 diabetes. In another embodiment, a decrease in frequency of the
20 at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing decreased susceptibility to, or protection against, Type 2 diabetes.

Another aspect of the invention relates to a method of genotyping a nucleic acid
25 sample obtained from a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in the sample, wherein the at least one marker is selected rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32),
30 rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, and wherein determination of the presence or
35 absence of the at least one allele of the at least one polymorphic marker is predictive of a susceptibility of Type 2 diabetes.

In one embodiment, genotyping comprises amplifying a segment of a nucleic acid that comprises the at least one polymorphic marker by Polymerase Chain Reaction (PCR),

using a nucleotide primer pair flanking the at least one polymorphic marker. In another embodiment, genotyping is performed using a process selected from allele-specific probe hybridization, allele-specific primer extension, allele-specific amplification, nucleic acid sequencing, 5'-exonuclease digestion, molecular beacon assay, oligonucleotide ligation assay, size analysis, and single-stranded conformation analysis. In one particular embodiment, the process comprises allele-specific probe hybridization. In another embodiment, the process comprises DNA sequencing. In a preferred embodiment, the method comprises:

- 1) contacting copies of the nucleic acid with a detection oligonucleotide probe and an enhancer oligonucleotide probe under conditions for specific hybridization of the oligonucleotide probe with the nucleic acid;

wherein

- a) the detection oligonucleotide probe is from 5-100 nucleotides in length and specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site;
 - b) the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;
 - c) the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid; and
 - d) a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides;
- 2) treating the nucleic acid with an endonuclease that will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid; and
 - 3) measuring free detectable label, wherein the presence of the free detectable label indicates that the detection probe specifically hybridizes to the first segment of the nucleic acid, and indicates the sequence of the polymorphic site as the complement of the detection probe.

In a particular embodiment, the copies of the nucleic acid are provided by amplification by Polymerase Chain Reaction (PCR). In another embodiment, the susceptibility determined is increased susceptibility. In another embodiment, the susceptibility determined is decreased susceptibility.

5 Another aspect of the invention relates to a method of assessing an individual for probability of response to a therapeutic agent for preventing and/or ameliorating symptoms associated with Type 2 diabetes, comprising: determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected
10 from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37),
15 rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele of the at least one marker is indicative of a probability of a positive response to the Type 2 diabetes therapeutic agent. In one embodiment, the Type 2 diabetes therapeutic agent
20 is selected from the agents set forth in Agent Table 1 and Agent Table 2.

Yet another aspect of the invention relates to a method of predicting prognosis of an individual diagnosed with, Type 2 diabetes, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is
25 selected from the group consisting of rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36),
30 rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele is indicative of a worse prognosis of the Type 2 diabetes in the individual.

35 A further aspect of the invention relates to a method of monitoring progress of a treatment of an individual undergoing treatment for Type 2 diabetes, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of rs2497304 (SEQ ID

NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35),
 5 rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele is indicative of the treatment outcome of the individual.

10 In one embodiment, the method further comprises assessing at least one biomarker in a sample from the individual. In another embodiment, the method further comprises analyzing non-genetic information to make risk assessment, diagnosis, or prognosis of the individual. The non-genetic information is in one embodiment selected from age, gender, ethnicity, socioeconomic status, previous disease diagnosis, medical
 15 history of subject, family history of Type 2 diabetes, biochemical measurements, and clinical measurements. In a particular preferred embodiment, a further step comprising calculating overall risk is employed.

The invention also relates to a kit for assessing susceptibility to Type 2 diabetes in a human individual, the kit comprising reagents for selectively detecting the presence or
 20 absence of at least one allele of at least one polymorphic marker in the genome of the individual, wherein the polymorphic marker is selected from the group consisting of polymorphic markers within the nucleic acid segments whose sequences are set forth in SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3, and markers in linkage disequilibrium therewith, and wherein the presence of the at least one allele is indicative of a
 25 susceptibility to Type 2 diabetes.

In one embodiment, the at least one polymorphic marker is selected from the group of markers set forth in Tables 10 - 12, and markers in linkage disequilibrium therewith. In another embodiment, the at least one polymorphic marker is selected from the group of markers set forth in Tables 10 - 12 and Table 14, and markers in linkage
 30 disequilibrium therewith. In another embodiment, the at least one polymorphic markers is selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34),
 35 rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In another embodiment, the at least one polymorphic markers is selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID

NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15),
 rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6),
 rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34),
 rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37),
 5 rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9),
 rs2191113 (SEQ ID NO:13), and rs9890889 (SEQ ID NO:31).

In one embodiment, the reagents comprise at least one contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising the at least one polymorphic marker, a buffer and a detectable label. In one embodiment, the reagents
 10 comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic nucleic acid segment obtained from the subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes one polymorphic marker, and wherein the fragment is at least 30 base pairs in size. In a particular embodiment the at least one oligonucleotide is completely
 15 complementary to the genome of the individual. In another embodiment, the at least one oligonucleotide can comprise at least one mismatch to the genome of the individual. In one embodiment, the oligonucleotide is about 18 to about 50 nucleotides in length. In another embodiment, the oligonucleotide is 20-30 nucleotides in length.

In one preferred embodiment, the kit comprises:

20 a detection oligonucleotide probe that is from 5-100 nucleotides in length; an enhancer oligonucleotide probe that is from 5-100 nucleotides in length; and an endonuclease enzyme;

wherein the detection oligonucleotide probe specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site; and
 25 wherein the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus; wherein the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the
 30 oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid; wherein a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single
 35 base gap exists between the oligonucleotides; and wherein treating the nucleic acid with the endonuclease will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid.

A further aspect of the invention relates to the use of an oligonucleotide probe in the manufacture of a diagnostic reagent for diagnosing and/or assessing susceptibility to Type 2 diabetes in a human individual, wherein the probe hybridizes to a segment of a nucleic acid whose nucleotide sequence is given by SEQ ID NO: 1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site, wherein the fragment is 15-500 nucleotides in length. In one embodiment, the polymorphic site is selected from the polymorphic markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and polymorphisms in linkage disequilibrium therewith.

Yet another aspect of the invention relates to a computer-readable medium on which is stored: an identifier for at least one polymorphic marker; an indicator of the frequency of at least one allele of said at least one polymorphic marker in a plurality of individuals diagnosed with Type 2 diabetes; and an indicator of the frequency of the least one allele of said at least one polymorphic markers in a plurality of reference individuals; wherein the at least one polymorphic marker is selected from the polymorphic markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and polymorphisms in linkage disequilibrium therewith. In one embodiment, linkage disequilibrium is defined as defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8.

In one embodiment, information about the ancestry of the plurality of individuals is included. In another embodiment, the plurality of individuals diagnosed with Type 2 diabetes and the plurality of reference individuals is of a specific ancestry.

Another aspect relates to an apparatus for determining a genetic indicator for Type 2 diabetes in a human individual, comprising: a computer readable memory; and a routine stored on the computer readable memory; wherein the routine is adapted to be executed on a processor to analyze marker and/or haplotype information for at least one human individual with respect to at least one polymorphic marker selected from the markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4),

rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15),
 rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6),
 rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34),
 rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37),
 5 rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9),
 rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage
 disequilibrium therewith, as defined by numerical values of r^2 of at least 0.2 and/or values
 of $|D'|$ of at least 0.8, and generate an output based on the marker or haplotype
 information, wherein the output comprises a risk measure of the at least one marker or
 10 haplotype as a genetic indicator of Type 2 diabetes for the human individual.

In one embodiment, the routine further comprises an indicator of the frequency of
 at least one allele of at least one polymorphic marker or at least one haplotype in a
 plurality of individuals diagnosed with Type 2 diabetes, and an indicator of the frequency
 of at the least one allele of at least one polymorphic marker or at least one haplotype in a
 15 plurality of reference individuals, and wherein a risk measure is based on a comparison of
 the at least one marker and/or haplotype status for the human individual to the indicator
 of the frequency of the at least one marker and/or haplotype information for the plurality
 of individuals diagnosed with Type 2 diabetes.

In certain embodiments of the methods, uses, apparatus or kits of the invention,
 20 linkage disequilibrium is characterized by numeric values for $|D'|$ of greater than 0.8
 and/or r^2 of greater than 0.2. However, other values for the r^2 and $|D'|$ measures are also
 possible in other embodiments and such embodiments are also within the scope of the
 claimed invention, as described in further detail herein.

In certain other embodiments of the methods, uses, apparatus or kits of the
 25 invention, the individual is of a specific human ancestry. In one embodiment, the
 ancestry is selected from black African ancestry, Caucasian ancestry and Chinese
 ancestry. In another embodiment, the ancestry is black African ancestry. In another
 embodiment, the ancestry is European ancestry. In another embodiment, the ancestry is
 Caucasian ancestry. The ancestry is in certain embodiment self-reported by the individual
 30 who undergoes genetic analysis or genotyping. In other embodiments, the ancestry is
 determined by genetic determination comprising detecting at least one allele of at least
 one polymorphic marker in a nucleic acid sample from the individual, wherein the
 presence or absence of the allele is indicative of the ancestry of the individual.

In particular other embodiments of the methods, uses, apparatus or kits of the
 35 invention, the individual is obese. In other embodiments, the individual is non-obese.
 Obesity is in one embodiment determined by values of BMI (Body Mass Index) of greater
 than 25. In another embodiment, obesity is defined by values of BMI greater than 30.
 Other cutoff integer or fractional values of BMI are also possible and within scope of the

invention, including, but not limited to BMI of greater than 23, 24, 25.5, 26, 26.5, 27, 27.5 and so on. Non-obese individuals are in one embodiment defined as all those individuals who do not fulfill the criteria of obesity by BMI. In other embodiments, non-obese individuals are those with a particular cutoff of BMI, such as BMI less than 25, less than 24, less than 23, less than 22, less than 21 or less than 20. Non-integer cutoff values of BMI values are also useful for defining non-obese individuals. In general, the obese and non-obese groups do not overlap in terms of their BMI values. In certain embodiments, the cutoff employed to define the groups is the same, *e.g.*, greater than or smaller than BMI of 25. In other embodiments, a different cutoff is used, *e.g.*, greater than 27 for obese individuals and smaller than 23 for non-obese individuals. All relevant ranges of BMI that are suitable for defining obese and non-obese individuals are also possible and within scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

FIG 1 shows a plot linkage disequilibrium pattern in the region of chromosome 6p22.3 containing markers associated with Type 2 diabetes. (a) The X-axis shows positions with respect to NCBI Build 35 genome assembly (identical to Build 36), and the Y-axis shows a measure of linkage disequilibrium in the region. The span of the CDKAL1 gene is indicated by the arrows, and the locations of exons by black bars perpendicular to the diagonal line. The SNP markers are plotted equidistantly rather than according to their physical positions. The figure shows the r^2 measure of linkage disequilibrium, wherein the shading is proportional to pair-wise values of r^2 between markers. (b) A close-up of the 5' end of the CDKAL gene, showing the LD Block C06 region (SEQ ID NO:1) within which several markers have been found to be associated with Type 2 diabetes. The location of several of the associated SNP markers is indicated on the figure.

FIG 2 shows linkage disequilibrium in the region of chromosome 10q23.33 containing markers associated with Type 2 diabetes. The X-axis shows positions with respect to NCBI Build 35 genome assembly, and the Y-axis shows a measure of linkage disequilibrium in the region. The location of four associated SNP markers rs2497304, rs947591, rs10882091 and rs7914814 is indicated as well as the span and exons of the three genes within the LD block, IDE, KIF11 and HHEX. The figure shows the r^2 measure of linkage disequilibrium, wherein the shading is proportional to pair-wise values of r^2 between markers.

FIG 3 shows linkage disequilibrium in the region of chromosome 17q24.3 containing markers associated with diabetes in non-obese and all patients. The location of five SNP markers, rs1860316, rs1981647, rs1843622, rs2191113 and rs9890889, is indicated. The figure shows the r^2 measure of linkage disequilibrium, wherein the shading is proportional to pair-wise values of r^2 between markers.

FIG 4 shows a Q-Q plot of the 653,025 adjusted χ^2 -statistics (circles) from the analysis of single SNPs and two marker haplotypes. The equiangular line (black line) is included in the plot for reference purpose. The dashed horizontal line indicates the threshold for genome-wide significance assuming a Bonferroni correction for the 653,025 SNPs / haplotypes and three phenotypes tested.

FIG 5 presents a schematic view of the association of T2D to 6p22.3. a) The pair-wise correlation structure in a 1 Mb interval (20.5 – 21.5 Mb, NCBI Build34) on chromosome 6. The upper plot includes pair-wise D' for 1047 common SNPs (with MAF > 5%) from the HapMap release 19 for the CEU population, while the lower plot includes pair-wise r^2 values for the same set of SNPs. b) Location of recombination hot-spots in this interval based on the HapMap dataset (*Nature* **437**, 1299-1320 (27 October 2005)). c) Location of exons (vertical bars) of the two genes, *E2F3* and *CDKAL1*, that map to the interval. d) Schematic view of the genome-wide association results in the interval for all T2D cases (black dots), non-obese T2D cases (open circles) and obese T2D cases (open triangles), respectively. Plotted is $-\log P$, where P is the adjusted P value, against the chromosomal location of the markers. All four panels use the same horizontal Mb scale indicated at the bottom of panel d).

FIG 6 shows *CDKAL1* cDNA from INS-1 cells. Lanes 1 and 2 contain *CDKAL1* cDNA amplified from exons 2 to 8 and exons 7 to 13, giving a band size of 596bp and 738bp, respectively. β -actin (837bp) serves as a positive control in lane 3 and lane 4 is a negative control reaction without primers. Size standard is given on the left.

FIG 7 shows the association of rs7756992 and rs13266634 to insulin secretion. Mean log-transformed insulin secretion levels, estimated by corrected insulin response (see Methods), for the three different genotypes of the two SNPs, rs7756992 and rs13266634. Results are shown for 3982 individuals (231 T2D cases and 3751 controls) from the Danish Inter99 study that had an oral glucose tolerance test. The number of individuals is included under each column, and the standard error (s.e.m.) is indicated as horizontal bars. The included P values are from regression of the log-transformed insulin secretion levels on genotype status, adjusting for age, sex and affection status, assuming either an additive model (P_{add}) or a recessive model (P_{rec}).

FIG 8 presents further analysis of association of rs7756992 and rs13266634 with insulin secretion. a) Mean log-transformed insulin secretion levels, estimated by corrected

insulin response (CIR) for the three different genotypes for the SNP rs7756992. The insulin secretion levels are estimated for a group of 3938 individuals from the Danish Inter99 cohort (223 T2D cases and 3715 controls) that had an OGTT. Results are shown for all individuals (leftmost bars) and males (middle bars) and females (rightmost bars) separately. The number of individuals behind each estimate is indicated in parenthesis below the columns together with the corresponding genotype. The standard error of the mean is indicated with a bar on top of each column. b) Corresponding estimates for the different genotypes of the SNP rs13266634 for 3926 individuals (228 T2D cases and 3698 controls).

10

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

The present invention discloses polymorphic markers and haplotypes that have been found to be associated with Type 2 diabetes. Particular alleles at certain polymorphic SNP markers and haplotypes comprising such alleles have been found to be associated with Type 2 diabetes. Such markers and haplotypes are useful for assessing susceptibility to Type 2 diabetes, as described in further detail herein. Further applications of the present invention include methods for assessing response to Type 2 diabetes therapeutic agents utilizing the polymorphic markers of the invention, as well as kits for assessing susceptibility of an individual to Type 2 diabetes.

20

Definitions

The following terms shall, in the present context, have the meaning as indicated:

A "polymorphic marker", sometime referred to as a "marker", as described herein, refers to a genomic polymorphic site. Each polymorphic marker has at least two sequence variations characteristic of particular alleles at the polymorphic site. Thus, genetic association to a polymorphic marker implies that there is association to at least one specific allele of that particular polymorphic marker. The marker can comprise any allele of any variant type found in the genome, including SNPs, microsatellites, insertions, deletions, duplications and translocations.

30

An "allele" refers to the nucleotide sequence of a given locus (position) on a chromosome. A polymorphic marker allele thus refers to the composition (i.e., sequence) of the marker on a chromosome. Genomic DNA from an individual contains two alleles for any given polymorphic marker, representative of each copy of the marker on each

chromosome. Sequence codes for nucleotides used herein are: A = 1, C = 2, G = 3, T = 4.

Sequence conucleotide ambiguity as described herein is as proposed by IUPAC-IUB. These codes are compatible with the codes used by the EMBL, GenBank, and PIR
5 databases.

IUB	Meaning
A	Adenosine
C	Cytidine
G	Guanine
T	Thymidine
R	G or A
Y	T or C
K	G or T
M	A or C
S	G or C
W	A or T
B	C G or T
D	A G or T
H	A C or T
V	A C or G
N	A C G or T (Any base)

A nucleotide position at which more than one sequence is possible in a population (either a natural population or a synthetic population, *e.g.*, a library of synthetic molecules) is referred to herein as a "polymorphic site".

10 A "Single Nucleotide Polymorphism" or "SNP" is a DNA sequence variation occurring when a single nucleotide at a specific location in the genome differs between members of a species or between paired chromosomes in an individual. Most SNP polymorphisms have two alleles. Each individual is in this instance either homozygous for one allele of the polymorphism (i.e. both chromosomal copies of the individual have the
15 same nucleotide at the SNP location), or the individual is heterozygous (i.e. the two sister chromosomes of the individual contain different nucleotides). The SNP nomenclature as reported herein refers to the official Reference SNP (rs) ID identification tag as assigned to each unique SNP by the National Center for Biotechnological Information (NCBI).

A "variant", as described herein, refers to a segment of DNA that differs from the
20 reference DNA. A "marker" or a "polymorphic marker", as defined herein, is a variant. Alleles that differ from the reference are referred to as "variant" alleles.

A "microsatellite" is a polymorphic marker that has multiple small repeats of bases that are 2-8 nucleotides in length (such as CA repeats) at a particular site, in which the number of repeat lengths varies in the general population. An "indel" is a common form

of polymorphism comprising a small insertion or deletion that is typically only a few nucleotides long.

A "haplotype," as described herein, refers to a segment of genomic DNA that is characterized by a specific combination of alleles arranged along the segment. For diploid
5 organisms such as humans, a haplotype comprises one member of the pair of alleles for each polymorphic marker or locus. In a certain embodiment, the haplotype can comprise two or more alleles, three or more alleles, four or more alleles, or five or more alleles. Haplotypes are described herein in the context of the marker name and the allele of the marker in that haplotype, e.g., "3 rs7758851" refers to the 3 allele of marker rs7758851
10 being in the haplotype, and is equivalent to "rs7758851 allele 3". Furthermore, allelic codes in haplotypes are as for individual markers, i.e. 1 = A, 2 = C, 3 = G and 4 = T.

The term "susceptibility", as described herein, encompasses both increased susceptibility and decreased susceptibility. Thus, particular alleles at polymorphic markers and/or haplotypes of the invention may be characteristic of increased
15 susceptibility (i.e., increased risk) of Type 2 diabetes, as characterized by a relative risk (RR) or odds ratio (OR) of greater than one for the particular allele or haplotype. Alternatively, the markers and/or haplotypes of the invention are characteristic of decreased susceptibility (i.e., decreased risk) of Type 2 diabetes, as characterized by a relative risk of less than one.

20 A "nucleic acid sample" is a sample obtained from an individuals that contains nucleic acid. In certain embodiments, i.e. the detection of specific polymorphic markers and/or haplotypes, the nucleic acid sample comprises genomic DNA. Such a nucleic acid sample can be obtained from any source that contains genomic DNA, including as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from
25 skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs.

The term "Type 2 diabetes therapeutic agent" refers to an agent that can be used to ameliorate or prevent symptoms associated with Type 2 diabetes.

The term "Type 2 diabetes-associated nucleic acid", as described herein, refers to
30 a nucleic acid that has been found to be associated to Type 2 diabetes. This includes, but is not limited to, the markers and haplotypes described herein and markers and haplotypes in strong linkage disequilibrium (LD) therewith. In one embodiment, a Type 2 diabetes-associated nucleic acid refers to an LD-block found to be associated with Type 2 diabetes through at least one polymorphic marker located within the LD block.

35 The term "non-obese" refers, as described herein, to an individual with calculated Body Mass Index (BMI) below a pre-determined threshold, such as a threshold of 30 or

lower. Other thresholds useful for defining the term are also possible, as described in more detail herein. The formula for calculating BMI is given by $[\text{body weight (in kg)}]/[\text{height (in m)}]^2$. The term "obese" refers to an individual with BMI above a certain pre-determined threshold, such as a threshold of 30.

5 The term "LD Block C06", as described herein, refers to the Linkage Disequilibrium (LD) block on Chromosome 6 between markers rs4429936 and rs6908425, corresponding to position 20,634,996 – 20,836,710 of NCBI (National Center for Biotechnology Information) Build 35 (SEQ ID NO:1).

10 The term "LD Block C10", as described herein, refers to the Linkage Disequilibrium (LD) block on Chromosome 10 between markers rs2798253 and rs11187152, corresponding to position 94,192,885 – 94,490,091 of NCBI (National Center for Biotechnology Information) Build 35 (SEQ ID NO:2).

15 The term "LD Block C17", as described herein, refers to the Linkage Disequilibrium (LD) block on Chromosome 17 between markers rs11077501 and rs4793497, corresponding to position 66,037,656 – 66,163,076 of NCBI (National Center for Biotechnology Information) Build 35 (SEQ ID NO:3).

 The term "CDKAL1", as described herein, refers to the CDK5 regulatory subunit associated protein 1-like 1 gene, which spans locations 20,642,736 – 21,340,611 in NCBI Build 35 of the human genome.

20 The term "SLC30A8", as described herein, refers to the Solute Carrier Family 30, member 8, gene. This gene is located on chromosome 8, its longest isoform spanning as much as 225kb between positions 118,032,398 and 118,258,134 in NCBI Build 36 of the human genome assembly, corresponding to position 117,919,805 and 118,145,541, respectively in NCBI Build 34. In both these builds, the gene spans 225,736 bp of
25 genomic sequence.

 Through genotyping of Icelandic Type 2 diabetes patients and population control individuals using the Illumina 330K chip that can be used to measure over 300,000 SNPs in the genome simultaneously, a number of variants associated with Type 2 diabetes have
30 been identified by the present invention. Association analysis using single SNPs, two marker haplotypes and extended haplotypes within areas of extensive linkage disequilibrium (LD blocks) was performed across the genome. After correcting the p-value for relatedness, 49 single markers and two marker haplotypes were initially identified at 21 loci (i.e. genetic susceptibility locations in the genome) that had a p-value
35 less than 5×10^{-5} (Table 1). In addition, 10 extended haplotypes at 8 additional loci were

selected by the same criteria (Table 2). Within the patient group, 700 individuals were non-obese (BMI<30) and those were tested separately for association. After correcting the p-value for relatedness, 36 single markers and two marker haplotypes at 20 loci had a p-value less than 5×10^{-5} (Table 3). Three of those loci were also identified when the total group was analyzed. In addition, 6 extended haplotypes at 4 additional loci were selected by the same criteria (Table 4). The obese group of 531 patients (BMI >30) was also analyzed separately for association. After correcting the p-value for relatedness, 38 single markers and two marker haplotypes at 16 loci had a p-value less than 5×10^{-5} (Table 5). One of those loci was also identified when the total group was analyzed but no overlap was found between the non-obese and obese groups using this criteria. In addition 10 extended haplotypes at 7 additional loci had a p-value less than 5×10^{-5} in association analysis of obese diabetics (Table 6).

These single-marker association and two-marker and extended haplotype association results represent evidence for multiple susceptibility variants for Type 2 diabetes. It should be noted that for single-marker SNP analysis as presented herein, susceptibility variants can be represented by increased risk, wherein one allele is overrepresented in the patient group compared with controls. Alternatively, the susceptibility variants can be represented by the other allele of the SNP in question – for that allele, under-representation in patients compared with controls is expected. This is a natural consequence of association analysis to genetic elements comprising two alleles. For multi-marker haplotypes or for polymorphic markers comprising more than one marker, at-risk association may be observed to one (or more) at-risk allele or haplotype. Protective variants in form of association (with RR-values less than unity) to one (or more) protective variants or haplotypes may also be observed, depending on the genetic composition and haplotype structure in the genetic region in question.

One of the most significant association signals was identified by two single markers (rs1569699 and rs7756992) and three 2 marker haplotypes mapping to chromosome 6p22.3 (3 rs7758851 2 rs1569699, 1 rs4712527 3 rs7756992, 1 rs7756992 3 rs9295478 ; see Table 3). These markers are located within an area of extensive LD (LD block) between position 20634996 and 20836710 on chromosome 6 (NCBI Build 35; SEQ ID NO:1) between markers rs4429936 and rs6908425 (Figure 1). This region contains the 5' end including exons 1-5 of the gene CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1) (NM_017774). The association of these markers was verified in two additional Type 2 diabetes cohorts (see Table 7).

Follow up studies of the association of rs7756992 allele G with increased risk of Type 2 diabetes have established association of the marker to Type 2 diabetes in individuals of European ancestry (allele specific odds ratio (OR) = 1.16; $P = 3.9 \times 10^{-10}$), in individuals from Hong Kong of Han Chinese ancestry (OR = 1.25; $P = 0.00018$) (see

Tables 14, 15 and 17). Additional variants within LD block C06 (SEQ ID NO:1) in LD with rs7756992 that have also been shown to be associated with Type 2 diabetes in European and Chinese populations include rs1569699, rs7752906, rs9350271, rs9356744, rs9368222, rs10440833 and rs6931514 (Table 18). The genotype odds ratio of the rs7756992 allele G variant supports a nearly recessive mode of inheritance (Table 20). In particular, the OR for the homozygote is 1.45 and 1.55 in the European and Hong Kong groups, respectively. The rs7756992 allele G at-risk variant has been found to be correlated with decreased insulin response in carriers (Table 21, Figures 7 and 8). Homozygous carriers of the variant have been found to have an estimated 24% less insulin response than heterozygotes or non-carriers suggesting that this variant confers risk of T2D through reduced insulin secretion. The rs7756992 marker, and markers in linkage disequilibrium therewith (including, but not limited to, rs1569699, rs7752906, rs9350271, rs9356744, rs9368222, rs10440833 and rs6931514) can therefore be used to assess increased susceptibility to Type 2 diabetes in an individual.

The function of the gene product of *CDKAL1* is not known. However, as implied in the gene name the protein product is similar to another protein, CDK5 regulatory subunit associated protein 1 (*CDK5RAP1*). *CDK5RAP1* is expressed in neuronal tissues where it inhibits cyclin dependent kinase 5 (CDK5) activity by binding to the CDK5 regulatory subunit p35 (Ching, Y.P., Pang, A.S., Lam, W.H., Qi, R.Z. & Wang, J.H. *J Biol Chem* **277**, 15237-40 (2002)). In pancreatic beta cells, CDK5 has been shown to play a role in the loss of beta cell function under glucotoxic conditions (Wei, F.Y. et al. *Nat Med* **11**, 1104-8 (2005). Furthermore, inhibition of the CDK5/p35 complex prevents decrease of insulin gene expression that results from glucotoxicity (Ubeda, M., Rukstalis, J.M. & Habener, J.F. *J Biol Chem* **281**, 28858-64 (2006)). *CDKAL1* might play a role in the inhibition of CDK5/p35 in pancreatic beta cells similar to that of *CDK5RAP1* in neuronal tissue. Reduced expression of *CDKAL1* or reduced inhibitory function thus could lead to an impaired response to glucotoxicity. The present data shows that *CDKAL1* is expressed in the rat pancreatic beta cell line INS-1 (Figure 6).

Based on the predicted function of *CDKAL1* and known function of *SLC30A8* we would expect both rs7756992 and rs13266634 to affect insulin secretion. To evaluate the effects of the two SNPs on insulin secretion we analyzed the effect of genotype status on corrected insulin response (CIR) in a set of individuals from the Inter99 study (part of Denmark B) that had undergone an oral glucose tolerance test (OGTT). For rs7756992, we demonstrated that the homozygote carriers of the risk allele had an estimated 24% less CIR than the heterozygote carriers or non-carriers ($P < 0.00001$, Fig. 7). This observation is consistent with the variant's nearly recessive mode of inheritance with respect to disease risk. Furthermore, the effect observed on CIR is present in both males and females (Figure 8) and in T2D patients as well as controls, and adjusting for BMI status did not affect the results (Table 21). The effect of rs13266634 on insulin response

was smaller but significant and for this risk variant the reduction in CIR was consistent with an additive effect. No effect on insulin sensitivity was observed for either variant (Table 21).

5 The identification of *CDKAL1* as a susceptibility gene for T2D adds a new piece to the puzzle of how genetic factors may predispose to T2D. Although the function of this gene remains to be elucidated we have shown that it is expressed in pancreatic beta cells and that a variant within the gene is correlated with insulin secretion. The similarity to CDK5RAP1 further indicates that CDKAL1 may facilitate insulin production under glucotoxic conditions through interaction with CDK5. In conclusion, we have identified a
10 variant in the *CDKAL1* gene that in a nearly recessive manner blunts the insulin response and predisposes to T2D.

The present invention has identified seven single markers and seven two marker haplotypes in a region on chromosome 10q23.33 to be associated with Type 2 diabetes (Table 1). Most of those markers are also associated to diabetes with elevated RR values
15 when obese patients are analyzed separately (Table 5). These markers are located within one LD block between positions 94192885 and 94490091 (NCBI Build 35), corresponding to the genomic segment bridged by markers rs2798253 and rs11187152 (Figure 2). This LD block contains three genes, Insulin-degrading enzyme (IDE) (NM_004969), Kinesin family member 11 (KIF11) (NM_004523) and Homeobox, hematopoietically expressed
20 (HHEX) (NM_002729).

IDE may belong to a protease family responsible for intercellular peptide signaling. Though its role in the cellular processing of insulin has not yet been defined, insulin-degrading enzyme is thought to be involved in the termination of the insulin response (Fakhrai-Rad et al, Human Molecular Genetics 9:2149-2158, 2000). Genetic analysis of
25 the diabetic GK rat has revealed 2 amino acid substitutions in the IDE gene (H18R and A890V) in the GK allele which reduced insulin-degrading activity by 31% in transfected cells. However, when the H18R and A890V variants were studied separately, no effects were observed, suggesting a synergistic effect of the 2 variants on insulin degradation. No effect on insulin degradation was observed in cell lysates, suggesting that the effect may
30 be coupled to receptor-mediated internalization of insulin. Congenic rats with the IDE GK allele displayed postprandial hyperglycemia, reduced lipogenesis in fat cells, blunted insulin-stimulated glucose transmembrane uptake, and reduced insulin degradation in isolated muscle. Analysis of additional rat strains demonstrated that the dysfunctional IDE allele was unique to GK rats. The authors concluded that IDE plays an important role in
35 the diabetic phenotype in GK rats. IDE has been studied as a candidate gene for Type 2 diabetes in humans with inconsistent results. Two large studies have recently analyzed the association of IDE to Type 2 diabetes by mutation screening and haplotype analysis using tagging SNPs over the gene (Groves et al, Diabetes 52:1300-1305, 2003; Florez et

al, Diabetes 55:128-135, 2006). Both studies conclude that common variants in IDE are unlikely to confer significant risk of Type 2 diabetes. These studies did however, not include the whole LD block as defined in figure 2 and at least some of the markers identified in our study as associated with Type 2 diabetes are outside the regions analyzed in those previous studies. Based on the results reported here, markers in LD with IDE are associated with Type 2 diabetes, providing genetic evidence for the role of IDE in the etiology of Type 2 diabetes.

KIF11 encodes a motor protein that belongs to the kinesin-like protein family. Members of this protein family are known to be involved in various kinds of spindle dynamics. The function of this gene product includes chromosome positioning, centrosome separation and establishing a bipolar spindle during cell mitosis. This gene is not a good functional candidate for diabetes but has to be considered as a positional candidate due to its location within the associated LD block.

HHEX encodes a member of the homeobox family of transcription factors, many of which are involved in developmental processes. Expression in specific hematopoietic lineages suggests that this protein may play a role in hematopoietic differentiation. HHEX is essential for pancreatic development; in HHEX negative mouse embryos there is a complete failure in ventral pancreatic specification (Bort et al, Development 131, 797-806, 2004). Other transcription factors involved in pancreatic development include the MODY genes as well as other factors that have been implicated in late onset diabetes. HHEX is also an essential effector of Wnt antagonist for heart induction (Foley and Mercola, GENES & DEVELOPMENT 19:387-396, 2005). This puts HHEX in the same pathway as the recently established Type 2 diabetes gene TCF7L2 and together these data make HHEX a functional as well as positional candidate for Type 2 diabetes.

The association of rs2497304, rs947591, rs10882091 and rs7914814 to Type 2 diabetes was verified in a Danish Type 2 diabetes case – control cohort and also in a US Caucasian cohort Type 2 diabetes cohort from the PENN CATH study (Table 8). When the two cohorts are combined the association of rs947591 reaches significance at the 0.05 level, with a risk of 1.1 in the combined cohort. When all the cohorts are combined the risk is 1.15 for the rs947591 marker. These results indicate that variants within the LD block on Chromosome 10 that includes IDE and HHEX are susceptibility variants for Type 2 diabetes.

Five single markers and two marker haplotypes in a region of chromosome 17q24.3 were furthermore found to be associated with Type 2 diabetes in non-obese patients (Table 3). Some of these markers show the strongest association reported in Table 3 and association to this region was also observed when all diabetics were analyzed (Table 1). These markers are located within two adjacent LD blocks located between

positions 66037656 and 66163076 (NCBI Build 35) on chromosome 17, between markers rs11077501 and rs4793497 (Figure 3). The association is significant at the genome-wide level. No known genes are located within these LD blocks. However, it is possible that variants in this region affect genes in neighboring regions including KCNJ2 and KCNJ16.

5 Alternatively these variants may affect unknown genes within these LD blocks.

Further evidence for the association of rs7756992, and correlated markers within the LD block C06 that contains the 5' end including exons 1-5 of the CDKAL1 gene (NM_017774) on chromosome 6p22.3, with Type 2 diabetes has come from additional association studies. Two equivalent markers, rs7754840 and rs10946398, highly
10 correlated with rs7756992 (r^2 0,68; D' 0,95) were shown to be significantly associated with Type II diabetes in three large studies (Saxena, R et al. Science 2007;316:1331-6; Zeggini, E et al. Science 2007;316:1336-41; Scott, LJ et al. Science 2007;316:1341-5). These studies thus further support the involvement of the CDKAL gene in Type 2 diabetes.

Association of rs10882091 and correlated markers on chromosome 10q23.33 with
15 Type II diabetes is also supported by recent publications. A highly correlated marker, rs1111875 (r^2 0,51; $D' = 1$) was found to be significantly associated with Type II diabetes in four large studies (Sladek, R et al. Nature. 2007;445:828-30; Saxena, R et al. Science 2007;316:1331-6; Zeggini, E et al. Science 2007;316:1336-41; Scott, LJ et al. Science 2007;316:1341-5). Thus, recent studies provide additional support to the discoveries by
20 the present inventors that markers in the LD Block C10 region as described herein are risk factors for Type 2 diabetes.

The genomic sequence within populations is not identical when individuals are compared. Rather, the genome exhibits sequence variability between individuals at
25 many locations in the genome. Such variations in sequence are commonly referred to as polymorphisms, and there are many such sites within each genome. For example, the human genome exhibits sequence variations which occur on average every 500 base pairs. The most common sequence variant consists of base variations at a single base position in the genome, and such sequence variants, or polymorphisms, are commonly
30 called Single Nucleotide Polymorphisms ("SNPs"). These SNPs are believed to have occurred in a single mutational event, and therefore there are usually two possible alleles possible at each SNP site; the original allele and the mutated allele. Due to natural genetic drift and possibly also selective pressure, the original mutation has resulted in a polymorphism characterized by a particular frequency of its alleles in any given
35 population. Many other types of sequence variants are found in the human genome, including microsatellites, insertions, deletions, inversions and copy number variations. A polymorphic microsatellite has multiple small repeats of bases (such as CA repeats, TG on

the complimentary strand) at a particular site in which the number of repeat lengths varies in the general population. In general terms, each version of the sequence with respect to the polymorphic site represents a specific allele of the polymorphic site. These sequence variants can all be referred to as polymorphisms, occurring at specific polymorphic sites characteristic of the sequence variant in question. In general terms, polymorphisms can comprise any number of specific alleles. Thus in one embodiment of the invention, the polymorphism is characterized by the presence of two or more alleles in any given population. In another embodiment, the polymorphism is characterized by the presence of three or more alleles. In other embodiments, the polymorphism is characterized by four or more alleles, five or more alleles, six or more alleles, seven or more alleles, nine or more alleles, or ten or more alleles. All such polymorphisms can be utilized in the methods and kits of the present invention, and are thus within the scope of the invention.

In some instances, reference is made to different alleles at a polymorphic site without choosing a reference allele. Alternatively, a reference sequence can be referred to for a particular polymorphic site. The reference allele is sometimes referred to as the "wild-type" allele and it usually is chosen as either the first sequenced allele or as the allele from a "non-affected" individual (*e.g.*, an individual that does not display a trait or disease phenotype).

Alleles for SNP markers as referred to herein refer to the bases A, C, G or T as they occur at the polymorphic site in the SNP assay employed. The allele codes for SNPs used herein are as follows: 1 = A, 2 = C, 3 = G, 4 = T. The person skilled in the art will however realise that by assaying or reading the opposite DNA strand, the complementary allele can in each case be measured. Thus, for a polymorphic site (polymorphic marker) characterized by an A/G polymorphism, the assay employed may be designed to specifically detect the presence of one or both of the two bases possible, *i.e.* A and G. Alternatively, by designing an assay that is designed to detect the opposite strand on the DNA template, the presence of the complementary bases T and C can be measured. Quantitatively (for example, in terms of relative risk), identical results would be obtained from measurement of either DNA strand (+ strand or - strand).

Typically, a reference sequence is referred to for a particular sequence. Alleles that differ from the reference are sometimes referred to as "variant" alleles. A variant sequence, as used herein, refers to a sequence that differs from the reference sequence but is otherwise substantially similar. Alleles at the polymorphic genetic markers described herein are variants. Additional variants can include changes that affect a polypeptide. Sequence differences, when compared to a reference nucleotide sequence, can include the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift; the change of at least one nucleotide, resulting in a

change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of a reading frame; duplication of all or a part of a sequence; transposition; or a rearrangement of a nucleotide sequence,. Such sequence changes can alter the polypeptide encoded by the nucleic acid. For example, if the change in the nucleic acid sequence causes a frame shift, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or trait can be a synonymous change in one or more nucleotides (*i.e.*, a change that does not result in a change in the amino acid sequence). Such a polymorphism can, for example, alter splice sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of an encoded polypeptide. It can also alter DNA to increase the possibility that structural changes, such as amplifications or deletions, occur at the somatic level. The polypeptide encoded by the reference nucleotide sequence is the "reference" polypeptide with a particular reference amino acid sequence, and polypeptides encoded by variant alleles are referred to as "variant" polypeptides with variant amino acid sequences.

A haplotype refers to a segment of DNA that is characterized by a specific combination of alleles arranged along the segment. For diploid organisms such as humans, a haplotype comprises one member of the pair of alleles for each polymorphic marker or locus . In a certain embodiment, the haplotype can comprise two or more alleles, three or more alleles, four or more alleles, or five or more alleles, each allele corresponding to a specific polymorphic marker along the segment. Haplotypes can comprise a combination of various polymorphic markers, *e.g.*, SNPs and microsatellites, having particular alleles at the polymorphic sites. The haplotypes thus comprise a combination of alleles at various genetic markers.

Detecting specific polymorphic markers and/or haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites. For example, standard techniques for genotyping for the presence of SNPs and/or microsatellite markers can be used, such as fluorescence-based techniques (Chen, X. *et al.*, *Genome Res.* 9(5): 492-98 (1999)), utilizing PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. Specific methodologies available for SNP genotyping include, but are not limited to, TaqMan genotyping assays and SNPLEX platforms (Applied Biosystems), mass spectrometry (*e.g.*, MassARRAY system from Sequenom), mini-sequencing methods, real-time PCR, Bio-Plex system (BioRad), CEQ and SNPstream systems (Beckman), Molecular Inversion Probe array technology (*e.g.*, Affymetrix GeneChip), BeadArray Technologies (*e.g.*, Illumina GoldenGate and Infinium assays) and

Centaurus assay (Nanogen). By these or other methods available to the person skilled in the art, one or more alleles at polymorphic markers, including microsatellites, SNPs or other types of polymorphic markers, can be identified.

In certain methods described herein, an individual who is at an increased susceptibility (i.e., increased risk) for Type 2 diabetes, is an individual in whom at least one specific allele at one or more polymorphic marker or haplotype conferring increased susceptibility for Type 2 diabetes is identified (i.e., at-risk marker alleles or haplotypes). In one aspect, the at-risk marker or haplotype is one that confers a significant increased risk (or susceptibility) of Type 2 diabetes. In one embodiment, significance associated with a marker or haplotype is measured by a relative risk (RR). In another embodiment, significance associated with a marker or haplotype is measured by an odds ratio (OR). In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant increased risk is measured as a risk (relative risk and/or odds ratio) of at least 1.2, including but not limited to: at least 1.2, at least 1.3, at least 1.4, at least 1.5, at least 1.6, at least 1.7, 1.8, at least 1.9, at least 2.0, at least 2.5, at least 3.0, at least 4.0, and at least 5.0. In a particular embodiment, a risk (relative risk and/or odds ratio) of at least 1.2 is significant. In another particular embodiment, a risk of at least 1.3 is significant. In yet another embodiment, a risk of at least 1.4 is significant. In a further embodiment, a relative risk of at least about 1.5 is significant. In another further embodiment, a significant increase in risk is at least about 1.7 is significant. However, other cutoffs are also contemplated, e.g. at least 1.15, 1.25, 1.35, and so on, and such cutoffs are also within scope of the present invention. In other embodiments, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 300%, and 500%. In one particular embodiment, a significant increase in risk is at least 20%. In other embodiments, a significant increase in risk is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% and at least 100%. Other cutoffs or ranges as deemed suitable by the person skilled in the art to characterize the invention are however also contemplated, and those are also within scope of the present invention.

An at-risk polymorphic marker or haplotype of the present invention is one where at least one allele of at least one marker or haplotype is more frequently present in an individual at risk for the disease or trait (affected), compared to the frequency of its presence in a comparison group (control), and wherein the presence of the marker or haplotype is indicative of susceptibility to the disease or trait. The control group may in one embodiment be a population sample, i.e. a random sample from the general population. In another embodiment, the control group is represented by a group of individuals who are disease-free. Such disease-free control may in one embodiment be characterized by the absence of one or more specific disease-associated symptoms. In

another embodiment, the disease-free control group is characterized by the absence of one or more disease-specific risk factors. Such risk factors are in one embodiment at least one environmental risk factor. Representative environmental factors are natural products, minerals or other chemicals which are known to affect, or contemplated to affect, the risk of developing the specific disease or trait. Other environmental risk factors are risk factors related to lifestyle, including but not limited to food and drink habits, geographical location of main habitat, and occupational risk factors. In another embodiment, the risk factors are at least one genetic risk factor.

As an example of a simple test for correlation would be a Fisher-exact test on a two by two table. Given a cohort of chromosomes, the two by two table is constructed out of the number of chromosomes that include both of the markers or haplotypes, one of the markers or haplotypes but not the other and neither of the markers or haplotypes.

In other embodiments of the invention, an individual who is at a decreased susceptibility (i.e., at a decreased risk) for Type 2 diabetes is an individual in whom at least one specific allele at one or more polymorphic marker or haplotype conferring decreased susceptibility for Type 2 diabetes is identified. The marker alleles and/or haplotypes conferring decreased risk are also said to be protective. In one aspect, the protective marker or haplotype is one that confers a significant decreased risk (or susceptibility) of the disease or trait. In another embodiment, the absence of an at-risk allele in a nucleic acid sample from the individual is also indicative of a protection against disease, by virtue of the absence of at-risk alleles. In one embodiment, significant decreased risk is measured as a relative risk of less than 0.9, including but not limited to less than 0.9, less than 0.8, less than 0.7, less than 0.6, less than 0.5, less than 0.4, less than 0.3, less than 0.2 and less than 0.1. In one particular embodiment, significant decreased risk is less than 0.7. In another embodiment, significant decreased risk is less than 0.5. In yet another embodiment, significant decreased risk is less than 0.3. In another embodiment, the decrease in risk (or susceptibility) is at least 20%, including but not limited to at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% and at least 98%. In one particular embodiment, a significant decrease in risk is at least about 30%. In another embodiment, a significant decrease in risk is at least about 50%. In another embodiment, the decrease in risk is at least about 70%. Other cutoffs or ranges as deemed suitable by the person skilled in the art to characterize the invention are however also contemplated, and those are also within scope of the present invention.

The person skilled in the art will appreciate that for markers with two alleles present in the population being studied (such as SNPs), and wherein one allele is found in increased frequency in a group of individuals with a trait or disease in the population, compared with controls, the other allele of the marker will be found in decreased frequency in the group of

individuals with the trait or disease, compared with controls. In such a case, one allele of the marker (the one found in increased frequency in individuals with the trait or disease) will be the at-risk allele, while the other allele will be a protective allele.

5 *Linkage Disequilibrium*

The natural phenomenon of recombination, which occurs on average once for each chromosomal pair during each meiotic event, represents one way in which nature provides variations in sequence (and biological function by consequence). It has been discovered that recombination does not occur randomly in the genome; rather, there are large variations in the frequency of recombination rates, resulting in small regions of high recombination frequency (also called recombination hotspots) and larger regions of low recombination frequency, which are commonly referred to as Linkage Disequilibrium (LD) blocks (Myers, S. *et al.*, *Biochem Soc Trans* 34:526-530 (2006); Jeffreys, A.J., *et al.*, *Nature Genet* 29:217-222 (2001); May, C.A., *et al.*, *Nature Genet* 31:272-275(2002)).

Linkage Disequilibrium (LD) refers to a non-random assortment of two genetic elements. For example, if a particular genetic element (*e.g.*, an allele of a polymorphic marker, or a haplotype) occurs in a population at a frequency of 0.50 (50%) and another element occurs at a frequency of 0.50 (50%), then the predicted occurrence of a person's having both elements is 0.25 (25%), assuming a random distribution of the elements. However, if it is discovered that the two elements occur together at a frequency higher than 0.25, then the elements are said to be in linkage disequilibrium, since they tend to be inherited together at a higher rate than what their independent frequencies of occurrence (*e.g.*, allele or haplotype frequencies) would predict. Roughly speaking, LD is generally correlated with the frequency of recombination events between the two elements. Allele or haplotype frequencies can be determined in a population by genotyping individuals in a population and determining the frequency of the occurrence of each allele or haplotype in the population. For populations of diploids, *e.g.*, human populations, individuals will typically have two alleles for each genetic element (*e.g.*, a marker, haplotype or gene).

Many different measures have been proposed for assessing the strength of linkage disequilibrium (LD). Most capture the strength of association between pairs of biallelic sites. Two important pairwise measures of LD are r^2 (sometimes denoted Δ^2) and $|D'|$. Both measures range from 0 (no disequilibrium) to 1 ('complete' disequilibrium), but their interpretation is slightly different. $|D'|$ is defined in such a way that it is equal to 1 if just two or three of the possible haplotypes are present, and it is <1 if all four possible haplotypes are present. Therefore, a value of $|D'|$ that is <1 indicates that historical recombination may have occurred between two sites (recurrent mutation can also cause

$|D'|$ to be <1 , but for single nucleotide polymorphisms (SNPs) this is usually regarded as being less likely than recombination). The measure r^2 represents the statistical correlation between two sites, and takes the value of 1 if only two haplotypes are present.

The r^2 measure is arguably the most relevant measure for association mapping, because there is a simple inverse relationship between r^2 and the sample size required to detect association between susceptibility loci and SNPs. These measures are defined for pairs of sites, but for some applications a determination of how strong LD is across an entire region that contains many polymorphic sites might be desirable (e.g., testing whether the strength of LD differs significantly among loci or across populations, or whether there is more or less LD in a region than predicted under a particular model). Measuring LD across a region is not straightforward, but one approach is to use the measure r , which was developed in population genetics. Roughly speaking, r measures how much recombination would be required under a particular population model to generate the LD that is seen in the data. This type of method can potentially also provide a statistically rigorous approach to the problem of determining whether LD data provide evidence for the presence of recombination hotspots. For the methods, kits, procedures, media and apparatus described herein, a significant r^2 value can be at least 0.05, such as at least 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99 or 1.0. In one preferred embodiment, the significant r^2 value can be at least 0.2. Alternatively, linkage disequilibrium as described herein, refers to linkage disequilibrium characterized by values of $|D'|$ of at least 0.2, such as 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.85, 0.9, 0.95, 0.96, 0.97, 0.98, 0.99. Thus, linkage disequilibrium represents a correlation between alleles of distinct markers. It is measured by correlation coefficient or $|D'|$ (r^2 up to 1.0 and $|D'|$ up to 1.0). In certain embodiments, linkage disequilibrium is defined in terms of values for both the r^2 and $|D'|$ measures. In one such embodiment, a significant linkage disequilibrium is defined as $r^2 > 0.1$ and $|D'| > 0.8$. In another embodiment, a significant linkage disequilibrium is defined as $r^2 > 0.2$ and $|D'| > 0.9$. Other combinations and permutations of values of r^2 and $|D'|$ for determining linkage disequilibrium are also possible, and within the scope of the invention. Linkage disequilibrium can be determined in a single human population, as defined herein, or it can be determined in a collection of samples comprising individuals from more than one human population. In one embodiment of the invention, LD is determined in a sample from one or more of the HapMap populations (caucasian, african, japanese, chinese), as defined (<http://www.hapmap.org>). In one such embodiment, LD is determined in the CEU population of the HapMap samples. In another embodiment, LD is determined in the YRI population. In yet another embodiment, LD is determined in samples from the Icelandic population.

If all polymorphisms in the genome were identical at the population level, then every single one of them would need to be investigated in association studies. However, due to linkage disequilibrium between polymorphisms, tightly linked polymorphisms are strongly correlated, which reduces the number of polymorphisms that need to be
5 investigated in an association study to observe a significant association. Another consequence of LD is that many polymorphisms may give an association signal due to the fact that these polymorphisms are strongly correlated.

Genomic LD maps have been generated across the genome, and such LD maps have been proposed to serve as framework for mapping disease-genes (Risch, N. &
10 Merkiangas, K, *Science* 273:1516-1517 (1996); Maniatis, N., *et al.*, *Proc Natl Acad Sci USA* 99:2228-2233 (2002); Reich, DE *et al.*, *Nature* 411:199-204 (2001)).

It is now established that many portions of the human genome can be broken into series of discrete haplotype blocks containing a few common haplotypes; for these blocks, linkage disequilibrium data provides little evidence indicating recombination (see, e.g.,
15 Wall., J.D. and Pritchard, J.K., *Nature Reviews Genetics* 4:587-597 (2003); Daly, M. *et al.*, *Nature Genet.* 29:229-232 (2001); Gabriel, S.B. *et al.*, *Science* 296:2225-2229 (2002); Patil, N. *et al.*, *Science* 294:1719-1723 (2001); Dawson, E. *et al.*, *Nature* 418:544-548 (2002); Phillips, M.S. *et al.*, *Nature Genet.* 33:382-387 (2003)).

There are two main methods for defining these haplotype blocks: blocks can be
20 defined as regions of DNA that have limited haplotype diversity (see, e.g., Daly, M. *et al.*, *Nature Genet.* 29:229-232 (2001); Patil, N. *et al.*, *Science* 294:1719-1723 (2001); Dawson, E. *et al.*, *Nature* 418:544-548 (2002); Zhang, K. *et al.*, *Proc. Natl. Acad. Sci. USA* 99:7335-7339 (2002)), or as regions between transition zones having extensive historical recombination, identified using linkage disequilibrium (see, e.g., Gabriel, S.B. *et al.*, *Science* 296:2225-2229 (2002); Phillips, M.S. *et al.*, *Nature Genet.* 33:382-387
25 (2003); Wang, N. *et al.*, *Am. J. Hum. Genet.* 71:1227-1234 (2002); Stumpf, M.P., and Goldstein, D.B., *Curr. Biol.* 13:1-8 (2003)). More recently, a fine-scale map of recombination rates and corresponding hotspots across the human genome has been generated (Myers, S., *et al.*, *Science* 310:321-32324 (2005); Myers, S. *et al.*, *Biochem*
30 *Soc Trans* 34:526530 (2006)). The map reveals the enormous variation in recombination across the genome, with recombination rates as high as 10-60 cM/Mb in hotspots, while closer to 0 in intervening regions, which thus represent regions of limited haplotype diversity and high LD. The map can therefore be used to define haplotype blocks/LD blocks as regions flanked by recombination hotspots. As used herein, the terms
35 "haplotype block" or "LD block" includes blocks defined by any of the above described characteristics, or other alternative methods used by the person skilled in the art to define such regions.

Haplotype blocks can be used to map associations between phenotype and haplotype status, using single markers or haplotypes comprising a plurality of markers. The main haplotypes can be identified in each haplotype block, and then a set of "tagging" SNPs or markers (the smallest set of SNPs or markers needed to distinguish among the haplotypes) can then be identified. These tagging SNPs or markers can then be used in assessment of samples from groups of individuals, in order to identify association between phenotype and haplotype. If desired, neighboring haplotype blocks can be assessed concurrently, as there may also exist linkage disequilibrium among the haplotype blocks.

It has thus become apparent that for any given observed association to a polymorphic marker in the genome, it is likely that additional markers in the genome also show association. This is a natural consequence of the uneven distribution of LD across the genome, as observed by the large variation in recombination rates. The markers used to detect association thus in a sense represent "tags" for a genomic region (i.e., a haplotype block or LD block) that is associating with a given disease or trait, and as such are useful for use in the methods and kits of the present invention. One or more causative (functional) variants or mutations may reside within the region found to be associating to the disease or trait. Such variants may confer a higher relative risk (RR) or odds ratio (OR) than observed for the tagging markers used to detect the association. The present invention thus refers to the markers used for detecting association to the disease, as described herein, as well as markers in linkage disequilibrium with the markers. Thus, in certain embodiments of the invention, markers that are in LD with the markers and/or haplotypes of the invention, as described herein, may be used as surrogate markers. The surrogate markers have in one embodiment relative risk (RR) and/or odds ratio (OR) values smaller than for the markers or haplotypes initially found to be associating with the disease, as described herein. In other embodiments, the surrogate markers have RR or OR values greater than those initially determined for the markers initially found to be associating with the disease, as described herein. An example of such an embodiment would be a rare, or relatively rare (< 10% allelic population frequency) variant in LD with a more common variant (> 10% population frequency) initially found to be associating with the disease, such as the variants described herein. Identifying and using such markers for detecting the association discovered by the inventors as described herein can be performed by routine methods well known to the person skilled in the art, and are therefore within the scope of the present invention.

It is possible that certain polymorphic markers in linkage disequilibrium with the markers shown herein to be associated with Type 2 diabetes are located outside the physical boundaries of the LD block as defined. This is a consequence of the historical recombination rates in the region in question, which may have led to a region of strong LD (the LD block), with residual markers outside the block in LD with markers within the

block. Such markers are also within scope of the present invention, as they are equally useful for practicing the invention by virtue of their genetic relationship with the markers shown herein to be associated with Type 2 diabetes. Examples are shown in Table 22 (rs17234378; SEQ ID NO:44), Table 23 (rs7086285; SEQ ID NO:43) and Table 24 (rs9890889; SEQ ID NO:31; rs2009802; SEQ ID NO:38; rs17718938; SEQ ID NO:39; ,
5 rs2109050; SEQ ID NO:41; rs1962801; SEQ ID NO:42.

Determination of haplotype frequency

The frequencies of haplotypes in patient and control groups can be estimated
10 using an expectation-maximization algorithm (Dempster A. *et al.*, *J. R. Stat. Soc. B*, 39:1-38 (1977)). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase can be used. Under the null hypothesis, the patients and the controls are assumed to have identical frequencies. Using a likelihood approach, an alternative hypothesis is tested, where a candidate at-risk-haplotype, which can include
15 the markers described herein, is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses and a corresponding 1-df likelihood ratio statistic is used to evaluate the statistical significance.

To look for at-risk and protective markers and haplotypes within a region of
20 interest, for example, association of all possible combinations of genotyped markers is studied, provided those markers span a practical region. The combined patient and control groups can be randomly divided into two sets, equal in size to the original group of patients and controls. The marker and haplotype analysis is then repeated and the most significant p-value registered is determined. This randomization scheme can be repeated,
25 for example, over 100 times to construct an empirical distribution of p-values. In a preferred embodiment, a p-value of <0.05 is indicative of a significant marker and/or haplotype association.

Haplotype Analysis

One general approach to haplotype analysis involves using likelihood-based
30 inference applied to NEsted MOdels (Gretarsdottir S., *et al.*, *Nat. Genet.* 35:131-38 (2003)). The method is implemented in the program NEMO, which allows for many polymorphic markers, SNPs and microsatellites. The method and software are specifically designed for case-control studies where the purpose is to identify haplotype groups that
35 confer different risks. It is also a tool for studying LD structures. In NEMO, maximum

likelihood estimates, likelihood ratios and p-values are calculated directly, with the aid of the EM algorithm, for the observed data treating it as a missing-data problem.

Even though likelihood ratio tests based on likelihoods computed directly for the observed data, which have captured the information loss due to uncertainty in phase and missing genotypes, can be relied on to give valid p-values, it would still be of interest to know how much information had been lost due to the information being incomplete. The information measure for haplotype analysis is described in Nicolae and Kong (Technical Report 537, Department of Statistics, University of Statistics, University of Chicago; *Biometrics*, 60(2):368-75 (2004)) as a natural extension of information measures defined for linkage analysis, and is implemented in NEMO.

For single marker association to a disease or trait (e.g., Type 2 diabetes), the Fisher exact test can be used to calculate two-sided p-values for each individual allele. Usually, all p-values are presented unadjusted for multiple comparisons unless specifically indicated. The presented frequencies (for microsatellites, SNPs and haplotypes) are allelic frequencies as opposed to carrier frequencies. To minimize any bias due the relatedness of the patients who were recruited as families for the linkage analysis, first and second-degree relatives can be eliminated from the patient list. Furthermore, the test can be repeated for association correcting for any remaining relatedness among the patients, by extending a variance adjustment procedure described in Risch, N. & Teng, J. (*Genome Res.*, 8:1273-1288 (1998)), DNA pooling (*ibid*) for sibships so that it can be applied to general familial relationships, and present both adjusted and unadjusted p-values for comparison. The differences are in general very small as expected. To assess the significance of single-marker association corrected for multiple testing we can carry out a randomization test using the same genotype data. Cohorts of patients and controls can be randomized and the association analysis redone multiple times (e.g., up to 500,000 times) and the p-value is the fraction of replications that produced a p-value for some marker allele that is lower than or equal to the p-value we observed using the original patient and control cohorts.

For both single-marker and haplotype analyses, relative risk (RR) and the population attributable risk (PAR) can be calculated assuming a multiplicative model (haplotype relative risk model) (Terwilliger, J.D. & Ott, J., *Hum. Hered.* 42:337-46 (1992) and Falk, C.T. & Rubinstein, P, *Ann. Hum. Genet.* 51 (Pt 3):227-33 (1987)), i.e., that the risks of the two alleles/haplotypes a person carries multiply. For example, if RR is the risk of A relative to a, then the risk of a person homozygote AA will be RR times that of a heterozygote Aa and RR^2 times that of a homozygote aa. The multiplicative model has a nice property that simplifies analysis and computations — haplotypes are independent, i.e., in Hardy-Weinberg equilibrium, within the affected population as well as within the control population. As a consequence, haplotype counts of the affecteds and controls

each have multinomial distributions, but with different haplotype frequencies under the alternative hypothesis. Specifically, for two haplotypes, h_i and h_j , $\text{risk}(h_i)/\text{risk}(h_j) = (f_i/p_i)/(f_j/p_j)$, where f and p denote, respectively, frequencies in the affected population and in the control population. While there is some power loss if the true model is not
 5 multiplicative, the loss tends to be mild except for extreme cases. Most importantly, p -values are always valid since they are computed with respect to null hypothesis.

Risk assessment and Diagnostics

As described herein, certain polymorphic markers and haplotypes comprising such
 10 markers are found to be useful for risk assessment of Type 2 diabetes. Risk assessment can involve the use of the markers for diagnosing a susceptibility to Type 2 diabetes. Particular alleles of polymorphic markers are found more frequently in individuals with Type 2 diabetes, than in individuals without diagnosis of Type 2 diabetes. Therefore, these marker alleles have predictive value for detecting Type 2 diabetes, or a
 15 susceptibility to Type 2 diabetes, in an individual. Tagging markers within haplotype blocks or LD blocks comprising at-risk markers, such as the markers of the present invention, can be used as surrogates for other markers and/or haplotypes within the haplotype block or LD block. Markers with values of r^2 equal to 1 are perfect surrogates for the at-risk variants, i.e. genotypes for one marker perfectly predicts genotypes for the
 20 other. Markers with smaller values of r^2 than 1 can also be surrogates for the at-risk variant, or alternatively represent variants with relative risk values as high as or possibly even higher than the at-risk variant.

The at-risk variant identified may not be the functional variant itself, but is in this instance in linkage disequilibrium with the true functional variant. The present invention
 25 encompasses the assessment of such surrogate markers for the markers as disclosed herein. Such markers are annotated, mapped and listed in public databases (e.g., dbSNP), as well known to the skilled person, or can alternatively be readily identified by sequencing the region or a part of the region identified by the markers of the present invention in a group of individuals, and identify polymorphisms in the resulting group of
 30 sequences. As a consequence, the person skilled in the art can readily and without undue experimentation genotype surrogate markers in linkage disequilibrium with the markers and/or haplotypes as described herein. The tagging or surrogate markers in LD with the at-risk variants detected, also have predictive value for detecting association to Type 2 diabetes, or a susceptibility to Type 2 diabetes, in an individual.

35 The markers and haplotypes as described herein, e.g., the markers presented in Tables 1 - 24, may be useful for risk assessment and diagnostic purposes for, either alone or in combination. The markers and haplotypes can also be combined with other markers

conferring increased risk for Type 2 diabetes. Even in cases where the increase in risk by individual markers is relatively modest, i.e. on the order of 10-30%, the association may have significant implications. Thus, relatively common variants may have significant contribution to the overall risk (Population Attributable Risk is high), or combination of markers can be used to define groups of individual who, based on the combined risk of the markers, is at significant combined risk of developing the disease. The markers described herein to be associated with Type 2 diabetes can therefore be combined with other polymorphic markers or haplotypes reported or found to be associated with Type 2 diabetes, so as to obtain an overall risk of the disease based on a plurality of genetic markers.

In one such embodiment, the polymorphic markers or haplotypes described herein are assessed together with information about markers within the TCF7L2 gene. Association of variants within this gene is well established (Grant S.F., *et al.*, *Nat Genet.* - 38:320-3 (2006)) and has been replicated in a large number of populations (Florez, J.C., *Curr Opin Clin Nutr Metabol Care* 10:391-396 (2007)). The marker rs7903146 within the TCF7L2 gene, or other markers in LD with the marker (e.g., rs12255372) can be used to determine the genetic risk conferred by the at-risk variant in the gene (OR about 1.44).

Markers in other genes have recently been implicated in the etiology of Type 2 diabetes as risk factors, including PPARG (rs1801282), KCNJ11 (rs5215), TCF2 (rs4430796), WFS1 (rs10010131), CDKN2A-2B (rs1081161), IGF2BP2 (rs4402960) and FTO (rs805136) (Frayling, T.M. *Nature Reviews Genetics* 8:657-662 (2007)). These markers, or markers in linkage disequilibrium therewith can likewise also be used in methods combining determination of the presence or absence of at-risk variants for Type 2 diabetes with the variants reported herein, so as to obtain an overall risk assessment of Type 2 diabetes.

Thus, in one embodiment of the invention, a plurality of variants (genetic markers and/or biomarkers and/or haplotypes) is used for overall risk assessment. These variants are in one embodiment selected from the variants as disclosed herein. Other embodiments include the use of the variants of the present invention in combination with other variants known to be useful for diagnosing a susceptibility to Type 2 diabetes. In such embodiments, the genotype status of a plurality of markers and/or haplotypes is determined in an individual, and the status of the individual compared with the population frequency of the associated variants, or the frequency of the variants in clinically healthy subjects, such as age-matched and sex-matched subjects. Methods known in the art, such as multivariate analyses or joint risk analyses, may subsequently be used to determine the overall risk conferred based on the genotype status at the multiple loci. Assessment of risk based on such analysis may subsequently be used in the methods and kits of the invention, as described herein.

As described in the above, the haplotype block structure of the human genome has the effect that a large number of variants (markers and/or haplotypes) in linkage disequilibrium with the variant originally associated with a disease or trait may be used as surrogate markers for assessing association to the disease or trait. The number of such surrogate markers will depend on factors such as the historical recombination rate in the region, the mutational frequency in the region (i.e., the number of polymorphic sites or markers in the region), and the extent of LD (size of the LD block) in the region. These markers are usually located within the physical boundaries of the LD block or haplotype block in question as defined using the methods described herein, or by other methods known to the person skilled in the art. However, sometimes marker and haplotype association is found to extend beyond the physical boundaries of the haplotype block as defined. Such markers and/or haplotypes may in those cases be also used as surrogate markers and/or haplotypes for the markers and/or haplotypes physically residing within the haplotype block as defined. As a consequence, markers and haplotypes in LD (typically characterized by r^2 greater than 0.1, such as r^2 greater than 0.2, including r^2 greater than 0.3, also including r^2 greater than 0.4) with the markers and haplotypes of the present invention are also within the scope of the invention, even if they are physically located beyond the boundaries of the haplotype block as defined. This includes markers that are described herein (e.g., markers listed in Tables 22, 23 and 24), but may also include other markers that are in linkage disequilibrium (e.g., characterized by r^2 greater than 0.2 and/or $|D'| > 0.8$) with one or more of the markers listed in Tables 22, 23 and 24.

For the SNP markers described herein, the opposite allele to the allele found to be in excess in patients (at-risk allele) is found in decreased frequency in Type 2 diabetes. These markers and haplotypes in LD and/or comprising such markers, are thus protective for Type 2 diabetes, i.e. they confer a decreased risk or susceptibility of individuals carrying these markers and/or haplotypes developing Type 2 diabetes. Alternatively speaking, the absence of at-risk alleles of at-risk variants implies the presence of the alternate allele for biallelic markers such as SNPs. Thus, the absence of at-risk variants as described herein is indicative of a protection against Type 2 diabetes.

As described herein, haplotypes comprising a combination of genetic markers, e.g., SNPs and microsatellites, can be useful for risk assessment. Detecting haplotypes can be accomplished by methods known in the art and/or described herein for detecting sequences at polymorphic sites. Furthermore, correlation between certain haplotypes or sets of markers and disease phenotype can be verified using standard techniques. A representative example of a simple test for correlation would be a Fisher-exact test on a two by two table.

In specific embodiments, a marker or haplotype found to be associated with Type 2 diabetes, is one in which a marker or haplotype is more frequently present in an individual at risk for Type 2 diabetes (*e.g.*, an affected person), compared to the frequency of its presence in a healthy individual (control) or in a randomly selected individual from the population (population control), wherein the presence of the marker allele or haplotype is indicative of Type 2 diabetes or a susceptibility to Type 2 diabetes. In other embodiments, at-risk markers in linkage disequilibrium with one or more markers found to be associated with Type 2 diabetes are tagging markers that are more frequently present in an individual at risk for Type 2 diabetes (*e.g.*, affected individuals), compared to the frequency of their presence in controls, wherein the presence of the tagging markers is indicative of increased susceptibility to Type 2 diabetes. In a further embodiment, at-risk markers alleles (*i.e.* conferring increased susceptibility) in linkage disequilibrium with one or more markers found to be associated with Type 2 diabetes are markers comprising one or more allele that is more frequently present in an individual at risk for Type 2 diabetes, compared to the frequency of their presence in controls, wherein the presence of the markers is indicative of increased susceptibility to Type 2 diabetes.

Study population

In a general sense, the methods and kits of the invention can be utilized from samples containing genomic DNA from any source, *i.e.* any individual. In preferred embodiments, the individual is a human individual. The individual can be an adult, child, or fetus. The present invention also provides for assessing markers and/or haplotypes in individuals who are members of a target population. Such a target population is in one embodiment a population or group of individuals at risk of developing the disease, based on other genetic factors, biomarkers, biophysical parameters (*e.g.*, weight, BMD, blood pressure), or general health and/or lifestyle parameters (*e.g.*, history of disease or related diseases, previous diagnosis of disease, family history of disease).

The invention provides for embodiments that include individuals from specific age subgroups, such as those over the age of 40, over age of 45, or over age of 50, 55, 60, 65, 70, 75, 80, or 85. Other embodiments of the invention pertain to other age groups, such as individuals aged less than 85, such as less than age 80, less than age 75, or less than age 70, 65, 60, 55, 50, 45, 40, 35, or age 30. Other embodiments relate to individuals with age at onset of the disease in any of the age ranges described in the above. It is also contemplated that a range of ages may be relevant in certain embodiments, such as age at onset at more than age 45 but less than age 60. Other age ranges are however also contemplated, including all age ranges bracketed by the age

values listed in the above. The invention furthermore relates to individuals of either gender, males or females.

The Icelandic population is a Caucasian population of Northern European ancestry. A large number of studies reporting results of genetic linkage and association in the Icelandic population have been published in the last few years. Many of those studies show replication of variants, originally identified in the Icelandic population as being associating with a particular disease, in other populations (Stacey, S.N., *et al.*, *Nat Genet.* May 27 2007 (Epub ahead of print; Helgadóttir, A., *et al.*, *Science* **316**:1491-93 (2007); Steinthorsdóttir, V., *et al.*, *Nat Genet.* **39**:770-75 (2007); Gudmundsson, J., *et al.*, *Nat Genet.* **39**:631-37 (2007); Amundadóttir, L.T., *et al.*, *Nat Genet.* **38**:652-58 (2006); Grant, S.F., *et al.*, *Nat Genet.* **38**:320-23 (2006)). Thus, genetic findings in the Icelandic population have in general been replicated in other populations, including populations from Africa and Asia. The variants described herein to be associated to the CDKAL gene, in particular the LD Block C06 (SEQ ID NO:1) have been replicated in several populations of European, American, and Chinese (Hong Kong) origin. This supports the belief that these variants (rs7756992 and markers in linkage disequilibrium therewith) are at-risk variants for Type 2 diabetes in most populations.

Particular embodiments comprising individual human populations are thus also contemplated and within the scope of the present invention. Such embodiments relate to human subjects that are from one or more human population including, but not limited to, Caucasian populations, European populations, American populations, Eurasian populations, Asian populations, Central/South Asian populations, East Asian populations, Middle Eastern populations, African populations, Hispanic populations, and Oceanian populations. European populations include, but are not limited to, Swedish, Norwegian, Finnish, Russian, Danish, Icelandic, Irish, Kelt, English, Scottish, Dutch, Belgian, French, German, Spanish, Portuguese, Italian, Polish, Bulgarian, Slavic, Serbian, Bosnian, Czech, Greek and Turkish populations. The invention furthermore in other embodiments can be practiced in specific human populations that include Bantu, Mandenk, Yoruba, San, Mbuti Pygmy, Orcadian, Adygel, Russian, Sardinian, Tuscan, Mozabite, Bedouin, Druze, Palestinian, Balochi, Brahui, Makrani, Sindhi, Pathan, Burusho, Hazara, Uygur, Kalash, Han, Dai, Daur, Hezhen, Lahu, Miao, Oroqen, She, Tujia, Tu, Xibo, Yi, Mongolan, Naxi, Cambodian, Japanese, Yakut, Melanesian, Papuan, Karitinan, Surui, Columbian, Maya and Pima.

In one preferred embodiment, the invention relates to populations that include black African ancestry such as populations comprising persons of African descent or lineage. Black African ancestry may be determined by self reporting as African-Americans, Afro-Americans, Black Americans, being a member of the black race or being a member of the negro race. For example, African Americans or Black Americans are

those persons living in North America and having origins in any of the black racial groups of Africa. In another example, self-reported persons of black African ancestry may have at least one parent of black African ancestry or at least one grandparent of black African ancestry.

5 The racial contribution in individual subjects may also be determined by genetic analysis. Genetic analysis of ancestry may be carried out using unlinked microsatellite markers such as those set out in Smith *et al.* (*Am J Hum Genet* **74**, 1001-13 (2004)).

 In certain embodiments, the invention relates to markers and/or haplotypes identified in specific populations, as described in the above. The person skilled in the art
10 will appreciate that measures of linkage disequilibrium (LD) may give different results when applied to different populations. This is due to different population history of different human populations as well as differential selective pressures that may have led to differences in LD in specific genomic regions. It is also well known to the person skilled in the art that certain markers, *e.g.* SNP markers, have different population frequency in
15 different populations, or are polymorphic in one population but not in another. The person skilled in the art will however apply the methods available and as thought herein to practice the present invention in any given human population. This may include assessment of polymorphic markers in the LD region of the present invention, so as to identify those markers that give strongest association within the specific population.
20 Thus, the at-risk variants of the present invention may reside on different haplotype background and in different frequencies in various human populations. However, utilizing methods known in the art and the markers of the present invention, the invention can be practiced in any given human population.

25 *Utility of Genetic Testing*

 The knowledge about a genetic variant that confers a risk of developing Type 2 diabetes offers the opportunity to apply a genetic test to distinguish between individuals with increased risk of developing the disease (i.e. carriers of the at-risk variant) and those with decreased risk of developing the disease (i.e. carriers of the protective variant). The
30 core values of genetic testing, for individuals belonging to both of the above mentioned groups, are the possibilities of being able to diagnose the disease at an early stage and provide information to the clinician about prognosis/aggressiveness of the disease in order to be able to apply the most appropriate treatment.

 For example, the application of a genetic test for Type 2 diabetes can identify high
35 risk individuals among people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). It is well established that while around a third of people who are found to

have IFG/IGT develop Type 2 diabetes, glucose levels return to normal for an equal proportion of individuals. Identification of individuals within this group that are carriers of genetic risk variants will allow targeting of those individuals by preventive measures. For example, these individuals may benefit from a closer monitoring of blood glucose levels to aid in early diagnosis. They may also need more stringent lifestyle intervention advice since individuals with certain genetic risk factors develop Type 2 diabetes at lower BMI levels than those without those factors.

Individuals with a family history of Type 2 diabetes and carriers of at-risk variants may benefit from genetic testing since the knowledge of the presence of a genetic risk factor, or evidence for increased risk of being a carrier of one or more risk factors, may provide increased incentive for implementing a healthier lifestyle. Furthermore, closer monitoring of glucose levels should be advised for such individuals, facilitating early diagnosis and/or preventative treatment.

Genetic testing of Type 2 diabetes patients may furthermore give valuable information about the primary cause of the disease and can aid the clinician in selecting the best treatment options and medication for each individual. For instance, patients with genetic risk factors for reduced insulin secretion may be likely to benefit from medication increasing insulin secretion while increasing insulin sensitivity in those individuals may be less effective.

20

METHODS OF THE INVENTION

Methods for risk assessment of Type 2 diabetes are described herein and are encompassed by the invention. The invention also encompasses methods of assessing an individual for probability of response to a therapeutic agent for Type 2 diabetes, as well as methods for predicting the effectiveness of a therapeutic agent for Type 2 diabetes. Kits for assaying a sample from a subject to detect susceptibility to Type 2 diabetes are also encompassed by the invention.

DIAGNOSTIC AND SCREENING ASSAYS OF THE INVENTION

In certain embodiments, the present invention pertains to methods of assessing risk or diagnosing, or aiding in risk assessment or diagnosis of, Type 2 diabetes or a susceptibility to Type 2 diabetes, by detecting particular alleles at genetic markers that appear more frequently in Type 2 diabetes subjects or subjects who are susceptible to Type 2 diabetes. In a particular embodiment, the invention is a method of assessing susceptibility to Type 2 diabetes by detecting at least one allele of at least one

polymorphic marker (*e.g.*, the markers described herein). The present invention describes methods whereby detection of particular alleles of particular markers or haplotypes is indicative of a susceptibility to Type 2 diabetes. Such prognostic or predictive assays can also be used to determine prophylactic treatment of a subject prior
5 to the onset of symptoms of Type 2 diabetes.

The present invention pertains in some embodiments to methods of clinical applications of diagnosis, *e.g.*, diagnosis performed by a medical professional, which may include an assessment or determination of genetic risk variants. In other embodiments, the invention pertains to methods of risk assessment (or diagnosis) performed by a
10 layman. Recent technological advances in genotyping technologies, including high-throughput genotyping of SNP markers, such as Molecular Inversion Probe array technology (*e.g.*, Affymetrix GeneChip), and BeadArray Technologies (*e.g.*, Illumina GoldenGate and Infinium assays) have made it possible for individuals to have their own genome assessed for up to one million SNPs. The resulting genotype information, made
15 available to the individual can be compared to information from the public literature about disease or trait risk associated with various SNPs. The diagnostic application of disease-associated alleles as described herein, can thus be performed either by a health professional based on results of a clinical test or by a layman, including an individual providing service for performing an whole-genome assessment of SNPs. In other words,
20 the diagnosis or assessment of a susceptibility based on genetic risk can be made by health professionals, genetic counselors, genotype services providers or by the layman, based on information about his/her genotype and publications on various risk factors. In the present context, the term "diagnosing", and "diagnose a susceptibility", is meant to refer to any available diagnostic method, including those mentioned above.

25 In addition, in certain other embodiments, the present invention pertains to methods of diagnosing, or aiding in the diagnosis of, a decreased susceptibility to Type 2 diabetes, by detecting particular genetic marker alleles or haplotypes that appear less frequently in Type 2 diabetes patients than in individual not diagnosed with Type 2 diabetes or in the general population.

30 As described and exemplified herein, particular marker alleles or haplotypes (*e.g.* the markers and haplotypes as listed in Tables 1-24, *e.g.*, the markers and haplotypes as listed in Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith) are associated with Type 2 diabetes. In one embodiment, the marker allele or haplotype is one that confers a significant risk or susceptibility to Type 2 diabetes. In another
35 embodiment, the invention relates to a method of diagnosing a susceptibility to Type 2 diabetes in a human individual, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected

from the group consisting of the polymorphic markers listed in Table 9, Table 10, Table 11, and Table 12, and markers in linkage disequilibrium (defined as $r^2 > 0.2$) therewith. In another embodiment, the invention pertains to methods of diagnosing or assessing a susceptibility to Type 2 diabetes in a human individual, by screening for at least one
5 marker allele or haplotype as listed in Tables 1-6 and 9 – 12, or markers in linkage disequilibrium therewith. In another embodiment, the marker allele or haplotype is more frequently present in a subject having, or who is susceptible to, Type 2 diabetes (affected), as compared to the frequency of its presence in a healthy subject (control, such as population controls). In certain embodiments, the significance of association of
10 the at least one marker allele or haplotype is characterized by a p value < 0.05 . In other embodiments, the significance of association is characterized by smaller p-values, such as < 0.01 , < 0.001 , < 0.0001 , < 0.00001 , < 0.000001 , < 0.0000001 , < 0.00000001 or < 0.000000001 .

In these embodiments, the presence of the at least one marker allele or
15 haplotype is indicative of a susceptibility to Type 2 diabetes. These diagnostic methods involve detecting the presence or absence of at least one marker allele or haplotype that is associated with Type 2 diabetes. The haplotypes described herein include combinations of alleles at various genetic markers (e.g., SNPs, microsatellites). The detection of the particular genetic marker alleles that make up the particular haplotypes can be performed
20 by a variety of methods described herein and/or known in the art. For example, genetic markers can be detected at the nucleic acid level (e.g., by direct nucleotide sequencing or by other means known to the skilled in the art) or at the amino acid level if the genetic marker affects the coding sequence of a protein encoded by a Type 2 diabetes -associated nucleic acid (e.g., by protein sequencing or by immunoassays using antibodies that
25 recognize such a protein). The marker alleles or haplotypes of the present invention correspond to fragments of a genomic DNA sequence associated with Type 2 diabetes. Such fragments encompass the DNA sequence of the polymorphic marker or haplotype in question, but may also include DNA segments in strong LD (linkage disequilibrium) with the marker or haplotype (e.g., as determined by a value of r^2 greater than 0.2 and/or $|D'|$
30 > 0.8).

In one embodiment, diagnosis or assessment of a susceptibility to Type 2 diabetes can be accomplished using hybridization methods, such as Southern analysis, Northern analysis, and/or *in situ* hybridizations (see Current Protocols in Molecular Biology, Ausubel, F. *et al.*, eds., John Wiley & Sons, including all supplements). The presence of a
35 specific marker allele can be indicated by sequence-specific hybridization of a nucleic acid probe specific for the particular allele. The presence of more than specific marker allele or a specific haplotype can be indicated by using several sequence-specific nucleic acid probes, each being specific for a particular allele. In one embodiment, a haplotype can be indicated by a single nucleic acid probe that is specific for the specific haplotype (i.e.,

hybridizes specifically to a DNA strand comprising the specific marker alleles characteristic of the haplotype). A sequence-specific probe can be directed to hybridize to genomic DNA, RNA, or cDNA. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe that hybridizes to a complementary sequence. One of skill in the art would
5 know how to design such a probe so that sequence specific hybridization will occur only if a particular allele is present in a genomic sequence from a test sample.

To diagnose a susceptibility to Type 2 diabetes, a hybridization sample is formed by contacting the test sample containing an Type 2 diabetes -associated nucleic acid, such as a genomic DNA sample, with at least one nucleic acid probe. A non-limiting example of
10 a probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe that is capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length that is sufficient to specifically hybridize under stringent conditions to appropriate mRNA or
15 genomic DNA. For example, the nucleic acid probe can comprise all or a portion of the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2) (e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes), LD Block C17 (SEQ ID NO:3) or the CDKAL1 gene, or the SLC30A8 gene, as described herein, optionally comprising at least one allele of a marker described herein, or at least one haplotype
20 described herein, or the probe can be the complementary sequence of such a sequence. In a particular embodiment, the nucleic acid probe is a portion of the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2) (e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes), LD Block C17 (SEQ ID NO:3) or the CDKAL1 gene, or the SLC30A8 gene as described herein, optionally comprising at
25 least one allele of a marker described herein, or at least one allele contained in the haplotypes described herein, or the probe can be the complementary sequence of such a sequence. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization can be performed by methods well known to the person skilled in the art (see, e.g., Current Protocols in Molecular Biology, Ausubel, F. et al., eds.,
30 John Wiley & Sons, including all supplements). In one embodiment, hybridization refers to specific hybridization, i.e., hybridization with no mismatches (exact hybridization). In one embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is detected using standard methods. If specific
35 hybridization occurs between the nucleic acid probe and the nucleic acid in the test sample, then the sample contains the allele that is complementary to the nucleotide that is present in the nucleic acid probe. The process can be repeated for any markers of the present invention, or markers that make up a haplotype of the present invention, or multiple probes can be used concurrently to detect more than one marker alleles at a

time. It is also possible to design a single probe containing more than one marker alleles of a particular haplotype (e.g., a probe containing alleles complementary to 2, 3, 4, 5 or all of the markers that make up a particular haplotype). Detection of the particular markers of the haplotype in the sample is indicative that the source of the sample has the particular haplotype (e.g., a haplotype) and therefore is susceptible to DISEASE.

In one preferred embodiment, a method utilizing a detection oligonucleotide probe comprising a fluorescent moiety or group at its 3' terminus and a quencher at its 5' terminus, and an enhancer oligonucleotide, is employed, as described by Kuttyavin *et al.* (*Nucleic Acid Res.* **34**:e128 (2006)). The fluorescent moiety can be Gig Harbor Green or Yakima Yellow, or other suitable fluorescent moieties. The detection probe is designed to hybridize to a short nucleotide sequence that includes the SNP polymorphism to be detected. Preferably, the SNP is anywhere from the terminal residue to -6 residues from the 3' end of the detection probe. The enhancer is a short oligonucleotide probe which hybridizes to the DNA template 3' relative to the detection probe. The probes are designed such that a single nucleotide gap exists between the detection probe and the enhancer nucleotide probe when both are bound to the template. The gap creates a synthetic abasic site that is recognized by an endonuclease, such as Endonuclease IV. The enzyme cleaves the dye off the fully complementary detection probe, but cannot cleave a detection probe containing a mismatch. Thus, by measuring the fluorescence of the released fluorescent moiety, assessment of the presence of a particular allele defined by nucleotide sequence of the detection probe can be performed.

The detection probe can be of any suitable size, although preferably the probe is relatively short. In one embodiment, the probe is from 5-100 nucleotides in length. In another embodiment, the probe is from 10-50 nucleotides in length, and in another embodiment, the probe is from 12-30 nucleotides in length. Other lengths of the probe are possible and within scope of the skill of the average person skilled in the art. In a preferred embodiment, the DNA template containing the SNP polymorphism is amplified by Polymerase Chain Reaction (PCR) prior to detection. In such an embodiment, the amplified DNA serves as the template for the detection probe and the enhancer probe.

Certain embodiments of the detection probe, the enhancer probe, and/or the primers used for amplification of the template by PCR include the use of modified bases, including modified A and modified G. The use of modified bases can be useful for adjusting the melting temperature of the nucleotide molecule (probe and/or primer) to the template DNA, for example for increasing the melting temperature in regions containing a low percentage of G or C bases, in which modified A with the capability of forming three hydrogen bonds to its complementary T can be used, or for decreasing the melting temperature in regions containing a high percentage of G or C bases, for example by using modified G bases that form only two hydrogen bonds to their complementary C

base in a double stranded DNA molecule. In a preferred embodiment, modified bases are used in the design of the detection nucleotide probe. Any modified base known to the skilled person can be selected in these methods, and the selection of suitable bases is well within the scope of the skilled person based on the teachings herein and known bases available from commercial sources as known to the skilled person.

In another hybridization method, Northern analysis (see Current Protocols in Molecular Biology, Ausubel, F. *et al.*, eds., John Wiley & Sons, *supra*) is used to identify the presence of a polymorphism associated with Type 2 diabetes. For Northern analysis, a test sample of RNA is obtained from the subject by appropriate means. As described herein, specific hybridization of a nucleic acid probe to RNA from the subject is indicative of a particular allele complementary to the probe. For representative examples of use of nucleic acid probes, see, for example, U.S. Patent Nos. 5,288,611 and 4,851,330.

Additionally, or alternatively, a peptide nucleic acid (PNA) probe can be used in addition to, or instead of, a nucleic acid probe in the hybridization methods described herein. A PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P., *et al.*, *Bioconjug. Chem.* 5:3-7 (1994)). The PNA probe can be designed to specifically hybridize to a molecule in a sample suspected of containing one or more of the marker alleles or haplotypes that are associated with Type 2 diabetes. Hybridization of the PNA probe is thus diagnostic for Type 2 diabetes or a susceptibility to Type 2 diabetes.

In one embodiment of the methods of the invention, diagnosis of Type 2 diabetes or a susceptibility to Type 2 diabetes is accomplished through enzymatic amplification of a nucleic acid from the subject. For example, a test sample containing genomic DNA can be obtained from the subject and the polymerase chain reaction (PCR) can be used to amplify a fragment comprising one or more markers or haplotypes of the present invention found to be associated with Type 2 diabetes. As described herein, identification of a particular marker allele or haplotype associated with Type 2 diabetes can be accomplished using a variety of methods (*e.g.*, sequence analysis, analysis by restriction digestion, specific hybridization, single stranded conformation polymorphism assays (SSCP), electrophoretic analysis, etc.). In another embodiment, diagnosis is accomplished by expression analysis using quantitative PCR (kinetic thermal cycling). This technique can, for example, utilize commercially available technologies, such as TaqMan® (Applied Biosystems, Foster City, CA), to allow the identification of polymorphisms and haplotypes. The technique can assess the presence of an alteration in the expression or composition of a polypeptide or splicing variant(s) that is encoded by a Type 2 diabetes-associated nucleic acid. Further, the expression of the variant(s) can be quantified as physically or functionally different.

In another embodiment of the methods of the invention, analysis by restriction digestion can be used to detect a particular allele if the allele results in the creation or elimination of a restriction site relative to a reference sequence. A test sample containing genomic DNA is obtained from the subject. PCR can be used to amplify particular regions that are associated with Type 2 diabetes (e.g. the polymorphic markers and haplotypes of Tables 1-21, e.g., the polymorphic markers and haplotypes of Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith) nucleic acid in the test sample from the test subject. Restriction fragment length polymorphism (RFLP) analysis can be conducted, e.g., as described in Current Protocols in Molecular Biology, *supra*. The digestion pattern of the relevant DNA fragment indicates the presence or absence of the particular allele in the sample.

Sequence analysis can also be used to detect specific alleles at polymorphic sites associated with Type 2 diabetes (e.g. the polymorphic markers and haplotypes of Tables 1-24, e.g., the polymorphic markers and haplotypes of Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith, e.g., the markers set forth in Tables 22, 23 and 24). Therefore, in one embodiment, determination of the presence or absence of a particular marker alleles or haplotypes comprises sequence analysis. For example, a test sample of DNA or RNA can be obtained from the test subject. PCR or other appropriate methods can be used to amplify a portion of a Type 2 diabetes-associated nucleic acid, and the presence of a specific allele can then be detected directly by sequencing the polymorphic site (or multiple polymorphic sites) of the genomic DNA in the sample.

Allele-specific oligonucleotides can also be used to detect the presence of a particular allele at a Type 2 diabetes-associated nucleic acid (e.g. the polymorphic markers and haplotypes of Tables 1-21, e.g., the polymorphic markers and haplotypes of Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith), through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. *et al.*, *Nature*, 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs or approximately 15-30 base pairs, that specifically hybridizes to a Type 2 diabetes-associated nucleic acid, and which contains a specific allele at a polymorphic site (e.g., a polymorphism described herein). An allele-specific oligonucleotide probe that is specific for one or more particular a Type 2 diabetes-associated nucleic acid can be prepared using standard methods (see, e.g., Current Protocols in Molecular Biology, *supra*). PCR can be used to amplify the desired region a Type 2 diabetes-associated nucleic acid. The DNA containing the amplified region can be dot-blotted using standard methods (see, e.g., Current Protocols in Molecular Biology, *supra*), and the blot can be contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified region can then be detected. Specific hybridization of an allele-specific

oligonucleotide probe to DNA from the subject is indicative of a specific allele at a polymorphic site associated with Type 2 diabetes (see, e.g., Gibbs, R. *et al.*, *Nucleic Acids Res.*, 17:2437-2448 (1989) and WO 93/22456).

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from a subject, can be used to identify polymorphisms in a Type 2 diabetes-associated nucleic acid (e.g. the polymorphic markers and haplotypes of Tables 1-24, e.g. the polymorphic markers and haplotypes of Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith). For example, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "Genechips™," have been generally described in the art (see, e.g., U.S. Patent No. 5,143,854, PCT Patent Publication Nos. WO 90/15070 and 92/10092). These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods (Fodor, S. *et al.*, *Science*, 251:767-773 (1991); Pirrung *et al.*, U.S. Patent No. 5,143,854 (see also published PCT Application No. WO 90/15070); and Fodor, S. *et al.*, published PCT Application No. WO 92/10092 and U.S. Patent No. 5,424,186, the entire teachings of each of which are incorporated by reference herein). Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, e.g., U.S. Patent No. 5,384,261; the entire teachings of which are incorporated by reference herein. In another example, linear arrays can be utilized.

Additional descriptions of use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patent Nos. 5,858,659 and 5,837,832, the entire teachings of both of which are incorporated by reference herein. Other methods of nucleic acid analysis can be used to detect a particular allele at a polymorphic site associated with Type 2 diabetes (e.g. the polymorphic markers and haplotypes of Tables 1-24, e.g. the polymorphic markers and haplotypes of Tables 1-6 and Tables 9-12, and markers in linkage disequilibrium therewith). Representative methods include, for example, direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA*, 81: 1991-1995 (1988); Sanger, F., *et al.*, *Proc. Natl. Acad. Sci. USA*, 74:5463-5467 (1977); Beavis, *et al.*, U.S. Patent No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V., *et al.*, *Proc. Natl. Acad. Sci. USA*, 86:232-236 (1989)), mobility shift analysis (Orita, M., *et al.*, *Proc. Natl. Acad. Sci. USA*, 86:2766-2770 (1989)), restriction enzyme analysis (Flavell, R., *et al.*, *Cell*, 15:25-41 (1978); Geever, R., *et al.*, *Proc. Natl. Acad. Sci. USA*, 78:5081-5085 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton, R., *et al.*, *Proc. Natl. Acad. Sci. USA*, 85:4397-4401 (1985)); RNase protection

assays (Myers, R., *et al.*, *Science*, 230:1242-1246 (1985); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of Type 2 diabetes or a susceptibility to Type 2 diabetes can be made by examining expression and/or composition of a polypeptide encoded by Type 2 diabetes-associated nucleic acid in those instances where the genetic marker(s) or haplotype(s) of the present invention result in a change in the composition or expression of the polypeptide. Thus, diagnosis of a susceptibility to Type 2 diabetes can be made by examining expression and/or composition of one of these polypeptides, or another polypeptide encoded by a Type 2 diabetes-associated nucleic acid, in those instances where the genetic marker or haplotype of the present invention results in a change in the composition or expression of the polypeptide. The haplotypes and markers of the present invention that show association to Type 2 diabetes may play a role through their effect on one or more of these nearby genes. Possible mechanisms affecting these genes include, *e.g.*, effects on transcription, effects on RNA splicing, alterations in relative amounts of alternative splice forms of mRNA, effects on RNA stability, effects on transport from the nucleus to cytoplasm, and effects on the efficiency and accuracy of translation.

A variety of methods can be used to make such a detection, including enzyme linked immunosorbent assays (ELISA), Western blots, immunoprecipitation and immunofluorescence. A test sample from a subject is assessed for the presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by a Type 2 diabetes-associated nucleic acid. An alteration in expression of a polypeptide encoded by a Type 2 diabetes-associated nucleic acid can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced). An alteration in the composition of a polypeptide encoded by a Type 2 diabetes-associated nucleic acid is an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant polypeptide or of a different splicing variant). In one embodiment, diagnosis of a susceptibility to Type 2 diabetes is made by detecting a particular splicing variant encoded by a Type 2 diabetes-associated nucleic acid, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An "alteration" in the polypeptide expression or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared to the expression or composition of polypeptide encoded by a Type 2 diabetes-associated nucleic acid in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from a subject who is not affected by, and/or who does not have a susceptibility to, Type 2 diabetes (*e.g.*, a subject that does not possess a marker allele or haplotype as described herein). Similarly, the presence of one or more

different splicing variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, can be indicative of a susceptibility to Type 2 diabetes. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, can be indicative of a specific allele in the instance where the allele alters a splice site relative to the reference in the control sample. Various means of examining expression or composition of a polypeptide encoded by a Type 2 diabetes-associated nucleic acid can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and immunoassays (*e.g.*, David *et al.*, U.S. Pat. No. 4,376,110) such as immunoblotting (see, *e.g.*, Current Protocols in Molecular Biology, particularly chapter 10, *supra*).

For example, in one embodiment, an antibody (*e.g.*, an antibody with a detectable label) that is capable of binding to a polypeptide encoded by a Type 2 diabetes-associated nucleic acid can be used. Antibodies can be polyclonal or monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fv, Fab, Fab', F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a labeled secondary antibody (*e.g.*, a fluorescently-labeled secondary antibody) and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin.

In one embodiment of this method, the level or amount of polypeptide encoded by a Type 2 diabetes-associated nucleic acid in a test sample is compared with the level or amount of the polypeptide encoded by a Type 2 diabetes-associated nucleic acid in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the Type 2 diabetes-associated nucleic acid, and is diagnostic for a particular allele or haplotype responsible for causing the difference in expression. Alternatively, the composition of the polypeptide encoded by a Type 2 diabetes-associated nucleic acid in a test sample is compared with the composition of the polypeptide encoded by a Type 2 diabetes-associated nucleic acid in a control sample. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample.

In another embodiment, the diagnosis of a susceptibility to Type 2 diabetes is made by detecting at least one Type 2 diabetes-associated marker allele or haplotype (*e.g.*, associated alleles or haplotypes of the markers listed in Tables 1-21, such as Tables

1-6 and Tables 9-12), in combination with an additional protein-based, RNA-based or DNA-based assay. The methods of the invention can also be used in combination with an analysis of a subject's family history and risk factors (e.g., environmental risk factors, lifestyle risk factors).

5

Kits

Kits useful in the methods of the invention comprise components useful in any of the methods described herein, including for example, primers for nucleic acid amplification, hybridization probes, restriction enzymes (e.g., for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to an altered polypeptide encoded by a nucleic acid of the invention as described herein (e.g., a genomic segment comprising at least one polymorphic marker and/or haplotype of the present invention) or to a non-altered (native) polypeptide encoded by a nucleic acid of the invention as described herein, means for amplification of a nucleic acid associated with Type 2 diabetes, means for analyzing the nucleic acid sequence of a nucleic acid associated with Type 2 diabetes, means for analyzing the amino acid sequence of a polypeptide encoded by a nucleic acid associated with Type 2 diabetes (e.g., the Type 2 diabetes protein encoded by the Type 2 diabetes gene), etc. The kits can for example include necessary buffers, nucleic acid primers for amplifying nucleic acids of the invention (e.g., a nucleic acid segment comprising one or more of the polymorphic markers as described herein), and reagents for allele-specific detection of the fragments amplified using such primers and necessary enzymes (e.g., DNA polymerase). Additionally, kits can provide reagents for assays to be used in combination with the methods of the present invention, e.g., reagents for use with other Type 2 diabetes diagnostic assays.

In one embodiment, the invention is a kit for assaying a sample from a subject to detect the presence of Type 2 diabetes, symptoms associated with Type 2 diabetes, or a susceptibility to Type 2 diabetes in a subject, wherein the kit comprises reagents necessary for selectively detecting at least one allele of at least one polymorphism of the present invention in the genome of the individual. In a particular embodiment, the reagents comprise at least one contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising at least one polymorphism of the present invention. In another embodiment, the reagents comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic segment obtained from a subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes at least one polymorphism, wherein the polymorphism is selected from the group consisting of the polymorphisms as listed in Tables 1-6 and 9-12, and polymorphic markers in linkage disequilibrium

therewith (e.g., the markers set forth in Tables 22, 23 and 24). In yet another embodiment the fragment is at least 20 base pairs in size. Such oligonucleotides or nucleic acids (e.g., oligonucleotide primers) can be designed using portions of the nucleic acid sequence flanking polymorphisms (e.g., SNPs or microsatellites) that are indicative of Type 2 diabetes. In another embodiment, the kit comprises one or more labeled nucleic acids capable of allele-specific detection of one or more specific polymorphic markers or haplotypes associated with Type 2 diabetes, and reagents for detection of the label. Suitable labels include, e.g., a radioisotope, a fluorescent label, an enzyme label, an enzyme co-factor label, a magnetic label, a spin label, an epitope label.

In particular embodiments, the polymorphic marker or haplotype to be detected by the reagents of the kit comprises one or more markers, two or more markers, three or more markers, four or more markers or five or more markers selected from the group consisting of the markers set forth in Tables 9-12. In another embodiment, the marker or haplotype to be detected comprises the markers set forth in Tables 22-24. In another embodiment, the marker or haplotype to be detected comprises markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), and rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith. In one such embodiment, linkage disequilibrium is defined by values of r^2 greater than 0.2.

In one preferred embodiment, the kit for detecting the markers of the invention comprises a detection oligonucleotide probe, that hybridizes to a segment of template DNA containing a SNP polymorphisms to be detected, an enhancer oligonucleotide probe and an endonuclease. As explained in the above, the detection oligonucleotide probe comprises a fluorescent moiety or group at its 3' terminus and a quencher at its 5' terminus, and an enhancer oligonucleotide, is employed, as described by Kuttyavin *et al.* (*Nucleic Acid Res.* **34**:e128 (2006)). The fluorescent moiety can be Gig Harbor Green or Yakima Yellow, or other suitable fluorescent moieties. The detection probe is designed to hybridize to a short nucleotide sequence that includes the SNP polymorphism to be detected. Preferably, the SNP is anywhere from the terminal residue to -6 residues from the 3' end of the detection probe. The enhancer is a short oligonucleotide probe which hybridizes to the DNA template 3' relative to the detection probe. The probes are designed such that a single nucleotide gap exists between the detection probe and the enhancer nucleotide probe when both are bound to the template. The gap creates a synthetic abasic site that is recognized by an endonuclease, such as Endonuclease IV.

The enzyme cleaves the dye off the fully complementary detection probe, but cannot cleave a detection probe containing a mismatch. Thus, by measuring the fluorescence of the released fluorescent moiety, assessment of the presence of a particular allele defined by nucleotide sequence of the detection probe can be performed.

5 The detection probe can be of any suitable size, although preferably the probe is relatively short. In one embodiment, the probe is from 5-100 nucleotides in length. In another embodiment, the probe is from 10-50 nucleotides in length, and in another embodiment, the probe is from 12-30 nucleotides in length. Other lengths of the probe are possible and within scope of the skill of the average person skilled in the art.

10 In a preferred embodiment, the DNA template containing the SNP polymorphism is amplified by Polymerase Chain Reaction (PCR) prior to detection, and primers for such amplification are included in the reagent kit. In such an embodiment, the amplified DNA serves as the template for the detection probe and the enhancer probe.

 Certain embodiments of the detection probe, the enhancer probe, and/or the
15 primers used for amplification of the template by PCR include the use of modified bases, including modified A and modified G. The use of modified bases can be useful for adjusting the melting temperature of the nucleotide molecule (probe and/or primer) to the template DNA, for example for increasing the melting temperature in regions containing a low percentage of G or C bases, in which modified A with the capability of
20 forming three hydrogen bonds to its complementary T can be used, or for decreasing the melting temperature in regions containing a high percentage of G or C bases, for example by using modified G bases that form only two hydrogen bonds to their complementary C base in a double stranded DNA molecule. In a preferred embodiment, modified bases are used in the design of the detection nucleotide probe. Any modified base known to the
25 skilled person can be selected in these methods, and the selection of suitable bases is well within the scope of the skilled person based on the teachings herein and known bases available from commercial sources as known to the skilled person.

 In one such embodiments, the presence of the marker or haplotype is indicative of a susceptibility (increased susceptibility or decreased susceptibility) to Type 2 diabetes.
30 In another embodiment, the presence of the marker or haplotype is indicative of response to a Type 2 diabetes therapeutic agent. In another embodiment, the presence of the marker or haplotype is indicative of prognosis of Type 2 diabetes. In yet another embodiment, the presence of the marker or haplotype is indicative of progress of treatment of Type 2 diabetes. Such treatment may include intervention by surgery,
35 medication or by other means (e.g., lifestyle changes).

Therapeutic agents for Type 2 diabetes

Currently available Type 2 diabetes medication (apart from insulin) falls into six main classes of drugs: sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors and a new class of drugs called DPP-4 inhibitors. These classes of drugs work in different ways to lower blood glucose levels.

1. *Sulfonylureas*. Sulfonylureas stimulate the beta cells of the pancreas to release more insulin.
2. *Meglitinides*. Meglitinides are drugs that also stimulate the beta cells to release insulin.
3. *Biguanides*. Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed.
4. *Thiazolidinediones*. These drugs help insulin work better in the muscle and fat and also reduce glucose production in the liver.
5. *Alpha-glucosidase inhibitors*. These drugs help the body to lower blood glucose levels by blocking the breakdown of starches, such as bread, potatoes, and pasta in the intestine. They also slow the breakdown of some sugars, such as table sugar. Their action slows the rise in blood glucose levels after a meal. They should be taken with the first bite of a meal.
6. *DPP-4 Inhibitors*. A new class of medications called DPP-4 inhibitors help improve A1C without causing hypoglycemia. They work by preventing the breakdown of a naturally occurring compound in the body, GLP-1. GLP-1 reduces blood glucose levels in the body, but is broken down very quickly so it does not work well when injected as a drug itself. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow it to remain active in the body longer, lowering blood glucose levels only when they are elevated.

Examples of available drugs in these classes are listed in Agent Table 1.

Agent Table 1.

Drug Class	Generic name	Brand name
Biguanides	metformin	Glucophage, Glucophage XR, Glycon
	metformin plus glyburide	Glucovance
Thiazolidinediones	pioglitazone	Actos
	rosiglitazone	Avandia
Sulfonylureas	acetohexamide	Dymelor

Drug Class	Generic name	Brand name
	chlorpropamide	Diabinese
	gliclazide Diamicon	Diamicon MR
	glimepiride	Amaryl
	glipizide	Glucotrol, Glucotrol XL
	glyburide	Micronase, DiaBeta, Glynase PresTab
	glyburide plus metformin	Glucovance
	tolazamide	Tolinase
	tolbutamide	Orinase, Tol-Tab
Meglitinides	nateglinide	Starlix
	repaglinide	Prandin, Gluconorm
Alpha-glucosidase inhibitors	acarbose	Precose, Prandase
	miglitol	Glyset
DPP-4 Inhibitors	sitagliptin	Januvia

Additionally, a combination therapy comprising Biguanide and Sulphonylureas has been used for treatment of Type 2 diabetes.

Additional Type 2 diabetes drugs are listed Agent Table 2.

5

Agent Table 2

Compound name(s)	Compound name (generated using Autonom, ISIS Draw version 2.5 from MDL Information Systems)	Company	Compound Reference	Indications
AR-0133418 (SN-4521)	1-(4-Methoxy-benzyl)-3-(5-nitro-thiazol-2-yl)-urea	AstraZeneca		AD
AR-025028	NSD	AstraZeneca		
CT-98023	N-[4-(2,4-Dichloro-phenyl)-5-(1H-imidazol-2-yl)-pyrimidin-2-yl]-N'-(5-nitro-pyridin-2-yl)-ethane-1,2-diamine	Chiron Corp		non-insulin dependent diabetes
CT-20026	NSD	Chiron Corp	Wagman et al., Curr Pharm. Des 2004: 10(10) 1105-37	non-insulin dependent diabetes
CT-21022	NSD	Chiron Corp		non-insulin dependent diabetes
CT-20014	NSD	Chiron Corp		non-insulin dependent diabetes
CT-21018	NSD	Chiron Corp		non-insulin dependent diabetes
CHIR-98025	NSD	Chiron Corp		non-insulin dependent diabetes
CHIR-99021	NSD	Chiron Corp	Wagman et al., Curr Pharm. Des 2004: 10(10) 1105-37	non-insulin dependent diabetes
CG-100179	NSD	CrystalGenomics and Yuyu	WO-2004065370	diabetes mellitus (Korea)

Compound name(s)	Compound name (generated using Autonom, ISIS Draw version 2.5 from MDL Information Systems)	Company	Compound Reference	Indications
	4-[2-(4-Dimethylamino-3-nitro-phenylamino)-pyrimidin-4-yl]-3,5-dimethyl-1H-pyrrole-2-carbonitrile	Cyclacel Ltd.		non-insulin dependent diabetes, among others.
NP-01139, NP-031112, NP-03112, NP-00361	4-Benzyl-2-methyl-[1,2,4]thiadiazolidine-3,5-dione	Neuropharma SA		CNS disorders, AD
	3-[9-Fluoro-2-(piperidine-1-carbonyl)-1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-7-yl]-4-imidazo[1,2-a]pyridin-3-yl-pyrrole-2,5-dione	Eli Lilly & Co		non-insulin dependent diabetes
GW-784752x, GW-784775, SB-216763, SB-415286	Cyclopentanecarboxylic acid (6-pyridin-3-yl-furo[2,3-d]pyrimidin-4-yl)-amide	GSK	WO-03024447 (compound referenced: 4-[2-(2-bromophenyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl]pyridine	non-insulin dependent diabetes, neurodegenerative disease
NNC-57-0511, NNC-57-0545, NNC-57-0588	1-(4-Amino-furazan-3-yl)-5-piperidin-1-ylmethyl-1H-[1,2,3]triazole-4-carboxylic acid [1-pyridin-4-yl-meth-(E)-ylidene]-hydrazide	Novo Nordisk		non-insulin dependent diabetes,
CP-70949	NSD	Pfizer		Hypoglycemic agent
VX-608	NSD			Cerebrovascular ischemia, non-insulin dependent diabetes
KP-403 class	NSD	Kinetek		Nuclear factor kappa B modulator, Anti-inflammatory, Cell cycle inhibitor, Glycogen synthase kinase-3 beta inhibitor
BYETTA (exenatide)	Exenatide: C ₁₈₄ H ₂₈₂ N ₅₀ O ₆₀ S - Amino acid sequence: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH ₂	Amylin / Eli Lilly & Co		non-insulin dependent diabetes
Vildagliptin (LAF237)	NSD	Novartis		non-insulin dependent diabetes - DPP-4 inhibitor

Therapeutic agents of the invention

Variants of the present invention (e.g., the markers and/or haplotypes as described herein) can be used to identify novel therapeutic targets for Type 2 diabetes.

- 5 For example, genes containing, or in linkage disequilibrium with, variants (markers and/or haplotypes) associated with Type 2 diabetes, or their products, as well as genes or their products that are directly or indirectly regulated by or interact with these variant genes or their products, can be targeted for the development of therapeutic agents to treat Type 2 diabetes, or prevent or delay onset of symptoms associated with Type 2 diabetes.
- 10 Therapeutic agents may comprise one or more of, for example, small non-protein and non-nucleic acid molecules, proteins, peptides, protein fragments, nucleic acids (DNA, RNA), PNA (peptide nucleic acids), or their derivatives or mimetics which can modulate the function and/or levels of the target genes or their gene products.

- The nucleic acids and/or variants of the invention, or nucleic acids comprising their
15 complementary sequence, may be used as antisense constructs to control gene expression in cells, tissues or organs. The methodology associated with antisense techniques is well known to the skilled artisan, and is described and reviewed in *Antisense Drug Technology: Principles, Strategies, and Applications*, Crooke, ed., Marcel Dekker Inc., New York (2001). In general, antisense nucleic acid molecules are designed
20 to be complementary to a region of mRNA expressed by a gene, so that the antisense molecule hybridizes to the mRNA, thus blocking translation of the mRNA into protein. Several classes of antisense oligonucleotide are known to those skilled in the art, including cleavers and blockers. The former bind to target RNA sites, activate intracellular nucleases (e.g., RnaseH or Rnase L), that cleave the target RNA. Blockers bind to target
25 RNA, inhibit protein translation by steric hindrance of the ribosomes. Examples of blockers include nucleic acids, morpholino compounds, locked nucleic acids and methylphosphonates (Thompson, *Drug Discovery Today*, 7:912-917 (2002)). Antisense oligonucleotides are useful directly as therapeutic agents, and are also useful for determining and validating gene function, for example by gene knock-out or gene knock-
30 down experiments. Antisense technology is further described in Lavery *et al.*, *Curr. Opin. Drug Discov. Devel.* 6:561-569 (2003), Stephens *et al.*, *Curr. Opin. Mol. Ther.* 5:118-122 (2003), Kurreck, *Eur. J. Biochem.* 270:1628-44 (2003), Dias *et al.*, *Mol. Cancer Ter.* 1:347-55 (2002), Chen, *Methods Mol. Med.* 75:621-636 (2003), Wang *et al.*, *Curr. Cancer Drug Targets* 1:177-96 (2001), and Bennett, *Antisense Nucleic Acid Drug.Dev.* 12:215-24
35 (2002)

The variants described herein can be used for the selection and design of antisense reagents that are specific for particular variants. Using information about the variants described herein, antisense oligonucleotides or other antisense molecules that

specifically target mRNA molecules that contain one or more variants of the invention can be designed. In this manner, expression of mRNA molecules that contain one or more variant of the present invention (markers and/or haplotypes) can be inhibited or blocked. In one embodiment, the antisense molecules are designed to specifically bind a particular allelic form (i.e., one or several variants (alleles and/or haplotypes)) of the target nucleic acid, thereby inhibiting translation of a product originating from this specific allele or haplotype, but which do not bind other or alternate variants at the specific polymorphic sites of the target nucleic acid molecule.

As antisense molecules can be used to inactivate mRNA so as to inhibit gene expression, and thus protein expression, the molecules can be used to treat a disease or disorder, such as Type 2 diabetes. The methodology can involve cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Such mRNA regions include, for example, protein-coding regions, in particular protein-coding regions corresponding to catalytic activity, substrate and/or ligand binding sites, or other functional domains of a protein.

The phenomenon of RNA interference (RNAi) has been actively studied for the last decade, since its original discovery in *C. elegans* (Fire *et al.*, *Nature* 391:806-11 (1998)), and in recent years its potential use in treatment of human disease has been actively pursued (reviewed in Kim & Rossi, *Nature Rev. Genet.* 8:173-204 (2007)). RNA interference (RNAi), also called gene silencing, is based on using double-stranded RNA molecules (dsRNA) to turn off specific genes. In the cell, cytoplasmic double-stranded RNA molecules (dsRNA) are processed by cellular complexes into small interfering RNA (siRNA). The siRNA guide the targeting of a protein-RNA complex to specific sites on a target mRNA, leading to cleavage of the mRNA (Thompson, *Drug Discovery Today*, 7:912-917 (2002)). The siRNA molecules are typically about 20, 21, 22 or 23 nucleotides in length. Thus, one aspect of the invention relates to isolated nucleic acid molecules, and the use of those molecules for RNA interference, i.e. as small interfering RNA molecules (siRNA). In one embodiment, the isolated nucleic acid molecules are 18-26 nucleotides in length, preferably 19-25 nucleotides in length, more preferably 20-24 nucleotides in length, and more preferably 21, 22 or 23 nucleotides in length.

Another pathway for RNAi-mediated gene silencing originates in endogenously encoded primary microRNA (pri-miRNA) transcripts, which are processed in the cell to generate precursor miRNA (pre-miRNA). These miRNA molecules are exported from the nucleus to the cytoplasm, where they undergo processing to generate mature miRNA molecules (miRNA), which direct translational inhibition by recognizing target sites in the 3' untranslated regions of mRNAs, and subsequent mRNA degradation by processing P-bodies (reviewed in Kim & Rossi, *Nature Rev. Genet.* 8:173-204 (2007)).

Clinical applications of RNAi include the incorporation of synthetic siRNA duplexes, which preferably are approximately 20-23 nucleotides in size, and preferably have 3' overlaps of 2 nucleotides. Knockdown of gene expression is established by sequence-specific design for the target mRNA. Several commercial sites for optimal design and
5 synthesis of such molecules are known to those skilled in the art.

Other applications provide longer siRNA molecules (typically 25-30 nucleotides in length, preferably about 27 nucleotides), as well as small hairpin RNAs (shRNAs; typically about 29 nucleotides in length). The latter are naturally expressed, as described in Amarzguioui *et al.* (*FEBS Lett.* 579:5974-81 (2005)). Chemically synthetic siRNAs and
10 shRNAs are substrates for *in vivo* processing, and in some cases provide more potent gene-silencing than shorter designs (Kim *et al.*, *Nature Biotechnol.* 23:222-226 (2005); Siolas *et al.*, *Nature Biotechnol.* 23:227-231 (2005)). In general siRNAs provide for transient silencing of gene expression, because their intracellular concentration is diluted by subsequent cell divisions. By contrast, expressed shRNAs mediate long-term, stable
15 knockdown of target transcripts, for as long as transcription of the shRNA takes place (Marques *et al.*, *Nature Biotechnol.* 23:559-565 (2006); Brummelkamp *et al.*, *Science* 296: 550-553 (2002)).

Since RNAi molecules, including siRNA, miRNA and shRNA, act in a sequence-dependent manner, the variants of the present invention (*e.g.*, the markers and
20 haplotypes as described herein) can be used to design RNAi reagents that recognize specific nucleic acid molecules comprising specific alleles and/or haplotypes (*e.g.*, the alleles and/or haplotypes of the present invention), while not recognizing nucleic acid molecules comprising other alleles or haplotypes. These RNAi reagents can thus recognize and destroy the target nucleic acid molecules. As with antisense reagents, RNAi
25 reagents can be useful as therapeutic agents (*i.e.*, for turning off disease-associated genes or disease-associated gene variants), but may also be useful for characterizing and validating gene function (*e.g.*, by gene knock-out or gene knock-down experiments).

Delivery of RNAi may be performed by a range of methodologies known to those skilled in the art. Methods utilizing non-viral delivery include cholesterol, stable nucleic acid-lipid particle (SNALP), heavy-chain antibody fragment (Fab), aptamers and
30 nanoparticles. Viral delivery methods include use of lentivirus, adenovirus and adeno-associated virus. The siRNA molecules are in some embodiments chemically modified to increase their stability. This can include modifications at the 2' position of the ribose, including 2'-O-methylpurines and 2'-fluoropyrimidines, which provide resistance to Rnase
35 activity. Other chemical modifications are possible and known to those skilled in the art.

The following references provide a further summary of RNAi, and possibilities for targeting specific genes using RNAi: Kim & Rossi, *Nat. Rev. Genet.* 8:173-184 (2007),

Chen & Rajewsky, *Nat. Rev. Genet.* 8: 93-103 (2007), Reynolds, *et al.*, *Nat. Biotechnol.* 22:326-330 (2004), Chi *et al.*, *Proc. Natl. Acad. Sci. USA* 100:6343-6346 (2003), Vickers *et al.*, *J. Biol. Chem.* 278:7108-7118 (2003), Agami, *Curr. Opin. Chem. Biol.* 6:829-834 (2002), Lavery, *et al.*, *Curr. Opin. Drug Discov. Devel.* 6:561-569 (2003), Shi, *Trends Genet.* 19:9-12 (2003), Shuey *et al.*, *Drug Discov. Today* 7:1040-46 (2002), McManus *et al.*, *Nat. Rev. Genet.* 3:737-747 (2002), Xia *et al.*, *Nat. Biotechnol.* 20:1006-10 (2002), Plasterk *et al.*, *curr. Opin. Genet. Dev.* 10:562-7 (2000), Boshier *et al.*, *Nat. Cell Biol.* 2:E31-6 (2000), and Hunter, *Curr. Biol.* 9:R440-442 (1999).

A genetic defect leading to increased predisposition or risk for development of a disease, including Type 2 diabetes, or a defect causing the disease, may be corrected permanently by administering to a subject carrying the defect a nucleic acid fragment that incorporates a repair sequence that supplies the normal/wild-type nucleotide(s) at the site of the genetic defect. Such site-specific repair sequence may encompass an RNA/DNA oligonucleotide that operates to promote endogenous repair of a subject's genomic DNA. The administration of the repair sequence may be performed by an appropriate vehicle, such as a complex with polyethelenimine, encapsulated in anionic liposomes, a viral vector such as an adenovirus vector, or other pharmaceutical compositions suitable for promoting intracellular uptake of the administered nucleic acid. The genetic defect may then be overcome, since the chimeric oligonucleotides induce the incorporation of the normal sequence into the genome of the subject, leading to expression of the normal/wild-type gene product. The replacement is propagated, thus rendering a permanent repair and alleviation of the symptoms associated with the disease or condition.

The present invention provides methods for identifying compounds or agents that can be used to treat Type 2 diabetes. Thus, the variants of the invention are useful as targets for the identification and/or development of therapeutic agents. Such methods may include assaying the ability of an agent or compound to modulate the activity and/or expression of a nucleic acid that includes at least one of the variants (markers and/or haplotypes) of the present invention, or the encoded product of the nucleic acid. This in turn can be used to identify agents or compounds that inhibit or alter the undesired activity or expression of the encoded nucleic acid product. Assays for performing such experiments can be performed in cell-based systems or in cell-free systems, as known to the skilled person. Cell-based systems include cells naturally expressing the nucleic acid molecules of interest, or recombinant cells that have been genetically modified so as to express a certain desired nucleic acid molecule.

Variant gene expression in a patient can be assessed by expression of a variant-containing nucleic acid sequence (for example, a gene containing at least one variant of the present invention, which can be transcribed into RNA containing the at least one

variant, and in turn translated into protein), or by altered expression of a normal/wild-type nucleic acid sequence due to variants affecting the level or pattern of expression of the normal transcripts, for example variants in the regulatory or control region of the gene. Assays for gene expression include direct nucleic acid assays (mRNA), assays for
5 expressed protein levels, or assays of collateral compounds involved in a pathway, for example a signal pathway. Furthermore, the expression of genes that are up- or down-regulated in response to the signal pathway can also be assayed. One embodiment includes operably linking a reporter gene, such as luciferase, to the regulatory region of the gene(s) of interest.

10 Modulators of gene expression can in one embodiment be identified when a cell is contacted with a candidate compound or agent, and the expression of mRNA is determined. The expression level of mRNA in the presence of the candidate compound or agent is compared to the expression level in the absence of the compound or agent. Based on this comparison, candidate compounds or agents for treating Type 2 diabetes
15 can be identified as those modulating the gene expression of the variant gene. When expression of mRNA or the encoded protein is statistically significantly greater in the presence of the candidate compound or agent than in its absence, then the candidate compound or agent is identified as a stimulator or up-regulator of expression of the nucleic acid. When nucleic acid expression or protein level is statistically significantly less
20 in the presence of the candidate compound or agent than in its absence, then the candidate compound is identified as an inhibitor or down-regulator of the nucleic acid expression.

The invention further provides methods of treatment using a compound identified through drug (compound and/or agent) screening as a gene modulator (i.e. stimulator
25 and/or inhibitor of gene expression).

In a further aspect of the present invention, a pharmaceutical pack (kit) is provided, the pack comprising a therapeutic agent and a set of instructions for administration of the therapeutic agent to humans diagnostically tested for one or more variants of the present invention, as disclosed herein. The therapeutic agent can be a
30 small molecule drug, an antibody, a peptide, an antisense or RNAi molecule, or other therapeutic molecules. In one embodiment, an individual identified as a carrier of at least one variant of the present invention is instructed to take a prescribed dose of the therapeutic agent. In one such embodiment, an individual identified as a homozygous carrier of at least one variant of the present invention is instructed to take a prescribed
35 dose of the therapeutic agent. In another embodiment, an individual identified as a non-carrier of at least one variant of the present invention is instructed to take a prescribed dose of the therapeutic agent.

Methods of assessing probability of response to therapeutic agents, methods of monitoring progress of treatment and methods of treatment

As is known in the art, individuals can have differential responses to a particular therapy (e.g., a therapeutic agent or therapeutic method). Pharmacogenomics addresses the issue of how genetic variations (e.g., the variants (markers and/or haplotypes) of the present invention) affect drug response, due to altered drug disposition and/or abnormal or altered action of the drug. Thus, the basis of the differential response may be genetically determined in part. Clinical outcomes due to genetic variations affecting drug response may result in toxicity of the drug in certain individuals (e.g., carriers or non-carriers of the genetic variants of the present invention), or therapeutic failure of the drug. Therefore, the variants of the present invention may determine the manner in which a therapeutic agent and/or method acts on the body, or the way in which the body metabolizes the therapeutic agent.

Accordingly, in one embodiment, the presence of a particular allele at a polymorphic site or haplotype is indicative of a different, e.g. a different response rate, to a particular treatment modality. This means that a patient diagnosed with Type 2 diabetes, and carrying a certain allele at a polymorphic or haplotype of the present invention (e.g., the at-risk and protective alleles and/or haplotypes of the invention) would respond better to, or worse to, a specific therapeutic, drug and/or other therapy used to treat the disease. Therefore, the presence or absence of the marker allele or haplotype could aid in deciding what treatment should be used for a the patient. For example, for a newly diagnosed patient, the presence of a marker or haplotype of the present invention may be assessed (e.g., through testing DNA derived from a blood sample, as described herein). If the patient is positive for a marker allele or haplotype at (that is, at least one specific allele of the marker, or haplotype, is present), then the physician recommends one particular therapy, while if the patient is negative for the at least one allele of a marker, or a haplotype, then a different course of therapy may be recommended (which may include recommending that no immediate therapy, other than serial monitoring for progression of the disease, be performed). Thus, the patient's carrier status could be used to help determine whether a particular treatment modality should be administered. The value lies within the possibilities of being able to diagnose the disease at an early stage, to select the most appropriate treatment, and provide information to the clinician about prognosis/aggressiveness of the disease in order to be able to apply the most appropriate treatment.

In some embodiments, the treatment modality comprises administering at least one of the therapeutic agents set forth in Agent Table 1 and Agent Table 2. In one

embodiment, the therapeutic agent is selected from Biguanides, Thiazolidinediones, Sulfonylureas, Meglitinides, Alpha-glucosidase inhibitors and DPP-4 inhibitors. In one embodiment, the Biguanide is metformin or metformin plus glyburide. Other combination therapies comprising metformin, including combinations with thiazolidinediones, are also contemplated and within the scope of the invention. In another embodiment, the Sulfonylurea is selected from acetohexamide, chlorpropamide, gliclazide Diamicon, glimepiride, glipizide, glyburide, tolazamide and tolbutamide. In another embodiment, the Thiazolidinedione is selected from pioglitazone, rosiglitazone and mitoglitazone or other thiazolidinedione derivatives. In another embodiment, the therapeutic agent is selected from the agents set forth in Agent Table 2.

The present invention also relates to methods of monitoring progress or effectiveness of a treatment for Type 2 diabetes. This can be done based on the genotype and/or haplotype status of the markers and haplotypes of the present invention, i.e., by assessing the absence or presence of at least one allele of at least one polymorphic marker as disclosed herein, or by monitoring expression of genes that are associated with the variants (markers and haplotypes) of the present invention. The risk gene mRNA or the encoded polypeptide can be measured in a tissue sample (e.g., a peripheral blood sample, or a biopsy sample). Expression levels and/or mRNA levels can thus be determined before and during treatment to monitor its effectiveness. Alternatively, or concomitantly, the genotype and/or haplotype status of at least one risk variant for Type 2 diabetes presented herein is determined before and during treatment to monitor its effectiveness. Alternatively, biological networks or metabolic pathways related to the markers and haplotypes of the present invention can be monitored by determining mRNA and/or polypeptide levels. This can be done for example, by monitoring expression levels or polypeptides for several genes belonging to the network and/or pathway, in samples taken before and during treatment. Alternatively, metabolites belonging to the biological network or metabolic pathway can be determined before and during treatment. Effectiveness of the treatment is determined by comparing observed changes in expression levels/metabolite levels during treatment to corresponding data from healthy subjects.

The progress of therapy in individuals carrying at least one at-risk allele of at least one marker found to be associated with increased susceptibility or risk of Type 2 diabetes is thus monitored based on the genotype status of the individual. Individuals carrying at-risk variants as described herein may benefit from closer or more frequent monitoring of progress of therapy than non-carriers, alternatively in combination with a particular treatment modality or therapeutic agent being administered, as described in the above.

In a further aspect, the markers of the present invention can be used to increase power and effectiveness of clinical trials. Thus, individuals who are carriers of at least one

at-risk variant of the present invention, i.e. individuals who are carriers of at least one allele of at least one polymorphic marker conferring increased risk of developing Type 2 diabetes may be more likely to respond to a particular treatment modality. In one embodiment, individuals who carry at-risk variants for gene(s) in a pathway and/or metabolic network for which a particular treatment (e.g., small molecule drug) is targeting, are more likely to be responders to the treatment. In another embodiment, individuals who carry at-risk variants for a gene, which expression and/or function is altered by the at-risk variant, are more likely to be responders to a treatment modality targeting that gene, its expression or its gene product. This application can improve the safety of clinical trials, but can also enhance the chance that a clinical trial will demonstrate statistically significant efficacy, which may be limited to a certain sub-group of the population, e.g., individuals that are either carriers or non-carriers of the at-risk variants described herein. Thus, one possible outcome of such a trial is that carriers of certain genetic variants, e.g., the markers and haplotypes of the present invention, are statistically significantly likely to show positive response to the therapeutic agent, i.e. experience alleviation of symptoms associated with Type 2 diabetes when taking the therapeutic agent or drug as prescribed.

In a further aspect, the markers and haplotypes of the present invention can be used for targeting the selection of pharmaceutical agents for specific individuals. Personalized selection of treatment modalities, lifestyle changes or combination of the two, can be realized by the utilization of the at-risk variants of the present invention. Thus, the knowledge of an individual's status for particular markers of the present invention, can be useful for selection of treatment options that target genes or gene products affected by the at-risk variants of the invention. Certain combinations of variants may be suitable for one selection of treatment options, while other gene variant combinations may target other treatment options. Such combination of variant may include one variant, two variants, three variants, or four or more variants, as needed to determine with clinically reliable accuracy the selection of treatment module.

In addition to the diagnostic and therapeutic uses of the variants of the present invention, the variants (markers and haplotypes) can also be useful markers for human identification, and as such be useful in forensics, paternity testing and in biometrics. The specific use of SNPs for forensic purposes is reviewed by Gill (*Int. J. Legal Med.* 114:204-10 (2001)). Genetic variations in genomic DNA between individuals can be used as genetic markers to identify individuals and to associate a biological sample with an individual. Genetic markers, including SNPs and microsatellites, can be useful to distinguish individuals. The more markers that are analyzed, the lower the probability that the allelic combination of the markers in any given individual is the same as in an unrelated individual (assuming that the markers are unrelated, i.e. that the markers are in perfect linkage equilibrium). Thus, the variants used for these purposes are preferably

unrelated, i.e. they are inherited independently. Thus, preferred markers can be selected from available markers, such as the markers of the present invention, and the selected markers may comprise markers from different regions in the human genome, including markers on different chromosomes.

5 In certain applications, the SNPs useful for forensic testing are from degenerate codon positions (i.e., the third position in certain codons such that the variation of the SNP does not affect the amino acid encoded by the codon). In other applications, such for applications for predicting phenotypic characteristics including race, ancestry or physical characteristics, it may be more useful and desirable to utilize SNPs that affect the amino
10 acid sequence of the encoded protein. In other such embodiments, the variant (SNP or other polymorphic marker) affects the expression level of a nearby gene, thus leading to altered protein expression.

The present invention also relates to computer-implemented applications of the polymorphic markers and haplotypes described herein to be associated with Type 2
15 diabetes. Such applications can be useful for storing, manipulating or otherwise analyzing genotype data that is useful in the methods of the invention. One example pertains to storing genotype information derived from an individual on readable media, so as to be able to provide the genotype information to a third party (e.g., the individual), or for deriving information from the genotype data, e.g., by comparing the genotype data to
20 information about genetic risk factors contributing to increased susceptibility to Type 2 diabetes, and reporting results based on such comparison.

One such aspect relates to computer-readable media. In general terms, such medium has capabilities of storing (i) identifier information for at least one polymorphic marker or a haplotype; (ii) an indicator of the frequency of at least one allele of said at
25 least one marker, or the frequency of a haplotype, in individuals with Type 2 diabetes; and an indicator of the frequency of at least one allele of said at least one marker, or the frequency of a haplotype, in a reference population. The reference population can be a disease-free population of individuals. Alternatively, the reference population is a random sample from the general population, and is thus representative of the population at large.
30 The frequency indicator may be a calculated frequency, a count of alleles and/or haplotype copies, or normalized or otherwise manipulated values of the actual frequencies that are suitable for the particular medium.

Additional information about the individual can be stored on the medium, such as ancestry information, information about sex, physical attributes or characteristics
35 (including height and weight), biochemical measurements (such as blood pressure, blood lipid levels, fasting glucose levels, insulin response measurements), or other useful

information that is desirable to store or manipulate in the context of the genotype status of a particular individual.

The invention furthermore relates to an apparatus that is suitable for determination or manipulation of genetic data useful for determining a susceptibility to Type 2 diabetes in a human individual. Such an apparatus can include a computer-readable memory, a routine for manipulating data stored on the computer-readable memory, and a routine for generating an output that includes a measure of the genetic data. Such measure can include values such as allelic or haplotype frequencies, genotype counts, sex, age, phenotype information, values for odds ratio (OR) or relative risk (RR), population attributable risk (PAR), or other useful information that is either a direct statistic of the original genotype data or based on calculations based on the genetic data.

The above-described applications can all be practiced with the markers and haplotypes of the invention that have in more detail been described with respect to methods of assessing susceptibility to Type 2 diabetes. Thus, these applications can in general be reduced to practice using markers listed in Tables 1-6, and markers in linkage disequilibrium therewith, *e.g.* the markers set forth in Tables 22, 23 and 24. In one embodiment, the markers or haplotypes are present within the genomic segments whose sequences are set forth in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3. In another embodiment, the markers and haplotypes comprise at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), and rs9890889 (SEQ ID NO:31), optionally including markers in linkage disequilibrium therewith, wherein linkage disequilibrium is defined by numerical values for r^2 of greater than 0.2. In another embodiment, the marker or haplotype comprises at least one marker selected from rs2497304 allele A, rs947591 allele A, rs10882091 allele C, rs7914814 allele T, rs6583830 allele A, rs2421943 allele G, rs6583826 allele G, rs7752906 allele A, rs1569699 allele C, rs7756992 allele G, rs9350271 allele A, rs9356744 allele C, rs9368222 allele A, rs10440833 allele A, rs6931514 allele G, rs1860316 allele A, rs1981647 allele C, rs1843622 allele T, rs2191113 allele A, and rs9890889 allele A. In yet another embodiment, the at least one marker or haplotype comprises at least one marker selected from the markers set forth in Tables 22, 23 and 24.

Nucleic acids and polypeptides

The nucleic acids and polypeptides described herein can be used in methods of diagnosis of a susceptibility to Type 2 diabetes, as well as in kits useful for such diagnosis.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (e.g., as in an RNA library). For example, an isolated nucleic acid of the invention can be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material can be purified to essential homogeneity, for example as determined by polyacrylamide gel electrophoresis (PAGE) or column chromatography (e.g., HPLC). An isolated nucleic acid molecule of the invention can comprise at least about 50%, at least about 80% or at least about 90% (on a molar basis) of all macromolecular species present. With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 250 kb, 200 kb, 150 kb, 100 kb, 75 kb, 50 kb, 25 kb, 10 kb, 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of the nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells or heterologous organisms, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Such isolated nucleotide sequences are useful, for example, in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (e.g., from other mammalian species), for gene mapping (e.g., by *in situ* hybridization with chromosomes), or for detecting expression of the gene in tissue (e.g., human tissue), such as by Northern blot analysis or other hybridization techniques.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide

sequence described herein (e.g., nucleic acid molecules that specifically hybridize to a nucleotide sequence containing a polymorphic site associated with a haplotype described herein). In one embodiment, the invention includes variants that hybridize under high stringency hybridization and wash conditions (e.g., for selective hybridization) to a nucleotide sequence that comprises the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2; e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes) and LD Block C17 (SEQ ID NO:3), or the CDKAL1 gene or a fragment thereof (or a nucleotide sequence comprising the complement of the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2; e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes) and LD Block C17 (SEQ ID NO:3), or the CDKAL1 gene or a fragment thereof), wherein the nucleotide sequence comprises at least one polymorphic allele contained in the haplotypes (e.g., haplotypes) described herein.

Such nucleic acid molecules can be detected and/or isolated by allele- or sequence-specific hybridization (e.g., under high stringency conditions). Stringency conditions and methods for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (Ausubel, F. et al., "Current Protocols in Molecular Biology", John Wiley & Sons, (1998)), and Kraus, M. and Aaronson, S., *Methods Enzymol.*, 200:546-556 (1991), the entire teachings of which are incorporated by reference herein.

The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions x 100). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A non-limiting example of such a mathematical algorithm is described in Karlin, S. and Altschul, S., *Proc. Natl. Acad. Sci. USA*, 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0), as described in Altschul, S. et al., *Nucleic Acids Res.*, 25:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. See the website on the world wide web at ncbi.nlm.nih.gov. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (e.g., W=5 or W=20).

Other examples include the algorithm of Myers and Miller, CABIOS (1989), ADVANCE and ADAM as described in Torellis, A. and Robotti, C., *Comput. Appl. Biosci.* 10:3-5 (1994); and FASTA described in Pearson, W. and Lipman, D., *Proc. Natl. Acad. Sci. USA*, 85:2444-48 (1988). In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (Accelrys, Cambridge, UK).

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid that comprises, or consists of, the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2; e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes) and LD Block C17 (SEQ ID NO:3), or the CDKAL1 gene or a fragment thereof (or a nucleotide sequence comprising, or consisting of, the complement of the nucleotide sequence of LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2; e.g., the nucleotide sequence encoding the IDE, KIF11 and/or the HHEX genes) and LD Block C17 (SEQ ID NO:3), or the CDKAL1 gene or a fragment thereof), wherein the nucleotide sequence comprises at least one polymorphic allele contained in the haplotypes (e.g., haplotypes) described herein. The nucleic acid fragments of the invention are at least about 15, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200, 500, 1000, 10,000 or more nucleotides in length.

The nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of a nucleic acid molecule. In addition to DNA and RNA, such probes and primers include polypeptide nucleic acids (PNA), as described in Nielsen, P. *et al.*, *Science* 254:1497-1500 (1991). A probe or primer comprises a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid molecule. In one embodiment, the probe or primer comprises at least one allele of at least one polymorphic marker or at least one haplotype described herein, or the complement thereof. In particular embodiments, a probe or primer can comprise 100 or fewer nucleotides; for example, in certain embodiments from 6 to 50 nucleotides, or, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. In another embodiment, the probe or primer is capable of selectively hybridizing to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, e.g., a radioisotope, a fluorescent label, an enzyme label, an enzyme co-factor label, a magnetic label, a spin label, an epitope label.

The nucleic acid molecules of the invention, such as those described above, can be identified and isolated using standard molecular biology techniques well known to the skilled person. The amplified DNA can be labeled (*e.g.*, radiolabeled) and used as a probe for screening a cDNA library derived from human cells. The cDNA can be derived from mRNA and contained in a suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

In general, the isolated nucleic acid sequences of the invention can be used as molecular weight markers on Southern gels, and as chromosome markers that are labeled to map related gene positions. The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify Type 2 diabetes or a susceptibility to Type 2 diabetes, and as probes, such as to hybridize and discover related DNA sequences or to subtract out known sequences from a sample (*e.g.*, subtractive hybridization). The nucleic acid sequences can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using immunization techniques, and/or as an antigen to raise anti-DNA antibodies or elicit immune responses.

Antibodies

Polyclonal antibodies and/or monoclonal antibodies that specifically bind one form of the gene product but not to the other form of the gene product are also provided. Antibodies are also provided which bind a portion of either the variant or the reference gene product that contains the polymorphic site or sites. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain antigen-binding sites that specifically bind an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal

antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, polypeptide of the invention or a
5 fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain
10 the IgG fraction. At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today* 4: 72 (1983)), the EBV-hybridoma
15 technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan *et al.*, (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as
20 described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody
25 to a polypeptide of the invention (see, *e.g.*, *Current Protocols in Immunology*, *supra*; Galfre *et al.*, *Nature* 266:55052 (1977); R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.* 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be
30 useful.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind
35 the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™* Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use

in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology* 9: 1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*, *Science* 246: 1275-1281 (1989); and Griffiths *et al.*, *EMBO J.* 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies (*e.g.*, a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide. Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. The antibody can be coupled to a detectable substance to facilitate its detection. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Antibodies may also be useful in pharmacogenomic analysis. In such embodiments, antibodies against variant proteins encoded by nucleic acids as described herein, such as variant proteins that are encoded by nucleic acids that contain at least one polymorphic marker of the invention, can be used to identify individuals that require modified treatment modalities.

Antibodies can furthermore be useful for assessing expression of variant proteins in disease states, such as in active stages of Type 2 diabetes, or in an individual with a predisposition to Type 2 diabetes that is related to the function of the protein. Antibodies specific for a variant protein of the present invention that is encoded by a nucleic acid that
5 comprises at least one polymorphic marker or haplotype as described herein can be used to screen for the presence of the variant protein, for example to screen for a predisposition to Type 2 diabetes as indicated by the presence of the variant protein.

Antibodies can be used in other methods. Thus, antibodies are useful as diagnostic tools for evaluating proteins, such as variant proteins of the invention, in
10 conjunction with analysis by electrophoretic mobility, isoelectric point, tryptic or other protease digest, or for use in other physical assays known to those skilled in the art. Antibodies may also be used in tissue typing. In one such embodiment, a specific variant protein has been correlated with expression in a specific tissue type, and antibodies specific for the variant protein can then be used to identify the specific tissue type.

15 Subcellular localization of proteins, including variant proteins, can also be determined using antibodies, and can be applied to assess aberrant subcellular localization of the protein in cells in various tissues. Such use can be applied in genetic testing, but also in monitoring a particular treatment modality. In the case where treatment is aimed at correcting the expression level or presence of the variant protein or
20 aberrant tissue distribution or developmental expression of the variant protein, antibodies specific for the variant protein or fragments thereof can be used to monitor therapeutic efficacy.

Antibodies are further useful for inhibiting variant protein function, for example by blocking the binding of a variant protein to a binding molecule or partner. Such uses can
25 also be applied in a therapeutic context in which treatment involves inhibiting a variant protein's function. An antibody can be for example be used to block or competitively inhibit binding, thereby modulating (i.e., agonizing or antagonizing) the activity of the protein. Antibodies can be prepared against specific protein fragments containing sites required for specific function or against an intact protein that is associated with a cell or
30 cell membrane. For administration *in vivo*, an antibody may be linked with an additional therapeutic payload, such as radionuclide, an enzyme, an immunogenic epitope, or a cytotoxic agent, including bacterial toxins (diphtheria or plant toxins, such as ricin). The *in vivo* half-life of an antibody or a fragment thereof may be increased by pegylation through conjugation to polyethylene glycol.

35 The present invention will now be exemplified by the following non-limiting examples.

EXEMPLIFICATION

EXAMPLE 1

5 The following contains description of the identification of susceptibility factors found to be associated with Type 2 diabetes through single-point and haplotype analysis of SNP markers.

METHODS

10 Icelandic cohort

 The Data Protection Authority of Iceland and the National Bioethics Committee of Iceland approved the study. All participants in the study gave informed consent. All personal identifiers associated with blood samples, medical information and genealogy were first encrypted by the Data Protection Authority, using a third-party encryption system.

15 For this study, 2400 Type 2 diabetes patients were identified who were diagnosed either through a long-term epidemiologic study done at the Icelandic Heart Association over the past 30 years or at one of two major hospitals in Reykjavik over the past 12 years. Two-thirds of these patients were alive, representing about half of the population of known Type 2 diabetes patients in Iceland today. The majority of these patients were contacted for this
20 study, and the cooperation rate exceeded 80%. All participants in the study visited the Icelandic Heart Association where they answered a questionnaire, had blood drawn and a fasting plasma glucose measurements taken. Questions about medication and age at diagnosis were included. The Type 2 diabetes patients in this study were diagnosed as described in our previously published linkage study (Reynisdottir *et al.*, *Am J Hum Genet* 73, 323 (2003). In brief, the diagnosis of Type 2 diabetes was confirmed by study physicians
25 through previous medical records, medication history, and/or new laboratory measurements. For previously diagnosed Type 2 diabetes patients, reporting of the use of oral glucose-lowering agent confirmed Type 2 diabetes. Individuals who were currently treated with insulin were classified as having Type 2 diabetes if they were also using or had previously used oral
30 glucose-lowering agents. In this cohort the majority of patients on medication take oral glucose-lowering agents and only a small portion (9%) require insulin. For hitherto undiagnosed individuals, the diagnosis of Type 2 diabetes and impaired fasting glucose (IFG) was based on the criteria set by the American Diabetes Association (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). The average age of the Type 2
35 diabetes patients in this study was 69.7 years.

Replication cohorts

The Danish study group was a set of Type 2 diabetes patients from the Steno Diabetes Center in Copenhagen (N=1,018) and from the Inter99 population-based sample of 30-60 year old individuals living in the greater Copenhagen area and sampled at Research Centre for Prevention and Health28 (N=359). Diabetes and pre-diabetes categories were diagnosed according to the 1999 World Health Organization (WHO) criteria. An effectively random subset (N=2,400) of Danish controls with BMI measurements were obtained from the Inter99 collection. Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen County and was in accordance with the principles of the Helsinki Declaration.

The PENN CATH study in the US is a cross sectional study of the association of biochemical and genetic factors with coronary atherosclerosis in a consecutive cohort of patients undergoing cardiac catheterization at the University of Pennsylvania Medical Center between July 1998 and March 2003. Type 2 diabetes was defined as history of fasting blood glucose ≥ 126 mg/dl, 2-hour post-prandial glucose ≥ 200 mg/dl, use of oral hypoglycemic agents, or insulin and oral hypoglycemic in a subject greater than age 40. The University of Pennsylvania Institutional Review Board approved the study protocol and all subjects gave written informed consent. Ethnicity was determined through self-report. A total of 468 Caucasian Type 2 diabetes cases were derived from this cohort. Additionally, 1024 unaffected (with respect to Type 2 diabetes) Caucasian controls were randomly drawn from the same study.

The DNA used for genotyping was the product of whole-genome amplification, by use of the GenomiPhi Amplification kit (Amersham), of DNA isolated from the peripheral blood of the Danish and US Type 2 diabetes patients and controls.

Genotyping

A genome-wide scan of 1399 Icelandic diabetes patients was performed using Infinium HumanHap300 SNP chips from Illumina for assaying approximately 317,000 single nucleotide polymorphisms (SNPs) on a single chip (Illumina, San Diego, CA, USA). SNP genotyping for replication in other case-control cohorts was carried using the Centaurus platform (Nanogen).

Statistical Methods for Association Analysis

For single marker association to Type 2 diabetes, we used a likelihood ratio test to calculate a two-sided p-value for each allele. We calculated relative risk (RR) and population attributable risk (PAR) assuming a multiplicative model (C. T. Falk, P. Rubinstein, *Ann Hum Genet* 51 (Pt 3), 227 (1987); J. D. Terwilliger, J. Ott, *Hum Hered* 42, 337 (1992)). For the CEPH Caucasian HapMap data, we calculated LD between pairs of SNPs using the standard definition of D' (R. C. Lewontin, *Genetics* 50, 757 (1964)) and

R^2 W. G. Hill, A. Robertson, *Genetics* 60, 615 (Nov, 1968). When plotting all SNP combinations to elucidate the LD structure in a particular region, we plotted D' in the upper left corner and p-values in the lower right corner. In the LD plots we present, the markers are plotted equidistantly rather than according to their physical positions.

5

RESULTS

Genome-wide association study

We successfully genotyped 1399 Icelandic Type 2 diabetes patients and 5275 population control individuals using the Illumina 330K chip. Association analysis was performed using single SNPs, two marker haplotypes and extended haplotypes within LD blocks. After correcting the p-value for relatedness we identified 49 single markers and two marker haplotypes at 21 loci (i.e. genetic susceptibility locations in the genome) that had a p-value less than 5×10^{-5} (Table 1). In addition, 10 extended haplotypes at 8 additional loci were selected by the same criteria (Table 2). Within the patient group, 700 individuals were non-obese (BMI < 30) and those were tested separately for association. After correcting the p-value for relatedness, 36 single markers and two marker haplotypes at 20 loci had a p-value less than 5×10^{-5} (Table 3). Three of those loci were also identified when the total group was analysed. In addition 6 extended haplotypes at 4 additional loci were selected by the same criteria (Table 4). The obese group of 531 patients (BMI > 30) was also analysed separately for association. After correcting the p-value for relatedness 38 single markers and two marker haplotypes at 16 loci had a p-value less than 5×10^{-5} (Table 5). One of those loci was also identified when the total group was analysed but no overlap was found between the non-obese and obese groups using this criteria. In addition 10 extended haplotypes at 7 additional loci had a p-value less than 5×10^{-5} in association analysis of obese diabetics (Table 6).

The single-marker association and two-marker and extended haplotype association analysis presented in Tables 1-6 thus represents evidence for multiple susceptibility variants for Type 2 diabetes. It should be noted that for single-marker SNP analysis as presented herein, susceptibility variants can either be represented by increased risk, wherein one allele is overrepresented in the patient group compared with controls. Alternatively, the susceptibility variants can be represented by the other allele of the SNP in question – for that allele, under-representation in patients compared with controls is expected. This is a natural consequence of association analysis to genetic elements comprising two alleles. For multi-marker haplotypes or for polymorphic markers comprising more than one marker, at-risk association may be observed to one (or more) at-risk allele or haplotype. Protective variants in form of association (with RR-values less than unity) to one (or more) protective variants or haplotypes may also be observed, depending on the genetic composition and haplotype structure in the genetic region in question.

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Table 1. Single markers and two marker haplotypes associated with Type 2 Diabetes. Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Chr	Pos	Punadj	Padj	Risk	Aff.frq	Ctrl.frq	Haplotype
chr1	151511890	4.01E-06	4.49E-05	1.223	0.407	0.360	3 rs3738028
chr2	40560735	2.41E-06	3.06E-05	1.225	0.593	0.543	1 rs13414307
chr2	40560735	4.59E-07	8.27E-06	1.243	0.571	0.517	1 rs13414307 3 rs1990609
chr2	54969849	5.53E-08	1.56E-06	1.287	0.335	0.281	3 rs930493 4 rs10173697
chr2	54977961	3.12E-06	3.75E-05	1.224	0.553	0.503	4 rs10173697
chr3	89323970	2.60E-06	3.25E-05	1.380	0.904	0.872	4 rs12486049
chr6	6965113	1.00E-06	1.53E-05	1.705	0.072	0.044	1 rs490213 3 rs814174
chr6	31556294	3.22E-06	3.78E-05	1.232	0.372	0.325	2 rs2516424
chr6	31556294	1.93E-06	2.57E-05	1.240	0.368	0.320	2 rs2516424 2 rs4947324
chr6	132422361	3.10E-06	3.74E-05	1.262	0.278	0.234	3 rs9483377 2 rs997607
chr6	132422361	3.97E-06	4.54E-05	1.252	0.276	0.233	3 rs9483377 3 rs7745875
chr6	132422361	7.98E-07	1.25E-05	1.249	0.356	0.307	3 rs9483377
chr6	150460378	5.01E-07	8.86E-06	1.293	0.794	0.749	1 rs11155700
chr6	150461077	5.15E-07	9.05E-06	1.292	0.794	0.749	2 rs12213837
chr6	164474219	3.07E-06	3.63E-05	0.813	0.479	0.531	4 rs206732 2 rs933251
chr7	87951463	4.36E-06	4.89E-05	1.273	0.753	0.705	1 rs2192319
chr8	124196776	1.21E-06	1.78E-05	1.253	0.721	0.673	3 rs952656
chr8	124202699	5.97E-07	9.96E-06	0.722	0.108	0.143	4 rs13252935 3 rs7824293
chr9	90164936	2.03E-06	2.62E-05	1.304	0.192	0.154	1 rs10993008
chr9	95493692	2.38E-06	3.03E-05	1.253	0.309	0.263	3 rs10990568 3 rs4743148
chr9	95510129	5.85E-07	9.80E-06	1.252	0.365	0.315	3 rs4743148
chr10	53058229	1.39E-06	1.98E-05	1.240	0.377	0.328	4 rs7915186 4 rs3829170
chr10	53063104	1.37E-06	1.96E-05	1.239	0.386	0.336	4 rs3829170 3 rs7922112
chr10	94301795	2.54E-08	8.44E-07	1.276	0.614	0.555	3 rs2421943
chr10	94301795	2.11E-09	1.19E-07	1.297	0.585	0.521	3 rs2421943 2 rs7917359
chr10	94304784	1.49E-07	3.32E-06	0.797	0.443	0.499	3 rs7908111 3 rs2497304
chr10	94309972	6.60E-09	2.85E-07	0.779	0.455	0.517	3 rs1999763 4 rs10882091
chr10	94309972	6.60E-09	2.85E-07	0.779	0.455	0.517	3 rs1999763 3 rs6583830
chr10	94337810	1.36E-06	1.91E-05	1.228	0.518	0.467	3 rs6583826
chr10	94337810	7.18E-08	1.91E-06	1.262	0.449	0.393	3 rs6583826 2 rs10882091
chr10	94364357	7.76E-08	2.04E-06	1.259	0.466	0.410	2 rs10882091 3 rs7923837
chr10	94364357	9.33E-08	2.30E-06	1.256	0.472	0.415	2 rs10882091
chr10	94372930	9.81E-08	2.40E-06	1.256	0.472	0.415	4 rs7914814
chr10	94388098	9.33E-08	2.30E-06	1.256	0.472	0.415	1 rs6583830
chr10	94442410	8.41E-08	2.17E-06	1.256	0.527	0.470	1 rs2275729 3 rs1111875
chr10	94482696	7.56E-08	1.95E-06	1.258	0.542	0.485	1 rs2497304
chr10	94485733	1.64E-06	2.21E-05	1.225	0.526	0.475	1 rs947591
chr12	33373479	3.87E-06	4.37E-05	1.391	0.110	0.082	4 rs1905421
chr15	98156854	3.80E-06	4.30E-05	0.815	0.469	0.521	1 rs9920347 3 rs11635811
chr16	22705353	2.93E-06	3.57E-05	1.264	0.781	0.738	4 rs724466
chr16	72066252	4.23E-06	4.68E-05	0.625	0.038	0.059	2 rs1862773 4 rs825842
chr16	72086481	5.86E-07	9.82E-06	0.612	0.043	0.069	4 rs2432543 3 rs4887826
chr17	66072384	7.34E-07	1.20E-05	1.236	0.564	0.511	3 rs17763769 1 rs1860316
chr17	66117911	1.18E-07	2.77E-06	0.781	0.282	0.335	3 rs1860316 2 rs17763811
chr17	66117911	6.79E-08	1.83E-06	1.281	0.707	0.653	1 rs1860316

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chr17	66132788	1.80E-06	2.43E-05	1.226	0.563	0.513	2 rs1981647
chr17	66149102	1.39E-06	1.99E-05	1.239	0.665	0.615	4 rs1843622
chr17	66159416	7.32E-07	1.19E-05	1.266	0.744	0.696	1 rs2191113
chr20	36391335	2.09E-07	4.45E-06	1.250	0.550	0.495	3 rs4592915 2 rs2232580

Table 2. Multi - marker haplotypes associated with Type 2 Diabetes.

Chr	Pos	Punadj	Padj	Risk	Aff.frq	Ctrl.frq	Haplotype*
chr2	19652497	2.00E-08	6.98E-07	2.492	0.027	0.011	
3	rs1593746 3 rs4666491 3 rs12710718 4 rs1579204 1 rs824506 2 rs1344652 1 rs4109456 3 rs1427547 2 rs1522490 1 rs6757410 4 rs1863776						
chr2	74747736	1.95E-06	2.59E-05	1.903	0.036	0.019	
2	rs363674 2 rs759075 1 rs4853033 1 rs205651 4 rs363608 1 rs1063588 2 rs363612 1 rs150139 2 rs363617 4 rs1137 4 rs828902 1 rs205627						
chr9	29300367	5.32E-07	9.29E-06	1.813	0.042	0.024	
1	rs4879332 2 rs1928663 4 rs2183357 2 rs10813050 2 rs1928661 4 rs10491662 2 rs1169758 2 rs1169757 3 rs12378755						
chr9	32290296	4.13E-06	4.68E-05	1.489	0.075	0.052	
3	rs1537156 2 rs7024902 4 rs7037573 4 rs3928808 4 rs10970902 3 rs1331226 3 rs10758127 1 rs1331231 1 rs992710 2 rs1411866 3 rs10511901 3 rs2094703 1 rs7854942 4 rs2150637						
chr11	22912998	7.25E-07	1.19E-05	1.687	0.059	0.036	
3	rs11026796 1 rs1019216 2 rs2302423 4 rs4923035 1 rs2429777 4 rs12575930 3 rs887567 2 rs733295 3 rs7113718 1 rs7934814 4 rs3909703 4 rs3862134 3 rs10833917 1 rs6483890 2 rs2433454						
chr13	60726830	1.52E-06	2.12E-05	1.481	0.108	0.075	
4	rs1411145 4 rs9539100 3 rs991666 3 rs1026924 3 rs4886330 3 rs1411568 3 rs1028965 1 rs9670441						
chr16	72082296	1.71E-06	2.29E-05	0.595	0.033	0.054	
4	rs1424011 2 rs1862778 1 rs4888373 4 rs8053178 4 rs825842 4 rs2432543 2 rs6564272 3 rs4887826 3 rs825851						
chr17	66118095	3.46E-08	1.05E-06	0.762	0.229	0.281	
2	rs16913 2 rs10512540 3 rs17763769 1 rs2109051 3 rs1860316 3 rs9904090 4 rs1981647 2 rs1843622 2 rs4584866 3 rs17791650 3 rs9891997 3 rs2191113						
chr18	67477090	1.12E-06	1.64E-05	0.547	0.033	0.059	
2	rs9956771 4 rs8088887 2 rs10514019 4 rs719328 4 rs1942399 2 rs1942396 4 rs948665 3 rs11151691						
chrX	56884473	4.32E-06	4.85E-05	1.184	0.709	0.673	
1	rs12858633 1 rs5960235 3 rs5914036 3 rs6612746						

*Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Table 3. Single markers and two marker haplotypes associated with Type 2 Diabetes in non-obese patients

Chr	Pos	Punadj	Padj	Rrisk	Aff.frq	Ctrl.frq	Haplotype*
chr1	29759353	5.23E-06	3.18E-05	0.661	0.104	0.149	4 rs4949283 2 rs502545
chr2	53360168	8.51E-06	4.70E-05	1.411	0.855	0.807	1 rs1424963
chr5	87772535	1.95E-06	1.36E-05	1.394	0.244	0.188	3 rs10505855 2 rs12514611
chr6	6965113	5.76E-06	3.39E-05	1.891	0.080	0.044	1 rs490213 3 rs814174
chr6	20650200	8.46E-06	4.68E-05	1.327	0.307	0.250	3 rs7758851 2 rs1569699
chr6	20771314	1.06E-06	8.14E-06	1.369	0.292	0.232	1 rs4712527 3 rs7756992
chr6	20787289	4.47E-06	2.79E-05	1.333	0.315	0.256	2 rs1569699
chr6	20787688	1.78E-06	1.28E-05	0.741	0.682	0.743	1 rs7756992 3 rs9295478
chr6	20787688	1.11E-06	8.61E-06	1.368	0.292	0.232	3 rs7756992
chr9	95447272	6.08E-06	3.61E-05	0.764	0.469	0.536	2 rs10818991 2 rs10990303
chr11	23939149	3.05E-06	2.02E-05	1.525	0.128	0.088	4 rs1879230
chr11	130184827	9.00E-06	4.93E-05	1.303	0.416	0.353	4 rs11222327 1 rs1939905
chr13	26578564	2.15E-06	1.51E-05	0.723	0.220	0.281	1 rs565707 1 rs6491198
chr13	26578564	8.29E-07	6.63E-06	1.381	0.763	0.700	2 rs565707
chr13	26635031	3.14E-06	2.03E-05	1.309	0.606	0.540	2 rs7984685
chr13	26637643	3.37E-06	2.15E-05	1.308	0.606	0.540	2 rs7998347
chr13	26801814	9.09E-06	4.97E-05	1.340	0.771	0.716	1 rs1333350
chr13	26801814	1.29E-06	9.76E-06	0.709	0.195	0.254	3 rs1333350 4 rs7987436
chr13	108034018	9.08E-06	4.97E-05	1.322	0.732	0.674	2 rs4771591
chr16	12697094	8.10E-06	4.59E-05	0.616	0.068	0.105	2 rs6498353 3 rs9941146
chr17	66072384	2.10E-07	2.09E-06	1.347	0.585	0.511	3 rs17763769 1 rs1860316
chr17	66117911	1.01E-09	2.42E-08	0.677	0.254	0.335	3 rs1860316 2 rs17763811
chr17	66117911	1.20E-09	2.73E-08	1.462	0.734	0.653	1 rs1860316
chr17	66132788	7.18E-07	5.88E-06	1.329	0.583	0.513	2 rs1981647
chr17	66149102	4.33E-07	3.84E-06	1.355	0.684	0.615	4 rs1843622
chr17	66159416	4.49E-09	8.28E-08	1.467	0.771	0.696	1 rs2191113
chr17	66173475	4.75E-06	2.88E-05	1.472	0.885	0.839	1 rs9890889
chr18	41053807	4.27E-06	2.68E-05	1.389	0.218	0.167	3 rs10502860
chr18	63441694	8.25E-06	4.66E-05	0.687	0.121	0.167	4 rs764133 4 rs7237209
chr18	63465082	4.35E-06	2.67E-05	1.443	0.867	0.819	2 rs7237209
chr19	3316583	7.55E-06	4.33E-05	1.370	0.227	0.176	1 rs3810420
chr20	36391335	8.38E-06	4.65E-05	1.292	0.558	0.495	3 rs4592915 2 rs2232580
chr21	13769165	3.83E-06	2.40E-05	1.599	0.927	0.888	1 rs468601
chr21	33298252	1.17E-06	9.03E-06	1.358	0.311	0.249	3 rs2834061
chr21	39374906	4.04E-06	2.51E-05	1.308	0.631	0.566	4 rs369906
chr22	29580921	8.60E-06	4.75E-05	1.347	0.265	0.212	3 rs8142410 3 rs5994353

*Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Table 4. Multi- marker haplotypes associated with Type 2 Diabetes in non-obese patients

Chr	Pos	Punadj	Padj	Rrisk	Aff.frq	Ctrl.frq	Haplotype*
chr2	19652497	3.14E-07	2.93E-06	2.859	0.031	0.011	
3	rs1593746 3 rs4666491 3 rs12710718 4 rs1579204 1 rs824506 2 rs1344652 1 rs4109456 3 rs1427547 2 rs1522490 1 rs6757410 4 rs1863776						
chr5	2458281	6.12E-06	3.62E-05	0.077	0.001	0.017	
3	rs931283 1 rs160730 3 rs468085 4 rs464716 3 rs10052956 2 rs160729 3 rs315914 1 rs1039096						
chr6	137323498	6.46E-06	3.73E-05	2.566	0.040	0.016	
2	rs6570118 4 rs7743308 3 rs6928748 2 rs12214917 2 rs6936698 2 rs4896224 2 rs10872468						
chr11	32116221	4.15E-06	2.57E-05	1.362	0.266	0.211	
1	rs224633 3 rs581573 4 rs223070 4 rs10488686 4 rs4922579 2 rs110688 4 rs1605271 3 rs4922901 3 rs7950374 1 rs1033584 1 rs12788147 3 rs11031625 2 rs880587 4 rs989570 2 rs10835861						
chr17	66118095	7.82E-10	1.95E-08	0.660	0.205	0.281	
2	rs16913 2 rs10512540 3 rs17763769 1 rs2109051 3 rs1860316 3 rs9904090 4 rs1981647 2 rs1843622 2 rs4584866 3 rs17791650 3 rs9891997 3 rs2191113						
chr17	66204022	6.39E-06	3.76E-05	0.683	0.115	0.160	
2	rs9890889 4 rs2367005 2 rs2109054 3 rs17792120 1 rs7221340 4 rs1486293 2 rs1486296 2 rs17763811 4 rs9807096 3 rs10512541 3 rs8065001 2 rs4793501 3 rs929474 3 rs9907514						

*Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Table 5. Single markers and two marker haplotypes associated with Type 2 Diabetes in obese patients

Chr	Pos	Punadj	Padj	Risk	Aff.frq	Ctrl.frq	Haplotype*
chr1	104818519	5.60E-06	2.85E-05	1.343	0.466	0.394	2 rs7553985
chr1	104824377	4.76E-06	2.48E-05	1.346	0.466	0.393	4 rs2166890
chr1	104825870	6.28E-06	3.14E-05	1.355	0.396	0.317	4 rs7552405
chr3	147025256	7.11E-06	3.49E-05	1.696	0.097	0.059	3 rs7630694
chr3	197065940	2.81E-06	1.58E-05	1.396	0.737	0.668	1 rs9858622
chr4	140287637	4.41E-06	2.32E-05	1.431	0.804	0.741	1 rs13116075 1 rs6824182
chr4	140364285	1.05E-05	4.86E-05	0.708	0.194	0.254	4 rs2292837 2 rs11725721
chr4	140397800	8.21E-06	3.95E-05	0.704	0.194	0.254	3 rs3762864 2 rs11725721
chr5	76586085	9.46E-06	4.46E-05	0.750	0.438	0.510	1 rs832785 1 rs2859576
chr5	76586766	8.97E-06	4.26E-05	1.333	0.562	0.491	4 rs4704400
chr6	9509965	7.50E-06	3.66E-05	1.335	0.495	0.424	4 rs214447
chr6	22837279	1.03E-05	4.80E-05	1.430	0.824	0.766	2 rs10498713 3 rs4426986
chr6	41191330	3.22E-06	1.77E-05	1.360	0.637	0.563	1 rs10456499
chr8	128358773	4.94E-06	2.56E-05	0.692	0.190	0.254	2 rs283710 2 rs412835
chr8	128362648	6.35E-07	4.42E-06	1.495	0.822	0.755	3 rs185852
chr8	128376264	1.57E-06	9.59E-06	0.680	0.189	0.255	2 rs283718 1 rs283720
chr9	126494483	2.67E-06	1.51E-05	1.591	0.139	0.092	4 rs3814120
chr10	94301795	5.53E-07	3.93E-06	1.393	0.602	0.521	3 rs2421943 2 rs7917359
chr10	94304784	8.39E-06	4.02E-05	0.747	0.427	0.499	3 rs7908111 3 rs2497304
chr10	94309972	3.74E-06	2.01E-05	0.739	0.442	0.518	3 rs1999763 4 rs10882091
chr10	94309972	3.74E-06	2.01E-05	0.739	0.442	0.518	3 rs1999763 3 rs6583830
chr10	94337810	1.89E-06	1.12E-05	1.364	0.469	0.393	3 rs6583826 2 rs10882091
chr10	94364357	1.76E-06	1.05E-05	1.363	0.486	0.410	2 rs10882091 3 rs7923837
chr10	94364357	2.58E-06	1.47E-05	1.355	0.491	0.415	2 rs10882091
chr10	94372930	2.66E-06	1.51E-05	1.355	0.491	0.416	4 rs7914814
chr10	94388098	2.58E-06	1.47E-05	1.355	0.491	0.415	1 rs6583830
chr10	94482696	1.62E-06	9.85E-06	1.363	0.562	0.485	1 rs2497304
chr10	118562511	8.21E-06	3.95E-05	1.384	0.302	0.238	4 rs1681748 4 rs2170862
chr10	118610986	9.43E-06	4.45E-05	1.367	0.320	0.256	4 rs2170862
chr10	118880683	3.29E-06	1.80E-05	1.379	0.347	0.278	3 rs10787760
chr11	106441899	8.79E-06	4.18E-05	1.533	0.142	0.097	4 rs1455593
chr12	30340321	4.54E-06	2.38E-05	0.723	0.296	0.368	1 rs1429622 3 rs1506382
chr14	81787150	3.94E-06	2.10E-05	1.363	0.439	0.365	1 rs799099 3 rs4899801
chr14	81843593	8.25E-06	3.97E-05	1.339	0.437	0.367	3 rs2066041
chr14	81899972	9.32E-06	4.40E-05	1.331	0.530	0.459	1 rs10483957
chr14	87823315	9.69E-07	6.35E-06	1.605	0.891	0.836	3 rs419028
chr16	24287484	6.15E-06	3.08E-05	1.388	0.372	0.300	1 rs11074618 2 rs985729
chr19	3065864	1.02E-05	4.77E-05	1.433	0.825	0.767	3 rs3746069

*Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Table 6. Multi- marker haplotypes associated with Type 2 Diabetes in obese patients

Chr	Pos	Punadj	Padj	Rrisk	Aff.frq	Ctrl.frq	Haplotype*
chr2	2591675	4.35E-06	2.29E-05	0.654	0.126	0.181	
4	rs7576292 4 rs6548079 4 rs1451199 1 rs2385306 2 rs1020530 1 rs12714359 2 rs7556672 3 rs1451198						
chr4	112032007	7.13E-06	3.50E-05	1.699	0.097	0.060	
2	rs16997168 4 rs2723316 1 rs6419178 3 rs1448817 3 rs2634073 2 rs2200733 2 rs2220427 2 rs13105878 3 rs10033464						
chr8	128361033	7.34E-07	5.01E-06	0.671	0.178	0.244	
3	rs283709 2 rs283710 2 rs4871780 1 rs185852 2 rs412835						
chr10	68829632	4.50E-06	2.36E-05	2.428	0.039	0.017	
4	rs7094426 1 rs1904614 3 rs10823028 3 rs2620924 1 rs12359451 2 rs11815372 3 rs7083570 3 rs2394375 2 rs1875151 4 rs10823057 4 rs6480272 3 rs1911356						
chr11	106076550	9.88E-06	4.63E-05	0.655	0.114	0.164	
3	rs1791587 3 rs1793083 2 rs1791597 4 rs7104111 2 rs1793064 1 rs4523664 2 rs623018 4 rs631214 3 rs602159 2 rs10890568 2 rs4553343 4 rs1487906 3 rs4121676 1 rs4121677 4 rs6588924						
chr13	94045239	4.93E-06	2.55E-05	0.058	0.001	0.012	
1	rs726298 2 rs7339106 1 rs9556403 2 rs9590039 2 rs6492722 1 rs1572935 3 rs6492725						
chr14	81810554	9.82E-07	6.42E-06	1.408	0.341	0.269	
4	rs9323719 2 rs7143860 3 rs709900 2 rs10135954 1 rs799103 1 rs799099 3 rs8018202 4 rs709915 3 rs709918 3 rs2066041 1 rs1457990 3 rs4899801 1 rs10483957						
chr15	63410029	6.68E-06	3.31E-05	2.395	0.047	0.020	
4	rs2019185 2 rs920688 1 rs894494 3 rs665287 1 rs626163 2 rs639812 2 rs894491 1 rs581427 4 rs603439 1 rs678113 2 rs602192 3 rs7182756 1 rs2280345 3 rs11071841 1 rs2277582						
chr15	95944049	4.24E-06	2.25E-05	0.593	0.079	0.127	
2	rs8029926 4 rs649034 4 rs2036348						
chr18	38114511	4.94E-06	2.56E-05	0.555	0.055	0.094	
4	rs9304267 3 rs3763494 1 rs882291 2 rs898785 3 rs11082268 4 rs8088748 2 rs10502781 3 rs717127						
chr20	45233401	3.10E-06	1.71E-05	1.397	0.322	0.254	
1	rs6063073 4 rs6066209 3 rs2018876 2 rs3092781 4 rs6122563 3 rs8126262 1 rs6063083 3 rs6018337 4 rs7262634						

*Associating alleles are indicated in front of each marker (Allelic code: A=1, C=2, G=3, T=4)

Chromosome 6p22.3 locus

One of the most significant association signals for non-obese diabetic patients was identified by two single markers (rs1569699 and rs7756992) and two 2 marker haplotypes mapping to chromosome 6p22.3 (Table 3). These markers are located within one LD block at position 20634996-20836710 bases (NCBI Build 35) between markers rs4429936 and rs6908425 (SEQ ID NO:1; Figure 1). This LD block contains the 5' end including exons 1-5 of the gene CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1) (NM_017774). The CDKAL1 protein has catalytic activity as well as iron ion binding activity but the in vivo function is unknown. It is widely expressed including expression in pancreas.

To verify the association of rs1569699 and rs7756992 to Type 2 diabetes the two markers were genotyped in a Danish Type 2 diabetes case – control cohort and also in a US Caucasian cohort Type 2 diabetes cohort from the PENN CATH study (Table 7). The results show that the two markers are significantly associated with Type 2 diabetes in the Danish cohort and that it confers a similar risk in the US UPenn. cohort although the results do not reach statistical significance. When the two replication cohorts are combined the results are significant with a risk of around 1.2. When all the cohorts are combined the risk for each marker is over 1.2 comparing a group of nearly 3000 Type 2 diabetes patients (not accounting for BMI) and over 8000 controls. These results are genome wide significant.

Table 7. Association of rs1569699 and rs7756992 to Type 2 diabetes

Iceland									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Padj
rs1569699	2	chr6	20787289	1397	0.297	5264	0.256	1.224	0.000158
rs7756992	3	chr6	20787688	1398	0.270	5271	0.232	1.228	0.000204
Denmark (Steno)									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	P
rs1569699	2	chr6	20787289	1108	0.361	2346	0.321	1.200	0.00079
rs7756992	3	chr6	20787688	1131	0.320	2361	0.274	1.247	0.000078
Upenn									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	P
rs1569699	2	chr6	20787289	360	0.346	522	0.308	1.185	0.09944
rs7756992	3	chr6	20787688	392	0.293	690	0.261	1.176	0.103824
Combined replication cohorts									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Pmh
rs1569699	2	chr6	20787289	1468	-	2868	-	1.195	0.00002
rs7756992	3	chr6	20787688	1523	-	3051	-	1.221	2.8E-06
Combined all cohorts									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Pmh
rs1569699	2	chr6	20787289	2865	-	8132	-	1.207	1.1E-07
rs7756992	3	chr6	20787688	2921	-	8322	-	1.224	1.9E-09

These results show significant association to the 20634996-20836710 bp region (Build 34) on chromosome 6, between markers rs4429936 and rs6908425, in Type 2 diabetes. Values for relative risk (RR) are comparable in all three cohorts; the lack of significant association at the 0.05-level in the UPenn cohort is mainly due to lack of power compared with the other cohorts, although the RR value is slightly lower in this cohort as compared with Iceland (RR of 1.185 compared with 1.224 for rs1569699). Furthermore, RR-values for non-obese Type 2 diabetes patients in Iceland are even higher (RR = 1.33 for rs1569699).

Chromosome 10q23.33 locus

Seven single markers and seven two marker haplotypes in a region on chromosome 10q23.33 were found to be associated with Type 2 diabetes (Table 1). Most of those markers are also associated to diabetes with elevated RR values when obese patients are analysed separately (Table 5). These markers are located within one LD block between positions 94192885 and 94490091 (NCBI Build 35), corresponding to the genomic segment bridged by markers rs2798253 and rs11187152 (Figure 2). This LD block contains three genes, Insulin-degrading enzyme (IDE)

(NM_004969), Kinesin family member 11 (KIF11) (NM_004523) and Homeobox, hematopoietically expressed (HHEX) (NM_002729).

IDE may belong to a protease family responsible for intercellular peptide signalling. Though its role in the cellular processing of insulin has not yet been defined, insulin-degrading enzyme is thought to be involved in the termination of the insulin response (Fakhrai-Rad et al, Human Molecular Genetics 9:2149-2158, 2000). Genetic analysis of the diabetic GK rat has revealed 2 amino acid substitutions in the IDE gene (H18R and A890V) in the GK allele which reduced insulin-degrading activity by 31% in transfected cells. However, when the H18R and A890V variants were studied separately, no effects were observed, suggesting a synergistic effect of the 2 variants on insulin degradation. No effect on insulin degradation was observed in cell lysates, suggesting that the effect may be coupled to receptor-mediated internalization of insulin. Congenic rats with the IDE GK allele displayed postprandial hyperglycemia, reduced lipogenesis in fat cells, blunted insulin-stimulated glucose transmembrane uptake, and reduced insulin degradation in isolated muscle. Analysis of additional rat strains demonstrated that the dysfunctional IDE allele was unique to GK rats. The authors concluded that IDE plays an important role in the diabetic phenotype in GK rats. IDE has been studied as a candidate gene for Type 2 diabetes in humans with inconsistent results. Two large studies have recently analysed the association of IDE to Type 2 diabetes by mutation screening and haplotype analysis using tagging SNPs over the gene (Groves et al, Diabetes 52:1300-1305, 2003; Florez et al, Diabetes 55:128-135, 2006). Both studies conclude that common variants in IDE are unlikely to confer significant risk of Type 2 diabetes. These studies did however, not include the whole LD block as defined in figure 2 and at least some of the markers identified in our study as associated with Type 2 diabetes are outside the regions analysed in those previous studies. Based on the results reported here, markers in LD with IDE are associated with Type 2 diabetes, providing genetic evidence for the role of IDE in the etiology of Type 2 diabetes.

KIF11 encodes a motor protein that belongs to the kinesin-like protein family. Members of this protein family are known to be involved in various kinds of spindle dynamics. The function of this gene product includes chromosome positioning, centrosome separation and establishing a bipolar spindle during cell mitosis. This gene is not a good functional candidate for diabetes but has to be considered as a positional candidate due to its location within the associated LD block.

HHEX encodes a member of the homeobox family of transcription factors, many of which are involved in developmental processes. Expression in specific hematopoietic lineages suggests that this protein may play a role in hematopoietic differentiation. HHEX is essential for pancreatic development; in HHEX negative mouse embryos there is a complete failure in ventral pancreatic specification (Bort et al, Development 131, 797-806, 2004). Other transcription factors involved in pancreatic development include the MODY genes as well as other factors that have been implicated in late onset diabetes. HHEX is also an essential effector of Wnt antagonist for heart induction (Foley and Mercola, GENES & DEVELOPMENT 19:387-396, 2005). This puts HHEX in the same pathway as the recently established Type 2 diabetes gene TCF7L2 and together these data make HHEX a functional as well as positional candidate for Type 2 diabetes.

To verify the association of rs2497304, rs947591, rs10882091 and rs7914814 to Type 2 diabetes, the markers were genotyped in a Danish Type 2 diabetes case – control cohort and also in a US Caucasian cohort Type 2 diabetes cohort from the PENN CATH study (Table 8). The results show that the association is not replicated in either cohort independently. However, when the two cohorts are combined the association of rs947591 reaches significance at the 0.05 level, with a risk of 1.1 in the combined cohort. When all the cohorts are combined the risk is 1.15 for the rs947591 marker.

These results indicate that variants within the LD block on Chromosome 10 that includes IDE and HHEX are susceptibility variants for Type 2 diabetes.

Table 8. Association analysis of markers on Chromosome 10 to Type 2 diabetes in Iceland, Denmark, and the US.

Iceland									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Padj
rs10882091	2	chr10	94364357	1399	0.472	5275	0.415	1.257	0.0000023
rs7914814	4	chr10	94372930	1399	0.472	5275	0.416	1.256	0.0000024
rs2497304	1	chr10	94482696	1399	0.542	5275	0.485	1.257	0.0000019
rs947591	1	chr10	94485733	1399	0.526	5273	0.475	1.226	0.0000221
Denmark (Steno)									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	P
rs10882091	2	chr10	94364357	1115	0.431	2341	0.413	1.077	0.15
rs7914814	4	chr10	94372930	1141	0.430	2360	0.410	1.088	0.10
rs2497304	1	chr10	94482696	1145	0.528	2348	0.509	1.079	0.14
rs947591	1	chr10	94485733	1140	0.502	2361	0.478	1.103	0.055
Upenn									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	P
rs10882091	2	chr10	94364357	386	0.377	640	0.375	1.008	0.93
rs7914814	4	chr10	94372930	394	0.379	683	0.381	0.995	0.95
rs2497304	1	chr10	94482696	408	0.460	778	0.454	1.021	0.81
rs947591	1	chr10	94485733	393	0.480	687	0.459	1.089	0.34
Combined replication cohorts									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Pmh
rs10882091	2	chr10	94364357	1501	-	2981	-	1.052	0.19
rs7914814	4	chr10	94372930	1535	-	3043	-	1.053	0.16
rs2497304	1	chr10	94482696	1553	-	3126	-	1.057	0.16
rs947591	1	chr10	94485733	1533	-	3048	-	1.098	0.032
Combined all cohorts									
rs-Name	Allele	Chr	Pos (B35)	Aff.n	Aff.frq	Ctrl.n	Ctrl.frq	Rrisk	Pmh
rs10882091	2	chr10	94364357	2900	-	8256	-	1.136	0.000017
rs7914814	4	chr10	94372930	2934	-	8318	-	1.137	0.000012
rs2497304	1	chr10	94482696	2952	-	8401	-	1.139	0.000011
rs947591	1	chr10	94485733	2932	-	8321	-	1.152	9.7E-07

Chromosome 17q24.3 locus

Five single markers and two two marker haplotypes in a region of chromosome 17q24.3 were found to be associated with Type 2 diabetes in non-obese patients (Table 3). Some of these markers show the strongest association reported in Table 3 and association to this region was also observed when all diabetics were analysed (Table 1). These markers are located within two adjacent LD blocks located between positions 66037656 and 66163076 (NCBI Build 35) on

chromosome 17, between markers rs11077501 and rs4793497 (Figure 3). The association is significant after correction for the number of tests performed in the single marker association analysis; i.e., the association is significant at the genome-wide level. No known genes are located within these LD blocks. However, it is possible that variants in this region affect genes in neighboring regions including KCNJ2 and KCNJ16. Alternatively these variants may affect unknown genes within these LD block regions.

Table 9. SNPs located within the CDKAL1 gene (Located between position 20,642,736 and 21,340,611 bp on Chromosome 6 in NCBI Build 35 and NCBI Build 36)

Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID
20642787	rs41271303	20649183	rs12200834	20660836	rs11320714	20677060	rs12333291
20642953	rs11963450	20649236	rs34860173	20660918	rs9350256	20677967	rs2064321
20643397	rs981043	20649324	rs11754872	20661764	rs7756211	20677985	rs35546893
20643513	rs981042	20649498	rs6456356	20662069	rs9460520	20678018	rs4291090
20643675	rs16883895	20649517	rs9368199	20662498	rs34245467	20678121	rs2064320
20643753	rs17512225	20649682	rs2143406	20662930	rs9350257	20678268	rs9465810
20643840	rs35035071	20650176	rs10484634	20663855	rs11964554	20678275	rs9465811
20643949	rs6904566	20650200	rs7758851	20663990	rs9465806	20678423	rs9358344
20644073	rs6927356	20650398	rs34677076	20664109	rs11964635	20678756	rs10946390
20644093	rs35281412	20651447	rs6928571	20664190	rs13199421	20679114	rs6905281
20644313	rs35915788	20651461	rs12192584	20664314	rs6932320	20679339	rs16883932
20644314	rs34025398	20651608	rs34856684	20664570	rs12200078	20679612	rs34904067
20644319	rs34361235	20652015	rs9350255	20664659	rs13437555	20679660	rs7744002
20644335	rs6905138	20652091	rs9368200	20664884	rs9350258	20679763	rs35142564
20644499	rs13194858	20652136	rs12214002	20665256	rs12176441	20680095	rs9465812
20644717	rs2179551	20652245	rs9465797	20665260	rs12183826	20680678	rs7759094
20644727	rs2179550	20652300	rs9465798	20665264	rs9356738	20680784	rs9460522
20644787	rs9465794	20652574	rs28699301	20665272	rs9348434	20681538	rs7764551
20644787	rs9465795	20652650	rs13215844	20665343	rs9465807	20681585	rs10541455
20644848	rs7747962	20652678	rs12214315	20665804	rs4458667	20682409	rs16883935
20644858	rs6910725	20652722	rs11759517	20665995	rs7739402	20682542	rs13215603
20644918	rs965054	20652786	rs13218957	20667590	rs16883914	20682568	rs962576
20644971	rs2143407	20652806	rs13218962	20667591	rs16883916	20683235	rs1474720
20645032	rs10619380	20653186	rs10543744	20667900	rs9654584	20683797	rs16883944
20645431	rs2328525	20653201	rs12216047	20667999	rs9465808	20684155	rs34538343
20645661	rs13199286	20653447	rs9366354	20668414	rs17584626	20684269	rs9350260
20645841	rs10611252	20653890	rs9358342	20668565	rs7751682	20684353	rs16883951
20645940	rs7753499	20654091	rs9368201	20669667	rs11361279	20684645	rs9358345
20646023	rs7753956	20654382	rs34206163	20669681	rs34634263	20684862	rs1012627
20646024	rs34811195	20654506	rs9465799	20670059	rs12214549	20684890	rs9368203
20646024	rs7753670	20654794	rs34187071	20670364	rs7753519	20684939	rs35894322
20646107	rs3060613	20654867	rs9465800	20670575	rs28567007	20684965	rs4710932
20646109	rs11277970	20654890	rs6908974	20670597	rs7772137	20684984	rs6909117
20646110	rs11280099	20654992	rs13197372	20670719	rs12208597	20685540	rs1012626
20646114	rs6149468	20655361	rs13214145	20670998	rs9368202	20685748	rs1012625
20646139	rs16883900	20655793	rs16883910	20671877	rs2328526	20685760	rs7752194
20646175	rs7774291	20655968	rs12194705	20672452	rs34823358	20685958	rs9465813
20646441	rs10612082	20656271	rs35080661	20673287	rs28639914	20686014	rs12207923
20646476	rs9368198	20656465	rs7753467	20673363	rs34233572	20686355	rs16883963
20646502	rs13203336	20656466	rs7773488	20673415	rs4712506	20686831	rs13205786
20646504	rs13203631	20656986	rs34182285	20673935	rs13203450	20686887	rs35205364
20646619	rs6456355	20657084	rs34242699	20674280	rs9350259	20687102	rs10456232
20646644	rs10484635	20657780	rs9348433	20674435	rs6918457	20687189	rs9465814
20647190	rs12204173	20657942	rs9460519	20674595	rs35210537	20687201	rs35571892
20647320	rs13207544	20658083	rs12198377	20674749	rs11329887	20687740	rs9465815
20647851	rs12198728	20658096	rs9465801	20675016	rs9348435	20687753	rs36119371
20647984	rs28396084	20658195	rs9465802	20675068	rs35366106	20687921	rs28621813
20648327	rs12199073	20658822	rs28458932	20675342	rs16901563	20687926	rs9350261
20648500	rs9465796	20658823	rs9465803	20675352	rs12333229	20687928	rs7341226
20648561	rs12212600	20658981	rs2103682	20675520	rs9460521	20688175	rs6927481
20648596	rs13212040	20659321	rs9465804	20676092	rs10589899	20688323	rs35313444
20648663	rs35291340	20659580	rs34611621	20676351	rs2876573	20688373	rs6928198
20648722	rs12199324	20660058	rs12055423	20676957	rs6935461	20688404	rs6907897
20649085	rs12200871	20660653	rs9465805	20676963	rs6935465	20688545	rs6928586
20649159	rs9348432	20660829	rs11365187	20676968	rs10603174	20688872	rs9368204

Pos Build 35/36	Marker ID
20689021	rs9358346
20689589	rs11967546
20689593	rs34134803
20689772	rs10456233
20689807	rs7744833
20690122	rs9460523
20690123	rs9465816
20690432	rs6908077
20690630	rs9465817
20691069	rs11967445
20691263	rs34022950
20691793	rs9460524
20691994	rs34020592
20692003	rs11448102
20692339	rs9465818
20692402	rs9350262
20692513	rs13205241
20693000	rs12153939
20693100	rs6925593
20693119	rs4712507
20693225	rs10558806
20693267	rs35982532
20693276	rs11385529
20693360	rs9348436
20693416	rs9368206
20693438	rs13209542
20693452	rs9368207
20693630	rs13209907
20693635	rs6926658
20694018	rs12213132
20694182	rs4357125
20694554	rs6932944
20694607	rs6932962
20695026	rs9348437
20695332	rs12201857
20695356	rs9465819
20695447	rs6938955
20695539	rs9460525
20695827	rs9465820
20695964	rs10946391
20695968	rs9368208
20696003	rs9465821
20696183	rs6923790
20696399	rs10558139
20697309	rs6907459
20697320	rs6907767
20697321	rs9465822
20697349	rs6930283
20697706	rs6908042
20697741	rs6935317
20697761	rs35370102
20698266	rs9368209
20698366	rs13216746
20698367	rs13216747
20699007	rs35485532
20699747	rs13216324
20699817	rs4336434
20700046	rs4509107
20700428	rs9465823
20700465	rs6936705

Pos Build 35/36	Marker ID
20700679	rs34023799
20700929	rs6942313
20701057	rs28869917
20701318	rs34982231
20701631	rs9358349
20701770	rs9460526
20701829	rs9366356
20702163	rs36120092
20702181	rs9465824
20702519	rs4712512
20702561	rs4712513
20702646	rs4710934
20702658	rs9348438
20702902	rs9460529
20703363	rs13199587
20703470	rs13199384
20703526	rs10223680
20703606	rs9350263
20703768	rs9465825
20703832	rs10223876
20704100	rs35702271
20704171	rs9358350
20704432	rs12208985
20704771	rs12210459
20704892	rs35431707
20705144	rs36039523
20705297	rs11758281
20705350	rs28893199
20705757	rs34256347
20706019	rs12192740
20706282	rs13212326
20706486	rs12199184
20706753	rs10456234
20707009	rs4712514
20707422	rs9465826
20707607	rs9366357
20707867	rs2294809
20708549	rs2294808
20708813	rs7762750
20708976	rs4712515
20708998	rs10522824
20708999	rs35660518
20709002	rs10679950
20709003	rs34870864
20709022	rs4712516
20709145	rs4710935
20709386	rs9465827
20709388	rs12204865
20709672	rs10946393
20709764	rs12209806
20709894	rs10946394
20709921	rs1997778
20709971	rs35878587
20710359	rs1997777
20710378	rs2223622
20710776	rs11964057
20711246	rs9460530
20711344	rs9460531
20711376	rs34329159
20711640	rs7764558

Pos Build 35/36	Marker ID
20711804	rs4710936
20712056	rs12213940
20712228	rs13215038
20712739	rs10946395
20712832	rs6939917
20712975	rs9358351
20713800	rs6925097
20713924	rs9465828
20713955	rs9465829
20713961	rs6902661
20714057	rs34373680
20714281	rs35051096
20714508	rs932405
20714591	rs6926585
20714635	rs3938395
20715464	rs11964664
20715551	rs35964987
20715663	rs12206413
20715758	rs35990187
20715763	rs4991654
20715910	rs9460532
20715991	rs13328250
20716030	rs13328252
20716194	rs4712517
20716257	rs4712518
20717220	rs7758129
20717475	rs13206462
20717483	rs13192442
20717486	rs13206468
20717492	rs13192445
20717498	rs13192450
20717504	rs13206477
20717510	rs13206483
20717577	rs12179168
20717586	rs12180975
20717611	rs12179172
20717860	rs12179563
20718357	rs11355836
20718696	rs2328527
20718709	rs11452882
20718920	rs2876574
20719905	rs9465831
20720031	rs34877824
20720290	rs13212501
20720647	rs9358352
20720703	rs9358353
20720761	rs28756205
20720889	rs9350265
20720989	rs7750508
20721130	rs7771052
20721141	rs9460533
20721195	rs13200415
20721216	rs10550932
20721312	rs9465832
20721463	rs9368211
20721471	rs9350266
20721507	rs11752592
20721515	rs9350267
20721754	rs978988
20721898	rs978987

Pos Build 35/36	Marker ID
20721906	rs978986
20722036	rs5874773
20722196	rs5874774
20722500	rs7756788
20722659	rs9348439
20722661	rs9356739
20722693	rs9356740
20722738	rs7760894
20723021	rs2796913
20723046	rs2608613
20723121	rs10456710
20723139	rs9476286
20723140	rs28368538
20723140	rs9476287
20723141	rs28612622
20723142	rs9463660
20723146	rs9463661
20723162	rs9461022
20723193	rs9461021
20723235	rs34980442
20723239	rs34049080
20723258	rs35218684
20723260	rs12175876
20723270	rs10948323
20723287	rs34400313
20723292	rs36081550
20723304	rs12175878
20723305	rs34520184
20723305	rs34756989
20723322	rs4629736
20723322	rs9296917
20723324	rs28562027
20723333	rs9381823
20723346	rs34769771
20723346	rs34774640
20723346	rs36038896
20723365	rs13209195
20723369	rs12213541
20723369	rs34112320
20723371	rs34615869
20723379	rs35949519
20723381	rs9257498
20723383	rs34200576
20723393	rs4960519
20723396	rs9261905
20723402	rs9267103
20723404	rs17367677
20723416	rs9261906
20723421	rs9267104
20723424	rs9267105
20723434	rs28810763
20723438	rs12179121
20723438	rs4714959
20723439	rs10946636
20723439	rs28763327
20723439	rs28847950
20723439	rs3933247
20723449	rs28808723
20723451	rs9767082
20723452	rs35132675

Pos Build 35/36	Marker ID
20723452	rs35517166
20723452	rs4714297
20723456	rs12182737
20723456	rs36163804
20723460	rs35790973
20723464	rs35236694
20723469	rs35567559
20723469	rs9267106
20723471	rs9800557
20723484	rs12182463
20723489	rs10948322
20723489	rs34052284
20723489	rs9268999
20723490	rs9258377
20723495	rs9257499
20723498	rs9265816
20723500	rs28771402
20723501	rs28771401
20723502	rs12194731
20723502	rs4451188
20723502	rs9717323
20723502	rs9765920
20723503	rs9265815
20723504	rs28771400
20723506	rs12190813
20723506	rs12215416
20723507	rs12178527
20723510	rs35234761
20723510	rs35887156
20723512	rs28797321
20723515	rs28771399
20723522	rs13207682
20723522	rs36099432
20723531	rs28749543
20723535	rs13196506
20723535	rs35716308
20723536	rs28831180
20723536	rs34938144
20723537	rs36142967
20723541	rs35313792
20723542	rs9260904
20723543	rs34597832
20723545	rs9767740
20723546	rs28771398
20723550	rs34384951
20723554	rs12524128
20723554	rs12665124
20723554	rs34922643
20723555	rs9260903
20723557	rs28771397
20723557	rs6915279
20723559	rs9261907
20723559	rs9766798
20723559	rs9767242
20723560	rs6914835
20723560	rs9260902
20723560	rs9767101
20723562	rs9261908
20723563	rs12207064
20723563	rs12213193

Pos Build 35/36	Marker ID
20723563	rs35750154
20723566	rs9260901
20723570	rs9269000
20723579	rs12178368
20723579	rs13197714
20723579	rs28771396
20723579	rs34443697
20723579	rs9267107
20723582	rs35113301
20723582	rs3933248
20723583	rs28819830
20723586	rs10947899
20723586	rs9260900
20723588	rs13204671
20723588	rs34094007
20723588	rs34963756
20723588	rs4304158
20723589	rs4298351
20723590	rs12182307
20723590	rs12201487
20723590	rs34097573
20723595	rs13219021
20723596	rs34456153
20723596	rs9767597
20723597	rs9767102
20723598	rs9269001
20723601	rs12180097
20723603	rs12178465
20723603	rs35128115
20723607	rs4273681
20723609	rs12193754
20723617	rs813814
20723617	rs9689672
20723619	rs36173068
20723623	rs12202172
20723623	rs28862376
20723625	rs12178884
20723625	rs12203117
20723625	rs34250588
20723626	rs12182581
20723632	rs34147797
20723635	rs9688484
20723636	rs9269002
20723636	rs9767733
20723637	rs10948989
20723637	rs34732676
20723637	rs9260899
20723638	rs35686233
20723639	rs11753098
20723639	rs35156647
20723646	rs34719653
20723646	rs35575623
20723648	rs12192046
20723649	rs11759854
20723649	rs28771395
20723649	rs35563402
20723649	rs36016334
20723649	rs4555911
20723653	rs11965757
20723654	rs10948990

Pos Build 35/36	Marker ID
20723654	rs28808296
20723654	rs34995142
20723654	rs809919
20723657	rs11571978
20723659	rs12208488
20723662	rs11751374
20723663	rs13217613
20723667	rs12528735
20723668	rs35160656
20723668	rs35322569
20723668	rs9766221
20723670	rs35120225
20723670	rs511868
20723674	rs9269003
20723675	rs34290316
20723675	rs35735496
20723675	rs9689102
20723676	rs10948991
20723676	rs9269004
20723677	rs13220607
20723677	rs34700647
20723677	rs9260898
20723678	rs9260897
20723684	rs28771394
20723686	rs12213200
20723687	rs9717987
20723688	rs28771393
20723688	rs9717716
20723689	rs28771392
20723690	rs11758009
20723690	rs34159662
20723690	rs34683172
20723690	rs9717331
20723691	rs9717853
20723692	rs9765875
20723696	rs12178974
20723696	rs36003577
20723698	rs9767747
20723700	rs28771391
20723704	rs13216352
20723707	rs12200762
20723707	rs12206373
20723707	rs34570202
20723707	rs36197940
20723707	rs9265814
20723714	rs34131282
20723717	rs12175478
20723720	rs28772692
20723722	rs35516674
20723722	rs35704013
20723727	rs34691406
20723728	rs28771390
20723728	rs4374863
20723730	rs34826149
20723734	rs12207894
20723734	rs12662476
20723736	rs9260896
20723739	rs28771389
20723740	rs28771388
20723741	rs9382592

Pos Build 35/36	Marker ID
20723745	rs12173375
20723745	rs9268072
20723745	rs9382110
20723746	rs4715211
20723747	rs35961188
20723747	rs34128950
20723747	rs4620119
20723749	rs9767236
20723752	rs34717143
20723755	rs13201202
20723756	rs13201503
20723762	rs13197088
20723762	rs35347849
20723766	rs35650828
20723766	rs34663083
20723767	rs13199241
20723767	rs34205031
20723768	rs34469031
20723768	rs28749541
20723768	rs9279137
20723769	rs9260895
20723770	rs35446958
20723770	rs12212483
20723775	rs28380829
20723777	rs12525384
20723777	rs34576984
20723782	rs283541
20723785	rs28380828
20723788	rs10948698
20723790	rs9265813
20723791	rs9689173
20723792	rs28380827
20723795	rs35399169
20723799	rs9260894
20723800	rs12173388
20723800	rs9269005
20723802	rs28359816
20723803	rs28380826
20723807	rs280297
20723807	rs34507582
20723807	rs9261623
20723810	rs12174621
20723813	rs28380825
20723815	rs35197377
20723816	rs17362870
20723816	rs35071522
20723816	rs34562190
20723816	rs35179751
20723816	rs4458721
20723817	rs12180385
20723817	rs12206581
20723817	rs12333308
20723817	rs9269006
20723821	rs9688475
20723829	rs9269007
20723832	rs9269008
20723832	rs9269009
20723834	rs35899754
20723836	rs13211190
20723837	rs12216274

Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID
20723838	rs12191544	20724013	rs34552032	20724401	rs12202889	20731063	rs16883996
20723838	rs4337934	20724018	rs28890881	20724435	rs28840538	20731181	rs35073110
20723841	rs9279295	20724018	rs34478537	20724466	rs9473983	20731184	rs5028948
20723842	rs12178577	20724025	rs35191657	20724467	rs34220946	20731263	rs34201758
20723849	rs12215604	20724038	rs34450517	20724487	rs9261322	20731371	rs6456360
20723853	rs9395360	20724043	rs9689655	20724491	rs9261323	20731373	rs6456361
20723854	rs28749540	20724064	rs12180172	20724517	rs526092	20731380	rs6456362
20723855	rs28895226	20724068	rs28865015	20724564	rs9473982	20731584	rs6922571
20723855	rs9260893	20724071	rs9717839	20724566	rs34307764	20731925	rs35145358
20723861	rs4365925	20724072	rs9717836	20724626	rs34490559	20731950	rs9465836
20723864	rs9261912	20724074	rs9885593	20724665	rs4449621	20732013	rs7763304
20723865	rs28895227	20724082	rs28887572	20724685	rs4714818	20732158	rs9465837
20723870	rs9261913	20724083	rs13216113	20724698	rs4714817	20732218	rs7743314
20723873	rs12183502	20724083	rs35254115	20724722	rs682384	20732337	rs714831
20723873	rs34332895	20724084	rs10949190	20724738	rs682051	20732361	rs714830
20723873	rs9472692	20724085	rs6923503	20724753	rs12530056	20732484	rs7743789
20723876	rs35640475	20724087	rs12214411	20724756	rs35086683	20732584	rs5874776
20723884	rs9269010	20724091	rs28747986	20724888	rs12528468	20732589	rs5874777
20723888	rs12192337	20724096	rs1087363	20725092	rs10650195	20732965	rs16884003
20723888	rs35349786	20724096	rs1091092	20725092	rs35956126	20733079	rs9356741
20723891	rs34978372	20724104	rs12180759	20725109	rs6937578	20733080	rs9366358
20723893	rs280296	20724107	rs11758052	20725159	rs12530107	20733246	rs9356742
20723894	rs11755576	20724112	rs9261321	20725173	rs720448	20733430	rs11756987
20723903	rs35553517	20724113	rs28861738	20725176	rs9368212	20733470	rs9465838
20723903	rs28803616	20724113	rs36109104	20725250	rs35481531	20733613	rs2206579
20723904	rs4358654	20724123	rs13208115	20725253	rs720449	20733920	rs35111339
20723910	rs9260892	20724129	rs9472693	20725262	rs10650196	20734361	rs6917583
20723914	rs13196941	20724130	rs12208570	20725495	rs2064	20734388	rs6917599
20723914	rs9717238	20724130	rs28832660	20725499	rs2065	20734630	rs13437429
20723915	rs12175553	20724131	rs13200482	20725638	rs9368213	20735418	rs34307011
20723915	rs12191408	20724131	rs9260886	20725732	rs41455744	20735420	rs4515379
20723915	rs4460210	20724131	rs9472694	20726077	rs34960654	20735756	rs2223620
20723915	rs9260891	20724159	rs9260885	20726154	rs6900954	20735870	rs9465839
20723918	rs9395361	20724172	rs280295	20726168	rs6456359	20735993	rs12664972
20723920	rs9766917	20724172	rs28749538	20726176	rs7739405	20736790	rs28402356
20723926	rs35073779	20724174	rs13201041	20726601	rs7760508	20736798	rs6934727
20723931	rs9765884	20724184	rs1087362	20726684	rs10456007	20736873	rs35493429
20723931	rs9767229	20724187	rs12183850	20726987	rs9460534	20736881	rs11369825
20723932	rs35247846	20724190	rs12202552	20727168	rs11966749	20737261	rs4523079
20723932	rs9717328	20724208	rs9260884	20727353	rs9358354	20737470	rs7771213
20723936	rs28805674	20724210	rs9474341	20727809	rs9368214	20737568	rs9465840
20723936	rs9260890	20724211	rs9260883	20727982	rs9350268	20737687	rs9465841
20723938	rs34926348	20724222	rs34669820	20728095	rs2069013	20737767	rs9465842
20723938	rs9717233	20724225	rs12189886	20728160	rs2069014	20737837	rs9460535
20723945	rs35869128	20724234	rs12182114	20728290	rs2069015	20737992	rs34835908
20723946	rs12175941	20724266	rs9688643	20728292	rs11967475	20738060	rs9465843
20723951	rs9260889	20724272	rs12195237	20729096	rs10214549	20738139	rs13220465
20723952	rs9766686	20724281	rs35293595	20729217	rs2223621	20738159	rs13220352
20723956	rs10046203	20724281	rs9381428	20729281	rs9465835	20738321	rs4710937
20723957	rs9260888	20724306	rs34665644	20729984	rs35404829	20738375	rs9460536
20723958	rs12180540	20724309	rs12189599	20729995	rs10687080	20738376	rs13190734
20723961	rs9766115	20724311	rs12208503	20730233	rs6915936	20738451	rs9465844
20723968	rs6912019	20724312	rs9800791	20730331	rs9295472	20738712	rs35976895
20723969	rs9767458	20724330	rs12173681	20730732	rs1569660	20738713	rs11327958
20723976	rs13202161	20724337	rs12182094	20730929	rs7455009	20738932	rs13194407
20723989	rs13218048	20724343	rs12182119	20730945	rs1569659	20738990	rs10484633
20724000	rs13218040	20724352	rs12182102	20730946	rs5874775	20739524	rs2328528
20724001	rs13206557	20724392	rs12174506	20730948	rs10601252	20739789	rs35958155
20724002	rs13202152	20724393	rs9767809	20730983	rs1569658	20739809	rs4421185
20724013	rs12210049	20724394	rs12173703	20731030	rs34142400	20739932	rs2328529

Pos Build 35/36	Marker ID
20740089	rs9460537
20740745	rs17224527
20740886	rs34166991
20741024	rs17823073
20741276	rs12183074
20741316	rs9465845
20741844	rs35148963
20741886	rs7768642
20742320	rs9465846
20742407	rs9465847
20742551	rs17823127
20742594	rs16884021
20742630	rs4533976
20742865	rs7755830
20743005	rs7756031
20743139	rs35650451
20743188	rs10561117
20743241	rs6940200
20743799	rs9465848
20743808	rs34351919
20745083	rs4712519
20745285	rs9368215
20745566	rs12206285
20745853	rs34049994
20745988	rs7751957
20746702	rs9465849
20746857	rs7341291
20746957	rs6921014
20747388	rs9465850
20747583	rs7758612
20747681	rs35602526
20748295	rs9465851
20748399	rs34257578
20748403	rs11339738
20748516	rs9460538
20748850	rs4712520
20748883	rs4710938
20749084	rs35889049
20749315	rs9348440
20749879	rs9465852
20750054	rs12196009
20750306	rs11968248
20750353	rs34797179
20750764	rs6925328
20750913	rs36073053
20751140	rs36224625
20751145	rs35462488
20751150	rs3060659
20751153	rs5874778
20751155	rs11267861
20751201	rs4235999
20751230	rs16884038
20751706	rs2328530
20751731	rs2328531
20751750	rs28360636
20752162	rs6932676
20752183	rs9460539
20752303	rs6932876
20752346	rs34929755
20752359	rs28733367

Pos Build 35/36	Marker ID
20752360	rs11348111
20752473	rs6933219
20752702	rs6933165
20752872	rs35255583
20752901	rs34332316
20752923	rs4710939
20753486	rs11970417
20753659	rs11963217
20753670	rs11965473
20753833	rs2876575
20754049	rs7739974
20754976	rs7745175
20755173	rs7765784
20755178	rs6907731
20755250	rs35057896
20755313	rs7746072
20755639	rs10484632
20755770	rs35444529
20755849	rs17823571
20755941	rs11965062
20755962	rs6936199
20755965	rs6913126
20756178	rs6913509
20756613	rs34638218
20756673	rs35746011
20756741	rs9460540
20757090	rs36045545
20757129	rs35392790
20757233	rs6456364
20757260	rs2179553
20757513	rs9350269
20757531	rs9465854
20757787	rs2179552
20757936	rs6925233
20758033	rs2328532
20758248	rs7743970
20758317	rs13209457
20758318	rs34641285
20758344	rs13209538
20758387	rs2876576
20758479	rs13209572
20758653	rs28783153
20758712	rs9969037
20758800	rs7766844
20758969	rs7767133
20759291	rs7749464
20760100	rs2050225
20760696	rs9295474
20760744	rs9295475
20761529	rs2328545
20761548	rs28846771
20761779	rs2876582
20761899	rs10223446
20762094	rs13219723
20762095	rs13203489
20762154	rs13203583
20762172	rs13203887
20762279	rs6456366
20762876	rs9358355
20763089	rs9368216

Pos Build 35/36	Marker ID
20763375	rs9465855
20763384	rs9465856
20763463	rs16884070
20763482	rs16884072
20763647	rs13208604
20764169	rs9465857
20764307	rs9368217
20764559	rs9460541
20764746	rs9460542
20764765	rs11969955
20764779	rs4712522
20764924	rs16884074
20765172	rs34489684
20765324	rs2328546
20765543	rs4712523
20765844	rs4712524
20765898	rs35397753
20765991	rs4710940
20766197	rs13190727
20766215	rs35136485
20766311	rs35260725
20766335	rs35939620
20766566	rs17823996
20766713	rs16884082
20767438	rs6906327
20767566	rs6456367
20767785	rs6456368
20768202	rs7749083
20768344	rs6456369
20768669	rs10946396
20768672	rs10946397
20768710	rs11759505
20769000	rs13203361
20769013	rs10946398
20769122	rs7774594
20769229	rs7754840
20769249	rs9460543
20769508	rs9460544
20769529	rs9460545
20769711	rs2206740
20769806	rs5874779
20769807	rs33970890
20769815	rs5874780
20769816	rs35014292
20769816	rs35363501
20770092	rs6456370
20770102	rs979614
20770196	rs35456723
20770571	rs9368218
20770945	rs4712525
20771014	rs4712526
20771314	rs4712527
20771442	rs35191644
20771443	rs34470647
20771611	rs9460546
20771938	rs9465859
20772079	rs9465860
20772291	rs736425
20772508	rs3060776
20772509	rs34941928

Pos Build 35/36	Marker ID
20772512	rs5874781
20772761	rs35778487
20773060	rs742642
20773305	rs35248697
20773436	rs11967127
20773528	rs7748382
20773547	rs9688549
20773548	rs9689351
20773570	rs28665000
20773886	rs7752236
20773925	rs7772603
20774001	rs7752780
20774034	rs7752906
20774160	rs34184260
20774223	rs2206739
20774225	rs2206738
20774250	rs2206737
20774436	rs11970425
20774484	rs36034806
20774899	rs35042364
20775218	rs35540121
20775361	rs9358356
20775667	rs9356743
20775778	rs9350270
20776366	rs34929853
20778035	rs34971765
20778443	rs11970596
20779261	rs12527373
20779367	rs35916847
20780262	rs11968224
20780271	rs11968225
20780276	rs9465861
20780296	rs11968264
20780406	rs12189849
20780413	rs12209627
20780432	rs12189895
20780855	rs11968848
20781135	rs11963945
20781601	rs35677128
20781859	rs7451008
20782670	rs9368219
20782790	rs1012636
20782945	rs13217846
20783274	rs1012635
20783700	rs35665197
20783771	rs35261542
20783828	rs28823314
20783899	rs28890810
20784051	rs28871991
20784393	rs34499031
20784650	rs13208763
20784747	rs28719685
20784789	rs28856096
20785042	rs11961863
20785211	rs17824302
20785289	rs12660618
20786302	rs11371206
20786303	rs34152621
20786409	rs4712528
20786463	rs13217082

Pos Build 35/36	Marker ID
20786470	rs13217085
20786481	rs13217090
20786483	rs13217091
20786523	rs13200946
20786772	rs11968032
20786954	rs9465863
20787289	rs1569699
20787386	rs34168173
20787688	rs7756992
20788045	rs35312717
20788657	rs9348441
20788843	rs9368220
20788941	rs6931254
20789327	rs6911742
20790601	rs35612982
20791039	rs35816514
20791123	rs34612860
20791143	rs9350271
20791162	rs35657899
20791179	rs11364854
20791249	rs9460547
20791646	rs16884103
20791961	rs2206736
20793465	rs9356744
20794295	rs34987372
20794427	rs36005020
20794552	rs7766070
20794975	rs9368222
20795290	rs35566695
20795781	rs10440832
20796100	rs10440833
20796237	rs35747076
20796578	rs6900217
20797102	rs34433496
20797924	rs7748720
20797928	rs34175709
20798290	rs6911357
20800493	rs12200791
20800955	rs5874782
20800957	rs36119385
20801341	rs13219682
20802207	rs4710941
20802270	rs4620109
20802272	rs28459626
20802273	rs4712529
20802292	rs10577753
20802504	rs2223683
20802573	rs2206735
20802863	rs2206734
20802910	rs34530846
20803458	rs16884131
20804127	rs10806921
20805104	rs16884133
20805571	rs17824500
20805652	rs10946401
20806114	rs16884135
20806582	rs35711395
20807220	rs11969783
20807364	rs16884137
20808600	rs11970626

Pos Build 35/36	Marker ID
20809092	rs12190713
20809106	rs11398905
20809415	rs11961445
20809470	rs35982077
20809486	rs11305935
20810952	rs9356745
20811700	rs35043644
20811842	rs16884140
20811931	rs6931514
20812147	rs35443650
20813281	rs34671712
20813569	rs11753081
20814081	rs7739516
20814209	rs6901559
20815176	rs13196379
20815177	rs13212234
20816204	rs10536170
20817155	rs9465869
20817688	rs36070002
20818288	rs17226450
20818905	rs1073247
20819131	rs9465870
20819386	rs17226492
20819433	rs13213613
20819567	rs16884146
20819958	rs2206733
20820440	rs3749925
20821121	rs9460548
20821619	rs9460549
20821685	rs1040558
20821893	rs4712530
20822083	rs35629277
20822362	rs7451928
20822445	rs6456371
20822589	rs13220116
20822823	rs2206732
20823169	rs2179633
20823483	rs11963770
20823805	rs10946402
20823840	rs4712531
20824098	rs35738288
20824232	rs9295478
20824549	rs2328547
20824763	rs3060781
20824764	rs34686252
20824856	rs13215905
20824884	rs9368223
20824937	rs2328548
20825025	rs11427712
20825074	rs6935599
20825100	rs13216165
20825234	rs9465871
20825383	rs10946403
20826219	rs2328549
20826449	rs17226774
20827124	rs9358357
20827211	rs9368224
20827321	rs11756271
20827372	rs9358358
20827540	rs9460550

Pos Build 35/36	Marker ID
20827858	rs12110493
20827866	rs12193125
20828258	rs9356746
20828797	rs9350272
20829322	rs13219444
20829342	rs12111216
20829562	rs9350273
20829700	rs9368225
20830399	rs17825025
20831036	rs9368226
20832213	rs6903175
20832229	rs6903744
20832537	rs12111351
20832754	rs4712536
20832986	rs9356747
20833076	rs9356748
20833219	rs7767391
20833402	rs7747752
20833511	rs9350274
20833853	rs34170041
20833919	rs6915155
20834014	rs6914868
20834472	rs4538697
20835549	rs4712537
20836048	rs34097377
20836492	rs6928012
20836710	rs6908425
20837083	rs28713236
20837085	rs28570482
20837098	rs35373857
20837704	rs35980729
20838039	rs9465872
20838780	rs9942459
20838787	rs9942429
20838794	rs12197544
20839053	rs34407999
20839503	rs7741604
20840493	rs35573456
20840651	rs35633408
20841368	rs9465873
20841433	rs12211466
20842055	rs4712538
20842055	rs41413744
20842592	rs13213979
20842973	rs13217519
20843073	rs34169067
20843074	rs34773978
20843075	rs34104100
20843076	rs34790688
20843373	rs11753021
20843473	rs11753041
20843666	rs6938978
20844017	rs9295479
20844137	rs10484631
20844216	rs9358361
20844796	rs9688471
20844922	rs7744943
20844996	rs9295480
20845006	rs9368227
20845333	rs9465874

Pos Build 35/36	Marker ID
20845619	rs9358362
20845736	rs9368228
20845737	rs17839864
20845816	rs34427164
20846388	rs9368229
20846555	rs9295481
20846750	rs9368230
20846907	rs9356750
20846992	rs9366359
20847710	rs41272361
20847886	rs4710942
20847986	rs9465875
20847998	rs4710943
20848275	rs9350276
20848458	rs9465876
20848854	rs34604097
20849362	rs9688952
20849423	rs34933309
20849720	rs9350277
20850306	rs13204257
20850665	rs35106298
20851446	rs13194434
20851931	rs9358363
20852254	rs34929383
20852706	rs4710944
20852720	rs12529627
20853053	rs4710945
20853694	rs9350278
20854215	rs7738382
20854499	rs1474739
20854568	rs35432334
20854686	rs16884185
20855689	rs35345966
20856120	rs2745928
20856124	rs2745927
20856166	rs2473649
20856236	rs13215601
20856258	rs35386836
20856392	rs2819991
20856706	rs2819995
20856744	rs11752936
20856762	rs1543364
20856765	rs13203288
20856879	rs2473648
20856966	rs2473647
20856967	rs2473646
20857002	rs1543363
20857270	rs16884190
20857656	rs4644038
20858009	rs2819988
20858162	rs4475313
20858693	rs2745933
20858865	rs9460552
20859007	rs9460553
20859031	rs9350279
20859173	rs10568019
20859187	rs10598071
20859199	rs12199271
20859220	rs7765413
20859294	rs7747724

Pos Build 35/36	Marker ID
20859674	rs11756862
20859995	rs4712539
20860175	rs2819989
20860310	rs2819990
20860358	rs9465877
20860448	rs34996587
20860459	rs34744837
20861169	rs2819992
20861420	rs10946405
20861729	rs2745932
20861866	rs2819993
20861911	rs9465879
20861915	rs2819994
20861965	rs34164249
20862098	rs2493995
20862168	rs35908672
20862169	rs35525968
20862500	rs9358364
20862605	rs2745931
20862716	rs2745930
20862740	rs2745929
20863911	rs2819996
20864423	rs1012114
20864756	rs2473651
20864955	rs16901574
20865045	rs9358365
20865049	rs6913831
20865061	rs10652206
20865064	rs10652207
20865081	rs11281792
20865121	rs6934147
20865127	rs13200804
20865134	rs6934300
20865135	rs2473650
20865136	rs6913999
20865625	rs9465880
20866301	rs34767457
20866310	rs35499882
20866326	rs2819997
20866505	rs2819998
20866612	rs2819999
20866683	rs2820000
20866739	rs10946406
20866788	rs34291318
20866813	rs9465881
20866829	rs9465882
20866922	rs2820001
20867101	rs2820002
20867254	rs9350280
20867255	rs9356751
20868156	rs6909558
20868333	rs11415727
20868591	rs6910326
20869059	rs12664021
20869213	rs9295482
20869314	rs9465883
20869658	rs9465884
20870485	rs4437452
20871061	rs34235608
20871150	rs4712540

Pos Build 35/36	Marker ID
20871244	rs35450702
20872229	rs4351239
20872296	rs12190376
20872578	rs4710946
20873095	rs9465885
20873251	rs12192328
20873365	rs10536083
20873375	rs36210777
20873677	rs6149469
20874082	rs4585542
20874261	rs7751154
20874410	rs9356752
20874676	rs4510656
20875450	rs7452218
20875680	rs4320364
20876442	rs9465886
20876454	rs6926436
20877469	rs34127549
20877508	rs13214325
20877580	rs7750031
20877596	rs34801493
20877974	rs7772390
20878762	rs6900375
20879028	rs4712541
20879194	rs4710947
20879323	rs34893361
20879617	rs35938647
20879690	rs9465887
20879842	rs9368232
20879939	rs9350281
20880120	rs4132894
20880272	rs12195490
20880344	rs9465888
20880553	rs6941727
20880797	rs4712542
20880982	rs6923622
20881085	rs4712543
20881539	rs9358366
20881700	rs12211178
20881731	rs7453352
20881858	rs6929760
20881957	rs6929918
20882292	rs9465889
20882389	rs4712545
20882575	rs12193239
20882738	rs9465890
20883200	rs6936300
20883430	rs6936840
20883639	rs4493738
20883701	rs11965197
20884250	rs6899514
20884329	rs6456372
20885570	rs34358176
20886538	rs9465891
20886687	rs10946407
20887060	rs35581397
20887457	rs9358367
20887829	rs4076137
20888220	rs13207747
20888221	rs13208059

Pos Build 35/36	Marker ID
20888329	rs4074058
20888884	rs9350282
20888894	rs3193655
20888919	rs11545101
20888919	rs3193654
20889269	rs12199265
20889428	rs34113701
20889600	rs41272363
20890872	rs4478387
20891222	rs11752139
20891373	rs6910215
20891415	rs10690190
20891417	rs10647996
20891638	rs10946408
20892162	rs4710949
20892292	rs4712547
20892371	rs4712548
20892641	rs10550462
20892642	rs34372186
20893118	rs9368234
20893144	rs9348443
20893525	rs5874783
20893543	rs11344905
20893671	rs12210335
20893673	rs12210336
20893711	rs6902757
20893943	rs6456373
20894027	rs6927892
20894054	rs13210599
20894573	rs34563996
20895285	rs35066145
20897153	rs10498698
20898456	rs10806923
20898488	rs10806924
20898554	rs9368235
20898785	rs9368236
20898787	rs9368237
20899054	rs9356753
20899265	rs12111182
20899490	rs11752772
20899516	rs12661145
20899518	rs12665631
20899691	rs12208378
20900193	rs34964322
20901075	rs34430352
20901172	rs4299818
20901416	rs4495263
20901588	rs7773697
20901981	rs10684385
20901982	rs33967126
20902035	rs34171574
20902604	rs9460557
20902661	rs4492184
20902662	rs35025612
20903233	rs10946409
20903353	rs9295483
20903427	rs11751916
20904975	rs36025037
20905571	rs7738948
20905701	rs9465892

Pos Build 35/36	Marker ID
20905830	rs12211211
20906051	rs11968853
20906198	rs10456236
20906864	rs4712549
20906867	rs36194803
20906929	rs4712550
20907200	rs12213259
20907404	rs4496779
20907564	rs34432145
20907866	rs9358368
20908149	rs9368238
20908386	rs4524599
20908448	rs9465893
20908614	rs12215519
20909486	rs5874784
20909709	rs34686362
20910367	rs9460558
20910522	rs12664231
20910525	rs10946410
20911078	rs4710950
20911442	rs9465894
20911666	rs6925153
20911791	rs6456374
20912542	rs9465895
20913109	rs4712551
20913695	rs4607421
20913962	rs4293992
20913984	rs9460559
20914140	rs6942203
20914465	rs12189708
20914479	rs12660120
20914641	rs9465897
20914675	rs9465898
20915109	rs6905567
20915183	rs4580857
20915571	rs12191782
20915711	rs9358370
20916218	rs7748911
20916690	rs9350287
20916721	rs9356754
20917615	rs12525153
20917713	rs6456375
20917744	rs35117828
20917773	rs9348444
20917833	rs9465899
20917869	rs6902880
20918009	rs11756029
20918026	rs9348445
20918173	rs9358371
20918193	rs9348446
20918577	rs5874785
20918578	rs35532605
20918604	rs5874786
20918655	rs5874787
20918710	rs4373348
20918839	rs11966932
20918888	rs35887473
20918888	rs34206478
20919070	rs4330530
20919476	rs13198015

Pos Build 35/36	Marker ID
20919599	rs9465900
20919670	rs9465901
20919827	rs4710951
20919932	rs4710952
20920567	rs9358372
20920927	rs9358373
20920992	rs9368239
20921191	rs12192912
20921354	rs7747989
20921744	rs7752140
20921896	rs7752310
20922035	rs4710953
20922189	rs12662683
20922395	rs9465902
20922954	rs35040258
20922958	rs4710954
20923239	rs12661606
20923432	rs10946411
20923828	rs36037446
20924516	rs12212105
20925219	rs12213857
20925336	rs12213956
20925602	rs10946412
20925812	rs11759888
20925967	rs9366360
20926372	rs12665734
20926457	rs4712552
20926516	rs9465903
20926518	rs4712553
20927237	rs12190831
20927408	rs4334968
20927432	rs34237934
20927804	rs11961950
20927955	rs10806925
20929468	rs7753109
20929641	rs9465904
20929820	rs6931788
20929846	rs11304808
20930110	rs9465905
20930489	rs9465906
20930866	rs9465907
20931188	rs9465908
20931485	rs6938757
20931735	rs6923264
20931827	rs6900509
20932202	rs9460561
20932400	rs10946413
20932413	rs9465909
20932808	rs9460562
20932809	rs9465910
20932976	rs10806926
20932997	rs9460563
20933029	rs9465911
20933338	rs11404073
20933339	rs34199366
20933375	rs4712554
20933483	rs4712555
20933542	rs35893096
20933749	rs34260649
20933990	rs9465912

Pos Build 35/36	Marker ID
20934012	rs9368240
20934024	rs9368241
20934147	rs9368242
20934260	rs4395717
20934729	rs12209113
20935051	rs44446563
20935807	rs9348447
20936313	rs10806927
20936483	rs35622501
20936512	rs12211426
20936992	rs9368243
20937713	rs7768091
20937751	rs9356755
20938085	rs6917412
20938283	rs12215186
20938644	rs9348448
20938681	rs10570889
20938807	rs34799469
20938927	rs12190001
20938932	rs9465913
20939133	rs35997536
20939251	rs6901110
20939636	rs35810189
20940144	rs9368244
20940807	rs9350288
20940851	rs12210496
20941839	rs4568440
20942876	rs11964964
20943072	rs28616599
20943192	rs12201027
20943239	rs12194825
20943369	rs34826961
20943724	rs5874788
20943727	rs34317828
20944192	rs9465914
20944328	rs9465915
20946192	rs10592623
20946236	rs7749282
20946253	rs7769205
20946255	rs7749021
20946263	rs7769209
20946275	rs7749034
20946424	rs9295484
20946948	rs6456377
20947467	rs34883184
20948065	rs9465917
20948650	rs12210803
20948719	rs4345385
20949055	rs7764980
20949271	rs7765060
20949459	rs11967047
20949540	rs35943413
20949572	rs11967068
20949779	rs9460564
20950591	rs9465919
20950992	rs35578988
20951013	rs35344109
20952130	rs9356756
20952309	rs34656248
20952720	rs17234378

Pos Build 35/36	Marker ID
20952897	rs35541206
20952909	rs9366361
20952918	rs35392381
20953053	rs7751431
20953657	rs4336435
20953903	rs36065886
20954005	rs6920045
20954509	rs6941354
20954569	rs6941809
20954582	rs6941508
20954975	rs6903445
20955367	rs7742468
20956366	rs11417705
20956496	rs11281215
20956497	rs28533427
20956497	rs9295485
20956498	rs28588709
20956498	rs34068549
20956738	rs34367682
20957391	rs7753271
20957513	rs9460566
20957564	rs34204682
20957693	rs11962974
20957793	rs35879846
20957849	rs6921177
20958215	rs6456378
20958359	rs12663147
20958432	rs13192874
20958637	rs11294607
20958873	rs7763216
20959240	rs5874789
20959954	rs11966086
20960487	rs13208940
20960793	rs4397214
20961601	rs6908918
20961601	rs34610909
20961612	rs6908922
20961613	rs6908779
20962352	rs7771981
20962545	rs9465921
20962984	rs4236002
20963120	rs4236003
20963450	rs9350289
20963535	rs9350290
20963662	rs10558810
20963671	rs10608340
20963756	rs7761330
20963966	rs13209243
20964017	rs35463313
20964570	rs12211628
20964682	rs4712556
20965069	rs4710955
20965780	rs34481273
20965904	rs16884229
20966215	rs11965417
20966239	rs4712558
20966335	rs4712559
20966543	rs34865786
20966637	rs17826361
20966708	rs9366362

Pos Build 35/36	Marker ID
20966831	rs9366363
20967583	rs11966194
20968463	rs12524318
20968532	rs28412953
20968698	rs9358374
20968821	rs9350291
20968927	rs9350292
20969034	rs9350293
20969131	rs16901585
20969205	rs5007237
20969579	rs4383807
20969839	rs4330531
20970113	rs12662176
20970590	rs9356757
20970850	rs34873202
20970884	rs9368245
20970889	rs34101377
20971175	rs12201353
20971267	rs12214755
20972435	rs11269210
20973576	rs9465922
20973608	rs12191898
20973841	rs35647500
20973851	rs5874790
20973852	rs35372258
20974027	rs7749397
20974223	rs7454011
20974715	rs35244703
20974836	rs9368246
20974986	rs34062103
20975000	rs35487666
20975596	rs16884250
20975795	rs10554344
20976043	rs4370355
20976276	rs10588127
20976276	rs34382383
20977459	rs7766346
20977678	rs7766681
20977795	rs7770607
20978072	rs9350294
20978617	rs9350295
20978719	rs9366364
20978768	rs34447575
20978882	rs9366365
20980033	rs35505816
20980715	rs34113324
20981367	rs10946414
20981827	rs4645410
20982392	rs16884254
20982541	rs13197235
20983561	rs9350296
20983706	rs9368247
20984381	rs12665789
20984489	rs4077403
20984592	rs4077404
20984662	rs4077405
20984894	rs4529295
20984917	rs35499986
20985132	rs4618519
20985379	rs36002274

Pos Build 35/36	Marker ID
20985482	rs9368248
20985514	rs7742802
20985952	rs4236004
20986261	rs4712561
20986658	rs9358375
20986864	rs12194583
20986999	rs34923632
20987073	rs4537128
20987237	rs4626408
20987282	rs12194813
20987312	rs6915746
20988259	rs9350297
20988570	rs12210231
20988821	rs12198243
20989365	rs10946415
20989383	rs7763704
20989596	rs10589878
20990154	rs9465923
20990216	rs9465924
20990238	rs9460567
20990523	rs9465925
20990820	rs4612156
20991595	rs10946416
20992059	rs4546483
20992198	rs9460569
20993260	rs35314952
20993493	rs4131667
20993700	rs4334975
20993732	rs4272215
20994113	rs11756312
20994209	rs6926335
20995305	rs9366367
20995933	rs6938256
20996432	rs6938755
20996580	rs9465928
20996674	rs7773564
20996730	rs28843472
20996731	rs12210522
20996732	rs13191608
20996755	rs10806929
20996858	rs9268994
20996859	rs9268995
20996890	rs28895225
20996905	rs9268996
20996911	rs9268997
20996937	rs35328517
20996973	rs9268998
20997216	rs12055384
20997384	rs12055630
20997540	rs4947247
20998096	rs9460571
20998693	rs10946417
20998950	rs11752477
20999169	rs6913323
20999294	rs12194053
20999407	rs36009649
20999752	rs10594050
20999763	rs5874791
20999764	rs35553046
20999770	rs4363020

Pos Build 35/36	Marker ID
21000241	rs10456008
21000447	rs35294796
21000702	rs9368251
21001068	rs6916036
21001199	rs34587331
21001226	rs6456379
21001338	rs9368252
21001683	rs4626415
21002414	rs5874792
21002415	rs33925173
21002601	rs5874793
21002602	rs34720816
21002625	rs12528945
21004281	rs12206985
21004330	rs11757050
21004330	rs34449480
21004372	rs9368253
21004532	rs9295486
21004540	rs9465930
21004836	rs12208719
21005635	rs6918643
21005875	rs4712562
21006091	rs6456380
21006119	rs7759877
21006228	rs9358376
21006412	rs35620702
21006800	rs28665148
21006801	rs28599540
21007273	rs35400949
21007751	rs12153898
21007819	rs12154181
21007863	rs12154184
21008099	rs9368254
21008207	rs9368255
21009058	rs35958016
21009211	rs6456381
21009246	rs7758467
21009290	rs6456382
21009421	rs12153811
21009654	rs7739013
21009711	rs6922768
21009716	rs13191241
21009909	rs10640864
21009910	rs34135721
21010295	rs34154507
21010566	rs35386545
21010568	rs9368256
21010964	rs7740094
21010972	rs7758155
21011220	rs9366368
21011950	rs9358377
21012344	rs6908429
21012629	rs4712563
21012910	rs4710957
21013210	rs12214079
21013433	rs9460572
21013812	rs2876583
21013840	rs9465931
21014102	rs34068097
21014657	rs10080699

Pos Build 35/36	Marker ID
21014657	rs9460573
21014665	rs9460574
21014666	rs6920918
21015860	rs4413596
21016247	rs6909682
21016278	rs6910032
21016580	rs1498427
21016869	rs34713988
21017395	rs9368257
21017439	rs6939006
21017512	rs17236121
21017740	rs11753331
21018757	rs12198263
21018818	rs35916632
21018915	rs9350298
21018982	rs4710958
21019053	rs35886192
21019304	rs6456385
21019380	rs7763674
21019654	rs7746308
21020651	rs12190631
21020765	rs1498425
21021671	rs13197106
21022074	rs6913538
21022178	rs9460575
21022308	rs6914232
21022483	rs9460576
21022485	rs6914586
21022873	rs9465932
21022913	rs2030082
21022932	rs9350299
21023379	rs10536841
21023692	rs9465933
21024540	rs34537557
21025636	rs9368258
21026230	rs6938184
21026422	rs6938415
21026611	rs35678799
21028069	rs28440883
21028102	rs4712564
21028251	rs4712565
21028711	rs9366369
21028958	rs9465934
21029390	rs6913658
21030247	rs7765765
21030707	rs12662218
21030842	rs9460577
21030852	rs4712566
21030926	rs4712567
21030962	rs6936002
21031254	rs9460578
21031561	rs7771782
21032098	rs2328550
21032169	rs9465935
21033024	rs9460579
21033247	rs2328551
21033384	rs34787947
21033907	rs35164658
21034157	rs34463604
21034296	rs16884302

Pos Build 35/36	Marker ID
21034654	rs13215945
21034664	rs13215949
21034748	rs13202822
21034750	rs13203127
21034760	rs13203130
21035097	rs35259543
21035108	rs10687937
21035135	rs9358378
21035148	rs9465936
21035989	rs6903176
21036896	rs34272344
21037020	rs9366370
21037483	rs7747830
21037954	rs35552655
21038014	rs11970010
21038092	rs11970030
21038468	rs35341341
21038480	rs5874794
21038957	rs34094116
21039069	rs9366371
21039135	rs7775995
21040473	rs6916666
21041656	rs16884308
21042140	rs11395158
21042539	rs34100038
21042991	rs7768647
21043110	rs35030815
21043259	rs9350300
21044027	rs10946419
21044393	rs10946420
21044437	rs9465937
21044451	rs9368259
21044452	rs33911838
21044591	rs9358379
21044671	rs9460580
21044802	rs35523552
21044952	rs16884310
21046071	rs34741537
21046084	rs12526287
21046565	rs9465938
21046566	rs28734969
21046585	rs7747773
21046841	rs9465939
21046900	rs4144650
21047359	rs4712569
21047690	rs4712570
21047713	rs6939250
21047725	rs4710959
21047769	rs4710960
21047987	rs13191844
21048358	rs12196595
21048740	rs9350301
21049043	rs9350302
21049105	rs11964084
21049192	rs6927419
21049306	rs12198512
21049369	rs11450413
21049370	rs11409601
21049371	rs33942714
21050175	rs4307160

Pos Build 35/36	Marker ID
21050624	rs4712571
21051211	rs9465941
21051466	rs10946423
21051483	rs9465942
21051538	rs34759060
21051555	rs9295487
21051560	rs5874795
21051561	rs9358380
21051563	rs12174149
21051568	rs9350303
21051569	rs9358381
21052585	rs11279071
21052648	rs9465943
21053046	rs9465944
21053295	rs10690950
21053629	rs34879403
21053757	rs7772447
21053935	rs7773189
21054476	rs34602677
21054784	rs6901153
21054804	rs11361870
21054805	rs35132815
21055236	rs12203876
21055710	rs35896536
21055853	rs34881630
21055870	rs9368260
21056065	rs9460581
21056280	rs6930879
21056288	rs6930887
21056329	rs6931047
21056472	rs9350305
21058200	rs9350306
21058970	rs12197923
21059112	rs9460582
21059179	rs5874796
21059866	rs6922187
21060142	rs9465945
21060180	rs10558500
21060186	rs11289942
21060212	rs9348451
21060247	rs6922914
21060361	rs9358382
21060639	rs35863080
21061204	rs4631270
21061590	rs2015426
21061898	rs7749498
21062676	rs9350307
21062805	rs1004172
21063311	rs7775523
21064970	rs12199174
21066160	rs9368261
21067118	rs7738201
21067314	rs17236645
21067986	rs16884319
21068463	rs9918311
21068617	rs34769285
21068702	rs12205321
21068911	rs6456388
21069040	rs4712572
21069650	rs12524678

Pos Build 35/36	Marker ID
21069850	rs13211056
21070260	rs17236694
21070934	rs35382761
21071276	rs28612346
21071587	rs6915209
21071832	rs35420176
21072294	rs6940952
21072419	rs35708433
21072662	rs6941808
21072828	rs11966306
21073181	rs16884325
21073468	rs7743030
21073553	rs28429494
21074417	rs4712573
21074865	rs11752712
21075695	rs9460583
21075964	rs9460584
21076612	rs34425275
21076615	rs1112255
21076815	rs1112256
21077529	rs9348452
21077563	rs34660637
21077716	rs7746754
21077794	rs9350308
21078333	rs34215872
21079005	rs2030081
21079247	rs6940649
21079554	rs6941043
21079964	rs6913817
21080948	rs201361
21081289	rs34479545
21081631	rs1980458
21082363	rs13210151
21082946	rs34266759
21083025	rs34192233
21083039	rs11427521
21083189	rs35882882
21083211	rs11330322
21083279	rs1997685
21083363	rs10498699
21083433	rs201360
21085426	rs201359
21085653	rs201358
21085834	rs34764914
21087560	rs201357
21088272	rs4712575
21088448	rs4712576
21088450	rs4712577
21088472	rs365001
21088891	rs35829025
21089414	rs383684
21089616	rs444005
21090258	rs35693086
21090584	rs11961135
21091067	rs201356
21091773	rs201355
21091799	rs12193382
21091799	rs34391804
21091914	rs35723307
21091926	rs35448639

Pos Build 35/36	Marker ID
21093023	rs35957348
21093317	rs201354
21093369	rs201353
21093439	rs9350309
21093650	rs201352
21094109	rs201351
21094143	rs35853352
21094861	rs5874797
21094872	rs5874798
21094931	rs201350
21095014	rs1997684
21095425	rs4560627
21095482	rs10699637
21095654	rs7453577
21096171	rs11300877
21096223	rs201349
21096419	rs10694429
21096428	rs3223730
21096922	rs201348
21097026	rs35010661
21097035	rs201347
21097047	rs10701919
21097265	rs201346
21098132	rs6456389
21099063	rs12528036
21099645	rs201345
21099698	rs13199754
21099916	rs35504365
21100226	rs35586782
21100247	rs28418444
21100248	rs13196975
21100263	rs35586503
21100320	rs9356759
21100418	rs9366372
21100871	rs10946424
21100949	rs201344
21101200	rs11964880
21101281	rs11967584
21101513	rs201343
21102229	rs201342
21102283	rs9350310
21102377	rs9368262
21102486	rs9368263
21103236	rs35996844
21103858	rs201341
21103935	rs12660707
21104054	rs201340
21104291	rs201339
21105034	rs396308
21105044	rs4712578
21105348	rs449233
21107366	rs9358383
21107874	rs36078234
21108856	rs9368264
21109330	rs9368265
21109358	rs9368266
21109523	rs9368267
21109553	rs6940871
21109878	rs35240009
21110331	rs6914677

Pos Build 35/36	Marker ID
21110432	rs9350311
21110750	rs12195827
21110788	rs9366373
21110864	rs34620040
21111239	rs9350312
21111513	rs2038066
21111536	rs13191651
21111581	rs13191676
21111601	rs2038065
21112269	rs7744303
21112288	rs7744317
21112352	rs7762669
21113187	rs6932336
21113252	rs34002111
21113325	rs6932393
21113687	rs2839854
21114641	rs9348453
21115599	rs9358384
21115719	rs9348454
21115720	rs2473089
21115866	rs2494728
21116011	rs9358385
21116132	rs1498426
21116718	rs12192642
21116822	rs13200036
21116851	rs9368268
21116920	rs7750463
21116972	rs7750903
21117087	rs374654
21117572	rs6914615
21117867	rs9465946
21118124	rs364334
21118132	rs416688
21118300	rs11382802
21118547	rs1548145
21118567	rs201291
21119018	rs9465947
21119021	rs12197742
21119236	rs201292
21119698	rs35998561
21119973	rs201293
21120225	rs9358386
21120735	rs35254358
21120883	rs6905258
21121364	rs201294
21121603	rs201295
21121962	rs7748932
21121994	rs2494729
21122535	rs3966676
21122822	rs34834774
21122975	rs16884376
21123408	rs201308
21123602	rs8180606
21123934	rs201309
21123964	rs201310
21124001	rs6456390
21124511	rs201311
21124822	rs5874799
21124823	rs34733906
21124830	rs400514

Pos Build 35/36	Marker ID
21124882	rs3061573
21125298	rs16884385
21125848	rs34894804
21125898	rs9460586
21126295	rs16884389
21126495	rs35678732
21126634	rs10946425
21127516	rs6899729
21127744	rs16884394
21128114	rs36115181
21128124	rs5874800
21128307	rs34639729
21128419	rs35260082
21128533	rs7744010
21128746	rs201290
21129343	rs201289
21129647	rs34802324
21129981	rs201288
21130208	rs201287
21131340	rs34891710
21131348	rs11438527
21131431	rs34878496
21131727	rs16884396
21132081	rs9465948
21132220	rs16884399
21133062	rs11297091
21133400	rs169293
21133737	rs201307
21133815	rs12206158
21133964	rs34317920
21134374	rs34305502
21134401	rs35570989
21135019	rs13218003
21135740	rs12209877
21136038	rs6921781
21136172	rs16884406
21136940	rs201306
21136972	rs201305
21137253	rs201304
21137477	rs34243092
21137698	rs201303
21138072	rs201302
21138132	rs201301
21138504	rs35592283
21138790	rs10946426
21138980	rs6919322
21139058	rs4710961
21139068	rs9465949
21139350	rs398913
21139414	rs4710962
21139480	rs12526927
21139855	rs9460587
21140661	rs415446
21141104	rs35761643
21141617	rs11961096
21141944	rs201300
21142185	rs35161624
21142199	rs35206549
21142635	rs13210277
21142726	rs12198160

Pos Build 35/36	Marker ID
21142744	rs7766970
21143715	rs201299
21143786	rs35061829
21144118	rs201298
21144658	rs201297
21145049	rs201296
21145549	rs34771308
21145593	rs9295488
21145919	rs989969
21146291	rs34874522
21146814	rs201312
21146901	rs201313
21147026	rs201314
21147263	rs9350314
21147738	rs6918555
21147791	rs6918751
21147930	rs9295489
21148244	rs13190826
21148269	rs13190835
21148356	rs17662372
21148684	rs201315
21148701	rs16884415
21150019	rs16884420
21150116	rs17730046
21150139	rs201316
21151059	rs16884425
21151118	rs1555052
21151344	rs11753092
21151557	rs34254730
21151557	rs9465950
21151573	rs7756338
21151831	rs9348455
21151949	rs201317
21152589	rs6925617
21152677	rs201318
21152873	rs9460588
21152874	rs34536386
21152874	rs9460589
21152898	rs201319
21153050	rs201320
21153105	rs201321
21153294	rs201322
21153342	rs201323
21153387	rs201324
21153587	rs201325
21153907	rs9460590
21153987	rs201326
21154014	rs201327
21154069	rs201328
21154147	rs201329
21154297	rs201330
21154380	rs13217562
21154919	rs34472513
21154958	rs201331
21155233	rs201332
21155256	rs34312444
21155363	rs201333
21155639	rs201334
21155793	rs201335
21156103	rs201336

Pos Build 35/36	Marker ID
21156840	rs201337
21156885	rs201338
21157007	rs34847494
21157597	rs9942509
21157604	rs34987941
21158291	rs10806930
21158841	rs4712579
21160395	rs7775602
21160650	rs11760181
21160654	rs2056951
21160683	rs7758243
21160934	rs9358387
21160973	rs6456391
21160974	rs9465951
21161031	rs6903997
21162291	rs6933211
21162635	rs7748652
21162661	rs6456392
21162711	rs13215037
21162805	rs7752701
21163066	rs6456393
21163111	rs2328567
21163129	rs6456394
21163541	rs12661235
21163651	rs7754018
21163696	rs9350315
21163923	rs9918435
21165424	rs9465953
21165665	rs35560899
21165892	rs34142046
21166104	rs9465954
21166730	rs12202256
21166802	rs2206014
21167015	rs13219721
21167016	rs13205176
21167182	rs13219752
21167200	rs13205420
21167401	rs9350316
21167460	rs9368270
21167796	rs9465955
21169768	rs28532482
21170022	rs17237178
21170224	rs13209905
21170225	rs13209787
21170236	rs13210005
21170269	rs13210023
21170287	rs13210027
21170376	rs7744921
21170433	rs9465956
21170545	rs9465957
21170553	rs9465958
21170579	rs16884466
21170710	rs11969047
21170765	rs16884468
21170846	rs11969587
21171228	rs9465959
21171401	rs34908981
21172309	rs9460591
21173104	rs35603774
21173126	rs9465960

Pos Build 35/36	Marker ID
21173198	rs34559907
21173393	rs4710963
21173679	rs9465961
21173766	rs1001310
21173805	rs4712580
21174689	rs9460592
21174762	rs9460593
21176267	rs12209678
21177342	rs35738724
21177501	rs7762612
21177928	rs36174378
21177981	rs13199309
21178014	rs9295490
21178237	rs12660913
21178243	rs10946427
21178328	rs12199982
21178333	rs34600664
21178468	rs6932873
21178475	rs9356760
21178487	rs9465962
21178588	rs9356761
21178609	rs10650825
21179141	rs4382241
21179575	rs2013346
21179832	rs10498700
21180396	rs9350317
21180629	rs11757139
21180733	rs11757596
21181008	rs11757677
21181027	rs9465963
21181171	rs13203959
21181269	rs9366374
21181357	rs11968037
21181410	rs6918997
21181499	rs9368271
21181567	rs9460594
21181588	rs9460595
21182172	rs9295491
21182342	rs4283868
21182548	rs4413602
21183182	rs10541645
21183338	rs10541646
21183364	rs11407560
21183365	rs35953450
21183371	rs7766554
21183409	rs7766574
21183437	rs10541647
21183457	rs7766451
21183464	rs7766713
21183493	rs7766728
21183552	rs4280955
21183645	rs7767038
21183675	rs7766788
21183741	rs7770701
21184027	rs16884481
21184246	rs9295492
21184599	rs4367364
21184749	rs2068072
21184770	rs2068071
21185523	rs11963640

Pos Build 35/36	Marker ID
21185602	rs11961090
21185611	rs11963654
21185810	rs35119417
21186212	rs9358388
21186666	rs4599624
21187063	rs10080639
21187282	rs7749838
21187336	rs11967298
21187386	rs34700985
21187552	rs9366375
21187610	rs4310041
21187627	rs4496780
21187688	rs7750461
21187916	rs6917272
21188170	rs6917904
21188430	rs34700472
21188451	rs9350318
21189185	rs4323302
21189629	rs9366376
21189885	rs10456237
21189931	rs13219886
21190084	rs9368272
21190476	rs35189729
21191594	rs6904648
21191595	rs11751563
21191595	rs35898656
21192182	rs4593348
21192409	rs4421186
21192801	rs6915237
21193447	rs7773973
21193514	rs17834555
21193811	rs6901354
21194026	rs4130033
21194285	rs35287977
21194419	rs10806931
21194732	rs11964144
21194764	rs10946428
21196061	rs12200487
21196232	rs4712581
21196650	rs6456395
21196835	rs6456396
21197051	rs9368273
21197394	rs4712582
21198212	rs34465715
21198601	rs6904348
21199015	rs11433815
21199016	rs36110847
21199138	rs9368274
21199756	rs12197841
21199815	rs12197853
21199817	rs12197854
21200342	rs7762660
21200361	rs7762670
21200554	rs7762964
21200605	rs13210302
21200944	rs34756370
21201333	rs7768086
21201341	rs13214341
21202104	rs33945169
21202717	rs6939622

Pos Build 35/36	Marker ID
21202933	rs4454125
21203121	rs4401656
21204432	rs11969472
21204602	rs9358389
21204788	rs4712583
21205444	rs11757261
21205844	rs34430280
21206360	rs11757901
21206756	rs34764667
21206833	rs35866346
21207116	rs9465965
21207331	rs7744319
21207645	rs9368275
21207687	rs9356762
21208023	rs9350319
21208328	rs9350320
21208606	rs9366377
21208909	rs5874801
21209654	rs9368276
21210536	rs4712584
21210553	rs34092761
21210726	rs9366378
21211436	rs11968036
21211664	rs9465966
21211803	rs4569951
21212138	rs4130302
21212414	rs35081613
21212547	rs9358390
21212715	rs6925464
21212715	rs9460596
21212847	rs17834987
21213142	rs12529531
21213851	rs36086759
21214087	rs6936205
21215067	rs4574622
21215086	rs9465967
21215088	rs9358391
21215150	rs35347692
21215159	rs5874802
21215207	rs4624863
21215258	rs9465968
21215359	rs4526186
21215371	rs34865903
21215437	rs7739050
21215448	rs4326226
21216093	rs4712585
21216145	rs9356763
21216170	rs4710964
21216871	rs9460597
21218688	rs11963150
21218907	rs6923546
21219519	rs6924221
21220306	rs10456238
21222458	rs34418857
21222459	rs34251532
21222460	rs34219362
21222644	rs35962170
21223003	rs16884514
21223188	rs7773318
21223279	rs4340995

Pos Build 35/36	Marker ID
21223295	rs9356764
21224572	rs35468559
21224879	rs3935207
21224965	rs35629967
21225019	rs6927498
21225119	rs10613278
21225499	rs35372171
21225513	rs10554335
21225585	rs7764365
21225685	rs35234206
21225694	rs11418036
21225734	rs7768536
21226218	rs4389757
21227109	rs6456397
21227703	rs35183051
21228007	rs7741436
21228269	rs9356765
21228407	rs9366379
21228562	rs6926818
21228614	rs16884524
21228619	rs34425854
21228733	rs4074910
21228748	rs4076112
21229002	rs35885025
21229134	rs6909332
21229654	rs4438948
21229845	rs6905660
21230834	rs9358392
21231054	rs9368279
21231899	rs4315997
21231967	rs4479917
21232500	rs10946430
21232701	rs34821627
21232763	rs13191691
21232779	rs13207763
21232796	rs13207766
21232816	rs13191830
21233338	rs34857211
21234866	rs7750839
21235291	rs7751485
21235577	rs11757294
21235798	rs34183889
21236043	rs12055489
21236223	rs28421119
21237436	rs9295493
21237650	rs12055790
21237696	rs35692444
21237763	rs7766575
21237890	rs9356766
21237892	rs34802727
21237915	rs35927368
21238432	rs10708944
21238635	rs6932722
21238849	rs6937439
21238961	rs9986401
21239004	rs9465969
21239122	rs9986662
21239291	rs9295494
21239512	rs35030599
21240132	rs9460598

Pos Build 35/36	Marker ID
21240526	rs28403910
21241995	rs9465970
21242670	rs7760880
21242672	rs7761283
21242682	rs11463641
21242783	rs7765177
21242820	rs7765199
21242857	rs7764887
21243009	rs7765106
21243039	rs28610069
21243105	rs7765274
21243107	rs2446490
21243137	rs2493869
21243228	rs7765725
21243240	rs7765730
21243646	rs16884554
21243857	rs13216162
21244099	rs2446489
21244512	rs2446488
21244516	rs7771907
21245195	rs9350322
21245369	rs2446487
21246042	rs35201465
21246079	rs9358393
21246445	rs959712
21246447	rs35541643
21246451	rs34848377
21246456	rs5874803
21246457	rs33951051
21246458	rs5874804
21246459	rs35717786
21246466	rs5874805
21246467	rs35384149
21246474	rs959711
21246487	rs34589183
21246785	rs9688559
21246915	rs9689353
21246958	rs34154291
21246988	rs9688564
21246992	rs9688565
21247009	rs2446486
21247020	rs9688569
21247061	rs9688573
21247079	rs9295495
21247094	rs9465971
21247737	rs9460599
21247746	rs6916667
21247788	rs9465972
21248278	rs2446485
21248465	rs2446484
21249707	rs28665959
21249879	rs35583136
21249895	rs34896971
21249984	rs7746383
21250235	rs7746846
21250457	rs28360550
21250639	rs6932702
21251345	rs9348456
21251752	rs35724409
21251989	rs2328573

Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID	Pos Build 35/36	Marker ID
21252098	rs17835633	21265017	rs4712586	21279689	rs34012677	21297967	rs10452581
21252216	rs36008085	21265065	rs7761116	21279828	rs12178179	21298562	rs13192000
21252578	rs10498701	21265072	rs9358395	21279839	rs9465980	21298563	rs13191669
21252578	rs35938718	21265152	rs9368283	21280353	rs9358396	21298583	rs13192011
21252735	rs34957382	21265828	rs34689265	21281052	rs12194541	21298617	rs13192029
21253603	rs10708192	21266252	rs6931316	21281118	rs2061441	21298629	rs13192143
21254245	rs1466340	21267009	rs6916577	21281632	rs9460605	21298630	rs13207866
21255061	rs10710231	21267167	rs6937555	21281781	rs12525339	21298671	rs13191819
21255726	rs1466339	21267311	rs10645059	21282235	rs35462438	21298690	rs13192164
21255824	rs7740358	21267321	rs10652396	21282590	rs9465981	21298721	rs13192173
21256011	rs11405792	21267832	rs16884591	21282848	rs4637624	21298723	rs13191845
21256411	rs1471205	21268027	rs11442196	21282946	rs35969558	21299659	rs9465990
21256721	rs9368280	21268361	rs7739578	21283471	rs12525940	21299810	rs9460607
21257043	rs9295496	21268400	rs7739596	21283655	rs34603118	21299907	rs9465991
21257242	rs12206028	21268426	rs4527692	21283948	rs12528104	21299909	rs9366386
21257356	rs9368281	21268664	rs9295498	21284103	rs12526391	21299971	rs35944981
21258107	rs2168985	21268668	rs9295499	21284906	rs6939148	21300001	rs9366387
21258129	rs12207912	21268866	rs10080292	21284912	rs9460606	21300046	rs9366388
21258136	rs35882470	21268870	rs35915482	21285561	rs13219281	21300106	rs9368287
21258203	rs9368282	21268881	rs9465976	21285569	rs13219285	21300203	rs13193222
21258436	rs7752602	21268928	rs28581582	21285598	rs13219506	21300325	rs10080974
21258626	rs7752788	21268942	rs34844023	21285611	rs13219193	21300381	rs9295502
21258747	rs2446483	21269038	rs12179712	21285620	rs13219198	21300388	rs12528974
21258795	rs9356768	21269039	rs9465977	21285664	rs13219637	21300395	rs7759646
21258995	rs34495814	21269504	rs9465978	21285689	rs13205078	21300433	rs9465992
21259344	rs9350323	21271039	rs6929437	21285691	rs13205079	21300768	rs11964193
21259352	rs4530843	21271299	rs4995985	21285875	rs11308599	21301021	rs34456723
21259489	rs9460600	21271738	rs34031561	21286261	rs9465982	21301080	rs34094109
21259600	rs9460601	21271898	rs6914598	21288187	rs12214946	21301834	rs11759448
21260113	rs10946431	21272056	rs6935079	21288554	rs34495587	21302380	rs11962770
21260135	rs35088240	21272110	rs6935117	21289215	rs12523755	21303198	rs9366389
21260216	rs10946432	21272124	rs6935124	21289629	rs35642303	21303687	rs11753415
21260253	rs10946433	21272174	rs9368284	21290957	rs9295501	21304730	rs4712587
21260917	rs11961031	21272190	rs6915161	21291348	rs35815279	21304976	rs7748091
21261341	rs4144175	21272228	rs9356770	21291533	rs12527222	21305299	rs28469715
21261468	rs10604354	21272416	rs35558562	21291647	rs9465983	21305355	rs7748766
21261575	rs12203853	21272655	rs6916053	21291857	rs2493868	21305591	rs35164470
21261620	rs6901380	21272716	rs34191499	21291918	rs35979352	21305660	rs2125571
21261891	rs6906201	21273107	rs6941714	21292407	rs34248538	21305669	rs9465993
21262118	rs9460602	21273161	rs34326160	21292789	rs10946434	21306062	rs3793090
21262389	rs35396145	21273168	rs9460603	21292811	rs9465984	21307994	rs1531303
21262741	rs9350324	21273192	rs9348458	21293033	rs34599800	21308261	rs2305955
21262775	rs9295497	21273257	rs7776158	21293434	rs35442433	21308369	rs1459047
21262969	rs9366381	21273274	rs11965768	21293569	rs9465985	21309244	rs35662535
21263128	rs6456398	21274046	rs35674401	21294166	rs35712201	21309281	rs9767650
21263152	rs6456399	21274684	rs2125570	21294748	rs35539626	21309286	rs9767186
21263168	rs6456400	21275213	rs7768526	21294750	rs9465986	21309387	rs9460608
21263322	rs6456401	21275957	rs9368285	21294751	rs9465987	21309472	rs9465994
21263462	rs11456476	21276570	rs28360551	21294801	rs11961469	21310133	rs9465995
21263471	rs34116986	21277729	rs7763700	21295134	rs2446482	21310563	rs36067162
21263595	rs6913868	21277824	rs4425589	21295312	rs9465988	21310749	rs11965158
21263798	rs9366382	21277964	rs9348459	21295313	rs12191416	21311344	rs9350328
21263882	rs9348457	21278549	rs13197595	21295313	rs35985333	21311426	rs5874806
21264053	rs35931974	21278592	rs9460604	21295996	rs9465989	21311451	rs10616274
21264270	rs9366383	21278780	rs12180174	21296793	rs9350327	21311452	rs5874807
21264385	rs9366384	21278845	rs9465979	21297183	rs34750271	21311454	rs11288843
21264393	rs9356769	21279293	rs36058161	21297265	rs35013686	21311471	rs9350329
21264732	rs34306955	21279338	rs11969929	21297416	rs16884616	21311502	rs1824330
21264842	rs9350325	21279609	rs11965049	21297902	rs35898446	21311620	rs9717950
21264968	rs6924598	21279673	rs9295500	21297924	rs11751020	21311710	rs3898487

Pos Build 35/36	Marker ID
21311900	rs9350330
21311902	rs9350331
21312023	rs35603064
21312085	rs35615714
21312109	rs36017220
21312120	rs12196363
21312143	rs35881379
21312153	rs35710688
21312177	rs35017881
21312188	rs12196418
21312191	rs12196419
21312206	rs35883368
21312223	rs12196423
21312231	rs34046809
21312253	rs34108390
21312453	rs6921264
21312671	rs6921652
21312775	rs6926388
21312801	rs12527588
21313200	rs10456240
21313329	rs10456241
21313367	rs10456242
21313458	rs10456243
21313856	rs34046046
21313879	rs13213969
21313886	rs6932316
21313910	rs6932752
21313958	rs13214311
21313963	rs6932914
21313998	rs6932635
21314018	rs6912407
21314041	rs34849597
21314107	rs9366390
21314243	rs10223539
21314298	rs10223540
21314473	rs6913302
21315081	rs9366391
21315139	rs9356771
21315390	rs12530254
21315432	rs34085972

Pos Build 35/36	Marker ID
21315529	rs4291091
21315727	rs6940465
21315763	rs6901748
21316195	rs6902505
21316396	rs898167
21316398	rs898166
21316408	rs898165
21316820	rs34797264
21317102	rs9368288
21317206	rs9358397
21317611	rs2168984
21317978	rs1563728
21318135	rs4712588
21318266	rs11267610
21318399	rs4712589
21318666	rs6915037
21318882	rs12664336
21319431	rs9465998
21319494	rs10214790
21319776	rs12201217
21320060	rs9350332
21320905	rs9358398
21321149	rs9358399
21321286	rs9358400
21321533	rs10214694
21321733	rs10214716
21322176	rs9460609
21322179	rs6929219
21322517	rs12527686
21322561	rs12527673
21322733	rs9350333
21323322	rs10946436
21323380	rs6913136
21323400	rs13200114
21323464	rs13200422
21323815	rs2328572
21323949	rs9350334
21324672	rs34913347
21324713	rs10946437
21324725	rs10946438

Pos Build 35/36	Marker ID
21325164	rs9358401
21325261	rs34055473
21325350	rs34921405
21325357	rs6904880
21325395	rs6456403
21325653	rs2085654
21325832	rs9466000
21325853	rs9466001
21326033	rs2100707
21326158	rs12111402
21326366	rs4712590
21326649	rs4710965
21327416	rs6937610
21327459	rs12110862
21327488	rs35624914
21327606	rs11349673
21327854	rs16884681
21327895	rs7738425
21328030	rs16884685
21328355	rs16884688
21328398	rs35663664
21328510	rs12203389
21328818	rs12191541
21328946	rs34618548
21330074	rs1563726
21330730	rs16884693
21331119	rs2328574
21331209	rs16884699
21331264	rs16884705
21331267	rs6929141
21331293	rs16884709
21331392	rs16884713
21332034	rs9466002
21332081	rs9466003
21332103	rs9466004
21332139	rs9466005
21332272	rs9460610
21332409	rs7770316
21332488	rs11964983
21332496	rs7770752

Pos Build 35/36	Marker ID
21332625	rs7770637
21333229	rs1870421
21333556	rs6942273
21333618	rs9466006
21333709	rs9466007
21334500	rs7763249
21335731	rs9368289
21335750	rs9368290
21335782	rs13202305
21335903	rs34362358
21335906	rs11415596
21336317	rs28484932
21336582	rs7754027
21336699	rs34022115
21336867	rs4710966
21337512	rs16884722
21338182	rs35571136
21338184	rs35739791
21338815	rs9460611
21338986	rs9460612
21339013	rs12200511
21339097	rs35791563
21339201	rs34084405
21339207	rs34158326
21339453	rs1563727
21339524	rs3840416
21339530	rs11362523
21339688	rs7770664
21339861	rs35121088
21339935	rs4712591
21340199	rs35206923
21340202	rs28600127
21340213	rs4710967
21340214	rs4710968
21340218	rs13213171
21340219	rs13197226
21340225	rs12199601
21340594	rs1137970

Table 10. SNPs within LD block C06 (SEQ ID NO:1) between positions 20,634,996 and 20,836,710 bp on Chromosome 6 in NCBI Build 35 and NCBI Build 36

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20634996	1	rs4429936
20635028	33	rs9465780
20635060	65	rs7743222
20635066	71	rs7743223
20635241	246	rs4516938
20635285	290	rs4628090
20635339	344	rs9465781
20635349	354	rs28450063
20635350	355	rs9465782
20635834	839	rs4712503
20635845	850	rs9465783
20635860	865	rs4712504
20636037	1042	rs10946388
20636813	1818	rs9460517
20636939	1944	rs34086777
20637089	2094	rs9465785
20637215	2220	rs7754223
20637279	2284	rs34173688
20637287	2292	rs11459684
20637288	2293	rs35781726
20637303	2308	rs9460518
20637450	2455	rs11362835
20637521	2526	rs7772956
20637824	2829	rs1883641
20637875	2880	rs1883640
20637944	2949	rs11402844
20638219	3224	rs35198704
20638372	3377	rs6923683
20638762	3767	rs12181295
20638829	3834	rs9465788
20638961	3966	rs34578766
20639509	4514	rs2206578
20639662	4667	rs35530523
20639708	4713	rs2206577
20639710	4715	rs34553771
20639718	4723	rs34581322
20639719	4724	rs5874771
20639909	4914	rs6902897
20640005	5010	rs34607984
20640118	5123	rs6923201
20640162	5167	rs6903415
20640249	5254	rs9465790
20640425	5430	rs6923750
20640859	5864	rs10717803
20641038	6043	rs9465791
20641141	6146	rs6909467
20641248	6253	rs34525680
20641293	6298	rs35457534
20641299	6304	rs35731703
20641303	6308	rs10554680
20641320	6325	rs35239102
20641362	6367	rs9368197
20641413	6418	rs9465792
20641494	6499	rs12212722

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20641581	6586	rs7765611
20641590	6595	rs10566792
20641598	6603	rs10566793
20641718	6723	rs34275610
20641718	6723	rs10566794
20641724	6729	rs11347538
20641733	6738	rs5874772
20642073	7078	rs16883887
20642385	7390	rs34088191
20642428	7433	rs10806920
20642440	7445	rs11370426
20642441	7446	rs33915274
20642442	7447	rs11459775
20642443	7448	rs34576540
20642494	7499	rs10708068
20642586	7591	rs4712505
20642787	7792	rs41271303
20642953	7958	rs11963450
20643397	8402	rs981043
20643513	8518	rs981042
20643675	8680	rs16883895
20643753	8758	rs17512225
20643840	8845	rs35035071
20643949	8954	rs6904566
20644073	9078	rs6927356
20644093	9098	rs35281412
20644313	9318	rs35915788
20644314	9319	rs34025398
20644320	9325	rs34361235
20644335	9340	rs6905138
20644499	9504	rs13194858
20644717	9722	rs2179551
20644727	9732	rs2179550
20644787	9792	rs9465794
20644787	9792	rs9465795
20644848	9853	rs7747962
20644858	9863	rs6910725
20644918	9923	rs965054
20644971	9976	rs2143407
20645032	10037	rs10619380
20645431	10436	rs2328525
20645661	10666	rs13199286
20645841	10846	rs10611252
20645940	10945	rs7753499
20646023	11028	rs7753956
20646024	11029	rs34811195
20646024	11029	rs7753670
20646107	11112	rs3060613
20646107	11112	rs6149468
20646109	11114	rs11277970
20646110	11115	rs11280099
20646139	11144	rs16883900
20646175	11180	rs7774291
20646443	11448	rs10612082

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20646476	11481	rs9368198
20646502	11507	rs13203336
20646504	11509	rs13203631
20646619	11624	rs6456355
20646644	11649	rs10484635
20647190	12195	rs12204173
20647320	12325	rs13207544
20647851	12856	rs12198728
20647984	12989	rs28396084
20648327	13332	rs12199073
20648500	13505	rs9465796
20648561	13566	rs12212600
20648596	13601	rs13212040
20648663	13668	rs35291340
20648722	13727	rs12199324
20649085	14090	rs12200871
20649159	14164	rs9348432
20649183	14188	rs12200834
20649236	14241	rs34860173
20649324	14329	rs11754872
20649498	14503	rs6456356
20649517	14522	rs9368199
20649682	14687	rs2143406
20650176	15181	rs10484634
20650200	15205	rs7758851
20650398	15403	rs34677076
20651447	16452	rs6928571
20651461	16466	rs12192584
20651608	16613	rs34856684
20652015	17020	rs9350255
20652091	17096	rs9368200
20652136	17141	rs12214002
20652245	17250	rs9465797
20652300	17305	rs9465798
20652574	17579	rs28699301
20652650	17655	rs13215844
20652678	17683	rs12214315
20652722	17727	rs11759517
20652786	17791	rs13218957
20652806	17811	rs13218962
20653188	18193	rs10543744
20653201	18206	rs12216047
20653447	18452	rs9366354
20653890	18895	rs9358342
20654091	19096	rs9368201
20654382	19387	rs34206163
20654506	19511	rs9465799
20654794	19799	rs34187071
20654867	19872	rs9465800
20654890	19895	rs6908974
20654992	19997	rs13197372
20655361	20366	rs13214145
20655793	20798	rs16883910
20655968	20973	rs12194705
20656271	21276	rs35080661
20656465	21470	rs7753467
20656466	21471	rs7773488
20656986	21991	rs34182285
20657084	22089	rs34242699

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20657780	22785	rs9348433
20657942	22947	rs9460519
20658083	23088	rs12198377
20658096	23101	rs9465801
20658195	23200	rs9465802
20658822	23827	rs28458932
20658823	23828	rs9465803
20658981	23986	rs2103682
20659321	24326	rs9465804
20659580	24585	rs34611621
20660058	25063	rs12055423
20660653	25658	rs9465805
20660829	25834	rs11365187
20660836	25841	rs11320714
20660918	25923	rs9350256
20661764	26769	rs7756211
20662069	27074	rs9460520
20662498	27503	rs34245467
20662930	27935	rs9350257
20663855	28860	rs11964554
20663990	28995	rs9465806
20664109	29114	rs11964635
20664190	29195	rs13199421
20664314	29319	rs6932320
20664570	29575	rs12200078
20664659	29664	rs13437555
20664884	29889	rs9350258
20665256	30261	rs12176441
20665260	30265	rs12183826
20665264	30269	rs9356738
20665272	30277	rs9348434
20665343	30348	rs9465807
20665804	30809	rs4458667
20665995	31000	rs7739402
20667590	32595	rs16883914
20667591	32596	rs16883916
20667900	32905	rs9654584
20667999	33004	rs9465808
20668414	33419	rs17584626
20668565	33570	rs7751682
20669667	34672	rs11361279
20669681	34686	rs34634263
20670059	35064	rs12214549
20670364	35369	rs7753519
20670575	35580	rs28567007
20670597	35602	rs7772137
20670719	35724	rs12208597
20670998	36003	rs9368202
20671877	36882	rs2328526
20672452	37457	rs34823358
20673287	38292	rs28639914
20673363	38368	rs34233572
20673415	38420	rs4712506
20673935	38940	rs13203450
20674280	39285	rs9350259
20674435	39440	rs6918457
20674595	39600	rs35210537
20674749	39754	rs11329887
20675016	40021	rs9348435

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20675068	40073	rs35366106
20675342	40347	rs16901563
20675352	40357	rs12333229
20675520	40525	rs9460521
20676094	41099	rs10589899
20676351	41356	rs2876573
20676957	41962	rs6935461
20676963	41968	rs6935465
20676968	41973	rs10603174
20677060	42065	rs12333291
20677967	42972	rs2064321
20677985	42990	rs35546893
20678018	43023	rs4291090
20678121	43126	rs2064320
20678268	43273	rs9465810
20678275	43280	rs9465811
20678423	43428	rs9358344
20678756	43761	rs10946390
20679114	44119	rs6905281
20679339	44344	rs16883932
20679612	44617	rs34904067
20679660	44665	rs7744002
20679763	44768	rs35142564
20680095	45100	rs9465812
20680678	45683	rs7759094
20680784	45789	rs9460522
20681538	46543	rs7764551
20681585	46590	rs10541455
20682409	47414	rs16883935
20682542	47547	rs13215603
20682568	47573	rs962576
20683235	48240	rs1474720
20683797	48802	rs16883944
20684155	49160	rs34538343
20684269	49274	rs9350260
20684353	49358	rs16883951
20684645	49650	rs9358345
20684862	49867	rs1012627
20684890	49895	rs9368203
20684939	49944	rs35894322
20684965	49970	rs4710932
20684984	49989	rs6909117
20685540	50545	rs1012626
20685748	50753	rs1012625
20685760	50765	rs7752194
20685958	50963	rs9465813
20686014	51019	rs12207923
20686355	51360	rs16883963
20686831	51836	rs13205786
20686887	51892	rs35205364
20687102	52107	rs10456232
20687189	52194	rs9465814
20687201	52206	rs35571892
20687740	52745	rs9465815
20687753	52758	rs36119371
20687921	52926	rs28621813
20687926	52931	rs9350261
20687928	52933	rs7341226
20688175	53180	rs6927481

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20688323	53328	rs35313444
20688373	53378	rs6928198
20688404	53409	rs6907897
20688545	53550	rs6928586
20688872	53877	rs9368204
20689021	54026	rs9358346
20689589	54594	rs11967546
20689593	54598	rs34134803
20689772	54777	rs10456233
20689807	54812	rs7744833
20690123	55128	rs9460523
20690123	55128	rs9465816
20690432	55437	rs6908077
20690630	55635	rs9465817
20691069	56074	rs11967445
20691263	56268	rs34022950
20691793	56798	rs9460524
20691994	56999	rs34020592
20692003	57008	rs11448102
20692339	57344	rs9465818
20692402	57407	rs9350262
20692513	57518	rs13205241
20693000	58005	rs12153939
20693100	58105	rs6925593
20693119	58124	rs4712507
20693226	58231	rs10558806
20693267	58272	rs35982532
20693276	58281	rs11385529
20693360	58365	rs9348436
20693416	58421	rs9368206
20693438	58443	rs13209542
20693452	58457	rs9368207
20693630	58635	rs13209907
20693635	58640	rs6926658
20694018	59023	rs12213132
20694182	59187	rs4357125
20694554	59559	rs6932944
20694607	59612	rs6932962
20695026	60031	rs9348437
20695332	60337	rs12201857
20695356	60361	rs9465819
20695447	60452	rs6938955
20695539	60544	rs9460525
20695827	60832	rs9465820
20695964	60969	rs10946391
20695968	60973	rs9368208
20696003	61008	rs9465821
20696183	61188	rs6923790
20696401	61406	rs10558139
20697309	62314	rs6907459
20697320	62325	rs6907767
20697321	62326	rs9465822
20697349	62354	rs6930283
20697706	62711	rs6908042
20697741	62746	rs6935317
20697761	62766	rs35370102
20698266	63271	rs9368209
20698366	63371	rs13216746
20698367	63372	rs13216747

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20699007	64012	rs35485532
20699747	64752	rs13216324
20699817	64822	rs4336434
20700046	65051	rs4509107
20700428	65433	rs9465823
20700465	65470	rs6936705
20700679	65684	rs34023799
20700929	65934	rs6942313
20701057	66062	rs28869917
20701318	66323	rs34982231
20701631	66636	rs9358349
20701770	66775	rs9460526
20701829	66834	rs9366356
20702163	67168	rs36120092
20702181	67186	rs9465824
20702519	67524	rs4712512
20702561	67566	rs4712513
20702646	67651	rs4710934
20702658	67663	rs9348438
20702902	67907	rs9460529
20703363	68368	rs13199587
20703470	68475	rs13199384
20703526	68531	rs10223680
20703606	68611	rs9350263
20703768	68773	rs9465825
20703832	68837	rs10223876
20704100	69105	rs35702271
20704171	69176	rs9358350
20704432	69437	rs12208985
20704771	69776	rs12210459
20704892	69897	rs35431707
20705144	70149	rs36039523
20705297	70302	rs11758281
20705350	70355	rs28893199
20705757	70762	rs34256347
20706019	71024	rs12192740
20706282	71287	rs13212326
20706486	71491	rs12199184
20706753	71758	rs10456234
20707009	72014	rs4712514
20707422	72427	rs9465826
20707607	72612	rs9366357
20707867	72872	rs2294809
20708549	73554	rs2294808
20708813	73818	rs7762750
20708976	73981	rs4712515
20708998	74003	rs10522824
20708999	74004	rs35660518
20709002	74007	rs10679950
20709003	74008	rs34870864
20709022	74027	rs4712516
20709145	74150	rs4710935
20709386	74391	rs9465827
20709388	74393	rs12204865
20709672	74677	rs10946393
20709764	74769	rs12209806
20709894	74899	rs10946394
20709921	74926	rs1997778
20709971	74976	rs35878587

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20710359	75364	rs1997777
20710378	75383	rs2223622
20710776	75781	rs11964057
20711246	76251	rs9460530
20711344	76349	rs9460531
20711376	76381	rs34329159
20711640	76645	rs7764558
20711804	76809	rs4710936
20712056	77061	rs12213940
20712228	77233	rs13215038
20712739	77744	rs10946395
20712832	77837	rs6939917
20712975	77980	rs9358351
20713800	78805	rs6925097
20713924	78929	rs9465828
20713955	78960	rs9465829
20713961	78966	rs6902661
20714057	79062	rs34373680
20714281	79286	rs35051096
20714508	79513	rs932405
20714591	79596	rs6926585
20714635	79640	rs3938395
20715464	80469	rs11964664
20715551	80556	rs35964987
20715663	80668	rs12206413
20715758	80763	rs35990187
20715763	80768	rs4991654
20715910	80915	rs9460532
20715991	80996	rs13328250
20716030	81035	rs13328252
20716194	81199	rs4712517
20716257	81262	rs4712518
20717220	82225	rs7758129
20717475	82480	rs13206462
20717483	82488	rs13192442
20717486	82491	rs13206468
20717492	82497	rs13192445
20717498	82503	rs13192450
20717504	82509	rs13206477
20717510	82515	rs13206483
20717577	82582	rs12179168
20717586	82591	rs12180975
20717611	82616	rs12179172
20717860	82865	rs12179563
20718357	83362	rs11355836
20718696	83701	rs2328527
20718709	83714	rs11452882
20718920	83925	rs2876574
20719905	84910	rs9465831
20720031	85036	rs34877824
20720290	85295	rs13212501
20720647	85652	rs9358352
20720703	85708	rs9358353
20720761	85766	rs28756205
20720889	85894	rs9350265
20720989	85994	rs7750508
20721130	86135	rs7771052
20721141	86146	rs9460533
20721195	86200	rs13200415

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20721216	86221	rs10550932
20721312	86317	rs9465832
20721463	86468	rs9368211
20721471	86476	rs9350266
20721507	86512	rs11752592
20721515	86520	rs9350267
20721754	86759	rs978988
20721898	86903	rs978987
20721906	86911	rs978986
20722036	87041	rs5874773
20722196	87201	rs5874774
20722500	87505	rs7756788
20722659	87664	rs9348439
20722661	87666	rs9356739
20722693	87698	rs9356740
20722738	87743	rs7760894
20723021	88026	rs2796913
20723046	88051	rs2608613
20723121	88126	rs10456710
20723139	88144	rs9476286
20723140	88145	rs9476287
20723140	88145	rs28368538
20723141	88146	rs28612622
20723142	88147	rs9463660
20723146	88151	rs9463661
20723162	88167	rs9461022
20723193	88198	rs9461021
20723235	88240	rs34980442
20723239	88244	rs34049080
20723258	88263	rs35218684
20723260	88265	rs12175876
20723270	88275	rs10948323
20723287	88292	rs34400313
20723292	88297	rs36081550
20723304	88309	rs12175878
20723305	88310	rs34520184
20723305	88310	rs34756989
20723322	88327	rs4629736
20723322	88327	rs9296917
20723324	88329	rs28562027
20723333	88338	rs9381823
20723346	88351	rs34769771
20723346	88351	rs34774640
20723346	88351	rs36038896
20723365	88370	rs13209195
20723369	88374	rs12213541
20723369	88374	rs34112320
20723371	88376	rs34615869
20723379	88384	rs35949519
20723381	88386	rs9257498
20723383	88388	rs34200576
20723393	88398	rs4960519
20723396	88401	rs9261905
20723402	88407	rs9267103
20723404	88409	rs17367677
20723416	88421	rs9261906
20723421	88426	rs9267104
20723424	88429	rs9267105
20723434	88439	rs28810763

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723438	88443	rs12179121
20723438	88443	rs4714959
20723439	88444	rs10946636
20723439	88444	rs28763327
20723439	88444	rs28847950
20723439	88444	rs3933247
20723449	88454	rs28808723
20723451	88456	rs9767082
20723452	88457	rs35132675
20723452	88457	rs35517166
20723452	88457	rs4714297
20723456	88461	rs12182737
20723456	88461	rs36163804
20723460	88465	rs35790973
20723464	88469	rs35236694
20723469	88474	rs35567559
20723469	88474	rs9267106
20723471	88476	rs9800557
20723484	88489	rs12182463
20723489	88494	rs10948322
20723489	88494	rs34052284
20723489	88494	rs9268999
20723490	88495	rs9258377
20723495	88500	rs9257499
20723498	88503	rs9265816
20723500	88505	rs28771402
20723501	88506	rs28771401
20723502	88507	rs12194731
20723502	88507	rs4451188
20723502	88507	rs9717323
20723502	88507	rs9765920
20723503	88508	rs9265815
20723504	88509	rs28771400
20723506	88511	rs12190813
20723506	88511	rs12215416
20723507	88512	rs12178527
20723510	88515	rs35234761
20723510	88515	rs35887156
20723512	88517	rs28797321
20723515	88520	rs28771399
20723522	88527	rs13207682
20723522	88527	rs36099432
20723531	88536	rs28749543
20723535	88540	rs13196506
20723535	88540	rs35716308
20723536	88541	rs28831180
20723536	88541	rs34938144
20723537	88542	rs36142967
20723541	88546	rs35313792
20723542	88547	rs9260904
20723543	88548	rs34597832
20723545	88550	rs9767740
20723546	88551	rs28771398
20723550	88555	rs34384951
20723554	88559	rs12524128
20723554	88559	rs12665124
20723554	88559	rs34922643
20723555	88560	rs9260903
20723557	88562	rs28771397

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723557	88562	rs6915279
20723559	88564	rs9261907
20723559	88564	rs9766798
20723559	88564	rs9767242
20723560	88565	rs6914835
20723560	88565	rs9260902
20723560	88565	rs9767101
20723562	88567	rs9261908
20723563	88568	rs12207064
20723563	88568	rs12213193
20723563	88568	rs35750154
20723566	88571	rs9260901
20723570	88575	rs9269000
20723579	88584	rs12178368
20723579	88584	rs13197714
20723579	88584	rs28771396
20723579	88584	rs34443697
20723579	88584	rs9267107
20723582	88587	rs35113301
20723582	88587	rs3933248
20723583	88588	rs28819830
20723586	88591	rs10947899
20723586	88591	rs9260900
20723588	88593	rs13204671
20723588	88593	rs34094007
20723588	88593	rs34963756
20723588	88593	rs4304158
20723589	88594	rs4298351
20723590	88595	rs12182307
20723590	88595	rs12201487
20723590	88595	rs34097573
20723595	88600	rs13219021
20723596	88601	rs34456153
20723596	88601	rs9767597
20723597	88602	rs9767102
20723598	88603	rs9269001
20723601	88606	rs12180097
20723603	88608	rs12178465
20723603	88608	rs35128115
20723607	88612	rs4273681
20723609	88614	rs12193754
20723617	88622	rs813814
20723617	88622	rs9689672
20723619	88624	rs36173068
20723623	88628	rs12202172
20723623	88628	rs28862376
20723625	88630	rs12178884
20723625	88630	rs12203117
20723625	88630	rs34250588
20723626	88631	rs12182581
20723632	88637	rs34147797
20723635	88640	rs9688484
20723636	88641	rs9269002
20723636	88641	rs9767733
20723637	88642	rs10948989
20723637	88642	rs34732676
20723637	88642	rs9260899
20723638	88643	rs35686233
20723639	88644	rs11753098

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723639	88644	rs35156647
20723646	88651	rs35575623
20723646	88651	rs34719653
20723648	88653	rs12192046
20723649	88654	rs11759854
20723649	88654	rs28771395
20723649	88654	rs35563402
20723649	88654	rs36016334
20723649	88654	rs4555911
20723653	88658	rs11965757
20723654	88659	rs10948990
20723654	88659	rs28808296
20723654	88659	rs34995142
20723654	88659	rs809919
20723657	88662	rs11571978
20723659	88664	rs12208488
20723662	88667	rs11751374
20723663	88668	rs13217613
20723667	88672	rs12528735
20723668	88673	rs35160656
20723668	88673	rs35322569
20723668	88673	rs9766221
20723670	88675	rs35120225
20723670	88675	rs511868
20723674	88679	rs9269003
20723675	88680	rs34290316
20723675	88680	rs35735496
20723675	88680	rs9689102
20723676	88681	rs10948991
20723676	88681	rs9269004
20723677	88682	rs13220607
20723677	88682	rs34700647
20723677	88682	rs9260898
20723678	88683	rs9260897
20723684	88689	rs28771394
20723686	88691	rs12213200
20723687	88692	rs9717987
20723688	88693	rs28771393
20723688	88693	rs9717716
20723689	88694	rs28771392
20723690	88695	rs11758009
20723690	88695	rs34159662
20723690	88695	rs34683172
20723690	88695	rs9717331
20723691	88696	rs9717853
20723692	88697	rs9765875
20723696	88701	rs12178974
20723696	88701	rs36003577
20723698	88703	rs9767747
20723700	88705	rs28771391
20723704	88709	rs13216352
20723707	88712	rs12200762
20723707	88712	rs12206373
20723707	88712	rs34570202
20723707	88712	rs36197940
20723707	88712	rs9265814
20723714	88719	rs34131282
20723717	88722	rs12175478
20723720	88725	rs28772692

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723722	88727	rs35516674
20723722	88727	rs35704013
20723727	88732	rs34691406
20723728	88733	rs28771390
20723728	88733	rs4374863
20723730	88735	rs34826149
20723734	88739	rs12207894
20723734	88739	rs12662476
20723736	88741	rs9260896
20723739	88744	rs28771389
20723740	88745	rs28771388
20723741	88746	rs9382592
20723745	88750	rs12173375
20723745	88750	rs9268072
20723745	88750	rs9382110
20723746	88751	rs4715211
20723747	88752	rs34128950
20723747	88752	rs35961188
20723747	88752	rs4620119
20723749	88754	rs9767236
20723752	88757	rs34717143
20723755	88760	rs13201202
20723756	88761	rs13201503
20723762	88767	rs13197088
20723762	88767	rs35347849
20723766	88771	rs34663083
20723766	88771	rs35650828
20723767	88772	rs13199241
20723767	88772	rs34205031
20723768	88773	rs28749541
20723768	88773	rs34469031
20723768	88773	rs9279137
20723769	88774	rs9260895
20723770	88775	rs12212483
20723770	88775	rs35446958
20723775	88780	rs28380829
20723777	88782	rs12525384
20723777	88782	rs34576984
20723782	88787	rs283541
20723785	88790	rs28380828
20723788	88793	rs10948698
20723790	88795	rs9265813
20723791	88796	rs9689173
20723792	88797	rs28380827
20723795	88800	rs35399169
20723799	88804	rs9260894
20723800	88805	rs12173388
20723800	88805	rs9269005
20723802	88807	rs28359816
20723803	88808	rs28380826
20723807	88812	rs280297
20723807	88812	rs34507582
20723807	88812	rs9261623
20723810	88815	rs12174621
20723813	88818	rs28380825
20723815	88820	rs35197377
20723816	88821	rs17362870
20723816	88821	rs34562190
20723816	88821	rs35071522

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723816	88821	rs35179751
20723816	88821	rs4458721
20723817	88822	rs12180385
20723817	88822	rs12206581
20723817	88822	rs12333308
20723817	88822	rs9269006
20723821	88826	rs9688475
20723829	88834	rs9269007
20723832	88837	rs9269008
20723832	88837	rs9269009
20723834	88839	rs35899754
20723836	88841	rs13211190
20723837	88842	rs12216274
20723838	88843	rs12191544
20723838	88843	rs4337934
20723841	88846	rs9279295
20723842	88847	rs12178577
20723849	88854	rs12215604
20723853	88858	rs9395360
20723854	88859	rs28749540
20723855	88860	rs28895226
20723855	88860	rs9260893
20723861	88866	rs4365925
20723864	88869	rs9261912
20723865	88870	rs28895227
20723870	88875	rs9261913
20723873	88878	rs12183502
20723873	88878	rs34332895
20723873	88878	rs9472692
20723876	88881	rs35640475
20723884	88889	rs9269010
20723888	88893	rs12192337
20723888	88893	rs35349786
20723891	88896	rs34978372
20723893	88898	rs280296
20723894	88899	rs11755576
20723903	88908	rs28803616
20723903	88908	rs35553517
20723904	88909	rs4358654
20723910	88915	rs9260892
20723914	88919	rs13196941
20723914	88919	rs9717238
20723915	88920	rs12175553
20723915	88920	rs12191408
20723915	88920	rs4460210
20723915	88920	rs9260891
20723918	88923	rs9395361
20723920	88925	rs9766917
20723926	88931	rs35073779
20723931	88936	rs9765884
20723931	88936	rs9767229
20723932	88937	rs35247846
20723932	88937	rs9717328
20723936	88941	rs28805674
20723936	88941	rs9260890
20723938	88943	rs34926348
20723938	88943	rs9717233
20723945	88950	rs35869128
20723946	88951	rs12175941

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20723951	88956	rs9260889
20723952	88957	rs9766686
20723956	88961	rs10046203
20723957	88962	rs9260888
20723958	88963	rs12180540
20723961	88966	rs9766115
20723968	88973	rs6912019
20723969	88974	rs9767458
20723976	88981	rs13202161
20723989	88994	rs13218048
20724000	89005	rs13218040
20724001	89006	rs13206557
20724002	89007	rs13202152
20724013	89018	rs12210049
20724013	89018	rs34552032
20724018	89023	rs28890881
20724018	89023	rs34478537
20724025	89030	rs35191657
20724038	89043	rs34450517
20724043	89048	rs9689655
20724064	89069	rs12180172
20724068	89073	rs28865015
20724071	89076	rs9717839
20724072	89077	rs9717836
20724074	89079	rs9885593
20724082	89087	rs28887572
20724083	89088	rs13216113
20724083	89088	rs35254115
20724084	89089	rs10949190
20724085	89090	rs6923503
20724087	89092	rs12214411
20724091	89096	rs28747986
20724096	89101	rs1087363
20724096	89101	rs1091092
20724104	89109	rs12180759
20724107	89112	rs11758052
20724112	89117	rs9261321
20724113	89118	rs28861738
20724113	89118	rs36109104
20724123	89128	rs13208115
20724129	89134	rs9472693
20724130	89135	rs12208570
20724130	89135	rs28832660
20724131	89136	rs13200482
20724131	89136	rs9260886
20724131	89136	rs9472694
20724159	89164	rs9260885
20724172	89177	rs280295
20724172	89177	rs28749538
20724174	89179	rs13201041
20724184	89189	rs1087362
20724187	89192	rs12183850
20724190	89195	rs12202552
20724208	89213	rs9260884
20724210	89215	rs9474341
20724211	89216	rs9260883
20724222	89227	rs34669820
20724225	89230	rs12189886
20724234	89239	rs12182114

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20724266	89271	rs9688643
20724272	89277	rs12195237
20724281	89286	rs35293595
20724281	89286	rs9381428
20724306	89311	rs34665644
20724309	89314	rs12189599
20724311	89316	rs12208503
20724312	89317	rs9800791
20724330	89335	rs12173681
20724337	89342	rs12182094
20724343	89348	rs12182119
20724352	89357	rs12182102
20724392	89397	rs12174506
20724393	89398	rs9767809
20724394	89399	rs12173703
20724401	89406	rs12202889
20724435	89440	rs28840538
20724466	89471	rs9473983
20724467	89472	rs34220946
20724487	89492	rs9261322
20724491	89496	rs9261323
20724517	89522	rs526092
20724564	89569	rs9473982
20724566	89571	rs34307764
20724626	89631	rs34490559
20724665	89670	rs4449621
20724685	89690	rs4714818
20724698	89703	rs4714817
20724722	89727	rs682384
20724738	89743	rs682051
20724753	89758	rs12530056
20724756	89761	rs35086683
20724888	89893	rs12528468
20725092	90097	rs10650195
20725092	90097	rs35956126
20725109	90114	rs6937578
20725159	90164	rs12530107
20725173	90178	rs720448
20725176	90181	rs9368212
20725250	90255	rs35481531
20725253	90258	rs720449
20725262	90267	rs10650196
20725495	90500	rs2064
20725499	90504	rs2065
20725638	90643	rs9368213
20725732	90737	rs41455744
20726077	91082	rs34960654
20726154	91159	rs6900954
20726168	91173	rs6456359
20726176	91181	rs7739405
20726601	91606	rs7760508
20726684	91689	rs10456007
20726987	91992	rs9460534
20727168	92173	rs11966749
20727353	92358	rs9358354
20727809	92814	rs9368214
20727982	92987	rs9350268
20728095	93100	rs2069013
20728160	93165	rs2069014

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20728290	93295	rs2069015
20728292	93297	rs11967475
20729096	94101	rs10214549
20729217	94222	rs2223621
20729281	94286	rs9465835
20729984	94989	rs35404829
20729995	95000	rs10687080
20730233	95238	rs6915936
20730331	95336	rs9295472
20730732	95737	rs1569660
20730929	95934	rs7455009
20730945	95950	rs1569659
20730946	95951	rs5874775
20730948	95953	rs10601252
20730983	95988	rs1569658
20731030	96035	rs34142400
20731063	96068	rs16883996
20731181	96186	rs35073110
20731184	96189	rs5028948
20731263	96268	rs34201758
20731371	96376	rs6456360
20731373	96378	rs6456361
20731380	96385	rs6456362
20731584	96589	rs6922571
20731925	96930	rs35145358
20731950	96955	rs9465836
20732013	97018	rs7763304
20732158	97163	rs9465837
20732218	97223	rs7743314
20732337	97342	rs714831
20732361	97366	rs714830
20732484	97489	rs7743789
20732584	97589	rs5874776
20732589	97594	rs5874777
20732965	97970	rs16884003
20733079	98084	rs9356741
20733080	98085	rs9366358
20733246	98251	rs9356742
20733430	98435	rs11756987
20733470	98475	rs9465838
20733613	98618	rs2206579
20733920	98925	rs35111339
20734361	99366	rs6917583
20734388	99393	rs6917599
20734630	99635	rs13437429
20735418	100423	rs34307011
20735420	100425	rs4515379
20735756	100761	rs2223620
20735870	100875	rs9465839
20735993	100998	rs12664972
20736790	101795	rs28402356
20736798	101803	rs6934727
20736873	101878	rs35493429
20736881	101886	rs11369825
20737261	102266	rs4523079
20737470	102475	rs7771213
20737568	102573	rs9465840
20737687	102692	rs9465841
20737767	102772	rs9465842

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20737837	102842	rs9460535
20737992	102997	rs34835908
20738060	103065	rs9465843
20738139	103144	rs13220465
20738159	103164	rs13220352
20738321	103326	rs4710937
20738375	103380	rs9460536
20738376	103381	rs13190734
20738451	103456	rs9465844
20738712	103717	rs35976895
20738713	103718	rs11327958
20738932	103937	rs13194407
20738990	103995	rs10484633
20739524	104529	rs2328528
20739789	104794	rs35958155
20739809	104814	rs4421185
20739932	104937	rs2328529
20740089	105094	rs9460537
20740745	105750	rs17224527
20740886	105891	rs34166991
20741024	106029	rs17823073
20741276	106281	rs12183074
20741316	106321	rs9465845
20741844	106849	rs35148963
20741886	106891	rs7768642
20742320	107325	rs9465846
20742407	107412	rs9465847
20742551	107556	rs17823127
20742594	107599	rs16884021
20742630	107635	rs4533976
20742865	107870	rs7755830
20743005	108010	rs7756031
20743139	108144	rs35650451
20743192	108197	rs10561117
20743241	108246	rs6940200
20743799	108804	rs9465848
20743808	108813	rs34351919
20745083	110088	rs4712519
20745285	110290	rs9368215
20745566	110571	rs12206285
20745853	110858	rs34049994
20745988	110993	rs7751957
20746702	111707	rs9465849
20746857	111862	rs7341291
20746957	111962	rs6921014
20747388	112393	rs9465850
20747583	112588	rs7758612
20747681	112686	rs35602526
20748295	113300	rs9465851
20748399	113404	rs34257578
20748403	113408	rs11339738
20748516	113521	rs9460538
20748850	113855	rs4712520
20748883	113888	rs4710938
20749084	114089	rs35889049
20749315	114320	rs9348440
20749879	114884	rs9465852
20750054	115059	rs12196009
20750306	115311	rs11968248

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20750353	115358	rs34797179
20750764	115769	rs6925328
20750913	115918	rs36073053
20751137	116142	rs35462488
20751140	116145	rs36224625
20751150	116155	rs3060659
20751153	116158	rs5874778
20751155	116160	rs11267861
20751201	116206	rs4235999
20751230	116235	rs16884038
20751706	116711	rs2328530
20751731	116736	rs2328531
20751750	116755	rs28360636
20752162	117167	rs6932676
20752183	117188	rs9460539
20752303	117308	rs6932876
20752346	117351	rs34929755
20752359	117364	rs28733367
20752360	117365	rs11348111
20752473	117478	rs6933219
20752702	117707	rs6933165
20752872	117877	rs35255583
20752901	117906	rs34332316
20752923	117928	rs4710939
20753486	118491	rs11970417
20753659	118664	rs11963217
20753670	118675	rs11965473
20753833	118838	rs2876575
20754049	119054	rs7739974
20754976	119981	rs7745175
20755173	120178	rs7765784
20755178	120183	rs6907731
20755250	120255	rs35057896
20755313	120318	rs7746072
20755639	120644	rs10484632
20755770	120775	rs35444529
20755849	120854	rs17823571
20755941	120946	rs11965062
20755962	120967	rs6936199
20755965	120970	rs6913126
20756178	121183	rs6913509
20756613	121618	rs34638218
20756673	121678	rs35746011
20756741	121746	rs9460540
20757090	122095	rs36045545
20757129	122134	rs35392790
20757233	122238	rs6456364
20757260	122265	rs2179553
20757513	122518	rs9350269
20757531	122536	rs9465854
20757787	122792	rs2179552
20757936	122941	rs6925233
20758033	123038	rs2328532
20758248	123253	rs7743970
20758317	123322	rs13209457
20758318	123323	rs34641285
20758344	123349	rs13209538
20758387	123392	rs2876576
20758479	123484	rs13209572

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20758653	123658	rs28783153
20758712	123717	rs9969037
20758800	123805	rs7766844
20758969	123974	rs7767133
20759291	124296	rs7749464
20760100	125105	rs2050225
20760696	125701	rs9295474
20760744	125749	rs9295475
20761529	126534	rs2328545
20761548	126553	rs28846771
20761779	126784	rs2876582
20761899	126904	rs10223446
20762094	127099	rs13219723
20762095	127100	rs13203489
20762154	127159	rs13203583
20762172	127177	rs13203887
20762279	127284	rs6456366
20762876	127881	rs9358355
20763089	128094	rs9368216
20763375	128380	rs9465855
20763384	128389	rs9465856
20763463	128468	rs16884070
20763482	128487	rs16884072
20763647	128652	rs13208604
20764169	129174	rs9465857
20764307	129312	rs9368217
20764559	129564	rs9460541
20764746	129751	rs9460542
20764765	129770	rs11969955
20764779	129784	rs4712522
20764924	129929	rs16884074
20765172	130177	rs34489684
20765324	130329	rs2328546
20765543	130548	rs4712523
20765844	130849	rs4712524
20765898	130903	rs35397753
20765991	130996	rs4710940
20766197	131202	rs13190727
20766215	131220	rs35136485
20766311	131316	rs35260725
20766335	131340	rs35939620
20766566	131571	rs17823996
20766713	131718	rs16884082
20767438	132443	rs6906327
20767566	132571	rs6456367
20767785	132790	rs6456368
20768202	133207	rs7749083
20768344	133349	rs6456369
20768669	133674	rs10946396
20768672	133677	rs10946397
20768710	133715	rs11759505
20769000	134005	rs13203361
20769013	134018	rs10946398
20769122	134127	rs7774594
20769229	134234	rs7754840
20769249	134254	rs9460543
20769508	134513	rs9460544
20769529	134534	rs9460545
20769711	134716	rs2206740

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20769806	134811	rs5874779
20769807	134812	rs33970890
20769815	134820	rs5874780
20769816	134821	rs35014292
20769816	134821	rs35363501
20770092	135097	rs6456370
20770102	135107	rs979614
20770196	135201	rs35456723
20770571	135576	rs9368218
20770945	135950	rs4712525
20771014	136019	rs4712526
20771314	136319	rs4712527
20771442	136447	rs35191644
20771442	136447	rs34470647
20771611	136616	rs9460546
20771938	136943	rs9465859
20772079	137084	rs9465860
20772291	137296	rs736425
20772508	137513	rs3060776
20772509	137514	rs34941928
20772512	137517	rs5874781
20772761	137766	rs35778487
20773060	138065	rs742642
20773305	138310	rs35248697
20773436	138441	rs11967127
20773528	138533	rs7748382
20773547	138552	rs9688549
20773548	138553	rs9689351
20773570	138575	rs28665000
20773886	138891	rs7752236
20773925	138930	rs7772603
20774001	139006	rs7752780
20774034	139039	rs7752906
20774160	139165	rs34184260
20774223	139228	rs2206739
20774225	139230	rs2206738
20774250	139255	rs2206737
20774436	139441	rs11970425
20774484	139489	rs36034806
20774899	139904	rs35042364
20775218	140223	rs35540121
20775361	140366	rs9358356
20775667	140672	rs9356743
20775778	140783	rs9350270
20776366	141371	rs34929853
20778035	143040	rs34971765
20778443	143448	rs11970596
20779261	144266	rs12527373
20779367	144372	rs35916847
20780262	145267	rs11968224
20780271	145276	rs11968225
20780276	145281	rs9465861
20780296	145301	rs11968264
20780406	145411	rs12189849
20780413	145418	rs12209627
20780432	145437	rs12189895
20780855	145860	rs11968848
20781135	146140	rs11963945
20781601	146606	rs35677128

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20781859	146864	rs7451008
20782670	147675	rs9368219
20782790	147795	rs1012636
20782945	147950	rs13217846
20783274	148279	rs1012635
20783700	148705	rs35665197
20783771	148776	rs35261542
20783828	148833	rs28823314
20783899	148904	rs28890810
20784051	149056	rs28871991
20784393	149398	rs34499031
20784650	149655	rs13208763
20784747	149752	rs28719685
20784789	149794	rs28856096
20785042	150047	rs11961863
20785211	150216	rs17824302
20785289	150294	rs12660618
20786302	151307	rs11371206
20786303	151308	rs34152621
20786409	151414	rs4712528
20786463	151468	rs13217082
20786470	151475	rs13217085
20786481	151486	rs13217090
20786483	151488	rs13217091
20786523	151528	rs13200946
20786772	151777	rs11968032
20786954	151959	rs9465863
20787289	152294	rs1569699
20787386	152391	rs34168173
20787688	152693	rs7756992
20788045	153050	rs35312717
20788657	153662	rs9348441
20788843	153848	rs9368220
20788941	153946	rs6931254
20789327	154332	rs6911742
20790601	155606	rs35612982
20791039	156044	rs35816514
20791123	156128	rs34612860
20791143	156148	rs9350271
20791162	156167	rs35657899
20791179	156184	rs11364854
20791249	156254	rs9460547
20791646	156651	rs16884103
20791961	156966	rs2206736
20793465	158470	rs9356744
20794295	159300	rs34987372
20794427	159432	rs36005020
20794552	159557	rs7766070
20794975	159980	rs9368222
20795290	160295	rs35566695
20795781	160786	rs10440832
20796100	161105	rs10440833
20796237	161242	rs35747076
20796578	161583	rs6900217
20797104	162109	rs34433496
20797924	162929	rs7748720
20797928	162933	rs34175709
20798290	163295	rs6911357
20800493	165498	rs12200791

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20800955	165960	rs5874782
20800957	165962	rs36119385
20801341	166346	rs13219682
20802207	167212	rs4710941
20802270	167275	rs4620109
20802272	167277	rs28459626
20802273	167278	rs4712529
20802294	167299	rs10577753
20802504	167509	rs2223683
20802573	167578	rs2206735
20802863	167868	rs2206734
20802910	167915	rs34530846
20803458	168463	rs16884131
20804127	169132	rs10806921
20805104	170109	rs16884133
20805571	170576	rs17824500
20805652	170657	rs10946401
20806114	171119	rs16884135
20806582	171587	rs35711395
20807220	172225	rs11969783
20807364	172369	rs16884137
20808600	173605	rs11970626
20809092	174097	rs12190713
20809106	174111	rs11398905
20809415	174420	rs11961445
20809470	174475	rs35982077
20809486	174491	rs11305935
20810952	175957	rs9356745
20811700	176705	rs35043644
20811842	176847	rs16884140
20811931	176936	rs6931514
20812147	177152	rs35443650
20813281	178286	rs34671712
20813569	178574	rs11753081
20814081	179086	rs7739516
20814209	179214	rs6901559
20815176	180181	rs13196379
20815177	180182	rs13212234
20816204	181209	rs10536170
20817155	182160	rs9465869
20817688	182693	rs36070002
20818288	183293	rs17226450
20818905	183910	rs1073247
20819131	184136	rs9465870
20819386	184391	rs17226492
20819433	184438	rs13213613
20819567	184572	rs16884146
20819958	184963	rs2206733
20820440	185445	rs3749925
20821121	186126	rs9460548
20821619	186624	rs9460549
20821685	186690	rs1040558
20821893	186898	rs4712530
20822083	187088	rs35629277
20822362	187367	rs7451928
20822445	187450	rs6456371
20822589	187594	rs13220116
20822823	187828	rs2206732
20823169	188174	rs2179633

Position in Build 35/36	Position in SEQ ID NO:1	Marker ID
20823483	188488	rs11963770
20823805	188810	rs10946402
20823840	188845	rs4712531
20824098	189103	rs35738288
20824232	189237	rs9295478
20824549	189554	rs2328547
20824763	189768	rs3060781
20824764	189769	rs34686252
20824856	189861	rs13215905
20824884	189889	rs9368223
20824937	189942	rs2328548
20825025	190030	rs11427712
20825074	190079	rs6935599
20825100	190105	rs13216165
20825234	190239	rs9465871
20825383	190388	rs10946403
20826219	191224	rs2328549
20826449	191454	rs17226774
20827124	192129	rs9358357
20827211	192216	rs9368224
20827321	192326	rs11756271
20827372	192377	rs9358358
20827540	192545	rs9460550
20827858	192863	rs12110493
20827866	192871	rs12193125
20828258	193263	rs9356746
20828797	193802	rs9350272
20829322	194327	rs13219444
20829342	194347	rs12111216
20829562	194567	rs9350273
20829700	194705	rs9368225
20830399	195404	rs17825025
20831036	196041	rs9368226
20832213	197218	rs6903175
20832229	197234	rs6903744
20832537	197542	rs12111351
20832754	197759	rs4712536
20832986	197991	rs9356747
20833076	198081	rs9356748
20833219	198224	rs7767391
20833402	198407	rs7747752
20833511	198516	rs9350274
20833853	198858	rs34170041
20833919	198924	rs6915155
20834014	199019	rs6914868
20834472	199477	rs4538697
20835549	200554	rs4712537
20836048	201053	rs34097377
20836492	201497	rs6928012
20836710	201715	rs6908425

Table 11. SNPs within LD block C10 (SEQ ID NO:2) between positions 94,192,885 and 94,490,091 bp on Chromosome 10 in NCBI Build 35 and NCBI Build 36

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94192885	1	rs2798253
94193597	713	rs36087110
94193803	919	rs35771118
94193950	1066	rs12359552
94193961	1077	rs11186999
94194166	1282	rs7916460
94194775	1891	rs10882065
94195841	2957	rs11187000
94196162	3278	rs4933231
94196306	3422	rs11187001
94196353	3469	rs4933725
94196465	3581	rs11187002
94196477	3593	rs4933726
94196509	3625	rs4933232
94196716	3832	rs11187003
94196844	3960	rs34115369
94197028	4144	rs10786047
94197152	4268	rs11814521
94197347	4463	rs11814555
94198457	5573	rs7476275
94198727	5843	rs3118967
94199011	6127	rs11187004
94199856	6972	rs7910977
94199919	7035	rs6583813
94199932	7048	rs511985
94200269	7385	rs7911558
94200789	7905	rs12415807
94201174	8290	rs35125831
94201284	8400	rs2251101
94201876	8992	rs7896688
94202516	9632	rs5786996
94202722	9838	rs913648
94203071	10187	rs5786997
94203072	10188	rs35771235
94203255	10371	rs34872659
94203768	10884	rs34266748
94204339	11455	rs4646958
94204560	11676	rs11187007
94205437	12553	rs11459510
94205449	12565	rs35832015
94206153	13269	rs12356364
94206407	13523	rs11593933
94206490	13606	rs3781241
94206524	13640	rs3781240
94206594	13710	rs10562725
94206599	13715	rs10617641
94206609	13725	rs28641489
94207018	14134	rs11187009
94207224	14340	rs36119168
94207391	14507	rs11594562
94207777	14893	rs3781239
94208177	15293	rs3824738
94208228	15344	rs12782629
94208261	15377	rs12261501
94208278	15394	rs12781670
94208383	15499	rs568657

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94208423	15539	rs509954
94209484	16600	rs489517
94209509	16625	rs9420586
94209578	16694	rs11187010
94209597	16713	rs2247348
94209748	16864	rs307638
94210585	17701	rs35118791
94210625	17741	rs520711
94211102	18218	rs7098739
94211382	18498	rs7081224
94211591	18707	rs7093437
94212604	19720	rs551266
94213696	20812	rs1042444
94213766	20882	rs7087334
94214145	21261	rs1887922
94214615	21731	rs7898862
94214726	21842	rs10882066
94214869	21985	rs11187011
94214932	22048	rs7916011
94214997	22113	rs7899603
94215212	22328	rs34934289
94215235	22351	rs12242504
94215277	22393	rs2275218
94215373	22489	rs538469
94215528	22644	rs35640611
94215823	22939	rs11187012
94216140	23256	rs11187013
94216829	23945	rs7893352
94217818	24934	rs11187014
94218798	25914	rs544537
94218805	25921	rs12243622
94219607	26723	rs11187015
94219726	26842	rs7920976
94219892	27008	rs4646957
94220409	27525	rs11187016
94221786	28902	rs2250090
94222227	29343	rs2149632
94222398	29514	rs35959170
94222860	29976	rs35551274
94222881	29997	rs7087153
94222964	30080	rs12762802
94223038	30154	rs12763971
94223085	30201	rs11187017
94223100	30216	rs2249960
94223275	30391	rs12262931
94223719	30835	rs11187018
94223794	30910	rs11323400
94223971	31087	rs7092468
94224735	31851	rs12245118
94224789	31905	rs35223317
94226905	34021	rs35637537
94227236	34352	rs35291821
94227390	34506	rs7073248
94227405	34521	rs7091270
94227647	34763	rs12251346
94227782	34898	rs6583815

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94227902	35018	rs12411941
94227937	35053	rs17875326
94228149	35265	rs7077626
94228919	36035	rs35864975
94229152	36268	rs5030982
94229349	36465	rs3831274
94229366	36482	rs35611772
94229773	36889	rs7910605
94231074	38190	rs12356508
94231328	38444	rs34093069
94231497	38613	rs35831196
94232484	39600	rs35250835
94232485	39601	rs5786998
94232486	39602	rs35368064
94233186	40302	rs12243214
94233203	40319	rs7917817
94233597	40713	rs2421940
94234183	41299	rs35120790
94234248	41364	rs10882067
94234880	41996	rs35436518
94234881	41997	rs34615998
94234883	41999	rs11595475
94235591	42707	rs35243007
94236972	44088	rs35426658
94237227	44343	rs6583817
94237240	44356	rs35863982
94237312	44428	rs35532620
94238290	45406	rs11187019
94238346	45462	rs12219139
94238396	45512	rs12219148
94238509	45625	rs34930778
94238512	45628	rs36015364
94238730	45846	rs11187020
94239054	46170	rs35650880
94239749	46865	rs7093418
94239850	46966	rs11596251
94239962	47078	rs3737225
94241364	48480	rs11444132
94241365	48481	rs34841034
94242628	49744	rs11187021
94243163	50279	rs3837333
94243164	50280	rs34838821
94243184	50300	rs3781238
94243185	50301	rs35973022
94243185	50301	rs3781237
94243606	50722	rs10882068
94244183	51299	rs1855917
94244263	51379	rs1855916
94245019	52135	rs10882069
94245021	52137	rs9420151
94245023	52139	rs11187022
94245061	52177	rs10882070
94245384	52500	rs7075073
94246000	53116	rs11187024
94246773	53889	rs11598525
94246972	54088	rs34822156
94247198	54314	rs7084090
94247956	55072	rs11187025
94247994	55110	rs6583818

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94249045	56161	rs34666358
94249117	56233	rs11187026
94249160	56276	rs11187027
94249226	56342	rs34459034
94249288	56404	rs11187028
94249316	56432	rs36049328
94249679	56795	rs7097800
94249948	57064	rs10786048
94250085	57201	rs10882071
94250350	57466	rs12249976
94250507	57623	rs7068618
94250611	57727	rs11187029
94250692	57808	rs10882072
94250983	58099	rs11187030
94251771	58887	rs11187031
94251786	58902	rs11187032
94252339	59455	rs11187033
94252515	59631	rs11187034
94252799	59915	rs11442945
94253137	60253	rs11187035
94253203	60319	rs1970244
94253341	60457	rs11187037
94253515	60631	rs1970245
94253764	60880	rs5786999
94253765	60881	rs34057954
94253766	60882	rs10716816
94254606	61722	rs34708742
94254765	61881	rs35101389
94254975	62091	rs11187038
94255082	62198	rs34174850
94256325	63441	rs34053974
94256855	63971	rs11296200
94257747	64863	rs11460471
94258212	65328	rs11286004
94258296	65412	rs5787000
94258297	65413	rs33917554
94258314	65430	rs1832196
94258319	65435	rs34194084
94258381	65497	rs1832195
94258980	66096	rs35636429
94259168	66284	rs4256898
94259346	66462	rs34663898
94259587	66703	rs6583819
94259670	66786	rs11324773
94259792	66908	rs11187039
94260389	67505	rs34662862
94260838	67954	rs35891632
94260859	67975	rs10882073
94260983	68099	rs11498516
94261156	68272	rs17445028
94261438	68554	rs35831688
94262303	69419	rs11373926
94262304	69420	rs35405697
94262311	69427	rs35377675
94262679	69795	rs34457657
94262685	69801	rs34774587
94262844	69960	rs11187040
94263091	70207	rs7086558
94263344	70460	rs7910569

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94263586	70702	rs34673600
94264572	71688	rs35270297
94264650	71766	rs4646956
94264789	71905	rs17875327
94265538	72654	rs9633693
94266128	73244	rs12780132
94266506	73622	rs7895832
94266635	73751	rs6583820
94267645	74761	rs7093773
94267750	74866	rs12257226
94267766	74882	rs7075851
94267846	74962	rs10509645
94268591	75707	rs35693308
94271124	78240	rs11812558
94271625	78741	rs11187042
94271665	78781	rs10882074
94271861	78977	rs11187043
94272258	79374	rs11187044
94272698	79814	rs7915971
94273091	80207	rs4933233
94273288	80404	rs35361515
94273349	80465	rs11187045
94273885	81001	rs35296767
94273981	81097	rs11187046
94274088	81204	rs11813097
94274094	81210	rs10882075
94274100	81216	rs10882076
94274121	81237	rs11187047
94274127	81243	rs11187048
94274129	81245	rs11187049
94274135	81251	rs11187050
94274143	81259	rs11187051
94274150	81266	rs11187052
94274183	81299	rs11818981
94274184	81300	rs11818982
94274213	81329	rs11187053
94274245	81361	rs12355280
94274246	81362	rs12359894
94274253	81369	rs11187054
94274787	81903	rs12358677
94275109	82225	rs35688800
94275207	82323	rs12261046
94275338	82454	rs12261114
94275379	82495	rs12261174
94275382	82498	rs7894448
94275487	82603	rs12262694
94275508	82624	rs4641376
94275509	82625	rs35586301
94276174	83290	rs11187055
94276314	83430	rs7089987
94276400	83516	rs7073833
94276465	83581	rs10882077
94276595	83711	rs11459412
94276596	83712	rs34975586
94277360	84476	rs2421942
94280464	87580	rs7078413
94280662	87778	rs7079099
94280746	87862	rs12258487
94281644	88760	rs34747737

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94281681	88797	rs7901064
94282086	89202	rs17107709
94282197	89313	rs868057
94283137	90253	rs34880105
94283469	90585	rs35455474
94283592	90708	rs11819413
94283667	90783	rs11187056
94283823	90939	rs1855915
94283919	91035	rs12268712
94284271	91387	rs4646955
94285010	92126	rs7898114
94285220	92336	rs11450948
94285221	92337	rs35571064
94285296	92412	rs7898493
94285778	92894	rs7077418
94286057	93173	rs11187057
94286438	93554	rs34460166
94286967	94083	rs2275221
94288311	95427	rs1832197
94288480	95596	rs17107721
94288514	95630	rs5787001
94288515	95631	rs34593706
94288516	95632	rs11187059
94288531	95647	rs12249288
94290376	97492	rs12416180
94292030	99146	rs10882078
94292741	99857	rs11815736
94293623	100739	rs5004594
94293624	100740	rs1970243
94293625	100741	rs33928713
94293625	100741	rs5787002
94293956	101072	rs12218329
94294112	101228	rs11187060
94294428	101544	rs7915349
94295169	102285	rs17445328
94295389	102505	rs11187061
94295397	102513	rs17107734
94296406	103522	rs11187062
94296563	103679	rs10218994
94296625	103741	rs17445419
94296937	104053	rs12219325
94297315	104431	rs11286362
94297863	104979	rs10786049
94297879	104995	rs7900822
94298098	105214	rs11187063
94298233	105349	rs11187064
94298446	105562	rs10219017
94299005	106121	rs34494546
94299843	106959	rs7909636
94300255	107371	rs34330550
94300414	107530	rs10882079
94300889	108005	rs12220493
94301795	108911	rs2421943
94301904	109020	rs11187065
94302165	109281	rs4406744
94302446	109562	rs35156639
94303116	110232	rs1987122
94303124	110240	rs9420144
94303675	110791	rs35707435

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94304293	111409	rs11418454
94304299	111415	rs11424864
94304548	111664	rs6583821
94304589	111705	rs10882080
94304784	111900	rs7908111
94305004	112120	rs10882081
94306623	113739	rs7902106
94306803	113919	rs12415874
94306808	113924	rs7917163
94307486	114602	rs4933728
94307610	114726	rs12412249
94307630	114746	rs3051565
94307851	114967	rs11187066
94307892	115008	rs10882082
94308049	115165	rs7098744
94308378	115494	rs12777622
94308408	115524	rs12779093
94308409	115525	rs12777974
94309312	116428	rs11187067
94309594	116710	rs12765408
94309595	116711	rs34052181
94309972	117088	rs1999763
94310119	117235	rs1999764
94310400	117516	rs11187068
94310514	117630	rs7078418
94310644	117760	rs35429533
94310846	117962	rs11187069
94311213	118329	rs34630015
94311876	118992	rs12264361
94311953	119069	rs10882083
94312407	119523	rs12264682
94312615	119731	rs11187070
94312726	119842	rs12266443
94312981	120097	rs12776190
94313002	120118	rs4933729
94313190	120306	rs12774925
94313202	120318	rs12774931
94314015	121131	rs11187071
94314384	121500	rs35009022
94314389	121505	rs11187072
94314566	121682	rs12241107
94314708	121824	rs11187073
94314816	121932	rs12763871
94314968	122084	rs35418143
94315124	122240	rs12411517
94315147	122263	rs11308616
94315157	122273	rs33935672
94315157	122273	rs5787003
94315491	122607	rs7076966
94315748	122864	rs5787004
94315751	122867	rs35925526
94315930	123046	rs5787005
94315944	123060	rs34378303
94316148	123264	rs2901598
94316150	123266	rs2421944
94316175	123291	rs34777726
94316176	123292	rs3051566
94316766	123882	rs12253172
94316799	123915	rs12253177

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94316926	124042	rs11187074
94317075	124191	rs7082686
94317136	124252	rs7100623
94317536	124652	rs12255048
94317963	125079	rs12355977
94318001	125117	rs35616984
94318580	125696	rs35826224
94318582	125698	rs10584127
94318582	125698	rs7915220
94318992	126108	rs11437287
94318993	126109	rs35875721
94319093	126209	rs10882084
94320200	127316	rs7097014
94321033	128149	rs12415246
94321119	128235	rs4304670
94321321	128437	rs2421945
94321612	128728	rs12252447
94321742	128858	rs10736067
94322696	129812	rs7909487
94323150	130266	rs34093946
94323222	130338	rs12783634
94323807	130923	rs4646954
94323935	131051	rs4646953
94323955	131071	rs35380063
94324493	131609	rs17875328
94324556	131672	rs34867369
94324758	131874	rs3758505
94325575	132691	rs11379220
94325779	132895	rs7099761
94326009	133125	rs11187075
94326342	133458	rs35628053
94326394	133510	rs3758504
94326684	133800	rs3758503
94326943	134059	rs11187076
94327161	134277	rs35376801
94327403	134519	rs12762388
94327431	134547	rs12762406
94327438	134554	rs12764060
94327683	134799	rs4933730
94327871	134987	rs7900584
94328020	135136	rs12414433
94328211	135327	rs7900991
94328632	135748	rs7921325
94328678	135794	rs7905037
94330087	137203	rs11187077
94330685	137801	rs11187078
94330689	137805	rs11273566
94331181	138297	rs6583822
94331572	138688	rs11187079
94331642	138758	rs7069538
94331770	138886	rs7087423
94332643	139759	rs2901597
94332963	140079	rs7092522
94332992	140108	rs12766927
94333545	140661	rs11187080
94334378	141494	rs34210106
94334395	141511	rs6583823
94334850	141966	rs7084215
94334897	142013	rs6583824

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94335207	142323	rs6583825
94335889	143005	rs2421941
94336041	143157	rs12262994
94336117	143233	rs12263054
94336859	143975	rs12573146
94337053	144169	rs11187081
94337295	144411	rs34143873
94337314	144430	rs11455878
94337315	144431	rs35480775
94337549	144665	rs7921210
94337810	144926	rs6583826
94338024	145140	rs12776949
94338180	145296	rs7922041
94338205	145321	rs34073794
94338626	145742	rs10701812
94338815	145931	rs7911019
94339556	146672	rs7898478
94340196	147312	rs4611114
94340487	147603	rs1889894
94340661	147777	rs12355158
94341882	148998	rs17875329
94341915	149031	rs11595187
94341951	149067	rs17875331
94342066	149182	rs17875332
94342135	149251	rs11595260
94342136	149252	rs11599701
94342406	149522	rs7092778
94342485	149601	rs11187083
94342495	149611	rs17875333
94342598	149714	rs11187084
94342803	149919	rs2297743
94343099	150215	rs36015451
94343258	150374	rs12256435
94343418	150534	rs11818332
94343843	150959	rs3781236
94344062	151178	rs3824736
94344184	151300	rs3824735
94344608	151724	rs11429679
94344609	151725	rs34491012
94344692	151808	rs11187085
94344951	152067	rs11187086
94345504	152620	rs11817798
94345575	152691	rs12240557
94345783	152899	rs35583124
94345930	153046	rs12262350
94346261	153377	rs11187087
94346544	153660	rs7099635
94346892	154008	rs4604791
94346932	154048	rs11556038
94347159	154275	rs7082683
94348003	155119	rs6583827
94349194	156310	rs11187089
94349700	156816	rs12218324
94349861	156977	rs11498685
94350652	157768	rs11187090
94350841	157957	rs12411873
94351226	158342	rs7068118
94351364	158480	rs35624581
94351461	158577	rs35982149

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94352267	159383	rs35452156
94352383	159499	rs35807258
94352546	159662	rs10564653
94352561	159677	rs7095250
94352562	159678	rs7095369
94352579	159695	rs10564753
94352593	159709	rs3980475
94352908	160024	rs7096101
94353042	160158	rs9733604
94353107	160223	rs12266122
94353183	160299	rs7096520
94353519	160635	rs35612167
94353973	161089	rs4933731
94354724	161840	rs11187091
94354862	161978	rs10882085
94354869	161985	rs12763703
94355005	162121	rs10882086
94355421	162537	rs11812310
94355638	162754	rs11187092
94355673	162789	rs12242681
94355721	162837	rs12257279
94356330	163446	rs11393423
94356331	163447	rs35558317
94356578	163694	rs12244660
94356605	163721	rs12244573
94356815	163931	rs12244809
94356878	163994	rs12259474
94356984	164100	rs17875334
94357013	164129	rs17107758
94357210	164326	rs10786050
94357829	164945	rs12246900
94357847	164963	rs10882087
94357897	165013	rs12261518
94357989	165105	rs11187093
94358032	165148	rs12247024
94358158	165274	rs11187094
94358195	165311	rs12261697
94358568	165684	rs10882088
94358636	165752	rs12248860
94359005	166121	rs3835295
94359040	166156	rs10882089
94359040	166156	rs34446454
94359042	166158	rs11187095
94359042	166158	rs3835294
94359044	166160	rs12767141
94359496	166612	rs12250905
94359568	166684	rs11187096
94359915	167031	rs12356724
94360614	167730	rs11599330
94361073	168189	rs35352564
94362686	169802	rs2275220
94362922	170038	rs2275219
94363760	170876	rs10882090
94364357	171473	rs10882091
94364583	171699	rs11187097
94364871	171987	rs11187098
94364977	172093	rs11187099
94365856	172972	rs12252642
94366308	173424	rs12252836

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94366409	173525	rs17875338
94366437	173553	rs17875337
94366604	173720	rs33921491
94366606	173722	rs10550249
94366638	173754	rs34075743
94366848	173964	rs7069647
94367517	174633	rs11187100
94367754	174870	rs11187101
94367943	175059	rs12415792
94368029	175145	rs3980476
94368183	175299	rs12767059
94368830	175946	rs6583828
94368857	175973	rs11517020
94369044	176160	rs34515231
94369203	176319	rs10882092
94369352	176468	rs6583829
94369694	176810	rs12260688
94369814	176930	rs12781567
94370112	177228	rs7084441
94371113	178229	rs17875339
94371489	178605	rs11187102
94371558	178674	rs11187103
94371597	178713	rs34942989
94371629	178745	rs11817621
94371641	178757	rs11815573
94371998	179114	rs11187104
94372020	179136	rs7894183
94372150	179266	rs12254289
94372405	179521	rs36031409
94372432	179548	rs12262063
94372442	179558	rs7914248
94372445	179561	rs12254474
94372736	179852	rs7898027
94372930	180046	rs7914814
94372946	180062	rs7898506
94373054	180170	rs17367408
94373182	180298	rs10082524
94373409	180525	rs7091887
94373424	180540	rs7073868
94373661	180777	rs7095585
94373838	180954	rs12772554
94373970	181086	rs12772956
94374055	181171	rs10882093
94374407	181523	rs11187105
94374449	181565	rs12258463
94374494	181610	rs35518831
94374496	181612	rs34197740
94374497	181613	rs35008887
94374498	181614	rs35083945
94375670	182786	rs11187106
94376102	183218	rs7071905
94376134	183250	rs7087860
94376451	183567	rs35368950
94376836	183952	rs7915915
94376918	184034	rs12264372
94377314	184430	rs1573051
94377656	184772	rs10882094
94378087	185203	rs12244924
94378491	185607	rs17875340

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94379385	186501	rs11417254
94379401	186517	rs7068540
94379725	186841	rs28692618
94380110	187226	rs35297001
94380403	187519	rs7073739
94380415	187531	rs11595797
94380535	187651	rs12243009
94380591	187707	rs7077137
94381028	188144	rs9731595
94381254	188370	rs7078403
94381345	188461	rs7078179
94381677	188793	rs11187107
94382267	189383	rs2275217
94382439	189555	rs17107764
94382499	189615	rs10639509
94382499	189615	rs17875342
94382500	189616	rs34767899
94382708	189824	rs11818705
94382761	189877	rs11818708
94382810	189926	rs11818750
94382815	189931	rs5787006
94383610	190726	rs11187108
94383671	190787	rs3051599
94383672	190788	rs35996949
94383672	190788	rs2421946
94383672	190788	rs5787007
94383674	190790	rs34710486
94383765	190881	rs28615450
94383941	191057	rs10736068
94383978	191094	rs11819282
94384075	191191	rs11819301
94384310	191426	rs11819351
94384382	191498	rs10882095
94384580	191696	rs7070990
94385075	192191	rs7089765
94385373	192489	rs10736069
94385475	192591	rs12257072
94385728	192844	rs7900689
94386335	193451	rs11812813
94386492	193608	rs4933732
94386500	193616	rs11594678
94386540	193656	rs11813238
94386568	193684	rs1972360
94386594	193710	rs11816962
94386703	193819	rs4558084
94386890	194006	rs34948996
94387372	194488	rs1547818
94387496	194612	rs34497717
94387741	194857	rs7069680
94387964	195080	rs7085790
94388094	195210	rs36015190
94388098	195214	rs6583830
94388569	195685	rs7090402
94388954	196070	rs11187109
94389669	196785	rs35137137
94389736	196852	rs35494689
94390313	197429	rs6583831
94390339	197455	rs11187110
94390489	197605	rs11187111

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94390602	197718	rs4933733
94390673	197789	rs34848251
94390842	197958	rs7922902
94391081	198197	rs11282830
94391082	198198	rs35084253
94391352	198468	rs6583832
94391366	198482	rs10882096
94391873	198989	rs7079583
94391950	199066	rs7079602
94391966	199082	rs11187112
94392278	199394	rs12244429
94393212	200328	rs35312216
94393281	200397	rs28576319
94393578	200694	rs7088685
94394524	201640	rs17107776
94394677	201793	rs7902436
94394804	201920	rs7917359
94395324	202440	rs36070037
94395344	202460	rs34647366
94395706	202822	rs33915127
94396217	203333	rs11187114
94396832	203948	rs7069619
94397097	204213	rs34629164
94397263	204379	rs11187115
94397647	204763	rs7073957
94397851	204967	rs10686721
94397859	204975	rs34357393
94397981	205097	rs36046902
94398388	205504	rs12264712
94398585	205701	rs34132402
94398837	205953	rs12358273
94398866	205982	rs35625726
94398869	205985	rs11285704
94399729	206845	rs7067733
94399780	206896	rs6583833
94399806	206922	rs35230377
94400137	207253	rs10430651
94400806	207922	rs12262781
94400870	207986	rs12359115
94401006	208122	rs12359131
94401155	208271	rs7898318
94401180	208296	rs12359158
94401236	208352	rs12359159
94401240	208356	rs12764793
94401245	208361	rs12764800
94401246	208362	rs12241432
94401250	208366	rs11383128
94401253	208369	rs7898430
94401708	208824	rs35738968
94401710	208826	rs10537782
94401720	208836	rs36000362
94401732	208848	rs7893798
94402105	209221	rs11187116
94402138	209254	rs11187117
94402166	209282	rs11187118
94402579	209695	rs12411448
94402726	209842	rs35910196
94402828	209944	rs34963356
94403360	210476	rs17875344

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94403488	210604	rs34417963
94403643	210759	rs41290170
94403647	210763	rs17875345
94403675	210791	rs41290172
94403774	210890	rs41290174
94403917	211033	rs1044146
94403990	211106	rs17875346
94404243	211359	rs7078243
94404370	211486	rs11187119
94404390	211506	rs36107638
94404547	211663	rs4933734
94404618	211734	rs17875347
94405058	212174	rs1044153
94405646	212762	rs11187120
94405813	212929	rs35698103
94406209	213325	rs7071912
94406381	213497	rs11597699
94406501	213617	rs11598250
94406519	213635	rs35135018
94406834	213950	rs12242617
94407185	214301	rs12264496
94407201	214317	rs11814562
94407283	214399	rs7916594
94407322	214438	rs7093043
94407327	214443	rs7092669
94407904	215020	rs12244738
94408110	215226	rs12573394
94408195	215311	rs34223527
94408405	215521	rs7921040
94408480	215596	rs35583259
94408734	215850	rs2901599
94409046	216162	rs11187122
94409276	216392	rs6583834
94410546	217662	rs7076842
94411653	218769	rs9804194
94411998	219114	rs7914504
94412220	219336	rs35580348
94412694	219810	rs7079361
94412743	219859	rs7095377
94413406	220522	rs7096187
94413485	220601	rs6583835
94413764	220880	rs6583836
94413791	220907	rs7100344
94414053	221169	rs2153827
94414178	221294	rs6583837
94414402	221518	rs35978445
94414724	221840	rs2497321
94414758	221874	rs2497320
94415097	222213	rs11187124
94415101	222217	rs7913315
94415116	222232	rs2497319
94415147	222263	rs7071919
94416183	223299	rs2488058
94416216	223332	rs2488057
94417125	224241	rs34940159
94417197	224313	rs12776166
94417669	224785	rs11187125
94418089	225205	rs7910187
94418694	225810	rs7914114

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94418703	225819	rs11554568
94418859	225975	rs7914143
94418888	226004	rs1832887
94418890	226006	rs1418391
94418990	226106	rs7914507
94419062	226178	rs17875348
94419074	226190	rs7899695
94419424	226540	rs12414381
94419447	226563	rs7918084
94419491	226607	rs7903302
94419506	226622	rs11187126
94419569	226685	rs11187127
94419688	226804	rs11187128
94419689	226805	rs12772782
94419887	227003	rs11187129
94420477	227593	rs2185756
94420505	227621	rs9419741
94420766	227882	rs34709928
94420766	227882	rs34848369
94420877	227993	rs35250649
94421300	228416	rs9419742
94421540	228656	rs11594482
94421980	229096	rs2497318
94422308	229424	rs2488055
94422330	229446	rs6583838
94422446	229562	rs2488054
94423353	230469	rs7909334
94423442	230558	rs35288203
94423443	230559	rs7897560
94423460	230576	rs35413668
94423462	230578	rs7897565
94423473	230589	rs12761997
94423750	230866	rs34831256
94424074	231190	rs4421685
94425223	232339	rs28514404
94425223	232339	rs28591207
94425307	232423	rs35885794
94425468	232584	rs7098199
94425577	232693	rs34985734
94425653	232769	rs35906730
94425663	232779	rs4933735
94425739	232855	rs7098638
94426831	233947	rs7911264
94427225	234341	rs11187131
94427575	234691	rs11187132
94428318	235434	rs11448446
94428319	235435	rs34215006
94428322	235438	rs11439271
94428328	235444	rs35808040
94429339	236455	rs34911167
94429434	236550	rs11599074
94429447	236563	rs12774356
94429484	236600	rs12779070
94430250	237366	rs28757342
94430530	237646	rs35299744
94431405	238521	rs7089358
94431962	239078	rs35828108
94432143	239259	rs34615602
94432674	239790	rs7914280

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94432723	239839	rs17875349
94432994	240110	rs34669790
94434773	241889	rs10882098
94434827	241943	rs12778051
94434836	241952	rs11187133
94434881	241997	rs11187134
94435923	243039	rs2497317
94436021	243137	rs2488087
94436103	243219	rs12262390
94436615	243731	rs10786052
94437076	244192	rs10522178
94437120	244236	rs10531158
94437559	244675	rs12251379
94437891	245007	rs949579
94438736	245852	rs11187135
94438875	245991	rs34593856
94439140	246256	rs12781513
94439449	246565	rs7475059
94439530	246646	rs4075563
94439906	247022	rs34266926
94439912	247028	rs2229328
94439992	247108	rs1418387
94440106	247222	rs2901618
94440107	247223	rs2901619
94440209	247325	rs34372348
94440213	247329	rs9420589
94441710	248826	rs41290176
94442254	249370	rs17851141
94442322	249438	rs2275730
94442410	249526	rs2275729
94443456	250572	rs11319879
94443457	250573	rs34616944
94444237	251353	rs34433040
94445202	252318	rs35423905
94445857	252973	rs34619410
94448868	255984	rs3076219
94449333	256449	rs34231544
94449598	256714	rs35657492
94450261	257377	rs11187138
94450630	257746	rs10882099
94450667	257783	rs10882100
94451033	258149	rs7100035
94451324	258440	rs7100357
94451790	258906	rs12263166
94451929	259045	rs12263147
94451954	259070	rs12218257
94451963	259079	rs2488085
94451965	259081	rs2497316
94452407	259523	rs10882101
94452569	259685	rs5787008
94452862	259978	rs1111875
94453437	260553	rs7921459
94453671	260787	rs35245232
94453759	260875	rs1977832
94453925	261041	rs1977833
94453943	261059	rs35396842
94453943	261059	rs11309330
94453950	261066	rs34470242
94454287	261403	rs12778642

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94454556	261672	rs7911447
94454563	261679	rs7894796
94454564	261680	rs7911455
94454571	261687	rs7895123
94455183	262299	rs4933234
94455211	262327	rs34991559
94455539	262655	rs5015480
94456086	263202	rs2497315
94456407	263523	rs11187139
94456419	263535	rs12219514
94456475	263591	rs10882102
94456646	263762	rs12572190
94456890	264006	rs11187140
94456999	264115	rs7904159
94457006	264122	rs7904279
94457011	264127	rs7904508
94457018	264134	rs7904513
94457029	264145	rs7904292
94457125	264241	rs11187141
94457267	264383	rs34744311
94458157	265273	rs9419743
94458159	265275	rs12254229
94458272	265388	rs12246641
94458305	265421	rs12246541
94458432	265548	rs11813799
94458665	265781	rs11187142
94458914	266030	rs11187143
94459172	266288	rs28590736
94459519	266635	rs28428943
94459960	267076	rs11187144
94460495	267611	rs10882104
94460975	268091	rs34859807
94460979	268095	rs2497314
94461575	268691	rs4933736
94462185	269301	rs34966020
94462949	270065	rs34290965
94463018	270134	rs11817277
94463116	270232	rs34600815
94463139	270255	rs34793711
94463609	270725	rs7087591
94464077	271193	rs10786053
94464091	271207	rs10882105
94464476	271592	rs1578672
94465084	272200	rs35705157
94465091	272207	rs2901609
94465573	272689	rs34405337
94465640	272756	rs4545448
94466041	273157	rs4504977
94466253	273369	rs4262638
94466275	273391	rs12777206
94466575	273691	rs12782663
94466582	273698	rs12782667
94466623	273739	rs12781544
94467199	274315	rs10748582
94467336	274452	rs11378649
94467337	274453	rs33926570
94467472	274588	rs2488082
94467519	274635	rs1832886
94467850	274966	rs7898054

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94468084	275200	rs11187145
94468335	275451	rs11187146
94468644	275760	rs2488081
94468673	275789	rs2488080
94469087	276203	rs1112718
94469812	276928	rs12260097
94469857	276973	rs34383024
94470058	277174	rs35816895
94470314	277430	rs10882106
94470371	277487	rs2497313
94470482	277598	rs7086841
94470666	277782	rs2497312
94471062	278178	rs9420591
94471614	278730	rs4933235
94471897	279013	rs7923837
94471924	279040	rs10673051
94471925	279041	rs35275238
94471968	279084	rs35606816
94471975	279091	rs2497311
94472056	279172	rs7923866
94472115	279231	rs12780253
94472584	279700	rs35282244
94473140	280256	rs36026029
94473357	280473	rs11187147
94473463	280579	rs2488079
94473656	280772	rs10529320
94473689	280805	rs2497310
94473690	280806	rs2488078
94473695	280811	rs3221117
94473956	281072	rs2497309
94474172	281288	rs870786
94474324	281440	rs2497308
94474328	281444	rs2488077
94474418	281534	rs5787009
94474440	281556	rs5787010
94474442	281558	rs5787011
94474472	281588	rs11187148
94474486	281602	rs1418390
94474604	281720	rs2497307
94474750	281866	rs7081035
94474783	281899	rs7081294
94474989	282105	rs7081351
94475058	282174	rs7081745
94475060	282176	rs10568596
94475063	282179	rs7099393
94475082	282198	rs10665748
94475086	282202	rs34350311
94475191	282307	rs2497306
94475601	282717	rs2497305
94475656	282772	rs34372918
94475743	282859	rs11187149
94476016	283132	rs11597458
94476061	283177	rs2488076
94476146	283262	rs11593164
94476357	283473	rs34848929
94476358	283474	rs11597547
94476822	283938	rs11187150
94477781	284897	rs1544210
94478596	285712	rs35619602

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94479180	286296	rs10630735
94479181	286297	rs35097519
94479192	286308	rs34237492
94479194	286310	rs11309242
94480154	287270	rs2488075
94480323	287439	rs12762754
94480347	287463	rs11593631
94480992	288108	rs9730884
94481595	288711	rs11379031
94481781	288897	rs10615317
94481897	289013	rs35598412
94482696	289812	rs2497304
94482730	289846	rs9419745
94482914	290030	rs35849687
94483045	290161	rs34009238
94483719	290835	rs2488074
94484440	291556	rs11187151
94484498	291614	rs35406218
94485046	292162	rs34249712
94485097	292213	rs2497303

Position in Build 35/36	Position in SEQ ID NO:2	Marker ID
94485259	292375	rs4933738
94485733	292849	rs947591
94485978	293094	rs7916355
94486361	293477	rs2051004
94488416	295532	rs4933236
94488811	295927	rs17107841
94488843	295959	rs33985961
94488845	295961	rs10578040
94488955	296071	rs2488073
94489325	296441	rs2488072
94489493	296609	rs34209030
94489557	296673	rs2488071
94489846	296962	rs7917254
94490010	297126	rs11318190
94490015	297131	rs34994435
94490015	297131	rs10588167
94490091	297207	rs11187152

Table 12. SNPs within LD block C17 between positions 66,037,656 and 66,163,076 bp on Chromosome 17 in NCBI build 35 and NCBI Build 36.)

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66037656	1	rs11077501
66038245	590	rs10445229
66038446	791	rs8067115
66038456	801	rs10445230
66038691	1036	rs10445231
66039757	2102	rs28569992
66039800	2145	rs4606755
66039816	2161	rs4435300
66039936	2281	rs35154837
66039942	2287	rs9630701
66040960	3305	rs12165045
66040982	3327	rs7359539
66041088	3433	rs7359543
66042479	4824	rs365813
66043002	5347	rs4261590
66043301	5646	rs7223187
66043481	5826	rs6146132
66043562	5907	rs721249
66043745	6090	rs5821786
66043746	6091	rs33957619
66043759	6104	rs5821787
66043760	6105	rs33961999
66043764	6109	rs12950870
66044207	6552	rs350605
66044302	6647	rs10559381
66044390	6735	rs11650835
66044411	6756	rs7209364
66044489	6834	rs350604
66044496	6841	rs11657696
66044614	6959	rs11651554
66044626	6971	rs11657734
66045245	7590	rs350603
66045317	7662	rs2307760
66045722	8067	rs11653245
66045948	8293	rs11653355
66047524	9869	rs34832542
66047547	9892	rs2567294
66047580	9925	rs11655558
66047597	9942	rs184783
66047621	9966	rs353452
66047646	9991	rs9897791
66047700	10045	rs11655611
66047739	10084	rs1825672
66047807	10152	rs35941755
66047887	10232	rs9896649
66048278	10623	rs34984463
66048288	10633	rs11374691
66048300	10645	rs11868103
66048450	10795	rs7220610
66048799	11144	rs7216368
66048942	11287	rs16913
66049292	11637	rs34941209
66049692	12037	rs8069108
66049716	12061	rs420762
66050080	12425	rs2630640
66050452	12797	rs34793380

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66050707	13052	rs1817630
66050903	13248	rs11077502
66050915	13260	rs7218450
66051172	13517	rs411602
66051859	14204	rs16975882
66051914	14259	rs41450951
66052282	14627	rs17780198
66052347	14692	rs10512540
66052398	14743	rs2630639
66052474	14819	rs4793432
66052546	14891	rs34696190
66052699	15044	rs12952273
66053325	15670	rs350612
66053541	15886	rs1284043
66053695	16040	rs1298182
66053988	16333	rs1092528
66054007	16352	rs1091892
66054019	16364	rs1092390
66054025	16370	rs1092391
66054076	16421	rs276805
66054488	16833	rs164784
66055098	17443	rs164785
66056158	18503	rs350611
66057036	19381	rs9736449
66057065	19410	rs1161565
66057065	19410	rs350610
66057184	19529	rs36160618
66057341	19686	rs28835946
66057721	20066	rs350609
66057907	20252	rs36143257
66058061	20406	rs164786
66058223	20568	rs4506943
66058544	20889	rs164787
66058598	20943	rs35063328
66058616	20961	rs35629111
66058724	21069	rs35654390
66058733	21078	rs350608
66058804	21149	rs589894
66059113	21458	rs512280
66059121	21466	rs512274
66059131	21476	rs512241
66059267	21612	rs35813361
66059431	21776	rs34292805
66060049	22394	rs671190
66060102	22447	rs671117
66060111	22456	rs35419562
66060172	22517	rs8080393
66060192	22537	rs509784
66060244	22589	rs509924
66060364	22709	rs510865
66060367	22712	rs669895
66060401	22746	rs8075249
66060403	22748	rs8080759
66060407	22752	rs511552
66060416	22761	rs511578
66060618	22963	rs11326414

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66061168	23513	rs350607
66061287	23632	rs8081864
66061435	23780	rs8066762
66063324	25669	rs10048191
66063794	26139	rs34162560
66063983	26328	rs350606
66064178	26523	rs8078924
66065291	27636	rs4793451
66065798	28143	rs350613
66066258	28603	rs10432003
66066436	28781	rs350614
66066465	28810	rs34703743
66066481	28826	rs35908278
66066608	28953	rs11654062
66067303	29648	rs350615
66067453	29798	rs16975891
66067482	29827	rs17823280
66067699	30044	rs350616
66068320	30665	rs350617
66068798	31143	rs1991680
66069274	31619	rs9896037
66069554	31899	rs16975893
66069880	32225	rs8081551
66070068	32413	rs11654475
66071319	33664	rs11651609
66071575	33920	rs34132957
66071603	33948	rs12603169
66071721	34066	rs8073324
66072276	34621	rs1431455
66072384	34729	rs17763769
66073012	35357	rs350618
66073300	35645	rs1991679
66073592	35937	rs34134043
66073862	36207	rs7208933
66074000	36345	rs11655478
66074367	36712	rs35062489
66074796	37141	rs9900305
66075575	37920	rs16975908
66076138	38483	rs7224554
66076400	38745	rs35795750
66076402	38747	rs5821788
66076579	38924	rs350619
66076797	39142	rs34028570
66076805	39150	rs5821789
66076806	39151	rs35251724
66077103	39448	rs7210525
66077477	39822	rs2567296
66077488	39833	rs1843621
66077930	40275	rs34077265
66077984	40329	rs528669
66078111	40456	rs8067160
66078127	40472	rs350620
66078527	40872	rs191621
66079419	41764	rs350621
66079437	41782	rs350622
66079660	42005	rs12452538
66079935	42280	rs17176093
66079969	42314	rs350623
66079990	42335	rs11077503

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66080024	42369	rs11077504
66080067	42412	rs350624
66080672	43017	rs35072892
66080920	43265	rs11657749
66080984	43329	rs16975914
66081110	43455	rs34693986
66081370	43715	rs350625
66081556	43901	rs818765
66081568	43913	rs415298
66081576	43921	rs376750
66081612	43957	rs10652573
66081700	44045	rs350626
66082086	44431	rs28590672
66083526	45871	rs16975922
66083670	46015	rs481417
66083783	46128	rs191622
66083825	46170	rs482515
66083858	46203	rs367218
66083931	46276	rs402214
66084484	46829	rs483543
66084515	46860	rs484253
66084734	47079	rs486202
66084769	47114	rs610662
66084772	47117	rs11310950
66084781	47126	rs12936985
66084782	47127	rs12945927
66084808	47153	rs610730
66084932	47277	rs1825669
66084935	47280	rs1825670
66084954	47299	rs1825671
66085342	47687	rs8077690
66085473	47818	rs12602288
66086152	48497	rs16975937
66086744	49089	rs28694321
66087301	49646	rs35353185
66087527	49872	rs41486747
66087994	50339	rs718950
66088026	50371	rs718951
66089255	51600	rs11654235
66089418	51763	rs11077506
66090535	52880	rs1431454
66090620	52965	rs5821790
66090782	53127	rs1367748
66090958	53303	rs12603995
66091042	53387	rs16975939
66091117	53462	rs11434683
66091324	53669	rs8081186
66091594	53939	rs149309
66091687	54032	rs184806
66091693	54038	rs149380
66091704	54049	rs151727
66091719	54064	rs189541
66091741	54086	rs11651021
66091844	54189	rs416121
66091912	54257	rs9302918
66092080	54425	rs9302919
66092700	55045	rs35618929
66092813	55158	rs35870620
66092904	55249	rs11652089

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66093601	55946	rs12938026
66093669	56014	rs12948379
66094196	56541	rs9911671
66094376	56721	rs16975941
66094422	56767	rs7220885
66094832	57177	rs601297
66094858	57203	rs601615
66094862	57207	rs601617
66094892	57237	rs601656
66095313	57658	rs418402
66096181	58526	rs35417478
66097168	59513	rs16975944
66097631	59976	rs34913709
66097633	59978	rs9894781
66097634	59979	rs9914075
66097640	59985	rs11658937
66097733	60078	rs8078784
66097760	60105	rs9915992
66098070	60415	rs10634138
66098071	60416	rs34728014
66098073	60418	rs34864826
66098076	60421	rs10551730
66098084	60429	rs5821791
66098085	60430	rs34310496
66098092	60437	rs34563419
66098173	60518	rs7503632
66098597	60942	rs9902449
66098928	61273	rs9894881
66098930	61275	rs9894882
66098976	61321	rs11656877
66099163	61508	rs5821792
66099494	61839	rs16975946
66099600	61945	rs17779190
66099816	62161	rs11650015
66100055	62400	rs10607347
66100062	62407	rs11372958
66100081	62426	rs34073356
66100089	62434	rs36104345
66100401	62746	rs2109051
66100605	62950	rs2159312
66101242	63587	rs990043
66101267	63612	rs576754
66101396	63741	rs2035582
66101665	64010	rs9905624
66101895	64240	rs693914
66102064	64409	rs558507
66102168	64513	rs35142117
66102168	64513	rs10596869
66102213	64558	rs560206
66102221	64566	rs12949221
66102269	64614	rs560368
66102315	64660	rs1911969
66102441	64786	rs35550717
66102450	64795	rs34779818
66102555	64900	rs9892329
66102591	64936	rs11658215
66102896	65241	rs35815207
66103027	65372	rs9914225
66103236	65581	rs9894021

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66103495	65840	rs9891523
66103561	65906	rs720877
66103923	66268	rs720876
66103928	66273	rs35174251
66104116	66461	rs9892968
66104437	66782	rs17779357
66104493	66838	rs34287249
66105315	67660	rs3042758
66105827	68172	rs1872599
66106415	68760	rs7218838
66106622	68967	rs7209535
66106911	69256	rs9896809
66107082	69427	rs28507887
66107150	69495	rs8067542
66107151	69496	rs10641487
66107152	69497	rs33989506
66107167	69512	rs8081487
66108291	70636	rs4793495
66108545	70890	rs8073162
66108565	70910	rs8072591
66108901	71246	rs9905537
66108905	71250	rs8073114
66108924	71269	rs8072003
66108980	71325	rs35155940
66108991	71336	rs11459300
66108997	71342	rs36029337
66109457	71802	rs11656223
66110309	72654	rs6501400
66110507	72852	rs8074266
66110586	72931	rs388304
66110881	73226	rs4544280
66111138	73483	rs12601471
66111335	73680	rs12603574
66111468	73813	rs11077507
66111545	73890	rs11077508
66111926	74271	rs28546453
66112148	74493	rs412877
66112202	74547	rs391223
66112205	74550	rs7224183
66112227	74572	rs173318
66112234	74579	rs192147
66112749	75094	rs34361437
66113023	75368	rs12449913
66114764	77109	rs28496807
66114858	77203	rs7220084
66114926	77271	rs7224857
66115366	77711	rs7221542
66115371	77716	rs7221545
66115377	77722	rs34466876
66115416	77761	rs10610236
66115835	78180	rs1979538
66116621	78966	rs8067103
66116703	79048	rs7216053
66116880	79225	rs12949351
66117903	80248	rs9913650
66117911	80256	rs1860316
66118086	80431	rs9914115
66118200	80545	rs9908443
66118485	80830	rs8079029

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66118495	80840	rs12601922
66118737	81082	rs10545098
66118737	81082	rs12603987
66119589	81934	rs9897225
66119616	81961	rs35975623
66119642	81987	rs9895773
66119822	82167	rs9898518
66119823	82168	rs28422091
66119823	82168	rs36094553
66119863	82208	rs3220372
66119992	82337	rs41408048
66120631	82976	rs28373290
66120827	83172	rs41459950
66121181	83526	rs36013413
66121413	83758	rs10564191
66121468	83813	rs7221715
66121873	84218	rs12940023
66122077	84422	rs4019476
66122410	84755	rs7222670
66122508	84853	rs7211934
66122635	84980	rs7212243
66122801	85146	rs11655139
66123046	85391	rs4793317
66123283	85628	rs171384
66123342	85687	rs4793496
66123566	85911	rs507683
66123595	85940	rs507607
66123682	86027	rs41528454
66123714	86059	rs41381246
66123879	86224	rs192146
66123955	86300	rs34149626
66123959	86304	rs35260054
66125089	87434	rs9908077
66125154	87499	rs11077509
66125233	87578	rs35234488
66125360	87705	rs11871352
66125993	88338	rs7209850
66126471	88816	rs421333
66126699	89044	rs413073
66126766	89111	rs2035581
66126795	89140	rs392974
66126799	89144	rs28532132
66126840	89185	rs3931227
66126841	89186	rs16975961
66126875	89220	rs532348
66127256	89601	rs11867791
66127283	89628	rs11871014
66127312	89657	rs34866225
66127313	89658	rs35958830
66128191	90536	rs9904090
66128304	90649	rs16975968
66129127	91472	rs9911708
66129806	92151	rs34448828
66129814	92159	rs11398461
66130210	92555	rs9907685
66130284	92629	rs9914666
66130455	92800	rs17717654
66131911	94256	rs16975970
66131995	94340	rs1981646

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66132156	94501	rs11656723
66132225	94570	rs16975976
66132788	95133	rs1981647
66133032	95377	rs16975979
66133370	95715	rs16975981
66134231	96576	rs9909661
66134831	97176	rs9890554
66135283	97628	rs11077510
66135627	97972	rs9302920
66135758	98103	rs34975186
66136201	98546	rs11870545
66136484	98829	rs9906234
66136910	99255	rs10621796
66136920	99265	rs11328278
66136922	99267	rs11328279
66137329	99674	rs35402203
66137331	99676	rs6501401
66137347	99692	rs10596163
66137437	99782	rs35029611
66137784	100129	rs35985303
66137798	100143	rs10595957
66137965	100310	rs10221271
66138452	100797	rs10221225
66138713	101058	rs34005576
66139441	101786	rs9913463
66139476	101821	rs9915148
66139800	102145	rs11650683
66140108	102453	rs34335723
66140414	102759	rs11654495
66141319	103664	rs35607820
66141543	103888	rs12601304
66141933	104278	rs1486290
66142011	104356	rs12452862
66142106	104451	rs35317540
66142226	104571	rs11077511
66142325	104670	rs35278774
66142329	104674	rs7216457
66142581	104926	rs11077512
66142607	104952	rs35634443
66142648	104993	rs11454851
66142729	105074	rs11654670
66142794	105139	rs34926966
66143200	105545	rs8078302
66143897	106242	rs562472
66144028	106373	rs28420303
66144129	106474	rs28542473
66144170	106515	rs28526433
66144232	106577	rs12185220
66144972	107317	rs7350903
66145018	107363	rs7350904
66145022	107367	rs7350905
66145067	107412	rs35353467
66145660	108005	rs16975985
66145765	108110	rs16975987
66145912	108257	rs412981
66145914	108259	rs412980
66145925	108270	rs9907746
66146236	108581	rs432688
66146640	108985	rs540331

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66146722	109067	rs473792
66146816	109161	rs2630644
66146912	109257	rs12949591
66146954	109299	rs2109053
66147095	109440	rs35296857
66147167	109512	rs17791270
66147246	109591	rs16975989
66147343	109688	rs17791282
66147436	109781	rs17718124
66147660	110005	rs16975993
66147678	110023	rs35106633
66147754	110099	rs34429407
66147913	110258	rs2240749
66147960	110305	rs16975998
66148045	110390	rs3217050
66148046	110391	rs2240750
66148178	110523	rs16976000
66148512	110857	rs16976002
66148962	111307	rs189580
66149102	111447	rs1843622
66149149	111494	rs543765
66149213	111558	rs434729
66149222	111567	rs375709
66149257	111602	rs11656782
66149348	111693	rs11653519
66149386	111731	rs190256
66149859	112204	rs4584866
66150283	112628	rs16976008
66150360	112705	rs16976009
66150511	112856	rs16976011
66150609	112954	rs17718380
66150898	113243	rs11652208
66150909	113254	rs11652209
66151294	113639	rs10491179
66151858	114203	rs16976019
66152747	115092	rs35499697
66152804	115149	rs17791650
66152863	115208	rs16976023
66152963	115308	rs16976024
66152998	115343	rs9891997
66153185	115530	rs12942978
66153557	115902	rs16976027
66153631	115976	rs17718538
66154056	116401	rs16976031
66155045	117390	rs34736208
66155048	117393	rs12952540
66155070	117415	rs34389302
66155101	117446	rs189581
66155303	117648	rs9910837
66155784	118129	rs17718586
66156561	118906	rs544680
66156593	118938	rs8066818
66157022	119367	rs408448
66157073	119418	rs11650843

Position in Build 35/36	Position in SEQ ID NO:3	Marker ID
66157111	119456	rs367742
66157179	119524	rs550945
66157197	119542	rs183590
66157224	119569	rs551058
66157327	119672	rs34098284
66157893	120238	rs183591
66157917	120262	rs183059
66157976	120321	rs404774
66158027	120372	rs11657329
66158091	120436	rs405068
66158109	120454	rs35166389
66158247	120592	rs16976038
66158414	120759	rs183592
66159001	121346	rs34458687
66159262	121607	rs35760966
66159416	121761	rs2191113
66159464	121809	rs5821793
66159546	121891	rs5821794
66159547	121892	rs35222039
66159556	121901	rs10648023
66159562	121907	rs3048626
66159637	121982	rs8072436
66159764	122109	rs2215270
66159891	122236	rs16976043
66160076	122421	rs8074760
66160292	122637	rs11657599
66160331	122676	rs34281212
66160370	122715	rs36074213
66160438	122783	rs171385
66160451	122796	rs412353
66160480	122825	rs422923
66160492	122837	rs11654012
66160668	123013	rs35429609
66160721	123066	rs2367004
66161977	124322	rs35222003
66161994	124339	rs11867678
66162691	125036	rs12953137
66162852	125197	rs10642929
66162854	125199	rs34937331
66162869	125214	rs10585639
66163076	125421	rs4793497
66037656	1	rs11077501
66038245	590	rs10445229
66038446	791	rs8067115
66038456	801	rs10445230
66038691	1036	rs10445231
66039757	2102	rs28569992
66039800	2145	rs4606755
66039816	2161	rs4435300
66039936	2281	rs35154837

Table 13. Key to Sequence listing provided herein.

SEQ ID NO	Name
1	LD block C06
2	LD block C10
3	LD block C17
4	rs10882091
5	rs1111875
6	rs1569699
7	rs17763769
8	rs17763811
9	rs1843622
10	rs1860316
11	rs1981647
12	rs1999763
13	rs2191113
14	rs2275729
15	rs2421943
16	rs2497304
17	rs3829170
18	rs4712527
19	rs6583826
20	rs6583830
21	rs7756992
22	rs7758851

SEQ ID NO	Name
23	rs7908111
24	rs7914814
25	rs7915186
26	rs7917359
27	rs7922112
28	rs7923837
29	rs9295478
30	rs947591
31	rs9890889
32	rs7752906
33	rs9350271
34	rs9356744
35	rs9368222
36	rs10440833
37	rs6931514
38	rs2009802
39	rs17718938
40	rs17223216
41	rs2109050
42	rs1962801
43	rs7086285
44	rs17234378

EXAMPLE 2

VARIANTS IN THE *CDKAL1* GENE INFLUENCE INSULIN RESPONSE AND THE RISK OF TYPE 2 DIABETES

We have recently described a variant in *TCF7L2* associated to T2D (Grant, S.F. *et al. Nat Genet* **38**, 320-3 (2006); Helgason, A. *et al. Nat Genet* (2007)). In the following, we describe a genome-wide association study on Icelandic T2D patients, using the Illumina Hap300 chip. We individually tested 313,179 SNPs for association to T2D in a sample of 1399 T2D patients and 5275 controls. We further tested 339,846 two-marker haplotypes identified as efficient surrogates ($r^2 > 0.8$) for a set of SNPs which were not included on the Hap300 chip but were typed in the HapMap project (Pe'er, I. *et al. Nat Genet* **38**, 663-7 (2006)). In addition to analyzing the entire group of T2D patients we separately tested 700 non-obese T2D patients and 531 obese T2D patients for association. Overall, a total of 1,959,075 (653,025 variants $\times$ 3 phenotypes) tests were performed. The results were adjusted for relatedness between individuals and potential population stratification by genomic control (Devlin, B. & Roeder, K. *Biometrics* **55**, 997-1004 (1999)) (see *Methods*). Specifically, the (unadjusted) chi-square statistics were divided by 1.287, 1.204 and 1.184 respectively for the analyses of all, non-obese and obese T2D cases. A previously identified SNP rs7903146 in the *TCF7L2* gene gave the most significant results with OR = 1.38 and $P = 1.82 \times 10^{-10}$ in all T2D patients. Although no other SNP or haplotype was significant after adjustment for the number of tests performed, more borderline significant signals were observed than expected by chance alone (**Fig. 4**). Hence we decided to further pursue the top signals.

METHODS

Icelandic study population

The Icelandic T2D group has been described previously (Reynisdottir, I. *et al. Am J Hum Genet* **73**, 323-35 (2003)). A total of 1500 T2D patients were recruited for this genome-wide association study, using the Infinium II assay method and the Sentrix HumanHap300 BeadChip (Illumina, San Diego, CA, USA). Thereof, 1399 were successfully genotyped according to our quality control criteria (see Supplementary Methods) and used in the present case control-analysis; 531 of the genotyped cases were obese (BMI ≥ 30). The controls used in this study consisted of 599 controls randomly selected from the Icelandic genealogical database and 4676 individuals from other ongoing genome-wide association studies at deCODE. The study was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. Written informed consent was obtained from all cases and controls.

Other study populations

The Danish female study group of 282 cases and 629 controls, herein termed Denmark A, was selected from the Prospective Epidemiological Risk Factor (PERF) study in Denmark (Tanko, L.B., *et al. Bone* **32**, 8-14 (2003)). This is a group of postmenopausal women who took part in various screening placebo-controlled clinical trials and epidemiological studies performed at the Center for Clinical and Basic Research. At a follow-up examination of 5847 women in 2000-2001 medical history including diabetes type I and type II, family history, and current or previous long-term use of drugs were gathered during personal interviews using a preformed questionnaire. If subject was diagnosed as diabetes of either type I or type II, the time of diagnosis or treatment was also collected. The study was approved by the Ethical Committee of Copenhagen County and was in accordance with the principles of the Helsinki Declaration.

The second Danish study population of 1359 T2D cases and 4858 control individuals with normal glucose tolerance was from the Steno Diabetes Center in Copenhagen and from the Inter99 population-based sample of 30- to 60-year-old individuals living in the greater Copenhagen area and sampled at Research Centre for Prevention and Health (Jorgensen, T. *et al. Eur J Cardiovasc Prev Rehabil* **10**, 377-86 (2003)). This dataset is referred to in the text as Denmark B. Diabetes and pre-diabetes categories were diagnosed according to the 1999 World Health Organization (WHO) criteria. An oral glucose tolerance test was performed on participants in the Inter99 study as described (Jorgensen, T. *et al. Eur J Cardiovasc Prev Rehabil* **10**, 377-86 (2003)). Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen County and was in accordance with the principles of the Helsinki Declaration.

The Philadelphia study population consisted of 468 T2D cases and 1024 control individuals. The study population was selected from the PENN CATH study, a cross-sectional study of the association of biochemical and genetic factors to coronary atherosclerosis in a study population of consecutive individuals undergoing cardiac catheterization at the University of Pennsylvania Medical Center. T2D was defined as a history of fasting blood glucose ≥ 126 mg dl⁻¹, 2 h postprandial glucose ≥ 200 mg dl⁻¹, use of oral hypoglycemic agents, or use of insulin and oral hypoglycemic in a subject older than age 40. The University of Pennsylvania Institutional Review Board approved the study protocol, and all subjects gave written informed consent. All cases and controls were of European ancestry. Ethnicity was determined through self-report.

The Dutch Breda study population consisted of 370 T2D cases and 916 control individuals. The cases were recruited in 1998-1999 in collaboration with the Diabetes Service Breda and 80 general practitioners from the region around Breda. All patients are diagnosed according to WHO criteria (plasma glucose levels >11.1 mmol/l or a fasting plasma glucose level ≥ 7.0 mmol/l), and undergo clinical and laboratory evaluations for their diabetes at regular 3-month intervals. The

Medical Ethics Committee of the University Medical Centre in Utrecht approved the study protocol. All probands filled out an informed consent and a questionnaire on clinical data, including their diabetes related medication, height and weight at present and at the age of 20 year. The controls are Dutch blood bank donors with an average age of 48.

The Scottish study population consisted of type 2 diabetic cases and non-diabetic controls from the Wellcome Trust UK T2D case-control collection (Go-DARTS2) which is a sub-study of Diabetes Audit and Research Tayside (DARTS) (Morris, A.D. *et al. BMJ* **315**, 524-8 (1997)). All T2D patients were physician-diagnosed T2D cases recruited at primary or secondary care diabetes clinics, or invited to participate from primary care registers and have not been characterized for GAD anti-bodies or MODY gene mutations. The controls were invited to participate through the primary care physicians or through their workplace occupational health departments. Controls did not have a previous diagnosis of diabetes, but the glucose tolerance status of the controls is unknown. All individuals in this ongoing study were recruited in Tayside between October 2004 and July 2006. This study was approved by the Tayside Medical Ethics Committee and informed consent was obtained from all subjects.

All subjects in the Hong Kong study population were of southern Han Chinese ancestry residing in Hong Kong. The cases consisted of 1500 individuals with T2D selected from the Prince of Wales Hospital Diabetes Registry. Of these, 682 patients had young-onset diabetes (age-at-diagnosis ≤ 40 years) with positive family history. An additional 818 cases were randomly selected from the same registry. The controls consisted of 1000 subjects with normal glucose tolerance (fasting plasma glucose < 6.1 mmol/l). Of these, 617 were recruited from the general population participating in a community-based cardiovascular risk screening program as well as hospital staff. In addition, 383 subjects were recruited from a cardiovascular risk screening program for adolescents. Informed consent was obtained for each participating subject. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

The African study population comes from the Africa America Diabetes Mellitus study, which was originally designed as an affected sibling pair study with enrollment of available spouses as controls. It has since been expanded to include other family members of the affected pairs and population controls. Recruitment strategies and eligibility criteria for the families enrolled in this report have been described previously (Rotimi, C.N. *et al. Ann Epidemiol* **11**, 51-8 (2001)). This West African case-control series consisted of individuals from the Yoruba (233 affected individuals, 432 controls) and Igbo (237 affected individuals, 276 controls) groups from Nigeria and the Akan (257 affected individuals, 248 controls), Ewe (22 affected individuals, 30 controls) and Gaa-Adangbe (123 affected individuals, 141 controls) groups from Ghana.

With the exception of the Scottish Go-DARTS study population the DNA used for genotyping in all replication study populations was the product of whole-genome amplification (GenomiPhi Amplification kit, Amersham) of DNA isolated from the peripheral blood.

Statistical analysis

Illumina Genome-Wide Genotyping. All Icelandic case- and control-samples were assayed with the Infinium HumanHap300 SNP chips (Illumina, San Diego, CA, USA), containing 317,503 haplotype tagging SNPs derived from phase I of the International HapMap project. Of the SNPs assayed on the chip, 4,324 SNPs were excluded as they had (a) yield lower than 95% in cases or controls; (b) minor allele frequency less than 1% in the population; or (c) showed significant distortion from Hardy-Weinberg equilibrium in the controls (P -value < 0.001). Any samples with a call rate below 98% were excluded from the analysis. Thus, the final analyses presented in the text utilizes 313,179 SNPs.

Single SNP genotyping. Single SNP genotyping for all population studied, except for the Scottish Go-DARTS population, was carried out at deCODE Genetics in Reykjavik, Iceland by the Centaurus (Nanogen) platform (Kutyavin, I.V. *et al. Nucleic Acids Res* **34**, e128 (2006)). The quality of each Centaurus SNP assay was evaluated by genotyping each assay in the CEU and/or YRI HapMap samples and comparing the results with the HapMap data. Assays with $>1.5\%$ mismatch rate were not used and a linkage disequilibrium (LD) test was used for markers known to be in LD. Single SNP genotyping for the Scottish population was carried out at the Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee, Scotland, by the TaqMan® method.

Association analysis. For association analysis we utilized a standard likelihood ratio statistics, implemented in the NEMO software (Gretarsdottir, S. *et al. Nat Genet* **35**, 131-8 (2003)) to calculate two-sided p -values and allele specific OR for each individual allele, assuming a multiplicative model for risk, i.e., that the risks of the two alleles a person carries multiply. Allelic frequencies, rather than carrier frequencies are presented for the markers, and p -values are given after adjustment for the relatedness of the subjects. When estimating genotype specific OR (**Table 19**) genotype frequencies in the population were estimated assuming HWE.

In general, allele/haplotype frequencies are estimated by maximum likelihood and tests of differences between cases and controls are performed using a generalized likelihood ratio test (Rice, J.A. *Mathematical Statistics and Data Analysis*, (Wadsworth Inc., Belmont, CA, 1995)). This method is particularly useful in situations where there are some missing genotypes for the marker of interest and genotypes of another marker, which is in strong LD with the marker of interest, are used to provide some partial information. This was used in the association tests presented in **Table**

17 to ensure that the comparison of the highly correlated markers was done using the same number of individuals. To handle uncertainties with phase and missing genotypes, maximum likelihood estimates, likelihood ratios and p-values are computed directly for the observed data, and hence the loss of information due to uncertainty in phase and missing genotypes is automatically captured by the likelihood ratios.

Results from multiple case-control groups were combined using a Mantel-Haenszel model (Mantel, N. & Haenszel, W. *J Natl Cancer Inst* **22**, 719-48 (1959)) in which the groups were allowed to have different population frequencies for alleles, and genotypes but were assumed to have common relative risks.

Correction for relatedness of the subjects and Genomic Control. Some of the individuals in both the Icelandic patient and control groups are related to each other, causing the chi-square test statistic to have a mean >1 and median $>0.675^2$. We estimated the inflation factor by calculating the average of the 653,025 chi-square statistics, which was a method of genomic control⁴ to adjust for both relatedness and potential population stratification. The inflation factor was estimated as 1.287, 1.204 and 1.184, for the analysis of all, non-obese and obese T2D cases, respectively. The results presented are based on adjusting the chi-square statistics by dividing each of them by the corresponding inflation factor.

Quantitative analysis. Data from oral glucose tolerance test on individuals from the Danish Inter99 study were used to calculate insulin secretion as corrected insulin response (CIR) using the following equation: $(100 \times \text{insulin at 30 minutes}) \div [\text{glucose at 30 minutes} \times (\text{glucose at 30 minutes} - 3.89 \text{ mmol})]$. Insulin sensitivity was estimated as the reciprocal of the insulin resistance according to the homeostasis model assessment (HOMA): $22.5 / [\text{fasting insulin} \times \text{fasting glucose}]$ (Matthews, D.R. *et al. Diabetologia* **28**, 412-9 (1985)). The association between CIR (HOMA) and genotype status was tested using a multiple regression where the log-transformed CIR (HOMA) were taken as the response variable and the explanatory variable was either the number of copies of risk allele an individual carries (an additive model) or an indicator variable for homozygous carriers of the risk allele (a recessive model). Adjustment for sex, age and affection status was done by including the appropriate terms as explanatory variables. For comparison insulin secretion was also calculated as $(\text{insulin at 30 minutes} - \text{insulin at 0 minutes}) \div (\text{glucose at 30 minutes} - \text{glucose at 0 minutes})$, yielding comparable results.

Cell lines. The INS1 cells were provided by Hoffmann-LaRoche. They were grown in RPMI1640 (Invitrogen) supplemented with 10% fetal bovine serum (Invitrogen), 50 µg/ml penicillin-streptomycin (Invitrogen), 50 µM 2-mercaptoethanol (SIGMA), 1 mM MEM sodium pyruvate (Invitrogen) and 10 mM Hepes buffer solution (Invitrogen). They were split 1:2 twice per week by washing once in 1X Hanks Balanced Salt Solution (Invitrogen) and then trypsinized (trypsin-EDTA; Invitrogen).

Preparation of RNA and cDNA amplification. INS1 cells were incubated for 48h in normal growth medium containing 10 mM glucose. At the time of harvest there were 2×10^7 cells, which were used for the preparation of total RNA. RNA was extracted using RNeasy Midi Kit (Quiagen). cDNA was prepared using High-Capacity cDNA Archive Kit (Applied Biosystems). *CDKAL1* cDNA was amplified using two different primer pairs between exons 2 and 8 (forward: 5'-GGGGCTGCTCACATAATAATTCA-3'; reverse: 5'-TGTGCCAATGTCTCTGCCATA-3') and between exons 7 and 13 (forward: 5'-ACCTGGCCAGCTATCCCATT-3'; reverse: 5'-CCATTTTCCCATGAATGCAG-3'). Primers from beta-actin served as positive controls (forward 5'-ATCTGGCACCACCTCCTACAATGAGCTGC-3'; reverse: 5'-CGTCATACTCCTGCTTGCTGATCCACATCTGC-3').

RESULTS AND DISCUSSION

For each phenotype tested we selected all single SNPs and two marker haplotypes with $P < 0.00005$ for replication in a case-control sample from Denmark (Denmark B). After eliminating redundant markers a total of 46 SNPs were taken further for the attempt at replication (**Table 14**). In addition, we included the five most significant non-synonymous SNPs present on the Illumina Hap300 chip. Out of those 51 SNPs, 47 were successfully genotyped in 1110 Danish T2D cases and 2272 controls. In the Danish group SNPs rs7756992 and rs13266634 stood out and were significantly replicated with $P = 0.00013$ and OR = 1.24 and $P = 0.0012$ and OR = 1.20, respectively, in the Danish group of all T2D patients (**Table 15**). This is compared to $P = 0.00021$ and OR = 1.23 and $P = 0.000061$ and OR = 1.19, respectively in the initial Icelandic study. All of the other SNPs genotyped had $P > 0.01$ in the Danish group and were not pursued further. The first SNP, rs7756992, is located in intron 5 of the CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*) gene on 6p22.3. It resides in a large LD block of 201.7 kb that includes exons 1-5 of the *CDKAL1* gene as well as the minimal promoter region but no other known genes (**Figure 5**). The second SNP, rs13266634, is a non-synonymous SNP causing an arginine 325 to tryptophan change in the last exon of the solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*) gene on 8q24. The gene product of *SLC30A8* is specific to the pancreas and it is expressed in beta

cells where it facilitates the accumulation of zinc from the cytoplasm into intracellular vesicles (Chimienti, F., *et al. Diabetes* **53**, 2330-7 (2004)). The risk allele of rs13266634 on 8q24 has recently been found to confer risk of T2D in a genome wide association study of French T2D cases and controls (Sladek, R. *et al. Nature* **445**, 881-5 (2007)). Of other significantly associated SNPs in that study, we also replicated, in the initial Icelandic samples, association to two SNPs close to the *HHEX* gene (**Table 16**). However, we did not replicate the reported association to markers in the *LOC387761* and *EXT2* genes also described in that study.

We typed the SNPs rs7756992 and rs13266634 in four other T2D case-control groups of European ancestry from Denmark (Denmark A), Scotland, the Netherlands and Philadelphia, US as well as case-control groups from Hong Kong and West Africa. Furthermore, the size of the Denmark B study group was expanded mostly by increasing the number of genotyped controls. The association of the G allele of rs7756992 was replicated with significance in the Scottish (OR = 1.11; $P = 0.0042$) and the Hong Kong (OR = 1.25; $P = 0.00018$) case-control groups (**Table 17**). Association in other study groups was not individually significant, but all were in the same direction. The observed association from combining all eight case-control groups gave an OR of 1.15 with a corresponding P of 9.0×10^{-12} (**Table 17**). Given that approximately 2 million tests were performed in the initial genome-scan, this association remained highly significant with Bonferonni adjustment ($P_{adj} = 1.8 \times 10^{-5}$) (Skol, A.D., *et al. Nat Genet* **38**, 209-13 (2006)). Attempts at refining the association observed with rs7756992 by genotyping additional markers that correlate with the original signal in the HapMap CEPH (CEU) dataset, did not yield more significant results (**Table 18**). As could be expected the linkage disequilibrium observed for the West African population was considerably less than that seen for the Icelandic and Hong Kong groups (**Table 19**). Further work is needed to determine if an associated variant with a higher OR than observed for rs7756992 can be identified in the West African group. Likewise, for allele C of the non-synonymous SNP rs13266634 the association to T2D was replicated with significance in three of the six additional groups (from Scotland, Philadelphia and Hong Kong) (**Table 17**). Even though the OR for Denmark B decreased with the larger sample size and the estimated effect was in the opposite direction (only slightly and non-significant) for Denmark A, the combined results from all study group yielded a genome-wide significant P of 2.5×10^{-11} and an OR of 1.16 (**Table 17**).

In the Icelandic study the association to rs7756992 was more significant in non-obese T2D patients (OR = 1.37; $P = 9.0 \times 10^{-6}$) than in the group of all patients (OR = 1.23; $P = 0.00021$) (**Table 14** and **Table 17**). A higher OR in non-obese than in obese T2D patients was also observed for this variant in the other populations studied. For the combined populations of European origin the OR was 1.19; $P = 7.29 \times 10^{-9}$ for the non-obese T2D patients compared to OR = 1.12; $P = 0.00017$ for the obese group. An even stronger effect was seen in the Hong Kong non-obese T2D group (OR = 1.36; $P = 7.48 \times 10^{-6}$), compared to the obese group (OR = 1.13; $P = 0.094$), where obesity was defined as BMI ≥ 25 . When the results for all groups were combined, relative to

controls, OR = 1.19; $P = 1.93 \times 10^{-11}$ and OR = 1.13; $P = 2.68 \times 10^{-5}$ was obtained for the non-obese and obese T2D patient groups, respectively. These results indicate that this variant does not confer increased risk of T2D through increased BMI.

Genotype odds ratio was estimated for each of the two loci (**Table 20**). Based on the results for the combined Caucasian study populations rs7756992 deviates significantly from the multiplicative model with OR for the heterozygote = 1.09 compared to OR = 1.45 for the homozygote, supporting a nearly recessive mode of inheritance. The same trend, although non-significant, was seen for the Hong Kong samples with heterozygote OR = 1.13 and OR = 1.55 for the homozygote. Conversely, a multiplicative model for the genotype relative risk provided an adequate fit for rs13266634.

The function of the gene product of *CDKAL1* is not known. However, as implied in the gene name the protein product is similar to another protein, CDK5 regulatory subunit associated protein 1 (*CDK5RAP1*). *CDK5RAP1* is expressed in neuronal tissues where it inhibits cyclin dependent kinase 5 (CDK5) activity by binding to the CDK5 regulatory subunit p35 (Ching, Y.P., *et al. J Biol Chem* **277**, 15237-40 (2002)). In pancreatic beta cells, CDK5 has been shown to play a role in the loss of beta cell function under glucotoxic conditions (Wei, F.Y. *et al. Nat Med* **11**, 1104-8 (2005)). Furthermore, inhibition of the CDK5/p35 complex prevents decrease of insulin gene expression that results from glucotoxicity (Ubeda, M., *et al. J Biol Chem* **281**, 28858-64 (2006)). It is tempting to speculate that *CDKAL1* might play a role in the inhibition of CDK5/p35 in pancreatic beta cells similar to that of *CDK5RAP1* in neuronal tissue. Reduced expression of *CDKAL1* or reduced inhibitory function thus could lead to an impaired response to glucotoxicity. In this study we showed that *CDKAL1* is expressed in the rat pancreatic beta cell line INS-1 (**Figure 6**). Further studies are needed to determine if the effect of *CDKAL1* on increasing the risk of T2D is exerted through this pathway.

Based on the predicted function of *CDKAL1* and known function of *SLC30A8* we would expect both rs7756992 and rs13266634 to affect insulin secretion. To evaluate the effects of the two SNPs on insulin secretion we analyzed the effect of genotype status on corrected insulin response (CIR) in a set of individuals from the Inter99 study (part of Denmark B) that had undergone an oral glucose tolerance test (OGTT). For rs7756992, we demonstrated that the homozygote carriers of the risk allele had an estimated 24% less CIR than the heterozygote carriers or non-carriers ($P < 0.00001$, **Fig. 7**). This observation is consistent with the variant's nearly recessive mode of inheritance with respect to disease risk. Furthermore, the effect observed on CIR is present in both males and females (**Figure 8**) and in T2D patients as well as controls, and adjusting for BMI status did not affect the results (**Table 21**). The effect of rs13266634 on insulin response was smaller but significant and for this risk variant the reduction in CIR was consistent with an additive effect. No effect on insulin sensitivity was observed for either variant (**Table 21**).

The identification of *CDKAL1* as a susceptibility gene for T2D adds a new piece to the puzzle of how genetic factors may predispose to T2D. Although the function of this gene remains to be elucidated we have shown that it is expressed in pancreatic beta cells and that a variant within the gene is correlated with insulin secretion. The similarity to CDK5RAP1 further indicates that CDKAL1 may facilitate insulin production under glucotoxic conditions through interaction with CDK5. In conclusion, we have identified a variant in the *CDKAL1* gene that in a nearly recessive manner blunts the insulin response and predisposes to T2D.

Table 14. Association to T2D in the Icelandic discovery group.

The upper table includes association results for all SNPs or two-marker haplotypes that have an adjusted *P* value less than 10⁻⁵ for either all T2D cases, non-obese T2D cases or obese T2D cases. Included in the table is the chromosome, the position of the markers (or the midpoint for two-marker haplotypes) in NCBI Build 34, the markers and alleles tested, the corresponding surrogate SNP for two-markers haplotypes selected for replication, the frequency in controls and the frequency in cases, the odds ratio (OR) and adjusted *P*-value for the three case groups tested. The number of T2D cases in each of the three groups is included in parenthesis and the same set of 5275 controls is used in all tests. Note that information on BMI is missing for 168 of the cases. The lower table includes the corresponding values for the five most significant non-synonymous SNPs selected for replication. Included in column five are the corresponding genes and the codon changes. In both tables markers selected for further testing in the first replication group (Denmark B) are indicated with bold typesetting. Other markers / haplotypes were excluded from the replication study as they were a) highly correlated with another marker selected for replication, or b) belong to the *TCF7L2* locus that has been studied previously.

Chr	Position	Markers	Allele	Surrogate ^a (<i>r</i> ²)	Con.frq	All T2D cases (1399)				NonObese T2D cases (700)				Obese T2D cases (531)			
						Case.frq	OR	<i>P</i> ^b	Case.frq	OR	<i>P</i> ^b	Case.frq	OR	<i>P</i> ^b	Case.frq	OR	<i>P</i> ^b
C01	29602516	rs4949283 rs502545	TC	rs10798895 G (1)	0.149	0.117	0.76	0.00016	0.104	0.66	0.00033	0.133	0.88	0.21			
C01	104461151	rs7553985	C	-	0.394	0.430	1.16	0.0023	0.419	1.11	0.11	0.466	1.34	0.00027			
C01	104467009	rs2166890	T	-	0.393	0.430	1.16	0.0018	0.419	1.11	0.091	0.466	1.35	0.00024			
C01	104468502	rs7552405	T	-	0.317	0.355	1.19	0.00078	0.346	1.14	0.047	0.386	1.35	0.00030			
C01	151915609	rs3738028	G	-	0.360	0.407	1.22	0.00046	0.417	1.27	0.00016	0.409	1.23	0.0038			
C02	40632580	rs13414307 rs1990609	AG	-	0.517	0.571	1.24	0.000089	0.568	1.23	0.0011	0.582	1.30	0.00026			
C02	40623619	rs13414307	A	-	0.543	0.593	1.22	0.00033	0.589	1.21	0.0028	0.603	1.28	0.00056			
C02	55036788	rs930493 rs10173697	GT	-	0.281	0.335	1.29	0.0000017	0.325	1.23	0.0024	0.333	1.27	0.0016			
C02	55040844	rs10173697	T	-	0.503	0.553	1.22	0.000040	0.545	1.18	0.0086	0.560	1.25	0.0014			
C03	89162181	rs12486049	T	-	0.872	0.904	1.38	0.000035	0.907	1.43	0.00043	0.901	1.34	0.0095			
C03	146863467	rs7630694	G	-	0.060	0.070	1.20	0.065	0.056	0.93	0.60	0.097	1.70	0.000033			
C03	196904151	rs9858622	A	-	0.668	0.701	1.17	0.0028	0.682	1.07	0.34	0.737	1.40	0.000016			
C04	140508134	rs13116075 rs6824182	AA	rs10033117 C (1)	0.741	0.763	1.13	0.036	0.734	0.96	0.60	0.804	1.43	0.000024			
C04	140604420	rs2292837 rs11725721	TC	-	0.254	0.232	0.89	0.038	0.259	1.03	0.69	0.194	0.71	0.000047			
C04	140621178	rs3762864 rs11725721	GC	-	0.254	0.233	0.89	0.042	0.262	1.04	0.60	0.194	0.70	0.000038			

C05	76637396	rs832785 rs2859576	AA	-	0.510	0.470	0.85	0.00082	0.489	0.92	0.18	0.438	0.75	0.000043
C05	76635083	rs4704400	T	-	0.490	0.530	1.18	0.0008	0.511	1.09	0.18	0.562	1.33	0.000043
C05	87882885	rs10505855 rs12514611	GC	rs10452479 G (0.94)	0.188	0.224	1.25	0.00023	0.244	1.39	0.000015	0.200	1.08	0.38
C06	6967990	rs490213 rs814174	AG	rs12201780 A (1)	0.044	0.072	1.71	0.000016	0.080	1.89	0.000037	0.063	1.48	0.033
C06	9509965	rs214447	T	-	0.424	0.449	1.11	0.034	0.416	0.97	0.61	0.495	1.34	0.000035
C06	20779501	rs4712527 rs7756992	AG	-	0.232	0.270	1.23	0.00021	0.292	1.37	0.000090	0.250	1.11	0.21
C06	20805960	rs7756992 rs9295478	AG	-	0.743	0.701	0.81	0.000089	0.682	0.74	0.000013	0.718	0.88	0.11
C06	20787688	rs7756992	G	-	0.232	0.270	1.23	0.00021	0.292	1.37	0.000090	0.250	1.11	0.20
C06	31552682	rs2516424	C	-	0.325	0.372	1.23	0.000039	0.375	1.25	0.00080	0.376	1.25	0.0020
C06	31592562	rs2516424 rs4947324	CC	-	0.320	0.368	1.24	0.000027	0.370	1.25	0.00074	0.373	1.26	0.0016
C06	41130207	rs10456499	A	-	0.563	0.597	1.15	0.0040	0.575	1.05	0.43	0.637	1.36	0.000018
C06	132387934	rs9483377 rs997607	GC	-	0.234	0.278	1.26	0.000040	0.272	1.22	0.0067	0.276	1.25	0.0065
C06	132379686	rs9483377 rs7745875	GG	-	0.233	0.276	1.25	0.000048	0.271	1.22	0.0052	0.273	1.23	0.0087
C06	132361238	rs9483377	G	-	0.307	0.356	1.25	0.000013	0.348	1.20	0.0052	0.354	1.24	0.0040
C06	150399255	rs11155700	A	-	0.749	0.794	1.29	0.000095	0.786	1.23	0.0049	0.801	1.35	0.00039
C06	150399954	rs12213837	C	-	0.749	0.794	1.29	0.000097	0.786	1.23	0.0049	0.801	1.35	0.00040
C06	164421443	rs206732 rs933251	TC	rs10085202 A (1)	0.531	0.479	0.81	0.000037	0.469	0.78	0.00015	0.497	0.87	0.058
C08	124084183	rs952656	G	-	0.673	0.721	1.25	0.000019	0.706	1.17	0.021	0.725	1.28	0.0012
C08	124092339	rs13252935 rs7824293	TG	-	0.143	0.108	0.72	0.000010	0.116	0.78	0.0099	0.104	0.69	0.00067
C08	128249239	rs283710 rs412835	CC	-	0.254	0.222	0.84	0.0024	0.245	0.95	0.51	0.190	0.69	0.000025
C08	128250055	rs185852	G	-	0.755	0.791	1.22	0.00050	0.764	1.05	0.49	0.822	1.49	0.0000046
C08	128265112	rs283718 rs283720	CA	-	0.255	0.223	0.84	0.0026	0.256	1.01	0.94	0.189	0.68	0.0000092
C09	88426790	rs10993008	A	-	0.154	0.192	1.30	0.000027	0.181	1.21	0.019	0.194	1.32	0.0020
C09	93768899	rs10818991 rs10990303	CC	rs10985640 A (0.85)	0.537	0.490	0.83	0.00019	0.469	0.76	0.000037	0.513	0.91	0.18
C09	93802193	rs10990568 rs4743148	GG	-	0.263	0.309	1.25	0.000032	0.314	1.28	0.00038	0.306	1.23	0.0076
C09	93810412	rs4743148	G	-	0.315	0.365	1.25	0.000010	0.371	1.28	0.00013	0.358	1.21	0.0092
C09	124790974	rs3814120	T	-	0.093	0.113	1.25	0.0046	0.094	1.01	0.91	0.140	1.59	0.000014
C10	52735263	rs7915186 rs3829170	TT	-	0.328	0.377	1.24	0.000021	0.374	1.22	0.0021	0.375	1.23	0.0049
C10	52746400	rs3829170 rs7922112	TG	rs12247188 T (0.9)	0.336	0.386	1.24	0.000021	0.381	1.22	0.0027	0.387	1.24	0.0027
C10	93976392	rs2421943	G	-	0.555	0.614	1.28	9.1×10 ⁻⁷	0.600	1.20	0.0043	0.621	1.31	0.00017
C10	94022896	rs2421943 rs7917359	GC	-	0.521	0.585	1.30	1.3×10 ⁻⁸	0.565	1.19	0.0052	0.602	1.39	0.0000041
C10	94068337	rs7908111 rs2497304	GG	-	0.499	0.443	0.80	0.0000034	0.456	0.84	0.0072	0.427	0.75	0.000039

C10	94011761	rs1999763 rs10882091	GT	-	0.517	0.455	0.78	2.9×10^{-7}	0.472	0.83	0.0038	0.442	0.74	0.000019
C10	94023632	rs1999763 rs6583830	GG	-	0.517	0.455	0.78	2.9×10^{-7}	0.472	0.83	0.0038	0.442	0.74	0.000019
C10	94012407	rs6583826	G	-	0.467	0.518	1.23	0.000020	0.508	1.18	0.0080	0.527	1.28	0.000048
C10	94025680	rs6583826 rs10882091	GC	-	0.393	0.449	1.26	0.0000021	0.435	1.19	0.0062	0.469	1.36	0.000012
C10	94092724	rs10882091 rs7923837	CG	-	0.410	0.466	1.26	0.0000022	0.452	1.19	0.0063	0.486	1.36	0.000011
C10	94038954	rs10882091	C	-	0.415	0.472	1.26	0.0000024	0.456	1.18	0.0079	0.491	1.36	0.000014
C10	94047527	rs7914814	T	-	0.416	0.472	1.26	0.0000025	0.456	1.18	0.0081	0.491	1.35	0.000014
C10	94062695	rs6583830	A	-	0.415	0.472	1.26	0.0000024	0.456	1.18	0.0079	0.491	1.36	0.000014
C10	94122233	rs2275729 rs1111875	AG	-	0.470	0.527	1.26	0.0000023	0.519	1.22	0.0018	0.534	1.29	0.000025
C10	94157293	rs2497304	A	-	0.530	0.473	0.80	0.0000	0.481	0.82	0.00	0.466	0.77	0.000251
C10	94160330	rs947591	A	-	0.475	0.526	1.23	0.000023	0.521	1.21	0.0028	0.545	1.33	0.000053
C10	114441018	rs7895307 rs12255372	GT	-	0.257	0.308	1.29	0.0000049	0.330	1.42	4.5×10^{-7}	0.269	1.06	0.45
C10	114422936	rs7903146	T	-	0.300	0.372	1.38	1.9×10^{-10}	0.396	1.53	2.4×10^{-11}	0.342	1.21	0.010
C10	114434905	rs7903146 rs11196192	TT	-	0.220	0.282	1.39	3.4×10^{-9}	0.298	1.51	9.4×10^{-9}	0.263	1.27	0.0042
C10	114438514	rs7904519	G	-	0.480	0.522	1.18	0.00045	0.553	1.34	0.0000026	0.483	1.01	0.84
C10	114455586	rs7904519 rs10885409	GC	-	0.474	0.516	1.18	0.00055	0.549	1.35	0.0000018	0.476	1.01	0.90
C10	114455586	rs7904519 rs10885409	AT	-	0.510	0.471	0.86	0.0013	0.441	0.76	0.000011	0.510	1.00	0.99
C10	114472659	rs10885409	C	-	0.484	0.523	1.17	0.0014	0.555	1.33	0.0000060	0.483	0.99	0.94
C10	114473489	rs12255372	T	-	0.294	0.351	1.29	4.9×10^{-7}	0.371	1.41	1.6×10^{-7}	0.317	1.11	0.15
C10	118261345	rs1681748 rs2170862	TT	-	0.238	0.265	1.15	0.013	0.245	1.04	0.59	0.302	1.38	0.000041
C10	118285583	rs2170862	T	-	0.256	0.281	1.13	0.020	0.259	1.02	0.82	0.320	1.37	0.000043
C10	118555280	rs10787760	G	-	0.278	0.300	1.12	0.037	0.269	0.96	0.53	0.347	1.38	0.000017
C11	23946882	rs1879230	T	-	0.088	0.111	1.30	0.00097	0.128	1.53	0.000021	0.093	1.07	0.57
C11	106474406	rs1455593	T	-	0.097	0.114	1.20	0.021	0.087	0.89	0.29	0.142	1.54	0.000040
C12	30390375	rs1429622 rs1506382	AG	rs794598 C (0.9)	0.368	0.321	0.82	0.000083	0.341	0.89	0.092	0.296	0.72	0.000023
C12	33373479	rs1905421	T	-	0.082	0.110	1.39	0.000044	0.116	1.47	0.00020	0.107	1.35	0.011
C13	25558690	rs565707 rs6491198	AA	-	0.281	0.249	0.85	0.0039	0.220	0.72	0.000016	0.274	0.97	0.69
C13	25478564	rs565707	C	-	0.700	0.734	1.19	0.0016	0.763	1.38	0.0000073	0.710	1.05	0.53
C13	25535031	rs7984685	C	-	0.540	0.582	1.19	0.00043	0.606	1.31	0.000022	0.568	1.12	0.11
C13	25537643	rs7998347	C	-	0.540	0.582	1.19	0.00046	0.606	1.31	0.000024	0.568	1.12	0.11
C13	25715179	rs1333350 rs7987436	GT	-	0.254	0.216	0.81	0.00030	0.195	0.71	0.000010	0.251	0.98	0.82
C14	80759910	rs799099 rs4899801	AG	-	0.365	0.390	1.11	0.037	0.359	0.97	0.64	0.439	1.36	0.000022

C14	80763881	rs2066041	G	-	0.367	0.394	1.12	0.021	0.368	1.01	0.92	0.437	1.34	0.000038
C14	80820260	rs10483957	A	-	0.459	0.493	1.15	0.0042	0.476	1.07	0.28	0.530	1.33	0.000042
C15	98094991	rs9920347 rs11635811	AG	rs2045107 C (0.9)	0.521	0.469	0.81	0.000044	0.475	0.84	0.0056	0.468	0.81	0.0041
C16	12811478	rs6498353 rs9941146	CG	-	0.105	0.080	0.74	0.00054	0.068	0.62	0.000047	0.082	0.75	0.026
C16	22764405	rs724466	T	-	0.738	0.781	1.26	0.000038	0.781	1.27	0.0012	0.783	1.29	0.0025
C16	24353768	rs11074618 rs985729	AC	rs11644596 G (1)	0.299	0.342	1.21	0.00044	0.332	1.16	0.040	0.372	1.39	0.000032
C16	73296557	rs1862773 rs825842	CT	-	0.059	0.038	0.63	0.000048	0.041	0.67	0.0075	0.039	0.64	0.0072
C16	73311680	rs2432543 rs4887826	TG	-	0.069	0.043	0.61	0.000010	0.042	0.60	0.00046	0.049	0.69	0.019
C17	69180675	rs17763769 rs1860316	GA	-	0.511	0.564	1.24	0.000013	0.585	1.35	0.0000023	0.543	1.14	0.069
C17	69203439	rs1860316	A	-	0.653	0.707	1.28	0.0000020	0.734	1.46	3.2×10 ⁻⁸	0.687	1.17	0.039
C17	69242752	rs1860316 rs17763811	GC	-	0.335	0.282	0.78	0.0000028	0.254	0.68	2.6×10 ⁻⁸	0.301	0.86	0.039
C17	69218316	rs1981647	C	-	0.513	0.563	1.23	0.000026	0.583	1.33	0.0000065	0.544	1.14	0.071
C17	69234630	rs1843622	T	-	0.615	0.665	1.24	0.000021	0.684	1.35	0.0000043	0.640	1.11	0.14
C17	69244944	rs2191113	A	-	0.696	0.744	1.27	0.000013	0.771	1.47	9.5×10 ⁻⁸	0.713	1.08	0.30
C17	69259003	rs9890889	A	-	0.839	0.869	1.27	0.00053	0.885	1.47	0.000032	0.857	1.14	0.17
C18	41051796	rs10502860	G	-	0.167	0.194	1.20	0.0035	0.218	1.39	0.000028	0.174	1.05	0.61
C18	63451377	rs764133 rs7237209	TT	-	0.167	0.132	0.76	0.00010	0.121	0.69	0.000048	0.135	0.78	0.014
C18	63463071	rs7237209	C	-	0.819	0.852	1.27	0.00028	0.867	1.44	0.000029	0.847	1.22	0.037
C19	3316583	rs3810420	A	-	0.176	0.189	1.09	0.16	0.227	1.37	0.000045	0.146	0.80	0.021
C20	37651862	rs4592915 rs2232580	GC	rs6127771 C (1)	0.495	0.550	1.25	0.0000048	0.558	1.29	0.000051	0.543	1.21	0.0060
C21	13769165	rs468601	A	-	0.888	0.908	1.25	0.0054	0.927	1.60	0.000026	0.895	1.08	0.48
C21	33296778	rs2834061	G	-	0.249	0.291	1.24	0.000076	0.311	1.36	0.0000094	0.271	1.12	0.15
C21	39373432	rs369906	T	-	0.566	0.613	1.21	0.00010	0.631	1.31	0.000028	0.587	1.09	0.24
Gene														
C03	69453958	rs10510980	A	ENST000000343145 (K211R)	0.808	0.840	1.25	0.00065	0.836	1.22	0.019	0.845	1.30	0.0061
C08	118141371	rs13266634	C	SLC30A8 (R325W)	0.646	0.685	1.19	0.00060	0.678	1.16	0.030	0.697	1.26	0.0020
C10	124472418	rs2495774	G	LOC390009 (Q27H)	0.547	0.594	1.21	0.00011	0.592	1.20	0.0039	0.597	1.22	0.0043
C11	3624302	rs2271586	T	ART5 (T284K)	0.176	0.208	1.23	0.00059	0.212	1.26	0.0033	0.203	1.20	0.042
C19	8669900	rs10410943	G	MGC33407 (A51V)	0.674	0.714	1.20	0.00043	0.713	1.20	0.0076	0.708	1.17	0.035

^aA surrogate of the corresponding two marker haplotype with a correlation coefficient r^2 . ^bP values adjusted for relatedness and population stratification using genomic control (see **Methods**).

Table 15. Association to T2D in the primary replication group (Denmark B).
Association results for the 47 SNPs tested in the primary replication cohort (Denmark B), consisting of 1110 T2D cases and 2272 controls. Included in the table is the chromosome, the position of the SNPs in NCBI Build 34, the marker and allele tested, frequency in controls and the frequency in cases, odds ratio (OR) and *P* value in all T2D cases, non-obese T2D cases and obese T2D cases, respectively. For all three groups of cases, the same group of controls is used and the number of cases is included in the parentheses. The two SNPs selected for replication in additional T2D case-control groups are highlighted with bold typesetting.

Chr	Position	Marker	Allele	All T2D cases (1110)			NonObese T2D cases (640)			Obese T2D cases (470)		
				Case.frq	OR	<i>P</i>	Case.frq	OR	<i>P</i>	Case.frq	OR	<i>P</i>
C01	29589307	rs10798895	A	0.832	0.828	0.97 0.68	0.831	0.99 0.94	0.824	0.94 0.55		
C01	104461151	rs7553985	C	0.367	0.379	1.05 0.34	0.375	1.03 0.62	0.385	1.08 0.30		
C01	151915609	rs3738028	G	0.385	0.410	1.11 0.050	0.419	1.15 0.029	0.397	1.05 0.47		
C02	40623619	rs13414307	A	0.537	0.540	1.01 0.84	0.544	1.03 0.67	0.534	0.99 0.86		
C03	69453958	rs10510980	A	0.826	0.833	1.05 0.50	0.835	1.06 0.50	0.831	1.03 0.74		
C03	89162181	rs12486049	T	0.878	0.872	0.94 0.47	0.871	0.93 0.49	0.873	0.96 0.70		
C03	146863467	rs7630694	G	0.053	0.054	1.02 0.85	0.051	0.95 0.72	0.059	1.12 0.46		
C03	196904151	rs9858622	A	0.656	0.667	1.05 0.39	0.662	1.02 0.73	0.674	1.08 0.29		
C04	140660180	rs10033117	C	0.740	0.746	1.03 0.65	0.747	1.04 0.65	0.744	1.02 0.81		
C05	76635083	rs4704400	T	0.472	0.456	0.94 0.23	0.452	0.92 0.22	0.461	0.96 0.55		
C05	87825021	rs10452479	G	0.229	0.238	1.05 0.43	0.240	1.06 0.43	0.235	1.04 0.68		
C06	6971276	rs12201780	A	0.043	0.048	1.12 0.36	0.049	1.16 0.32	0.045	1.07 0.71		
C06	9509965	rs214447	T	0.418	0.427	1.03 0.52	0.432	1.06 0.39	0.419	1.00 0.95		
C06	20787688	rs7756992	G	0.276	0.322	1.24 0.00013	0.321	1.24 0.0021	0.323	1.25 0.0044		
C06	31552682	rs2516424	C	0.363	0.380	1.07 0.19	0.374	1.05 0.48	0.387	1.11 0.18		
C06	41130207	rs10456499	A	0.581	0.579	0.99 0.92	0.576	0.98 0.78	0.583	1.01 0.87		
C06	132361238	rs9483377	G	0.306	0.331	1.12 0.039	0.334	1.14 0.061	0.327	1.10 0.20		
C06	150399255	rs11155700	A	0.758	0.734	0.88 0.043	0.737	0.90 0.14	0.731	0.87 0.089		
C06	164425224	rs10085202	G	0.430	0.426	0.99 0.78	0.424	0.98 0.73	0.428	0.99 0.94		
C08	118141371	rs13266634	C	0.664	0.704	1.20 0.0012	0.701	1.19 0.013	0.707	1.22 0.012		
C08	124084183	rs952656	G	0.672	0.672	1.00 0.98	0.680	1.04 0.56	0.660	0.95 0.51		
C08	128250055	rs185852	G	0.796	0.797	1.01 0.92	0.794	0.99 0.88	0.801	1.03 0.72		

C09	88426790	rs10993008	A	0.146	0.150	1.03	0.66	0.151	1.04	0.64	0.149	1.02	0.84
C09	93745181	rs10985640	G	0.430	0.434	1.01	0.78	0.421	0.96	0.57	0.451	1.09	0.25
C09	93810412	rs4743148	G	0.382	0.381	1.00	0.94	0.370	0.95	0.41	0.398	1.07	0.39
C09	124790974	rs3814120	T	0.089	0.090	1.02	0.84	0.076	0.85	0.16	0.109	1.27	0.052
C10	52758344	rs12247188	T	0.331	0.315	0.93	0.19	0.312	0.92	0.22	0.318	0.94	0.45
C10	94047527	rs7914814	T	0.413	0.432	1.08	0.14	0.434	1.09	0.18	0.429	1.07	0.35
C10	118555280	rs10787760	G	0.294	0.276	0.91	0.15	0.268	0.88	0.080	0.288	0.97	0.73
C10	124472418	rs2495774	G	0.524	0.540	1.07	0.22	0.542	1.07	0.27	0.538	1.06	0.46
C11	23946882	rs1879230	T	0.127	0.115	0.89	0.13	0.118	0.91	0.36	0.110	0.85	0.14
C11	3624302	rs2271586	T	0.190	0.201	1.07	0.28	0.194	1.02	0.77	0.211	1.14	0.13
C11	106474406	rs1455593	T	0.081	0.080	0.98	0.81	0.081	0.99	0.92	0.078	0.96	0.77
C12	30434349	rs794598	T	0.623	0.600	0.91	0.063	0.594	0.88	0.058	0.608	0.94	0.37
C12	33373479	rs1905421	T	0.099	0.097	0.98	0.79	0.086	0.85	0.17	0.113	1.16	0.24
C14	80763881	rs2066041	G	0.427	0.415	0.95	0.35	0.427	1.00	1.00	0.398	0.89	0.11
C15	98060278	rs2045107	G	0.524	0.527	1.01	0.78	0.522	0.99	0.92	0.534	1.04	0.55
C16	12756032	rs6498353	C	0.136	0.134	0.98	0.80	0.140	1.04	0.68	0.124	0.90	0.35
C16	22764405	rs724466	T	0.695	0.715	1.10	0.085	0.719	1.12	0.10	0.710	1.08	0.34
C16	24356412	rs11644596	G	0.324	0.323	1.00	0.94	0.336	1.06	0.43	0.305	0.92	0.27
C16	73314817	rs4887826	G	0.064	0.052	0.82	0.068	0.054	0.84	0.21	0.050	0.78	0.11
C17	69203439	rs1860316	A	0.679	0.682	1.01	0.82	0.684	1.02	0.74	0.679	1.00	1.00
C18	41051796	rs10502860	G	0.222	0.197	0.86	0.044	0.198	0.87	0.12	0.196	0.86	0.13
C18	63463071	rs7237209	C	0.861	0.852	0.92	0.29	0.848	0.89	0.22	0.857	0.97	0.74
C19	3316583	rs3810420	A	0.181	0.191	1.07	0.30	0.188	1.05	0.54	0.195	1.10	0.30
C20	37645161	rs6127771	C	0.447	0.451	1.02	0.77	0.442	0.98	0.77	0.462	1.06	0.39
C21	33296778	rs2834061	G	0.250	0.255	1.03	0.66	0.267	1.09	0.23	0.239	0.94	0.48

Table 16. Association results for SNPs with reported association to T2D in Sladek et al.

Shown are association results for T2D in the Icelandic study group for the eight SNPs identified by Sladek et al (*Nature* **445**, 881-5 (2007)) to associate with T2D. For the Icelandic group the table includes the frequency in cases and controls, odds ratio (OR) and adjusted *P* value for five of the eight SNP's. Corresponding values are shown for the replication cohort used in Sladek et al. Three of the markers, rs1113132, rs11037909 and rs3740878, are not on the Illumina 300K chip; however, a surrogate SNP rs729287 which has a correlation $r^2 = 1$ to rs11037909 and rs3740878 (based on HapMap CEU data) has been typed in the Icelandic study group and results for this marker are included in the table.

Icelandic study group										Sladek et al			
Chr	Position	Marker	Allele	Controls	Cases	OR	P	Controls	Cases	OR ^a	P ^b	Nearest gene	
C08	118141371	rs13266634	C	0.646	0.685	1.19	0.00060	0.699	0.746	1.26	5.0×10 ⁻⁷	SLC30A8	
C10	94127459	rs1111875	G	0.550	0.588	1.17	0.0014	0.598	0.642	1.21	9.1×10 ⁻⁶	HHEX	
C10	94146494	rs7923837	G	0.583	0.624	1.19	0.00058	0.623	0.665	1.20	2.2×10 ⁻⁵	HHEX	
C10	114422936	rs7903146	T	0.300	0.372	1.38	1.9×10 ⁻¹⁰	0.293	0.406	1.65	<1.0×10 ⁻⁷	TCF7L2	
C11	42211027	rs7480010	G	0.273	0.271	0.95	0.33	0.301	0.336	1.18	2.9×10 ⁻⁴	LOC387761	
C11	44207712	rs1113132	C	-	-	-	-	0.733	0.763	1.17	8.1×10 ⁻⁴	EXT2	
C11	44219923	rs11037909	T	-	-	-	-	0.729	0.760	1.18	4.5×10 ⁻⁴	EXT2	
C11	44222111	rs3740878	A	-	-	-	-	0.728	0.760	1.18	2.8×10 ⁻⁴	EXT2	
C11	44244399	rs729287	C	0.748	0.759	1.06	0.33	-	-	-	-	EXT2	

^a Allelic OR calculated from frequency information provided in Table 1 of Sladek et al. ^b *P* value (based on permutation) for Stage 2 in Table 1 in Sladek et al.

Table 17. Association results for the SNPs rs7756992 and rs13266634 in six Caucasian T2D case-control groups and in case-control groups from Hong Kong and from West-Africa.

Study population (<i>n/m</i>)	Frequency		OR (95% CI)	P value
Variant (allele)	Controls	Cases		
Iceland (1399/5275)				
rs7756992 (G)	0.232	0.270	1.23 (1.10-1.37)	0.00021
rs13266634 (C)	0.646	0.685	1.19 (1.08-1.31)	0.0006
Denmark A (263/597)				
rs7756992 (G)	0.297	0.331	1.17 (0.93-1.47)	0.18
rs13266634 (C)	0.686	0.672	0.94 (0.75-1.17)	0.58
Denmark B (1359/4825)				
rs7756992 (G)	0.279	0.320	1.21 (1.10-1.33)	0.000054
rs13266634 (C)	0.673	0.692	1.09 (0.99-1.19)	0.073
Philadelphia (447/950)				
rs7756992 (G)	0.262	0.295	1.18 (0.98-1.42)	0.073
rs13266634 (C)	0.678	0.760	1.51 (1.25-1.81)	1.5×10 ⁻⁵
Scotland (3742/3718)				
rs7756992 (G)	0.267	0.288	1.11 (1.03-1.19)	0.0042
rs13266634 (C)	0.682	0.710	1.14 (1.06-1.22)	0.00025
The Netherlands (368/915)				
rs7756992 (G)	0.270	0.280	1.05 (0.86-1.27)	0.64
rs13266634 (C)	0.717	0.736	1.10 (0.91-1.33)	0.33
Caucasian combined^a (7578/16280)				
rs7756992 (G)	0.264	0.293	1.16 (1.09-1.22)	3.9×10 ⁻¹⁰
rs13266634 (C)	0.675	0.700	1.15 (1.10-1.20)	3.3×10 ⁻⁹
Hong Kong(1457/986)				
rs7756992 (G)	0.462	0.517	1.25 (1.11-1.40)	0.00018
rs13266634 (C)	0.523	0.566	1.19 (1.06-1.33)	0.0035
West Africa^a (865/1106)				
rs7756992 (G)	0.612	0.625	1.02 (0.92-1.14)	0.72
rs13266634 (C)	0.962	0.971	1.26 (0.88-1.81)	0.21
All groups combined (9900/18372)				
rs7756992 (G)			1.15 (1.11-1.20)	9.0×10 ⁻¹²
rs13266634 (C)			1.16 (1.11-1.21)	2.5×10 ⁻¹¹

Shown are the number of T2D cases and controls (*n/m*), the allelic frequency in the affected and control individuals, the allelic odds-ratio (OR) with 95 confidence intervals (CI 95%) and two-sided *P* values based on the multiplicative model. ^aWhen combining results for the Caucasian groups and for the five West-African groups, OR's and *P* values are combined using a Mantel-Haenzsel model, while the frequency in cases and controls is estimated as a weighted average over the different study groups.

Table 18. Association of eight SNP's in *CDKAL1* to T2D in Iceland, Hong Kong and West-Africa.
Association to T2D for eight SNP's in the *CDKAL1* gene for three of the eight study groups; from Iceland, Hong Kong and West-Africa. The seven additional SNP's are all highly correlated to rs7756992.

SNP	Allele	Position ^b	Combined ^a				Iceland				Hong Kong				West-Africa ^c			
			OR (95% CI)	P	Con.frq	Case.frq	OR	P	Con.frq	Case.frq	OR	P	Con.frq	Case.frq	OR	P	Con.frq	Case.frq
rs7752906	A	20774034	1.19 (1.11-1.28)	6.5×10 ⁻⁷	0.296	0.338	1.22	0.00076	0.362	0.422	1.29	3.2×10 ⁻⁵	0.654	0.674	1.06	0.43	0.674	1.06
rs1569699	C	20787289	1.19 (1.12-1.27)	1.4×10 ⁻⁷	0.257	0.297	1.22	0.00018	0.463	0.519	1.25	0.00019	0.627	0.656	1.10	0.17	0.656	1.10
rs7756992	G	20787688	1.17 (1.09-1.25)	3.1×10 ⁻⁶	0.232	0.270	1.23	0.00023	0.462	0.517	1.25	0.00018	0.612	0.625	1.02	0.72	0.625	1.02
rs9350271	A	20791143	1.18 (1.11-1.26)	9.6×10 ⁻⁷	0.257	0.298	1.23	0.00016	0.356	0.406	1.23	0.00055	0.695	0.712	1.07	0.38	0.712	1.07
rs9356744	C	20793465	1.18 (1.11-1.26)	7.9×10 ⁻⁷	0.256	0.297	1.23	0.00014	0.357	0.407	1.24	0.00045	0.696	0.713	1.06	0.39	0.713	1.06
rs9368222	A	20794975	1.20 (1.12-1.28)	4.8×10 ⁻⁷	0.231	0.269	1.22	0.00029	0.355	0.405	1.24	0.00041	0.184	0.203	1.10	0.27	0.203	1.10
rs10440833	A	20796100	1.18 (1.11-1.27)	1.4×10 ⁻⁶	0.233	0.269	1.22	0.00046	0.354	0.407	1.25	0.00024	0.213	0.226	1.06	0.48	0.226	1.06
rs6931514	G	20811931	1.19 (1.11-1.27)	7.8×10 ⁻⁷	0.231	0.267	1.22	0.00047	0.464	0.520	1.25	0.00015	0.231	0.249	1.07	0.41	0.249	1.07

^aResults for the three groups were combined using a Mantel-Haenszel model. ^bBasepair position in NCBI Build 34. ^cResults for the five West-African groups were combined using Mantel-Haenszel model and the allele frequencies shown are a weighted average of the frequency for the five groups.

Table 19. Pair-wise correlation for SNP's typed in CDKAL1.

Pair-wise correlation, D' (lower left corner) and r^2 (upper right corner), for the eight SNP's in *CDKAL1* that were tested for association to T2D. The correlation is estimated for control individuals from the Icelandic, Hong Kong and West-African study groups, respectively.

$D' \backslash r^2$	rs7752906	rs1569699	rs7756992	rs9350271	rs9356744	rs9368222	rs10440833	rs6931514
Iceland								
rs7752906	-	0.55	0.66	0.56	0.56	0.67	0.66	0.65
rs1569699	0.83	-	0.87	0.99	0.98	0.85	0.83	0.83
rs7756992	0.98	1.00	-	0.86	0.86	0.99	0.97	0.96
rs9350271	0.84	1.00	1.00	-	1.00	0.86	0.85	0.84
rs9356744	0.84	1.00	1.00	1.00	-	0.87	0.86	0.85
rs9368222	0.99	1.00	1.00	1.00	1.00	-	0.98	0.97
rs10440833	0.96	0.97	1.00	0.98	0.99	1.00	-	0.99
rs6931514	0.96	0.97	0.99	0.98	0.99	0.99	1.00	-
Hong Kong								
rs7752906	-	0.45	0.46	0.77	0.76	0.77	0.77	0.46
rs1569699	0.84	-	0.99	0.63	0.63	0.62	0.62	0.98
rs7756992	0.84	1.00	-	0.63	0.62	0.64	0.64	0.99
rs9350271	0.89	1.00	0.99	-	1.00	0.99	0.99	0.62
rs9356744	0.88	0.99	0.99	1.00	-	0.99	0.99	0.62
rs9368222	0.89	0.99	1.00	1.00	1.00	-	1.00	0.63
rs10440833	0.89	1.00	1.00	1.00	1.00	1.00	-	0.63
rs6931514	0.84	0.99	1.00	0.99	0.99	1.00	1.00	-
West-Africa								
rs7752906	-	0.16	0.32	0.13	0.14	0.12	0.07	0.08
rs1569699	0.42	-	0.61	0.72	0.72	0.12	0.07	0.09
rs7756992	0.62	0.84	-	0.67	0.67	0.14	0.08	0.10
rs9350271	0.40	0.96	0.99	-	0.99	0.10	0.04	0.05
rs9356744	0.41	0.96	1.00	1.00	-	0.10	0.04	0.06
rs9368222	1.00	0.96	0.95	1.00	1.00	-	0.86	0.76
rs10440833	0.68	0.68	0.68	0.59	0.60	1.00	-	0.87
rs6931514	0.73	0.72	0.73	0.63	0.65	0.99	1.00	-

Table 20. Genotype specific odds ratio for rs7756992 and rs13266634.

Study population	Allelic		Genotype odds ratio ^a		<i>P</i> ^b
Variant (allele)	OR (95% CI)	00	0X (95% CI)	XX (95% CI)	
Caucasian					
rs7756992 (G)	1.16 (1.09-1.22)	1	1.09 (1.03-1.16)	1.45 (1.31-1.61)	0.00052
rs13266634 (C)	1.15 (1.11-1.20)	1	1.12 (1.03-1.23)	1.30 (1.18-1.43)	0.63
Hong Kong					
rs7756992 (G)	1.25 (1.11-1.40)	1	1.13 (0.97-1.31)	1.55 (1.23-1.95)	0.071
rs13266634 (C)	1.19 (1.06-1.33)	1	1.13 (0.96-1.34)	1.40 (1.11-1.76)	0.43

^aGenotype odds ratio for heterozygous (0X) and homozygous carrier (XX) compared with non-carriers (00). ^bTest of the multiplicative model (the null hypotheses) versus the full model, one degree of freedom.

Table 21. Association to insulin secretion and insulin sensitivity.

Association of the risk variants rs7756992 (G) and rs13266634 (C) to insulin secretion, estimated by corrected insulin response (CIR), and insulin sensitivity estimated the reciprocal of HOMA (homeostasis model assessment). The table includes number of T2D cases (*n*) and controls (*m*) used, the estimated effect and standard error and the *P* value obtained by regressing the log-transformed trait values on age, sex and either the number of risk alleles an individual carries (additive model) or an indicator variable for homozygous carriers of the risk allele (recessive model). When controls and T2D cases are analysed together an indicator variable for the affection status is included in the analysis. Also shown, for the combined group, is the corresponding *P* value obtained by adjusting for BMI status of the individuals in the analysis.

Trait	Analysis		Combined group			Controls		T2D	
	Group	(n/m)	Effect (se)	P	P ^a	Effect (se)	P	Effect (se)	P
Insulin Response (CIR)	rs7756992 (add)								
	All	(3715/223)	-0.083 (0.018)	4.0E-06	9.1E-06	-0.080 (0.018)	1.3E-05	-0.142 (0.095)	0.14
	Males	(1742/139)	-0.056 (0.025)	0.025	0.042	-0.058 (0.025)	0.021	-0.028 (0.119)	0.82
	Females	(1973/84)	-0.100 (0.025)	6.8E-05	0.00012	-0.088 (0.025)	0.00049	-0.342 (0.144)	0.02
	rs7756992 (rec)								
	All	(3715/223)	-0.243 (0.041)	3.3E-09	4.9E-09	-0.230 (0.042)	3.7E-08	-0.417 (0.199)	0.037
	Males	(1742/139)	-0.225 (0.055)	4.9E-05	0.00014	-0.222 (0.056)	7.5E-05	-0.250 (0.250)	0.32
	Females	(1973/84)	-0.232 (0.059)	7.5E-05	7.6E-05	-0.204 (0.060)	0.00063	-0.696 (0.301)	0.023
	rs13266634 (add)								
HOMA	All	(3698/228)	-0.061 (0.017)	0.0005	0.00056	-0.059 (0.018)	0.00075	-0.083 (0.094)	0.38
	Males	(1736/143)	-0.079 (0.024)	0.0011	0.00091	-0.062 (0.024)	0.011	-0.262 (0.109)	0.017
	Females	(1962/85)	-0.048 (0.024)	0.047	0.052	-0.058 (0.024)	0.016	0.233 (0.166)	0.16
	rs7756992 (add)								
HOMA	All	(4430/1164)	-0.013 (0.013)	0.33	0.7	0.002 (0.013)	0.85	-0.065 (0.038)	0.082
	Males	(2062/691)	-0.002 (0.019)	0.94	0.51	0.022 (0.020)	0.26	-0.070 (0.049)	0.15
	Females	(2368/473)	-0.026 (0.018)	0.14	0.22	-0.018 (0.018)	0.31	-0.061 (0.059)	0.3

rs13266634 (add)							
All (4411/1166)	-0.015 (0.013)	0.24	0.19	-0.013 (0.013)	0.31	-0.024 (0.039)	0.55
Males (2058/697)	-0.003 (0.019)	0.88	0.81	-0.010 (0.019)	0.61	0.019 (0.050)	0.7
Females (2353/469)	-0.028 (0.017)	0.11	0.087	-0.016 (0.017)	0.34	-0.092 (0.063)	0.14

^a P value after adjusting for BMI by including a log(BMI) term among the explanatory variables.

Table 22. Surrogate markers for marker rs7756992 on chromosome 6. The table shows markers with values for r^2 of greater than 0.2 in the HapMap Caucasian CEPH samples. The search was performed over a 2Mb region flanking rs77566992 (1Mb upstream and 1Mb downstream).

Surrogates for rs7756992 on chromosome 6				
SNP	D'	R2	Pos B36	Pos SEQ ID NO:1
rs9460517	0.82	0.30	20636813	1818
rs7772956	0.72	0.29	20637521	2526
rs6904566	0.73	0.32	20643949	8954
rs6927356	0.73	0.32	20644073	9078
rs6905138	0.73	0.32	20644335	9340
rs13194858	0.73	0.32	20644499	9504
rs6456356	1.00	0.22	20649498	14503
rs9366354	0.84	0.40	20653447	18452
rs9368201	0.84	0.41	20654091	19096
rs9348433	0.84	0.40	20657780	22785
rs13203450	0.73	0.32	20673935	38940
rs1012626	0.82	0.39	20685540	50545
rs9460523	0.55	0.23	20690122	55127
rs9350262	0.55	0.23	20692402	57407
rs4712507	0.56	0.24	20693119	58124
rs9366357	0.56	0.23	20707607	72612
rs1997777	1.00	0.22	20710359	75364
rs11964057	0.56	0.23	20710776	75781
rs12206413	1.00	0.22	20715663	80668
rs4515379	0.66	0.20	20735420	100425
rs9465841	0.66	0.20	20737687	102692
rs13190734	0.62	0.31	20738376	103381
rs2328528	0.67	0.21	20739524	104529
rs2328529	0.67	0.21	20739932	104937
rs7768642	0.67	0.21	20741886	106891
rs9465846	0.67	0.21	20742320	107325
rs9465847	0.67	0.21	20742407	107412
rs7755830	1.00	0.32	20742865	107870
rs6940200	0.67	0.21	20743241	108246
rs9465850	0.67	0.22	20747388	112393
rs4710938	1.00	0.34	20748883	113888
rs9348440	0.79	0.23	20749315	114320
rs4235999	1.00	0.33	20751201	116206
rs4710939	1.00	0.35	20752923	117928
rs11965062	1.00	0.33	20755941	120946
rs9460540	1.00	0.33	20756741	121746
rs6456364	0.79	0.23	20757233	122238
rs9295474	0.95	0.68	20760696	125701
rs2328545	0.79	0.23	20761529	126534
rs9368216	0.79	0.23	20763089	128094
rs16884072	0.66	0.33	20763482	128487
rs9460541	0.66	0.33	20764559	129564
rs9460542	0.66	0.33	20764746	129751
rs4712522	0.95	0.68	20764779	129784
rs16884074	0.66	0.32	20764924	129929

rs4712523	0.95	0.68	20765543	130548
rs4710940	0.95	0.52	20765991	130996
rs13190727	0.66	0.33	20766197	131202
rs6906327	0.95	0.52	20767438	132443
rs6456367	0.95	0.68	20767566	132571
rs6456368	0.95	0.67	20767785	132790
rs7749083	0.66	0.33	20768202	133207
rs6456369	0.95	0.52	20768344	133349
rs13203361	0.66	0.33	20769000	134005
rs10946398	0.95	0.68	20769013	134018
rs7774594	0.95	0.67	20769122	134127
rs7754840	0.95	0.68	20769229	134234
rs9460544	0.95	0.68	20769508	134513
rs9460545	0.95	0.68	20769529	134534
rs979614	1.00	0.34	20770102	135107
rs4712525	0.95	0.68	20770945	135950
rs4712526	0.95	0.68	20771014	136019
rs9460546	0.95	0.68	20771611	136616
rs736425	0.66	0.33	20772291	137296
rs742642	0.79	0.23	20773060	138065
rs7748382	0.95	0.68	20773528	138533
rs7772603	0.95	0.68	20773925	138930
rs7752780	0.95	0.68	20774001	139006
rs7752906	0.95	0.70	20774034	139039
rs11970425	0.66	0.33	20774436	139441
rs9358356	0.95	0.67	20775361	140366
rs9356743	0.79	0.23	20775667	140672
rs9368219	1.00	0.53	20782670	147675
rs1012635	1.00	0.42	20783274	148279
rs1569699	1.00	0.72	20787289	152294
rs9350271	1.00	0.78	20791143	156148
rs9356744	1.00	0.75	20793465	158470
rs7766070	1.00	1.00	20794552	159557
rs9368222	1.00	1.00	20794975	159980
rs10440833	1.00	1.00	20796100	161105
rs2206734	1.00	0.53	20802863	167868
rs6931514	1.00	1.00	20811931	176936
rs11753081	1.00	0.53	20813569	178574
rs1040558	1.00	0.53	20821685	186690
rs9295478	0.62	0.30	20824232	189237
rs2328548	1.00	0.53	20824937	189942
rs6935599	1.00	0.53	20825074	190079
rs9465871	1.00	0.53	20825234	190239
rs10946403	1.00	0.53	20825383	190388
rs2328549	1.00	0.30	20826219	191224
rs9358357	1.00	0.53	20827124	192129
rs9368224	1.00	0.53	20827211	192216
rs9358358	1.00	0.30	20827372	192377
rs9460550	1.00	0.53	20827540	192545
rs9356746	1.00	0.30	20828258	193263
rs9368226	1.00	0.50	20831036	196041
rs12111351	0.61	0.29	20832537	197542
rs9356747	0.60	0.29	20832986	197991
rs9356748	1.00	0.30	20833076	198081
rs7767391	1.00	0.50	20833219	198224
rs7747752	0.62	0.30	20833402	198407
rs17234378	0.80	0.24	20952720	

Table 23. Surrogate markers for marker rs10882091 on chromosome 10. The table shows markers with values for r^2 of greater than 0.2 in the HapMap Caucasian CEPH samples. The search was performed over a 2Mb region flanking rs10882091 (1Mb upstream and 1Mb downstream).

Surrogates for rs10882091 on chromosome 10				
SNP	D'	R2	Pos B36	Pos SEQ ID NO:2
rs7086285	0.71	0.23	94166068	
rs2798253	0.93	0.32	94192885	1
rs6583813	1.00	0.33	94199919	7035
rs11187007	1.00	0.35	94204560	11676
rs2149632	1.00	0.35	94222227	29343
rs11187025	0.95	0.48	94247956	55072
rs11187033	1.00	0.35	94252339	59455
rs10509645	1.00	0.35	94267846	74962
rs7078413	0.49	0.23	94280464	87580
rs4646955	0.75	0.37	94284271	91387
rs17445328	0.68	0.32	94295169	102285
rs11187064	0.68	0.31	94298233	105349
rs2421943	1.00	0.45	94301795	108911
rs11187065	0.95	0.48	94301904	109020
rs11187078	1.00	0.35	94330685	137801
rs6583823	1.00	0.52	94334395	141511
rs2421941	0.96	0.93	94335889	143005
rs6583826	0.95	0.57	94337810	144926
rs3824735	1.00	0.36	94344184	151300
rs10786050	1.00	1.00	94357210	164326
rs11187094	1.00	0.21	94358158	165274
rs11187096	1.00	0.35	94359568	166684
rs7914814	1.00	1.00	94372930	180046
rs12772554	1.00	0.23	94373838	180954
rs10882094	1.00	1.00	94377656	184772
rs10882095	1.00	0.37	94384382	191498
rs10736069	1.00	1.00	94385373	192489
rs7900689	1.00	1.00	94385728	192844
rs6583830	1.00	1.00	94388098	195214
rs10882096	1.00	0.35	94391366	198482
rs11187114	1.00	0.36	94396217	203333
rs6583833	1.00	0.76	94399780	206896
rs7078243	1.00	0.78	94404243	211359
rs4933734	1.00	1.00	94404547	211663
rs7911264	1.00	0.73	94426831	233947
rs2488087	1.00	0.74	94436021	243137
rs10882100	1.00	0.74	94450667	257783
rs1111875	1.00	0.51	94452862	259978
rs12778642	1.00	0.55	94454287	261403
rs5015480	1.00	0.51	94455539	262655
rs10882102	1.00	0.52	94456475	263591
rs11187144	1.00	0.40	94459960	267076
rs7087591	1.00	0.39	94463609	270725
rs10748582	1.00	0.39	94467199	274315
rs7923837	1.00	0.39	94471897	279013
rs7923866	1.00	0.39	94472056	279172
rs2497306	1.00	0.58	94475191	282307
rs2488075	1.00	0.60	94480154	287270
rs2497304	0.96	0.63	94482696	289812

rs947591	0.81	0.57	94485733	292849
rs2488071	0.62	0.24	94489557	296673

Table 24. Surrogate markers for marker rs2191113 on chromosome 17. The table shows markers with values for r^2 of greater than 0.2 in the HapMap Caucasian CEPH samples. The search was performed over a 2Mb region flanking rs2191113 (1Mb upstream and 1Mb downstream).

Surrogates for rs2191113 on chromosome 17				
SNP	D'	R2	Pos B36	Pos SEQ ID NO:3
rs350605	0.82	0.54	66044207	6552
rs350603	0.80	0.22	66045245	7590
rs420762	0.80	0.24	66049716	12061
rs350615	0.86	0.58	66067303	29648
rs350616	0.81	0.25	66067699	30044
rs350621	0.86	0.58	66079419	41764
rs350624	0.86	0.58	66080067	42412
rs12602288	1.00	0.36	66085473	47818
rs1431454	0.82	0.26	66090535	52880
rs9302918	1.00	0.23	66091912	54257
rs9302919	0.81	0.26	66092080	54425
rs9911671	0.86	0.61	66094196	56541
rs1911969	0.86	0.60	66102315	64660
rs9894021	1.00	0.21	66103236	65581
rs720877	1.00	0.23	66103561	65906
rs720876	1.00	0.23	66103923	66268
rs7218838	0.86	0.61	66106415	68760
rs9896809	1.00	0.21	66106911	69256
rs7220084	0.82	0.26	66114858	77203
rs1860316	0.86	0.61	66117911	80256
rs8079029	0.90	0.62	66118485	80830
rs4019476	0.87	0.63	66122077	84422
rs1981647	0.82	0.26	66132788	95133
rs9890554	0.80	0.21	66134831	97176
rs10221225	0.80	0.22	66138452	100797
rs11650683	0.84	0.22	66139800	102145
rs1486290	0.82	0.27	66141933	104278
rs8078302	0.85	0.23	66143200	105545
rs12949591	1.00	0.20	66146912	109257
rs1843622	1.00	0.61	66149102	111447
rs9891997	1.00	0.28	66152998	115343
rs9910837	1.00	0.28	66155303	117648
rs4793497	0.94	0.58	66163076	125421
rs9890889	0.89	0.24	66173475	
rs2009802	0.71	0.23	66178475	
rs17718938	1.00	0.28	66184700	
rs17223216	0.89	0.24	66207685	
rs2109050	0.89	0.24	66228633	
rs1962801	1.00	0.31	66236090	

CLAIMS

1. A method of determining a susceptibility to Type 2 diabetes in a human individual,
5 comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the markers set forth in Tables 10-12, and markers in linkage disequilibrium therewith, and wherein determination of the presence or absence of the at least one allele is
10 indicative of a susceptibility to Type 2 diabetes.
2. The method of Claim 1, wherein the at least one polymorphic marker is present within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.
3. The method of Claim 1 or 2, wherein the at least one polymorphic marker comprises at least one marker selected from rs2497304 (SEQ ID NO:16),
15 rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514
20 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith.
4. The method of any of the preceding Claims, wherein the at least one polymorphic marker comprises at least one marker in strong linkage disequilibrium, as defined
25 by numeric values for $|D' |$ of greater than 0.8 and/or r^2 of greater than 0.2, with one or more markers selected from the group consisting of the markers set forth in Table 22, Table 23 and Table 24.
5. The method of any of the preceding Claims, wherein the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID
30 NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), and markers in linkage disequilibrium therewith.
6. The method of Claim 5, wherein the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992
35 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34),

rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), and rs6931514 (SEQ ID NO:37).

7. The method of Claim 1, wherein the at least one marker is selected from marker rs7756992 (SEQ ID NO: 21), and markers in linkage disequilibrium therewith.
- 5 8. The method of Claim 7, wherein the at least one markers is selected from the markers set forth in Table 22.
9. The method of Claim 1, wherein the at least one marker is selected from marker rs10882091 (SEQ ID NO: 4), and markers in linkage disequilibrium therewith.
- 10 10. The method of Claim 9, wherein the at least one markers is selected from the markers set forth in Table 23.
11. The method of Claim 1, wherein the at least one marker is selected from marker rs2191113 (SEQ ID NO: 13), and markers in linkage disequilibrium therewith.
12. The method of Claim 11, wherein the at least one markers is selected from the markers set forth in Table 24.
- 15 13. The method of any of the preceding Claims, further comprising assessing the frequency of at least one haplotype in the individual.
14. The method of any of the preceding claims, wherein the presence of at least one at-risk allele of at least one polymorphic marker in a nucleic acid sample from the individual is indicative of an increased susceptibility to Type 2 diabetes.
- 20 15. The method of claim 14, wherein the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.15.
16. The method of Claim 14 or 15, wherein the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.20.
- 25 17. The method of any of the claims 14-16, wherein the presence of rs2497304 allele A, rs947591 allele A, rs10882091 allele C rs7914814 allele T, rs6583830 allele A, rs2421943 allele G, rs6583826 allele G, rs7752906 allele A, rs1569699 allele C, rs7756992 allele G, rs9350271 allele A, rs9356744 allele C, rs9368222 allele A, rs10440833 allele A, rs6931514 allele G, rs1860316 allele A, rs1981647 allele C, rs1843622 allele T, rs2191113 allele A, and/or rs9890889 allele A is indicative of
30 increased susceptibility of Type 2 diabetes.

18. The method of any of the claims 1-13, wherein the presence of at least one protective allele in a nucleic acid sample from the individual is indicative of a decreased susceptibility of Type 2 diabetes.
- 5 19. The method of any of the claims 1-13, wherein the absence of at least one at-risk allele in a nucleic acid sample from the individual is indicative of a decreased susceptibility of Type 2 diabetes.
20. The method of any of the preceding claims, wherein the at least one marker or haplotype is further associated with insulin response and/or impaired glucose tolerance in the individual.
- 10 21. The method of any of the Claims 14-17, wherein determination of the presence of at least one allele or haplotype in an at-risk marker is indicative of an increased susceptibility to Type 2 diabetes, and wherein the at least one allele or haplotype is further indicative of decreased insulin response and/or impaired glucose tolerance.
- 15 22. The method of any of the preceding claims, wherein linkage disequilibrium is characterized by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2.
- 20 23. A method of assessing a susceptibility to Type 2 diabetes in a human individual, comprising screening a nucleic acid from the individual for at least one polymorphic marker or haplotype in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, that correlates with increased occurrence of Type 2 diabetes in a human population,

wherein the presence of an at-risk marker allele in the at least one polymorphism or an at-risk haplotype in the nucleic acid identifies the individual as having elevated susceptibility to diabetes, and

wherein the absence of the at least one at-risk marker allele or at-risk haplotype in the nucleic acid identifies the individual as not having the elevated susceptibility.
- 25 24. The method of Claim 23, wherein the polymorphism or haplotype is selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699
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- (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, as characterized by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2.
- 5
25. The method of any of the preceding Claims, further comprising screening the nucleic acid for the presence of at least one at-risk genetic variant for Type 2
- 10 diabetes not associated with LD Block C06 (SEQ ID NO:1), LD Block C10 (SEQ ID NO:2) and LD Block C17 (SEQ ID NO:3).
26. The method of Claim 25, comprising screening the nucleic acid for the presence or absence of at least one at-risk allele of at least one at-risk variant for Type 2
- 15 diabetes in the TCF7L2 gene, wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility of Type 2 diabetes.
26. The method of Claim 25, wherein the at least one at-risk variant in the TCF7L2 gene is selected from marker DG10S478, rs12255372, rs7895340, rs11196205, rs7901695, rs7903146, rs12243326 and rs4506565, and markers in linkage disequilibrium therewith.
- 20 27. The method of any of the preceding Claims wherein the presence of the marker or haplotype is indicative of a different response rate of the subject to a particular treatment modality for Type 2 diabetes.
28. The method of any of the preceding claims, wherein the individual is of a specific human ancestry.
- 25 29. The method of Claim 28, wherein the ancestry is selected from black African ancestry, Caucasian ancestry and Chinese ancestry.
30. The method of Claim 28 or 29, wherein the ancestry is black African ancestry.
31. The method of Claim 28, wherein the ancestry is European ancestry.
32. The method of Claim 28 or 29, wherein the ancestry is Caucasian ancestry.
- 30 33. The method of any of the Claims 28-32, wherein the ancestry is self-reported.
34. The method of any of the Claims 28-32, wherein the ancestry is determined by genetic determination comprising detecting at least one allele of at least one

polymorphic marker in a nucleic acid sample from the individual, wherein the presence or absence of the allele is indicative of the ancestry of the individual.

35. The method of any of the preceding Claims, wherein the individual is obese.

36. The method of any of the claims 1-34, wherein the individual is non-obese.

5 37. A method of identification of a marker for use in assessing susceptibility to Type 2 diabetes in human individuals, the method comprising

a. identifying at least one polymorphic marker within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, or at least one polymorphic marker in linkage disequilibrium therewith;

10 b. determining the genotype status of a sample of individuals diagnosed with, or having a susceptibility to, Type 2 diabetes; and

c. determining the genotype status of a sample of control individuals;

15 wherein a significant difference in frequency of at least one allele in at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing susceptibility to Type 2 diabetes.

38. The method of Claim 37, wherein linkage disequilibrium is characterized by numerical values of r^2 of greater than 0.2 and/or $|D'|$ of greater than 0.8.

20 39. The method of Claim 37, wherein the at least one polymorphic marker is in linkage disequilibrium, as characterized by numerical values of r^2 of greater than 0.2 and/or $|D'|$ of greater than 0.8 with at least one marker selected from marker rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13),
25
30 rs9890889 (SEQ ID NO:31).

40. The method of any of the Claims 37 - 39, wherein an increase in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of

the at least one allele in the control sample, is indicative of the at least one polymorphism being useful for assessing increased susceptibility to Type 2 diabetes.

41. The method of any of the Claims 37 - 39, wherein a decrease in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, Type 2 diabetes, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing decreased susceptibility to, or protection against, Type 2 diabetes.
42. A method of genotyping a nucleic acid sample obtained from a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in the sample, wherein the at least one marker is selected rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, and wherein determination of the presence or absence of the at least one allele of the at least one polymorphic marker is predictive of a susceptibility of Type 2 diabetes.
43. The method of Claim 41 or 42, wherein linkage disequilibrium is determined by numerical values for r^2 of at least 0.2 and/or numerical values of $|D'|$ of at least 0.8.
44. The method of any of the Claims 41 - 43, wherein genotyping comprises amplifying a segment of a nucleic acid that comprises the at least one polymorphic marker by Polymerase Chain Reaction (PCR), using a nucleotide primer pair flanking the at least one polymorphic marker.
45. The method of any of the Claims 41 - 44, wherein genotyping is performed using a process selected from allele-specific probe hybridization, allele-specific primer extension, allele-specific amplification, nucleic acid sequencing, 5'-exonuclease digestion, molecular beacon assay, oligonucleotide ligation assay, size analysis, and single-stranded conformation analysis.

46. The method of Claim 45, wherein the process comprises allele-specific probe hybridization.
47. The method of Claim 45, wherein the process comprises DNA sequencing.
48. The method according to any of the Claims 45-47, comprising:
- 5 1. contacting copies of the nucleic acid with a detection oligonucleotide probe and an enhancer oligonucleotide probe under conditions for specific hybridization of the oligonucleotide probe with the nucleic acid;
- wherein
- 10 a) the detection oligonucleotide probe is from 5-100 nucleotides in length and specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site;
- b) the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;
- 15 c) the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid; and
- 20 d) a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides;
- 25 2. treating the nucleic acid with an endonuclease that will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid; and
3. measuring free detectable label, wherein the presence of the free detectable label indicates that the detection probe specifically hybridizes to the first segment of the nucleic acid, and indicates the sequence of the polymorphic site as the complement of the detection probe.
- 30
49. The method of Claim 48, wherein the copies of the nucleic acid are provided by amplification by Polymerase Chain Reaction (PCR)

50. The method of any of the Claims 37 - 49, wherein the susceptibility is increased susceptibility.
51. The method of any of the Claims 37 - 49, wherein the susceptibility is decreased susceptibility.
- 5 52. The method of any of the Claims 37 - 50, wherein the individual is of a specific human ancestry.
53. The method of Claim 52, wherein the ancestry is selected from black African ancestry, Caucasian ancestry and Chinese ancestry.
54. The method of Claim 52 or 53, wherein the ancestry is black African ancestry.
- 10 55. The method of Claim 52, wherein the ancestry is European ancestry.
56. The method of Claim 52 or 53, wherein the ancestry is Caucasian ancestry.
57. The method of any of the Claims 52 - 56, wherein the ancestry is self-reported.
58. The method of any of the Claims 52 - 56, wherein the ancestry is determined by genetic determination comprising detecting at least one allele of at least one polymorphic marker in a nucleic acid sample from the individual, wherein the presence or absence of the allele is indicative of the ancestry of the individual.
- 15 59. The method of any of the Claims 37 - 58, wherein the human individual is obese.
60. The method of any of the claims 37 - 58, wherein the individual is non-obese.
61. A method of assessing an individual for probability of response to a therapeutic agent for preventing and/or ameliorating symptoms associated with Type 2 diabetes, comprising: determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele of the at least one
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marker is indicative of a probability of a positive response to the Type 2 diabetes therapeutic agent.

62. The method of Claim 61, wherein the Type 2 diabetes therapeutic agent is selected from the agents set forth in Agent Table 1 and Agent Table 2.
- 5 63. A method of predicting prognosis of an individual diagnosed with, Type 2 diabetes, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20),
10 rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10),
15 rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele is indicative of a worse prognosis of the Type 2 diabetes in the individual.
- 20 64. A method of monitoring progress of a treatment of an individual undergoing treatment for Type 2 diabetes, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11),
25 rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele is indicative of the treatment outcome of the individual.
- 30 65. The method of any of the Claims 61 - 64, wherein linkage disequilibrium is defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8
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66. The method of any of the preceding Claims, further comprising assessing at least one biomarker in a sample from the individual.
67. The method of any of the preceding Claims, further comprising analyzing non-genetic information to make risk assessment, diagnosis, or prognosis of the individual.
68. The method of Claim 67, wherein the non-genetic information is selected from age, gender, ethnicity, socioeconomic status, previous disease diagnosis, medical history of subject, family history of Type 2 diabetes, biochemical measurements, and clinical measurements.
69. The method of any of the Claims 66 - 68, further comprising calculating overall risk.
70. A kit for assessing susceptibility to Type 2 diabetes in a human individual, the kit comprising reagents for selectively detecting the presence or absence of at least one allele of at least one polymorphic marker in the genome of the individual, wherein the polymorphic marker is selected from the group consisting of polymorphic markers within the nucleic acid segments whose sequences are set forth in SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3, and markers in linkage disequilibrium therewith, and wherein the presence of the at least one allele is indicative of a susceptibility to Type 2 diabetes.
71. The kit of Claim 70, wherein the at least one polymorphic marker is selected from the group of markers set forth in Tables 10 - 12, and markers in linkage disequilibrium therewith.
72. The kit of Claim 70 or 71, wherein the at least one polymorphic markers is selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith.
73. The kit of any of the Claims 69 - 72, wherein linkage disequilibrium is defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8.

74. The kit of any of the Claims 70 - 73, wherein the reagents comprise at least one contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising the at least one polymorphic marker, a buffer and a detectable label.
- 5 75. The kit of any of the Claims 70 - 74, wherein the reagents comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic nucleic acid segment obtained from the subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes one polymorphic marker, and wherein the fragment is at least 30 base
10 pairs in size.
76. The kit of Claim 74 or 75, wherein the at least one oligonucleotide is completely complementary to the genome of the individual.
77. The kit of any of the Claims 74 - 76, wherein the oligonucleotide is about 18 to about 50 nucleotides in length.
- 15 78. The kit of any of the Claims 74 - 77, wherein the oligonucleotide is 20-30 nucleotides in length.
79. The kit of any of the Claims 70 - 78, wherein the kit comprises:
- a. a detection oligonucleotide probe that is from 5-100 nucleotides in length;
 - b. an enhancer oligonucleotide probe that is from 5-100 nucleotides in
20 length; and
 - c. an endonuclease enzyme;
- wherein the detection oligonucleotide probe specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site; and
- 25 wherein the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;
- wherein the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3'
30 relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid;

wherein a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides; and

5 wherein treating the nucleic acid with the endonuclease will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid.

80. Use of an oligonucleotide probe in the manufacture of a diagnostic reagent for diagnosing and/or assessing susceptibility to Type 2 diabetes in a human
10 individual, wherein the probe hybridizes to a segment of a nucleic acid whose nucleotide sequence is given by SEQ ID NO: 1, SEQ ID NO:2 or SEQ ID NO:3 that comprises at least one polymorphic site, wherein the fragment is 15-500 nucleotides in length.

81. The use according to Claim 80, wherein the polymorphic site is selected from the
15 polymorphic markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21),
20 rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and polymorphisms in linkage disequilibrium therewith.

82. A computer-readable medium on which is stored:
25 a. an identifier for at least one polymorphic marker;
b. an indicator of the frequency of at least one allele of said at least one polymorphic marker in a plurality of individuals diagnosed with Type 2 diabetes; and
c. an indicator of the frequency of the least one allele of said at least one
30 polymorphic markers in a plurality of reference individuals;

wherein the at least one polymorphic marker is selected from the polymorphic markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID

- NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and polymorphisms in linkage disequilibrium therewith, as defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8.
- 5
83. The medium of Claim 82, further comprising information about the ancestry of the plurality of individuals.
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84. The medium of Claim 82 or 83, wherein the plurality of individuals diagnosed with Type 2 diabetes and the plurality of reference individuals is of a specific ancestry.
85. An apparatus for determining a genetic indicator for Type 2 diabetes in a human individual, comprising:
- a computer readable memory; and
- 15 a routine stored on the computer readable memory;
- wherein the routine is adapted to be executed on a processor to analyze marker and/or haplotype information for at least one human individual with respect to at least one polymorphic marker selected from the markers rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith, as defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8, and generate an output based on the marker or haplotype information, wherein the output comprises a risk measure of the at least one marker or haplotype as a genetic indicator of Type 2 diabetes for the human individual.
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- 25
- 30
86. The apparatus of Claim 85, wherein the routine further comprises an indicator of the frequency of at least one allele of at least one polymorphic marker or at least one haplotype in a plurality of individuals diagnosed with Type 2 diabetes, and an indicator of the frequency of at the least one allele of at least one polymorphic marker or at least one haplotype in a plurality of reference individuals, and
- 35

wherein a risk measure is based on a comparison of the at least one marker and/or haplotype status for the human individual to the indicator of the frequency of the at least one marker and/or haplotype information for the plurality of individuals diagnosed with Type 2 diabetes.

- 5 87. The apparatus of Claim 85 or 86, wherein the risk measure is characterized by an Odds Ratio (OR) or a Relative Risk (RR).
88. A method of determining a susceptibility to Type 2 diabetes in a human individual, comprising determining whether at least one at-risk allele in at least one polymorphic marker is present in a genotype dataset derived from the individual,
 - 10 wherein the at least one polymorphic marker is selected from the markers set forth in Tables 10-12, and markers in linkage disequilibrium therewith, and wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility to Type 2 diabetes in the individual.
89. The method of Claim 88, wherein the at least one polymorphic marker is present
 - 15 within SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.
90. The method of Claim 88 or 89, wherein the at least one polymorphic marker comprises at least one marker selected from rs2497304 (SEQ ID NO:16), rs947591 (SEQ ID NO:30), rs10882091 (SEQ ID NO:4), rs7914814 (SEQ ID NO:24), rs6583830 (SEQ ID NO:20), rs2421943 (SEQ ID NO:15), rs6583826
 - 20 (SEQ ID NO:19), rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514 (SEQ ID NO:37), rs1860316 (SEQ ID NO:10), rs1981647 (SEQ ID NO:11), rs1843622 (SEQ ID NO:9), rs2191113 (SEQ ID NO:13), rs9890889 (SEQ ID NO:31), and markers in linkage disequilibrium therewith.
 - 25
91. The method of any of the Claims 88 -90, wherein the at least one polymorphic marker comprises at least one marker in strong linkage disequilibrium, as defined by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2, with one or more markers selected from the group consisting of the markers set forth
 - 30 in Table 22, Table 23 and Table 24.
92. The method of any of the Claims 88 - 91, wherein the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), rs6931514
 - 35 (SEQ ID NO:37), and markers in linkage disequilibrium therewith.

- 5 93. The method of Claim 92, wherein the at least one polymorphic marker is selected from markers rs7752906 (SEQ ID NO:32), rs1569699 (SEQ ID NO:6), rs7756992 (SEQ ID NO:21), rs9350271 (SEQ ID NO:33), rs9356744 (SEQ ID NO:34), rs9368222 (SEQ ID NO:35), rs10440833 (SEQ ID NO:36), and rs6931514 (SEQ ID NO:37).
94. The method of Claim 88, wherein the at least one polymorphic marker is selected from marker rs7756992 (SEQ ID NO: 21), and markers in linkage disequilibrium therewith.
- 10 95. The method of Claim 94, wherein the at least one polymorphic marker is selected from the markers set forth in Table 22.
96. The method of Claim 88, wherein the at least one marker is selected from marker rs10882091 (SEQ ID NO: 4), and markers in linkage disequilibrium therewith.
97. The method of Claim 96, wherein the at least one markers is selected from the markers set forth in Table 23.
- 15 98. The method of Claim 88, wherein the at least one marker is selected from marker rs2191113 (SEQ ID NO: 13), and markers in linkage disequilibrium therewith.
99. The method of Claim 98, wherein the at least one markers is selected from the markers set forth in Table 24.
- 20 100. The method of any of the Claims 88 - 99, further comprising assessing the frequency of at least one at-risk haplotype in the individual, and wherein determination of the presence of the at-risk haplotype is indicative of increased susceptibility of Type 2 diabetes.
101. The method of any of the Claims 88 - 100, wherein the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.15.
- 25 102. The method of any of the Claims 88 - 101, wherein the increased susceptibility is characterized by a relative risk (RR) or odds ratio (OR) of at least 1.20.
- 30 103. The method of any of the claims 88- 102, wherein the presence of rs2497304 allele A, rs947591 allele A, rs10882091 allele C rs7914814 allele T, rs6583830 allele A, rs2421943 allele G, rs6583826 allele G, rs7752906 allele A, rs1569699 allele C, rs7756992 allele G, rs9350271 allele A, rs9356744 allele C, rs9368222 allele A, rs10440833 allele A, rs6931514 allele G, rs1860316 allele A, rs1981647 allele C, rs1843622 allele T, rs2191113 allele A, and/or rs9890889 allele A is indicative of increased susceptibility of Type 2 diabetes.

104. The method of Claim 88, wherein determination of the absence of an at-risk allele in a polymorphic marker in a genotype dataset derived from the individual is indicative of decreased susceptibility to Type 2 diabetes..
- 5 105. The method of any of the Claims 88 - 104, wherein linkage disequilibrium is characterized by numeric values for $|D'|$ of greater than 0.8 and/or r^2 of greater than 0.2.
106. The method of any of the Claims 88 - 105, further comprising expressing the susceptibility to Type 2 diabetes as a risk measure.
- 10 107. The method of Claim 106, wherein the risk measure is calculated as a relative risk (RR) or odds ratio (OR).

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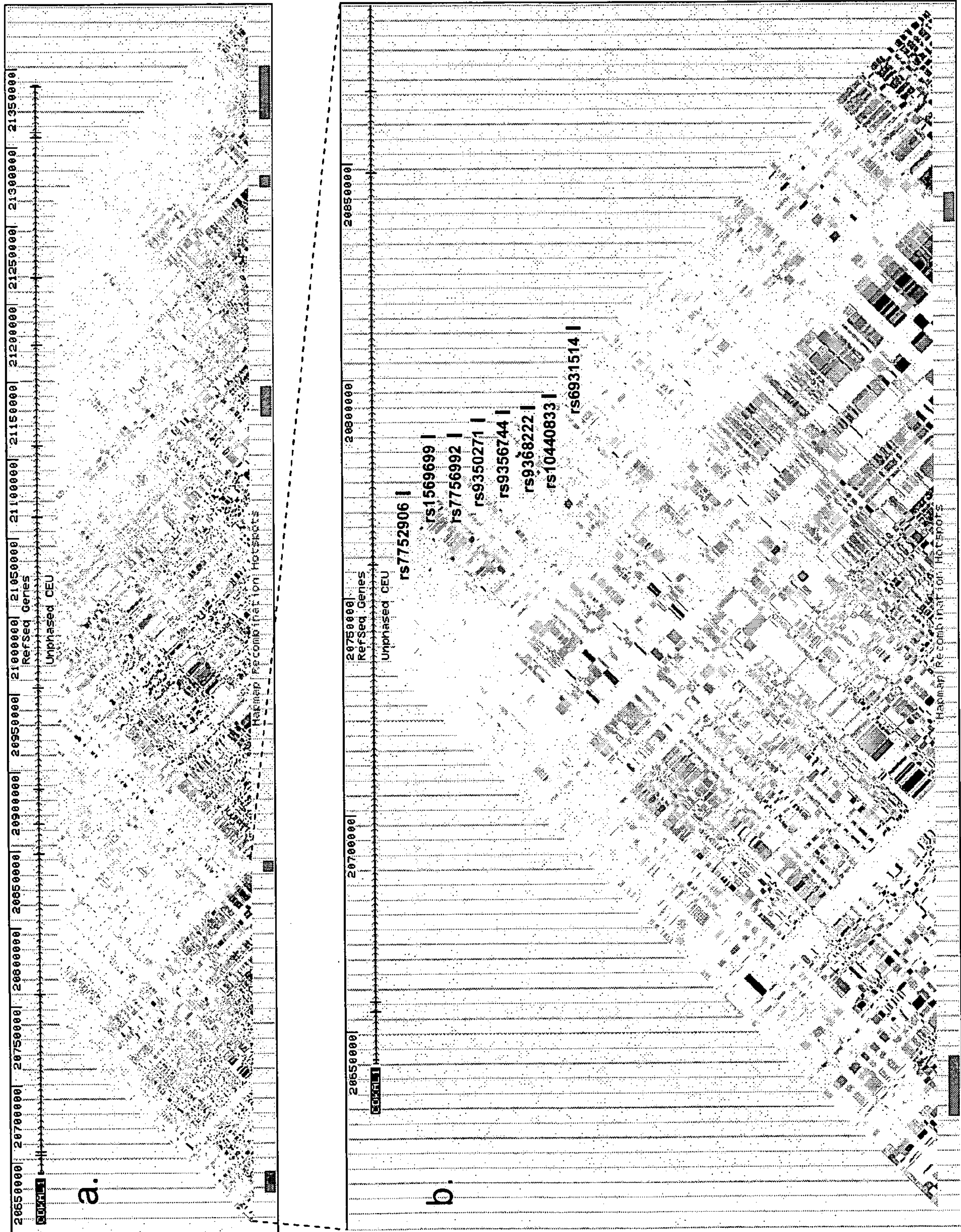


Fig. 1

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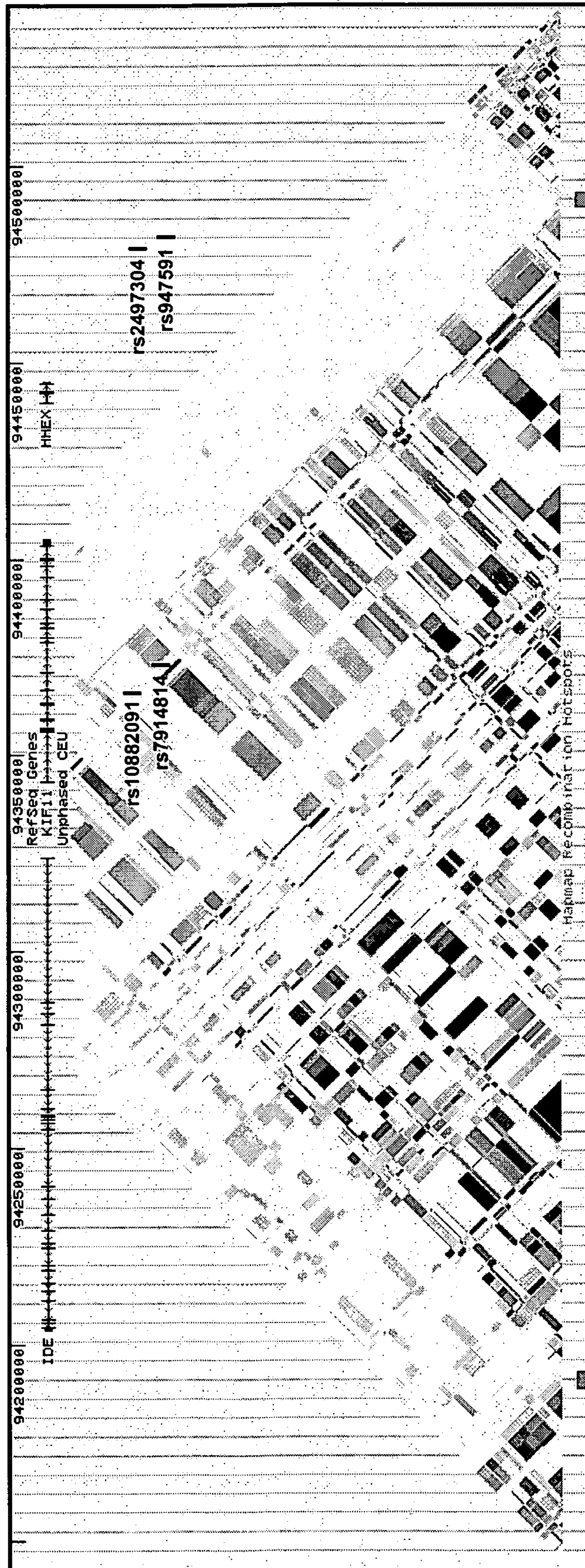


Fig. 2

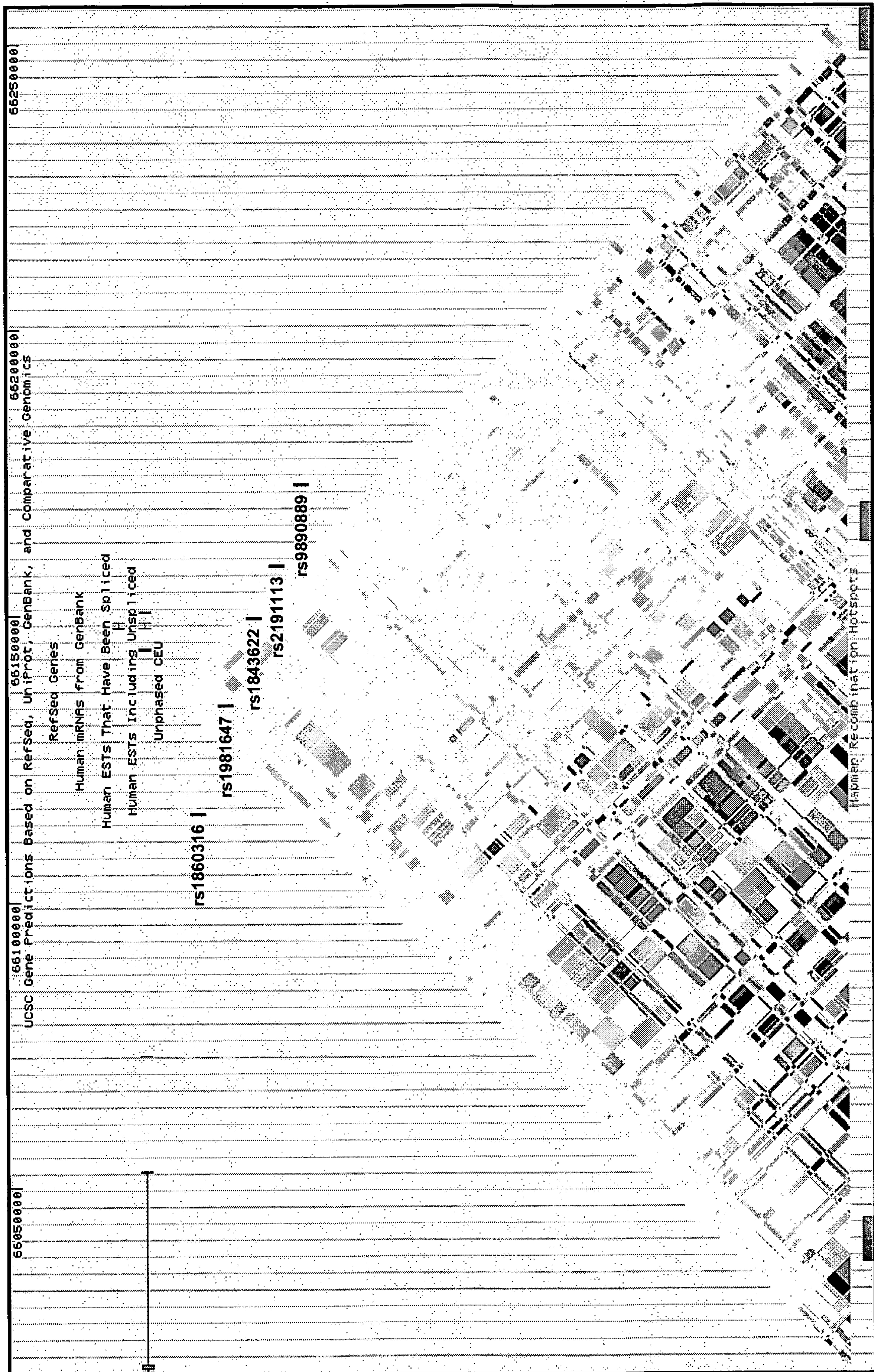


Fig. 3

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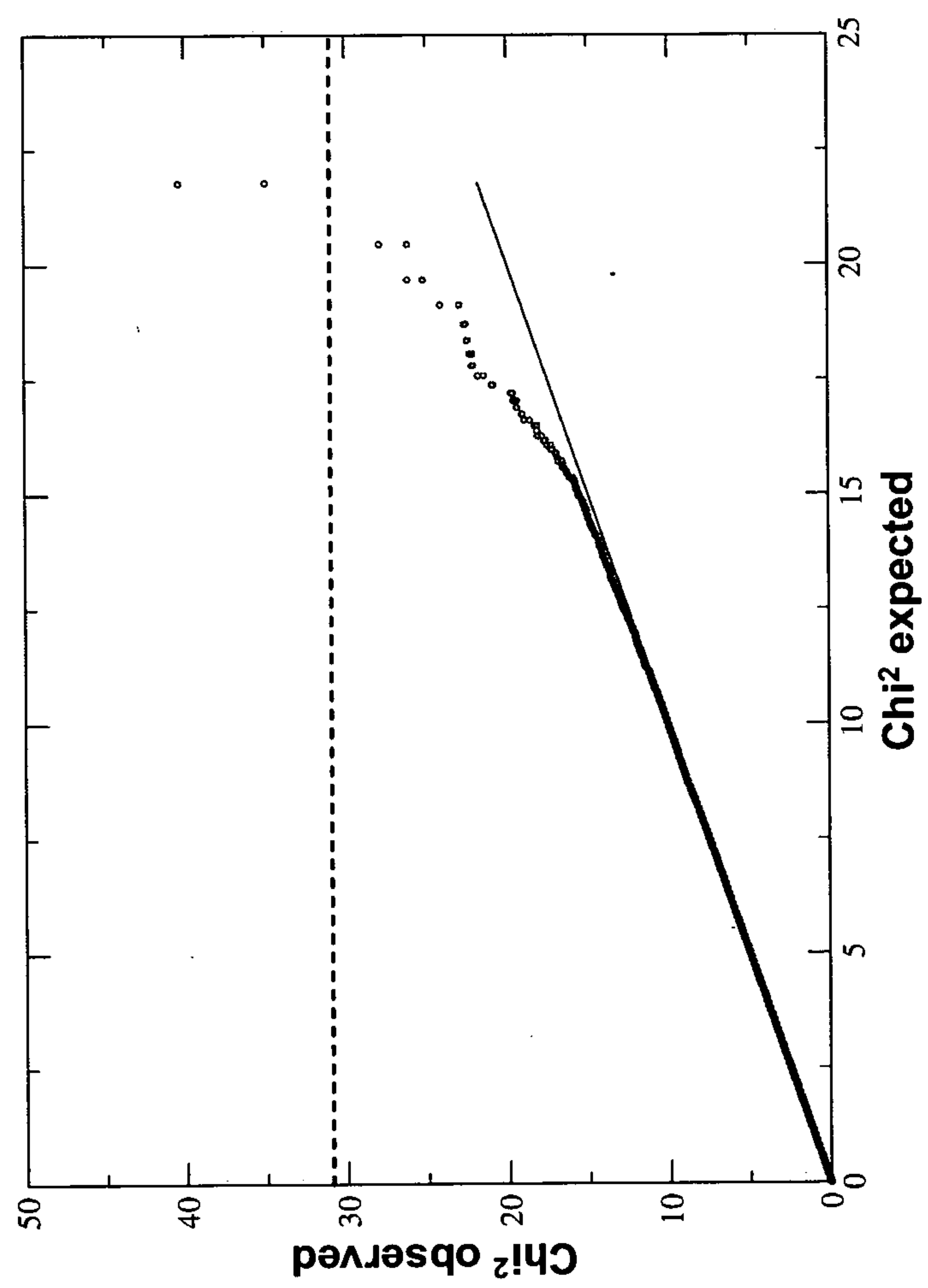
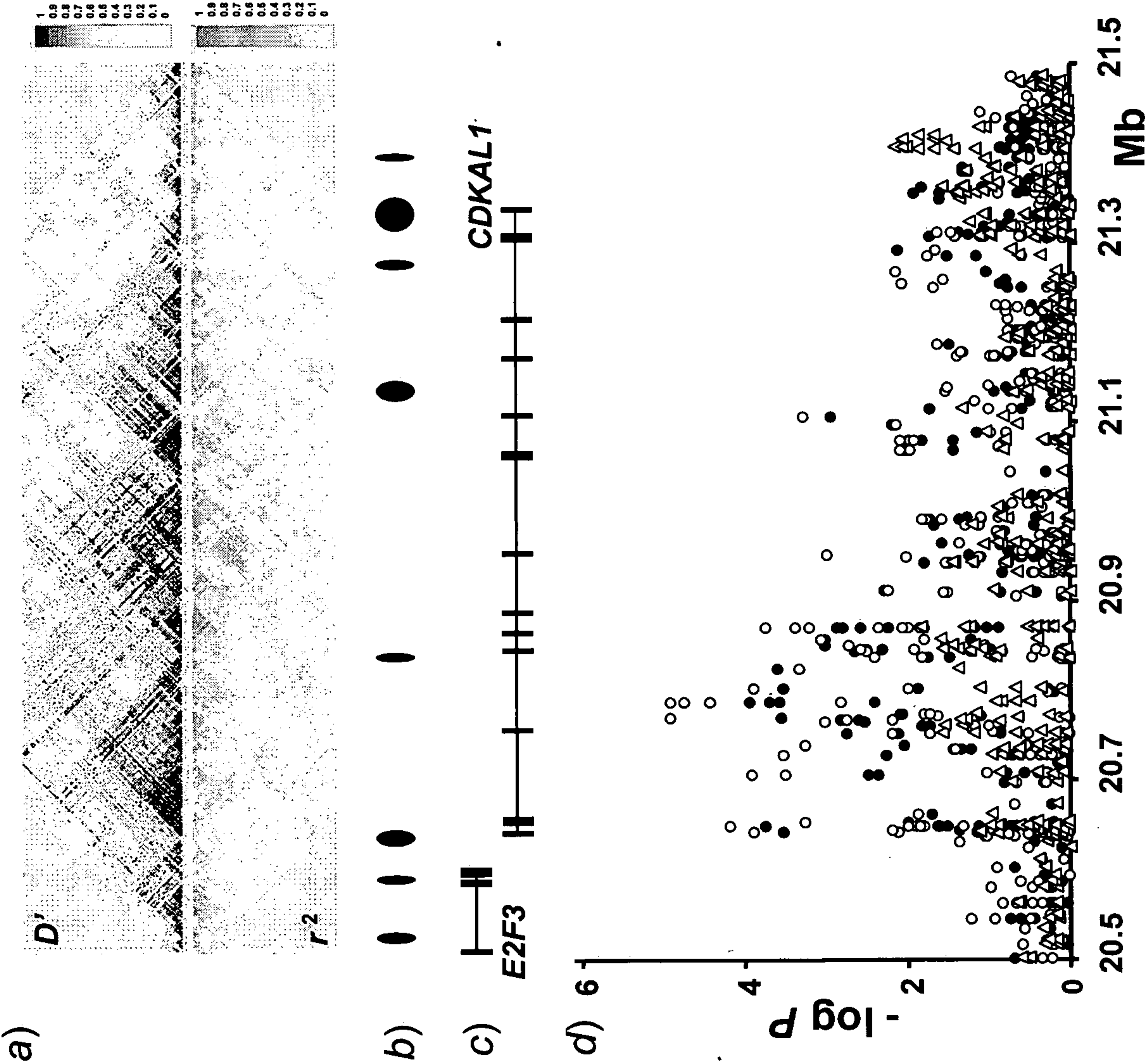


FIG. 4



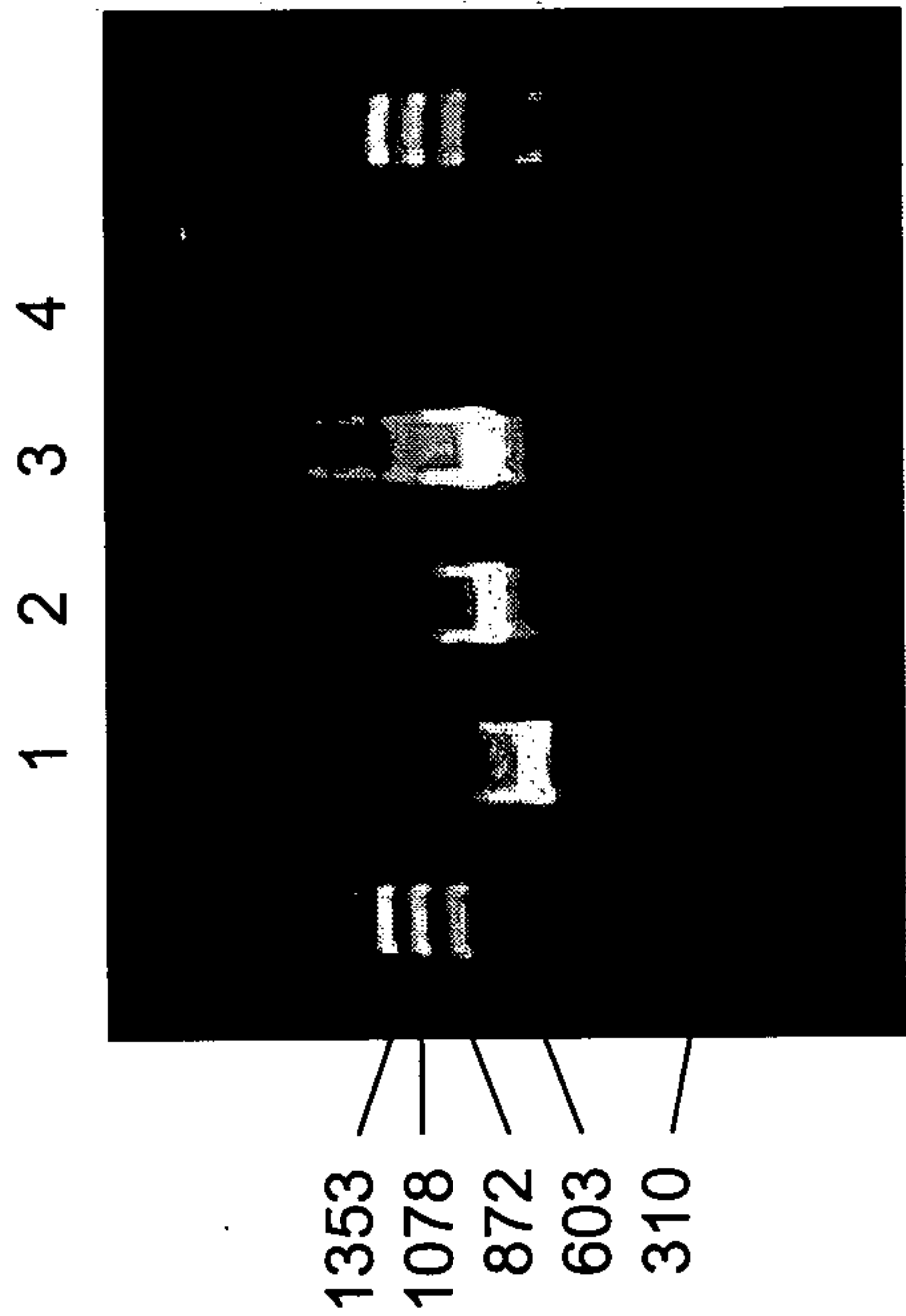


FIG. 6

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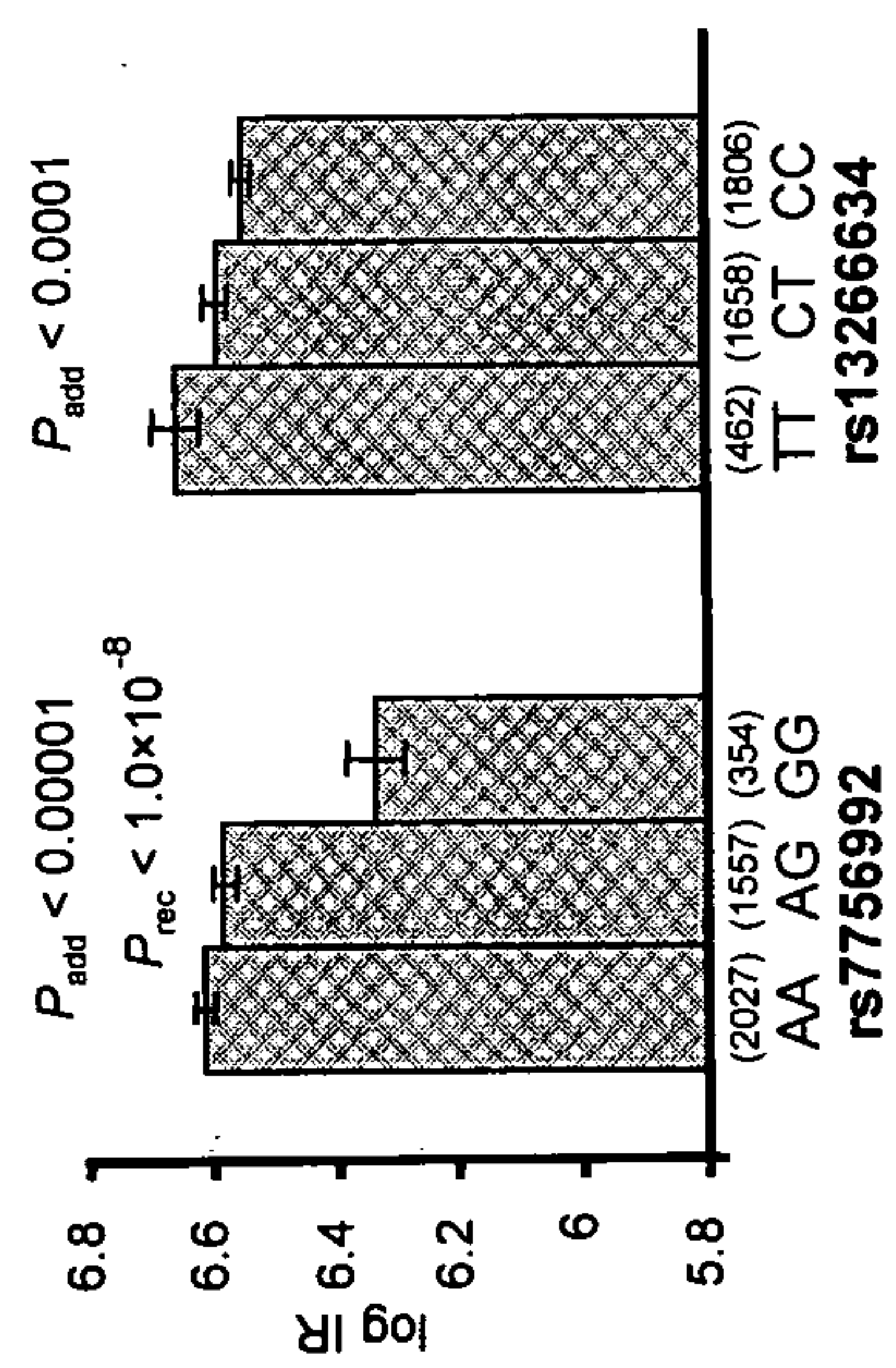


FIG. 7

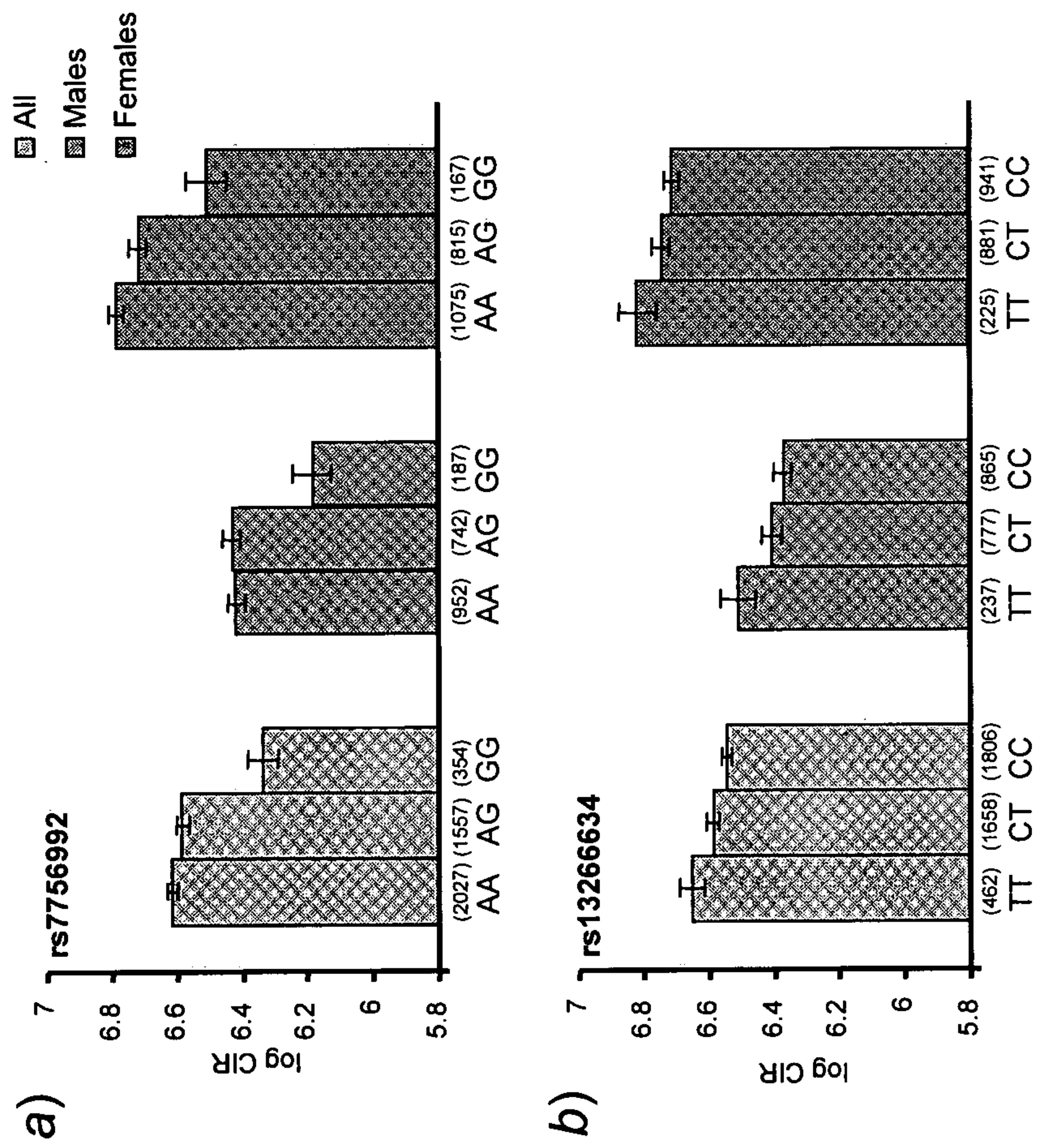


FIG. 8