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(71) Applicants: **THE CHINESE UNIVERSITY OF HONG KONG** [CN/CN]; Shatin, N.T., Hong Kong CN (CN). **BGI-HONG KONG CO., LTD.** [CN/CN]; Hong Kong (CN).

(72) Inventors: **CHAN, Juliana Chung-Ngor**; House 6, 14th Street, Hong Lok Yuen, Tai Po, N.T., Hong Kong (CN). **MA, Ronald Ching-Wan**; Flat 9B, Block 6, Cavendish Heights, 33 Perkins Road, Jardine's Lookout, Hong Kong (CN). **LEE, Heung Man**; Flat 2307, King Sam House, King Tin Court, Shatin, New Territories, Hong Kong (CN). **LIU, Xin**; No. 21, 3rd Hongan Street, Yantian District, Shenzhen, Guangdong 518083 (CN). **GAO, Zhi Bao**; Room 805, Zhongtie Building, Donghai Road, Yantian District, Shenzhen, Guangdong 518083 (CN). **WANG, Jun**; Main Building, Beishan Industrial Zone, Yantian District, Shenzhen, Guangdong 518083 (CN).

(74) Agent: **INSIGHT INTELLECTUAL PROPERTY LIMITED**; 19 A, Tower A, InDo Building, No. 48A Zhichun Road, Haidian District, Beijing 100098 (CN).

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(54) Title: USE OF MULTIOMIC SIGNATURE TO PREDICT DIABETES

(57) Abstract: Disclosed herein are methods of using genomic markers to predict the occurrence of diabetes in human subjects, and methods of using multiomic data to identify such markers.

USE OF MULTIOMIC SIGNATURE TO PREDICT DIABETES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/811,639, filed April 12, 2013, the contents of which are incorporated herein by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] There is a pandemic of type 2 diabetes (T2D) and obesity affecting an increasingly young population, especially in Asia [1, 2]. Type 2 diabetes is a complex disease due to interaction between genetic and environmental factors. Large scale family-based linkage analysis [3-6] and genome-wide association studies (GWAS) in case-control cohorts have identified multiple chromosomal regions and genetic variants associated with T2D [7-9], including genetic variants specific for the Chinese [10]. Most of the GWAS-T2D loci or nearby genes are implicated in β cell development, structure and function. Despite their replication in multiple populations, the low odds ratios of these SNPs (1.5-2) explained less than 10% of the heritability of T2D. Recent studies suggested epigenetics also plays a role in T2D. Using the FAIRE technique the GWAS SNP rs7903146 in the intron of TCF7L2 shows strong association in islet-specific open chromatins. Heterozygous carriers of rs7903146 showed marked allelic imbalance, the T allele is more open in islet chromatins and shows higher enhancer activity in functional luciferase activity assays [11]. Similarly, the risk-conferring A-allele of the intronic SNP rs8050136 of FTO, another T2D GWAS gene, is associated with increased DNA methylation in a 7.7Kb region harboring known conserved non-coding elements with regulatory activities [12]. Using a genome-wide approach, researchers have recently identified differentially methylated CpG in the first intron of FTO associated with T2D [13] supporting the importance of DNA methylation in T2D.

[0003] Recent advances in the next generation sequencing have enabled identification of all DNA methylation sites by whole genome bisulfite sequencing [14, 15]. In a proof-of-concept study to explain the missing heritability of T2D, we isolated DNA and RNA from peripheral blood mononuclear cells (PBMC) collected from a Chinese trio family consisting of an affected mother and daughter using the unaffected father as control. We applied whole

genome re-sequencing, bisulfite sequencing and RNA sequencing to obtain the genomes, methylomes, transcriptomes and microRNA expression profile in this trio family (**Figure 1**). We examined the correlations of methylome, transcriptome, microRNA expression and SNPs using pairwise comparisons to identify genes with the most consistent features. We also used an integrated network analysis incorporating genes with differential expression and methylation as well as being targets of differentially expressed microRNAs to discover the most connected genes. These discoveries were replicated in GWAS meta-analysis datasets [10] and independent case control cohort, accompanied by gene expression and DNA methylation assays in PBMC from 65 controls and 65 T2D cases (**Figure 2**). Using this multipronged approach, we discovered novel T2D associated genes with multiomic features implicated in chromatin modification and protein metabolism pathways in T2D.

[0004] Because of the enormous social and economic impact of type 2 diabetes and associated complications such as cardiovascular and renal diseases, there exist clear and immediate needs to develop new and effective means for accurate diagnosis or early assessment a patient's risk of developing these diseases in the future, such that early intervention may be performed to minimize the harmful effects associated with these diseases and/or the risk of developing the diseases. The present invention fulfills this and other related needs.

BRIEF SUMMARY OF THE INVENTION

[0005] Provided herein are methods, procedures, and systems for identifying and using genetic markers for diabetes. Multiomic data, including genomic, transciptomic, or methylomic data, can be obtained from individuals and compared between individals. Differences in these data, such as single-nucleotide polymorphisms, different patterns of DNA methylation, or different patterns of gene expression, can then be integrated and correlated with diabetes phenotypes. In some embodiments, the individuals are related, such as in a father-mother-daughter trio. In some embodiments, the integration or correlation is performed using network analysis. Multiomic signatures, including genes not previously associated with diabetes,areidentified for predicting the occurrence of diabetes in individuals and developing treatments for diabetes.

[0006] In the first aspect, a method is provided for detecting the presence or increased risk of developing T2D in a subject. The method includes these steps: (a) measuring, in a tissue

sample obtained from the subject, expression or DNA methylation levels of one or more T2D-associated genes; (b) comparing the expression or DNA methylation levels of the one or more T2D-associated genes with levels from the same genes in a standard control; and (c) detecting the presence or increased risk of developing T2D when the expression or DNA methylation levels of the one or more T2D-associated genes are higher or lower than the levels in the standard control. The T2D-associated genes are selected from the group consisting of *LRRC7*, *TXNDC12*, *TGFBR3*, *AJAPl*, *AGRN*, *APOB*, *EIF4E3*, *SLC35A4*, *PACRG*, *COL15A1*, *NR4A3*, *E2F8*, *PCDH17*, *PLEKHH3*, *SCARF2*, *CUEDC2*, *KDM2B*, *PDCD1*, *miR-16-1*, and *miR-16-2*.

[0007] In some embodiments of this method, step (a) includes measuring expression levels of the one or more T2D-associated genes, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, *EIF4E3*, *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*. Measuring expression levels can include measuring levels of RNA transcripts of the one or more T2D-associated genes. Alternatively or in addition, measuring expression levels can include measuring amounts of proteins or polypeptides resulting from translation of RNA transcripts of the one or more T2D-associated genes. In these embodiments, step (c) can include detecting the presence or increased risk of developing T2D when the expression levels of the one or more T2D-associated genes are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, and *EIF4E3*. Alternatively, step (c) can include detecting the presence or increased risk of developing T2D when the expression levels of the one or more T2D-associated genes are lower than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*.

[0008] In other embodiments of the method, step (a) includes measuring DNA methylation levels of the one or more T2D-associated genes and the T2D-associated genes are selected from the group consisting of *PDCD1*, *EIF4E3*, *PACRG*, and *KDM2B*. In these embodiments, step (c) can include detecting the presence or increased risk of developing T2D when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *PDCD1* and *EIF4E3*. In particular, the regions of the T2D-associated genes can be promoter regions. In other words, (c) can include detecting the presence or increased risk of developing T2D when the DNA methylation level of a promoter

region in the one or more T2D-associated genes is higher than the level in the standard control. Alternatively, step (c) can include detecting the presence or increased risk of developing T2D when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are lower than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *EIF4E3*, *PACRG*, and *KDM2B*. In some cases, step (c) includes detecting the presence or increased risk of developing T2D when the DNA methylation level of a promoter region in the one or more T2D-associated genes is lower than the level in the standard control.

[0009] In the second aspect, a method is provided for detecting the presence or increased risk of developing T2D in a subject. The method includes these steps: (a) determining, in a tissue sample obtained from the subject, a single-nucleotide genotype of the subject at a genomic locus, wherein the genomic locus is given by a SNP ID number provided in Table 9, 10, or 11; and (b) detecting the presence or increased risk of developing T2D in the subject if the single-nucleotide genotype matches a reference genotype associated with T2D.

[0010] In some embodiments of the method, the genomic locus is given by a SNP ID number provided in Table 11 and selected from the group consisting of rs1052637, rs748767, rs9998519, rs1534938, rs17497819, rs11597439, rs117510629, rs11065587, chr12:120395303, rs11065588, rs3743599, rs3743598, rs734409, rs3818744, rs17114359, rs220305, rs2839467, and rs93136. In these embodiments, the reference genotype associated with T2D for each genomic locus can be provided in a column A1 of Table 11. In one such embodiment, the genomic locus is given by the SNP ID number rs9998519 and the reference genotype is C. In another such embodiment, the genomic locus is given by the SNP ID number rs1534938 and the reference genotype is T.

[0011] In some embodiments of the method, the genomic locus is given by a SNP ID number provided in Table 9 and the reference genotype for the genomic locus is provided in the "risk genotype" column of Table 9. In some embodiments, the genomic locus is given by a SNP ID number provided in Table 10 and the reference genotype for the genomic locus is provided in the "risk allele" column of Table 10.

[0012] In some embodiments, steps (a) and (b) of the method are performed for a plurality of genomic loci.

[0013] In the methods of the first aspect or the second aspect, the sample can be a blood or saliva sample. The subject from whom the sample is obtained can be of Asian descent. In

some cases, the subject is a Chinese.In some cases, the subject is a Han Chinese. The subject can also have a family history of T2D but no diagnosis for T2D (i.e., the subject has not been diagnosed with T2D).

[0014] In some embodiments of the methods of the first and second aspects, step (a) includes an amplification reaction. The amplification reaction can be a polymerase chain reaction (PCR).

[0015] In the third aspect, a method of identifying genetic markers of T2D is provided. The method includes these steps: obtaining a multiomic data set from one or more T2D-positive subjects, wherein each T2D-positive subject has been diagnosed with T2D; obtaining a multiomic data set from one or more T2D-negative subjects, wherein each T2D-negative subject has not been diagnosed with T2D; identifying differences between the multiomic data sets obtained from the one or more T2D-positive subjects and the one or more T2D-negative subjects; and identifying one or more genetic markers based on the differences.

[0016] In some embodiments of this method, the T2D-positive subjects are related to the T2D-negative subjects. The T2D-positive subjects and T2D-negative subjects can together include a family trio, and the family trio can include a father, a mother, and an offspring. In some cases, one of the father and the mother is a T2D-positive subject, and the other of the father and the mother is a T2D-negative subject. In some cases, the father is a T2D-negative subject and the mother and the offspring are T2D-positive subjects. In one such case, the offspring is a daughter of the father and the mother.

[0017] In some embodiments of the method, each multiomic data set includes at least two of the following: DNA sequencing data, RNA sequencing data, and RNA expression level data. The DNA sequencing data can include genomic sequencing data or methylomic sequencing data. The RNA sequencing data can include transcriptomic sequencing data or microRNA sequencing data. The RNA expression level data can include mRNA expression level data or microRNA expression level data.

[0018] In some embodiments of the method, differences between the multiomic data sets from the one or more T2D-positive subjects and the one or more T2D-negative subjects are identified by comparing the multiomic data sets pair-wise. In some embodiments, the one or more genetic markers are identified using network analysis. The one or more genetic markers can include connected genes. In some embodiments, the genetic markers co-

segregate in the multiomic data sets obtained from the T2D-positive subjects or the T2D-negative subjects.

[0019] In some embodiments of the method, the genetic markers include differentially expressed genes, differentially expressed microRNAs, differentially methylated regions, or single-nucleotide polymorphisms. In these embodiments, the genetic markers can include a differentially expressed gene that contains or overlaps with a differentially methylated region. In some cases, the differentially methylated region occurs within or overlaps with the promoter of the gene. In some cases, the differentially methylated region occurs within or overlaps with the body of the gene.

[0020] Embodiments of the method can also include validating the genetic markers by comparing gene expression or methylation in T2D-positive and T2D-negative cohorts. Validating can include performing quantitative PCR.

[0021] In any aspect of the present invention, a method can be carried out in whole or in part using a computer system. For example, comparisons between or among gene expression levels, DNA methylation levels, or SNP genotypes can be performed computationally, as can preparation of multiomic data sets and multiomic or network analysis. In some embodiments, a computer product including a tangible computer readable medium is provided, and the medium stores a plurality of instructions that when executed control a computer system to perform a method as substantially described herein. In some embodiments, a system is provided that includes one or more processors configured to perform a method as substantially described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **Figure 1:** Summary of the study design. DNA from the PBMC of the trio will be subjected to whole genome sequencing and whole genome bisulfite sequencing. Whole genome sequencing identified the SNPs and indels from the trio. Bisulfite sequencing identified the DNA methylation sites. The RNA samples were subjected to RNA sequencing and microRNA sequencing to identify the gene expression profile and the microRNA expression pattern.

[0023] **Figure 2:**Summary of the multiomic data analysis of DNA methylation, gene expression from the trio. Interested gene loci were chosen for validation in DNA methylation and gene expression. Co-segregated SNPs in the interested gene loci will be checked against

the results of the Chinese GWAS meta-analysis to identify target SNPs for validation in independent case control cohort.

[0024] **Figure 3**: A computer system for use with some embodiments of the invention.

[0025] **Figure 4:** Summary of differential methylation regions (DMR) in the genome. Whole genome methylation analysis showed that there are over 1500 DMR in each member of the trio. 186 DMRs co-segregated only in the father-mother (FM) and father-daughter (FD) pairs. These 186 DMRs overlaps with 32 genes.

[0026] **Figure 5:** Summary of gene expression and microRNA expression in the trio. Venn diagram showed the number of expressed genes in the family trio (top left) and the pair wise comparison of expressed genes (top right). 413 Genes expressed differentially in both the FM and FD comparisons but not in the MD comparison. Expression of microRNA was summarized in the bottom. Over 500 microRNAs were expressed in each member of the trio (left) and 67 showed differential expression in only the FM and FD pairs (right).

[0027] **Figure 6:** Network analysis to discover genes associated with T2D. Network analysis constructed a gene network composed of thousands of genes. The sub-network contains the known T2D GWAS genes (left) contains 141 genes with 15 genes being the most connected genes shown in the table at right.

[0028] **Figure 7:** Discovery of T2D genes by multiomic approach. Whole genome bisulfite sequencing and RNA sequencing were applied to a family trio with T2D to reveal DNA methylation and gene expression change in PBMC associated with T2D. The CIRCOS diagram in centre summarizes the differentially methylated regions and differentially expressed genes. Key changes in both DNA methylation and gene expression in 5 gene regions were successfully validated in a 65 vs. 65 case control cohort.

DEFINITIONS

[0029] The term "**type 2 diabetes**" (T2D) refers to a metabolic disorder that is characterized by high blood glucose in the context of varying combinations of insulin resistance and insulin deficiency. Type 2 diabetes may becaused by a combination of lifestyle and genetic factors. Diabetes can be caused by distinct clinical entities such as endocrine disorders (*e.g.*, Cushing's syndrome) and chronic pancreatitis. However, the majority of people with diabetes have risk factors including but not limited to obesity,

hypertension, high blood cholesterol, metabolic syndrome (high triglyceride, low HDL-C, high blood glucose, high blood pressure, large waist), which may share common metabolic pathways, further amplified by aging, energy dense diets (*e.g.*, high-fat and high glucose),sedentary lifestyle and use of certain drugs (*e.g.*, beta blockers, steroids). On the other hand, having relatives (especially first degree) with T2D increases risks of developing T2D substantially. Symptoms of T2D often include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue, and weight loss. The abnormal neurohormonal and metabolic milieu characterized by hyperglycemia, dyslipidemia and low grade inflammation can trigger a cascade of signaling pathways, which can lead to cell death and dysregulated cell growth, giving rise to multiple morbidities including heart disease, strokes, limb amputation, visual loss, kidney failure, cancers, and cognitive impairment.

[0030] The term "**cardiovascular disease**" refers to a broad class of diseases that involve the heart or blood vessels (arteries and veins) and affect the cardiovascular system, such as conditions related to atherosclerosis (arterial disease). These include but not limited to stroke, coronary heart disease and peripheral vascular disease. Known risk factors for cardiovascular diseases include unhealthy eating, lack of exercise, obesity, suboptimally managed diabetes, abnormal blood lipids, high blood pressure, excessive consumption of alcohol, use of tobacco, as well as genetic background.

[0031] As used herein, the term "**body mass index**" or "**BMI**" refers to a number calculated from a person's weight and height to reflect the "fatness" or "thinness" of a person. More specifically, BMI = mass (kg) / (height (m))^2 or mass (lb) × 703 / (height (in))^2. Typically, in Caucasian populations, a BMI of 20 to 25 kg/m^{2}is considered optimal weight; a BMI lower than 20kg/m^2 suggests the person is underweight whereas a BMI above 25 kg/m^{2}may indicate the person is overweight; a BMI above 30 kg/m^{2}suggests the person is obese; and a BMI over 40 kg/m^{2}indicates the person to be morbidly obese. Compared to Caucasians, Asians have more body fat for the same degree of BMI and waist circumference. Thus, normal weight and obesity in Asians are defined as <23 kg/m^{2}and ≥25 kg/m^{2}respectively. While high BMI may predict risk for diabetes or prediabetes, people with low BMI, which correlates with beta cell function, are also at high risk, especially if these subjects develop central obesity, which tends to be associated with insulin resistance or reduced insulin sensitivity.

[0032] In this disclosure, the term "**biological sample**" or "**sample**" includes any section of tissue or bodily fluid taken from a test subject such as a biopsy and autopsy sample, and frozen section taken for histologic purposes, or processed forms of any of such samples. Biological samples include blood and blood fractions or products (*e.g.*, serum, plasma, platelets, white blood cells, red blood cells, and the like), sputum or saliva, lymph and tongue tissue, cultured cells, *e.g.*, primary cultures, explants, and transformed cells, stool, urine, stomach biopsy tissue *etc.* A biological sample is typically obtained from a eukaryotic organism, which may be a mammal, may be a primate and may be a human subject.

[0033] In this disclosure, the term "**biopsy**" refers to the process of removing a tissue sample for diagnostic or prognostic evaluation, and to the tissue specimen itself. Any biopsy technique known in the art can be applied to the methods of the present invention. The biopsy technique applied will depend on the tissue type to be evaluated (*e.g.*, tongue, colon, prostate, kidney, bladder, lymph node, liver, bone marrow, blood cell, stomach tissue, *etc.*) among other factors. Representative biopsy techniques include, but are not limited to, excisional biopsy, incisional biopsy, needle biopsy, surgical biopsy, and bone marrow biopsy and may comprise endoscopy such as colonoscopy. A wide range of biopsy techniques are well known to those skilled in the art who will choose between them and implement them with minimal experimentation.

[0034] In this disclosure, the term "**isolated**" nucleic acid molecule means a nucleic acid molecule that is separated from other nucleic acid molecules that are usually associated with the isolated nucleic acid molecule. Thus, an "isolated" nucleic acid molecule includes, without limitation, a nucleic acid molecule that is free of nucleotide sequences that naturally flank one or both ends of the nucleic acid in the genome of the organism from which the isolated nucleic acid is derived (*e.g.*, a cDNA or genomic DNA fragment produced by a polymerase chain reaction or restriction endonuclease digestion). Such an isolated nucleic acid molecule is generally introduced into a vector (*e.g.*, a cloning vector or an expression vector) for convenience of manipulation or to generate a fusion nucleic acid molecule. In addition, an isolated nucleic acid molecule can include an engineered nucleic acid molecule such as a recombinant or a synthetic nucleic acid molecule. A nucleic acid molecule existing among hundreds to millions of other nucleic acid molecules within, for example, a nucleic acid library (*e.g.*, a cDNA or genomic library) or a gel (*e.g.*, agarose, or polyacrylamine) containing restriction-digested genomic DNA, is not an "isolated" nucleic acid.

[0035] The term "**nucleic acid**" or "**polynucleotide**" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogs of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions), alleles, orthologs, single nucleotide polymorphisms (SNPs), and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, *Nucleic Acid Res.* **19**:5081 (1991); Ohtsuka *et al.*, *J. Biol. Chem.* **260**:2605-2608 (1985); and Rossolini *et al.*, *Mol. Cell. Probes* **8**:91-98 (1994)). The term nucleic acid is used interchangeably with gene, cDNA, and mRNA encoded by a gene.

[0036] The term "**gene**" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) involved in the transcription and/or translation of the gene product and the regulation of the transcription and/or translation, as well as intervening sequences (introns) between individual coding segments (exons).

[0037] *ADAT1, AGRN, AJAP1, AKAP7, ANKRD29, APOB, ASB13, C17orf64, C17orf81, C21orf56, C6orf138, CAMK1D, CBLN4, CCDC155, CCDC93, CDKN2B, CEMP1, CITED2, CLDN6, COL15A1, CUED2, CUEDC2, DDX18, E2F8, EIF4E3, FLT1, FMOD, GTF2A2, HEATR2, KCNK17, KDM2B, LHX8, LRRC7, MED7, miR-16-1, miR-16-2, NR4A3, PACRG, PCDH17, PDCD1, PDGFRL, PLEKHH3, PPP4R1L, PRR14, PTPN7, PTPRD, RABGGTB, RPS16, SCARF2, SLC22A20, SLC35A4, TARS, TGFBR3, TNFRSF12A, TXNDC12, U2AF1, UMODL1, WFS1,* and *XBP1*, as used herein, refer to the genes or proposed open reading frames (including their variants and mutants)and their polynucleotide transcripts as provided in publically accessible sequence databases of the human genome. In some context, these terms may also be used to refer to the polypeptides encoded by these genes or open reading frames.

[0038] In this application, the terms "**polypeptide**," "**peptide**," and "**protein**" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to

amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. As used herein, the terms encompass amino acid chains of any length, including full-length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds.

[0039] The term "**amino acid**" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. For the purposes of this application, amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. For the purposes of this application, amino acid mimetics refer to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0040] Amino acids may include those having non-naturally occurring D-chirality, as disclosed in WO01/12654, which may improve the stability (*e.g.*, half-life), bioavailability, and other characteristics of a polypeptide comprising one or more of such D-amino acids. In some cases, one or more, and potentially all of the amino acids of a therapeutic polypeptide have D-chirality.

[0041] Amino acids may be referred to herein by either the commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0042] The phrase "**specifically binds**," when used in the context of describing a binding relationship of a particular molecule to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated binding assay conditions, the specified binding agent(*e.g.*, an antibody) binds to a particular protein at least two times the background and

does not substantially bind in a significant amount to other proteins present in the sample. Specific binding of an antibody under such conditions may require an antibody that is selected for its specificity for a particular protein or a protein but not its similar "sister" proteins. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein or in a particular form. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (*see, e.g.*, Harlow & Lane, *Antibodies, A Laboratory Manual* (1988) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity). Typically a specific or selective binding reaction will be at least twice background signal or noise and more typically more than 10 to 100 times background. On the other hand, the term "specifically bind" when used in the context of referring to a polynucleotide sequence forming a double-stranded complex with another polynucleotide sequence describes "polynucleotide hybridization" based on the Watson-Crick base-pairing, as provided in the definition for the term "polynucleotide hybridization method."

[0043] A "**polynucleotide hybridization method**" as used herein refers to a method for detecting the presence and/or quantity of a pre-determined polynucleotide sequence based on its ability to form Watson-Crick base-pairing, under appropriate hybridization conditions, with a polynucleotide probe of a known sequence. Examples of such hybridization methods include Southern blot, Northern blot, and *in situ* hybridization.

[0044] "**Primers**" as used herein refer to oligonucleotides that can be used in an amplification method, such as a polymerase chain reaction (PCR), to amplify a nucleotide sequence based on the polynucleotide sequence corresponding to a gene of interest or a portion thereof. Typically, at least one of the PCR primers for amplification of a polynucleotide sequence is sequence-specific for that polynucleotidesequence. The exact length of the primer will depend upon many factors, including temperature, source of the primer, and the method used. For example, for diagnostic and prognostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains at least 10, or 15, or 20, or25 or more nucleotides, although it may contain fewer nucleotides or more nucleotides. The factors involved in determining the appropriate length of primer are readily known to one of ordinary skill in the art. In this disclosure the term "primer pair" means a pair of primers that hybridize to opposite strands a target DNA molecule or to regions of the target DNA which flank a nucleotide sequence to be amplified.

In this disclosure, the term "primer site" means the area of the target DNA or other nucleic acid to which a primer hybridizes.

[0045] A "**label**," "**detectable label**," or "**detectable moiety**" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (*e.g.*, as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins that can be made detectable, *e.g.*, by incorporating a radioactive component into the peptide or used to detect antibodies specifically reactive with the peptide. Typically a detectable label is attached to a probe or a molecule with defined binding characteristics (*e.g.*, a polypeptide with a known binding specificity or a polynucleotide), so as to allow the presence of the probe (and therefore its binding target) to be readily detectable.

[0046] The term "**amount**" as used in this application refers to the quantity of a polynucleotide of interest or a polypeptide of interest present in a sample. Such quantity may be expressed in the absolute terms, *i.e.*, the total quantity of the polynucleotide or polypeptide in the sample, or in the relative terms, *i.e.*, the concentration of the polynucleotide or polypeptide in the sample.

[0047] The term "**effective amount**" as used herein refers to an amount of a given substance that is sufficient in quantity to produce a desired effect. For example, an effective amount of a cholesterol lowering drug or a blood glucose lowering drug is the amount of said drug to achieve a decreased level of cholesterol or blood glucose, respectively, in a patient who has been given the drug for therapeutic purposes. An amount adequate to accomplish this is defined as the "therapeutically effective dose."The dosing range varies with the nature of the therapeutic agent being administeredand other factors such as the route of administration and the severity of a patient's condition.

[0048] The term "**expression level**" refers to the expression level ofa particular gene or genomic region in a sample obtained from an individual. Expression can be represented by the amount of transcribed RNA or translated protein or polypeptide associated with the gene or genomic region, or by a biological activity (e.g. enzymatic activity) resulting from expression of the gene or genomic region. Expression levels can be measured as desired, in absolute or relative terms, and can reflect the context of the measurement or the conditions under which the sample was obtained.

[0049] The term "**DNA methylation level**" refers to the extent to which a gene or genomic region is methylated in a sample obtained from an individual. A gene can be fully or partially methylated, and the pattern of methylation can be random, uniform, or specific to portions of the gene (for example, the promoter or body). Moreover, the pattern and extent of methylation of a gene can vary, for example between chromosomes in the same cell, tissues of the same individual, or different individuals. Thus, measuring a DNA methylation level in a sample can provide a detailed methylation pattern and can reflect the context in which the sample was obtained. The measured DNA methylation level can be used to determine whether a genomic region is differentially methylated, for example between T2D-positive and T2D-negative individuals.

[0050] **"Standard control"** as used herein refers to a sample suitable for the use of a method of the present invention, in order to quantitatively determine the level of expression (e.g., abundance of RNA transcripts or gene products) or DNA methylation in a test sample for one or more genomic regions of interest (for example, a gene or genomic locus). The standard control contains a known level or levels of expression or DNA methylation for the genomic region(s) of interest, such that the levels closely reflect those of an average healthy individual not suffering from T2D and not at an increased risk of later developing T2D. The standard control may be derived from one or more healthy individuals.

[0051] **"Higher or lower than levels in a standard control"** as used herein refers to differences between the level of expression or DNA methylation in test sample as compared with corresponding levels in a standard control, for the same genomic region of interest. A higher level is preferably at least 2-fold, more preferably at least 5-fold, and most preferably at least 10-fold higher than the level in the standard control. Similarly, a lower level is preferably less than 50%, more preferably less than 20%, and most preferably less than 10% of the level in the standard control.

[0052] The term "**subject**" or "**subject in need of treatment**," as used herein, includes individuals who seek medical attention due to risk of, or actual suffering from T2D, cancer, or cardiovascular disease. Subjects also include individuals currently undergoing therapy that seek manipulation of the therapeutic regimen. Subjects or individuals in need of treatment include those that demonstrate symptoms ofT2D or cardiovascular disease, or are at risk of suffering from T2D or cardiovascular disease or related symptoms. For example, a subject in need of treatment includes individuals with a genetic predisposition or family history for T2D,

cancer, or cardiovascular disease, those who have suffered relevant symptoms in the past, those who have been exposed to a triggering substance or event, as well as those suffering from chronic or acute symptoms of the condition. A "subject in need of treatment" may be at any age of life.

[0053] The term "**related,**" as it pertains to individuals, is used herein to refer to individuals who have common ancestry. For example, a child is related to its parents, grandparents, and siblings, and moreover all of these individuals are related to each other. Relatedness between individuals can be established through knowledge of family history, with genetic tests, or otherwise. Any number of generations can be considered when determining whether two or more people have common ancestry and are thus related, although this number can be limited if desired to provide a more stringent test.

[0054] As the term is used herein,a "**multiomic data set"** refers to data resulting from sequencing DNA and/or RNA obtained from a tissue sample of an individual. Without limitation, a multiomic data set can contain one or more of the following: all or a substantial part of the genomic DNA sequence of the individual; sequences or copy numbers of sites of interest within the genome; methylation patterns of genomic DNA; information about the accessibility of genomic DNA sequences to transcription; sequences of RNA transcripts, including coding and/or non-coding RNAs; and levels or relative abundances of RNA transcripts. In some embodiments, the multiomic data set contains sequencing data for the full genome, transcriptome, or methylome of the tissue sample. The DNA and RNA can be obtained from any kind of tissue, and the multiomic data set can have components that a skilled artisan would expect to be specific to the tissue (e.g. the presence of RNA transcripts for specific genes) or largely the same for all tissues of the individual (e.g. sequences of genomic DNA). Multiomic data sets from different individuals (e.g. individuals with different diabetes phenotypes) can be compared to identify genetic differences between the individuals, such as differences in genomic DNA sequence (e.g. single-nucleotide polymorphisms, insertions, deletions, differences in gene copy numbers), differences in genomic DNA structure (e.g. methylation, binding of DNA to histone proteins or transcription factors), and differences in gene expression (e.g. relative abundances of RNA transcripts or non-coding RNA).

[0055] As the term is used herein, a**"multiomic signature"** refers to a set of genetic markers, identified using multiomic data sets and the methods disclosed herein, that

characterizes or is possessed by an individual or group of individuals. A multiomic signature can be shared by individuals who are related to each other (for example, one being the offspring of another) or who have a common phenotype (for example, being diagnosed with T2D). A multiomic signature can include any number of identified genes, regions, or loci within the genome, as well as information about how the structure (e.g., sequence or methylation state) or expression (e.g., transcription levels) of these genes , regions, or loci differ between individuals who possess and do not possess the multiomic signature.

[0056] "**Network analysis**," as the term is used herein, refers to a method of integrating multiomic data sets from two or more individuals. In some embodiments, the individuals are related. For each individual, a gene can be represented as a vector made up of multiple data types from the multiomic data set, and connections between genes can be identified by correlating differences in the vectors between individuals. A set of connected genes with characteristics (e.g. expression level, DNA methylation level) that correlate with the presence or absence of a particular phenotype (e.g., T2D) can then be identified.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0057] Large scale studies like GWAS found multiple genes and SNPs associated with type 2 diabetes (T2D) but with limited effect size. We used a multiomic approach on a family trio to discover T2D associated genes.

[0058] DNA and RNA samples from peripheral blood mononuclear cells from a family trio consisting of T2D affected mother and daughter and non-T2D father were used for high throughput DNA sequencing, bisulfite sequencing, RNA sequencing and small RNA sequencing to obtain a complete profile on DNA methylation and gene expression. Pairwise comparisons (FM, father-mother, FD, father-daughter and MD, mother-daughter) were used to find differentially methylated and expressed genes. Network analysis was used to integrate these changes to discover key genes associated with T2D. Changes in DNA methylation and gene expression were validated in 65 controls and 65 T2D cases using Sequenom Epityper and qRT-PCR.

[0059] Bisulfite sequencing and RNA sequencing yielded high coverage and depth data for analysis. There were 413 differentially expressed genes and 186 differentially methylated regions (DMR) showed cosegregation in the FD and FM pairs but not in the MD pair. The

186 DMR overlapped with the promoter of 32 genes. Using the results from changes in gene and microRNA expression and DNA methylation, multiomic network analysis highlighted 15 most connected genes. Among these focus genes with correlated methylation/expression patterns, several of them showed association with T2D in a GWAS meta-analysis of 677 Chinese T2D cases and 955 controls. DNA methylation and gene expression changes in these genes were validated in 65 controls and 65 T2D cases. The confirmed genes suggested changes in chromatin modification and protein metabolism pathways in T2D.

[0060] Apart from emphasizing the importance of epigenetics and protein metabolism in T2D, this is a proof of concept study to use multiomic approach to discover pivotal genes in complex disease such as T2D.

II. General Methodology

[0061] Practicing this invention utilizes routine techniques in the field of molecular biology. Basic texts disclosing the general methods of use in this invention include Sambrook and Russell, *Molecular Cloning, A Laboratory Manual* (3rd ed. 2001); Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); and *Current Protocols in Molecular Biology* (Ausubel *et al.*, eds., 1994)).

[0062] For nucleic acids, sizes are given in either kilobases (kb) or base pairs (bp). These are estimates derived from agarose or acrylamide gel electrophoresis, from sequenced nucleic acids, or from published DNA sequences. For proteins, sizes are given in kilodaltons (kDa) or amino acid residue numbers. Protein sizes are estimated from gel electrophoresis, from sequenced proteins, from derived amino acid sequences, or from published protein sequences.

[0063] Oligonucleotides that are not commercially available can be chemically synthesized, *e.g.*, according to the solid phase phosphoramidite triester method first described by Beaucage and Caruthers, *Tetrahedron Lett.***22**:1859-1862 (1981), using an automated synthesizer, as described in Van Devanter *et. al.*, *Nucleic Acids Res.***12**:6159-6168 (1984). Purification of oligonucleotides is performed using any art-recognized strategy, *e.g.*, native acrylamide gel electrophoresis or anion-exchange high performance liquid chromatography (HPLC) as described in Pearson and Reanier, *J. Chrom.***255**: 137-149 (1983).

[0064] Standard next-generation DNA sequencing methods, including but not limited to those of Illumina, Ion Torrent, and Pacific Biosciences are well known in the art.

III. Multiomic Analysis

A. Subjects and sample preparation

[0065] A biological sample is obtained from a person to be tested or assessed for risk of developing type 2 diabetes or associated cardiovascular or renal disease using a method of the present invention. Collection of a tissue or fluid sample from an individual is performed in accordance with the standard protocol laboratories, hospitals or clinics generally follow, such as during a biopsy, blood drawing, saliva collection, or oral swab. An appropriate amount of sample is collected and may be stored according to standard procedures prior to further preparation.

[0066] The analysis of genomic DNA found in a subject's sample according to the present invention may be performed using essentially any tissue or bodily fluid, so long as genomic DNA is expected to be present in such sample. The methods for preparing tissue or fluid samples for nucleic acid extraction are well known among those of skill in the art. For example, a subject's epithelial tissue sample should be first treated to disrupt cellular membrane so as to release nucleic acids contained within the cells.

[0067] The Chinese family trio consisted of an affected mother (age: 69, age of diagnosis: 61) and daughter (age 48, age of diagnosis: 38) pair and an unaffected father (age 79). They were selected from the Hong Kong Family Diabetes Study which recruited over 180 families using an index patient with familial T2D diagnosed before the age of 40[16]. Peripheral blood samples were obtained from the family trio for isolation of PBMC using Ficoll-Paque stepwise gradient centrifugation. The isolated PBMC were divided for DNA and RNA extraction.

B. Whole genome sequencing and data analysis

1. DNA Extraction and Treatment

[0068] Methods for extracting DNA from a biological sample are well known and routinely practiced in the art of molecular biology, see, *e.g.*, Sambrook and Russell, *supra.* RNA contamination should be eliminated to avoid interference with DNA analysis. Optionally, other components (such as proteins and lipids) may be removed from the biological sample prior to further analysis of the genomic DNA.

2. Optional Amplification and Sequence Analysis

[0069] Following the desired processing of DNA/RNA in a biological sample, the DNA/RNA is then subjected to sequence-based analysis, such that the genomic sequence of one or more of the pertinent genes, or one or more of its transcripts, found in a test subject may be determined and then compared with a standard sequence to detect any possible sequence variation. An amplification reaction is optional prior to the sequence analysis. A variety of polynucleotide amplification methods are well established and frequently used in research. For instance, the general methods of polymerase chain reaction (PCR) for polynucleotide sequence amplification are well known in the art and are thus not described in detail herein. For a review of PCR methods, protocols, and principles in designing primers, *see, e.g.*, Innis, *et al.*, *PCR Protocols: A Guide to Methods and Applications*, Academic Press, Inc. N.Y., 1990. PCR reagents and protocols are also available from commercial vendors, such as Roche Molecular Systems.

[0070] Although PCR amplification is typically used in practicing the present invention, one of skill in the art will recognize that amplification of the relevant genomic sequence may be accomplished by any known method, such as the ligase chain reaction (LCR), transcription-mediated amplification, and self-sustained sequence replication or nucleic acid sequence-based amplification (NASBA), each of which provides sufficient amplification.

[0071] Techniques for polynucleotide sequence determination are also well established and widely practiced in the relevant research field. For instance, the basic principles and general techniques for polynucleotide sequencing are described in various research reports and treatises on molecular biology and recombinant genetics, such as Wallace *et al.*, *supra*; Sambrook and Russell, *supra*, and Ausubel *et al.*, *supra*. DNA sequencing methods routinely practiced in research laboratories, either manual or automated, can be used for practicing the present invention. Additional means suitable for determining the polynucleotide sequence of a genomic DNA for practicing the methods of the present invention include but are not limited to mass spectrometry, primer extension, polynucleotide hybridization, real-time PCR, melting curve analysis, high resolution melting analysis, heteroduplex analysis, pyrosequencing, and electrophoresis.

[0072] The DNA samples from the trio were subjected to 75bp pair-end sequencing using Solexa sequencer from Illumina. All procedures were performed in accordance to the specifications of manufacturer. All GA sequencing raw data was processed by the Illumina

Pipeline v1.3.1. After removing the low quality reads and adapter sequences, the filtered reads were aligned to the reference human genome hg18 using SOAP2 aligner developed by BGI[17]. The results were filtered and sorted. Variations in the sequence were identified by SOAPsnp v1.03[18]. Small indels in the sequence were identified by BWA aligner[19]. The identified variants were annotated and analyzed by SIFT (on the World Wide Web at sift-dna.org/)[20] to identify their functional implications.

C. Whole genome bisulfite sequencing and data analysis

[0073] Bisulfite sequencing was carried out to map the position of all methylcytosines in the genome. The DNA were fragmented and treated with bisulfite using standard protocol. DNA fragments in the size range of 320 to 380bp were gel purified for sequencing. All procedures were in accordance to the manufacturer's instructions. Converted DNA was subjected to 50bp pair-end Illumina GA sequencing using Solexa sequencer. All raw data was processed by the Illumina Pipeline v1.3.1.

[0074] The cleaned reads generated were aligned to the reference human genome hg18. Because DNA methylation is strand specific, the two strands of the reference human genome DNA was modified separately *in silico* to convert all 'C' to 'T' to generate a combined 6Gbp target genome to allow alignment after bisulfite conversion. The reads were also transformed using the following criteria: (1) observed 'C' in the forward reads was replaced by 'T'; (2) observed 'G' in the reverse reads was converted to 'A'. The transformed reads were then aligned to the modified target genome using SOAP2 aligner[17].

[0075] All the reads mapped to unique location with minimum mismatches and clear strand information were defined as uniquely matched reads and used to determine the methylated C. According to the SOAP alignment results, the unconverted C and G from the original read sequences were used to substitute the sequence in the corresponding positions of the aligned reads. Based on the aligned reads with all positions of the methylated C, the two strands of the DNA were transformed back to the original sequence with the methylated C marked. Potential CpG methylation sites were called when the 'C' positions were covered with cytosine in reads on the same strand or guanines from those on the opposite strand. Bases with quality scores lower than 14 were filtered out to exclude bases that were caused by sequencing errors.

D. Identification of differentially methylated regions (DMR)

[0076] The methylation levels were compared pairwise between two of the three samples to identify differentially methylated regions (DMR) using the following criteria. Firstly, we identified 'seed' regions containing at least 5 CpG sites with at least 2-fold change in methylation level ($P<0.05$, Fisher's exact test). We only included 'seed' regions with 20% or more CpG methylation in any one of the 3 subjects assuming that CpG sites with less than 20% methylation had no biological significance. Next, we extended the 'seed' region on both sides by adding the adjacent CpG sites until one of the following conditions were met: (1) the distance between two consecutive CpG was longer than 200 bp; (2) the average methylation fold change was less than 2; (3) both samples had less than 20% CpG methylation; (4) the P value from Chi-square test exceeded 0.01. The identified DMR were further filtered by the following criteria: (1) the statistical false discovery rate (FDR) was less than 0.05; (2) the DMR must be covered by 20 reads or more; (3) the CpG sites in the DMR must be covered by 10 reads or more. Differentially methylated regions fulfilling all these criteria were considered to be the authentic DMR.

E. mRNA Transcriptome sequencing and data analysis

[0077] Total RNA extracted from each sample was enriched by oligo-dT to obtain the polyA+ fraction for sequencing. The polyA+ mRNA was then fragmented and converted to cDNA by reverse transcription. After ligation of the 5' and 3' sequencing adaptors to the cDNA, DNA fragments were size selected for 75bp pair-end sequencing by Illumina Genome Analyzer II using standard procedures. All raw data was processed by the Illumina Pipeline v1.3.1. The generated reads were then mapped to the human genome hg18 using SOAP2 [17] and followed methods established from BGI [21, 22].

F. Identification of differentially expressed genes

[0078] All reads were mapped to the regions of known annotated genes expressed as reads per kilobase per million mapped reads (RPKM). The expression levels were compared pairwise between two of the three samples based on fold changes and p value of the difference using the method of Audic and Claverie [23]. Briefly, a difference in gene expression was considered significant if (1) fold change≥ 2; (2) P value≤ 0.001; (3) FDR≤ 0.001 and (4) expression level $\geq$ 10th percentile of all expressed transcripts in at least one of the 2 samples.

G. Small RNA sequencing and data analysis

[0079] Total RNA were fractionated by gel electrophoresis to isolate the small RNA portion corresponding to the size of 18 to 30 nucleotides for sequencing with Solexa Genome Analyzer II using standard procedures. Reads were filtered if (1) ≥ 4 bases with sequencing quality lower than 10 or ≥6 bases with sequencing quality lower than 13; (2) 5' adaptor was contaminated; (3) without 3' adaptor; (4) without insert tag; (5) with polyA or polyN; (6) shorter than 18 nt. The remaining 'clean reads' were then mapped back to the genome by SOAP2[17] to get the positions of small RNA tags along chromosomes. All the small RNA tags were also aligned by blastn (blastall -p blastn -F F -e 0.01) to the precursors and mature miRNA in the miRBase 15.0 to obtain the miRNA count for each miRNA expressed. Then the remaining small RNA tags were further aligned to the Rfam (by blastn, blastall -p blastn -F F -e 0.01), mRNA and piRNA from NCBI database to identify other small RNA species and small RNA fragments from degraded mRNA (exons and introns).

H. Identification of differentially expressed micro RNA

[0080] To identify the differential expression of miRNA, the number of tags mapping to known miRNA were considered as the expression level of the corresponding miRNA. The counts of each expressed miRNA were normalized to the total number of clean reads for comparison. The expression levels were compared pairwise between two of the three samples based on fold changes and the P value using published method [23].

I. Multiomic network analysis

[0081] We performed candidate gene prioritization of T2D through network analysis by integration of multiomic data. The difference networks of mother vs. father (M/F network) and daughter vs. father (D/F network) were constructed separately. Then the common parts of these two networks were considered as M/F and D/F co-segregated network or T2D relevant network. Characteristics of each gene could be represented by a vector (6 elements) corresponding to the multiomic data. These 6 elements are log2 ratios of gene expression, methylation level of gene body, methylation level of promoter region, tDMR in gene body, tDMR in promoter region and being the target genes of the miRNA showing the most significant difference in gene expression. We used 4 database to predict miRNA target genes: (1) MicroCosm_Targets (on the World Wide Web at ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/), (2) TargetScanHuman (on the World Wide Web at targetscan.org/vert_60/), (3) microRNA.org (on the World Wide Web at

microrna.org/microrna/getDownloads.do), and (4) TarBase_V5.0_human (on the World Wide Web at diana.cslab.ece.ntua.gr/tarbase/tarbase_download.php). Only target genes identified by at least 3 out of the 4 databases will be included for analysis. After discarding genes with too many missing elements (≥2), the M/F and D/F networks included 3,180 and 3,091 genes separately.

[0082] We used modified RV-coefficient [24], which is a generalization of Pearson correlation coefficient, as a measure of similarity of genes. Herein, RV-coefficients were computed for all pair of genes. From a network perspective, genes were taken as nodes, and edges were added between genes if they were significantly correlated. Scale-free is considered as robustness, which is one of the most prominent characteristics of biological network [25]. In order to make the T2D relevant network (the common parts of M/F and D/F networks) scale-free network, we chose $p<0.035$ (RV-coefficient) to simplify the relationship of genes in M/F and D/F networks. Finally, the T2D relevant network included 2,375 notes and 121,368 edges.

[0083] Corresponding to topology structure of network, betweenness centrality (BC) [26] and closeness centrality (CC) [27] hubs, are very crucial for maintaining network architecture and functionality [28]. Also, there were 17 known T2D GWAS genes in the T2D relevant network. So, hubs located on the shortest way between known T2D GWAS genes were selected for further study [25].

J. Gene expression validated by qRT-PCR

[0084] The gene expression level changes found in the RNA transcriptome analysis and microRNA expression were validated by real-time quantitative PCR (qRT-PCR) in 65 controls and 65 T2D cases. First strand cDNA was synthesized by the High-Capacity cDNA Reverse Transcription Kit (ABI Biosystems) using 0.5 μg total RNA as template. The SYBR Green method was used for qRT-PCR using an ABI 7900HT Real-time PCR machine and SYBP® Premix Ex Taq™ (Perfect Real Time) from Takara. The expression levels of each tested gene were tested by real time qPCR for 40 cycles. The expression levels of mRNA were normalized to the expression level of β-actin. The expression level of microRNA were normalized to the expression level of U6 small RNA.

K. DNA Methylation validated by Sequenom MassARRAY

[0085] DNA methylation changes were validated by the Sequenom MassARRAY Compact System (Sequenom, Inc.) using the EpiTYPER assay. Genomic sequences from interested regions were used to design the primers for the assay. DNA samples were extracted from the PBMCs of 65 controls and 65 T2D cases. For each sample, 1 ug of DNA was treated with sodium bisulfite using the EZ DNA MethylationTM kit (Zymo Research) according to manufacturer's procedure. The treated DNA were PCR amplified and tested for DNA methylation for individual CpG diculeotides at the interested genomic regions using EpiTYPER (Sequenom, Inc.) according to manufacturer's standard protocols.

IV. Therapeutic and Preventive Measures

[0086] By illustrating the correlation between genomic sequence or expression variation and the presence or heightened risk of developing type 2 diabetes or cardiovascular and renal diseases among related subjects, especially those fitting certain profiles, such as those of Asian descent, in particular Han Chinese, the present inventors have provided a valuable tool for clinicians to determine, often in combination with other information and diagnostic or predictive or screening test results, how a subject having certain genomic characteristics should be monitored and/or treated for type 2 diabetes and diabetic cardiovascular or renal disease such that the symptoms of these conditions may be prevented, eliminated, ameliorated, reduced in severity and/or frequency, or delayed in their onset. For example, a physician may arrange for regular monitoring of various symptoms oftype 2 diabetes or diabetic cardiovascular and renal diseases in a subject who has been deemed by the method of the present invention to have an elevated risk of developing type 2 diabetes. The physician may also prescribe both pharmacological and non-pharmacological treatments such as lifestyle modification (*e.g.*, reduce body weight by 5%, high fiber diet, walking for at least 150 minutes weekly) and medicines known to reduce risk of onset of diabetes (*e.g.*, metformin, alpha glucosidase inhibitors, lipase inhibitors) to a subject who has been deemed by the method of the present invention to have an elevated risk of developing type 2 diabetes. For a subject who has been deemedby the method of the present invention to suffer from or at risk of developing diabetic cardiovascular or renal disease, the attending physician may prescribe medications to control risk factors such as high levels of blood cholesterol and triglycerol (*e.g.*, statins and fibrates) and reduce angiotensin II activity (*e.g.*, Angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB)), as well as

place the subject under regular testing and monitoring of coronary artery condition and kidney function.

[0087] Multiomic signatures obtained using the methods described herein can also be used to develop and screen new therapies for diabetes and its comorbidities.

V. Kits and Devices

[0088] The presentinvention provides compositions and kits for practicing the methods described herein to detect possible genomic sequence variation of certain gene(s) and the transcripts thereof in a subject, which can be used for various purposes such as detecting or diagnosing the presence of type 2 diabetes and diabetic cardiovascular or renal disease in a subject, determining the risk of developing type 2 diabetes and diabetic cardiovascular or renal disease in a subject, and guiding the treatment plan for these conditions in the subject.

[0089] Kits for carrying out assays for determining the nucleotide sequence of a relevant genomic sequence typically include at least one oligonucleotide useful for specific hybridization with a predetermined segment of a pertinent genomic sequence. Optionally, this oligonucleotide is labeled with a detectable moiety. In some cases, the oligonucleotide specifically hybridizes with the standard sequence only but not with any of the variant sequences. In other cases, the oligonucleotide specifically hybridizes with one particular version of the variant sequence but not with other versions, nor with the standard sequence.

[0090] In some cases, the kits may include at least two oligonucleotide primers that can be used in the amplification of at least one segment of a pertinent genomic sequence or transcripts thereof by PCR. In some examples, at least one of the oligonucleotide primers is designed to anneal only to the standard sequence or only to a particular version of the variant sequences.

[0091] In addition, the kits of this invention may provide instruction manuals (*e.g.*, internet-based decision support tools) to guide users in analyzing test samples and assessing the presence or future risk of type 2 diabetes and diabetic cardiovascular or renal disease in a test subject.

VI. Computer Systems

[0092] Any of the computer systems mentioned herein may utilize any suitable number of subsystems. Examples of such subsystems are shown in **Figure 3** in computer apparatus 300. In some embodiments, a computer system includes a single computer apparatus, where the

subsystems can be the components of the computer apparatus. In other embodiments, a computer system can include multiple computer apparatuses, each being a subsystem, with internal components.

[0093] The subsystems shown in **Figure 3** are interconnected via a system bus 375. Additional subsystems such as a printer 374, keyboard 378, storage device(s) 379, monitor 376, which is coupled to display adapter 382, and others are shown. Peripherals and input/output (I/O) devices, which couple to I/O controller 371, can be connected to the computer system by any number of means known in the art, such as serial port 377. For example, serial port 377 or external interface 381 (e.g. Ethernet, Wi-Fi, etc.) can be used to connect computer system 300 to a wide area network such as the Internet, a mouse input device, or a scanner. The interconnection via system bus 375 allows the central processor 373 to communicate with each subsystem and to control the execution of instructions from system memory 372 or the storage device(s) 379 (e.g., a fixed disk, such as a hard drive or optical disk), as well as the exchange of information between subsystems. The system memory 372 and/or the storage device(s) 379 may embody a computer readable medium. Any of the data mentioned herein can be output from one component to another component and can be output to the user.

[0094] A computer system can include a plurality of the same components or subsystems, e.g., connected together by external interface 381 or by an internal interface. In some embodiments, computer systems, subsystem, or apparatuses can communicate over a network. In such instances, one computer can be considered a client and another computer a server, where each can be part of a same computer system. A client and a server can each include multiple systems, subsystems, or components.

[0095] It should be understood that any of the embodiments of the present invention can be implemented in the form of control logic using hardware (e.g. an application specific integrated circuit or field programmable gate array) and/or using computer software with a generally programmable processor in a modular or integrated manner. As user herein, a processor includes a multi-core processor on a same integrated chip, or multiple processing units on a single circuit board or networked. Based on the disclosure and teachings provided herein, a person of ordinary skill in the art will know and appreciate other ways and/or methods to implement embodiments of the present invention using hardware and a combination of hardware and software.

[0096] Any of the software components or functions described in this application may be implemented as software code to be executed by a processor using any suitable computer language such as, for example, Java, C++ or Perl using, for example, conventional or object-oriented techniques. The software code may be stored as a series of instructions or commands on a computer readable medium for storage and/or transmission, suitable media include random access memory (RAM), a read only memory (ROM), a magnetic medium such as a hard-drive or a floppy disk, or an optical medium such as a compact disk (CD) or DVD (digital versatile disk), flash memory, and the like. The computer readable medium may be any combination of such storage or transmission devices.

[0097] Such programs may also be encoded and transmitted using carrier signals adapted for transmission via wired, optical, and/or wireless networks conforming to a variety of protocols, including the Internet. As such, a computer readable medium according to an embodiment of the present invention may be created using a data signal encoded with such programs. Computer readable media encoded with the program code may be packaged with a compatible device or provided separately from other devices (e.g., via Internet download). Any such computer readable medium may reside on or within a single computer product (e.g. a hard drive, a CD, or an entire computer system), and may be present on or within different computer products within a system or network. A computer system may include a monitor, printer, or other suitable display for providing any of the results mentioned herein to a user.

[0098] Any of the methods described herein may be totally or partially performed with a computer system including one or more processors, which can be configured to perform the steps. Thus, embodiments can be directed to computer systems configured to perform the steps of any of the methods described herein, potentially with different components performing a respective steps or a respective group of steps. Although presented as numbered steps, steps of methods herein can be performed at a same time or in a different order. Additionally, portions of these steps may be used with portions of other steps from other methods. Also, all or portions of a step may be optional. Additionally, any of the steps of any of the methods can be performed with modules, circuits, or other means for performing these steps.

EXAMPLE

[0099] The following example is provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

Methylome of the trio and differential methylation regions (DMRs) in the genome

[0100] The present inventors used whole genome bisulfite sequencing to obtain single-base resolution DNA methylome of human PBMC of the trio. Over 140 Gbp of DNA sequences were obtained from each member of the triowith about 30× effective coverage of the human genome (**Table 1**). Mapped DNA sequences were used to calculate the degree of ^{m}C coverage at each position of C in the human genome. About 95% of the C in all autosomes was covered. Most of the DNA methylation were found in CG sites with a minority being, non-CG methylation. Differences in CG DNA methylation were identified by pairwise comparisons in the trio. Using a stringent seed expansion method, the inventors identified 2686, 2040 and 1514 DMRs in the corresponding FM, FD and MD pair wise comparisons (**Figure 4**). To identify DMR possibly related to T2D, we selected 186 DMRs present in both FM and FD comparisons but not in the MD comparison (**Table 2**). If 50% or more of the DMR sequence overlapped with the 2Kb promoter region of a gene, the latter was considered to be linked to the DMR. From these 186 DMRs, 32 genes were identified**(Table 3)**with promoter regions overlapping with the DMR. The inventors calculated the ^{m}C methylation coverage in the 2Kb promoter regions and found that the DNA ^{m}C methylation in these promoter regions showed a general trend in agreement with the DMRs identified.

Transcriptome by RNA-Seq and differentially expressed genes

[0101] In order to ascertain the functional significance of changes in DNA methylation, RNA sequencing was performed on the RNA samples from PBMC. Most of the sequence reads were mapped to the annotated human reference genes successfully (**Table 1**). The mapped sequences represented expression of 16469, 16732 and 16916 annotated gene loci from the father, mother and daughter respectively with the majority of transcripts expressed in all 3 subjects. Using 2-fold difference as the criterion in pair wise comparisons, 1097, 848 and 548 genes were differentially expressed in the FM, FD and MD pairs respectively. In the Venn diagram, 413 genes (listed in **Table 4**) showed differential expression in the FD and FM pairs but not in the MD comparison (**Figure 5**). Of these, 15 were located on the Y chromosome. In the remaining 398 genes, 200 showed decreased expression in the FM and FD pairs and 198 showed increased expression.

MicroRNA expression profile

[0102] Small RNA, especially microRNA, is a key regulator of many cellular pathways. Sequencing of the small RNA from the trio identified small RNA from different categories including scRNA, snoRNA, microRNA, snRNA, srpRNA, piRNA and parts of other RNA components of the cell, including tRNA, rRNA, repeat sequences as well as exon and intron sequences. Among the RNA sequence reads, microRNA sequences accounted for 70% of the total sequence reads. From these aligned RNA sequence reads, 616, 581 and 591 microRNAs were identified for the father, mother and daughter respectively. Among these expressed microRNAs, 540 were expressed in all 3 members. Pair wise comparisons showed that 67 microRNAs (listed in **Table 5**) were differentially expressed only in the FM and FD pairs but not the MD pair (**Figure 5**).

Multiomic features and network analysis

[0103] The inventors used network analysis to integrate these multiomic features to identify key regulatory genes and their pathways.Using the information on DNA methylation and gene expression and being the target of differentially expressed microRNA, two networks were constructed using pair wise comparison data from FM and FD pairs. The common components of the two networks were used as the putative T2D gene network. From this network a subnetwork containing a maximum of 17 of the known T2D GWAS genes was constructed. This T2D related network contains 141 genes located at the shortest connection with these 17 T2D GWAS genes (**Figure 6**). On this T2D gene network 15 genes (listed in **Table 6**) are the hub genes that are mostly used for connection. Among the 32 genes (listed in **Table 3**) with promoter regions overlapping the DMRs, *PDCD1* (Programmed cell death 1) is the only one overlapped with the 413 genes showing differential expression. *PDCD1* showed increased DNA methylation with decreased gene expression. This pattern of change can be validated in 65 controls versus 65 T2D cases (**Figure 7; Table 7, Table 8**) using quantitative PCR (qRT-PCR) and Sequenom EpiTYPER DNA methylation assays. The expression and DNA methylation of two additional genes discovered by network analysis, *EIF4E3* and *PACRG*, were also validated. *KDM2B* is a chromatin modifying enzyme showing differential methylation (DMR) in the trio. *KDM2B* is also a regulatory gene for the expression of the T2D GWAS gene *CDKN2A/B*. Both the expression and DNA methylation of *KDM2B* and *CDKN2B* showed significant changes in the 65 vs 65 case control cohort (**Figure 7**).

Discovery of T2D SNPs from multiomic and network analysis

[0104] Network analysis and multiomic analysis discovered genes associated with T2D. From the millions of SNPs called in the trio, many of them are co-segregated in the mother daughter pair. Such SNPs were correlated with gene expression (**Table 9**) and DNA methylation (**Table 10**) data, and SNP genotypes associated with a T2D risk were identified.The co-segregated SNPs in the focus gene regions were checked against the results of the 4 million SNPs in the Chinese GWAS meta-analysis consisted of 955 controls and 677 T2D cases [10]. Many of them showed significance in association with T2D (**Table 2**) and chosen for additional round of independent genotyping in 421 controls and 1144 T2D cases. Two SNPs, rs9998519 from the known T2D GWAS gene *WFS1* and rs1534938 from *PACRG*, a gene involved in cytoskeleton and protein folding, showed significance in association with T2D (**Table 11**).

Conclusion

[0105] By using a multiomic approach to ascertain the correlations of different features in a trio family, coupled with network analysis, the present inventors were able to discover novel loci for T2D implicated in chromatin modification, protein folding and intracellular trafficking. Given the increasing affordability of high throughput sequencing, advances in computational analysis as well as availability of multiple cohorts, GWAS datasets and bioinformatics tools, our integrated experiments have provided a template to use DNA and RNA extracted from PBMC to discover novel loci for complex diseases such as T2D.

[0106] All patents, patent applications, and other publications, including GenBank Accession Numbers, cited in this application are incorporated by reference in the entirety for all purposes.

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TABLES

Table 1 Sequencing summary of the trio.

		Father		Mother		Daughter	
		Bases (G)	Depth*1	Bases (G)	Depth*1	Bases (G)	Depth*1
Genome sequencing	Raw data	96.7	32×	91.9	31×	101.2	34×
	Filtered data*1	89.5	30×	85.3	28×	94.6	32×
	Mapped data*2	82.3	28×	78.5	26×	87.0	29×
Transcriptome sequencing	Raw data	7.9	15.8	9.9	19.8	12.7	25.4
	Filtered data*1	5.5	11.0	7.9	15.8	10.2	20.4
	Mapped data*2	4.9	9.8	7.5	15.0	9.5	19.0
Methylome sequencing	Raw data	152.4	51.3×	140.5	47.3×	141.8	47.7×
	Filtered data*1	142.4	47.9×	129.8	43.7×	129.7	43.7×
	Mapped data*2	96.5	32.5×	77.5	26.1×	88.9	29.9×
		Reads		Reads		Reads	
MicroRNA sequencing	Raw data	17418802		19351315		15739336	
	Filtered data	14636972		16853914		13122669	
	Mapped data*2	11643536		13370576		10318337	

*1. Calculation was based on the genome size of 2.97 Gb. And for transcriptome data, the total coding sequence length was set as 500 Mb.

*2. Adaptor contaminated, low quality, duplicated reads were filtered.

Table 1 Summary of the sequencing results. Over 90G of whole genome sequencing and over 140G of bisulfite sequencing data were generated for each member of the trio. All sequencing data generated from whole genome sequencing, bisulfite sequencing, RNA sequencing and microRNA sequencing were subjected to QC procedure to remove low quality reads and then mapped to human genome build 36 (hg18).

Table 2 List of the FM and FD common DMRs identified from the family trio

Chr	Start	End	Size (bp)	Log2 FM fold	Log2 FD fold	Direction
chr1	921095	921456	361	1.00	1.14	up
chr1	2532436	2532762	326	-1.05	-1.17	down
chr1	7518557	7519090	533	-1.08	-1.08	down
chr1	17297219	17297455	236	1.08	1.19	up
chr1	19122980	19123204	224	1.13	1.22	up
chr1	62524841	62525284	443	-1.13	-1.04	down
chr1	147436457	147437055	598	1.00	1.08	up
chr1	164078594	164078806	212	3.36	2.86	up
chr1	206404699	206404984	285	1.14	1.26	up
chr1	215153254	215153703	449	1.10	1.24	up
chr1	227573038	227573523	485	1.08	1.00	up
chr1	246166806	246167654	848	1.43	1.86	up
chr2	458658	458934	276	1.07	1.07	up
chr2	7782836	7783104	268	1.05	1.21	up
chr2	21121080	21121329	249	1.05	1.03	up
chr2	37085602	37086100	498	1.24	1.31	up
chr2	46587206	46587418	212	1.58	1.66	up
chr2	70555952	70556161	209	1.14	1.04	up
chr2	105758647	105759621	974	1.13	1.21	up
chr2	106570233	106570535	302	1.10	1.00	up
chr2	112350810	112351207	397	2.22	1.56	up
chr2	136605518	136606363	845	-1.32	-1.15	down
chr2	149716003	149716545	542	1.26	1.09	up
chr2	167174820	167176108	1288	1.08	1.00	up
chr2	236319809	236320070	261	-1.32	-1.32	down
chr2	241493598	241493802	204	1.03	1.06	up
chr3	2781806	2782020	214	1.00	1.20	up
chr3	69485053	69485404	351	1.08	1.04	up
chr3	72479591	72480181	590	1.45	1.32	up
chr3	141322442	141322837	395	-1.58	-1.87	down
chr3	197809458	197809848	390	1.96	2.07	up
chr4	9629836	9630267	431	1.06	1.13	up
chr4	38187472	38187720	248	-1.08	-1.08	down
chr4	55000809	55001457	648	1.43	1.53	up
chr4	109916433	109916723	290	1.30	1.30	up
chr4	147773215	147773660	445	1.22	1.14	up
chr4	165865588	165865979	391	1.69	1.34	up
chr4	182668242	182668877	635	1.20	1.02	up
chr4	186413669	186414272	603	1.74	1.12	up
chr4	186762687	186763063	376	1.12	1.09	up
chr5	1155445	1155675	230	1.00	1.05	up
chr5	3156310	3156774	464	1.05	1.05	up
chr5	111855865	111856249	384	2.19	1.72	up
chr5	111903540	111903937	397	2.04	1.69	up
chr5	150598935	150599610	675	1.44	1.53	up
chr5	180018484	180018784	300	2.06	2.22	up
chr6	2508898	2509217	319	1.00	1.20	up

chr6	33980643	33981169	526	-1.65	-1.87	down
chr6	36194298	36194610	312	1.15	1.00	up
chr6	37817757	37818191	434	1.15	1.44	up
chr6	42013004	42013252	248	1.00	1.32	up
chr6	48144802	48145295	493	1.00	1.38	up
chr6	91700987	91701347	360	1.00	1.00	up
chr6	131613039	131613256	217	1.06	1.24	up
chr6	156758934	156759638	704	-1.06	-1.00	down
chr6	158815623	158815945	322	1.27	1.07	up
chr6	164715221	164715627	406	1.09	1.30	up
chr7	1945557	1945918	361	1.18	0.95	up
chr7	2026322	2026543	221	1.05	1.10	up
chr7	2026336	2026566	230	1.05	1.05	up
chr7	3153139	3153517	378	1.04	1.20	up
chr7	5083914	5084118	204	1.13	1.00	up
chr7	7602342	7602573	231	1.28	1.44	up
chr7	27143376	27143579	203	1.21	1.05	up
chr7	29184327	29184683	356	-1.27	-1.05	down
chr7	38315887	38316125	238	2.42	2.00	up
chr7	52053577	52053838	261	-1.21	-1.40	down
chr7	53254086	53254368	282	1.00	1.14	up
chr7	53254086	53254368	282	1.00	1.14	up
chr7	57210018	57210231	213	1.14	1.07	up
chr7	134996929	134997597	668	2.10	1.54	up
chr8	1443332	1443655	323	-1.10	-1.10	down
chr8	17553311	17553617	306	1.32	1.20	up
chr8	54158684	54159076	392	-1.31	-1.00	down
chr8	99092907	99093223	316	1.07	1.20	up
chr8	103681814	103682114	300	1.05	1.05	up
chr8	103743690	103744673	983	1.04	1.38	up
chr8	134799815	134800128	313	-1.74	-1.64	down
chr8	137096242	137096495	253	-1.32	-1.15	down
chr8	142624198	142624654	456	1.00	1.07	up
chr8	143806564	143807239	675	1.06	1.12	up
chr8	144785690	144786286	596	1.06	1.18	up
chr9	6706207	6706410	203	1.00	1.00	up
chr9	15283820	15284025	205	1.05	1.05	up
chr9	124208107	124208940	833	-1.57	-1.12	down
chr9	135390134	135390330	196	1.06	1.05	up
chr10	1401177	1401531	354	1.10	1.14	up
chr10	1675605	1675846	241	1.07	1.07	up
chr10	1704796	1705002	206	-1.03	-1.05	down
chr10	3586433	3586747	314	-1.15	-1.15	down
chr10	23531781	23532257	476	0.93	1.00	up
chr10	23532652	23532908	256	1.00	1.11	up
chr10	33647636	33647903	267	1.05	1.05	up
chr10	45415837	45416085	248	1.00	1.03	up
chr10	71627118	71627572	454	1.06	1.06	up
chr10	75404348	75404613	265	-1.40	-1.12	down
chr10	80367359	80367682	323	1.00	1.12	up

chr10	80430872	80431071	199	1.04	1.08	up
chr10	95232526	95232919	393	1.51	2.12	up
chr10	104184192	104184393	201	1.13	1.13	up
chr10	114139165	114139539	374	1.52	1.52	up
chr10	119483997	119484297	300	1.00	1.14	up
chr10	126336367	126336593	226	1.10	1.15	up
chr10	129679019	129679273	254	1.05	1.05	up
chr10	131645374	131645928	554	-1.00	-1.16	down
chr11	6054942	6055284	342	-1.02	-1.47	down
chr11	10250169	10250444	275	1.08	1.25	up
chr11	65403818	65404312	494	1.24	1.05	up
chr11	110606489	110606807	318	1.24	1.13	up
chr11	112618724	112619284	560	-1.58	-1.30	down
chr12	4086923	4087167	244	4.86	5.09	up
chr12	19827764	19828029	265	1.02	1.05	up
chr12	52661188	52661478	290	1.07	1.00	up
chr12	74071092	74072128	1036	2.37	1.74	up
chr12	93162392	93162710	318	1.11	1.14	up
chr12	99634239	99634611	372	0.96	1.04	up
chr12	129209003	129209346	343	1.14	1.14	up
chr13	18847052	18847261	209	1.29	1.10	up
chr13	48004011	48004553	542	1.00	1.06	up
chr14	22842253	22842456	203	-1.00	-1.00	down
chr14	23111526	23111774	248	1.07	1.04	up
chr14	24020632	24021014	382	1.03	1.03	up
chr14	31529981	31530353	372	-1.37	-1.37	down
chr14	49619439	49619992	553	-1.04	-1.22	down
chr14	50328609	50328838	229	-1.05	-1.05	down
chr14	51580080	51580451	371	1.10	1.06	up
chr14	65473951	65474285	334	-1.00	-1.05	down
chr14	86479260	86479549	289	1.32	1.17	up
chr14	90914202	90914533	331	1.14	1.26	up
chr14	105066551	105066903	352	1.12	1.22	up
chr14	105600101	105600480	379	-1.26	-1.50	down
chr15	49278173	49278541	368	1.28	1.34	up
chr15	81128937	81129286	349	-1.07	-1.02	down
chr15	84096976	84097196	220	1.08	1.08	up
chr15	87375140	87375442	302	1.20	1.00	up
chr15	92669570	92669911	341	1.36	1.11	up
chr16	2523224	2523529	305	1.65	1.94	up
chr16	3008436	3008773	337	1.30	1.09	up
chr16	4085871	4086286	415	1.14	1.14	up
chr16	31078350	31078815	465	1.00	1.00	up
chr16	32034495	32034713	218	-1.13	-1.00	down
chr16	32034713	32035184	471	-1.81	-1.58	down
chr16	73870822	73871059	237	1.10	1.07	up
chr16	84876755	84877006	251	1.09	1.13	up
chr17	6295619	6295936	317	1.13	1.09	up
chr17	6496186	6497030	844	1.15	1.20	up
chr17	7095416	7095781	365	-1.39	-2.81	down

chr17	7883043	7883385	342	1.00	1.00	up
chr17	9569464	9569996	532	1.22	1.18	up
chr17	9963837	9964477	640	1.14	1.14	up
chr17	15626944	15627404	460	1.39	1.55	up
chr17	18413439	18413964	525	1.07	1.20	up
chr17	33970216	33970492	276	1.17	1.06	up
chr17	35331147	35331396	249	1.26	1.20	up
chr17	51009270	51010015	745	1.11	1.10	up
chr17	51009303	51010023	720	1.13	1.10	up
chr17	51009303	51010023	720	1.13	1.14	up
chr17	51010132	51010355	223	1.00	1.13	up
chr17	61800967	61801177	210	1.03	0.97	up
chr18	2316914	2317296	382	-1.10	-1.10	down
chr18	53933941	53934153	212	-1.34	-1.48	down
chr18	61993521	61993982	461	1.61	1.13	up
chr18	74268559	74269040	481	1.13	1.49	up
chr19	8580174	8580449	275	1.07	1.14	up
chr19	13179526	13179767	241	1.62	1.06	up
chr19	13833100	13833336	236	1.07	1.00	up
chr19	21056736	21057475	739	3.12	3.46	up
chr19	44622900	44623233	333	-1.09	-1.03	down
chr19	53692512	53692762	250	0.98	1.00	up
chr19	53692571	53692858	287	1.00	0.98	up
chr19	55610054	55610321	267	-1.32	-1.11	down
chr19	56327108	56327937	829	1.09	1.25	up
chr19	56585747	56586331	584	1.15	1.10	up
chr19	58392487	58392887	400	-1.03	-1.03	down
chr19	58392494	58392892	398	-1.03	-1.05	down
chr19	62167264	62167564	300	2.62	2.81	up
chr20	28138120	28139087	967	1.00	1.38	up
chr20	30527006	30527358	352	1.00	1.04	up
chr20	49450353	49450708	355	-1.00	-1.00	down
chr20	59341098	59341305	207	-1.00	-1.10	down
chr21	36408020	36408315	295	1.00	1.04	up
chr21	46428315	46428789	474	-2.49	-1.64	down
chr22	18132706	18133148	442	1.05	1.11	up
chr22	19281307	19281516	209	2.77	2.68	up
chr22	36902057	36902645	588	1.12	1.22	up
chr22	38974092	38974308	216	-1.46	-1.00	down

Table 3 List of genes with promoters overlapped with the DMRs

Gene ID	Symbol	Cytoband	strand	DMR Methylation	Father Expression	Mother Expression	Daughter Expression	Father Promoter Methylation	Mother Promoter Methylation	Daughter Promoter Methylation
5876	*RABGGTB*	1p31	+	Up	30.82	33.13	32.83	0.219	0.256	0.257
431707	*LHX8*	1p31.1	+	Up	0.00	0.00	0.00	0.137	0.213	0.272
2331	*FMOD*	1q32	-	Up	0.01	0.00	0.01	0.613	0.632	0.621
5778	*PTPN7*	1q32.1	-	Up	17.04	19.47	15.41	0.097	0.158	0.153
338	*APOB*	2p24-p23	-	Up	0.00	0.00	0.00	0.486	0.611	0.632
5133	*PDCD1*	2q37.3	-	Down	0.45	0.90	1.31	0.455	0.334	0.345
6897	*TARS*	5p13.2	+	Up	22.30	24.91	21.77	0.135	0.177	0.187
9443	*MED7*	5q33.3	-	Up	11.72	10.23	10.48	0.287	0.320	0.355
442213	*C6orf138*	6p12.3	-	Up	0.00	0.00	0.00	0.00	0.00	0.00
9465	*AKAP7*	6q23	+	Up	7.09	6.64	7.14	0.506	0.570	0.567
10370	*CITED2*	6q23.3	-	Up	38.74	53.76	47.78	0.025	0.034	0.039
54919	*HEATR2*	7p22.3	+	Up	3.50	4.02	4.38	0.323	0.445	0.383
5157	*PDGFRL*	8p22-p21.3	+	Up	0.00	0.00	0.04	0.178	0.241	0.273
79754	*ASB13*	10p15.1	-	Up	4.30	4.20	4.93	0.124	0.148	0.172
79004	*CUEDC2*	10q24.32	-	Up	13.89	17.24	16.86	0.288	0.356	0.334
440044	*SLC22A20*	11q13.1	+	Up	0.04	0.05	0.06	0.454	0.488	0.525
84678	*KDM2B*	12q24.31	-	Up	14.16	15.79	14.54	0.125	0.164	0.202
2321	*FLT1*	13q12	-	Up	0.63	0.36	0.43	0.170	0.207	0.227
2958	*GTF2A2*	15q22.2	-	Up	21.36	22.15	19.48	0.432	0.473	0.505
78994	*PRR14*	16p11.2	+	Up	16.24	18.53	17.77	0.276	0.296	0.307
9074	*CLDN6*	16p13.3	-	Up	0.00	0.06	0.03	0.399	0.430	0.452

51330	*TNFRSF12A*	16p13.3	+	Up	1.35	1.13	0.83	0.404	0.445	0.450
752014	*CEMP1*	16p13.3	-	Up	2.39	4.06	4.22	0.012	0.016	0.020
23587	*C17orf81*	17p13.1	+	Down	9.37	12.15	9.80	0.115	0.073	0.059
124773	*C17orf64*	17q23.2	+	Down	0.06	0.06	0.00	0.220	0.159	0.169
147463	*ANKRD29*	18q11.2	-	Up	0.07	0.05	0.14	0.339	0.395	0.381
6217	*RPS16*	19q13.1	-	Up	909.75	1631.30	1545.58	0.303	0.366	0.362
147872	*CCDC155*	19q13.33	+	Up	0.03	0.00	0.02	0.502	0.556	0.650
140689	*CBLN4*	20q13.13-q13.33	-	Up	0.00	0.00	0.00	0.203	0.268	0.265
7307	*U2AF1*	21q22.3	-	Up	52.18	57.21	51.10	0.058	0.082	0.091
84221	*C21orf56*	21q22.3	-	Down	0.80	1.64	1.37	0.441	0.304	0.342
7494	*XBP1*	22q12.1|22q12	-	Up	83.52	89.63	69.25	0.066	0.080	0.086

Expression levels are expressed as RPKM (reads per kilobase per million mapped reads); methylation levels are expressed as the proportion of ^{m}C in the region as 0.0 being no methylation and 1.0 being 100% methylated.

Table 4 FM and FD differentially expressed genes in the family trio

Gene ID	Symbol	Cytoband	Father expression	Mother expression	Daughter expression	Change
777	*CACNA1E*	1q25-q31	0.28	0.06	0.08	Down
1266	*CNN3*	1p22-p21	0.47	1.10	1.02	Up
1380	*CR2*	1q32	0.74	2.27	3.14	Up
3399	*ID3*	1p36.13-p36.12	1.75	4.11	4.78	Up
3915	*LAMC1*	1q31	0.52	1.15	1.05	Up
6097	*RORC*	1q21	1.10	2.89	4.25	Up
6375	*XCL1*	1q23	4.00	1.81	1.05	Down
8991	*SELENBP1*	1q21.3	0.75	1.84	3.34	Up
9636	*ISG15*	1p36.33	7.89	21.32	36.18	Up
9672	*SDC3*	1pter-p22.3	0.36	0.74	0.92	Up
10158	*PDZK1IP1*	1p33	20.96	4.98	7.81	Down
11004	*KIF2C*	1p34.1	0.79	0.39	0.38	Down
23127	*GLT25D2*	1q25	3.82	0.67	0.92	Down
25790	*CCDC19*	1q22	1.79	0.53	0.52	Down
27184	*DISC2*	1q42.1	0.30	0.10	0.12	Down
51127	*TRIM17*	1q42	1.41	0.65	0.65	Down
54344	*DPM3*	1q22	4.17	12.45	9.54	Up
55924	*C1orf183*	1p13.2	9.96	3.95	4.15	Down
79368	*FCRL2*	1q21	3.74	14.25	11.62	Up
79639	*TMEM53*	1p34.1	0.34	1.13	1.20	Up
79656	*BEND5*	1p33	0.34	1.40	1.24	Up
79762	*C1orf115*	1q41	0.74	2.06	1.97	Up
83416	*FCRL5*	1q21	1.19	4.53	3.67	Up
84809	*CROCCL1*	1p36.13	8.91	23.84	22.75	Up
84824	*FCRLA*	1q23.3	4.64	14.92	10.64	Up
116496	*FAM129A*	1q25	69.39	29.27	30.75	Down
127254	*C1orf173*	1p31.1	0.17	0.07	0.06	Down
256435	*ST6GALNAC3*	1p31.1	0.93	1.99	1.93	Up
257101	*ZNF683*	1p36.11	0.96	3.12	3.71	Up
339483	*MTMR9L*	1p35.1	0.68	0.33	0.22	Down
348378	*FAM159A*	1p32.3	2.39	5.70	4.88	Up
374946	*C1orf187*	1p36.22	2.35	0.76	0.60	Down
375790	*AGRN*	1p36.33	0.18	0.43	0.68	Up
388698	*FLG2*	1q21.3	0.34	0.16	0.14	Down
785	*CACNB4*	2q22-q23	1.63	0.40	0.47	Down
1285	*COL4A3*	2q36-q37	0.15	0.71	0.86	Up
1286	*COL4A4*	2q35-q37	0.21	0.55	0.62	Up
1496	*CTNNA2*	2p12-p11.1	0.26	0.01	0.01	Down
1593	*CYP27A1*	2q33-qter	6.97	18.67	17.74	Up
1674	*DES*	2q35	0.04	0.67	0.54	Up
2498	*FTHL3P*	2p23.3	7.45	1.65	3.06	Down
2817	*GPC1*	2q35-q37	0.04	0.20	0.26	Up
3485	*IGFBP2*	2q33-q34	1.40	0.16	0.11	Down
3577	*IL8RA*	2q35	74.66	23.03	17.27	Down
3579	*IL8RB*	2q35	182.14	53.93	39.07	Down
4084	*MXD1*	2p13-p12	64.88	31.90	29.55	Down
5133	*PDCD1*	2q37.3	0.45	0.90	1.31	Up
5212	*VIT*	2p22.2	0.65	0.21	0.10	Down
7850	*IL1R2*	2q12	15.23	6.41	3.25	Down
9173	*IL1RL1*	2q12	1.48	0.38	0.59	Down

53353	*LRP1B*	2q21.2	0.05	0.01	0.01	Down
55137	*FIGN*	2q24.3	0.17	0.00	0.01	Down
57520	*HECW2*	2q32.3	0.83	0.20	0.36	Down
79586	*CHPF*	2q35	0.21	0.67	0.55	Up
79623	*GALNT14*	2p23.1	0.53	0.13	0.14	Down
80097	*FAM128B*	2q21.1	10.14	24.65	23.48	Up
80326	*WNT10A*	2q35	0.42	0.94	0.92	Up
84913	*ATOH8*	2p11.2	0.03	0.45	0.45	Up
90134	*KCNH7*	2q24.2	0.36	0.10	0.12	Down
129642	*MBOAT2*	2p25.1	8.24	3.13	3.69	Down
130162	*C2orf63*	2p16.1	0.70	1.72	1.52	Up
130271	*PLEKHH2*	2p21	0.15	0.36	0.43	Up
440905	*LOC440905*	2q21.1	2.00	0.35	0.21	Down
653784	*FAM128A*	2q21.1	4.82	14.57	13.51	Up
941	*CD80*	3q13.3-q21	0.24	0.58	0.72	Up
1359	*CPA3*	3q21-q25	27.23	7.49	10.81	Down
1776	*DNASE1L3*	3p14.3	2.91	1.12	1.32	Down
2047	*EPHB1*	3q21-q23	1.33	0.34	0.50	Down
3568	*IL5RA*	3p26-p24	3.32	1.21	1.34	Down
4057	*LTF*	3p21.31	18.46	49.36	57.20	Up
4311	*MME*	3q25.1-q25.2	26.93	9.13	5.24	Down
54762	*GRAMD1C*	3q13.31	3.63	0.95	0.87	Down
57501	*KIAA1257*	3q21.3	0.99	0.21	0.18	Down
84239	*ATP13A4*	3q29	0.98	0.43	0.48	Down
114884	*OSBPL10*	3p22.3	1.35	4.81	4.01	Up
132014	*IL17RE*	3p25.3	0.10	0.33	0.52	Up
151963	*C3orf59*	3q29	0.86	1.83	2.32	Up
152189	*CMTM8*	3p22.3	0.39	1.80	2.06	Up
200958	*MUC20*	3q29	0.31	1.63	1.05	Up
253559	*CADM2*	3p12.1	0.21	0.01	0.05	Down
259173	*ALS2CL*	3p21.31	1.34	3.31	3.04	Up
339855	*KY*	3q22.2	0.57	0.19	0.19	Down
344787	*ZNF860*	3p23	0.65	1.66	2.00	Up
402135	*OR5K2*	3q11.2	0.06	0.86	0.77	Up
5593	*PRKG2*	4q13.1-q21.1	0.28	0.09	0.07	Down
6286	*S100P*	4p16	1.37	8.32	4.41	Up
7222	*TRPC3*	4q27	0.63	0.09	0.09	Down
8470	*SORBS2*	4q35.1	0.16	0.03	0.02	Down
11107	*PRDM5*	4q25-q26	0.69	0.15	0.08	Down
27306	*HPGDS*	4q22.3	1.58	0.49	0.65	Down
79633	*FAT4*	4q28.1	0.51	0.16	0.20	Down
79730	*NSUN7*	4p14	1.56	0.42	0.37	Down
114905	*C1QTNF7*	4p15.3	0.17	0.01	0.04	Down
389206	*BEND4*	4p13	0.18	0.55	0.48	Up
1879	*EBF1*	5q34	0.46	1.70	1.21	Up
4131	*MAP1B*	5q13	0.42	0.14	0.16	Down
5159	*PDGFRB*	5q33.1	3.52	1.43	1.04	Down
6569	*SLC34A1*	5q35	0.44	0.14	0.03	Down
10917	*BTNL3*	5q35.3	2.71	0.00	0.00	Down
11346	*SYNPO*	5q33.1	0.36	1.20	1.25	Up
23138	*N4BP3*	5q35.3	0.14	0.44	0.51	Up
56100	*PCDHGB6*	5q31	0.24	0.03	0.05	Down
56101	*PCDHGB5*	5q31	0.13	0.02	0.03	Down
56105	*PCDHGA11*	5q31	0.12	0.03	0.01	Down

56106	*PCDHGA10*	5q31	0.36	0.03	0.02	Down
134285	*TMEM171*	5q13.2	0.24	0.95	1.67	Up
153579	*BTNL9*	5q35.3	0.12	0.99	1.01	Up
383	*ARG1*	6q23	1.03	3.34	3.00	Up
1300	*COL10A1*	6q21-q22	0.83	0.38	0.34	Down
3117	*HLA-DQA1*	6p21.3	79.60	31.48	18.24	Down
3127	*HLA-DRB5*	6p21.3	200.83	47.95	39.28	Down
3139	*HLA-L*	6p21.3	1.26	3.73	3.09	Up
4646	*MYO6*	6q13	3.30	1.33	0.87	Down
5169	*ENPP3*	6q22	3.97	1.69	1.88	Down
5190	*PEX6*	6p21.1	3.46	7.75	7.40	Up
5796	*PTPRK*	6q22.2-q22.3	0.41	0.91	1.00	Up
6648	*SOD2*	6q25.3	301.34	130.45	139.49	Down
8347	*HIST1H2BC*	6p22.1	19.07	5.09	9.21	Down
9308	*CD83*	6p23	21.49	10.67	7.49	Down
9856	*KIAA0319*	6p22.3-p22.2	0.48	0.10	0.14	Down
10231	*RCAN2*	6p12.3	0.36	0.74	0.94	Up
10279	*PRSS16*	6p21	0.11	0.37	0.47	Up
10321	*CRISP3*	6p12.3	2.46	6.50	6.78	Up
26575	*RGS17*	6q25.3	0.91	0.40	0.29	Down
27242	*TNFRSF21*	6p21.1	2.17	0.93	1.08	Down
55510	*DDX43*	6q12-q13	1.83	0.30	0.52	Down
80129	*C6orf97*	6q25.1	2.94	1.34	1.33	Down
80867	*HCG2P7*	6p21.3	0.78	0.37	0.36	Down
116369	*SLC26A8*	6p21	1.79	0.51	0.70	Down
221481	*C6orf81*	6p21.31	0.31	0.97	0.98	Up
221687	*RNF182*	6p23	0.06	0.31	0.29	Up
221711	*SYCP2L*	6p24.2	0.91	0.18	0.23	Down
285852	*TREML4*	6p21.1	0.91	0.25	0.37	Down
340146	*SLC35D3*	6q23.3	0.75	0.15	0.32	Down
165	*AEBP1*	7p13	1.30	3.33	2.64	Up
358	*AQP1*	7p14	0.30	0.08	0.05	Down
2041	*EPHA1*	7q34	1.93	4.43	4.03	Up
3206	*HOXA10*	7p15.2	2.21	0.81	0.49	Down
3696	*ITGB8*	7p21.1	1.78	0.55	0.71	Down
4846	*NOS3*	7q36	0.20	0.58	0.43	Up
8972	*MGAM*	7q34	17.73	8.23	5.32	Down
10135	*NAMPT*	7q22.3	219.69	62.68	68.21	Down
51351	*ZNF117*	7q11.21	17.11	6.04	6.50	Down
64101	*LRRC4*	7q31.3	5.51	2.12	2.71	Down
79689	*STEAP4*	7q21.12	31.03	14.76	14.47	Down
91584	*PLXNA4*	7q32.3	1.13	0.53	0.53	Down
93432	*LOC93432*	7q34	0.38	0.00	0.06	Down
221981	*THSD7A*	7p21.3	0.18	0.01	0.06	Down
259286	*TAS2R40*	7q34	0.72	0.07	0.14	Down
286006	*C7orf53*	7q31.1	5.77	1.87	2.34	Down
401431	*LOC401431*	7q36.1	0.40	1.01	0.84	Up
441250	*TYW1B*	7q11.23	1.01	3.78	2.47	Up
100124692	*LOC100124692*	7q34	0.58	0.11	0.10	Down
1807	*DPYS*	8q22	0.49	0.02	0.02	Down
2675	*GFRA2*	8p21.3	0.24	0.64	0.52	Up
4856	*NOV*	8q24.1	1.80	0.80	0.67	Down
8794	*TNFRSF10C*	8p22-p21	54.45	21.09	16.66	Down
9639	*ARHGEF10*	8p23	1.00	9.53	7.84	Up

51312	*SLC25A37*	8p21.2	51.11	19.78	21.34	Down
79660	*PPP1R3B*	8p23.1	12.06	5.20	5.43	Down
80005	*DOCK5*	8p21.2	22.88	9.42	10.79	Down
83648	*FAM167A*	8p23-p22	0.23	1.38	1.07	Up
85453	*TSPYL5*	8q22.1	1.73	0.81	0.75	Down
93100	*NAPRT1*	8q24.3	3.64	9.74	10.20	Up
114822	*RHPN1*	8q24.3	0.34	1.14	1.18	Up
137075	*CLDN23*	8p23.1	1.32	0.55	0.50	Down
203054	*ADCK5*	8q24.3	1.01	2.70	2.10	Up
254778	*C8orf46*	8q13.1	0.37	1.24	0.84	Up
286046	*XKR6*	8p23.1	0.00	0.10	0.12	Up
286122	*C8orf31*	8q24.3	0.11	0.89	0.73	Up
216	*ALDH1A1*	9q21.13	32.99	66.26	72.78	Up
5004	*ORM1*	9q31-q32	1.01	3.48	3.20	Up
6019	*RLN2*	9p24.1	1.26	3.26	2.55	Up
7010	*TEK*	9p21	0.10	0.00	0.00	Down
7436	*VLDLR*	9p24	0.91	0.26	0.24	Down
8013	*NR4A3*	9q22	0.27	0.09	0.11	Down
9833	*MELK*	9p13.2	0.73	0.30	0.29	Down
10811	*NOXA1*	9q34.3	0.71	1.53	1.59	Up
11094	*C9orf7*	9q34	0.55	1.17	1.23	Up
23349	*KIAA1045*	9p13.3	0.30	0.09	0.05	Down
56654	*NPDC1*	9q34.3	0.68	2.57	1.98	Up
58499	*ZNF462*	9q31.2	0.01	0.06	0.11	Up
79937	*CNTNAP3*	9p13.1	4.33	0.51	0.62	Down
80380	*PDCD1LG2*	9p24.2	0.73	0.28	0.32	Down
89891	*WDR34*	9q34.11	0.63	1.42	1.34	Up
140803	*TRPM6*	9q21.13	3.31	1.18	1.28	Down
158228	*C9orf122*	9p13.1	0.14	0.87	0.51	Up
286343	*C9orf150*	9p23	0.16	0.00	0.01	Down
387328	*ZNF322B*	9q22.33	0.22	0.01	0.00	Down
401562	*LCNL1*	9q34.3	0.56	0.15	0.06	Down
414332	*LCN10*	9q34.3	0.89	3.81	3.28	Up
441478	*NRARP*	9q34.3	0.73	0.20	0.20	Down
654466	*KGFLP2*	9p12	0.20	1.01	0.52	Up
728489	*DNLZ*	9q34.3	1.30	3.27	2.92	Up
105	*ADARB2*	10p15.3	0.24	0.00	0.00	Down
150	*ADRA2A*	10q24-q26	0.39	0.11	0.12	Down
1305	*COL13A1*	10q22	1.00	0.21	0.14	Down
5328	*PLAU*	10q24	0.56	0.24	0.24	Down
5654	*HTRA1*	10q26.3	0.54	1.53	1.91	Up
5979	*RET*	10q11.2	0.25	0.10	0.10	Down
8644	*AKR1C3*	10p15-p14	31.32	13.12	8.08	Down
25805	*BAMBI*	10p12.3-p11.2	0.99	0.27	0.43	Down
159686	*CCDC147*	10q25.1	0.44	0.15	0.17	Down
338596	*ST8SIA6*	10p12.33	3.41	0.97	1.27	Down
387707	*CC2D2B*	10q24.1	0.99	0.40	0.41	Down
389941	*C1QL3*	10p13	1.64	0.35	0.39	Down
133	*ADM*	11p15.4	8.26	3.03	3.42	Down
741	*ZNHIT2*	11q13	0.49	1.20	1.25	Up
838	*CASP5*	11q22.2-q22.3	6.27	1.59	3.00	Down
931	*MS4A1*	11q12	41.30	129.24	105.34	Up

932	*MS4A3*	11q12.1	46.12	16.65	20.02	Down
2900	*GRIK4*	11q22.3	0.02	0.37	0.27	Up
3046	*HBE1*	11p15.5	0.60	0.00	0.03	Down
3047	*HBG1*	11p15.5	3.64	0.61	1.00	Down
4647	*MYO7A*	11q13.5	0.37	0.77	1.11	Up
5029	*P2RY2*	11q13.5-q14.1	0.73	1.50	2.03	Up
5450	*POU2AF1*	11q23.1	6.05	13.63	13.32	Up
5553	*PRG2*	11q12	0.28	1.11	0.99	Up
5790	*PTPRCAP*	11q13.3	33.66	69.47	73.73	Up
6947	*TCN1*	11q11-q12	18.11	5.10	6.95	Down
9638	*FEZ1*	11q24.2	7.88	3.69	2.97	Down
27087	*B3GAT1*	11q25	7.36	3.64	3.10	Down
54503	*ZDHHC13*	11p15.1	24.15	8.29	7.86	Down
84304	*NUDT22*	11q13.1	4.92	9.84	9.85	Up
84649	*DGAT2*	11q13.5	19.86	9.29	8.88	Down
116071	*BATF2*	11q13.1	0.50	1.02	1.96	Up
117195	*MRGPRX3*	11p15.1	0.09	0.64	0.42	Up
120071	*GYLTL1B*	11p11.2	0.55	1.90	1.91	Up
147199	*SCGB1C1*	11p15.5	2.04	0.33	0.70	Down
338440	*ANO9*	11p15.5	3.31	7.82	7.90	Up
341208	*HEPHL1*	11q21	0.08	0.01	0.00	Down
41	*ACCN2*	12q12	0.12	0.79	0.73	Up
94	*ACVRL1*	12q11-q14	0.21	0.54	0.56	Up
1240	*CMKLR1*	12q24.1	17.85	8.30	7.34	Down
1634	*DCN*	12q21.33	0.50	0.10	0.05	Down
1663	*DDX11*	12p11	0.71	4.21	3.74	Up
1840	*DTX1*	12q24.13	0.55	2.60	2.35	Up
3741	*KCNA5*	12p13	0.34	0.05	0.04	Down
4060	*LUM*	12q21.3-q22	0.50	0.03	0.17	Down
8082	*SSPN*	12p11.2	0.26	0.84	1.05	Up
8435	*SOAT2*	12q13.13	0.09	0.53	0.48	Up
8843	*GPR109B*	12q24.31	14.19	5.19	4.11	Down
9891	*NUAK1*	12q23.3	2.26	0.37	0.37	Down
11247	*NXPH4*	12q13.3	0.00	0.22	0.25	Up
23416	*KCNH3*	12q13	0.32	0.75	0.68	Up
79365	*BHLHE41*	12p12.1	0.26	1.10	0.75	Up
84698	*CAPS2*	12q14.1	0.74	0.12	0.29	Down
84727	*SPSB2*	12p13.31	0.27	2.59	1.40	Up
121355	*GTSF1*	12q13.13	14.29	5.03	3.69	Down
283420	*CLEC9A*	12p13.2	2.51	1.15	0.79	Down
338442	*GPR109A*	12q24.31	10.94	3.97	2.77	Down
100287569	*NCRNA00173*	12q24.22	6.45	2.23	2.82	Down
2259	*FGF14*	13q34	0.25	0.02	0.07	Down
10257	*ABCC4*	13q32	7.17	2.45	3.20	Down
10562	*OLFM4*	13q14.3	2.95	6.94	7.47	Up
121952	*LOC121952*	13q33.1	1.72	0.51	0.58	Down
122011	*CSNK1A1L*	13q13.3	0.28	0.07	0.08	Down
1690	*COCH*	14q11.2-q13	0.62	1.86	2.27	Up
9787	*DLGAP5*	14q22.3	0.72	0.22	0.31	Down
26534	*OR10G2*	14q11.2	0.07	0.55	0.54	Up
51016	*FAM158A*	14q11.2	2.18	4.76	5.17	Up
57596	*BEGAIN*	14q32.2	0.00	0.17	0.17	Up
79820	*CATSPERB*	14q32.12	0.20	0.77	0.65	Up

114088	*TRIM9*	14q22.1	0.38	0.17	0.15	Down
123096	*SLC25A29*	14q32.2	2.61	5.95	5.49	Up
643866	*CBLN3*	14q12	0.73	1.69	1.52	Up
366	*AQP9*	15q	110.32	44.63	49.95	Down
2038	*EPB42*	15q15-q21	0.23	0.88	1.00	Up
2628	*GATM*	15q21.1	0.48	1.36	1.42	Up
3067	*HDC*	15q21-q22	34.26	12.66	16.46	Down
6263	*RYR3*	15q14-q15	0.33	0.12	0.13	Down
64410	*KLHL25*	15q25.3	0.31	0.70	0.80	Up
145864	*HAPLN3*	15q26.1	2.58	7.33	6.78	Up
246777	*SPESP1*	15q23	0.48	0.09	0.02	Down
930	*CD19*	16p11.2	3.16	10.42	10.37	Up
1632	*DCI*	16p13.3	3.02	6.22	6.72	Up
4502	*MT2A*	16q13	12.21	24.88	28.79	Up
4913	*NTHL1*	16p13.3	0.88	2.14	2.10	Up
8912	*CACNA1H*	16p13.3	0.06	0.24	0.16	Up
10101	*NUBP2*	16p13.3	3.36	7.88	6.84	Up
51005	*AMDHD2*	16p13.3	0.75	1.62	2.27	Up
51327	*AHSP*	16p11.2	1.44	4.05	3.77	Up
54550	*NECAB2*	16q23.3	0.76	0.31	0.21	Down
54768	*HYDIN*	16q22.2	0.02	0.12	0.11	Up
58189	*WFDC1*	16q24.3	0.20	0.00	0.00	Down
63922	*CHTF18*	16p13.3	0.69	1.40	1.43	Up
64180	*DPEP3*	16q22.1	1.42	0.62	0.37	Down
64386	*MMP25*	16p13.3	29.20	8.75	9.86	Down
65990	*FAM173A*	16p13.3	1.56	3.38	4.62	Up
79007	*DBNDD1*	16q24.3	0.67	3.20	2.31	Up
84080	*C16orf48*	16q22.1	0.85	1.71	1.75	Up
84331	*FAM195A*	16p13.3	0.80	2.12	2.22	Up
84706	*GPT2*	16q12.1	0.29	0.65	0.70	Up
114984	*FLYWCH2*	16p13.3	2.22	5.14	4.46	Up
116028	*C16orf75*	16p13.13	0.49	1.14	1.09	Up
123904	*NRN1L*	16q22.1	0.24	1.09	1.46	Up
222487	*GPR97*	16q21	11.21	5.06	3.55	Down
260429	*PRSS33*	16p13.3	0.91	0.19	0.27	Down
245	*ALOX12P2*	17p13	0.49	0.20	0.21	Down
246	*ALOX15*	17p13.3	2.13	0.32	0.38	Down
924	*CD7*	17q25.2-q25.3	8.19	19.96	20.65	Up
974	*CD79B*	17q23	17.28	36.54	36.76	Up
990	*CDC6*	17q21.3	0.75	0.34	0.35	Down
2584	*GALK1*	17q24	1.94	4.01	4.07	Up
3959	*LGALS3BP*	17q25	5.69	12.05	11.83	Up
5026	*P2RX5*	17p13.3	6.33	23.91	17.52	Up
6521	*SLC4A1*	17q21-q22	1.45	3.05	3.98	Up
8639	*AOC3*	17q21	1.61	0.55	0.34	Down
9720	*CCDC144A*	17p11.2	0.26	0.69	1.08	Up
10610	*ST6GALNAC2*	17q25.1	4.33	1.59	1.98	Down
10750	*GRAP*	17p11.2	4.93	16.07	12.03	Up
23495	*TNFRSF13B*	17p11.2	0.92	3.87	3.25	Up
51655	*RASD1*	17p11.2	0.89	0.38	0.33	Down
57332	*CBX8*	17q25.3	0.76	1.66	1.91	Up
79148	*MMP28*	17q21.1	0.35	1.59	0.98	Up
91107	*TRIM47*	17q25	0.48	1.55	1.08	Up

113026	*PLCD3*	17q21.31	0.26	0.56	0.54	Up
162466	*PHOSPHO1*	17q21.32	13.53	4.75	4.29	Down
162632	*LOC162632*	17p11.2	0.65	3.36	5.09	Up
284047	*CCDC144B*	17p11.2	0.20	0.51	0.82	Up
80816	*ASXL3*	18q11	0.05	0.00	0.01	Down
54	*ACP5*	19p13.3-p13.2	4.75	13.76	9.65	Up
513	*ATP5D*	19p13.3	3.72	8.15	8.68	Up
828	*CAPS*	19p13.3	2.55	6.61	5.51	Up
970	*CD70*	19p13	0.17	1.10	0.76	Up
973	*CD79A*	19q13.2	17.19	51.42	49.75	Up
1084	*CEACAM3*	19q13.2	13.20	3.41	5.70	Down
2867	*FFAR2*	19q13.1	25.33	8.03	9.54	Down
3816	*KLK1*	19q13.3	0.14	1.46	0.97	Up
4051	*CYP4F3*	19p13.2	11.67	4.95	3.09	Down
6141	*RPL18*	19q13	233.91	491.10	671.41	Up
6320	*CLEC11A*	19q13.3	0.47	1.19	1.06	Up
6689	*SPIB*	19q13.3-q13.4	4.55	9.86	11.53	Up
10045	*SH2D3A*	19p13.3	2.63	5.68	5.36	Up
10597	*TRAPPC2P1*	19q13.4	1.70	4.01	3.91	Up
27134	*TJP3*	19p13.3	0.23	1.03	1.09	Up
27181	*SIGLEC8*	19q13.33-q13.41	0.63	0.18	0.14	Down
29997	*GLTSCR2*	19q13.3	85.38	206.70	183.62	Up
53615	*MBD3*	19p13.3	3.86	9.69	8.22	Up
56971	*CEACAM19*	19q13.31	0.43	1.03	1.02	Up
57469	*PNMAL2*	19q13.32	0.02	0.23	0.12	Up
59285	*CACNG6*	19q13.4	1.25	0.33	0.48	Down
84266	*ALKBH7*	19p13.3	1.67	3.95	4.99	Up
84658	*EMR3*	19p13.1	25.77	9.78	10.77	Down
89858	*SIGLEC12*	19q13.4	0.37	2.28	1.30	Up
90011	*KIR3DX1*	19q13.42	2.18	1.03	0.61	Down
148223	*C19orf25*	19p13.3	2.61	5.30	5.47	Up
162963	*ZNF610*	19q13.41	0.40	2.69	2.25	Up
284415	*VSTM1*	19q13.42	1.84	19.57	10.68	Up
374291	*NDUFS7*	19p13.3	4.17	9.13	10.89	Up
400668	*PRSSL1*	19p13.3	1.47	0.35	0.40	Down
440503	*PLIN5*	19p13.3	1.73	0.54	0.37	Down
645191	*LINGO3*	19p13.3	0.84	0.35	0.31	Down
653583	*PHLDB3*	19q13.31	0.55	1.12	1.22	Up
729359	*PLIN4*	19p13.3	0.84	0.32	0.28	Down
100128569	*C19orf71*	19p13.3	0.82	2.09	2.01	Up
671	*BPI*	20q11.23	3.14	9.14	8.09	Up
3787	*KCNS1*	20q12	0.21	0.04	0.03	Down
3911	*LAMA5*	20q13.2-q13.3	0.04	0.15	0.16	Up
5266	*PI3*	20q13.12	46.31	3.84	3.50	Down
6590	*SLPI*	20q12	19.20	4.49	3.85	Down
7056	*THBD*	20p11.2	7.21	2.93	2.91	Down
9751	*SNPH*	20p13	0.94	3.10	2.01	Up
11065	*UBE2C*	20q13.12	1.57	0.67	0.70	Down
22981	*NINL*	20p11.22-p11.1	1.75	0.57	0.39	Down
54923	*LIME1*	20q13.3	4.31	13.73	11.48	Up

54976	*C20orf27*	20p13	8.28	17.55	21.03	Up
85508	*SCRT2*	20p13	0.17	0.01	0.02	Down
116154	*PHACTR3*	20q13.32-q13.33	0.56	0.12	0.25	Down
140733	*MACROD2*	20p12.1	0.34	1.01	0.72	Up
140823	*ROMO1*	20q11.22	8.30	17.61	18.86	Up
391257	*SUMO1P1*	20q13.2	2.14	1.04	0.73	Down
1291	*COL6A1*	21q22.3	0.37	1.39	1.15	Up
3772	*KCNJ15*	21q22.2	20.62	6.67	7.16	Down
10215	*OLIG2*	21q22.11	0.22	0.04	0.02	Down
54033	*RBM11*	21q11	0.60	2.11	1.23	Up
193629	*NCRNA00189*	21q22.11	2.84	0.19	0.23	Down
706	*TSPO*	22q13.31	14.07	30.32	31.65	Up
4282	*MIF*	22q11.23	4.82	10.59	17.66	Up
10343	*PKDREJ*	22q13.31	0.33	0.16	0.14	Down
25787	*DGCR9*	22q11.21	0.06	0.40	0.27	Up
25812	*POM121L1P*	22q11.22	0.02	0.18	0.21	Up
27443	*CECR2*	22q11.2	0.04	0.14	0.17	Up
29802	*VPREB3*	22q11.23	2.24	5.77	9.51	Up
56666	*PANX2*	22q13.33	0.89	0.40	0.40	Down
85376	*RIMBP3*	22q11.21	0.01	0.12	0.11	Up
115650	*TNFRSF13C*	22q13.1-q13.31	2.24	5.51	5.55	Up
3730	*KAL1*	Xp22.32	0.37	0.05	0.03	Down
5358	*PLS3*	Xq23	0.37	0.15	0.13	Down
7503	*XIST*	Xq13.2	0.00	29.03	37.30	Up
8277	*TKTL1*	Xq28	5.34	2.19	1.61	Down
9185	*REPS2*	Xp22.2	4.76	2.17	2.04	Down
23630	*KCNE1L*	Xq22.3	0.50	0.13	0.10	Down
79983	*POF1B*	Xq21.2	0.11	0.31	0.37	Up
139189	*DGKK*	Xp11.22	1.09	0.08	0.03	Down
256714	*MAP7D2*	Xp22.12	0.03	0.70	0.52	Up
347404	*LANCL3*	Xp21.1	1.11	0.36	0.50	Down
441531	*PGAM4*	Xq13	0.60	0.14	0.22	Down
6192	*RPS4Y1*	Yp11.3	256.96	0.00	0.00	Down
7404	*UTY*	Yq11	9.23	0.03	0.02	Down
7544	*ZFY*	Yp11.3	5.13	0.00	0.00	Down
8284	*KDM5D*	Yq11	20.64	0.00	0.00	Down
8287	*USP9Y*	Yq11.2	13.49	0.00	0.00	Down
8653	*DDX3Y*	Yq11	59.06	0.00	0.00	Down
9086	*EIF1AY*	Yq11.223	31.32	0.00	0.00	Down
9087	*TMSB4Y*	Yq11.221	4.79	0.00	0.00	Down
22829	*NLGN4Y*	Yq11.221	0.10	0.00	0.00	Down
55410	*NCRNA00185*	Yq11.222	0.41	0.00	0.00	Down
64595	*TTTY15*	Yq11.1	3.03	0.01	0.01	Down
84663	*CYorf15B*	Yq11.222	30.98	0.00	0.00	Down
140032	*RPS4Y2*	Yq11.223	0.27	0.00	0.00	Down
246126	*CYorf15A*	Yq11.222	20.96	0.00	0.00	Down
286554	*BCORL2*	Yq11.222	2.80	0.00	0.00	Down

Expression levels are expressed as RPKM (reads per kilobase per million mapped reads).

Table 5. FM and FD differentially expressed miRNA in the family trio

miRNA	Father Expression Level	Mother Expression Level	Daughter Expression Level	Family
hsa-miR-1	2541.58	908.99	845.41	mir-1
hsa-miR-106a	39.08	4.33	8.00	mir-17
hsa-miR-106b	321.17	125.37	154.47	mir-17
hsa-miR-1308	9.56	1.72	1.52	
hsa-miR-134	8.13	1.42	2.59	mir-134
hsa-miR-144	15.78	3.26	6.17	mir-144
hsa-miR-148b	451.19	143.53	121.85	mir-148
hsa-miR-15a	1324.80	160.62	200.72	mir-15
hsa-miR-15b	1817.79	166.07	193.63	mir-15
hsa-miR-16	3654.38	706.07	929.08	mir-15
hsa-miR-17	361.21	66.51	105.47	mir-17
hsa-miR-181a	5050.16	1168.10	1392.48	mir-181
hsa-miR-181b	1229.90	193.90	243.40	mir-181
hsa-miR-181c	85.26	24.80	30.48	mir-181
hsa-miR-181d	186.31	40.35	48.62	mir-181
hsa-miR-18a	32.04	7.77	8.76	mir-17
hsa-miR-18b	6.15	2.20	1.91	mir-17
hsa-miR-190b	7.11	1.96	1.91	mir-190
hsa-miR-193a-3p	25.69	11.33	7.24	mir-193
hsa-miR-194	13.60	3.74	6.40	mir-194
hsa-miR-197	30.61	8.37	7.16	mir-197
hsa-miR-19b	174.76	34.06	51.59	mir-19
hsa-miR-20a	114.78	30.02	52.58	mir-17
hsa-miR-20b	12.16	2.37	3.35	mir-17
hsa-miR-210	6.15	0.89	1.60	mir-210
hsa-miR-22	448.25	107.45	156.75	mir-22
hsa-miR-223	7806.46	2486.48	1842.69	mir-223
hsa-miR-23a	4941.25	1489.57	1899.16	mir-23
hsa-miR-25	3338.87	842.00	755.11	mir-25
hsa-miR-29b	1440.80	295.18	528.17	mir-29
hsa-miR-29c	2660.25	624.66	969.39	mir-29
hsa-miR-30b	201.27	44.20	51.21	mir-30
hsa-miR-32	31.50	7.42	9.22	mir-32
hsa-miR-324-3p	7.58	1.13	1.22	mir-324
hsa-miR-324-5p	28.35	5.70	10.90	mir-324
hsa-miR-338-3p	99.27	16.73	13.03	mir-338
hsa-miR-361-5p	93.87	17.74	22.56	mir-361
hsa-miR-362-5p	10.32	4.21	4.50	mir-362
hsa-miR-365	30.06	4.09	3.43	mir-365
hsa-miR-374b	403.50	73.57	84.89	mir-374
hsa-miR-376b	5.88	0.89	1.30	mir-368
hsa-miR-382	22.14	7.06	9.37	mir-154

hsa-miR-424	216.10	36.91	45.04	mir-322
hsa-miR-425	196.90	42.19	44.35	mir-425
hsa-miR-454	10.73	3.62	4.50	mir-454
hsa-miR-487b	27.60	3.20	6.17	mir-154
hsa-miR-501-3p	12.78	6.17	4.12	mir-500
hsa-miR-505	27.60	9.32	8.46	mir-505
hsa-miR-532-3p	26.85	7.36	8.69	mir-188
hsa-miR-556-3p	7.04	2.79	1.98	mir-556
hsa-miR-574-3p	32.59	6.29	4.95	mir-574
hsa-miR-576-5p	37.51	4.45	5.41	mir-576
hsa-miR-584	32.32	6.05	5.03	mir-584
hsa-miR-590-5p	19.40	5.46	7.54	mir-590
hsa-miR-618	2.25	1.01	0.61	mir-618
hsa-miR-629	40.10	8.90	7.62	
hsa-miR-660	63.81	26.70	26.44	mir-188
hsa-miR-664	57.39	10.15	14.78	mir-664
hsa-miR-766	5.81	1.19	1.83	mir-766
hsa-miR-873	30.47	2.49	1.45	mir-873
hsa-miR-93	750.57	253.89	341.78	mir-17
hsa-miR-96	4.58	1.01	1.14	mir-96
hsa-let-7c	317.35	746.00	644.08	let-7
hsa-miR-122	12.78	36.85	58.52	mir-122
hsa-miR-1254	1.37	3.98	3.35	mir-1254
hsa-miR-125a-5p	65.18	205.00	240.80	mir-125
hsa-miR-185	4189.05	10857.66	12601.17	mir-185

Table 6. Expression and promoter methylation of the 15 network genes in the family trio

Symbol	Gene ID	Cytoband	Father Expression	Mother Expression	Daughter Expression	Father Promoter Methylation	Mother Promoter Methylation	Daughter Promoter Methylation
LRRC7	57554	1p31.1	0.11	0.04	0.05	0.724	0.696	0.756
TXNDC12	51060	1p32.3	56.08	53.37	49.20	0.005	0.002	0.006
TGFBR3	7049	1p33-p32	23.63	18.15	13.47	0.241	0.225	0.281
AJAP1	55966	1p36.32	0.05	0.02	0.03	0.097	0.106	0.116
AGRN	375790	1p36.33	0.18	0.43	0.68	0.423	0.391	0.435
APOB	338	2p24-p23	0.00	0.00	0.00	0.486	0.611	0.632
EIF4E3	317649	3p14	23.18	14.98	19.15	0.076	0.098	0.113
SLC35A4	113829	5q31.3	22.40	25.92	24.38	0.138	0.166	0.151
PACRG	135138	6q26	0.17	0.07	0.13	0.637	0.635	0.715
COL15A1	1306	9q21-q22	0.12	0.04	0.07	0.394	0.466	0.480
NR4A3	8013	9q22	0.27	0.09	0.11	0.004	0.006	0.005
E2F8	79733	11p15.1	0.30	0.11	0.22	0.095	0.118	0.127
PCDH17	27253	13q21.1	0.00	0.00	0.00	0.059	0.083	0.101
PLEKHH3	79990	17q21.2	0.04	0.10	0.06	0.027	0.026	0.034
SCARF2	91179	22q11.21	0.08	0.11	0.14	0.314	0.323	0.321

Expression levels are expressed as RPKM (reads per kilobase per million mapped reads); methylation levels are expressed as the proportion of ^{m}C in the region as 0.0 being no methylation and 1.0 being 100% methylated.

Table 7. List of genes showing changed expression in type 2 diabetes

Gene	Reason	Change in type 2 diabetes	Known to associate with type 2 diabetes
PTPRD	GWAS-T2D gene with > 2 fold expression change	40% decrease	Yes
KCNK17	GWAS-T2D gene with > 2 fold expression change	44% decrease	Yes
CUEDC2	Genes from multiomic analysis	18% decrease	No
KDM2B	Genes from multiomic analysis	22% increase	No
PDCD1	Genes from multiomic analysis	22% decrease	No
CDKN2B	GWAS-T2D gene and *KDM2B* target gene	43% increase	Yes
rRNA	*KDM2B* target gene	27% decrease	No
TXNDC12	Genes from network analysis	18% increase	No
PACRG	Genes from network analysis	20% decrease	No
EIF4E3	Genes from network analysis	38% increase	No
miR-16-1	top signal from microRNA expression	16% decrease	No
miR-16-2	top signal from microRNA expression	30% decrase	No

Table 8. List of genes showed changed DNA methylation in type 2 diabetes

Gene	Region	Change in type 2 diabetes	Known to associate with type 2 diabetes
PDCD1	chr2:242450726	increase	No
PDCD1	chr2:242450767:242450772	increase	No
PDCD1	chr2:242450889	increase	No
EIF4E3	chr3:71884942	decrease	No
EIF4E3	chr3:71885111	decrease	No
EIF4E3	chr3:71885141	increase	No
EIF4E3	chr3:71886723	decrease	No
EIF4E3	chr3:71886895	decrease	No
PACRG	chr6:163522932	decrease	No
PACRG	chr6:163593238	decrease	No
CDKN2B	chr9:22001075-22001081	increase	Yes
CDKN2B	chr9:22001091-22001093	increase	Yes
CDKN2B	chr9:22001115	increase	Yes
CDKN2B	chr9:22001207	increase	Yes
KDM2B	chr12:120504330-120504336	decrease	No

Table 9. SNPs co-segregated in the mother-daughter pair of the trio and correlated with gene expression data.

ID RS#	Chromosome	Position	Allele 1	Allele 2	Risk allele (High expressed in affected individual)	Risk genotype (High expressed in affected individual)	Gene ID
rs2275408	chr1	54450893	C	G	Allele 1	C	MRPL37
rs17464525	chr1	114245422	G	A	Allele 1	G	AP4B1
rs11563	chr1	25767440	G	T	Allele 2	T	LDLRAP1
rs35058101	chr1	17266635	T	A	Allele 2	A	PADI2
rs1804999	chr1	154486074	A	G	Allele 1	A	SMG5
rs72633678	chr1	159762101	A	T	Allele 1	A	HSPA6
rs2272867	chr1	207996202	C	A	Allele 1	C	TRAF3IP3
rs11256474	chr10	5721789	C	T	Allele 1	C	ASB13
rs11009140	chr10	33240564	G	A	Allele 1	G	ITGB1
rs1141862	chr10	91090238	T	A	Allele 1	T	IFIT3
rs35359667	chr10	91169674	G	A	Allele 2	A	IFIT5
rs2291289	chr11	72086305	C	T	Allele 2	T	CENTD2
rs7931870	chr11	95465445	A	G	Allele 1	A	MAML2
rs7270	chr12	10743039	A	T	Allele 1	A	CSDA
rs41291993	chr12	55325347	C	T	Allele 1	C	ATP5B
rs707577	chr20	43487763	T	C	Allele 1	T	PIGT
rs2075624	chr15	38498015	G	A	Allele 2	A	IVD
rs6499496	chr16	69874313	A	G	Allele 2	G	FLJ11171
rs2357306	chr14	51505681	A	T	Allele 1	A	GNG2
rs734138	chr16	2939219	C	T	Allele 2	T	FLYWCH1
rs8064024	chr16	4795280	A	G	Allele 1	A	N-PAC
rs17875563	chr15	79391348	A	T	Allele 2	T	IL16
rs247861	chr16	83157522	T	C	Allele 2	C	COTL1
rs1061032	chr17	8004808	T	G	Allele 1	T	VAMP2
rs2277698	chr17	74378612	C	T	Allele 1	C	TIMP2
rs7146	chr19	965398	A	G	Allele 1	A	C19orf6
rs2229920	chr19	10800792	T	C	Allele 1	T	DNM2
rs8616	chr19	11422629	T	C	Allele 1	T	PRKCSH
rs8810	chr19	16299315	A	T	Allele 1	A	KLF2
rs1885097	chr14	22619159	A	G	Allele 2	G	ACIN1
rs10194289	chr2	235067395	G	T	Allele 1	G	ARL4C
rs13848	chr2	240595439	T	C	Allele 2	C	NDUFA10
rs4842	chr21	34203291	T	C	Allele 1	T	ATP5O
rs8132624	chr21	46812792	C	T	Allele 1	C	DIP2A
rs132806	chr22	40400739	C	T	Allele 1	C	NHP2L1
rs1056964	chr22	49364342	A	G	Allele 2	G	CPT1B
rs3804766	chr3	51405697	A	C	Allele 1	A	RBM15B
rs11552301	chr4	936226	T	C	Allele 1	T	MGC4618
rs2294108	chr4	4288592	T	A	Allele 2	A	TMEM128
rs3733633	chr4	108795438	G	A	Allele 1	G	PAPSS1
rs8752	chr4	175649052	C	T	Allele 1	C	HPGD
rs13181449	chr5	6657787	C	T	Allele 1	C	NSUN2
rs26821	chr5	102548299	A	C	Allele 2	C	HISPPD1
rs2228458	chr5	150499181	G	A	Allele 1	G	ANXA6
rs1048719	chr5	150613025	G	A	Allele 1	G	GM2A
rs13196459	chr6	2834070	A	C	Allele 1	A	SERPINB9

rs318486	chr6	2835282	A	G	Allele 2	G	SERPINB9
rs115640156	chr6	30262178	T	C	Allele 1	T	TRIM26
rs3748177	chr9	116162023	C	T	Allele 1	C	AKNA
rs117888214	chr7	141275138	T	C	Allele 2	C	CLEC5A
rs2016465	chr8	82067952	A	G	Allele 1	A	PAG1
rs3826100	chr16	12571771	A	C	Allele 1	A	LOC92017
rs10609	chr16	12574577	A	G	Allele 1	A	LOC92017
rs7722287	chr5	1116998	G	A	Allele 1	G	SLC12A7

5

Table 10. SNPs co-segregated in the mother-daughter pair of the trio and correlated with DNA methylation data.

ASM CpG		Representing SNP				
Chromosome	Position	Chromosome	Position	RS# ID	Allele 1	Risk allele
chr22	15862847	chr22	15862847	rs5746958	C	T
chr22	21235786	chr22	21235672	rs11090148	C	T
chr22	21244300	chr22	21244300	rs62226018	C	T
chr22	22199908	chr22	22199899	rs6003780	G	A
chr22	22971202	chr22	22971203	rs2078191	G	A
chr22	23782434	chr22	23782421	.	G	A
chr22	25857498	chr22	25857498	rs2880346	C	T
chr22	26084801	chr22	26084774	rs2179099	A	G
chr22	27491007	chr22	27491007	rs4820792	C	T
chr22	32557271	chr22	32557271	rs2413204	C	T
chr22	32827993	chr22	32827983	rs13058033	G	A
chr22	37008396	chr22	37008397	rs62230170	G	A
chr22	38202652	chr22	38202646	rs5757690	C	T
chr22	41521312	chr22	41521284	rs5758945	G	A
chr22	41627340	chr22	41627341	rs9611957	G	A
chr22	42627705	chr22	42627705	rs4823156	C	T
chr22	43010150	chr22	43010151	rs112276918	G	A
chr22	43144621	chr22	43144621	rs78084875	C	T
chr22	43230438	chr22	43230430	rs133752	C	G
chr22	43579739	chr22	43579651	rs5765029	C	T
chr22	47277877	chr22	47277878	rs5768686	G	A
chr22	47393020	chr22	47393020	rs59674167	C	T
chr22	47672424	chr22	47672413	rs28661982	C	T
chr22	47947622	chr22	47947623	rs56395290	G	A
chr22	47951530	chr22	47951498	rs929029	G	T
chr22	47961507	chr22	47961507	rs17825671	C	T
chr22	48235392	chr22	48235392	rs79544241	C	T
chr22	48937749	chr22	48937749	rs10427578	C	T
chr14	20245118	chr14	20244990	rs34721199	T	G
chr14	24785576	chr14	24785576	rs17278020	C	T
chr14	27398647	chr14	27398647	rs61972797	C	T
chr14	31896798	chr14	31896798	rs10135655	C	T
chr14	35676224	chr14	35676219	rs12897066	A	G
chr14	47241766	chr14	47241766	rs77506553	C	T
chr14	51497958	chr14	51497958	rs1253649	C	T
chr14	51828091	chr14	51828092	rs75832675	G	A
chr14	55538299	chr14	55538300	rs1188203	G	A
chr14	55579266	chr14	55579267	rs241537	G	A
chr14	55893314	chr14	55893315	rs4901675	G	A

chr14	56230691	chr14	56230594	rs74052638	G	A
chr14	67053237	chr14	67053238	rs7160944	G	A
chr14	71536910	chr14	71536910	.	C	T
chr14	71536927	chr14	71536910	.	C	T
chr14	76084828	chr14	76084813	rs28431939	A	G
chr14	77468644	chr14	77468644	rs11159309	C	T
chr14	81257445	chr14	81257461	rs8015680	T	C
chr14	83315655	chr14	83315655	rs17119051	C	T
chr14	92138268	chr14	92138174	rs11160078	C	T
chr14	92230309	chr14	92230310	rs11849325	G	A
chr14	94989664	chr14	94989664	rs7151678	C	T
chr14	95103019	chr14	95103019	rs8010459	C	T
chr14	100572054	chr14	100572021	rs10134016	T	C
chr14	101373044	chr14	101373045	rs76697013	G	A
chr14	104083010	chr14	104083021	rs58381709	C	T
chr14	104083019	chr14	104083021	rs58381709	C	T
chr14	104088425	chr14	104088426	rs10136519	G	A
chr14	105797731	chr14	105797717	rs61995548	C	A
chr8	819360	chr8	819361	rs6993875	G	A
chr8	858517	chr8	858518	.	G	A
chr8	1762233	chr8	1762233	rs17756439	C	T
chr8	1767227	chr8	1767228	rs118103924	G	A
chr8	1774286	chr8	1774287	rs117299306	G	A
chr8	2077144	chr8	2077045	rs67769214	G	A
chr8	3186094	chr8	3186095	rs1549313	G	A
chr8	3186508	chr8	3186509	rs1348266	G	C
chr8	3907095	chr8	3907096	rs13253871	G	A
chr8	4247951	chr8	4247952	.	G	A
chr8	4613571	chr8	4613553	rs12550274	C	T
chr8	4920875	chr8	4920869	rs56685768	A	C
chr8	8297855	chr8	8297834	rs2945874	C	G
chr8	8372826	chr8	8372802	rs17152705	G	A
chr8	11653758	chr8	11653758	rs78334561	C	T
chr8	12958132	chr8	12958133	rs2466263	G	A
chr8	17791118	chr8	17791118	rs2106036	C	T
chr8	17817761	chr8	17817740	rs13278127	G	T
chr8	18311233	chr8	18311199	rs7818999	G	A
chr8	22140465	chr8	22140448	rs11547656	C	T
chr8	22775344	chr8	22775344	rs6557597	C	T
chr8	22885562	chr8	22885563	rs56276231	G	A
chr8	24149079	chr8	24149079	rs12549111	C	T
chr8	26896960	chr8	26896960	rs56135074	C	T
chr8	30517476	chr8	30517467	rs2979513	G	C
chr8	34595954	chr8	34595954	rs72640996	C	T

chr8	38882873	chr8	38882873	rs2056170	C	T
chr8	41713189	chr8	41713201	rs77677893	A	T
chr8	41713228	chr8	41713201	rs77677893	A	T
chr8	42405298	chr8	42405298	.	C	T
chr8	52367026	chr8	52367027	rs12542002	G	A
chr8	52368233	chr8	52368233	rs7012256	C	T
chr8	56019859	chr8	56019859	rs78116834	C	T
chr8	56691043	chr8	56691043	rs28577254	C	T
chr8	59295417	chr8	59295418	rs11777995	G	A
chr8	62654016	chr8	62654016	rs12674869	C	T
chr8	71717564	chr8	71717565	rs117937985	G	A
chr8	90271980	chr8	90271981	.	G	A
chr8	99057256	chr8	99057257	rs117598487	G	A
chr8	101125154	chr8	101125155	rs115353454	G	A
chr8	102172873	chr8	102172873	rs35655532	C	T
chr8	110280811	chr8	110280811	rs4734206	C	T
chr8	117711533	chr8	117711534	rs12056883	G	A
chr8	117998854	chr8	117998855	rs2921738	G	C
chr8	120047115	chr8	120047115	.	C	T
chr8	121033918	chr8	121033906	rs4871815	A	G
chr8	125171600	chr8	125171600	rs117193397	C	T
chr8	134570089	chr8	134570090	rs11776026	G	A
chr8	138647406	chr8	138647407	rs55711768	G	A
chr8	142945696	chr8	142945696	.	C	T
chr8	144471411	chr8	144471411	rs11780593	C	T
chr1	1876343	chr1	1876361	rs2748976	C	A
chr1	2006537	chr1	2006537	rs74697444	C	T
chr1	2247745	chr1	2247746	rs72642149	G	C
chr1	4185556	chr1	4185557	rs4654516	G	C
chr1	4471999	chr1	4471883	rs10915549	G	A
chr1	4857229	chr1	4857229	rs58851741	C	T
chr1	5225907	chr1	5225910	rs536995	T	C
chr1	9261200	chr1	9261200	rs9442515	C	T
chr1	10487930	chr1	10487930	rs61192982	C	T
chr1	12679477	chr1	12679470	rs7547122	G	A
chr1	16891271	chr1	16891185	rs676167	A	G
chr1	16891281	chr1	16891185	rs676167	A	G
chr1	16891294	chr1	16891185	rs676167	A	G
chr1	16891349	chr1	16891271	rs113256629	C	G
chr1	18103606	chr1	18103607	.	G	A
chr1	18348072	chr1	18348072	rs9660184	C	T
chr1	18348109	chr1	18348110	rs2027530	G	A
chr1	18353027	chr1	18352934	rs9662824	A	G
chr1	18414685	chr1	18414686	rs55715295	G	A

chr1	19553119	chr1	19553119	rs12751502	C	T
chr1	21233995	chr1	21233889	rs6426659	G	A
chr1	25251065	chr1	25251066	rs435820	G	A
chr1	25398467	chr1	25398468	rs742393	G	A
chr1	30031499	chr1	30031500	rs74356443	G	A
chr1	30662721	chr1	30662721	rs7516250	C	T
chr1	31894771	chr1	31894772	.	G	A
chr1	33476662	chr1	33476663	rs79084040	G	A
chr1	34135103	chr1	34135104	rs111677570	G	T
chr1	37557298	chr1	37557299	rs1571789	G	A
chr1	38500761	chr1	38500761	rs77814891	C	T
chr1	44753510	chr1	44753510	rs16832024	C	T
chr1	47832521	chr1	47832510	.	G	T
chr1	48895565	chr1	48895565	rs60162645	C	T
chr1	53366518	chr1	53366401	rs899976	G	A
chr1	53384559	chr1	53384552	rs1679934	G	A
chr1	54260864	chr1	54260864	.	C	T
chr1	55194862	chr1	55194862	rs11206486	C	T
chr1	55246903	chr1	55246913	rs6682884	A	C
chr1	56062110	chr1	56062111	rs4129669	G	A
chr1	59734223	chr1	59734153	rs667634	A	T
chr1	62442182	chr1	62442182	rs10889297	C	T
chr1	66473368	chr1	66473368	rs74873498	C	T
chr1	70661698	chr1	70661699	.	G	A
chr1	70689135	chr1	70689136	rs77759767	G	C
chr1	71179278	chr1	71179279	rs475468	G	A
chr1	77548809	chr1	77548809	rs2799550	C	T
chr1	78940451	chr1	78940439	rs75417281	G	C
chr1	79035617	chr1	79035618	rs10873997	G	A
chr1	90697666	chr1	90697666	rs56661730	C	G
chr1	90717979	chr1	90717979	rs117868251	C	T
chr1	91377181	chr1	91377182	rs347003	G	A
chr1	97570651	chr1	97570651	rs4950027	C	T
chr1	101774939	chr1	101774939	rs1343363	C	T
chr1	105508681	chr1	105508678	rs12029517	A	G
chr1	107024800	chr1	107024803	rs41346254	T	C
chr1	112156332	chr1	112156333	rs60237243	G	A
chr1	115646879	chr1	115646880	rs7542555	G	A
chr1	116889025	chr1	116889025	rs12044773	C	A
chr1	119314192	chr1	119314193	rs10458418	G	A
chr1	120141016	chr1	120140994	rs1163545	C	A
chr1	153007502	chr1	153007488	rs12404994	A	C
chr1	159762077	chr1	159762101	rs72633678	A	T
chr1	160199671	chr1	160199672	rs2499846	G	A

chr1	160713532	chr1	160713533	rs469970	G	A
chr1	166035874	chr1	166035874	rs6695245	C	T
chr1	169805739	chr1	169805740	rs72717840	G	A
chr1	177548350	chr1	177548351	rs7543894	G	C
chr1	178131379	chr1	178131379	rs555755	C	T
chr1	179601261	chr1	179601268	rs4651102	A	G
chr1	180005330	chr1	180005331	rs771329	G	C
chr1	185420925	chr1	185420926	rs6425080	G	C
chr1	185790902	chr1	185790903	rs1339082	G	A
chr1	186708283	chr1	186708284	rs10912405	G	T
chr1	201062471	chr1	201062472	rs41264010	G	A
chr1	201910656	chr1	201910657	rs11240720	G	A
chr1	205852774	chr1	205852775	rs7519119	G	A
chr1	206144266	chr1	206144266	rs656801	C	T
chr1	220582366	chr1	220582367	.	G	A
chr1	226029787	chr1	226029776	rs6697054	C	T
chr1	226031764	chr1	226031764	rs115617436	C	T
chr1	226782545	chr1	226782546	rs10916338	G	A
chr1	228328438	chr1	228328438	rs77945324	C	T
chr1	230075732	chr1	230075733	rs9432028	G	A
chr1	231875624	chr1	231875624	rs3843251	C	T
chr1	232596175	chr1	232596175	rs2175594	C	T
chr1	233092225	chr1	233092226	rs4920161	G	A
chr1	233102933	chr1	233102933	rs67435549	C	T
chr1	235358771	chr1	235358771	rs2490381	C	T
chr1	237274246	chr1	237274246	rs10925799	C	T
chr1	240625579	chr1	240625579	rs79799056	C	T
chr1	240919734	chr1	240919735	rs35575216	G	A
chr1	241156158	chr1	241156159	rs2491852	G	A
chr1	242849516	chr1	242849517	rs2806619	G	A
chr1	242987340	chr1	242987341	.	G	A
chr1	243791931	chr1	243791932	rs79726121	G	A
chr1	243926698	chr1	243926699	rs884987	G	C
chr1	243926832	chr1	243926828	rs2008766	C	A
chr1	244912807	chr1	244912807	rs72764608	C	T
chr17	3607498	chr17	3607499	rs220475	G	A
chr17	4253789	chr17	4253789	.	C	T
chr17	4401910	chr17	4401911	rs76953250	G	A
chr17	4877622	chr17	4877622	rs2304445	C	T
chr17	5040598	chr17	5040598	rs34765532	C	T
chr17	6059147	chr17	6059147	rs78870150	C	T
chr17	6554098	chr17	6554098	rs16956192	C	T
chr17	7861378	chr17	7861359	rs11655691	G	T
chr17	8215726	chr17	8215726	rs2909439	C	T

chr17	9558164	chr17	9558165	rs408537	G	A
chr17	12053514	chr17	12053514	rs7219462	C	T
chr17	13330112	chr17	13330112	rs111375519	C	T
chr17	17280694	chr17	17280581	rs78267649	A	G
chr17	21138951	chr17	21138936	rs2363227	G	T
chr17	21140135	chr17	21140108	rs5025581	C	T
chr17	21148099	chr17	21148094	rs57988116	G	A
chr17	21863440	chr17	21863440	rs12602066	C	T
chr17	24440749	chr17	24440750	rs4965415	G	A
chr17	24447352	chr17	24447352	rs869718	C	T
chr17	30341705	chr17	30341705	.	C	T
chr17	30578496	chr17	30578496	rs11870733	C	T
chr17	42421364	chr17	42421266	rs3851798	G	A
chr17	45523136	chr17	45523137	rs77510864	G	A
chr17	56920243	chr17	56920266	rs59159776	C	G
chr17	61754846	chr17	61754846	rs67828405	C	T
chr17	61755223	chr17	61755223	rs12938072	C	T
chr17	62365467	chr17	62365455	rs62072186	G	T
chr17	64303834	chr17	64303835	rs4968953	G	A
chr17	67130990	chr17	67130991	rs72841221	G	A
chr17	67578077	chr17	67578078	rs114978079	G	A
chr17	71102412	chr17	71102412	rs2305524	C	T
chr17	71120706	chr17	71120707	rs820142	G	A
chr17	71955651	chr17	71955652	rs59035745	G	A
chr17	71965707	chr17	71965707	rs4789300	C	T
chr17	72424575	chr17	72424548	rs12603183	G	A
chr17	73018709	chr17	73018710	rs2574863	G	A
chr17	74553146	chr17	74553146	rs78111110	C	T
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chr17	77264962	chr17	77264949	.	G	T
chr21	20860496	chr21	20860501	rs6517976	T	G
chr21	22123150	chr21	22123151	rs13046513	G	A
chr21	29036225	chr21	29036225	rs2832026	C	T
chr21	29371294	chr21	29371295	rs2853831	G	C
chr21	30167731	chr21	30167731	rs2832468	C	T
chr21	30733956	chr21	30733962	rs4816363	C	G
chr21	30756832	chr21	30756833	rs2000513	G	A
chr21	30886767	chr21	30886768	rs79025761	G	A
chr21	31741783	chr21	31741784	rs567943	G	A
chr21	36040302	chr21	36040303	rs60334620	G	A
chr21	38934537	chr21	38934540	rs461679	T	C
chr21	39876954	chr21	39876955	rs11700626	G	A
chr21	39942471	chr21	39942471	rs596618	C	T
chr21	40580199	chr21	40580208	rs12626576	C	G

chr21	41833869	chr21	41833869	rs55788142	C	T
chr21	42245907	chr21	42245902	rs13046500	G	A
chr21	43989429	chr21	43989430	rs117369905	G	A
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chr21	45108566	chr21	45108538	rs4818738	T	C
chr21	46301118	chr21	46301129	rs915808	A	C
chr16	5558903	chr16	5558905	rs11647221	C	T
chr16	6777187	chr16	6777188	rs62016111	G	C
chr16	6805163	chr16	6805163	rs115094998	C	T
chr16	7201743	chr16	7201744	rs117447259	G	A
chr16	7441130	chr16	7441131	.	G	A
chr16	8544969	chr16	8544969	rs76834968	C	T
chr16	11134805	chr16	11134806	rs75810024	G	A
chr16	11188593	chr16	11188593	rs78252181	C	T
chr16	12395276	chr16	12395277	rs8044113	G	A
chr16	12549828	chr16	12549829	.	G	A
chr16	12682060	chr16	12682064	rs1651006	G	C
chr16	13032468	chr16	13032451	rs4780494	A	G
chr16	13032470	chr16	13032451	rs4780494	A	G
chr16	19259863	chr16	19259863	rs4782231	C	T
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chr16	26563774	chr16	26563775	rs2008983	G	A
chr16	29206910	chr16	29206910	rs13337460	C	T
chr16	32545547	chr16	32545548	rs28686921	G	A
chr16	47587188	chr16	47587179	rs1420589	C	T
chr16	48177209	chr16	48177210	rs11642742	G	C
chr16	48863864	chr16	48863857	rs7193434	G	T
chr16	52757714	chr16	52757715	rs12447727	G	A
chr16	54735180	chr16	54735181	rs8063856	G	A
chr16	55649907	chr16	55649907	rs1627144	C	T
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chr16	58762853	chr16	58762854	rs55950120	G	T
chr16	62287580	chr16	62287593	rs2319434	T	C
chr16	64472868	chr16	64472868	rs77659387	C	T
chr16	64472874	chr16	64472868	rs77659387	C	T
chr16	64690121	chr16	64690121	rs8053639	C	T
chr16	67361336	chr16	67361345	rs28628339	A	G
chr16	76692144	chr16	76692145	rs79416778	G	T
chr16	76970453	chr16	76970453	rs72796059	C	T
chr16	76971805	chr16	76971805	rs72796067	C	T
chr16	76977015	chr16	76977016	rs72796083	G	A
chr16	77436189	chr16	77436189	.	C	T
chr16	77493230	chr16	77493231	rs11864605	G	A
chr16	77696228	chr16	77696228	rs4888926	C	T

chr16	78621364	chr16	78621246	rs13333795	A	G
chr16	80758906	chr16	80758906	rs4889478	C	T
chr16	80777559	chr16	80777553	rs7192638	T	C
chr16	81202293	chr16	81202175	rs35666337	A	G
chr16	81624421	chr16	81624422	rs35444894	G	A
chr16	82451098	chr16	82451099	rs76032180	G	A
chr16	84585884	chr16	84585885	rs6540244	G	A
chr16	84861643	chr16	84861643	rs62053617	C	T
chr16	85276016	chr16	85276016	rs62042107	C	T
chr16	85302663	chr16	85302663	rs300009	C	T
chr16	86430971	chr16	86430972	rs33967518	G	A
chr16	86653704	chr16	86653704	rs12919293	C	T
chr16	87092532	chr16	87092533	rs12447946	G	A
chr16	87293669	chr16	87293669	rs55780854	C	T
chr16	87828265	chr16	87828265	rs56135239	C	T
chr18	1057456	chr18	1057457	rs72859353	G	C
chr18	3692208	chr18	3692208	rs113277345	C	T
chr18	5008786	chr18	5008786	rs8095458	C	T
chr18	5878948	chr18	5878948	.	C	T
chr18	5893626	chr18	5893626	rs4797235	C	T
chr18	8436223	chr18	8436220	rs7242589	C	A
chr18	9766279	chr18	9766279	rs12966230	C	T
chr18	12997346	chr18	12997346	rs9957933	C	A
chr18	21097568	chr18	21097569	.	G	A
chr18	24043267	chr18	24043267	rs1988880	C	T
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chr18	42059645	chr18	42059645	.	C	T
chr18	48464643	chr18	48464632	rs8090718	A	G
chr18	52865095	chr18	52865096	rs61747862	G	A
chr18	58755881	chr18	58755881	.	C	T
chr18	60543074	chr18	60543074	rs12963425	C	T
chr18	61940561	chr18	61940561	rs34407336	C	T
chr18	61947536	chr18	61947536	rs11873967	C	A
chr18	61949363	chr18	61949349	rs62087667	G	T
chr18	66867150	chr18	66867151	rs75472619	G	A
chr18	66956359	chr18	66956360	rs74513032	G	A
chr18	71875809	chr18	71875810	rs73972485	G	A
chr18	71899497	chr18	71899497	rs76341020	C	T
chr18	72832706	chr18	72832697	rs73968250	G	C
chr18	72888539	chr18	72888539	rs112900430	C	T
chr18	73054287	chr18	73054273	rs35828995	G	A
chr18	73054272	chr18	73054273	rs35828995	G	A
chr18	73500430	chr18	73500430	rs183598	C	G
chr18	74258992	chr18	74258974	.	G	T

chr18	74919181	chr18	74919182	rs12709636	G	A
chr18	75413796	chr18	75413797	rs694732	G	A
chr3	7954065	chr3	7954066	.	G	A
chr3	8700097	chr3	8700097	rs34685587	C	T
chr3	10524847	chr3	10524848	rs113222553	G	A
chr3	13697642	chr3	13697636	rs4383497	A	G
chr3	14358255	chr3	14358256	rs73022213	G	C
chr3	16295376	chr3	16295265	rs111386922	C	G
chr3	18959026	chr3	18959027	rs61617737	G	A
chr3	23311984	chr3	23311972	rs903518	A	G
chr3	32192770	chr3	32192770	rs9838910	C	T
chr3	46577602	chr3	46577602	rs4683244	C	T
chr3	52840632	chr3	52840633	rs28552648	G	A
chr3	52970615	chr3	52970615	rs58515094	C	T
chr3	53946115	chr3	53946083	rs118025032	T	C
chr3	54166572	chr3	54166496	rs77060447	T	G
chr3	68306206	chr3	68306207	rs7618868	G	A
chr3	68322855	chr3	68322856	rs4459906	G	A
chr3	72003526	chr3	72003526	rs35644218	C	T
chr3	72337579	chr3	72337580	rs9790178	G	A
chr3	72604836	chr3	72604837	.	G	A
chr3	85023617	chr3	85023617	rs452496	C	T
chr3	101540791	chr3	101540792	rs166747	G	A
chr3	106498094	chr3	106498095	rs9842100	G	A
chr3	116644167	chr3	116644183	rs1353909	G	A
chr3	120003662	chr3	120003663	.	G	A
chr3	122660374	chr3	122660374	rs3843345	C	T
chr3	127410450	chr3	127410451	rs9822040	G	A
chr3	128973743	chr3	128973744	rs9852837	G	A
chr3	129196683	chr3	129196658	rs9289323	A	C
chr3	131634167	chr3	131634167	rs62281866	C	T
chr3	132323485	chr3	132323485	rs1964083	C	T
chr3	140834494	chr3	140834494	rs73869367	C	T
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chr3	152612802	chr3	152612803	rs6440740	G	A
chr3	154959094	chr3	154959090	rs641042	C	T
chr3	174750478	chr3	174750478	rs766004	C	T
chr3	178435565	chr3	178435565	rs6806734	C	T
chr3	178681500	chr3	178681408	rs7356095	G	A
chr3	185837799	chr3	185837799	rs4074989	C	T
chr3	185870867	chr3	185870867	rs4234609	C	T
chr3	193640185	chr3	193640186	rs7651615	G	A
chr3	194995299	chr3	194995197	rs472356	A	G
chr3	195360371	chr3	195360371	rs9869342	C	T

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chr12	116462	chr12	116388	rs73036139	C	T
chr12	249032	chr12	249032	rs555512	C	T
chr12	1282063	chr12	1282064	rs56362023	G	T
chr12	2478743	chr12	2478744	rs1004207	G	A
chr12	5303065	chr12	5303066	rs4766356	G	A
chr12	5559867	chr12	5559868	rs11063763	G	A
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chr12	31848937	chr12	31848937	rs116894325	C	T
chr12	42254508	chr12	42254503	rs61925207	G	A
chr12	50568327	chr12	50568327	rs697634	C	T
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chr12	51149480	chr12	51149480	rs412533	C	T
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chr12	60035695	chr12	60035696	rs68067046	G	T
chr12	71393626	chr12	71393627	rs10879481	G	A
chr12	73099856	chr12	73099857	.	G	A
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chr12	95759743	chr12	95759639	rs7138120	C	A
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chr12	103634684	chr12	103634684	rs4514507	C	T
chr12	110094145	chr12	110094146	rs3809296	G	A
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chr12	113423935	chr12	113423916	rs16944407	A	T
chr12	113468744	chr12	113468748	rs838314	T	G
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chr12	123456184	chr12	123456184	rs10846670	C	T
chr12	123743705	chr12	123743705	rs12579740	C	T
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chr12	125895218	chr12	125895219	rs12316600	G	A
chr12	128837216	chr12	128837216	rs10734971	C	T
chr12	129058376	chr12	129058377	rs7135364	G	A
chr12	129189268	chr12	129189268	rs10848013	C	T

chr12	129196987	chr12	129196988	rs10773744	G	A
chr12	129530149	chr12	129530149	rs11060934	C	T
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chr15	19347770	chr15	19347779	rs114113680	G	A
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chr15	19928411	chr15	19928411	rs1533331	C	T
chr15	22981746	chr15	22981747	rs72546347	G	A
chr15	29579000	chr15	29579001	rs16956797	G	A
chr15	29579055	chr15	29579056	rs72724993	G	T
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chr15	31109770	chr15	31109770	rs12903271	C	T
chr15	43809295	chr15	43809296	rs58712480	G	A
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chr15	79427835	chr15	79427836	rs7170663	G	A
chr15	85910576	chr15	85910577	rs79388227	G	A
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chr15	90375023	chr15	90375023	rs59913727	C	T
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chr2	151488	chr2	151489	rs300738	G	A
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chr2	3113856	chr2	3113856	rs4854193	C	T
chr2	3946516	chr2	3946516	rs6755953	C	T
chr2	6716348	chr2	6716348	rs752383	C	T
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chr2	23241714	chr2	23241715	rs13022502	G	A
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chr2	51517516	chr2	51517516	rs7568061	C	T
chr2	52093631	chr2	52093632	rs4971778	G	A
chr2	72107780	chr2	72107780	rs4852838	C	T
chr2	76092016	chr2	76092017	rs1822108	G	A
chr2	83606423	chr2	83606423	rs10210196	C	T
chr2	86941714	chr2	86941711	rs6713248	C	T
chr2	99640992	chr2	99640992	rs117984084	C	T
chr2	100603111	chr2	100603112	rs1879121	G	A
chr2	100888208	chr2	100888209	rs2117714	G	A
chr2	101594445	chr2	101594445	rs10177367	C	T
chr2	104695098	chr2	104695098	rs4605392	C	T
chr2	109613796	chr2	109613798	rs12614336	C	T
chr2	113099154	chr2	113099155	rs6758898	G	A
chr2	113871048	chr2	113870956	rs12711769	A	G
chr2	114622863	chr2	114622857	rs56036335	A	G
chr2	118794607	chr2	118794593	rs73947787	A	T
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chr2	137450730	chr2	137450712	rs7587475	C	T
chr2	137488476	chr2	137488477	rs1347033	G	A
chr2	150314358	chr2	150314359	rs1526287	G	A
chr2	152477087	chr2	152477088	rs6733800	G	A
chr2	153481719	chr2	153481620	rs61026505	A	G
chr2	153920617	chr2	153920611	rs11689374	A	G
chr2	161612945	chr2	161612946	rs197262	G	A
chr2	161887438	chr2	161887443	rs57090160	G	A
chr2	163748770	chr2	163748771	rs16848125	G	A
chr2	168866218	chr2	168866219	rs2466561	G	A
chr2	192299354	chr2	192299355	rs6746000	G	C
chr2	192739040	chr2	192739045	rs61025859	C	T
chr2	195387582	chr2	195387582	rs79898226	C	T
chr2	202548778	chr2	202548774	rs62195522	G	A
chr2	206530884	chr2	206530778	rs12618329	T	G
chr2	215155192	chr2	215155083	rs10169894	C	T
chr2	216856675	chr2	216856662	rs876771	C	A
chr2	217161987	chr2	217161988	rs11690415	G	A
chr2	220895890	chr2	220895890	rs1454551	C	T
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chr2	227124322	chr2	227124322	rs76885413	C	T
chr2	227198508	chr2	227198509	rs1273824	G	A

chr2	231520204	chr2	231520205	.	G	A
chr2	232603576	chr2	232603577	rs11902551	G	A
chr2	233744810	chr2	233744810	rs6741388	C	T
chr2	234373308	chr2	234373309	rs11563069	G	A
chr2	234373367	chr2	234373368	rs13018934	G	A
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chr2	237240258	chr2	237240258	rs12475884	C	T
chr2	239695925	chr2	239695926	rs3828204	G	A
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chr13	28524447	chr13	28524444	rs9508239	A	C
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chr13	47780343	chr13	47780343	rs1981435	C	T
chr13	49917042	chr13	49917042	.	C	T
chr13	52421953	chr13	52421953	rs2018259	C	T
chr13	56788341	chr13	56788341	rs9316919	C	T
chr13	63842896	chr13	63842897	rs9571183	G	A
chr13	65312735	chr13	65312735	rs9592432	C	T
chr13	65637622	chr13	65637616	rs9540671	G	C
chr13	72165298	chr13	72165298	rs9543078	C	T
chr13	73640651	chr13	73640651	rs12867877	C	T
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chr13	92949923	chr13	92949924	rs9301886	G	A
chr13	96051366	chr13	96051367	rs625346	G	A
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chr13	100346369	chr13	100346370	rs9518200	G	A
chr13	100394275	chr13	100394282	rs7984634	A	G
chr13	101613809	chr13	101613809	.	C	T
chr13	102120704	chr13	102120596	rs603929	T	C
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chr13	112052245	chr13	112052246	rs61960761	G	A
chr13	112055146	chr13	112055138	rs9604304	A	G
chr13	112145361	chr13	112145362	rs9577369	G	A
chr13	112575967	chr13	112575968	rs1320525	G	A
chr13	113838817	chr13	113838686	rs9525226	T	G
chr13	113964995	chr13	113964995	rs116889516	C	T
chr10	1864736	chr10	1864736	rs35325935	C	T
chr10	1902802	chr10	1902803	rs4242735	G	A
chr10	2333859	chr10	2333859	rs78333966	C	T
chr10	2566950	chr10	2566950	rs10903799	C	T
chr10	4053985	chr10	4053979	rs12769283	G	T
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chr10	16755791	chr10	16755768	rs61842277	A	G
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chr10	23849845	chr10	23849846	rs4570482	G	A
chr10	27052102	chr10	27052102	rs11015250	C	T
chr10	27866042	chr10	27866042	rs11015857	C	T
chr10	28288545	chr10	28288546	rs115092513	G	A
chr10	28615002	chr10	28615002	rs74741916	C	T
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chr10	35030767	chr10	35030768	rs3002035	G	A
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chr10	44366697	chr10	44366678	rs2152635	T	C
chr10	44409926	chr10	44409943	rs34118524	T	C
chr10	44496487	chr10	44496488	rs12358198	G	C
chr10	56056854	chr10	56056864	rs11004420	T	C
chr10	57232141	chr10	57232142	rs77220716	G	A
chr10	62185895	chr10	62185897	rs7077201	G	T
chr10	63787013	chr10	63786997	.	A	G
chr10	65318842	chr10	65318842	rs1916450	C	T
chr10	67256157	chr10	67256158	rs7477944	G	A
chr10	72032085	chr10	72032086	rs3758562	G	A
chr10	72187843	chr10	72187836	rs10999516	G	A
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chr10	80702560	chr10	80702471	rs10824737	G	A
chr10	82331162	chr10	82331145	rs11186151	T	G
chr10	83582387	chr10	83582387	rs11191455	C	T
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chr10	85266299	chr10	85266300	rs4471365	G	A
chr10	85371798	chr10	85371799	rs12414182	G	A
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chr10	105328811	chr10	105328812	rs11815048	G	A
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chr10	124407375	chr10	124407375	rs3013180	C	T
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chr10	131403271	chr10	131403272	rs78815056	G	A
chr10	132428171	chr10	132428172	.	G	C
chr10	132913126	chr10	132913126	rs74817440	C	T
chr10	133430053	chr10	133430054	.	G	A
chr10	134737876	chr10	134737876	rs4074092	C	T
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chr10	135075473	chr10	135075450	rs7906765	G	T
chr10	135192304	chr10	135192305	rs1536828	G	C
chr10	135192633	chr10	135192634	rs8192770	G	A
chr7	180344	chr7	180344	rs10253011	C	T
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chr7	227597	chr7	227597	rs12540429	C	T
chr7	848384	chr7	848384	rs6415241	C	T
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chr7	3694519	chr7	3694422	rs7778346	A	C
chr7	4107798	chr7	4107798	rs17134377	C	T
chr7	4994057	chr7	4994057	rs111957975	C	T
chr7	5136058	chr7	5136058	rs6972792	C	T
chr7	24085207	chr7	24085208	.	G	A
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chr7	33577181	chr7	33577181	rs2256309	C	T
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chr7	45516100	chr7	45516101	rs17172585	G	A
chr7	46136039	chr7	46136044	rs10255580	C	T
chr7	51922317	chr7	51922318	rs11238145	G	A
chr7	54479686	chr7	54479687	rs117604640	G	A
chr7	55686196	chr7	55686196	rs10244823	C	T
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chr7	67026359	chr7	67026345	rs6460413	C	T
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chr7	69847235	chr7	69847221	rs79808556	C	T
chr7	71515973	chr7	71515974	rs12540434	G	C
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chr7	90892275	chr7	90892276	rs713317	G	A
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chr7	101072837	chr7	101072838	rs11975626	G	A
chr7	104627725	chr7	104627726	.	G	A
chr7	107198953	chr7	107198952	rs41668	G	A
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chr7	116677136	chr7	116677235	rs10953839	A	C
chr7	117541782	chr7	117541783	rs10263991	G	A
chr7	122427336	chr7	122427337	rs9770283	G	A
chr7	123943094	chr7	123943095	rs17132872	G	C
chr7	129659119	chr7	129659129	rs13229387	T	C
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chr7	131788343	chr7	131788344	rs10954376	G	A
chr7	136552370	chr7	136552283	rs832973	C	T
chr7	138230550	chr7	138230550	rs74700697	C	T
chr7	148139033	chr7	148139034	.	G	A
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chr20	43755974	chr20	43755975	.	G	A
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chr19	13466552	chr19	13466561	rs1363343	T	C
chr19	16028975	chr19	16028975	rs17722606	C	T
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chr19	40236802	chr19	40236803	rs2451996	G	A
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chr6	3665281	chr6	3665282	rs226967	G	A
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chr6	15030518	chr6	15030514	rs367558	T	C
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chr6	152084984	chr6	152084983	rs3020340	A	G
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chr11	5890010	chr11	5890010	rs2198445	C	T
chr11	5890111	chr11	5889993	rs2198444	T	G
chr11	6737527	chr11	6737528	rs4757969	G	T
chr11	7926543	chr11	7926544	rs1510998	G	A
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chr11	19499355	chr11	19499355	rs17597260	C	T
chr11	20003681	chr11	20003680	rs11825935	G	C
chr11	24638115	chr11	24638108	rs3923615	G	T
chr11	24638136	chr11	24638108	rs3923615	G	T
chr11	26586186	chr11	26586187	rs10835012	G	C
chr11	30808609	chr11	30808610	rs3741026	G	A
chr11	36194135	chr11	36194136	rs11605921	G	A
chr11	42853579	chr11	42853499	rs10837957	A	C
chr11	42881323	chr11	42881279	rs79598717	C	T
chr11	43929787	chr11	43929788	rs66616283	G	A
chr11	43971264	chr11	43971264	rs10400220	C	T
chr11	44606989	chr11	44606989	rs7127343	C	T
chr11	44855135	chr11	44855135	rs4755908	C	T
chr11	61914644	chr11	61914627	rs2302361	T	A
chr11	62653400	chr11	62653316	rs2097075	G	C
chr11	64738413	chr11	64738413	rs12420456	C	T
chr11	65249688	chr11	65249688	rs481482	C	T
chr11	66026555	chr11	66026555	.	C	T
chr11	68353461	chr11	68353447	rs77818363	A	G
chr11	68829223	chr11	68829224	.	G	A
chr11	69511500	chr11	69511475	rs61885142	T	A
chr11	69570099	chr11	69570099	rs7947026	C	T
chr11	74191076	chr11	74191076	rs536823	C	T
chr11	78356329	chr11	78356330	rs681267	G	A
chr11	79683029	chr11	79683030	rs10792476	G	A
chr11	80299348	chr11	80299348	rs4945458	C	T
chr11	80393911	chr11	80393886	rs10792530	G	A
chr11	80524400	chr11	80524401	rs2512104	G	A
chr11	86328959	chr11	86328960	rs11234888	G	A
chr11	86411474	chr11	86411445	rs11234911	T	C
chr11	86568788	chr11	86568788	rs7946112	C	T
chr11	88005197	chr11	88005198	rs67163709	G	A
chr11	91573544	chr11	91573545	.	G	A

chr11	98580740	chr11	98580742	rs7938173	T	C
chr11	108395653	chr11	108395644	rs7927335	T	C
chr11	111831541	chr11	111831541	.	C	T
chr11	123999512	chr11	123999513	rs2156155	G	A
chr11	125749828	chr11	125749805	.	A	G
chr11	126024189	chr11	126024190	rs4937169	G	C
chr11	128158107	chr11	128158108	rs2284785	G	A
chr11	129290825	chr11	129290804	rs3734073	G	A
chr11	130480464	chr11	130480465	rs79528350	G	A
chr11	131926781	chr11	131926781	rs4400825	C	T
chr11	131958536	chr11	131958551	rs75470688	G	A
chr11	131986396	chr11	131986383	rs9787796	C	T
chr11	133193474	chr11	133193483	rs58888419	G	A
chr11	134119657	chr11	134119657	rs4937946	C	T
chr4	868048	chr4	868048	rs899387	C	T
chr4	1218946	chr4	1218947	rs73793145	G	A
chr4	1219071	chr4	1219071	rs73793148	C	T
chr4	1235385	chr4	1235277	rs2279281	T	G
chr4	1348894	chr4	1348895	rs79873757	G	A
chr4	3679320	chr4	3679320	.	C	T
chr4	4445519	chr4	4445519	rs10017186	C	T
chr4	5508174	chr4	5508111	rs3821926	A	G
chr4	6217443	chr4	6217357	rs6824225	A	G
chr4	7795563	chr4	7795564	rs13130675	G	A
chr4	9724236	chr4	9724219	rs4393994	C	T
chr4	10613189	chr4	10613190	rs16876870	G	A
chr4	13441393	chr4	13441393	rs77764276	C	T
chr4	13710915	chr4	13710898	rs3843431	C	A
chr4	15351689	chr4	15351690	rs1807250	G	C
chr4	15572770	chr4	15572771	rs2286461	G	A
chr4	15634935	chr4	15634935	rs17478336	C	T
chr4	24710495	chr4	24710495	rs6819784	C	T
chr4	24970264	chr4	24970265	.	G	C
chr4	30810032	chr4	30810032	rs1587410	C	T
chr4	37878854	chr4	37878738	rs4833008	G	A
chr4	39482965	chr4	39482965	rs59496471	C	T
chr4	43797868	chr4	43797869	rs7656241	G	A
chr4	44321394	chr4	44321395	rs80199883	G	A
chr4	55517623	chr4	55517624	rs11728462	G	A
chr4	55559063	chr4	55559064	rs77772711	G	T
chr4	59819066	chr4	59819065	rs5027239	A	G
chr4	60591058	chr4	60591059	rs76979826	G	A
chr4	65851368	chr4	65851368	rs11737511	C	T
chr4	78356258	chr4	78356228	rs4629478	A	G

chr4	78631735	chr4	78631736	rs6856567	G	A
chr4	111417683	chr4	111417683	rs2713947	C	T
chr4	113971463	chr4	113971463	rs72906881	C	T
chr4	114578185	chr4	114578185	rs117751698	C	T
chr4	116609419	chr4	116609388	rs10027287	G	A
chr4	116629029	chr4	116629029	rs9884192	C	T
chr4	120441740	chr4	120441739	rs113434765	G	A
chr4	124606908	chr4	124606909	rs17807333	G	A
chr4	127289521	chr4	127289521	.	C	T
chr4	133358739	chr4	133358740	rs168339	G	A
chr4	133381018	chr4	133381019	rs13126205	G	C
chr4	139662612	chr4	139662612	rs1450432	C	T
chr4	148244491	chr4	148244491	.	C	T
chr4	150184734	chr4	150184735	rs4355369	G	A
chr4	163740399	chr4	163740400	rs62326271	G	A
chr4	182328617	chr4	182328617	.	C	T
chr4	186015738	chr4	186015649	rs111420399	T	C
chr4	188330197	chr4	188330198	rs55761513	G	T
chr4	190270951	chr4	190270953	rs35316875	A	G
chr4	190395130	chr4	190395130	rs10021138	C	A
chr9	672944	chr9	672945	rs16922510	G	A
chr9	830970	chr9	830971	rs942073	G	A
chr9	1730278	chr9	1730278	rs4741586	C	T
chr9	1788528	chr9	1788529	rs16934186	G	A
chr9	2186734	chr9	2186734	rs1886264	C	T
chr9	2198793	chr9	2198793	rs10965207	C	T
chr9	7928329	chr9	7928329	.	C	T
chr9	9977332	chr9	9977333	rs10978149	G	A
chr9	12292804	chr9	12292805	rs79962943	G	T
chr9	12319961	chr9	12319961	rs79334083	C	T
chr9	13694539	chr9	13694539	rs1998584	C	T
chr9	16872284	chr9	16872285	rs61202585	G	A
chr9	22544603	chr9	22544601	rs1158382	G	A
chr9	27885371	chr9	27885371	rs1930021	C	T
chr9	44173605	chr9	44173606	rs28829650	G	A
chr9	85528826	chr9	85528826	rs4877803	C	T
chr9	85923713	chr9	85923713	rs11140389	C	T
chr9	89228881	chr9	89228882	rs115072974	G	C
chr9	89671061	chr9	89671065	rs11142008	T	C
chr9	90503718	chr9	90503719	rs4559317	G	A
chr9	90504278	chr9	90504296	rs1573234	T	C
chr9	91634970	chr9	91634970	rs73649344	C	T
chr9	92040775	chr9	92040775	rs1475628	C	T
chr9	92142496	chr9	92142497	rs2254787	G	A

chr9	94639659	chr9	94639660	rs61743154	G	A
chr9	99310684	chr9	99310667	rs7044880	A	G
chr9	100069864	chr9	100069865	.	G	A
chr9	100807123	chr9	100807124	rs16918128	G	A
chr9	100855291	chr9	100855291	rs74483774	C	T
chr9	103563252	chr9	103563252	rs1572563	C	T
chr9	106427883	chr9	106427898	rs2417536	G	A
chr9	107818719	chr9	107818720	rs16925120	G	A
chr9	110589628	chr9	110589580	rs7870428	G	T
chr9	114055802	chr9	114055802	rs10817303	C	T
chr9	124818467	chr9	124818468	rs653441	G	A
chr9	125158942	chr9	125158942	.	C	T
chr9	125997371	chr9	125997372	rs73575777	G	A
chr9	129336197	chr9	129336197	rs10987675	C	T
chr9	130617908	chr9	130617908	rs7025290	C	T
chr9	133967698	chr9	133967699	rs111479389	G	A
chr9	134017310	chr9	134017311	rs11243644	G	A
chr9	134032016	chr9	134031987	rs3829759	G	A
chr9	138279423	chr9	138279424	rs35302005	G	C
chr9	139425484	chr9	139425484	.	C	T
chr5	1136420	chr5	1136421	rs117206816	G	A
chr5	1180318	chr5	1180318	rs56221185	C	T
chr5	2061988	chr5	2061988	rs74365793	C	T
chr5	2188252	chr5	2188252	rs73027534	C	T
chr5	2194959	chr5	2194944	rs10056878	G	A
chr5	2194964	chr5	2194944	rs10056878	G	A
chr5	2738550	chr5	2738550	rs13170001	C	T
chr5	3184398	chr5	3184398	rs160899	C	T
chr5	3269672	chr5	3269672	rs57572328	C	T
chr5	3303986	chr5	3303987	rs62338472	G	A
chr5	3304117	chr5	3304118	rs77583350	G	A
chr5	5360238	chr5	5360239	rs34029195	G	C
chr5	6406001	chr5	6406001	rs271416	C	T
chr5	6406017	chr5	6406001	rs271416	C	T
chr5	6776546	chr5	6776546	rs274714	C	T
chr5	8114221	chr5	8114222	rs79587908	G	A
chr5	9019159	chr5	9019162	rs6863266	C	T
chr5	9197643	chr5	9197644	rs16882093	G	A
chr5	9900752	chr5	9900753	rs10462870	G	A
chr5	11335256	chr5	11335257	rs4702796	G	A
chr5	19243058	chr5	19243058	rs6865590	C	T
chr5	28167021	chr5	28167022	rs10472602	G	A
chr5	40815447	chr5	40815448	rs154276	G	A
chr5	40903405	chr5	40903387	rs364443	A	G

chr5	46257191	chr5	46257191	rs10052784	C	T
chr5	56857856	chr5	56857856	rs72765423	C	T
chr5	57111930	chr5	57111930	rs1432477	C	T
chr5	58085398	chr5	58085399	.	G	A
chr5	68465953	chr5	68465954	rs164707	G	A
chr5	78657453	chr5	78657453	rs3733885	C	T
chr5	79599567	chr5	79599567	rs79747351	C	T
chr5	90074285	chr5	90074285	rs4916818	C	T
chr5	116611972	chr5	116611972	.	C	T
chr5	119173180	chr5	119173174	rs7709933	C	T
chr5	123259371	chr5	123259373	rs11745800	C	T
chr5	125918889	chr5	125918774	rs34731336	G	A
chr5	132902616	chr5	132902616	rs461418	C	T
chr5	132902642	chr5	132902643	rs462330	G	A
chr5	133223255	chr5	133223255	rs1644312	C	T
chr5	133276022	chr5	133276023	rs62373722	G	A
chr5	135113312	chr5	135113312	rs4495176	C	T
chr5	135403503	chr5	135403372	rs4141306	A	G
chr5	136738011	chr5	136738012	rs34825120	G	A
chr5	143346948	chr5	143346949	rs312615	G	T
chr5	145309192	chr5	145309173	rs999237	T	C
chr5	146968646	chr5	146968647	rs114906228	G	A
chr5	150508726	chr5	150508726	rs55797624	C	T
chr5	157102545	chr5	157102546	rs6867670	G	A
chr5	160980854	chr5	160980854	rs79615688	C	T
chr5	161515354	chr5	161515355	rs647625	G	A
chr5	166025924	chr5	166025925	rs17067407	G	A
chr5	166760140	chr5	166760140	rs9313378	C	T
chr5	179480297	chr5	179480298	rs72813638	G	A

5

5 **Table 11. Summary of genotyping results of the trio.**

SNP rs#	Gene	Chr	HK GWAS (955 control vs 677 T2D)				HK Genotyping (421 control vs 1144 T2D)			
			A1	A2	OR	*P* value	A1	A2	OR	*P* value
rs1052637	*DDX18*	2	C	G	1.35	0.0025	C	G	0.98	0.873
rs748767	*CCDC93*	2	G	A	0.78	0.0062	G	A	1.00	0.959
rs9998519	*WFS1*	4	C	T	0.62	0.0059	C	T	0.76	**0.035**
rs1534938	*PACRG*	6	T	G	0.72	1.82e-04	T	G	0.84	**0.039**
rs17497819	*CAMK1D*	10	G	T	2.27	0.0026	T	G	0.98	0.912
rs11597439	*CUED2*	10	C	G	1.95	0.0029	G	C	1.01	0.915
rs117510629	*KDM2B*	12	T	A	1.43	0.038	A	T	1.01	0.926
rs11065587	*KDM2B*	12	G	C	1.43	0.038	C	G	1.01	0.933
chr12:120395303	*KDM2B*	12	G	A	1.43	0.038	A	G	1.00	0.999
rs11065588	*KDM2B*	12	G	A	1.39	0.041	A	G	1.03	0.833
rs3743599	*ADAT1*	16	T	G	0.77	0.0041	C	A	0.86	0.086
rs3743598	*ADAT1*	16	T	G	0.71	0.002	C	A	0.82	0.057
rs734409		17	T	C	0.78	0.0081	G	A	1.13	0.178
rs3818744	*PPP4R1L*	20	G	A	0.83	0.03	G	A	0.88	0.127
rs17114359	*UMODL1*	21	A	C	1.25	0.01	C	A	0.97	0.689
rs220305	*UMODL1*	21	G	A	1.37	2.72e-04	T	C	1.03	0.697
rs2839467	*UMODL1*	21	G	A	1.25	0.011	A	G	0.93	0.403
rs93136	*UMODL1*	21	G	A	1.36	2.87e-04	T	C	1.02	0.788

Table 11.Summary of the genotyping results. Co-segregated mother-daughter SNPs from focus gene regions showing nominally significant *P* values in the Chinese GWAS meta-analysis were genotyped independently in 1144 Chinese T2D cases and 421 controls.

WHAT IS CLAIMED IS:

1. A method for detecting the presence or increased risk of developing type 2 diabetes (T2D) in a subject, the method comprising:

(a) measuring, in a tissue sample obtained from the subject, expression or DNA methylation levels of one or more T2D-associated genes, wherein the T2D-associated genes are selected from the group consisting of *LRRC7, TXNDC12*, *TGFBR3, AJAPl, AGRN, APOB, EIF4E3, SLC35A4, PACRG, COL15A1, NR4A3, E2F8, PCDH17*, *PLEKHH3, SCARF2, CUEDC2*, *KDM2B*, *PDCD1*, *miR-16-1*, and *miR-16-2*;

(b) comparing the expression or DNA methylation levels of the one or more T2D-associated genes with levels from the same genes in a standard control; and

(c) detecting the presence or increased risk of developing T2D when the expression or DNA methylation levels of the one or more T2D-associated genes are higher or lower than the levels in the standard control.

2. The method of claim **1**, wherein step (a) comprises measuring expression levels of the one or more T2D-associated genes, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, *EIF4E3*, *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*.

3. The method of claim **2**, wherein measuring expression levels comprises measuring levels of RNA transcripts of the one or more T2D-associated genes.

4. The method of claim **2**, wherein measuring expression levels comprises measuring amounts of proteins or polypeptides resulting from translation of RNA transcripts of the one or more T2D-associated genes.

5. The method of claim **2**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the expression levels of the one or more T2D-associated genes are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, and *EIF4E3*.

6. The method of claim **2**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the expression levels of the one or more T2D-associated genes are lower than the levels in the standard control, and the T2D-

associated genes are selected from the group consisting of *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*.

7. The method of claim **1**, wherein step (a) comprises measuring DNA methylation levels of the one or more T2D-associated genes and the T2D-associated genes are selected from the group consisting of *PDCD1*, *EIF4E3*, *PACRG*, and *KDM2B*.

8. The method of claim **7**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *PDCD1* and *EIF4E3*.

9. The method of claim **8**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the DNA methylation level of a promoter region in the one or more T2D-associated genes is higher than the level in the standard control.

10. The method of claim **7**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are lower than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *EIF4E3*, *PACRG*, and *KDM2B*.

11. The method of claim **10**, wherein step (c) comprises detecting the presence or increased risk of developing T2D when the DNA methylation level of a promoter region in the one or more T2D-associated genes is lower than the level in the standard control.

12. A method for detecting the presence or increased risk of developing T2Din a subject, the method comprising:

(a) determining, in a tissue sample obtained from the subject, a single-nucleotide genotype of the subject at a genomic locus, wherein the genomic locus is given by a SNP ID number provided in Table 9, 10, or 11; and

(b) detecting the presence or increased risk of developing T2D in the subject if the single-nucleotide genotype matches a reference genotype associated with T2D.

13. The method of claim **12**, wherein the genomic locus is given by a SNP ID number provided in Table 11 and selected from the group consisting of rs1052637,

rs748767, rs9998519, rs1534938, rs17497819, rs11597439, rs117510629, rs11065587, chr12:120395303, rs11065588, rs3743599, rs3743598, rs734409, rs3818744, rs17114359, rs220305, rs2839467, and rs93136.

14. The method of claim **13**, wherein the reference genotype associated with T2D for each genomic locus is provided in a column A1 of Table 11.

15. The method of claim **13**, wherein the genomic locus is given by the SNP ID number rs9998519 and the reference genotype is C.

16. The method of claim **13**, wherein the genomic locus is given by the SNP ID number rs1534938 and the reference genotype is T.

17. The method of claim **12**, wherein the genomic locus is given by a SNP ID number provided in Table 9 and the reference genotype for the genomic locus is provided in the "risk genotype" column of Table 9.

18. The method of claim **12**, wherein the genomic locus is given by a SNP ID number provided in Table 10 and the reference genotype for the genomic locus is provided in the "risk allele" column of Table 10.

19. The method of claim **12**, wherein steps (a) and (b) are performed for a plurality of genomic loci.

20. The method of claim **1** or **12**, wherein the sample is a blood or saliva sample.

21. The method of claim **1** or **12**, wherein the subject is of Asian descent.

22. The method of claim **21**, wherein the subject is a Chinese.

23. The method of claim **22**,wherein the subjectis a Han Chinese.

24. The method of claim **1** or **12**,wherein the subjecthas a family history of T2D but has not been diagnosed with T2D.

25. The method of claim **1** or **12**, wherein step (a) comprises an amplification reaction.

26. The method of claim **25**, wherein the amplification reaction is a polymerase chain reaction (PCR).

27. A method of identifying genetic markers of T2D, the method comprising:

obtaining a multiomic data set from one or more T2D-positive subjects, wherein each T2D-positive subject has been diagnosed with T2D;

obtaining a multiomic data set from one or more T2D-negative subjects, wherein each T2D-negative subject has not been diagnosed with T2D;

identifying differences between the multiomic data sets obtained from the one or more T2D-positive subjects and the one or more T2D-negative subjects; and

identifying one or more genetic markers based on the differences.

28. The method of claim **27**, wherein the T2D-positive subjects and T2D-negative subjects together comprise a family trio, and the family trio comprises a father, a mother, and an offspring.

29. The method of claim **27**, wherein each multiomic data set comprises at least two of the following: DNA sequencing data, RNA sequencing data, and RNA expression level data.

30. The method of claim **27**, wherein differences between the multiomic data sets from the one or more T2D-positive subjects and the one or more T2D-negative subjects are identified by comparing the multiomic data sets pair-wise.

31. The method of claim **27**, wherein the one or more genetic markers are identified using network analysis.

32. The method of claim **27**, wherein the genetic markers comprise differentially expressed genes, differentially expressed microRNAs, differentially methylated regions, or single-nucleotide polymorphisms.

33. The method of claim **32**, wherein the genetic markers comprise a differentially expressed gene that contains or overlaps with a differentially methylated region.

34. A kit for detecting the presence or increased risk of developing type 2 diabetes (T2D) in a subject, the kit comprising: reagents for measuring, in a tissue sample obtained from the subject, expression or DNA methylation levels of one or more T2D-

associated genes, wherein the T2D-associated genes are selected from the group consisting of *LRRC7, TXNDC12*, *TGFBR3, AJAPl, AGRN, APOB, EIF4E3, SLC35A4, PACRG, COL15A1, NR4A3, E2F8, PCDH17*, *PLEKHH3, SCARF2, CUEDC2*, *KDM2B*, *PDCD1*, *miR-16-1*, and *miR-16-2*; and a standard control,

wherein the presence or increased risk of developing T2D is detected when the expression or DNA methylation levels of the one or more T2D-associated genes are higher or lower than the levels in the standard control.

35. The kit of claim 34, wherein the reagents are used for measuring expression levels of the one or more T2D-associated genes, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, *EIF4E3*, *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*.

36. The kit of claim 35, wherein the presence or increased risk of developing T2D is detected when the expression levels of the one or more T2D-associated genes are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *KDM2B*, *TXNDC12*, and *EIF4E3*.

37. The kit of claim 35, wherein the presence or increased risk of developing T2D is detected when the expression levels of the one or more T2D-associated genes are lower than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *CUEDC2*, *PDCD1*, *PACRG*, *miR-16-1*, and *miR-16-2*.

38. The kit of claim 34, wherein the reagents are used for measuring DNA methylation levels of the one or more T2D-associated genes and the T2D-associated genes are selected from the group consisting of *PDCD1*, *EIF4E3*, *PACRG*, and *KDM2B*.

39. The kit of claim 38, wherein the presence or increased risk of developing T2D is detected when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are higher than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *PDCD1* and *EIF4E3*.

40. The kit of claim 38, wherein the presence or increased risk of developing T2D is detected when the DNA methylation levels of the one or more T2D-associated genes, or regions of these genes, are lower than the levels in the standard control, and the T2D-associated genes are selected from the group consisting of *EIF4E3*, *PACRG*, and *KDM2B*.

41. A kit for detecting the presence or increased risk of developing T2D in a subject, the kit comprising: reagents for determining, in a tissue sample obtained from the subject, a single-nucleotide genotype of the subject at a genomic locus, wherein the genomic locus is given by a SNP ID number provided in Table 9, 10, or 11; and wherein the presence or increased risk of developing T2D in the subject is detected if the single-nucleotide genotype matches a reference genotype associated with T2D.

42. The kit of claim 41, wherein the genomic locus is given by the SNP ID number rs9998519 and the reference genotype is C.

43. The kit of claim 41, wherein the genomic locus is given by the SNP ID number rs1534938 and the reference genotype is T.

44. The kit of claim 41, wherein the genomic locus is given by a SNP ID number provided in Table 9 and the reference genotype for the genomic locus is provided in the "risk genotype" column of Table 9.

45. The kit of claim 41, wherein the genomic locus is given by a SNP ID number provided in Table 10 and the reference genotype for the genomic locus is provided in the "risk allele" column of Table 10.

46. The kit of claim 34 or 41, wherein the reagents comprises those used for an amplification reaction.

47. A device of identifying genetic markers of T2D, the device comprising:

a component for obtaining a multiomic data set from one or more T2D-positive subjects, wherein each T2D-positive subject has been diagnosed with T2D;

a component for obtaining a multiomic data set from one or more T2D-negative subjects, wherein each T2D-negative subject has not been diagnosed with T2D;

a component for identifying differences between the multiomic data sets obtained from the one or more T2D-positive subjects and the one or more T2D-negative subjects; and

a component for identifying one or more genetic markers based on the differences.

48. The device of claim 47, wherein the T2D-positive subjects and T2D-negative subjects together comprise a family trio, and the family trio comprises a father, a mother, and an offspring.

49. The device of claim 47, wherein each multiomic data set comprises at least two of the following: DNA sequencing data, RNA sequencing data, and RNA expression level data.

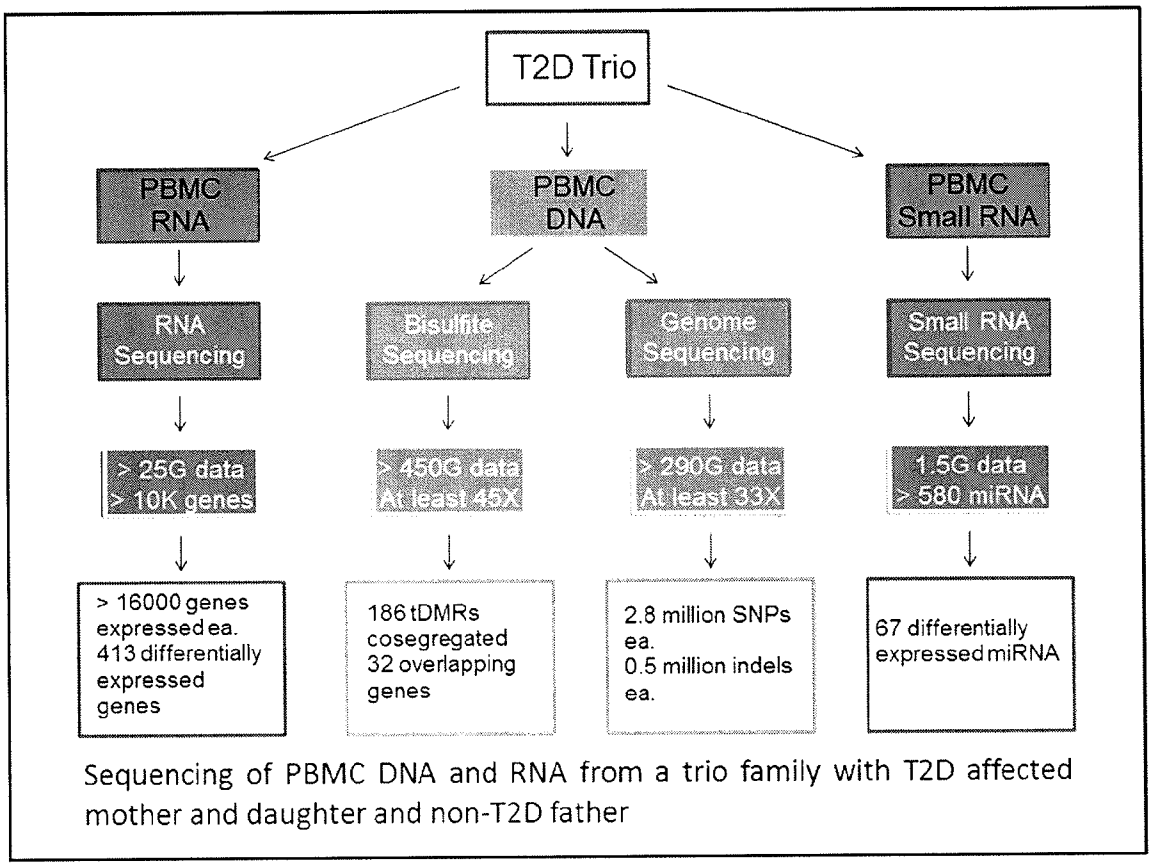

T2D Trio
PBMC RNA
PBMC DNA
PBMC Small RNA
RNA Sequencing
Bisulfite Sequencing
Genome Sequencing
Small RNA Sequencing
> 25G data
> 10K genes
> 450G data
At least 45X
> 290G data
At least 33X
1.5G data
> 580 miRNA
> 16000 genes expressed ea.
413 differentially expressed genes
186 tDMRs cosegregated
32 overlapping genes
2.8 million SNPs ea.
0.5 million indels ea.
67 differentially expressed miRNA
Sequencing of PBMC DNA and RNA from a trio family with T2D affected mother and daughter and non-T2D father

Figure 1

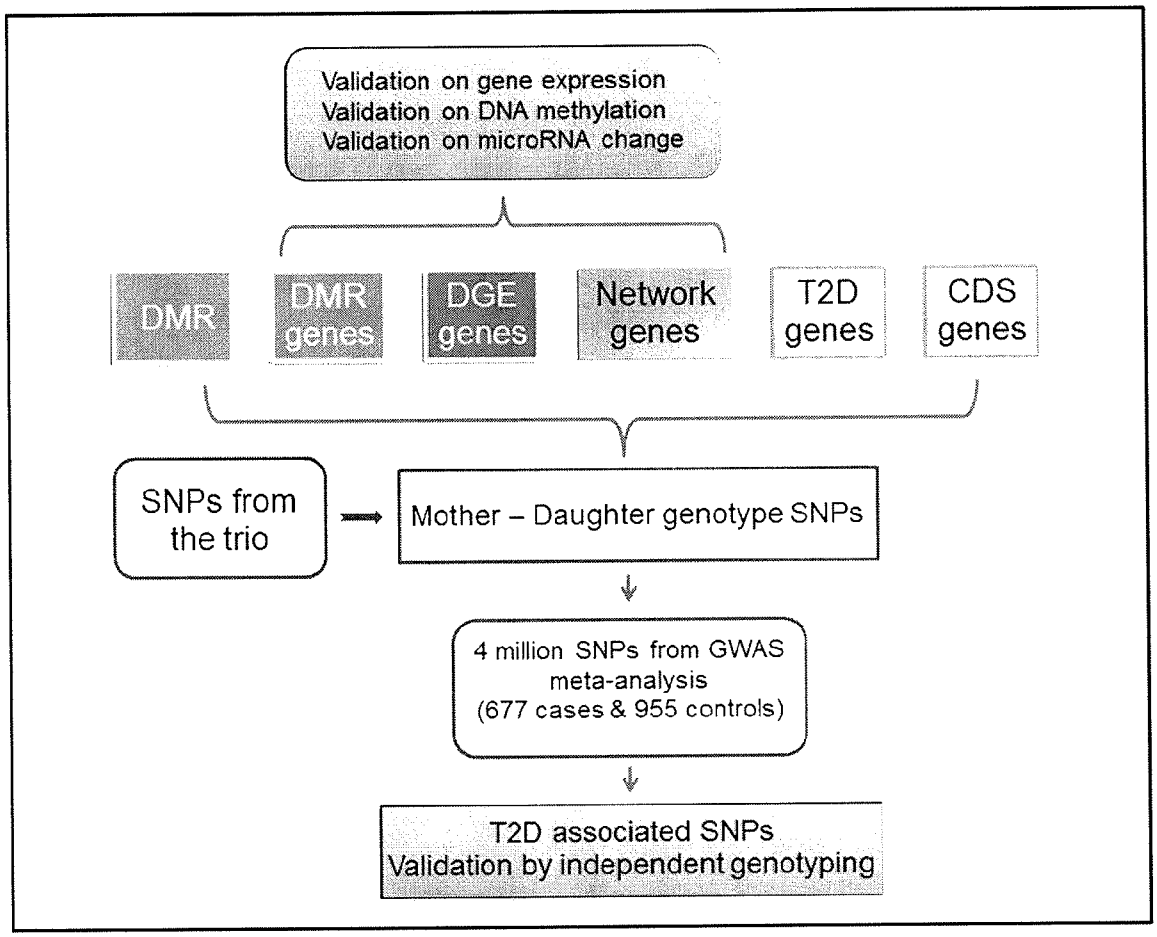

Validation on gene expression
Validation on DNA methylation
Validation on microRNA change
DMR
DMR genes
DGE genes
Network genes
T2D genes
CDS genes
SNPs from the trio
Mother – Daughter genotype SNPs
4 million SNPs from GWAS meta-analysis (677 cases & 955 controls)
T2D associated SNPs Validation by independent genotyping

Figure 2

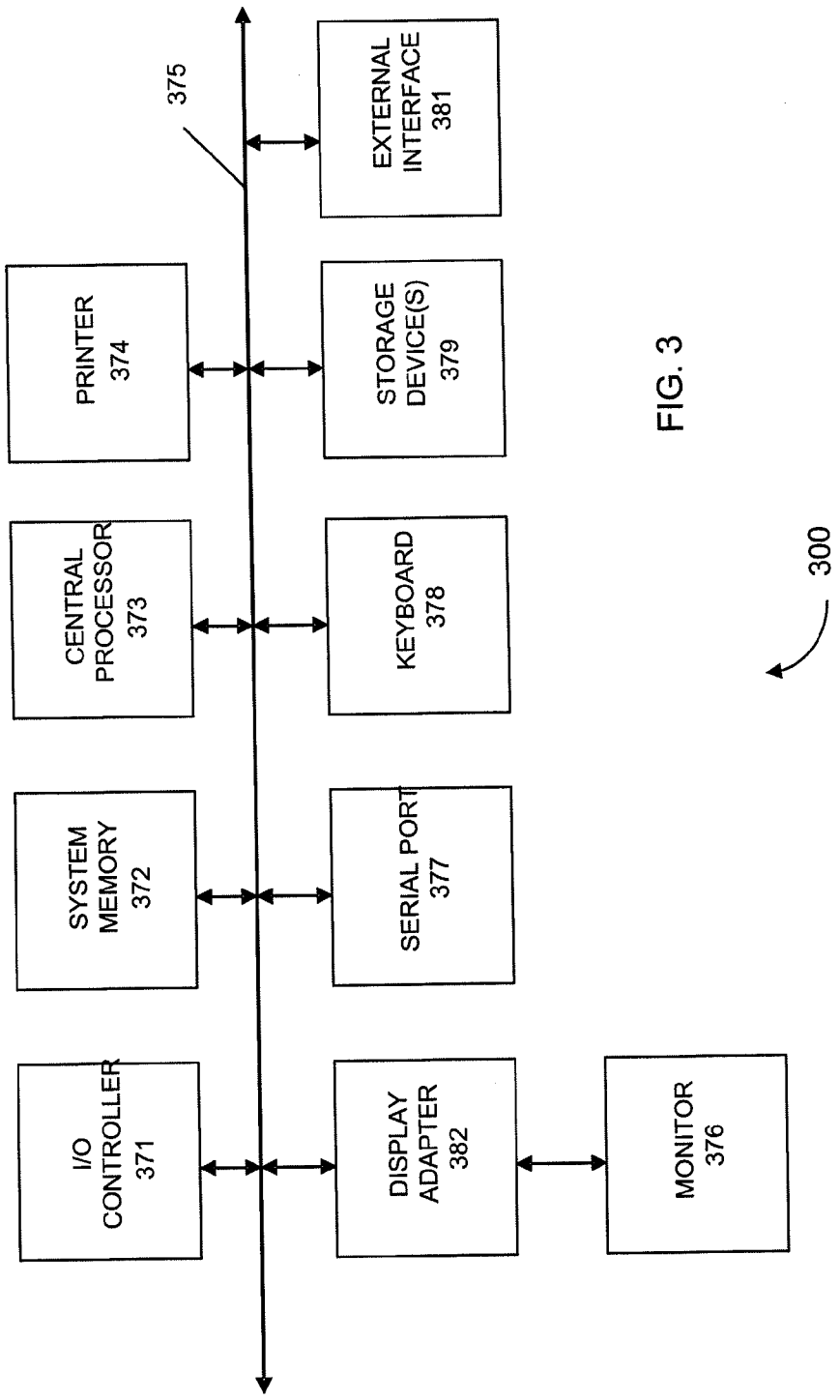

375
EXTERNAL INTERFACE 381
PRINTER 374
STORAGE DEVICE(S) 379
CENTRAL PROCESSOR 373
KEYBOARD 378
SYSTEM MEMORY 372
SERIAL PORT 377
I/O CONTROLLER 371
DISPLAY ADAPTER 382
MONITOR 376
300

FIG. 3

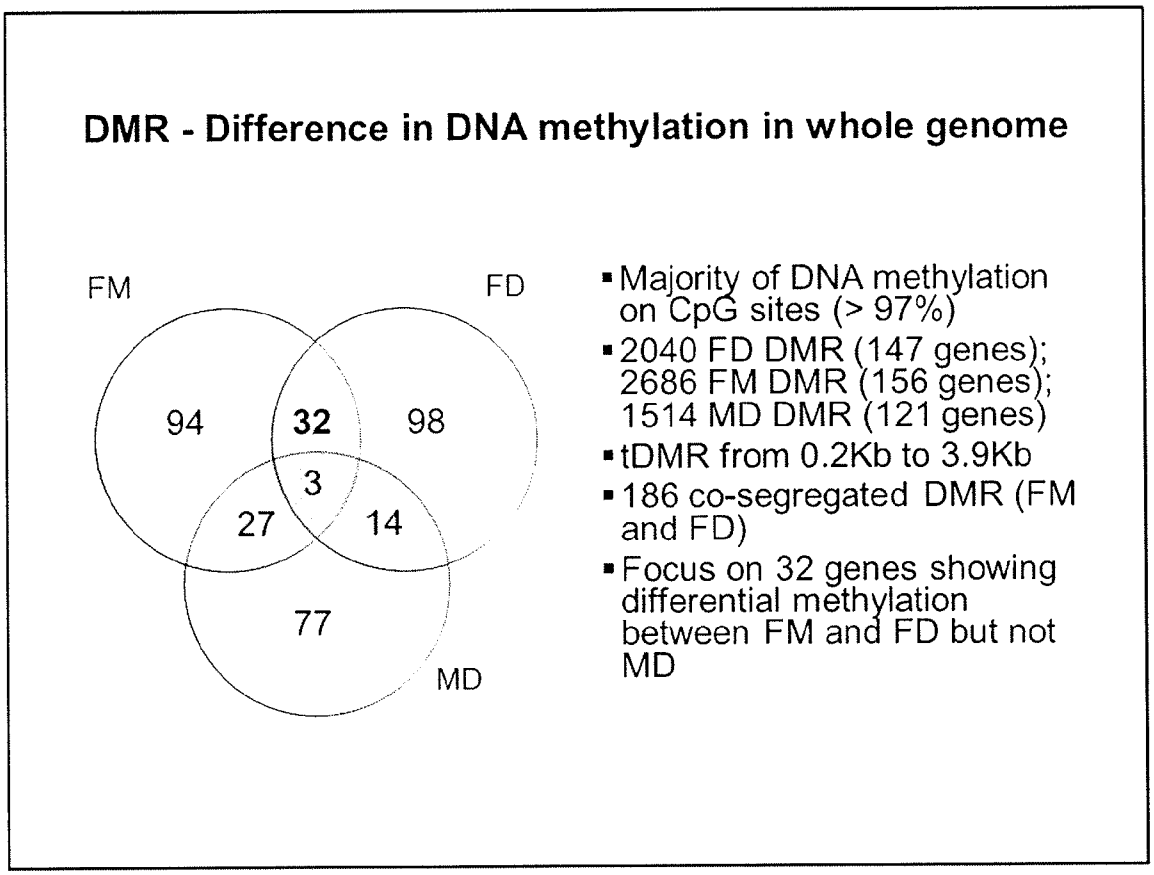
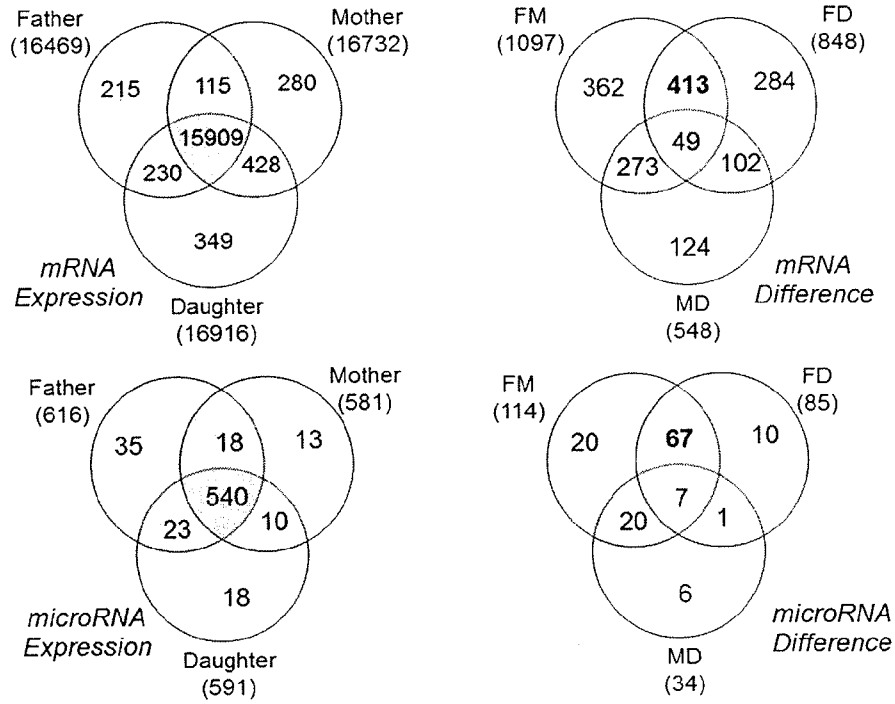
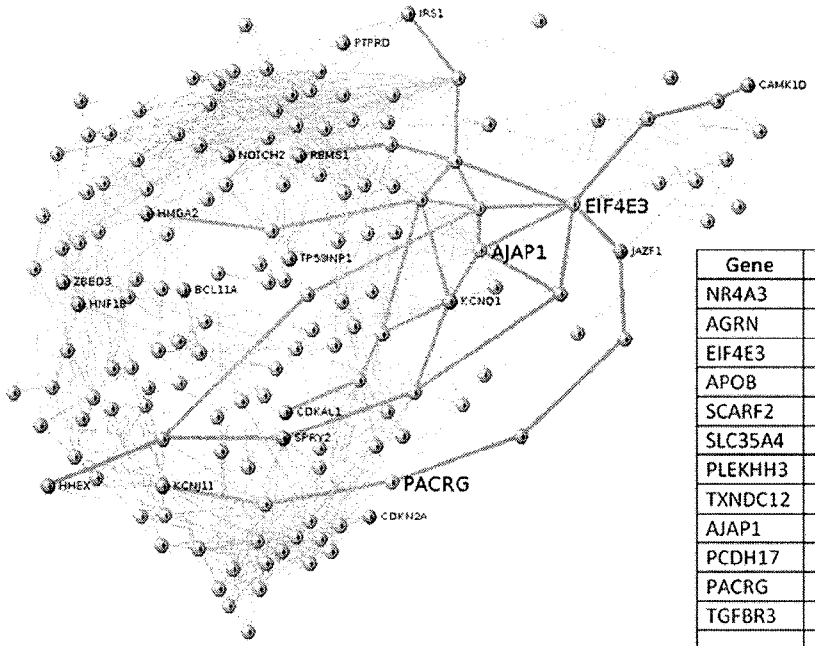

DMR - Difference in DNA methylation in whole genome
FM
FD
MD
94
32
98
3
27
14
77
Majority of DNA methylation on CpG sites (> 97%)
2040 FD DMR (147 genes); 2686 FM DMR (156 genes); 1514 MD DMR (121 genes)
tDMR from 0.2Kb to 3.9Kb
186 co-segregated DMR (FM and FD)
Focus on 32 genes showing differential methylation between FM and FD but not MD

Figure 4



Venn diagram summary of RNA transcriptome and microRNA expression. Top: Over 16,000 genes are expressed (left) and 413 showed differential expression (right). Bottom: About 600 microRNA are expressed (left) and 67 showed differential expression (right).

Figure 5



Gene	Cytoband	BC Score
NR4A3	9q22	216123.43
AGRN	1p36.3	137472.39
EIF4E3	3p14	117920.72
APOB	2p24-p23	72583.81
SCARF2	22q11.22	64638.43
SLC35A4	5q31.3	57333.21
PLEKHH3	17q21.2	51767.46
TXNDC12	1p32.3	47618.06
AJAP1	1p36.32	46505.04
PCDH17	13q21.1	42346.42
PACRG	6q26	38251.94
TGFBR3	1p33-p32	34293.94
		CC Score
LRRC7	1p31.1	0.000160
COL15A1	9q21	0.000156
E2F8	11p15.1	0.000156

Network analysis of multiomic genes. Multiomic network analysis using information on methylation, expression and microRNA targets discovered 15 most connected genes (Table).

Figure 6

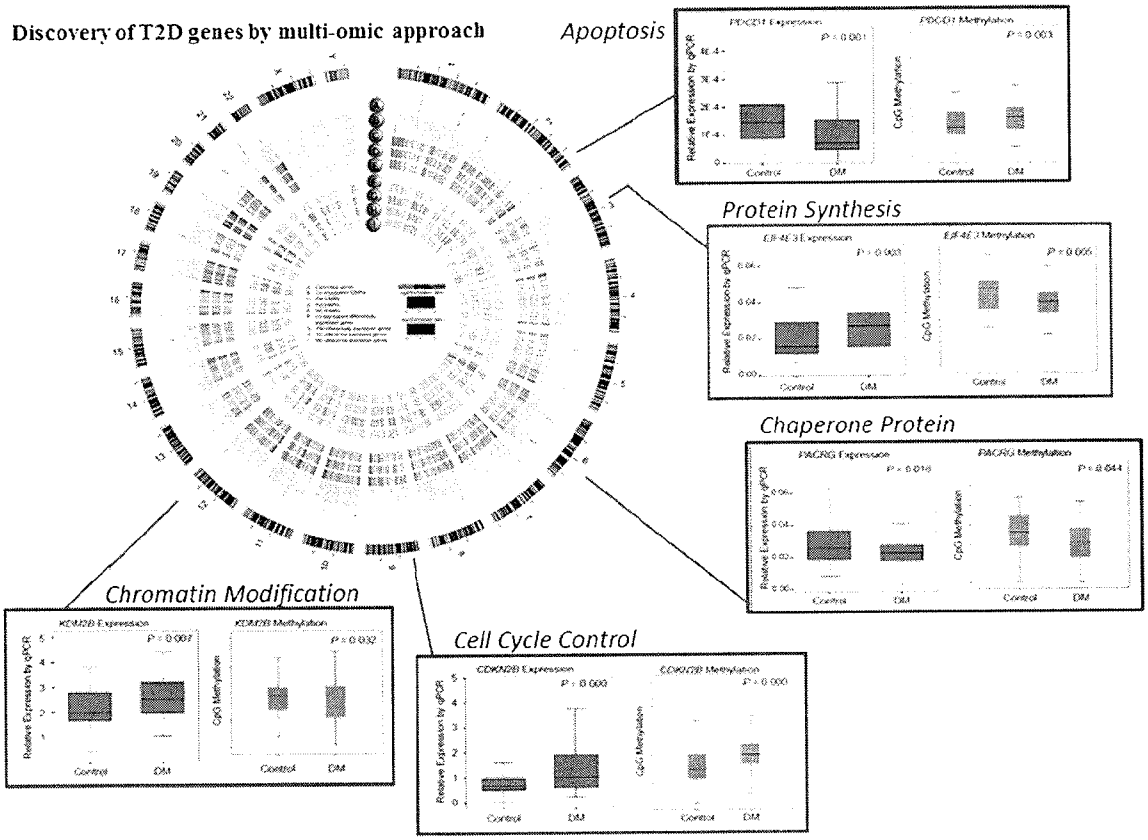

Discovery of T2D genes by multi-omic approach
Apoptosis
Protein Synthesis
Chaperone Protein
Chromatin Modification
Cell Cycle Control

Figure 7