Abstract

Type 2 diabetes (T2D) has become a major health problem throughout the world and the epidemic is particularly severe in Asian countries. Compared with European populations, Asians tend to develop diabetes at a younger age and at much higher incidence rates given the same amount of weight gain. Genome-wide association studies (GWAS) have identified over 70 loci associated with T2D. Although the majority of GWAS results were conducted in populations of European ancestry, recent GWAS in Asians have made important contributions to the identification of T2D susceptibility loci. These studies not only confirmed T2D susceptibility loci initially identified in European populations, but also identified novel susceptibility loci that provide new insights into the pathophysiology of diseases. In this article, we review GWAS results of T2D conducted in East and South Asians and compare them to those of European populations. Currently identified T2D genetic variants do not appear to explain the phenomenon that Asians are more susceptible to T2D than European populations, suggesting further studies in Asian populations are needed.

Introduction

Type 2 diabetes (T2D) has become a leading health problem throughout the world and the epidemic is particularly severe in developing countries. According to estimates by the International Diabetes Federation, the total number of people with diabetes worldwide is projected to rise from 366 million to 552 million by the year 2030, with two-thirds of all new diabetes cases occurring in low- to middle-income countries [1]. Accounting for roughly 60% of the world’s population, Asia’s rapid economic development and urbanization have made it an epicenter of the epidemic [2], with explosive increases in diabetes prevalence in recent decades [3]. In 1980, for example, less than 1% of Chinese adults had T2D. By 2008, the prevalence had reached nearly 10%, or more than 92 million Chinese adults, and another 148 million were prediabetic [4]. Compared with European populations, Asians develop diabetes at younger ages, and at much higher rates given the same amount of weight gain [2]. Several factors contribute to the accelerated diabetes epidemic in Asians, including a high prevalence of smoking and heavy alcohol use; high intake of refined carbohydrates (e.g. white rice); and dramatically lower physical activity levels [2].

It has long been recognized that there are strong genetic influences of T2D, as revealed through classical genetic research, including twin, adoption, and family studies. With the rapid development of modern genotyping techniques, a number of T2D loci have been identified and established by genome-wide association studies (GWAS) among the world’s major ethnic populations, mostly in European and Asian populations. In this article, we aimed to summarize recent progress on the GWAS of T2D in Asians. We also compared these identified T2D susceptibility loci between European and Asian populations and discussed whether currently known genetic variants can explain ethnic differences in T2D risk.

Genetic studies of T2D prior to GWAS

Candidate gene and genome-wide linkage studies (or large-scale association studies), the two major approaches for identifying genes that predispose to common complex diseases before the GWAS era, were limited by small sample sizes and lack of replication of results [5, 6]. In Asian populations, despite identification of numerous T2D susceptibility loci through candidate gene approach, few went on to be validated in other studies. The first signals associated with T2D to be robustly replicated in European populations were the P12 A polymorphism (rs1801282)
GWAS for T2D

With rapid improvements in high-throughput single nucleotide polymorphisms (SNPs) genotyping technology and development of the Hap Map project, methods for identifying susceptibility genes have changed dramatically. The GWAS is currently the most commonly-used approach for uncovering novel loci associated with T2D and related traits. To date, over 70 loci have been associated with T2D at a genome-wide significance level ($P < 5 \times 10^{-8}$). Although the majority of existing GWAS of T2D have been conducted among populations of European ancestry [13-15, 20-32], more recent GWAS in Asians have also successfully identified a number of novel T2D loci [33-45] (Table 1).

| Locus   | SNP     | Chr | Allele (+/-) | RAF | OR (95% CI) | Reference          |
|---------|---------|-----|--------------|-----|-------------|-------------------|
| **East Asians** |
| KCNQ1   | rs2237892 | 11  | C/T          | 0.61 | 1.42 (1.34-1.49) | Yasuda et al., 2008 [33]; Unoki et al., 2008 [34] |
| PTPRD   | rs17584499 | 9   | T/C          | 0.07 | 1.57 (1.36-1.82) | Tsai et al., 2010 [35] |
| SRR     | rs391300  | 17  | G/A          | 0.63 | 1.28 (1.18-1.39) | Tsai et al., 2010 [35] |
| SPRY2   | rs1359790 | 13  | G/A          | 0.71 | 1.15 (1.10-1.20) | Shu et al., 2010 [36] |
| UBE2E2  | rs6780569 | 3   | G/A          | 0.83 | 1.17 (1.11-1.23) | Yamauchi et al., 2010 [37] |
| C2CD4A/B| rs7172432 | 15  | A/G          | 0.59 | 1.12 (1.08-1.16) | Yamauchi et al., 2010 [37] |
| PSMD6   | rs835171  | 3   | C/T          | 0.61 | 1.09 (1.06-1.12) | Cho et al., 2012 [38] |
| MAEA    | rs6815464 | 4   | C/G          | 0.58 | 1.13 (1.10-1.16) | Cho et al., 2012 [38] |
| ZFAND3  | rs9470794 | 6   | C/T          | 0.27 | 1.12 (1.08-1.16) | Cho et al., 2012 [38] |
| KCNK16  | rs1353500 | 6   | T/G          | 0.42 | 1.08 (1.05-1.11) | Cho et al., 2012 [38] |
| GCC1/PAX4| rs6467136 | 7   | G/A          | 0.79 | 1.11 (1.07-1.14) | Cho et al., 2012 [38] |
| GLI3    | rs7041847 | 9   | A/G          | 0.41 | 1.10 (1.07-1.13) | Cho et al., 2012 [38] |
| PEPD    | rs3786897 | 19  | A/G          | 0.56 | 1.10 (1.07-1.14) | Cho et al., 2012 [38] |
| HNF4A   | rs6017317 | 20  | G/T          | 0.48 | 1.09 (1.07-1.12) | Cho et al., 2012 [38] |
| ANK1    | rs515071  | 8   | C/T          | 0.81 | 1.18 (1.12-1.25) | Imamura et al., 2012 [39] |
| GRK5    | rs10886471 | 10  | C/T          | 0.79 | 1.12 (1.08-1.16) | Li et al., 2013 [40] |
| RAIGRP1 | rs7403353 | 15  | T/C          | 0.33 | 1.10 (1.06-1.13) | Li et al., 2013 [40] |
| PA4X4   | rs10229583 | 7   | G/A          | 0.83 | 1.14 (1.09, 1.19) | Ma et al., 2013 [41] |
| MIR129-LEP| rs791595  | 7   | A/G          | 0.08 | 1.17 (1.12, 1.22) | Hara et al. 2014 [42] |
| GPSM1   | rs11787792 | 9   | A/G          | 0.87 | 1.15 (1.10, 1.20) | Hara et al. 2014 [42] |
| SLC16A13| rs312457  | 17  | G/A          | 0.08 | 1.20 (1.14, 1.26) | Hara et al. 2014 [42] |
| **South Asians** |
| ST6GAL1 | rs16861329 | 3   | G/A          | 0.75 | 1.09 (1.06-1.12) | Kooner et al., 2011 [43] |
| UPS2A6  | rs1802295 | 10  | A/G          | 0.26 | 1.08 (1.05-1.12) | Kooner et al., 2011 [43] |
| HMG20A  | rs7178572 | 15  | G/A          | 0.52 | 1.09 (1.06-1.12) | Kooner et al., 2011 [43] |
| AP5X2   | rs2052899 | 15  | C/A          | 0.31 | 1.10 (1.07-1.13) | Kooner et al., 2011 [43] |
| HNF4A   | rs4812829 | 20  | A/G          | 0.29 | 1.09 (1.06-1.12) | Kooner et al., 2011 [43] |
| SGGG    | rs9552911 | 13  | G/A          | 0.92 | 1.49 (1.30-1.72) | Saxena et al. 2013 [44] |
| TMEM163 | rs6723108 | 2   | T/G          | 0.86 | 1.31 (1.20-1.44) | Tabassum et al. 2013 [45] |

SNP, single nucleotide polymorphism; Chr, chromosome; +/-, risk/reference allele; RAF, risk allele frequency; OR, odds ratio.
between KCNQ1 variants and risk of T2D in East Asian populations have suggested that KCNQ1 variants might confer T2D risk through impaired beta-cell function [48-50]. A second, independent signal in this locus was identified in European populations by a meta-analysis in the Diabetes, Genetics, Replication and Meta-analysis Consortium (DIAGRAM) [31].

In 2010, Tsai et al. [35] reported a two-stage GWAS for T2D in Han Chinese from Taiwan. They confirmed the previously reported association between KCNQ1 and T2D, and also identified two novel T2D susceptibility loci, PTRPRD and SRR. PTRPRD belongs to the receptor type IIa (R2A) subfamily of protein tyrosine phosphatases (PTPs), which have been implicated in neural development, cancer, and diabetes [51]. SRR encodes a serine racemase that synthesizes D-serine from L-serine and may play a role in regulating insulin and/or glucagon secretion through glutamate signaling in the pancreas [52]. In addition, Shu et al. [36] reported another novel T2D susceptibility locus, SPRY2, in a multistage-GWAS in Chinese populations. They also found an independent genetic variant (rs10906115) near CDC123, a known T2D locus previously identified in European populations [15] at the genomewide significance level. SPRY2 encodes a protein belonging to the sprouty family and inhibits receptor tyrosine kinase-induced signaling and is required for growth factor stimulated translocation of the protein to membrane ruffles. SPRY4, a homolog of SPRY2, inhibits the insulin receptor-transduced MAPK signaling pathway and regulates development of the pancreas [53].

Yamauchi et al. [37] conducted a three-stage GWAS for T2D in a Japanese population and identified T2D susceptibility loci at UBE2E2 and C2CD4A/B. UBE2E2 encodes the ubiquitin-conjugating enzyme E2E2, and it has been suggested that the ubiquitin-proteasome system may play important roles in insulin secretion [54]. Indeed, the risk allele of UBE2E2 SNP rs7612463 was associated with lower homeostasis model assessment of beta-cell function (HOMA-β) among 872 non-diabetic control subjects [37]. C2CD4A/B encodes C2 calcium-dependent domain containing proteins 4A and 4B, nuclear factors with a role in regulating genes that control cellular architecture [55]. However, evidence for a role of C2CD4A/B in conferring susceptibility to T2D is lacking. Of note, follow-up studies in European populations confirmed the C2CD4A/B locus to be associated with T2D, whereas the UBE2E2 locus was not associated with T2D [37].

In 2012, Cho et al. [38] conducted a meta-analysis of eight T2D GWAS followed by 2-stage replication analyses with a total of roughly 25,000 cases and 30,000 controls in East Asian populations. The combined analysis identified eight new T2D loci reaching genome-wide significance level, mapping in or near GLI3, PEPD, HTIM2-R3HDM1-HNF4A, KCNK16, MAEA, GCC1, PAX4, PSMD6, and ZFAND3. PEPD, encoding peptidase D involved in insulin secretion [56], as well as, HNF4A, encoding hepatocyte nuclear factor 4 alpha, have been reported to be associated with maturity-onset diabetes of the young type 1 (MODY1) diseases and T2D [57-60]. GLI3 encodes a Krüppel-like zinc finger transcription factor that has been proposed as a key player in the regulation of pancreatic beta cell development and insulin gene expression [61]. KCNK16 encodes a potassium channel protein containing two pore-forming P domains, and potassium channels inhibited by ATP regulate glucose-dependent insulin secretion in pancreatic beta-cells [62]. MAEA encodes a protein with a role in erythroblast enucleation and in the development of mature macrophages [63]. GCC1 encodes a GRIP-domain-containing protein that might have a role in the organization of the trans-Golgi network [64]. PAX4 encodes paired box 4 which is involved in pancreatic islet development [65]. PSMD6 encodes 26S proteasome non-ATPase regulatory subunit 6, which is probably involved in the ATP-dependent degradation of ubiquitinated proteins [66]. The function of ZFAND3, which encodes zinc finger AN1-type domain 3, has not been fully elucidated.

Imamura et al. [39] conducted an imputation-based GWAS in Japanese populations and reported ANKI as a new T2D susceptibility locus. ANKI encodes a member of the ankyrin family which plays a critical role in stabilizing the membrane structure of erythrocytes [67]. The role of the gene in T2D was further validated in a recent study demonstrating that two additional SNPs in ANKI were associated with HbA1c levels in European, non-diabetic adults [68].

In 2013, Li et al. [40] performed a three-stage GWAS for T2D in a total of 8,569 cases and 8,923 controls of Han Chinese, followed by an in silico replication in the aforementioned East Asian meta-analysis [38]. This analysis confirmed seven T2D loci previously identified in Europeans (such as CDKAL1, CDKN2A/B, CDC123, HNF1B, and DUSP9) and East Asians (such as KCNQ1 and GLI3) at genomewide significance, and identified two novel T2D loci at GRK3 and RASGRP1. The T2D risk allele of RASGRP1 was also associated with higher HbA1c and lower homeostasis model assessment of beta-cell function, whereas the T2D risk allele of GRK3 was associated with higher fasting insulin. GRK5 encodes G-protein coupled receptor (GPCR) kinase 5 which plays a crucial role in phosphorylation of multiple GPCRs and non-GPCR substrates. These receptors and substrates, such as glucagon receptor [69], b2-adrenergic receptor [70, 71], Hsp70-interacting protein [72], and nuclear factor-kB1/p105 [73], are all important regulators of glucose homeostasis and inflammation. RASGRP1 encodes the RAS guanyl releasing protein which is involved in the development and function of lymphocytes. Its dysfunction in beta-cells was also reported to lead to islet inflammation and impaired beta-cell function [74].

A further GWAS conducted in Southern Han Chinese by Ma et al. [41], identified a novel T2D locus at 7q32 near PAX4, with successful replications in other Chinese and East Asians. The risk allele of the PAX4 variant was also associated with elevated fasting glucose and impaired beta-cell function. PAX4 plays an important role in the differentiation and development of pancreatic beta cells [75]. Previous studies have reported that diabetic patients carrying PAX4 mutation have serious defects in first-phase insulin secretion [76], and mutations in PAX4 may cause rare monogenic forms of young-onset diabetes, including maturity-onset diabetes of the young type 9 (MODY9) diseases [77].

In 2014, Hara et al. [42] performed a three-stage GWAS in Japanese and other East Asians where they identified three new loci for T2D: MIR129/LEP, GPM1, and SLC16A13. Lep, encoded by LEP, is responsible for regulating of body weight by inhibiting food intake and stimulating energy expenditure [78]. GPM1 might be a biologically plausible obesity gene with the evidence that Gpm1 null mice have a lean phenotype with reduced fat mass and increased nocturnal energy expenditure [79]. Intestinal expression of SLC16A13 has been suggested to be up-regulated by peroxisome proliferator-activated receptor - α agonists [80].
Interestingly, there was no association between these three novel loci and T2D in European populations [81].

South Asians

In 2011, Kooner et al. [43] reported the first GWAS for T2D in cases and controls with ancestry from the Indian Subcontinent (India, Pakistan, Sri Lanka, and Bangladesh). They identified six T2D susceptibility loci: GRB14, ST6GAL1, VPS26A, HMG20A, AP332, and HNF4A. They also reported that SNPs at GRB14 were associated with insulin sensitivity, and SNPs at ST6GAL1 and HNF4A with beta-cell function [43]. GRB14 encodes growth factor receptor-bound protein 14, an adaptor protein that binds to insulin receptors and insulin-like growth-factor receptors to inhibit tyrosine kinase signaling [82]. ST6GAL1, encoding an enzyme predominantly located in the Golgi apparatus, is involved in post-translational glycosylation of cell-surface components. Glycosylation through addition of sialic acid residues is reported to influence both insulin action and cell surface trafficking [83].

In 2013, Saxena et al. [44] conducted a GWAS and multistage meta-analysis in Punjabi Sikhs from Northern India. They identified a novel locus at 13q12 in the SGCG gene associated with T2D. Interestingly, the associated SNP is monomorphic in Europeans, suggesting this locus might be specific to the Indian Punjabi Sikh population. SGCG is a member of the sarcoglycan complex of transmembrane glycoproteins mutated in autosomal recessive muscular dystrophy [44]. Mice lacking sarcoglycan complex in adipose and skeletal muscle have been shown to be glucose intolerant and displayed whole body insulin resistance because of impaired insulin-stimulated glucose uptake in skeletal muscle [84]. In addition, Tabassum et al. [45], through a two-stage GWAS in Indians, reported a new T2D-associated locus in TMEM163 gene at 2q21. TMEM163, encoding a synaptic vesicle membrane protein with six putative transmembrane helices, has been shown to play an important role in reducing fasting insulin levels and HOMA-IR [45].

Most T2D loci initially identified in European populations have been replicated in Asians [38, 43]. Kooner et al. [43] investigated 42 T2D loci in both South Asians and Europeans, and found that 37 loci showed consistent direction of effect in South Asians and Europeans, and that 27 loci were associated with T2D at P < 0.05 in South Asians. Top signals observed in the East Asian T2D stage 1 meta-analysis [38], such as CDKAL1, CDKN2A/B, HHEX/IDE, KCNJ11, KCNQ1, and FTO, were similar to those identified in European populations (the DIAGRAM+ stage 1 meta-analysis) [31], though additional genetic loci have been identified in genetic populations that have not been tested in Asians. In addition, a GWAS of T2D in multi-ethnic cohorts from South-east Asia (including Chinese, Malays and Asian Indians) observed consistent direction of effect for many T2D SNPs identified in European populations [85].

However, there were some inter-ethnic differences in the risk allele frequencies (RAFs) and genetic variant locations of top T2D loci among European and South and East Asian populations. With the exception of SNPs in CDKAL1 and KCNQ1, the RAFs of most SNPs in East Asians are lower than those in Europeans and South Asians (Figure 1). For example, the risk allele of the SNP rs7903146 in TCF7L2 is common in European and South Asian populations (20-30%), but rare in East Asians (~2%). Other common genetic variants in TCF7L2 (e.g., SNPs rs290487 and rs11196218) with RAFs of 30-40% were reported to confer risk for T2D that is exclusive to the Chinese population [18, 19].

Despite heterogeneity in risk allele frequency of genetic variants with the strongest T2D association signals, the effect sizes appear to be similar across populations. Only a handful of SNPs showed potential heterogeneity between European and Asian populations (Figure 1). The association between TCF7L2 SNP rs7903146 and risk of T2D is stronger in Europeans (odds ratio [OR] 1.37 [1.31-1.43]) compared to East Asians (OR 1.16 [1.02-1.31]), P for heterogeneity = 0.14. Nevertheless, the effects are similar across all three populations, with no significant differences in ORs or 95% CIs between European and Asian populations (results not shown).

Figure 1. Risk allele frequency and effect size of top Type 2 diabetes susceptibility loci in European and Asian populations.

Bars represent risk allele frequency of each SNP (or its proxy) in Europeans (blue, derived from HapMapCEU), South Asians (green, derived from Kooner et al. [43]) and East Asians (red, derived from HapMap CHB/JPT). Square boxes and vertical bars represent odds ratio and 95% CI of each SNP (or its proxy) for T2D risk in Europeans (blue), South Asians (green) and East Asians (red), derived from reported GWAS studies [13-15, 31, 33, 38, 43]. CI = confidence interval.
Further, several combined analyses of multiple genetic variants using genetic risk scores in Asians have shown similar results with those in European populations, in which each risk allele increment was associated with a 10-20% increased risk of T2D [88-95]. For example, Meigs et al. [88] investigated the combined effect of 18 T2D genetic variants in participants of European ancestry from the Framingham Offspring Study and found that the OR per risk allele for T2D was 1.12. Similarly, in a combined analysis of 17 T2D genetic variants in a population-based Han Chinese cohort, each risk allele was associated with an 18% increased risk for T2D [93]. More recently, Janipalli et al. [95] reported an OR per risk allele of 1.11 for T2D in Indians by using a genetic risk score based on 32 T2D genetic variants. These data suggest that the overall contribution of the identified genetic loci to T2D is similar between European and Asian populations and that these genetic loci do not appear to explain ethnic differences in diabetes risk.

Very recently, a trans-ethnic meta-analysis of GWAS evaluated 69 established T2D loci among four major ethnic groups (European, East Asian, South Asian and Mexican ancestry) and found significant excess in directional consistency of T2D risk alleles across MPHOSPH9, FAF1 and including loci without heterogeneity across ethnic groups were identified, is strongest in populations of European ancestry, whereas the association was stronger in Japanese than in European Americans [86]. Other studies have observed similarly stronger associations among East Asians compared to Europeans [56, 87]. By comparing the data from three large-scale meta-analyses [31, 38, 43], the magnitude of the effect of CDKAL1 for T2D is stronger in East Asians (OR 1.20 [1.14-1.25]) compared to Europeans (OR 1.12 [1.08-1.16], P for heterogeneity = 0.02 between East and South Asians) and South Asians (OR 1.08 [1.02-1.14], P for heterogeneity = 0.004 between East and South Asians).

Thriftier Genotype

In 1962, Neel [101] suggested that famine exposure during human evolutionary history resulted in positive selection for thrifty genotypes characterized by high efficiency of energy metabolism and fat storage during periods of feast. Thus, obesity and T2D might be a result of a thrifty genotype that leads to advantageous phenotypes in the modern setting of food over abundance and sedentary lifestyles. The thrifty genotype hypothesis has been widely used to explain the extraordinarily high rates of diabetes seen among some indigenous populations such as Pima Indians of North America, since these populations may have an enhanced genetic predisposition to obesity and diabetes due to evolutionary selection for thrifty genotypes. In contrast, Europeans are thought less likely to possess thrifty genotypes as they evolved in environments that were less affected by feast and famine cycles. However, based on an analysis of 30 SNP data (17 T2D loci and 13 obesity loci) among African, European and East Asian populations from Hap Map, Southam et al. [102] found no clear evidence for over representation of derived alleles (versus ancestral alleles) for the T2D or obesity loci, nor did they find a greater concentration of these loci in a particular ethnic group. Moreover, in a recent analysis of 30 SNPs in 16 T2D loci and 28 SNPs in obesity loci among 53 populations from the Human Genome Diversity Panel, Klimentidis et al. [103] found no evidence that risk alleles associated with either phenotype tend to be either ancestral or derived. They did find a high degree of differentiation for the ensemble of T2D loci in East Asians and sub-Saharan Africans, however, suggesting that these groups might have experienced natural selection at T2D loci. These analyses provide some evidence for natural selection, but the validity of the thrifty genotype hypothesis remains largely unclear.

Speakman [104] proposed the “drifty” genotype hypothesis as an alternative to the thrifty genotype hypothesis. He argued that the existence of obesity- or diabetes-related genetic variants is simply because of random genetic drift over millions of years, as there is little evidence that humans were under strong selective pressure by famine throughout evolutionary history. Whether obesity and T2D loci represent thrifty or drifty genotypes is yet to be determined. Currently identified loci only represent a small part of the genetic architecture of obesity and T2D, and the causal genes or causal variants are largely unknown. Identification of more loci and more casual variants through ongoing fine-mapping efforts and whole-genome sequencing analyses will further illuminate the genetic basis of T2D in different ethnic groups.
Conclusion and Future Perspective

Significant progress in understanding the genetic determinants of T2D has been made through multiple waves of GWAS over a relatively short time. Although a majority of established T2D susceptibility loci were identified in European populations, recent GWAS in Asians have also made important contributions to the identification of susceptibility genes. These studies not only confirmed T2D susceptibility loci initially identified in European populations, but also identified novel susceptibility loci that provide new insights into the pathophysiology of diseases. At this juncture, however, currently known genetic variants do not appear to explain the excess susceptibility to T2D in Asians compared to European populations.

Several possibilities may explain this phenomenon. The casual genes/variants at known T2D loci, and their biological functions, are largely unclearly. Further studies with fine-mapping and sequencing analysis, and functional experiments, are needed to identify the causal genes/variants and mechanisms underlying the associations. Clearly, more genetic loci associated with T2D remain to be discovered since the currently known loci explained only a fraction of the heritability for T2D. More studies with large meta-analysis of GWAS, especially in Asian populations, are needed to identify loci that might be specific to Asians. Multi-ethnic meta-analysis would be helpful to identify new loci and population-specific loci for T2D. In addition, rare (low-frequency) variants with larger effect size might account for some of the unexplained heritability. Thus, deep-sequencing of the exomes or the whole genomes is needed. It is widely acknowledged that T2D is a result of the interplay between genetic and environmental factors.

Abbreviations and full names of genes.

| Abbreviations | Full Names |
|---------------|------------|
| ANK1          | Ankyrin 1, erythrocytic |
| AP3S2         | Adaptor-related protein complex 3, sigma 2 subunit |
| ARLI5         | ADP-riboseylation factor-like 15 |
| AMY1          | Amylase, alpha 1 |
| CDKAL1        | CDK5 regulatory subunit associated protein 1-like 1 |
| CDKN2A/B      | Cyclin-dependent kinase inhibitor 2A |
| C2CD4A/B      | C2 calcium-dependent domain containing 4B |
| FTO           | Fat mass and obesity associated |
| FAFI          | Fas (TNFRSF6) associated factor 1 |
| GCC1/PAX4     | GRIP and coiled-coil domain containing 1/ paired box 4 |
| GLIS3         | GLIS family zinc finger 3 |
| GPM1          | G-protein signaling modulator 1 |
| GRK5          | G protein-coupled receptor kinase 5 |
| HNF4A         | Hepatocyte nuclear factor 4, alpha |
| HMG20A        | High mobility group 20A |
| HHEX/IDE      | Hematopoietically expressed homeobox/insulin-degrading enzyme |
| KCNK16        | Potassium channel, subfamily K, member 16 |
| KCNQ1         | Potassium voltage-gated channel, KQT-like subfamily, member 1 |
| KCNJ11        | Potassium inwardly-rectifying channel, subfamily J, member 11 |
| KLF14         | Kruppel-like factor 14 |
| LPP           | LIM domain containing preferred translocation partner in lipoma |
| MAEA          | Macrophage erythroblast attacher |
| MIR129-LEP    | Mirl129-leptin |
| MPHOSPH9      | M-phase phosphoprotein 9 |
| PPARG         | Peroxisome proliferator-activated receptor gamma |
| PTPRD         | Protein tyrosine phosphatase, receptor type, D |
| PSMD6         | Proteasome (prosome, macropain) 26S subunit, non-ATPase, 6 |
| PEPD          | Peptidase D |
| PAX4          | Paired box 4 |
| POU5F1/TCF19  | POU class 5 homeobox 1/ transcription factor 19 |
| RAASGRF1      | RAS guanyl releasing protein 1 (calcium and DAG-regulated) |
| SRR           | Serine racemase |
| SPRY2         | Sprouty homolog 2 (Drosophila) |
| SLC16A13      | Solute carrier family 16, member 13 |

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