The Search for Genetic Risk Factors of Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is caused by complex interplay between multiple genetic and environmental factors. The three major approaches used to identify the genetic susceptibility include candidate gene approach, familial linkage analysis and genome-wide association analysis. Recent advance in genome-wide association studies have greatly improved our understanding of the pathophysiology of T2DM. As of the end of 2010, there are more than 40 confirmed T2DM-associated genetic loci. Most of the T2DM susceptibility genes were implicated in decreased β-cell function. However, these genetic variations have a modest effect and their combination only explains less than 10% of the T2DM heritability. With the advent of the next-generation sequencing technology, we will soon identify rare variants of larger effect as well as causal variants. These advances in understanding the genetics of T2DM will lead to the development of new therapeutic and preventive strategies and individualized medicine.

Keywords: Diabetes mellitus, type 2; Gene; Genome-wide association studies; Heritability; Next generation sequencing; Single nucleotide polymorphism

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a multi-factorial disease caused by complex interplay between genetic predisposition and environmental factors [1]. Environmental factors such as increased calorie intake, physical inactivity or obesity certainly contribute to the recent diabetes epidemic. However, genetic factors are also key determinants of the individual susceptibility to T2DM. The importance of genetic risk factors for T2DM is supported by two major findings. First, there are ethnic differences in the prevalence of T2DM. Asians or Pima Indians residing in Western countries have at least a two-fold increased risk of T2DM compared to European natives [2]. Second, there is strong family history of T2DM. The offspring of T2DM parents have 40% chance of having T2DM, which is a 6-fold increased risk compared to a population risk of 7% [2].

There has been a tremendous effort to reveal the genetic predisposition of T2DM over the past 30 years or so. The three approaches adopted for identifying genetic risk factors include: 1) focusing on linkage peaks from family studies, 2) targeting candidate genes on the biological basis, and 3) genome-wide association analysis. Since the recent advent of genome-wide...
association studies (GWAS), there has been remarkable progress in our understanding of the genetic basis of T2DM. More than 40 genetic variations that modify the risk of T2DM development have been identified. In this article, I will review the current approaches and progress in understanding the genetics of T2DM.

**FAMILY-BASED LINKAGE ANALYSIS**

Family-based linkage analysis relies on genetic markers in a family pedigree to identify the chromosomal regions showing linkage with T2DM. This approach is most useful when the disease under investigation follows a monogenic form of inheritance. Causative genetic variations of several monogenic forms of diabetes, including maturity-onset diabetes of the young, neonatal diabetes and maternally inherited diabetes and deafness were successfully identified using this approach [3-5]. However, this approach failed to identify causative genes for the common form of T2DM. There have been several reports suggesting linkage peaks near CAPN10 and ACRP30 [6,7]. Unfortunately, these results were not consistent across the study population and no high-risk variation was found to be associated with T2DM near these regions.

**THE CANDIDATE GENE APPROACH**

The candidate gene approach refers to case-control association studies focusing on specific candidate gene or a selected genetic region, chosen based on known biological function. More than hundred of candidate genes have been investigated by this approach. However, only a few genes such as PPARG and KCNJ11 have been shown to be associated with T2DM [8,9].

The PPARG gene encodes the peroxisome proliferator-activated receptor γ, which plays a fundamental role in adipogenesis and insulin sensitivity by regulating transcriptional activity of various genes. A variation with proline at the 12th amino acid (P12A) was confirmed to be associated with a modest odds ratio [OR] of 1.25, but significant increase in T2DM risk [8].

The KCNJ11 gene, located on the short arm of chromosome 11, encodes the pore-forming subunit of the ATP-sensitive potassium channel Kir6.2 of the pancreatic β-cells. Gain-of-function mutations of KCNJ11 open the potassium channel and inhibit the depolarization of β-cells, leading to a defect in insulin secretion [10]. Studies in various populations have consistently reported that substitution of lysine for glutamic acid at the 23rd amino acid (E23K) is associated with an increased risk of T2DM [11,12]. In recent reports of large-scale association studies and meta-analyses, the E23K variation was found to increase the risk of T2DM with an OR of 1.15 [9].

The most significant finding derived from the candidate gene approach is the strong association of TCF7L2 gene [13]. This gene was first discovered to increase the risk of T2DM through an effort to pinpoint the previously reported linkage peak [14]. The association between rs7903146T, an intronic variation, with T2DM was replicated in almost all ethnic groups and revealed to have the strongest effect in Europeans (OR, 1.46) [15-17]. A global meta-analysis showed that this variation had an OR of 1.45 and P-value of $5.4 \times 10^{-10}$ in a comparison of more than 46,000 cases and controls [18]. However, this allele had a significantly lower allele frequency in Asians and the resultant association was much weaker [19]. The functional role of TCF7L2 in the pathogenesis of T2DM is currently under thorough investigation. It is a crucial component of Wnt signaling and is implicated in β-cell proliferation and insulin secretion [20,21]. Furthermore, a recent study reported that TCF7L2 is important in maintaining the incretin effect [22].

**GWAS**

In the year 2007, there was a major breakthrough in identifying genetic risk factors of T2DM through the completion of GWAS. In GWAS, hundreds of thousands of single-nucleotide polymorphisms (SNPs) are tested for association with a disease, such as T2DM, in hundreds to thousands of individuals [23]. The three major advances that enabled this approach were 1) the improved knowledge of human genetic variations through the International HapMap project, 2) the technical advances in microarray genotyping methods, and 3) the progress in developing biostatistic methods to handle the large amount of data being produced. From the first six GWAS results reported in 2007, more than ten new genetic loci were reported to modify the risk of T2DM with genome-wide significance in Europeans [24-29]. These included variations in or near CDKAL1, CDKN2A/2B, SLC30A8, IGF2BP2, HHEX, and FTO. The variation in TCF7L2 was confirmed to have the strongest association in Europeans. In addition, the known association between variations in KCNJ11 and PPARG with T2DM were also replicated.

Based on the first GWAS reported by Sladek et al. [24], vari-
ations in SLC30A8 and near HHEX were found to be significantly associated with T2DM. Genetic variation of SLC30A8 is located in 8q24 and encodes an islet-specific zinc membrane transporter (ZnT8), which takes part in insulin synthesis and secretion [24]. Interestingly, the variation in SLC30A8, rs-13266634, results in a non-synonymous mutation of the protein [24]. One locus at 10q23-25 with large linkage disequilibrium block encompassing HHEX, IDE, and KIF11 were also significantly associated with T2DM. We have reported that variations in IDE, which encodes insulin degrading enzyme, are associated with the risk of T2DM in Koreans, as well as in a meta-analysis [30]. From the DGI study and FUSION study, variations in IGF2BP2 and CDKN2A/2B were found to be significantly associated with T2DM [25,27]. The IGF2BP2 gene located at 3q28, encodes insulin-like growth factor 2 mRNA-binding protein, which is thought to be involved in insulin signaling. A genetic variation located at 9p21 between CDKN2A and CDKN2B genes was also associated with T2DM. CDKN2A encodes p16\(^{INK4a}\) and its overexpression results in decreased \(\beta\)-cell mass in senescent mice [31]. Another variation near this locus was independently associated with the risk of coronary heart disease due to elevated low density lipoprotein

Table 1. Genetic variations associated with T2DM and related phenotypes in Koreans

| Associated trait | Gene symbol | Chromosome | SNP | \(P\) value | Predicted disease mechanism | Reference |
|------------------|-------------|------------|-----|-------------|----------------------------|-----------|
| Diabetes         | PPARGC1A    | 4p15       | rs3736265 | 0.04 | Insulin resistance, mitochondrial function | [55]      |
|                  | KCNJ11      | 11q15      | rs5219  | 0.01 | KATP (Insulin secretion) | [45]      |
|                  | PPARGCIB    | 5q32       | rs11959820 | 0.03 | Insulin resistance, mitochondrial function | [56]      |
|                  | NRF1        | 7q32       | rs1882094 | 0.01 | Mitochondrial function | [47]      |
|                  | PPARG       | 3p25       | rs1801282 | 0.02 | Insulin resistance | [46]      |
|                  | IDE         | 10q23      | rs4646957 | 0.02 | Insulin degradation | [30]      |
|                  | UCP2        | 11q13      | rs659366 | 0.02 | Mitochondrial function | [57]      |
|                  | LEPR        | 1q31       | rs3790419 | 0.05 | Appetite regulation | [57]      |
|                  | mtDNA       | Haplogroup N9a |       | 0.000003 | Mitochondrial function | [51]      |
| BMI              | PPARG       | 3p25       | rs1801282 | 0.01 | Insulin resistance | [46]      |
|                  | CD14        | 5q31       | rs2569190 | 0.003 | Systemic inflammation | [58]      |
|                  | HSD11B1     | 1q32       | rs846908  | 0.01 | Glucocorticoid metabolism | [59]      |
|                  | PPARD       | 6p21       | rs9658173 | 0.03 | Insulin resistance | [49]      |
|                  | LEPR        | 1q31       | rs1137100 | 0.02 | Appetite regulation | [60]      |
|                  | mtDNA       | Haplogroup N9a |       | 0.000003 | Mitochondrial function | [51]      |
| Waist circumference | ADIPOR2   | 12p13      | rs1044471 | 0.02 | Insulin resistance | [61]      |
| Fasting glucose  | HSD11B1     | 1q32       | rs701950  | 0.004 | Glucocorticoid metabolism | [59]      |
|                  | PPARD       | 6p21       | rs9794   | 0.04 | Insulin resistance | [49]      |
| HOMA-IR          | ADIPOR1     | 1p36       | rs75172865 | 0.004 | Insulin resistance | [61]      |
| SBP              | KCNJ11      | 11q15      | rs886288  | <0.001 | Insulin secretion | [45]      |
| Triglyceride     | PPARGC1B    | 5q32       | rs11959820 | 0.02 | Insulin resistance, mitochondrial function | [56]      |
|                  | PPARG       | 3p25       | rs1801282 | 0.05 | Insulin resistance | [46]      |
|                  | PCK1        | 20q13      | rs28359554 | 0.01 | Gluconeogenesis | [62]      |
|                  | CD14        | 5q31       | rs2569190 | 0.01 | Systemic inflammation | [58]      |
| HDL-C            | GHRELIN     | 3p25       | rs26311  | 0.0004 | Appetite regulation | [48]      |
|                  | PCK1        | 20q13      | rs28359554 | 0.000003 | Gluconeogenesis | [62]      |

T2DM, type 2 diabetes mellitus; SNP, single nucleotide polymorphism; BMI, body mass index; HOMA, homeostasis model assessment; IR, insulin resistance; SBP, systolic blood pressure; HDL-C, high density lipoprotein cholesterol.
cholesterol concentration [32,33]. A genetic variation located in 6p22.3 of the CDKAL1 gene was first discovered to be significantly associated with T2DM through the deCODE study [28]. CDKAL1 encodes CDK5 regulatory subunit-associated protein 1-like 1 [28], which is thought to inhibit cyclin-dependent kinase 5 (CDK5) activity by binding to the CDK5 activator p35 [34]. In a recent report, disruption of CDKAL1 in mouse β-cells resulted in impaired first-phase insulin secretion [35]. Subjects who had risk variants of CDKAL1 had decreased insulin secretion capacity.

After the initial GWAS results, meta-analyses with large-scale replication analyses were performed [36,37]. The DIAGRAM consortium, which includes more than 50,000 cases and controls, was able to identify six additional genetic loci associated with T2DM [36]. These included variations in or near JAZF1, CDC123-CDMK1D, TSPAN8-LGR5, THADA, ADAMTS9, NOTCH2 genes. It should be noted that GWAS carried out in Asians revealed new T2DM genetic loci that were not previously reported in Europeans [38-40]. These were in or near KCNQ1, UBE2E2 and C2CD4A/4B. The KCNQ1 gene encodes a subunit of a voltage-gated potassium channel that is expressed in β-cells. The variation in KCNQ1 is thought to modulate the risk of T2DM by inducing β-cell dysfunction [38,39]. The UBE2E2 gene encodes the ubiquitin-conjugating enzyme E2E, which plays an important role in insulin synthesis and secretion under conditions where endoplasmic reticulum stress is increased in β-cells [40]. In an effort to find common genetic variations affecting fasting plasma glucose, variation in MTNR1B was found to be significantly associated with elevated fasting glucose and risk of T2DM [41-43]. MTNR1B encodes the melatonin receptor 2 (MT2) and it is expressed in human pancreatic β-cells as well as in the brain [42]. Increased expression of MT2 in β-cells is thought to suppress glucose-stimulated insulin secretion [44]. As of the end of 2010, the results from the DIAGRAM+ study, with a sample size of 141,000, included an additional 12 genetic variations, adding up to a total of more than 40 confirmed T2DM genetic risk loci [37].

### GENETICS OF T2DM IN KOREANS

During the past ten years, my colleagues and I have focused on the candidate gene approach to find susceptibility genes for T2DM in Koreans. From these efforts, I have reported that variations in many genes, e.g., KCNJ11, PPARG, NRF1 and IDE are associated with T2DM (Table 1) [30,45-47]. We also have investigated the association of candidate genetic variations with quantitative metabolic traits such as fasting glucose, blood pressure, body mass index and dyslipidemia (Table 1) [45,48,49]. In addition, we have shown that mtDNA 16189T>C variation is associated with an increased risk of T2DM in Asians [50,51]. Among the mtDNA haplogroups, we showed that mitochondrial haplogroup N9a was significantly associated with resistance against T2DM, while D5 was significantly associated with a risk for T2DM [52]. Association of mito-

**Table 2. The most replicated T2DM genetic susceptibility loci confirmed by the initial six GWAS studies and comparison of their signals in Koreans [24-29]**

| Gene   | SNP            | Approach              | MAF in Europeans | OR in Europeans | MAF in Koreans | OR in Koreans | Predicted disease mechanism                  |
|--------|----------------|-----------------------|------------------|-----------------|----------------|---------------|---------------------------------------------|
| PPARG  | rs1801282(P12A)| Candidate gene        | 0.817 to 0.901   | 1.148           | 0.947          | 1.818         | Insulin resistance                          |
| KCNJ11 | rs5215(E23K)   | Candidate gene        | 0.351 to 0.461   | 1.093           | 0.456          | 1.225         | K<sub>ATP</sub> (Insulin secretion)         |
| TCF7L2 | rs7903146      | Linkage analysis      | 0.179 to 0.378   | 2.210           | 0.025          | 1.53          | β-cell function, incretin effect           |
| HHEX   | rs1111875      | GWAS                  | 0.526 to 0.626   | 1.172           | 0.186          | 1.22          | Pancreas development                        |
| SLC30A8| rs13266634     | GWAS                  | 0.604 to 0.724   | 1.149           | 0.585          | 1.18          | Insulin synthesis and secretion             |
| CDKAL1 | rs7754840      | GWAS                  | 0.293 to 0.373   | 1.185           | 0.464          | 1.24          | β-cell function and mass                    |
| CDK22A/2B | rs10811661    | GWAS                  | 0.810 to 0.844   | 1.191           | 0.546          | 1.25          | β-cell function and mass                    |
| IGF2BP2| rs4402960      | GWAS                  | 0.277 to 0.333   | 1.139           | 0.273          | 1.24          | mRNA processing in β-cells                  |
| FTO    | rs8050136      | GWAS                  | 0.373 to 0.420   | 1.116           | 0.118          | 1.06          | Obesity                                     |

The minor allele frequencies (MAF) and odds ratios (OR) of Europeans are adopted from the DIAGRAM+ study [37]. The MAF and OR of Koreans are adopted from reference [19].

T2DM, type 2 diabetes mellitus; SNP, single nucleotide polymorphism; GWAS, genome-wide association study.

http://e-dmj.org  Diabetes Metab J 2011;35:12-22
Mitochondrial DNA variation with T2DM was not observed in a European population [53,54]. For those genes identified by GWAS in Caucasians, we also confirmed the significant association between these gene variants with T2DM in Koreans (Table 2). Interestingly, the frequencies of risk alleles in Koreans were quite different from those of Caucasians, although the odds ratios of each gene variant were similar to those reported in Caucasians. These results suggest that there are important, but different contributions from genetic variants for T2DM between Caucasians and Asians (or Koreans). Fig. 1 summarizes the susceptibility genes of T2DM in the Korean population.

**FUTURE PERSPECTIVES**

It is evident that the success of the GWAS approach has revolutionized our understanding of the genetic risk factors of T2DM and has provided us with better insight into the pathogenesis of T2DM. Most of the genes identified from the initial T2DM GWAS were implicated in a defect in β-cell function, rather than increased insulin resistance. It should be noted that most genetic variations only have a modest effect and their combination only explains less than 10% of the T2DM heritability [23]. The underlying hypothesis based on the current GWAS and large-scale association studies is that common genetic variations are the cause of common complex disorders. Most of the common variations with a higher than 5% frequency reside in introns or inter-genic areas and they have a relatively small effect size.

The current and future strategies to identify T2DM risk loci include performing even larger GWAS in different ethnicities. This will lead to an increase in the number of common variations that are associated with T2DM, although the size of their effects is small. Finding rare variations with larger effect size is a rational strategy to discover additional T2DM genes. Deep sequencing around the GWAS signal might yield multiple rare variations that have functional consequences. With the advent of next generation sequencing technologies, it is now possible...
to perform whole exome sequencing. This will allow us to identify rare functional variation with large impact on a whole exome scale. Family studies will be used more frequently as rare variants will be enriched in the relatives of the index case and the affected status would be segregated by the causative genetic variation.

Although the progress in understanding the genetics of T2DM has already been immense, it seems that this is just the beginning of a new era. Further improvements in our understanding of T2DM genetics will eventually lead us to the development of new therapeutic and preventive methods as well as the basis for individualized medicine.

ACKNOWLEDGMENT

The author declares no conflict of interest.

REFERENCES

1. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005;365:1333-46.
2. Doria A, Patti ME, Kahn CR. The emerging genetic architecture of type 2 diabetes. Cell Metab 2008;8:186-200.
3. Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, Lesage S, Vionnet N, Clement K, Fougérousse F, Tanizawa Y, Weissbach J, Beckmann JS, Lathrop GM, Passa PH, Permutt MA, Cohen D. Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. Nature 1992;356:162-4.
4. Vaxillaire M, Froguel P. Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. Endocr Rev 2008;29:254-64.
5. Greeley SA, Tucker SE, Worrell HI, Skowron KB, Bell GI, Philpison LH. Update in neonatal diabetes. Curr Opin Endocrinol Diabetes Obes 2010;17:13-9.
6. Horikawa Y, Oda N, Cox NJ, Li X, Orho-Melander M, Hara M, Hinokio Y, Lindner TH, Mashima H, Schwarz PE, del Bosque-Plata L, Horikawa Y, Oda Y, Yoshiuchi I, Colilla S, Polonsky KS, Wei S, Concannon P, Iwasaki N, Schulze J, Baier LJ, Bogardus C, Groop L, Boerwinkle E, Hanis CL, Bell GI. Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. Nat Genet 2000;26:163-75.
7. Vionnet N, Hani EH, Dupont S, Gallina S, Francke S, Dotte S, De Matos F, Durand E, Lepretre F, Lecoeur C, Gallina P, Zekiri L, Dina C, Froguel P. Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2 diabetes locus on chromosome 1q21-q24. Am J Hum Genet 2000;67:1470-80.
8. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 2000;26:76-80.
9. Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, Walker M, Levy JC, Sampson M, Halford S, McCarthy MI, Hattersley AT, Frayling TM. Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 2003;52:568-72.
10. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JP, Sumnik Z, van Rhijn A, Wales JK, Clark P, Gorman S, Aisenberg J, Ellard S, Njolstad PR, Aschofot FM, Hattersley AT. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838-49.
11. Florez JC, Burtt N, de Bakker PI, Almgren P, Tuomi T, Holmkvist J, Gaudet D, Hudson TJ, Schaffner SF, Daly MJ, Hirschhorn JN, Groop L, Altshuler D. Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes 2004;53:1360-8.
12. Nielsen EM, Hansen L, Carstensen B, Echwald SM, Drivsholm T, Glumer C, Thorsteinsson B, Borch-Johnsen K, Hansen T, Pedersen O. The E23K variant of Kir6.2 associates with impaired post-OGTT serum insulin response and increased risk of type 2 diabetes. Diabetes 2003;52:573-7.
13. Grant SF, Thorleifsson G, Reynisdottir I, Benedikttson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir G, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes.
Diabetes Metab J 2011;35:12-22

14. Reynisdottir I, Thorleifsson G, Benediktsson R, Sigurdsson G, Emilsson V, Einarsdottir AS, Hjorleifsindottir EE, Orljysdottir GT, Bjornsdottir GT, Saemundsdottir J, Hallorsson S, Hrafnekisdottir S, Sigurjonsdottir SB, Steinsdottir S, Martin M, Kochan JP, Rhees BK, Grant SF, Frigge ML, Kong A, Gudnason V, Stefansson K, Gulcher JR. Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2. Am J Hum Genet 2003;73:323-35.

15. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altschuler D; Diabetes Prevention Program Research Group. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 2006;355:241-50.

16. Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjostrand M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Kotsopoulos L, Speliotes EK, Taskinen MR, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Niklasson L, Yu MC, Hastbacka B, Berglund G, Tuomi T, Nilsson P, Del Prato S, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S; Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336-41.

17. Chang YC, Chang TJ, Jiang YD, Kuo SS, Lee KC, Chiu KC, Chuang LM. Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. Diabetes 2007;56:2631-7.

18. Cauchi S, El Achhab Y, Choquet H, Dina C, Krempler F, Weitkamp E, Roix JJ, Kathiresan S, Hirschhorn JN, Ardlie KG, Groop LC, Altschuler D. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and redue the insulin response to glucose in nondiabetic individuals. Diabetes 2006;55:2890-5.

19. Ng MC, Park KS, Oh B, Tam CH, Cho YM, Shin HD, Lam VK, Ma RC, So WY, Cho YS, Kim HL, Lee HK, Chan JC, Cho NH. Implication of genetic variants near TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. Diabetes 2008;57:777-82.

20. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S, Groop L. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest 2007;117:2155-63.

21. Shu L, Sauter NS, Schulthess FT, Matveienko AV, Oberholzer J, Maedler K. Transcription factor 7-like 2 regulates beta-cell survival and function in human pancreatic islets. Diabetes 2008;57:645-53.

22. Schafer SA, Tschetter O, Machicao F, Thamer C, Stefan N, Gallwitz B, Holst JJ, Dekker JM, ’t Hart LM, Nijpels G, van Haeften TW, Haring HU, Fritsche A. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia 2007;50:2443-50.

23. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay T, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. Nature 2009;461:747-53.

24. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadijaj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Pretkni M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881-5.

25. Scott JT, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doherty KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341-5.

26. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS; Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336-41.

27. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altschuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Bostrom K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR,
Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarat A, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331-6.

28. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsdottir S, Emilsson V, Ghosh S, Baker A, Snorradottir S, Bjarnason H, Ng MC, Hansen T, Bagger Y, Wilensky RL, Reilly MP, Adeyemo A, Chen Y, Zhou J, Gundnason V, Chen G, Huang H, Lashley K, Doumatay A, So WY, Ma RC, Andersen G, Borch-Johnsen K, Jorgensen T, van Vliet-Ostaptchouk JV, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Rotimi C, Gurney M, Chan JC, Pedersen O, Sigurdsson G, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nat Genet 2007;39:770-5.

29. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661-78.

30. Kwak SH, Cho YM, Moon MK, Kim JH, Park BL, Cheong HS, Shin HD, Jang HC, Kim SY, Lee HK, Park KS. Association of polymorphisms in the insulin-degrading enzyme gene with insulin resistance and type 2 diabetes in the Korean population. Diabetes Res Clin Pract 2008;79:284-90.

31. Krishnamurthy J, Ramsey MR, Ligon KL, Torrice C, Koh A, Bonner-Weir S, Sharpless NE. p16INK4a induces an age-dependent decline in islet regenerative potential. Nature 2006;443:453-7.

32. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levy AI, Backman VM, Matthaisdottir S, Jonasdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007;316:1491-3.

33. McPherson R, Pertsemidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488-91.

34. Wei FY, Nagashima K, Oshime T, Saheki Y, Lu YF, Matsushita M, Yamada Y, Mikoshiba K, Seino Y, Matsu H, Tomizawa K. Cdk5-dependent regulation of glucose-stimulated insulin secretion. Nat Med 2005;11:1104-8.

35. Ohara-Imaizumi M, Yoshida M, Aoyagi K, Saito T, Okamura T, Takenaka H, Akimoto Y, Nakamichi Y, Takenashi-Yanobu R, Nishiwaki C, Kawakami H, Kato N, Hisanaga S, Kakei M, Nagamatsu S. Deletion of CDKAL1 affects mitochondrial ATP generation and first-phase insulin exocytosis. PLoS One 2010;5:e15553.

36. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Bostrum KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jorgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvella AF, Meisinger C, Midtbjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjogren M, Steinhorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ; Wellcome Trust Case Control Consortium, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638-45.

37. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Glyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinhorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga J, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumar M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P.
O’Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccasecca RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borgh-Johnsen K, Botcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crispiloni L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllensten U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Herberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinlin M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Leccoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolissi G, Pattaro C, Pearson D, Pedersen JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurdeathssson G, Sjöblom EJ, Silveira A, Simpson L, Singleton A, Smith NL, So WY, Solomon P, Sparks JA, Sydall H, Syvanen AC, Tanaka T, Thorand B, Tchet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varady AD, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nonjo K, Kadowaki T, Kasuga M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 2008;40:1092-7.

38. Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, Ng DP, Holmquist J, Borgh-Johnsen K, Jorgensen T, Sandbaek A, Lauritzen T, Hansen T, Nurbaya S, Tsunoda T, Kubo M, Babazono T, Hirose H, Hayashi M, Iwamoto Y, Kashiwagi A, Kaku K, Kawamori R, Tai ES, Pedersen O, Kamatani N, Kadowaki T, Kikkawa R, Nakamura Y, Maeda S. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet 2008;40:1098-102.

39. Yamauchi T, Hara K, Maeda S, Yasuda K, Takahashi A, Horikoshi M, Nakamura M, Fujita M, Grarup N, Cauchi S, Ng DP, Ma RC, Tsunoda T, Kubo M, Watada H, Maegawa H, Okada-Iwabu M, Iwabu M, Shojima N, Shin HD, Andersen G, Witte DR, Jorgensen T, Lauritzen T, Sandbaek A, Hansen T, Ohshima T, Omori S, Saito I, Kaku K, Hirose H, So WY, Beury D, Chan JC, Park KS, Tai ES, Ito C, Tanaka Y, Kashiwagi A, Kawamori R, Kasuga M, Fрогuel P, Pedersen O, Kamatani N, Nakamura Y, Kadowaki T. A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes mellitus. Nat Genet 2011;43:1242-22.
Genetics of type 2 diabetes

46. Moon MK, Cho YM, Jung HS, Park YJ, Yoon KH, Sung YA, Park BL, Lee HK, Park KS, Shin HD. Genetic polymorphisms in peroxisome proliferator-activated receptor gamma are associated with type 2 diabetes mellitus and obesity in the Korean population. Diabet Med 2005;22:1161-6.

47. Cho YM, Shin HD, Park BL, Kim JH, Park KS, Kim SY, Lee HK. Association between polymorphisms in the nuclear respiratory factor 1 gene and type 2 diabetes mellitus in the Korean population. Diabetologia 2005;48:2033-8.

48. Choi HJ, Cho YM, Moon MK, Choi HH, Shin HD, Jang HC, Kim SY, Lee HK, Park KS. Polymorphisms in the ghrelin gene are associated with serum high-density lipoprotein cholesterol level and not with type 2 diabetes mellitus in Koreans. J Clin Endocrinol Metab 2006;91:4657-63.

49. Shin HD, Park BL, Kim LH, Jung HS, Cho YM, Moon MK, Park YJ, Lee HK, Park KS. Genetic polymorphisms in peroxisome proliferator-activated receptor delta associated with obesity. Diabetes 2004;53:847-51.

50. Kim JH, Park KS, Cho YM, Kang BS, Kim SK, Jeon HJ, Kim SY, Lee HK. The prevalence of the mitochondrial DNA 16189 variant in non-diabetic Korean adults and its association with higher fasting glucose and body mass index. Diabet Med 2002;19:681-4.

51. Park KS, Chan JC, Chuang LM, Suzuki S, Araki E, Nanjo K, Ji L, Ng M, Nishi M, Furuta H, Shiratori T, Ahn BY, Chung SS, Min HK, Lee SW, Kim JH, Cho YM, Lee HK; Study Group of Molecular Diabetology in Asia. A mitochondrial DNA variant at position 16189 is associated with type 2 diabetes mellitus in Asians. Diabetologia 2008;51:602-8.

52. Fuku N, Park KS, Yamada Y, Nishigaki Y, Cho YM, Matsuho S, Segawa T, Watanabe S, Kato K, Yokoi K, Nozawa Y, Lee HK, Tanaka M. Mitochondrial haplogroup N9a confers resistance against type 2 diabetes in Asians. Am J Hum Genet 2007;80:407-15.

53. Chinnery PF, Elliott HR, Patel S, Lambert C,Keers SM, Durham SE, McCarthy MI, Hitman GA, Hattersley AT, Walker M. Role of the mitochondrial DNA 16184-16193 poly-C tract in type 2 diabetes. Lancet 2005;366:1650-1.

54. Saxena R, de Bakker PI, Singier K, Mootha V, Burtt N, Hirschhorn JN, Gaudet D, Isomaa B, Daly MJ, Groop L, Ardiie KG, Altshuler D. Comprehensive association testing of common mitochondrial DNA variation in metabolic disease. Am J Hum Genet 2006;79:54-61.

55. Park KS, Chan JC, Chuang LM, Suzuki S, Araki E, Nanjo K, Ji L, Ng M, Nishi M, Furuta H, Shiratori T, Ahn BY, Chung SS, Min HK, Lee SW, Kim JH, Cho YM, Lee HK; Study Group of Molecular Diabetology in Asia. A mitochondrial DNA variant at position 16189 is associated with type 2 diabetes mellitus in Asians. Diabetologia 2008;51:602-8.
early-onset type 2 diabetes mellitus in the Korean population. Diabetologia 2005;48:1323-30.

56. Park KS, Shin HD, Park BL, Cheong HS, Cho YM, Lee HK, Lee JY, Lee JK, Kim HT, Park CS, Han BG, Kimm K, Oh B. Putative association of peroxisome proliferator-activated receptor gamma co-activator 1beta (PPARGC1B) polymorphism with type 2 diabetes mellitus. Diabet Med 2006;23:635-42.

57. Lee HJ, Ryu HJ, Shin HD, Park BL, Kim JY, Cho YM, Park KS, Song J, Oh B. Associations between polymorphisms in the mitochondrial uncoupling proteins (UCPs) with T2DM. Clin Chim Acta 2008;398:27-33.

58. Shin HD, Park KS, Park BL, Cheong HS, Cho YM, Lee HK, Lee JY, Lee JK, Kim HT, Han BG, Kim JW, Koh I, Kim YJ, Oh B, Kimm K, Park C. Common promoter polymorphism in monocyte differentiation antigen CD14 is associated with serum triglyceride levels and body mass index in non-diabetic individuals. Diabet Med 2006;23:72-6.

59. Ku YH, Koo BK, Kwak SH, Cho YM, Shin HD, Lee HK, Kim Y, Choi JW, Oh B, Park KS. Regulatory effect of common promoter polymorphisms on the expression of the 11beta-hydroxysteroid dehydrogenase type 1 gene. Horm Res 2009;72:25-32.

60. Park KS, Shin HD, Park BL, Cheong HS, Cho YM, Lee HK, Lee JY, Lee JK, Oh B, Kimm K. Polymorphisms in the lepin receptor (LEPR): putative association with obesity and T2DM. J Hum Genet 2006;51:85-91.

61. Kim JT, Kim Y, Cho YM, Koo BK, Lee EK, Shin HD, Jang HC, Choi JW, Oh B, Park KS. Polymorphisms of ADIPOR1 and ADIPOR2 are associated with phenotypes of type 2 diabetes in Koreans. Clin Endocrinol (Oxf) 2009;70:66-74.

62. Shin HD, Park BL, Kim LH, Cheong HS, Kim JH, Cho YM, Lee HK, Park KS. Association of a polymorphism in the gene encoding phosphoenolpyruvate carboxykinase 1 with high-density lipoprotein and triglyceride levels. Diabetologia 2005;48:2025-32.

63. Korean Endocrine Society. Textbook of endocrinology and metabolism. 2nd ed. Seoul: Koonja Publishing; 2011. Section 9, Genetics of diabetes mellitus; p641-4.