*Endocrine Journal* 2011, **58** (9), 723-739

**REVIEW**

# Genetics of type 2 diabetes: the GWAS era and future perspectives

Minako Imamura and Shiro Maeda

*Laboratory for Endocrinology and Metabolism, RIKEN Center for Genomic Medicine, Yokohama 230-0045, Japan*

**Abstract.** Genome-wide association studies (GWAS) have facilitated a substantial and rapid rise in the number of confirmed genetic susceptibility variants for type 2 diabetes (T2D). Approximately 40 variants have been identified so far, many of which were discovered through GWAS. This success has led to widespread hope that the findings will translate into improved clinical care for the increasing numbers of patients with diabetes. Potential areas or clinical translation include risk prediction and subsequent disease prevention, pharmacogenetics, and the development of novel therapeutics. However, the genetic loci so far identified account for only a small fraction (approximately 10%) of the overall heritable risk for T2D. Uncovering the missing heritability is essential to the progress of T2D genetic studies and to the translation of genetic information into clinical practice.

*Key words*: Type 2 diabetes, Genetics, Genome-wide association studies, Clinical translation

**NEARLY** 300 million people worldwide are affected by diabetes mellitus, and its increasing prevalence is a serious concern in many countries. Type 2 diabetes (T2D) is characterized by insulin resistance in peripheral tissues and dysregulated insulin secretion by pancreatic beta-cells. Although the current rise in T2D prevalence is driven mainly by changes in life-style, complex genetic determinants are widely considered to contribute to an inherent susceptibility to this disease. The pathogenesis of T2D is heterogeneous, suggesting that the contribution from individual genetic factors is modest. Linkage analysis and the candidate gene approach were the primary methods to link genotype and phenotype before the development of genome-wide association studies (GWAS). Although these techniques can detect rare genetic variants that strongly influence disease susceptibility, they are not suitable to identify variants that have a smaller effect on disease susceptibility. Therefore, the discovery of novel T2D susceptible loci has been challenging, and a more powerful strategy was needed to overcome this difficulty. The development of high-throughput genotyping technologies and statistical and computational software has allowed remarkable progress over the past decade in the "genome-wide" search for genetic associations. Since the first GWAS for T2D identified novel susceptibility loci in 2007, approximately 40 T2D susceptibility loci have been identified so far, most of them through GWAS.

This review summarizes recent advances in the field of T2D genetics and discusses current obstacles to applying knowledge to clinical applications, as well as future investigations for further understanding of the genetic basis of T2D.

## Genetics of T2D: before the GWAS era

Prior to the GWAS era, the importance of genetic factors in the etiology of T2D had been well established through family and twin studies [1, 2]. The primary methods to identify susceptibility loci for diseases or phenotypic traits were linkage analysis and candidate-gene association studies. Linkage analysis is useful for identifying familial genetic variants that have large effects and was successfully used to discover several causal mutations for the monogenic forms of diabetes mellitus, such as maturity-onset diabetes of the young (MODY) [3]. For the common form of T2D, the dis-

Submitted Jul. 5, 2011; Accepted Jul. 7, 2011 as EJ11-0113
Released online in J-STAGE as advance publication Jul. 20, 2011

Correspondence to: Shiro Maeda, Laboratory for Endocrinology and Metabolism, RIKEN Center for Genomic Medicine, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan. E-mail: smaeda@src.riken.jp

covery of calpain 10 (*CAPN10*) in a Mexican-American population was the first reported success of linkage-positional cloning strategy for the disease [4], although the association could not be robustly replicated in other ethnic groups. Reynisdottir *et al*. identified segments in chromosomes 5 and 10 with suggestive linkage to T2D [5], and showed that the chromosome 10 region harbored the *TCF7L2* [6]. Five single nucleotide polymorphisms (SNPs) and 1 tetranucleotide repeat polymorphism (DG10S478) within *TCF7L2* showed strong association with T2D in 3 independent cohorts, and the SNPs (rs12255372 and rs7903146) showed strong linkage disequilibrium (LD) with composite at-risk alleles of the microsatellite marker (DG10S478). The association between the SNPs (rs12255372 and rs7903146) and decreased insulin secretion was also reported in American subjects with impaired glucose tolerance [7]. Subsequently, the association of *TCF7L2* with T2D was replicated not only in populations of European origin but also in other ethnic groups [8-13], including the Japanese [14, 15].

Candidate-gene association studies showed that the genes for the peroxisome proliferator activated receptor gamma (*PPARG*) [16] and the potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) [17] were 2 candidate susceptibility genes. Both genes encode targets of anti-diabetes medications (thiazolidinediones and sulphonylureas, respectively) and harbor missense variants associated with T2D: P12A in *PPARG* and E23K in *KCNJ11*. The successful identification of these genes encouraged the genetic study of T2D; however, the limitations of these classical approaches were also recognized. Thus, it has been challenging to identify the specific genetic variants associated with an increased risk for T2D, and until recently, these genes were largely unknown.

## The GWAS era of T2D genetics

A significant breakthrough in understanding the genetic basis of complex traits including T2D, was facilitated by the arrival of GWAS. GWAS is a powerful biology-agnostic method to detect genetic variations that predispose to a disease. In GWAS, the entire genomes of individuals with and without the disorder of interest (i.e., cases and controls) are screened for a large number of common SNPs. These studies have been facilitated by several recent developments including completion of the Human Genome Project and the International HapMap project. Several million SNPs were discovered and confirmed by the International HapMap project and have been deposited in a public database [18]. The HapMap project initially genotyped 3.9 million SNPs in 270 DNA samples from 4 different ethnic groups and defined the underlying patterns of the inheritance of genetic variation, as quantified by LD. Two SNPs with strong LD are thought to be co-inherited more frequently than SNPs with weak LD. Using this correlation structure, association analyses can be made in a more efficient and cost-effective manner by using a smaller subset of SNPs or "tag" SNPs to capture most of the remaining common genetic variations. Thus far, 1000 Genomes Project has been performed and has increased SNP information across the entire human genome, and more than 2 million directly genotyped and imputed SNPs (estimations based on the degree of LD in typed- alleles) can be examined in current GWAS.

The finding that a particular SNP is present at higher frequency in the disease cases *versus* the controls suggests that the SNP is associated with the disease, and a statistical *P* value of $5 \times 10^{-8}$ is required to satisfy genome-wide significance [19]. Because each GWAS typically involves hundreds of thousands of simultaneous tests of association, this stringent threshold reflects the standard *P* value of 0.05 with a Bonferroni correction for 1 million statistical tests and effectively reduces the number of false-positive SNPs identified. Even with such strict statistical thresholds, positive findings are routinely replicated in independent datasets to verify or refute the association of a SNP with the phenotype of interest. The data from several case-control collections can be merged and summarized by meta-analysis, and this has enabled identification of SNPs with smaller effect size by increasing the overall sample size. At present, 3 conditions must be satisfied to be considered susceptible loci through GWAS: (1) sufficient sample size in the genome-wide scan (at least 1000 each of cases and controls), (2) association *P*-value at the genome-wide significance level ($P < 5 \times 10^{-8}$), and (3) confirmation of the association by independent replication studies [19]. To date, GWAS have identified nearly 40 susceptibility loci for T2D in European and Asian populations (Table 1).

The first GWAS for T2D was conducted in a French cohort composed of 661 cases and 614 controls, covering 392,935 SNP loci. This study identified novel association signals at *SLC30A8, HHEX, LOC387761,*

**Table 1** Genetic loci associated with T2D

| Year | Locus | Marker | Chr | Type of SNP | Association in the Japanese | Risk allele frequencey | | Effect size odds ratio (95%CI) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | HapMap CEU | HapMap JPT | |
| 2000 | *PPARG* | rs1801282 [16] | 3 | Missense: Pro12Ala | Suggestive [65-67] | 0.9 | 0.97 | 1.14 (1.08-1.20) [22-24] |
| 2003 | *KCNJ11* | rs5219 [17] | 11 | Missense: Glu23Lys | Confirmed [67, 68] | 0.47[a] [17] | 0.34[a] [67] | 1.15 (1.09-1.21) [22] |
| 2006 | *TCF7L2* | rs7903146 [6] | 10 | Intronic | Confirmed [14, 15, 42] | 0.28 | 0.04 | 1.37 (1.28-1.47) [26] |
| 2007 | *IGF2BP2* | rs4402960 [22-24] | 3 | Intronic | Confirmed [36, 42, 67, 70] | 0.3 | 0.3 | 1.17 (1.10-1.25) [26] |
| | *WFS1* | rs10010131 [69] | 4 | Intronic | | 0.67 | 0.97 | 1.11 (1.07-1.16) |
| | | rs734312 [69] | 4 | Missense:Arg611His | | 0.65 | 0.84 | 1.08 (1.05-1.14) |
| | *CDKAL1* | rs7754840 [22-24] | 6 | Intronic | Confirmed [36, 42, 67, 70] | 0.34 | 0.39 | 1.12 (1.08-1.16) |
| | *SLC30A8* | rs13266634 [20] | 8 | Missense:Arg325Trp | Confirmed [67, 70] | 0.76 | 0.55 | 1.12 (1.07-1.16) ]27] |
| | *CDKN2A/B* | rs10811661 [22-24] | 9 | 125kb upstream | Confirmed [42, 67, 70] | 0.8 | 0.52 | 1.20 (1.14-1.25) |
| | *HHEX* | rs1111875 [20] | 10 | 7.7kb downstream | Confirmed [67, 70-72] | 0.58 | 0.33 | 1.13 (1.08-1.17) [22] |
| | *FTO* | rs8050136 [23,24] | 16 | Intronic | Suggestive [67] | 0.46 | 0.19 | 1.15 (1.09-1.22) [26] |
| | *HNF1B* | rs757210 [73] | 17 | Intronic | Confirmed [75] | 0.45 | 0.24 | 1.12 (1.07-1.18) [27] |
| | | rs7501939 [74] | 17 | Intronic | | 0.43 | 0.32 | 1.10 (1.06-1.15) |
| 2008 | *NOTCH2* | rs10923931 [26] | 1 | Intronic | | 0.09 | 0.03 | 1.13 (1.08-1.17) |
| | *THADA* | rs7578597 [26] | 2 | Missense:Thr1187Ala | | 0.87 | 0.99 | 1.15 (1.10-1.20) |
| | *ADAMSTS9* | rs4607103 [26] | 3 | 38kb upstream | | 0.81 | 0.65 | 1.09 (1.06-1.12) |
| | *JAZF1* | rs864745 [26] | 7 | Intronic | Suggestive [76] | 0.52 | 0.21 | 1.10 (1.07-1.13) |
| | *CDC123/CAMK1D* | rs12779790 [26] | 10 | Intergenic region | | 0.23 | 0.12 | 1.11 (1.07-1.14) |
| | *KCNQ1* | rs2237897 [36] | 11 | Intronic (intron15) | Confirmed [36] | 0.93 | 0.61[a] [36] | 1.41 (1.29-1.55) |
| | | rs2237892 [37] | 11 | Intronic (intron15) | Confirmed [36, 37, 42, 75] | 0.93 | 0.59 | 1.43 (1.34-1.52) |
| | *TSPAN8/LGR5* | rs7961581 [26] | 12 | Intergenic region | | 0.25 | 0.23 | 1.09 (1.06-1.12) |
| 2009 | *IRS1* | rs2943641 [77] | 2 | 502kb downstream | | 0.61 | 0.93 | 1.19 (1.13-1.25) |
| | *MTNR1B* | rs10830963 [78] | 11 | Intronic | | 0.3 | 0.45 | 1.09 (1.06-1.12) |
| | | rs1387153 [30] | 11 | Intronic | | 0.27 | 0.45 | 1.09 (1.06-1.11) |
| 2010 | *PROX1* | rs340874 [33] | 1 | 2kb upstream | | 0.56 | 0.35 | 1.07 (1.05-1.09) |
| | *BCL11A* | rs243021 [27] | 2 | 99kb downstream | | 0.48 | 0.7 | 1.08 (1.06-1.1) |
| | *GCKR* | rs780094 [33] | 2 | Intronic | Confirmed [75, 79] | 0.61 | 0.43 | 1.06 (1.04-1.08) |
| | *ADCY5* | rs11708067 [33] | 3 | Intronic | | 0.77 | 1 | 1.12 (1.09-1.15) |
| | *UBE2E2* | rs7612463 [42] | 3 | Intronic | Confirmed [42] | 0.86 | 0.84 | 1.19 (1.12-1.26) |
| | *ZBED3* | rs4457053 [27] | 5 | 41kb upstream | | 0.26 | 0.023 | 1.08 (1.06-1.11) |
| | *DGKB/TMEM195* | rs2191349 [33] | 7 | Intergenic region | Confirmed [42] | 0.48 | 0.73 | 1.06 (1.04-1.08) |
| | *GCK* | rs4607517 [33] | 7 | 36kb upstream | | 0.2 | 0.2 | 1.07 (1.05-1.10) |
| | *KLF14* | rs972283 [27] | 7 | 47kb upstream | | 0.55 | 0.71 | 1.07 (1.05-1.10) |
| | *TP53INP1* | rs896854 [27] | 8 | Intronic | | 0.44 | 0.32 | 1.06 (1.04-1.09) |
| | *CHCHD9* | rs13292136 [27] | 9 | 234kb upstream | | 0.93 | 0.87 | 1.11 (1.07-1.15) |
| | *CENTD2* | rs1552224 [27] | 11 | 5'UTR | | 0.88 | 0.96 | 1.14 (1.11-1.17) |
| | *KCNQ1*[b] | rs231362 [27] | 11 | Intronic (intron11) | | 0.52 | 0.86 | 1.08 (1.06-1.10) |
| | *HMGA2* | rs1531343 [27] | 12 | 43kb upstream | | 0.12 | 0.12 | 1.10 (1.07-1.14) |
| | *HNF1A* | rs7957197 [27] | 12 | 20kb downstream | | 0.85 | 1 | 1.07 (1.05-1.10) |
| | *PRC1* | rs8042680 [27] | 15 | Intronic | | 0.26 | 1 | 1.07 (1.05-1.10) |
| | *ZFAND6* | rs11634397 [27] | 15 | 1.5kb downstream | | 0.64 | 0.09 | 1.06 (1.04-1.08) |
| | *C2CD4A/B* | rs7172432 [42] | 15 | Intergenic region | Confirmed [42] | 0.58 | 0.58 | 1.13 (1.09-1.18) |
| | *DUSP9* | rs5945326 [27] | X | 8kb upstream | | 0.22 | 0.32 | 1.27 (1.18-1.37) |

[a] Data from references [b] This locus is thoght to be independent of the locus idenfiied by Japanese GWAS in 2008
References are in brackets

and *EXT2* and validated the previously identified association at *TCF7L2* [20]. Shortly after the initial GWAS, the Icelandic company deCODE Genetics and their collaborators confirmed the association between T2D and *SLC30A8*, *HHEX*, and the newly identified *CDKAL1* [21]. At the same time, 3 collaborating groups, the Wellcome Trust Case Control Consortium/United Kingdom Type 2 Diabetes Genetics consortium (WTCCC/UKT2D), the Finland-United States Investigation of NIDDM (FUSION), and the Diabetes Genetics Initiative (DGI), published their findings replicating the association of *SCL30A8* and *HHEX* with T2D and independently discovering novel associations at *CDKAL1*, *IGF2BP2*, and *CDKN2A*/*B* [22-24]. With the exception of *LOC387761* and *EXT2*, these novel loci and 2 previously-known variants, *PPARG* P12A and *KCNJ11* E23K, were confirmed by multiple replication studies composed of European and non-European populations. Thus, the first round of European GWAS confirmed 8 T2D susceptibility loci across multiple ethnic groups: *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *IGF2BP2*, *CDKN2A*/*B*, *PPARG*, and *KCNJ11*. In addition to these 8 loci, the WTCCC/UKT2D study identified a strong association between *FTO* variants and T2D, although the effect of *FTO* variants on conferring susceptibility to T2D was mostly mediated through increase in body weight [25].

After the first round of European GWAS, an effort was made to increase sample size so that common variants with lower effect sizes would be detectable. WTCCC/UKT2D, FUSION, and DGI combined their data to form the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium. Five additional novel loci, *JAZF1*, *CDC123*/*CAMK1D*, *TSPAN*/*LGR5*, *THADA*, and *ADAMSTS9*, were identified in a genome-wide scan comprising a substantial sample size (4,549 cases and 5,579 controls) followed by replication testing and more than 2.2 million SNPs (either directly genotyped or imputed) [26].

Most of the T2D genetics cohorts have now combined to form DIAGRAM+, which yields an effective sample size of more than 22,000 subjects of European origin. In a recent study, 2,426,886 imputed and genotyped autosomal SNPs, with additional interrogation of the X-chromosome, were examined for association with T2D as a categorical phenotype. Twelve new loci were identified as susceptibility loci for T2D with a genome-wide significance association ($P < 5 \times 10^{-8}$) [27].

## GWAS for continuous glycemic traits

Studies examining diabetes-related quantitative traits in participants without diabetes have also identified loci that influence beta-cell function and insulin resistance (Table 2). GWAS showed that *G6PC2* and *MTNR1B* were associated with fasting-glucose levels [28-30], and further studies confirmed the association of these 2 loci [29-31] and *GCK* which had been identified by the candidate-gene approach [32]. Recently, the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) examined 21 GWAS to identify loci associating with fasting glucose, fasting insulin, HOMA-β, and HOMA-IR [33]. Collectively, the GWAS included 46,186 participants of European descent and analyzed more than 2.5 million genotyped or imputed SNPs. After replication among 76,558 individuals from 34 additional cohorts, 9 new loci in or near *ADCY5*, *MADD*, *CRY2*, *ADRA2A*, *FADS1*, *PROX1*, *SLC2A2*, *GLIS3*, and *C2CD4B* were found to be associated with fasting glucose. In addition, *GCKR* and a SNP upstream of *IGF1* were found to be associated with fasting insulin and HOMA-IR. The meta-analysis also confirmed prior associations for glycemic traits with SNPs in or near *DGKB-TMEM195*, *GCKR*, *G6PC2*, *MTNR1B*, and *GCK*. An aggregate genotype score was constructed by summing the 16 risk variants and showed a clinically relevant difference in fasting glucose concentrations of about 7.2 mg/dL between groups with the highest and lowest scores. Five loci for 2-hour glucose levels, *GIPR*, *ADCY5*, *GCKR*, *VPS13C*, and *TCF7L2* were further identified in a meta-analysis of 9 GWAS for 2-hour glucose and subsequent replication studies [34].

Among the loci identified as being associated with glycemic traits, *MTNR1B*, *GCK*, *ADCY5*, *PROX1*, *DGKB-TMEM195*, and *GCKR* were also identified as novel loci associated with T2D.

## GWAS in groups of non-European descent

Over the past 2 decades, many Asian countries have experienced a dramatic increase in the incidence of T2D. Cumulative evidence suggests that Asians may be more susceptible than populations of European ancestry to insulin resistance and diabetes, which was thought to be due to interethnic genetic inheritance [35]. Several of the T2D loci identified by European GWAS, especially the first round of GWAS, have been con-

**Table 2** Genetic loci associated with glycemic traits

| Locus | Marker | Chr | Type of SNP | Trait | Risk allele frequencey | | Effect size Beta (S.E.) | References |
|---|---|---|---|---|---|---|---|---|
| | | | | | HapMap CEU | HapMap JPT | | |
| *PROX1* | rs340874 | 1 | 2kb upstream | FPG | 0.56 | 0.35 | 0.013 (0.003) | [33] |
| *G6PC2* | rs560887 | 2 | Intronic | FPG | 0.64 | 0.96 | 0.075 (0.003) | [28, 33] |
| | | | | HOMA-B | | | -0.042 (0.004) | |
| | | | | HbA1c | | | 0.032 (0.004) | |
| *GCKR* | rs1260326 | 2 | Missence:Leu446Pro | 2h-PG | 0.42 | 0.56 | 0.10 (0.01) | [22] |
| | rs780094 | 2 | Intronic | FPG | 0.61 | 0.43 | 0.029 (0.003) | [33] |
| | | | | FIRI | | | 0.032 (0.004) | |
| | | | | HOMA-IR | | | 0.035 (0.004) | |
| *ADCY5* | rs2877716 | 3 | Intronic | 2h-PG | 0.75 | 1 | 0.07 (0.01) | [34] |
| | rs11708067 | 3 | Intronic | FPG | 0.77 | 1 | 0.027 (0.003) | [33] |
| | | | | HOMA-B | | | -0.023 (0.004) | |
| *SLC2A2* | rs11920090 | 3 | Intronic | FPG | 0.86 | 0.99 | 0.02 (0.004) | [33] |
| *DGKB/ TMEM195* | rs2191349 | 7 | intergenic resion | FPG | 0.48 | 0.73 | 0.03 (0.003) | [33] |
| *GCK* | rs4607517 | 7 | 36kb upstream | FPG | 0.19 | 0.2 | 0.062 (0.004) | [33] |
| | | | | HbA1c | | | 0.041 (0.005) | |
| *SLC30A8* | rs13266634 | 8 | Missense:Arg325Trp | FPG | 0.76 | 0.55 | 0.027 (0.004) | [33] |
| *GLIS3* | rs7034200 | 9 | Intronic | FPG | 0.54 | 0.47 | 0.018 (0.003) | [33] |
| | | | | HOMA-B | | | -0.02 (0.004) | |
| *ARDA2A* | rs10885122 | 9 | 210kb downstream | FPG | 0.9 | 0.93 | 0.022 (0.004) | [33] |
| *TCF7L2* | rs7903146 | 10 | Intronic | FPG | 0.28 | 0.04 | 0.023 (0.004) | [33] |
| | rs12243326 | 10 | Intronic | 2h-PG | 0.24 | 0.03 | 0.07 (0.01) | [34] |
| *HK1* | rs7072268 | 10 | Intronic | HbA1c | 0.5 | 0.65 | 0.12 (N/A) | [80] |
| *CRY2* | rs11605924 | 11 | Intronic | FPG | 0.13 | 0.32 | 0.015 (0.003) | [33] |
| *FADS1* | rs174550 | 11 | Intronic | FPG | 0.66 | 0.69 | 0.017 (0.003) | [33] |
| | | | | HOMA-B | | | -0.020 (0.003) | |
| *MADD* | rs7944584 | 11 | Intronic | FPG | 0.71 | 0.98 | 0.021 (0.003) | [33] |
| *MTNR1B* | rs10830963 | 11 | Intronic | FPG | 0.3 | 0.45 | 0.067 (0.003) | [29, 30, 33] |
| | | | | HOMA-B | | | -0.034 (0.004) | |
| | | | | HbA1c | | | 0.024 (0.004) | |
| *IGF1* | rs35767 | 12 | 1.2kb upstream | FIRI | 0.89 | 0.7 | 0.01 (0.006) | [33] |
| | | | | HOMA-IR | | | 0.013 (0.006) | |
| *C2CD4B* | rs11071657 | 15 | 21kb downstream | FPG | 0.59 | 0.66 | 0.008 (0.003) | [33] |
| *VPS13C* | rs17271305 | 15 | Intronic | 2h-PG | 0.59 | 0.85 | 0.07 (0.01) | [34] |
| *GIPR* | rs10423928 | 19 | Intronic | 2h-PG | 0.18 | 0.21 | 0.11 (0.01) | [34] |

N/A; not available

firmed in Asian populations (Table 1). However, there are significant interethnic differences in the risk allele frequency at several loci. For example, risk allele frequencies of *TCF7L2* SNPs showing the strongest effect on T2D in European populations are very few in the Japanese (~5%) compared to populations of European descent (~40%). As a result, *TCF7L2* variants have a little effect on susceptibility to T2D in the Japanese (Table 3). In addition, the associations between T2D and some loci are not consistent in Japanese populations. Therefore, to explain T2D heritability in populations of Asian descent, it may be necessary to identify ethnic group-specific T2D susceptibility loci, those were not captured in the European study. In 2008, 2 independent Japanese GWAS identified the *KCNQ1* locus as a T2D susceptibility locus [36, 37]; these studies were the first GWAS for T2D using non-European populations. Subsequent replication studies performed in different ethnic groups revealed that variants within the *KCNQ1* had the strongest effects on conferring susceptibility to T2D in several East Asian populations [38-41]. The association of the *KCNQ1* locus with T2D could be replicated in European populations, but the minor allele frequencies were considerably lower

**Table 3** Interethnic differences in the allele frequencies of SNPs in *TCF7L2* and *KCNQ1*

| Locus | Marker | Allele (risk/other) | Risk allele frequency (control) | | Odds ratio (95%CI) | | Explained variance (%)[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | Japanese | European | Japanese | European | Japanese | European |
| *TCF7L2* | rs7903146 | T/C | 0.040 [42] | 0.26 [22] | 1.41 (1.26-1.58) [42] | 1.33 (1.17-1.50) [22] | 0.91 | 3.1 |
| | rs12255372 | T/G | 0.022 [14] | 0.29 [6] | 1.70 (1.20-2.41) [14] | 1.52 (1.38-1.68) [6] | 1.2 | 7.2 |
| *KCNQ1* | rs2237897 | C/T | 0.61 [36] | 0.96 [36] | 1.41 (1.29-1.55) [36] | 1.36 (1.16-1.60) [36] | 5.6 | 0.73 |
| | rs2237892 | C/T | 0.59 [37] | 0.93 [37] | 1.43 (1.34-1.52) [37] | 1.29 (1.11-1.50) [37] | 6.2 | 0.84 |

[a] heritability explained by indicated variants caliculated based on risk allele frequencies in control groups and odds ratios reported in the references. References are in brackets

than in East Asian populations (~7% *versus* ~40%, Table 3). Thus, in contrast to *TCF7L2*, the impact of the *KCNQ1* locus on T2D susceptibility was relatively small in European populations. Since the *KCNQ1* locus was not captured in the European studies, this finding emphasizes the importance of examining susceptibility loci in different ethnic groups.

Although the 2 previously mentioned Japanese GWAS successfully identified the *KCNQ1* locus, these studies had limited sample sizes at the initial stage of the genome-wide scan. The study of Unoki *et al.* [36] included 194 T2D cases *vs*. 1,558 controls, and the study by Yasuda *et al*. [37] had 187 T2D cases *vs*. 752 controls; thus, an adequately powered GWAS for T2D has not yet been performed in East Asian populations. Two additional T2D susceptibility loci, *UBE2E2* and *C2CD4A-C2CD4B*, were discovered in 2010 in a Japanese GWAS of a larger sample size (4,470 T2D *vs*. 3,071 controls) [42]. Associations between the *C2CD4A-C2CD4B* locus and T2D were confirmed by replication sets for both East Asian and European populations; however, no association between *UBE2E2* and *T2D* was observed in the European population. Therefore, the *UBE2E2* variants may affect development of T2D specifically in East Asian populations through interactions with specific environmental factors and/or specific genetic factors other than *UBE2E2*. However, the possibility that the same *UBE2E2* locus (perhaps through the same or different causal variants) is involved in the development of T2D in European populations cannot be excluded until the results of fine mapping and/or re-sequencing studies are available. Recently, the association of 4 loci, *PTPRD, SRR, CDC123*/*CAMK1D,* and *SPRY2* with T2D were shown to reach a genome-wide significance level in GWAS among Han Chinese in Taiwan and Shanghai [43, 44]. However, the association of these 4 loci remains to be evaluated in independent replication cohorts.

## What have GWAS brought about so far?

### *1. Identified loci for T2D linked more frequently to beta-cell function than to insulin sensitivity*

The etiology of T2D is a combination of beta-cell dysfunction and insulin resistance, which is promoted by either genetic or environmental factors (e.g., obesity, westernized diet, and life style). Interestingly, most of the known T2D susceptible variants appear to influence insulin secretion rather than insulin resistance. For example, risk variants of *CDKAL1*, *SLC30A8,* and *HHEX* were shown to be associated with an impaired insulin response in glucose tolerance tests [21, 45-48]. *CDKN2A*/*B* variants have been associated with impaired glucose-induced insulin secretion in healthy subjects [46]. In the MAGIC study, all the loci associated with T2D, *ADCY5*, *PROX1*, *GCK*, *GCKR,* and *DGKB-TMEM195* were associated with fasting glucose/HOMA-β, whereas only *GCKR* was associated with HOMA-IR [33]. Another large meta-analysis from DIAGRAM+ demonstrated that of 31 confirmed T2D susceptibility loci, 10 (*MTNR1B*, *SLC30A8*, *THADA*, *TCF7L2*, *KCNQ1*, *CAMK1D*, *CDKAL1*, *IGF2BP2*, *HNF1B*, and *CENTD2*) were nominally associated with reduced HOMA-β and only 3 (*PPARG*, *FTO*, and *KLF14*) were associated with HOMA-IR [27]. Furthermore, all loci identified in the Japanese GWAS, namely, *KCNQ1*, *UBE2E2*, and *C2CD4A-C2CD4B* were shown to be associated with decreased beta-cell function in non-diabetic control groups [37, 42, 49]. Prior to the accumulation of GWAS data, a genetic predisposition to insulin resistance had been considered to play the dominant role in development of T2D, especially in populations of European origin. The results obtained from GWAS, however, emphasize the crucial role of the pancreatic beta cells in the onset of T2D, and a genetic predisposition to reduced beta-cell function may contribute more to the susceptibility to T2D.

### *2. Missing heritability*

GWAS have successfully identified novel T2D susceptibility loci that had not been captured by classical approaches. However, based on the results of a European twin study, only ~10% of the known T2D heritability could be explained by those T2D susceptibility loci [27]. Although there is no information to estimate the T2D heritability in other ethnic populations, the sum of explained variance for all associated loci accounts for less than 20% heritability in the Japanese (our unpublished observation), suggesting the existence of a large portion of "missing heritability." To search for the missing heritability, several limitations of the current strategy for GWAS should be considered.

First, there are a considerable number of uncaptured SNPs in the public database, and there has been insufficient effort to perform GWAS for populations other than those of European origin. Second, the currently accepted significant threshold for GWAS ($P < 5 \times 10^{-8}$) may produce type 2 errors (false-negative results), and it is expected that many important loci are obscured among loci having only borderline associations; these could be captured in larger-scale analyses of different ethnic populations. A third limitation is the role of low-frequency risk variants that may have relatively large effects. The rationale of GWAS is based on the "common disease-common variant" hypothesis, and studies have focused on finding common variants associated with the disease; therefore, susceptibility variants having a minor allele frequency (MAF) of less than 1% are frequently missed.

Improving on the limitations of GWAS as they are currently performed will uncover other loci contributing to the disease. To overcome these limitations, the genome-wide exon (exome) sequencing strategy should be facilitated by ultra high-throughput sequencing technology (next-generation sequencers). In this analysis, a part of the missing heritability may be explained by identifying the clustering of rare variants within particular genes in the affected individuals. The introduction of next-generation sequencers will also help to solve missing heritability by accelerating studies of the transcriptome, large-scale sequence analysis of small RNAs, and/or epigenetic analyses such as the methylome.

### *3. Translation of T2D genetics into clinical practice: the possibility of disease prediction and prevention*

One of the most anticipated clinical uses of genetic information is to predict an individual's risk of developing T2D. This clinical application has been investigated in the Framingham Offspring Study [50], the Malmö Preventive Project (MPP), and the Botnia Study [51], among others [52, 53]. The studies examined 11 to 20 loci associated with T2D, and a genetic score was calculated based on the number of risk alleles in subjects who developed diabetes during the follow-up period and those who remained disease-free. The results of these analyses showed no clear improvement of predictive power by adding the genetic risk score to established risk prediction models composed of various clinical and biochemical factors including age, sex, family history, body mass index, fasting glucose level, systolic blood pressure, and lipid profile. The area under the receiver operating characteristics (ROC) curves was 0.74 and 0.75 with and without adding the genetic risk score, respectively [51].

Despite this, subset analyses of the study cohorts suggested that genetic testing might be beneficial in younger patients before clinical manifestation of the phenotypic characteristics associated with T2D. This possibility was recently examined by de Miguel-Yanes and colleagues, who re-calculated the genotype score of the Framingham Offspring Study using the updated list of 40 T2D susceptibility variants [54]. This study showed that the genetic score marginally improved the ability to predict future diabetes in subjects younger than 50 years; the increased risk was 24% per allele for individuals <50 years of age and 11% per allele for people ≥50 years of age.

A genetic investigation suggested no increased risk of T2D in homozygous carriers of the *TCF7L2* risk allele who were randomized to the lifestyle intervention arm of the Diabetes Prevention Program (DPP), although carrying both copies of the risk allele usually confers an 80% increased risk of developing diabetes [7]. This is a good example of the clinical usefulness of genetic testing to allow detection of high-risk individuals with whom physicians should aggressively intervene. At present, insufficient information is available to construct a genetic risk score for T2D and it is far from translating into clinical practice. One study, however, reported that a "high risk" result from genetic testing would inspire 71% of the 152 healthy subjects interviewed to adopt healthy lifestyle changes [55]. Therefore, despite the limited ability of genetic testing to predict T2D, genetic information may be more powerful in influencing behavior that will result in a subsequent health benefit.

***4. Translation of T2D genetics into clinical practice: the possibility of identifying novel therapeutic targets***

Although many new and interesting T2D susceptibility loci have been identified, it is challenging to translate them into clinical practice, especially for developing new drugs. A major obstacle is that disease-associated SNPs are usually annotated by the gene in closest proximity; however, the protein encoded by that gene may not have a causative role in the development of T2D in humans. In fact, for most of the identified T2D susceptibility loci, the causal variants and molecular mechanisms for diabetes risk are unknown. Furthermore, most genetic risk variants are found in the intronic or non-coding regions of genes and are more likely to affect regulation of transcription rather than gene function per se, thus being unlikely to be directly linked to the gene's biological function.

Nevertheless, GWAS have provided many useful insights into the pathophysiology of T2D. For example, the first T2D GWAS identified the T2D susceptibility variant rs13266634, which encodes an R →W change at position 325 in the *SLC30A8* gene [20]. The *SLC30A8* encodes ZnT-8, which transports zinc from the cytoplasm into secretory vesicles for insulin storage and secretion [56]. A therapeutic agent that enhances the intracellular function of this transporter could theoretically increase insulin secretion and lower blood glucose levels. In addition, other T2D susceptibility variants confirmed by GWAS include variants within the genes *PPARG* and *KCNJ11* that encode targets of the established oral hypoglycemic agents, thiazolidinediones and sulphonylureas, respectively [57, 58]. Therefore, elucidating the mechanisms by which each susceptibility locus contributes to T2D will improve our understanding of the pathophysiology of T2D and will provide new and useful information for the development of new drugs for the treatment and/or prevention of T2D.

## Future perspective

Ten years have passed since the first draft of the human genome sequence was published [59, 60]. During the past decade, the human genome (sequencing) project was completed, and a large body of information on the human genome has been accumulated. Simultaneously, several high-throughput genotyping technologies have been developed, as well as statistical methods and/or tools for handling innumerable datasets. The success of these missions, followed by the start of GWAS held out the hope that personalized medicine would be realized within the next several years. The first GWAS data were published in 2007 by WTCCC, and since then, more than 1,100 loci have been discovered [61]. Although this is excellent progress, it has also been recognized that the information obtained from GWAS has been insufficient to improve human health. In the field of T2D, GWAS has identified many new and convincing T2D susceptible loci. This too is an excellent start, but the entire heritability of T2D remains largely unexplained, despite the growing list of T2D susceptibility variants described here.

Over the next few years, certain modifications of the GWAS study design will be necessary. Much larger intra- or trans-ethnic sample sizes will be required to increase the power for detection, which may be conducted in meta-analyses. Examining populations of non-European descent is likely to identify additional T2D loci, and this should be performed more vigorously. An alternative option is subgroup analysis, which could eliminate the phenotypic variations that minimize the power for detection.

Association analyses of rarer variants for T2D are an additional option. In this regard, the search for low-frequency variants will be facilitated by the 1000 Genomes Project [62]. This international collaborative initiative is using next generation whole-genome sequencing technology to systematically catalog all variants with a minor allele frequency of greater than 1% in at least 1000 genomes. Exome sequencing is also an efficient strategy to selectively sequence the coding regions of the human genome to identify novel genes associated with rare and common disorders. Routine whole-genome sequencing of large numbers of individuals is still not feasible, in part due to the high cost associated with the technique, and the exome represents an enriched portion of the genome that can be used to search for variants with large effect sizes.

Further, examining non-additive gene-gene interactions and/or gene-environmental interactions may lead to the discovery of novel pathways that synergize to increase the risk of developing T2D.

Efforts must be made over the coming decade to translate new findings from GWAS to the clinic, which could attract the interest of most endocrinologists. One potential clinical application is the development of genetically based personalized susceptibility profiles to aid in the prediction, early identification, and pre-

vention of T2D or its complications.

Pharmacogenetics is also a promising clinical application of the genetic findings for T2D. Genetic profiling may allow personalized medicine by facilitating optimal treatment choices that maximize clinical efficacy and minimize toxicity. Recently, a GWAS of the glycemic response to metformin identified a SNP associated with treatment success at a locus containing the ataxia telangiectasia mutated gene (*ATM*) [63]. Although genetic background alone is insufficient to predict treatment response at an individual level, accumulation of these pharmacogenetic data is necessary for the future development of personalized medicine.

## Conclusion

The exciting results generated by GWAS have led to intense discussion of their clinical utility. The lack of clinical impact to date is not surprising as this branch of genetic research is still in its infancy, and it will be a challenge to translate the GWAS findings into improved care for patients with diabetes. The focus of ongoing research efforts include detailed functional characterization of the identified T2D susceptibility variants and the search for missing heritability. GWAS have produced a significant breakthrough in the field of common disease genetics, but this alone will not provide sufficient information. Translating information on the human genome into clinical practice has proven to be more challenging than was expected in 2003, when the Human Genome Project ended. According to the plan published by the National Human Genome Research Institute on February 2011, the impact of human genome data on health care will begin to build only after 2020 [64]. We still have a long way to go.

## References


1. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study. (1999) *Diabetologia* 42: 139-145.
2. Groop L, Forsblom C, Lehtovirta M,Tuomi T, Karanko S, Nissén M, Ehrnström BO, Forsén B, Isomaa B, Snickars B, Taskinen MR (1996) Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. *Diabetes* 45: 1585-1593.
3. Fajans SS, Bell GI, Polonsky KS (2001) Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med* 345: 971-980.
4. 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 (2000) Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 26: 163-175.
5. Reynisdottir I, Thorleifsson G, Benediktsson R, Sigurdsson G, Emilsson V, Einarsdottir AS, Hjorleifsdottir EE, Orlygsdottir GT, Bjornsdottir GT, Saemundsdottir J, Halldorsson S, Hrafnkelsdottir S, Sigurjonsdottir SB, Steinsdottir S, Martin M, Kochan JP, Rhees BK, Grant SF, Frigge ML, Kong A, Gudnason V, Stefansson K, Gulcher JR (2003) Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2. *Am J Hum Genet* 73: 323-335.
6. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, 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 (2006) Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nat Genet* 38: 320-323.
7. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D; Diabetes Prevention Program Research Group (2006) *TCF7L2* polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med* 355: 241-250.
8. Groves CJ, Zeggini E, Minton J, Frayling TM, Weedon MN, Rayner NW, Hitman GA, Walker M, Wiltshire S, Hattersley AT, McCarthy MI (2006) Association analysis of 6,736 U.K. subjects provides replication and confirms *TCF7L2* as a type 2 diabetes susceptibility gene with a substantial effect on individual risk. *Diabetes* 55: 2640-2644.
9. Zhang C, Qi L, Hunter DJ, Meigs JB, Manson JE, van Dam RM, Hu FB (2006) Variant of transcription factor 7-like 2 (*TCF7L2*) gene and the risk of type 2 diabetes in large cohorts of U.S. women and men. *Diabetes* 55: 2645-2648.

10. Scott LJ, Bonnycastle LL, Willer CJ, Sprau AG, Jackson AU, Narisu N, Duren WL, Chines PS, Stringham HM, Erdos MR, Valle TT, Tuomilehto J, Bergman RN, Mohlke KL, Collins FS, Boehnke M (2006) Association of transcription factor 7-like 2 (*TCF7L2*) variants with type 2 diabetes in a Finnish sample. *Diabetes* 55: 2649-2653.
11. Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, Mitchell BD, Shuldiner AR (2006) Polymorphisms in the transcription factor 7-like 2 (*TCF7L2*) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance. *Diabetes* 55: 2654-2659.
12. Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjögren M, Florez JC, Almgren P, Isomaa B, Orho-Melander M, Lindblad U, Daly MJ, Tuomi T, Hirschhorn JN, Ardlie KG, Groop LC, Altshuler D (2006) Common single nucleotide polymorphisms in *TCF7L2* are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. *Diabetes* 55: 2890-2895.
13. Cauchi S, Meyre D, Dina C, Choquet H, Samson C, Gallina S, Balkau B, Charpentier G, Pattou F, Stetsyuk V, Scharfmann R, Staels B, Frühbeck G, Froguel P (2006) Transcription factor *TCF7L2* genetic study in the French population: expression in human beta-cells and adipose tissue and strong association with type 2 diabetes. *Diabetes* 55: 2903-2908.
14. Hayashi T, Iwamoto Y, Kaku K, Hirose H, Maeda S (2007) Replication study for the association of *TCF7L2* with susceptibility to type 2 diabetes in a Japanese population. *Diabetologia* 50: 980-984.
15. Horikoshi M, Hara K, Ito C, Nagai R, Froguel P, Kadowaki T (2007) A genetic variation of the transcription factor 7-like 2 gene is associated with risk of type 2 diabetes in the Japanese population. *Diabetologia* 50: 747-751.
16. 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 (2000) The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26: 76-80.
17. 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 (2003) 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* 52: 568-572.
18. International HapMap Consortium (2005) A haplotype map of the human genome. *Nature* 437: 1299-1320.
19. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, Hirschhorn JN(2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nature Reviews Genetics* 9: 356-369.
20. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445: 881-885.
21. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir 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, Gudnason V, Chen G, Huang H, Lashley K, Doumatey 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 (2007) A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes. *Nat Genet* 39: 770-775.
22. 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, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, 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 (2007) Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316: 1331-1336.
23. 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 (2007) Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 316: 1336-1341.
24. Scott LJ, 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, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316: 1341-1345.

25. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI (2007) A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316: 889-894.
26. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström 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, Jørgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell 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, Sjögren M, Steinthorsdottir 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 (2008) Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* 40: 638-645.
27. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bengtsson Boström K, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Couper DJ, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jørgensen T, Kao WH, Klopp N, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Perry JR, Petersen AK, Platou C, Proença C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparsø T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllensten U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Mohlke KL, Morris AD, Palmer CN, Pramstaller PP, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Wareham NJ, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Hu FB, Meigs JB, Pankow JS, Pedersen O, Wichmann HE, Barroso I, Florez JC, Frayling TM, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI; MAGIC investigators; GIANT Consortium (2010) Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 42: 579-589.
28. Bouatia-Naji N, Rocheleau G, Van Lommel L, Lemaire K, Schuit F, Cavalcanti-Proença C, Marchand M, Hartikainen AL, Sovio U, De Graeve F, Rung J, Vaxillaire M, Tichet J, Marre M, Balkau B, Weill J, Elliott P, Jarvelin MR, Meyre D, Polychronakos C, Dina C, Sladek R, Froguel P (2008) A polymorphism within the *G6PC2* gene is associated with fasting plasma glucose levels. *Science* 320: 1085-1088.
29. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, Dehghan A, Deloukas P, Doney AS, Elliott P, Freimer N, Gateva V, Herder C, Hofman A, Hughes TE, Hunt S, Illig T, Inouye M, Isomaa B, Johnson T, Kong A, Krestyaninova M, Kuusisto J, Laakso M, Lim N, Lindblad U, Lindgren CM, McCann OT, Mohlke KL, Morris AD, Naitza S, Orrù M, Palmer CN, Pouta A, Randall J, Rathmann W, Saramies J, Scheet P, Scott LJ, Scuteri A, Sharp S, Sijbrands E, Smit JH, Song K, Steinthorsdottir V, Stringham HM, Tuomi T, Tuomilehto J, Uitterlinden AG, Voight BF, Waterworth

D, Wichmann HE, Willemsen G, Witteman JC, Yuan X, Zhao JH, Zeggini E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BW, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, Abecasis GR (2009) Variants in *MTNR1B* influence fasting glucose levels. *Nat Genet* 41: 77-81.

30. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chèvre JC, Borch-Johnsen K, Hartikainen AL, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Lévy-Marchal C, Pattou F, Meyre D, Blakemore AI, Jarvelin MR, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P(2009) A variant near *MTNR1B* is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* 41: 89-94.
31. Chen WM, Erdos MR, Jackson AU, Saxena R, Sanna S, Silver KD, Timpson NJ, Hansen T, Orrù M, Grazia Piras M, Bonnycastle LL, Willer CJ, Lyssenko V, Shen H, Kuusisto J, Ebrahim S, Sestu N, Duren WL, Spada MC, Stringham HM, Scott LJ, Olla N, Swift AJ, Najjar S, Mitchell BD, Lawlor DA, Smith GD, Ben-Shlomo Y, Andersen G, Borch-Johnsen K, Jørgensen T, Saramies J, Valle TT, Buchanan TA, Shuldiner AR, Lakatta E, Bergman RN, Uda M, Tuomilehto J, Pedersen O, Cao A, Groop L, Mohlke KL, Laakso M, Schlessinger D, Collins FS, Altshuler D, Abecasis GR, Boehnke M, Scuteri A, Watanabe RM (2008) Variations in the *G6PC2/ABCB11* genomic region are associated with fasting glucose levels. *J Clin Invest* 118: 2620-2628.
32. Weedon MN, Clark VJ, Qian Y, Ben-Shlomo Y, Timpson N, Ebrahim S, Lawlor DA, Pembrey ME, Ring S, Wilkin TJ, Voss LD, Jeffery AN, Metcalf B, Ferrucci L, Corsi AM, Murray A, Melzer D, Knight B, Shields B, Smith GD, Hattersley AT, Di Rienzo A, Frayling TM (2006) A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. *Am J Hum Genet* 79: 991-1001.
33. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Mägi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparsø T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proença C, Kumari 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, Borch-Johnsen K, Böttcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi 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, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jørgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martínez-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, Orrù M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden 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, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvänen AC, Tanaka T, Thorand B, Tichet J, Tönjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC; DIAGRAM Consortium; GIANT Consortium; Global BPgen Consortium, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Ríos M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF; Anders Hamsten on behalf of Procardis Consortium; MAGIC investigators, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J, Valle TT, Altshuler D, Rotter JI, Siscovick DS, Penninx

BW, Boomsma DI, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin MR, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC, Barroso I (2010) New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 42: 105-116.

34. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, Lyssenko V, Bouatia-Naji N, Dupuis J, Jackson AU, Kao WH, Li M, Glazer NL, Manning AK, Luan J, Stringham HM, Prokopenko I, Johnson T, Grarup N, Boesgaard TW, Lecoeur C, Shrader P, O'Connell J, Ingelsson E, Couper DJ, Rice K, Song K, Andreasen CH, Dina C, Köttgen A, Le Bacquer O, Pattou F, Taneera J, Steinthorsdottir V, Rybin D, Ardlie K, Sampson M, Qi L, van Hoek M, Weedon MN, Aulchenko YS, Voight BF, Grallert H, Balkau B, Bergman RN, Bielinski SJ, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Böttcher Y, Brunner E, Buchanan TA, Bumpstead SJ, Cavalcanti-Proença C, Charpentier G, Chen YD, Chines PS, Collins FS, Cornelis M, J Crawford G, Delplanque J, Doney A, Egan JM, Erdos MR, Firmann M, Forouhi NG, Fox CS, Goodarzi MO, Graessler J, Hingorani A, Isomaa B, Jørgensen T, Kivimaki M, Kovacs P, Krohn K, Kumari M, Lauritzen T, Lévy-Marchal C, Mayor V, McAteer JB, Meyre D, Mitchell BD, Mohlke KL, Morken MA, Narisu N, Palmer CN, Pakyz R, Pascoe L, Payne F, Pearson D, Rathmann W, Sandbaek A, Sayer AA, Scott LJ, Sharp SJ, Sijbrands E, Singleton A, Siscovick DS, Smith NL, Sparsø T, Swift AJ, Syddall H, Thorleifsson G, Tönjes A, Tuomi T, Tuomilehto J, Valle TT, Waeber G, Walley A, Waterworth DM, Zeggini E, Zhao JH; GIANT consortium; MAGIC investigators, Illig T, Wichmann HE, Wilson JF, van Duijn C, Hu FB, Morris AD, Frayling TM, Hattersley AT, Thorsteinsdottir U, Stefansson K, Nilsson P, Syvänen AC, Shuldiner AR, Walker M, Bornstein SR, Schwarz P, Williams GH, Nathan DM, Kuusisto J, Laakso M, Cooper C, Marmot M, Ferrucci L, Mooser V, Stumvoll M, Loos RJ, Altshuler D, Psaty BM, Rotter JI, Boerwinkle E, Hansen T, Pedersen O, Florez JC, McCarthy MI, Boehnke M, Barroso I, Sladek R, Froguel P, Meigs JB, Groop L, Wareham NJ, Watanabe RM (2010) Genetic variation in *GIPR* influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet* 42: 142-148.

35. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 301: 2129-2140.

36. Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, Ng DP, Holmkvist J, Borch-Johnsen K, Jørgensen 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 (2008) SNPs in *KCNQ1* are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet* 40: 1098-1102.

37. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, 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, Nanjo K, Kadowaki T, Kasuga M (2008) Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 40: 1092-1097.

38. Lee YH, Kang ES, Kim SH, Han SJ, Kim CH, Kim HJ, Ahn CW, Cha BS, Nam M, Nam CM, Lee HC (2008) Association between polymorphisms in *SLC30A8*, *HHEX*, *CDKN2A*/*B*, *IGF2BP2*, *FTO*, *WFS1*, *CDKAL1*, *KCNQ1* and type 2 diabetes in the Korean population. *J Hum Genet* 53: 991-998.

39. Tan JT, Nurbaya S, Gardner D, Ye S, Tai ES, Ng DP (2009) Genetic variation in *KCNQ1* associates with fasting glucose and beta-cell function: a study of 3,734 subjects comprising three ethnicities living in Singapore. *Diabetes* 58: 1445-1449.

40. Hu C, Wang C, Zhang R, Ma X, Wang J, Lu J, Qin W, Bao Y, Xiang K, Jia W(2009) Variations in *KCNQ1* are associated with type 2 diabetes and beta cell function in a Chinese population. *Diabetologia* 52: 1322-1325.

41. Liu Y, Zhou DZ, Zhang D, Chen Z, Zhao T, Zhang Z, Ning M, Hu X, Yang YF, Zhang ZF, Yu L, He L, Xu H (2009) Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes in the population of mainland China. *Diabetologia* 52: 1315-1321.

42. Yamauchi T, Hara K, Maeda S, Yasuda K, Takahashi A, Horikoshi M, Nakamura M, Fujita H, 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, Jørgensen T, Lauritzen T, Sandbæk A, Hansen T, Ohshige 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, Froguel P, Pedersen O, Kamatani N, Nakamura Y, Kadowaki T (2010) A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at *UBE2E2* and *C2CD4A-C2CD4B*. *Nat Genet* 42: 864-868.

43. Tsai FJ, Yang CF, Chen CC, Chuang LM, Lu CH, Chang CT, Wang TY, Chen RH, Shiu CF, Liu YM, Chang CC, Chen P, Chen CH, Fann CS, Chen YT, Wu JY (2010) A

genome-wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese. *PLoS Genet* 6: e1000847.

44. Shu XO, Long J, Cai Q, Qi L, Xiang YB, Cho YS, Tai ES, Li X, Lin X, Chow WH, Go MJ, Seielstad M, Bao W, Li H, Cornelis MC, Yu K, Wen W, Shi J, Han BG, Sim XL, Liu L, Qi Q, Kim HL, Ng DP, Lee JY, Kim YJ, Li C, Gao YT, Zheng W, Hu FB (2010) Identification of New Genetic Risk Variants for Type 2 Diabetes. *PLoS Genet* 6: e1001127.
45. Pascoe L, Tura A, Patel SK, Ibrahim IM, Ferrannini E, Zeggini E, Weedon MN, Mari A, Hattersley AT, McCarthy MI, Frayling TM, Walker M; RISC Consortium; U.K. Type 2 Diabetes Genetics Consortium (2007) Common variants of the novel type 2 diabetes genes *CDKAL1* and *HHEX*/*IDE* are associated with decreased pancreatic beta-cell function. *Diabetes* 56: 3101-3104.
46. Palmer ND, Goodarzi MO, Langefeld CD, Ziegler J, Norris JM, Haffner SM, Bryer-Ash M, Bergman RN, Wagenknecht LE, Taylor KD, Rotter JI, Bowden DW (2008) Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. *Diabetes* 57: 1093-1100.
47. Staiger H, Machicao F, Stefan N, Tschritter O, Thamer C, Kantartzis K, Schäfer SA, Kirchhoff K, Fritsche A, Häring HU (2007) Polymorphisms within novel risk loci for type 2 diabetes determine beta-cell function. *PLoS One* 2: e832.
48. Grarup N, Rose CS, Andersson EA, Andersen G, Nielsen AL, Albrechtsen A, Clausen JO, Rasmussen SS, Jørgensen T, Sandbaek A, Lauritzen T, Schmitz O, Hansen T, Pedersen O (2007) Studies of association of variants near the *HHEX, CDKN2A/B,* and *IGF2BP2* genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and extension of genome-wide association studies. *Diabetes* 56: 3105-3111.
49. Grarup N, Overvad M, Sparsø T, Witte DR, Pisinger C, Jørgensen T, Yamauchi T, Hara K, Maeda S, Kadowaki T, Hansen T, Pedersen O (2011) The diabetogenic *VPS13C*/*C2CD4A*/*C2CD4B* rs7172432 variant impairs glucose-stimulated insulin response in 5,722 non-diabetic Danish individuals. *Diabetologia* 54: 789-794.
50. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA (2008) Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 359: 2208-2219.
51. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, Berglund G, Altshuler D, Nilsson P, Groop L (2008) Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 359: 2220-2232.
52. Talmud PJ, Hingorani AD, Cooper JA, Marmot MG, Brunner EJ, Kumari M, Kivimäki M, Humphries SE (2010) Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. *BMJ* 340: b4838.
53. Lango H; UK Type 2 Diabetes Genetics Consortium, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI, Frayling TM, Weedon MN (2008) Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes* 57: 3129-3135.
54. de Miguel-Yanes JM, Shrader P, Pencina MJ, Fox CS, Manning AK, Grant RW, Dupuis J, Florez JC, D'Agostino RB Sr, Cupples LA, Meigs JB; MAGIC Investigators; DIAGRAM+ Investigators (2011) Genetic risk reclassification for type 2 diabetes by age below or above 50 years using 40 type 2 diabetes risk single nucleotide polymorphisms. *Diabetes Care* 34: 121-125.
55. Grant RW, Hivert M, Pandiscio JC, Florez JC, Nathan DM, Meigs JB (2009) The clinical application of genetic testing in type 2 diabetes: a patient and physician survey. *Diabetologia* 52: 2299-2305.
56. Chimienti F, Devergnas S, Favier A, Seve M (2004) Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. *Diabetes* 53: 2330-2337.
57. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA(1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 270: 12953-12956.
58. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, Abuelo D, Phornphutkul C, Molnes J, Bell GI, Gloyn AL, Hattersley AT, Molven A, Søvik O, Njølstad PR (2004) Permanent neonatal diabetes due to mutations in *KCNJ11* encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes* 53: 2713-2718.
59. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann N, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB,

Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Raymond C, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blöcker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C, Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowski J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ; International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome. *Nature* 409: 860-921.

60. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, Gocayne JD, Amanatides P, Ballew RM, Huson DH, Wortman JR, Zhang Q, Kodira CD, Zheng XH, Chen L, Skupski M, Subramanian G, Thomas PD, Zhang J, Gabor Miklos GL, Nelson C, Broder S, Clark AG, Nadeau J, McKusick VA, Zinder N, Levine AJ, Roberts RJ, Simon M, Slayman C, Hunkapiller M, Bolanos R, Delcher A, Dew I, Fasulo D, Flanigan M, Florea L, Halpern A, Hannenhalli S, Kravitz S, Levy S, Mobarry C, Reinert K, Remington K, Abu-Threideh J, Beasley E, Biddick K, Bonazzi V, Brandon R, Cargill M, Chandramouliswaran I, Charlab R, Chaturvedi K, Deng Z, Di Francesco V, Dunn P, Eilbeck K, Evangelista C, Gabrielian AE, Gan W, Ge W, Gong F, Gu Z, Guan P, Heiman TJ, Higgins ME, Ji RR, Ke Z, Ketchum KA, Lai Z, Lei Y, Li Z, Li J, Liang Y, Lin X, Lu F, Merkulov GV, Milshina N, Moore HM, Naik AK, Narayan VA, Neelam B, Nusskern D, Rusch DB, Salzberg S, Shao W, Shue B, Sun J, Wang Z, Wang A, Wang X, Wang J, Wei M, Wides R, Xiao C, Yan C, Yao A, Ye J, Zhan M, Zhang W, Zhang H, Zhao Q, Zheng L, Zhong F, Zhong W, Zhu S, Zhao S, Gilbert D, Baumhueter S, Spier G, Carter C, Cravchik A, Woodage T, Ali F, An H, Awe A, Baldwin D, Baden H, Barnstead M, Barrow I, Beeson K, Busam D, Carver A, Center A, Cheng ML, Curry L, Danaher S, Davenport L, Desilets R, Dietz S, Dodson K, Doup L, Ferriera S, Garg N, Gluecksmann A, Hart B, Haynes J, Haynes C, Heiner C, Hladun S, Hostin D, Houck J, Howland T, Ibegwam C, Johnson J, Kalush F, Kline L, Koduru S, Love A, Mann F, May D, McCawley S, McIntosh T, McMullen I, Moy M, Moy L, Murphy B, Nelson K, Pfannkoch C, Pratts E, Puri V, Qureshi H, Reardon M, Rodriguez R, Rogers YH, Romblad D, Ruhfel B, Scott R, Sitter C, Smallwood M, Stewart E, Strong R, Suh E, Thomas R, Tint NN, Tse S, Vech C, Wang G, Wetter J, Williams S, Williams M, Windsor S, Winn-Deen E, Wolfe K, Zaveri J, Zaveri K, Abril JF, Guigó R, Campbell MJ, Sjolander KV, Karlak B, Kejariwal A, Mi H, Lazareva B, Hatton T, Narechania A, Diemer K, Muruganujan A, Guo N, Sato S, Bafna V, Istrail S, Lippert R, Schwartz R, Walenz B, Yooseph S, Allen D, Basu A, Baxendale J, Blick L, Caminha M, Carnes-Stine J, Caulk P, Chiang YH, Coyne M, Dahlke C, Mays A, Dombroski M, Donnelly M, Ely D, Esparham S, Fosler C, Gire H, Glanowski S, Glasser K, Glodek A, Gorokhov M, Graham K, Gropman B, Harris M, Heil J, Henderson S, Hoover J, Jennings D, Jordan C, Jordan J, Kasha J, Kagan L, Kraft C, Levitsky A, Lewis M, Liu X, Lopez J, Ma D, Majoros W, McDaniel J, Murphy S, Newman M, Nguyen T, Nguyen N, Nodell M, Pan S, Peck J, Peterson M, Rowe W, Sanders R, Scott J, Simpson M, Smith T, Sprague A, Stockwell T, Turner R, Venter E, Wang M, Wen M, Wu D, Wu M, Xia A, Zandieh A, Zhu X (2001) The sequence of the human genome. *Science* 291: 1304-1351.

61. Lander ES (2011) Initial impact of the sequencing of the human genome. *Nature* 470: 187-197.

62. The 1000 Genomes Project Consortium (2010) A map of human genome variation from population-scale sequencing. *Nature* 467: 1061-1073.

63. GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group; Wellcome Trust Case Control Consortium 2, Zhou K, Bellenguez C, Spencer CC, Bennett AJ, Coleman RL, Tavendale R, Hawley SA, Donnelly LA, Schofield C, Groves CJ, Burch L, Carr F, Strange A, Freeman C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Gray E, Hunt S, Jankowski J, Langford C, Markus HS, Mathew CG, Plomin R,

Rautanen A, Sawcer SJ, Samani NJ, Trembath R, Viswanathan AC, Wood NW; MAGIC investigators, Harries LW, Hattersley AT, Doney AS, Colhoun H, Morris AD, Sutherland C, Hardie DG, Peltonen L, McCarthy MI, Holman RR, Palmer CN, Donnelly P, Pearson ER (2011) Common variants near *ATM* are associated with glycemic response to metformin in type 2 diabetes. *Nat Genet* 43: 117-120.

64. Green ED, Guyer MS; National Human Genome Research Institute (2011) Charting a course for genomic medicine from base pairs to bedside. *Nature* 470: 204-213.
65. Hara K, Okada T, Tobe K, Yasuda K, Mori Y, Kadowaki H, Hagura R, Akanuma Y, Kimura S, Ito C, Kadowaki T (2000) The Pro12Ala polymorphism in PPAR gamma2 may confer resistance to type 2 diabetes. *Biochem Biophys Res Commun* 271: 212-216.
66. Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, Takeda J, Inoue I, Seino Y, Yasuda K, Hanafusa T, Yamagata K, Awata T, Kadowaki T, Hara K, Yamada N, Gotoda T, Iwasaki N, Iwamoto Y, Sanke T, Nanjo K, Oka Y, Matsutani A, Maeda E, Kasuga M (2001) The Pro12 -->Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. *Diabetes* 50: 891-894.
67. Omori S, Tanaka Y, Takahashi A, Hirose H, Kashiwagi A, Kaku K, Kawamori R, Nakamura Y, Maeda S (2008) Association of *CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8,* and *KCNJ11* with susceptibility to type 2 diabetes in a Japanese population. *Diabetes* 57: 791-795.
68. Sakamoto Y, Inoue H, Keshavarz P, Miyawaki K, Yamaguchi Y, Moritani M, Kunika K, Nakamura N, Yoshikawa T, Yasui N, Shiota H, Tanahashi T, Itakura M(2007) SNPs in the *KCNJ11-ABCC8* gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. *J Hum Genet* 52: 781-793.
69. Sandhu MS, Weedon MN, Fawcett KA, Wasson J, Debenham SL, Daly A, Lango H, Frayling TM, Neumann RJ, Sherva R, Blech I, Pharoah PD, Palmer CN, Kimber C, Tavendale R, Morris AD, McCarthy MI, Walker M, Hitman G, Glaser B, Permutt MA, Hattersley AT, Wareham NJ, Barroso I (2007) Common variants in *WFS1* confer risk of type 2 diabetes. *Nat Genet* 39: 951-953.
70. Horikawa Y, Miyake K, Yasuda K, Enya M, Hirota Y, Yamagata K, Hinokio Y, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Yamamoto K, Tokunaga K, Takeda J, Kasuga M (2008) Replication of genome-wide association studies of type 2 diabetes susceptibility in Japan. *J Clin Endocrinol Metab* 93: 3136-3141.
71. Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, Froguel P, Kadowaki T (2007) Variations in the *HHEX* gene are associated with increased risk of type 2 diabetes in the Japanese population. *Diabetologia* 50: 2461-2466.
72. Furukawa Y, Shimada T, Furuta H, Matsuno S, Kusuyama A, Doi A, Nishi M, Sasaki H, Sanke T, Nanjo K (2008) Polymorphisms in the *IDE-KIF11-HHEX* gene locus are reproducibly associated with type 2 diabetes in a Japanese population. *J Clin Endocrinol Metab* 93: 310-314.
73. Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, Tuomi T, Gaudet D, Boström KB, Walker M, Hitman G, Hattersley AT, McCarthy MI, Ardlie KG, Hirschhorn JN, Daly MJ, Frayling TM, Groop L, Altshuler D (2007) Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. *Diabetes* 56: 685-693.
74. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K (2007) Two variants on chromosome 17 confer prostate cancer risk, and the one in *TCF2* protects against type 2 diabetes. *Nat Genet* 39: 977-983.
75. Miyake K, Yang W, Hara K, Yasuda K, Horikawa Y, Osawa H, Furuta H, Ng MC, Hirota Y, Mori H, Ido K, Yamagata K, Hinokio Y, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Wang HY, Tanahashi T, Nakamura N, Takeda J, Maeda E, Yamamoto K, Tokunaga K, Ma RC, So WY, Chan JC, Kamatani N, Makino H, Nanjo K, Kadowaki T, Kasuga M (2009) Construction of a prediction model for type 2 diabetes mellitus in the Japanese population based on 11 genes with strong evidence of the association. *J Hum Genet* 54: 236-241.
76. Omori S, Tanaka Y, Horikoshi M, Takahashi A, Hara K, Hirose H, Kashiwagi A, Kaku K, Kawamori R, Kadowaki T, Nakamura Y, Maeda S (2009) Replication study for the association of new meta-analysis-derived

risk loci with susceptibility to type 2 diabetes in 6,244 Japanese individuals. *Diabetologia* 52: 1554-1560.

77. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proença C, Bacot F, Balkau B, Belisle A, Borch-Johnsen K, Charpentier G, Dina C, Durand E, Elliott P, Hadjadj S, Järvelin MR, Laitinen J, Lauritzen T, Marre M, Mazur A, Meyre D, Montpetit A, Pisinger C, Posner B, Poulsen P, Pouta A, Prentki M, Ribel-Madsen R, Ruokonen A, Sandbaek A, Serre D, Tichet J, Vaxillaire M, Wojtaszewski JF, Vaag A, Hansen T, Polychronakos C, Pedersen O, Froguel P, Sladek R (2009) Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. *Nat Genet* 41: 1110-1115.
78. Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L (2009) Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat Genet* 41: 82-88.
79. Onuma H, Tabara Y, Kawamoto R, Shimizu I, Kawamura R, Takata Y, Nishida W, Ohashi J, Miki T, Kohara K, Makino H, Osawa H (2010) The *GCKR* rs780094 polymorphism is associated with susceptibility of type 2 diabetes, reduced fasting plasma glucose levels, increased triglycerides levels and lower HOMA-IR in Japanese population. *J Hum Genet* 55: 600-604.
80. Bonnefond A, Vaxillaire M, Labrune Y, Lecoeur C, Chèvre JC, Bouatia-Naji N, Cauchi S, Balkau B, Marre M, Tichet J, Riveline JP, Hadjadj S, Gallois Y, Czernichow S, Hercberg S, Kaakinen M, Wiesner S, Charpentier G, Lévy-Marchal C, Elliott P, Jarvelin MR, Horber F, Dina C, Pedersen O, Sladek R, Meyre D, Froguel P (2009) Genetic variant in *HK1* is associated with a proanemic state and A1C but not other glycemic control-related traits. *Diabetes* 58: 2687-2697.