The New Perspectives on Genetic Studies of Type 2 Diabetes and Thyroid Diseases

Min Xu, Yufang Bi, Bin Cui, Jie Hong, Weiqing Wang and Guang Ning*

'Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health, Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine, E-Institute of Shanghai Universities, Shanghai, China; 'Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Department of Endocrinology and Metabolism, Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Abstract: Recently, genome-wide association studies (GWAS) have led to the discovery of hundreds of susceptibility loci that are associated with complex metabolic diseases, such as type 2 diabetes and hyperthyroidism. The majority of the susceptibility loci are common across different races or populations; while some of them show ethnicity-specific distribution. Though the abundant novel susceptibility loci identified by GWAS have provided insight into biology through the discovery of new genes or pathways that were previously not known, most of them are in introns and the associated variants cumulatively explain only a small fraction of total heritability. Here we reviewed the genetic studies on the metabolic disorders, mainly type 2 diabetes and hyperthyroidism, including candidate genes-based findings and more recently the GWAS discovery; we also included the clinical relevance of these novel loci and the gene-environmental interactions. Finally, we discussed the future direction about the genetic study on the exploring of the pathogenesis of the metabolic diseases.

Received on: July 01, 2012- Revised on: November 16, 2012- Accepted on: November 19, 2012

Keywords: Genome wide association study, Gene-environmental interaction, Hyperthyroidism, Risk prediction, Type 2 diabetes.

INTRODUCTION

The genetic research of complex diseases has achieved remarkable leap during the past several years since the completion of the first genome-wide association study (GWAS) of age-related macular degeneration has been published in 2006 [1]. Such revolutionary progress in the field is largely due to the breakthrough in genotyping technology. GWAS has been extensively employed in genetic analysis of various human diseases (e.g., diabetes, obesity, cancers, cardiovascular diseases, dyslipidemia, neuropsychiatric diseases, autoimmune diseases, and infectious diseases) as well as disease-related quantitative traits (e.g., body height, blood glucose levels, body mass index (BMI) and waist circumference). GWAS has led to the discovery of hundreds of susceptibility loci that are associated with complex endocrine and metabolic traits, as long as diseases, such as type 2 diabetes (T2D), obesity and hyperthyroidism, and so on.

The metabolic diseases rose rapidly in the past decades and the number of adults with diabetes is expected to rise to about 440 million by 2030 almost 80% of whom will be from low-income and middle-income countries [2, 3]. T2D is a chronic complex metabolic disorder, the pathogenesis of which is not well elucidated though the impaired insulin sensitivity and islet β cell dysfunction being the two main mechanisms. Besides the environmental or lifestyle risk factors, like age, obesity, excess energy and longer sedentary time, etc, the genetic risk factors play a pivotal role in the incidence of T2D.

Hyperthyroidism is a condition in which the thyroid gland makes too much thyroid hormone, and the most common causes of hyperthyroidism are Graves' disease, followed by toxic multinodular goitre, whilst rarer causes include an autonomously functioning thyroid adenoma, or thyroiditis [4]. Hyperthyroidism is often referred to as an "overactive thyroid." Hyperthyroidism occurs when the thyroid releases too much of its hormones over a short (acute) or long (chronic) period of time. Many diseases and conditions can cause this problem, including: Graves disease (accounts for most cases of hyperthyroidism), inflammation (thyroiditis) of the thyroid due to viral infections or other causes, noncancerous growths of the thyroid gland or pituitary gland [5]. Graves' disease is a common organ-specific autoimmune disease, which is, to a significant extent, determined by genetic factors [6, 7]. The search for gene variations that predispose to such disease is complicated by their polygenic nature.

THE CANDIDATE GENE ASSOCIATION STUDIES OF T2D

Before the GWAS era, linkage analysis and candidate genes analysis are the two main methods to explore the effect of genetic factors on T2D. The unequivocal established susceptible loci for the common type of T2D have limited to...
CAPN10, TCF7L2, KCNJ11 and PPARG genes. CAPN10 and TCF7L2 are the two genes successfully identified by the linkage analysis. CAPN10, which encodes the cysteine protease calpain 10, was the first T2D susceptibility gene identified through a genome-wide linkage followed by positional cloning [8]. Many validated studies have been performed from Caucasians to East Asians [9-11]. TCF7L2, which encodes the transcription factor 7-like 2, was firstly found to be associated with T2D in Danish and US cohorts, through fine-mapping of a suggestive linkage to chromosome 10 [12]. After that, this gene was extensively and successfully replicated and validated in many populations, including the Indians, French and Asians, etc [13-17]. KCNJ11 and PPARG are the two proven susceptibility genes for T2D that was confirmed by candidate gene methods [18, 19]. The mostly studied polymorphisms associated with T2D are E23K in KCNJ11 and P12A in PPARG. KCNJ11, namely potassium inwardly-rectifying channel, subfamily J, member 11, encodes inward rectifier K(+) channel Kir6.2 (KIR6.2), which is important on the effect of anti-diabetic drug sulphonylureas. PPARG encodes peroxisome proliferator-activated receptor gamma, which is a target of thiazolidinediones. PPARG gene is one of the well-established susceptible genes of T2D. Interestingly, PPARG is one of the few genes that were confirmed to be associated with insulin resistance. Significantly greater insulin sensitivity was reported in not only nondiabetic alanine (Ala) carriers, but also the diabetic patients [20, 21].

**NEW SUSCEPTIBILITY GENES WERE IDENTIFIED BY GWAS**

Since the first GWAS, the number of susceptibility loci for T2D has grown up to more than 50 (Table 1) [22-45]. Most of the susceptibility loci are successfully validated in different races or ethnic groups. However, there are ethnicity-specific genetic loci have also been identified. Rs7903146 of TCF7L2 was widely accepted as one of the most relative susceptibility single nucleotide polymorphism (SNP) with T2D, which was replicated in almost all the GWAS [22, 24, 28, 29, 31, 34, 35]. However, they were mostly performed in Caucasians, and much less GWAS was conducted in Asian populations [27, 33, 37-39, 41, 46]. The minor allele frequency (MAF) of this variation may make the difference. The MAF of rs7903146 in the TCF7L2 gene in East Asians is 0.024–0.042 in control subjects and 0.023–0.055 in patients with T2D [17, 47-49]. In Caucasians, the MAF is 0.180–0.305 in control subjects and 0.220–0.425 in patients with T2D [12-16]. The less frequency of the polymorphisms may lead to less power to be detected in the association study.

Another discrepancy lies in KCNQ1 gene. KCNQ1 was thought to be an Asian-specific susceptibility gene for T2D when it was firstly detected by GWAS in Japanese [27, 33] and followed by multiple replication studies in other Asian populations [30, 38, 46]. The previously reported GWAS performed in Europeans and Caucasians did not identify KCNQ1 until the large-scale combining genome-wide association data from European descent reported a second independent signal of KCNQ1, rs231362 [50], which is different from the previously reported ones among Asian populations (rs2237892[33], rs2237895[38], rs2237897[27], rs163182 [46]). The MAF of rs231362 in Caucasians is 0.52, which is much higher than 0.08 for rs2237892 and 0.05 for rs2237897.

The remarkable findings from GWAS have inspired investigators and the medical professionals to think about the clinical utility and the impact of their results. One of these considerations is whether it could be effective to discover the functional variations, the ‘causal’ variants. Though GWAS is a powerful way to rapidly and systematically identify new associations, it cannot refine a direct association between a disease or trait and the “causal” DNA sequences (causal in the sense that altering these sequences would eliminate the diabetic phenotype). To the date, the role of GWAS loci in T2D development is less established. With few exceptions such as KCNJ11 and SLC30A8 whose functions are well studied, the causal variant(s), causal gene(s) and pathophysiological processes implicated in GWAS loci (independently and in combination) are little understood.

However, the present GWAS and primary functional studies have achieved some progression on genes in cell cycling control (CDKN2A/2B, CDKAL1), transcription factors (TCF7L2, HHEX), and ion channels (SLC30A8, KCNQ1). Two common variants (near or in FTO and MC4R) alter diabetes risk mediated by a primary effect of obesity [51]. There are many epidemiologic or in vivo function studies which have shown that most of the genetic loci of T2D are associated with the islet β cell function. The genes identified by GWAS are mostly involved in the process of insulin synthesis and secretion, and seldom are in the process of insulin effect on the target organs. This has been viewed as presumptive evidence that insulin secretion plays a more important etiologic role in T2D than insulin resistance. TCF7L2 is the mostly explored susceptible gene for T2D. Common SNPs in TCF7L2 are reproducibly associated with T2D and reduced insulin response to glucose in nondiabetic individuals [52-54]. Lyssenko and his colleagues extensively explored the predictive effect of 3 SNPs (rs7903146, rs12255372, and rs10885406) in TCF7L2 and the mechanisms in Scandinavians, Swedish and Finnish. They concluded that the increased risk of T2D conferred by variants in TCF7L2 involves the enteroinsular axis, enhanced expression of the gene in islets, and impaired insulin secretion [55]. The common variations of SLC30A8 also have also been extensively studied in a great deal of populations [24, 28, 32, 56, 57]. SLC30A8 encoded the zinc transporter 8 (ZnT8), a member of the zinc transporter (ZnT/Slc30) family [58, 59]. Both in vitro systems and in vivo studies in the knockout mice and humans, [60-63] have implicated ZnT8 in the development of T2D and are closely related to insulin synthesis and/or secretion. Another extensively studied susceptibility gene is KCNQ1, which was also reported to be highly related to β cell function [64, 65]. Many of the T2D susceptibility genes identified by GWAS affect β cell function (cell cycle regulation), and only a limited number of T2D GWAS loci are associated with insulin resistance (e.g., PPARG, FTO, IRS1 and KLF14) [34]. On one hand, these findings highlight the significant role of β cell dysfunction in T2D pathogenesis; on the other hand, the environmental impact on the development of insulin resistance and case-control design render it much more difficult to identify genetic loci associated with insulin resistance than those with β cell function [66].
### Table 1. The Susceptibility Genetic Loci for Type 2 Diabetes [by May-2012]. The References Listed Here Are Those That Firstly Reported the Significant Loci with P Value Less than 5 \times 10^{-8} for the GWAS

| Year | Genes | Location | SNP | Type of SNP | Odds Ratio, 95% Confidence Interval | P-values | References |
|------|-------|----------|-----|-------------|-----------------------------------|---------|------------|
| 1    | *CAPN10* | 2q37.3 | 9803A/G | Missense | - | - | [8] Horikawa Y, Nat Genet 2000 |
| 2    | *PPARG* | 3p25.2 | rs1801282-C | Missense | 1.25 [Not Reported] | 0.002 | [18] Altshuler D, Nat Genet 2000 |
| 3    | *KCNJ11* | 11p15.1 | rs5219-T | Missense | 1.23 [1.12–1.36] 1.14 [1.10–1.19] | 1.5 \times 10^{-5} 7 \times 10^{-31} | [19] Gloyn AL, Diabetes 2003 [20] Scott LJ, Science 2007 |
|      |        |          | rs5215-C | Missense | 1.14 [1.10–1.19] | 5.0 \times 10^{41} | [22] Zeggini E, Science 2007 |
| 4    | *TCF7L2* | 10q25.3 | rs7903146-T | Intron | 1.54 [Not Reported] 1.65 [1.28–2.02] 1.38 [Not Reported] | 2.1 \times 10^{-9} 2.0 \times 10^{-34} 2 \times 10^{-10} | [12] Grant SF, Nat Genet 2006; [24] Sladek R, Nature 2007 [29] Steinhorsdottir V, Nat Genet 2007 |
|      |        |          | rs7901695-C | Intron | 1.37 [1.31–1.43] | 1.0 \times 10^{-48} | [22] Zeggini E, Science 2007 |
|      |        |          | rs4506565-T | Intron | 1.36 [1.20–1.54] | 5 \times 10^{-12} | [23] WTCCC, Nature 2007 |
| 5    | *SLC30A8* | 8q24.11 | rs1326634-C | cds-synon | 1.18 [0.69–1.67] 1.12 [1.07–1.16] | 6 \times 10^{4} 5 \times 10^{4} | [24] Sladek R, Nature 2007 [22] Zeggini E, Science 2007 |
| 6    | *WFS1* | 4p16.1 | rs10010131-T | Intron | 0.90 [0.86–0.93] | 1.4 \times 10^{-7} | [25] Sandhu MS, Nat Genet 2007 |
|      |        |          | rs6446482-C | intron | 0.90 [0.87–0.94] | 3.4 \times 10^{-7} | [25] Sandhu MS, Nat Genet 2007 |
|      |        |          | rs1801214-T | cds-synon | 1.13 [1.08–1.18] | 3 \times 10^{4} | [34] Voight BF, Nat Genet 2010 |
| 7    | *TCF2 (HNF1β)* | 17q12 | rs7501939-C | intron | 0.91 [0.87–0.94] | 9.2 \times 10^{-7} | [26] Gudmundsson J, Nat Genet 2007 |
|      |        |          | rs4430796-A | intron | 0.91 [0.87–0.94] | 2.7 \times 10^{-7} | [26] Gudmundsson J, Nat Genet 2007 |
| 8    | *HHEX* | 10q23.33 | rs1111875-C | intergenic | 1.13 [1.08–1.17] | 6 \times 10^{-10} | [28] Scott LJ, Science 2007 |
|      |        |          | rs5015480-C | Intergenic | 1.18 [1.13–1.23] | 1 \times 10^{-13} | [34] Voight BF, Nat Genet 2010 |
| 9    | *IGF2BP2* | 3q27.2 | rs4402960-T | Intron | 1.14 [1.11–1.18] | 9 \times 10^{-16} | [22] Zeggini E, Science 2007 |
|      |        |          | rs6769511-C | Intron | 1.23 [1.15–1.31] | 1 \times 10^{-6} | [27] Unoki H, Nat Genet 2008 |
| 10   | *FTO* | 16q12.2 | rs8050136-A | Intron | 1.23 [1.18–1.32] | 9 \times 10^{-16} | [22] Zeggini E, Science 2007 |
|      |        |          | rs9939609-A | Intron | 1.34 [1.17–1.52] | 2 \times 10^{-7} | [23] WTCCC, Nature 2007 |
| 11   | *CDKAL1* | 6p22.3 | rs10946398-C | Intron | 1.16 [1.10–1.22] | 1 \times 10^{4} | [22] Zeggini E, Science 2007 |
|      |        |          | rs7754840-C | Intron | 1.12 [1.08–1.16] | 4 \times 10^{-12} | [28] Scott LJ, Science 2007 |
|      |        |          | rs7756992-G | Intron | 1.2 [1.13–1.27] | 8 \times 10^{-4} | [29] Steinhorsdottir V, Nat Genet 2007 |
|      |        |          | rs9465871-C | Intron | 1.18 [1.04–1.34] | 3 \times 10^{-7} | [23] WTCCC, Nature 2007 |
|      |        |          | rs4712524-G | intron | 1.22 [1.15–1.31] | 3 \times 10^{-10} | [27] Unoki H, Nat Genet 2008 |
| 12   | *CDKN2A, CDKN2B* | 9p21.3 | Rs564398-T | Intron | 1.13 [1.08–1.19] | 1 \times 10^{4} | [22] Zeggini E, Science 2007 |
|      |        |          | rs10811661-T | Intergenic | 1.2 [1.14–1.25] | 8 \times 10^{-13} | [28] Scott LJ, Science 2007 |
|      |        |          | rs2383208-A | Intergenic | 1.34 [1.27–1.41] | 2 \times 10^{-79} | [30] Takeuchi F, Diabetes 2009 |
|      |        |          | rs7018475-? | intergenic | 1.35 [1.18–1.56] | 3 \times 10^{4} | [45] Huang J, Eur J Hum Genet 2012 |
| Year | Genes | Location | SNP | Type of SNP | Odds Ratio, 95% Confidence Interval | P-values | References |
|-----|-------|----------|-----|-------------|-------------------------------------|----------|------------|
| 13  | JAZF1 | 7p15.1   | rs864745-T | Intron     | 1.1 [1.07-1.13]                    | 5x10^-14 | [31]       |
| 14  | CDC123 - CAMK1D | 10p13 | rs1277970-G | Intergenic | 1.11 [1.07-1.14]                    | 1x10^-10 | [31]       |
| 15  | TSPAN8 - LGR5 | 12q21.1 | rs7961581-C | Intergenic | 1.09 [1.06-1.12]                    | 1x10^-6  | [31]       |
| 16  | THADA  | 2p21     | rs7578597-T | Mssense    | 1.15 [1.10-1.20]                    | 1x10^-7  | [31]       |
| 17  | ADAMTS9 - MAGI1 | 3p14.1 | rs4607103-C | Intergenic | 1.09 [1.06-1.12]                    | 1x10^-7  | [31]       |
| 18  | NOTCH2 | 1p12     | rs10923931-T | Intron     | 1.13 [1.08-1.17]                    | 4x10^-9  | [31]       |
| 19  | KCNQ1  | 11p15.4  | rs2237892-C | Intron     | 1.4 [1.34-1.47]                     | 2x10^-42 | [33]       |
|     |        |          | rs2237897-C | intron     | 1.33 [1.24-1.41]                    | 1x10^-16 | [27]       |
|     |        |          | rs231362-G  | Intron     | 1.08 [1.06-1.10]                    | 3x10^-13 | [34]       |
|     |        |          | rs2237895-C | Intron     | 1.29 [1.19-1.40]                    | 1x10^-8  | [38]       |
| 20  | LOC64673, IRS1 | 2q36.3 | rs2943641-C | Intergenic | 1.19 [1.13-1.25]                    | 9x10^-12 | [35]       |
| 21  | RBMS1, ITGB6 | 2q24.2 | rs7593730-C | Intron     | 1.11 [1.08-1.16]                    | 4x10^-4  | [36]       |
| 22  | CENTD2 | 11q13.4  | rs1552224-A | Intergenic | 1.14 [1.11-1.17]                    | 1x10^-12 | [34]       |
| 23  | KIAA1486 - IRS1(IRS1) | 2q36.3 | rs7578326-A | Intergenic | 1.11 [1.08-1.13]                    | 5x10^-10 | [34]       |
| 24  | BCL11A | 2p16.1   | rs243021-A  | Intergenic | 1.08 [1.06-1.10]                    | 3x10^-13 | [34]       |
| 25  | MTVNR1B | 11q14.3  | rs1387153-T | Intergenic | 1.09 [1.06-1.11]                    | 8x10^-15 | [34]       |
| 26  | ZBED3  | 5q13.3   | rs4457053-G | Intergenic | 1.08 [1.06-1.11]                    | 3x10^-12 | [34]       |
| 27  | PRC1   | 15q26.1  | rs8042680-A | Intron     | 1.07 [1.05-1.09]                    | 2x10^-10 | [34]       |
| 28  | KLF14  | 7q32.3   | rs972283-G  | Intergenic | 1.07 [1.05-1.10]                    | 2x10^-10 | [34]       |
| 29  | DUSP9 | Xq28     | rs5945326-A | Intergenic | 1.27 [1.18-1.37]                    | 3x10^-10 | [34]       |
| 30  | TP53IP1 | 8q22.1   | rs896854-T | Intron     | 1.06 [1.04-1.09]                    | 1x10^-7  | [34]       |
| 31  | ZFAND6 | 15q25.1  | rs1163497-G | Intergenic | 1.06 [1.04-1.08]                    | 2x10^-9  | [34]       |
| 32  | HMG2A2 | 12q14.3  | rs1531343-C | UTR-3      | 1.11 [1.07-1.14]                    | 4x10^-7  | [34]       |
| 33  | HNF1A  | 12q24.31 | rs7957197-T | Intron     | 1.07 [1.05-1.10]                    | 2x10^-7  | [34]       |
| 34  | C2CD4A,C2CD4B | 15q22.2 | rs7172432-A | Intergenic | 1.11 [1.08-1.14]                    | 9x10^-14 | [37]       |
| 35  | PTPRD  | 9p24.1   | rs17584409-T | Intron     | 1.57 [1.36-1.82]                    | 9x10^-10 | [38]       |
| 36  | SRR    | 17p13.3  | rs3913000-G | Intron     | 1.28 [1.18-1.39]                    | 3x10^-8  | [38]       |
| 37  | CDC123,CAMK1D | 10p13 | rs10906115-A | Intergenic | 1.13 [1.08-1.18]                    | 1x10^-8  | [39]       |
| 38  | SPRY2  | 13q31.1  | rs1359790-G | Intergenic | 1.15 [1.10-1.20]                    | 6x10^-9  | [39]       |
| 39  | C6orf37 | 6q13     | rs1048886-G | missense   | 1.54 [1.32-1.80]                    | 3x10^-8  | [40]       |
| 40  | AP3S2  | 15q26.1  | rs2028299-C | UTR-3      | 1.11 [1.07-1.13]                    | 2x10^-12 | [41]       |
| 41  | HMG20A | 15q24.3  | rs7178572-G | Intron     | 1.09 [1.06-1.12]                    | 7x10^-11 | [41]       |
| 42  | GRB14  | 2q24.3   | rs3923113-A | Intergenic | 1.09 [1.06-1.13]                    | 1x10^-7  | [41]       |
| 43  | ST6GAL1 | 3q27.3   | rs18681329-G | Intron     | 1.09 [1.06-1.12]                    | 3x10^-8  | [41]       |
| 44  | VPS26A | 10q22.1  | rs1802295-A | UTR-3      | 1.08 [1.05-1.12]                    | 4x10^-8  | [41]       |
Insulin resistance and obesity are highly correlated, and thus by deliberately minimizing the confounding influence of obesity, those scans maximized the chances of identifying insulin secretion genes. One example is that the Welcome Trust Case Control Consortium (WTCCC) identified a locus near FTO associated with T2D in analysis without adjustment for BMI. When the BMI effect was statistically accounted for the association disappeared, indicating that the diabetes risk associated with the FTO locus is mediated by obesity [67]. Insulin resistance genes may also have smaller effect sizes which the current GWAS were underpowered to detect, may be relatively rare and not tagged by the current set of SNPs, or their manifestation may be subjected to stronger environmental influences [66].

### CLINICAL CORRELATION OF T2D SUSCEPTIBILITY LOCI IDENTIFIED BY GWAS

Clinical application of T2D GWAS loci is limited mainly due to the lack of information regarding biological function, the small proportion of the heritability explained by the common variants and the minor discrimination effect added to the conventional clinical factors.

Though the abundant novel susceptibility loci identified by GWAS have provided insight into biology through the discovery of new genes or pathways that were previously unknown, most of them are in introns, showing a moderate discovery of new genes or pathways that were previously by GWAS have provided insight into biology through the conventional clinical factors. Though the abundant novel susceptibility loci identified by GWAS are estimated to explain only 5-10% of the genetic heritability of T2D [68]. All in a sentence, these common variants have failed to explain most of the genetic contribution to disease [69].

Several clinical studies assessed the predictive value of these loci for the diabetes risk. For example, a 3-year follow-up study found that the risk allele homozygotes (TT) of TCF7L2 variant rs7903146 were more likely to develop diabetes from impaired glucose tolerance than the protective allele homozygotes [70]. Two independent studies in 2008 examined genotypes of 16 and 18 T2D loci respectively, and concluded that these newly identified T2D loci provided limited predictive information of T2D beyond the clinical risk factors (e.g., family history, BMI, hepatic enzymes, smoking status which were taken into consideration [71, 72]. A series of studies performed have tried to find out the predictive and discriminative effect of these loci on diseases risk and to identify high risk populations [57, 73]. The clinical T2D prediction models that consist of basic demographic, clinical, and laboratory predictors have C statistics ranging from 0.66 in the Rotterdam Study [74] to 0.90 in the Framingham Offspring Study [75], which were greater than the values when genotype scores alone were tested. Moreover, the addition of genotype risk scores to clinical prediction models only modestly improves the C statistic. For example, the C statistic improves from 0.903 to 0.906 with the addition of a 40-SNP score to the clinical model in the Framingham Offspring Study [74] and from 0.78 to 0.79 in participants of European ancestry from the Health Professionals Follow-up Study and Nurses’ Health Study [73] and from 0.71 to 0.73 in Han Chinese case control cohort [57]. There is one issue that should be concerned. Using genotype scores to predict T2D, it should probably be noted that many of the “clinical” risk factors which are stronger predictors of diabetes also have a genetic basis, such as obesity, smoking and family history. It could be more possible that the impact of genetics upon disease is too underestimated. Though the situation is a little bit disappointing, the future is promising. The big progress is thought to be on at least two research fronts that may improve the predictive performance of genotype information [76]. First, expanded GWAS efforts in non-European populations will allow targeted sequencing of risk loci and the identification of true causal variants. Second,
GENE-ENVIRONMENTAL INTERACTION

Another consideration of post GWAS era is study of gene environmental interaction. For most complex diseases including T2D, both genetic and environmental factors are involved in the pathogenesis processes. Genetic makeup does not change, but the environmental factors are changing over the lifetime. It is very essential to study the interaction of genetic factors and environmental factors in the diseases onset, prevention procedures and intervention methods. Great progress has been seen since GWAS has reported the abundant susceptibility loci. Lifestyle and diet habit are important environmental factors. A recent meta-analysis reported that the obesogenic effect of the FTO rs9939609 minor allele was substantially diminished by physical activity [82]. The analysis comprised up to 218,166 adults and provided strong statistical evidence supporting this gene-environmental interaction. Lifestyle intervention trials generally support beneficial responses on adiposity measures regardless of FTO genotype [83, 84]. Many studies focused on dietary intake and interventions have found significant interaction with genotypes. Recently, investigators of the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) [85, 86] have conducted two large-scale gene-diet interaction studies. In one study [85], they included 14 cohorts to assess the interaction of 20 genetic variants known to be related to glycemic traits and zinc metabolism with dietary zinc intake (food sources) and 5 cohorts to assess the interaction with total zinc intake (food sources and supplements) on fasting glucose levels among individuals of European ancestry without diabetes. A nominally significant yet biologically plausible interaction was observed between SLC30A8 (rs11558471) and total zinc intake. Higher total zinc intake may attenuate the glucose-raising effect of the rs11558471 SLC30A8 (zinc transporter) variant. In another study [86] it was found that higher wholegrain intake was associated with a smaller reduction in fasting insulin in those with the insulin-raising allele of rs780094 (GCKR). Several reports have studied the modification effect of T2D genetic variations, IRS1 (rs2943641 [87]) and GIPR (rs2287019 [88]) on weight loss and related improvement of insulin resistance in a 2-year randomized trial: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. The results may provide evidence for better choice of effective intervention. To use combined genetic effect (such as genetic risk score) in the gene-environmental interaction tests is a reasonable and effective way, especially when the individual genetic variation effect is minor or moderate. Qi et al. [90] assessed whether established genetic variants, mainly from GWAS, modify dietary patterns in predicting diabetes risk. A more Western dietary pattern significantly increased risk of T2D only among those with a high genetic risk score. Secondary analysis suggested the interaction was attributable to the red and processed meat component of the Western diet. No interaction with a prudent diet was observed. They concluded that genetic predisposition may synergistically interact with a Western dietary pattern in determining diabetes risk in men.

HYPERTHYROIDISM

The occurrence of Graves’ disease is related to the combined effect of genetic, environmental factors. Epidemiologic studies have confirmed that the incidence of Graves’ disease has a significant genetic predisposition [91-93]. Previous studies have identified many putative susceptibility variants for Graves’ disease. Until recently, only the major histo-compatibility complex (MHC) [94, 95] and cytotoxic-cyto-cyte antigen-4 (CTLA-4), TSHR and PTPN22 [96-100] have been consistently found associated with Graves’ disease. Recently, the WTCCC performed a study with a genome-wide set of non-synonymous coding variants and provided evidence that three loci (MHC, TSHR and FCRL3) were associated with Graves’ disease in individuals of European ancestry [101]. The exploration of genome wide susceptibility loci for Graves’ disease and other thyroid diseases achieved great progression since then. So far, there are more than 20 genes were reported to be associated with thyroid volume and function, thyroid cancer and Graves’ disease (Table 2, [102-109]). Most of them are identified and replicated in European ancestry except that two GWAS of Graves’ Diseases were performed in Chinese and Japanese. In the Chinese study, Chu et al. [108] conducted a GWAS in 1,536 individuals with Graves’ disease (cases) and 1,516 controls and followed by a further replication study which included 3,994 cases and 3,510 controls. Two new susceptibility loci (the RNA SET2-FGFR1 OP-CCR6 region at 6q27 were (Pcombined = 6.85 × 10^-10 for rs9355610)
Table 2. The Susceptibility Genetic Loci for Thyroid Diseases [by May-2012]

| Disease/Trait          | Gene(s)   | Location | Strongest SNP-Risk Allele | Initial/Replication Sample | Type of SNP | P-Value  | OR or beta | 95% Confidence Interval | References |
|------------------------|-----------|----------|---------------------------|----------------------------|-------------|----------|------------|--------------------------|------------|
| Thyroid function       | PDE8B     | 5q13.3   | rs2046045-T               | European/European Intron   | Intron      | 2.79x10^{-27} | -0.115 | [0.093-0.137] Unit decrease | [102] Rawal R, Hum Mol Genet. 2012 |
|                        | CAP2B     | 1p36     | rs10917477-A              | Intergenic                |             | 1.54x10^{-8} | -0.058 | [0.038-0.078] Unit decrease |            |
|                        | LOC440389 | 16q23    | rs3813582-T               | Intergenic                |             | 5.63x10^{-10} | 0.068  | [0.046-0.090] Unit increase |            |
|                        | NR3C2     | 4q31     | rs10028213-C              | Intergenic                |             | 2.88x10^{-10} | 0.084  | [0.059-0.109] Unit increase |            |
| Thyroid cancer         | MBIP      | 1q13.3   | rs16909374-T              | European/European Intron   | Intergenic  | 5x10^{-11}   | 2.09   | [1.68-2.60] |            |
|                        | NRG1      | 8p12     | rs2439302-G               | Intron                     |             | 2x10^{-9}    | 1.36   | [1.23-1.50] |            |
|                        | DIRR3     | 2q35     | rs966423-C                | Intron                     |             | 1x10^{-7}    | 1.34   | [1.22-1.47] |            |
|                        | FOXE1     | 9q22.33  | rs965513-A                | Intergenic                |             | 2x10^{-7}    | 1.75   | [1.59-1.94] |            |
|                        | NKX2-1    | 14q13.3  | rs944289-T                | Intergenic                |             | 2x10^{-7}    | 1.37   | [1.24-1.52] |            |
| Thyroid volume         | CAPZB     | 1p36.13  | rs12045440-T              | European/European Intron   | Intergenic  | 2x10^{-11} | 1.38   | [1.26-1.51] | [105] Teumer A, Am J Hum Genet 2011 |
|                        | CAPZB     | 1p36.13  | rs12138950-A              | Intergenic                |             | 3x10^{-18} | 0.1    | [0.08-0.12] Unit decrease |            |
|                        | MAF       | 16q23.2  | rs3813579-A               | Intergenic                |             | 4x10^{-10} | 1.32   | [1.21-1.44] |            |
|                        | MAF       | 16q23.2  | rs17767419-T              | Intergenic                |             | 9x10^{-15} | 0.07   | [0.05-0.09] Unit increase |            |
|                        | CAPZB     | 1p36.13  | rs10917468-C              | Intergenic                |             | 1x10^{-14} | 1.52   | [1.37-1.69] |            |
|                        | C15orf33, FGFI7 | 15q21.2  | rs4338740-C               | Intron; Intron            |             | 3x10^{-10} | 1.45   | [1.32-1.59] |            |
|                        | C15orf33, FGFI7 | 15q21.2  | rs4338740-T               | Intron; Intron            |             | 1x10^{-12} | 0.07   | [0.05-0.09] Unit decrease |            |
| Thyroid Stimulating Hormone | HACE1 | 6q16.3 | rs9322817-?               | Framingham/Intron          | Intron      | 7x10^{-6} | NR     | NR          | [106] Hwang SJ, BMC Med Genet 2007 |
|                        | RAPGEF5   | 7p15.3   | rs10499559-?              | Intergenic                |             | 8x10^{-6}   | NR     | NR          |            |
|                        | FOXE1     | 9q22.33  | rs7850258-?               | European/European Intron   | Intergenic  | 4x10^{-6}   | 1.23   | [1.04-1.47] | [107] Denny JC, Am J Hum Genet 2011 |
and an intergenic region at 4p14 ($P_{combined} = 1.08 \times 10^{-13}$ for rs6832151). The functional study showed that these newly associated SNPs were correlated with the expression levels of $RNASET2$ at 6q27, of $CHRNA9$ and of a previously uncharacterized gene at 4p14, respectively. Moreover, strong associations of $TSHR$ and major histocompatibility complex class II variants with persistently TRAb-positive Graves’ disease were confirmed in the study.

In addition to these GWAS, some studies focused on the candidate genes in pathogenesis pathway of thyroid diseases. These studies provide more evidence of genetic basis of the diseases and may cast light on the etiology of this autoimmune disease. Graves’ disease is an organ-specific autoimmune thyroid disease; the etiology of Graves’ disease may be multifactorial, but the immune response plays a central role. E-selectin, similar to L-selectin, is one of the three members of the selectin family and has been shown to mediate the recruitment of circulating leukocytes by physically supporting adhesive interactions, and participating in cell signalling and rolling. [110, 111] Furthermore, it was well documented that patients with untreated Graves’ disease had high serum levels of a soluble form of E-selectin (sE-selectin), and the concentrations of this adhesion molecule correlated with the activity of the disease, probably reflecting

| Disease/Trait   | Gene(s)          | Location | Strongest SNP-Risk Allele | Initial/Replication Sample | Type of SNP | P-Value | OR or beta | 95% Confidence Interval | References                  |
|-----------------|------------------|----------|---------------------------|---------------------------|-------------|---------|------------|--------------------------|------------------------------|
| Graves’ Disease | HLA, DPB1        | 6p21.32  | rs2281388-T               | Chinese/Chinese           | Intergenic  | $2 \times 10^{-65}$ | 1.64        | [1.55-1.74]              | [108] Chu X, Nat Genet 2011  |
|                 | HLA-B            | 6p21.33  | rs1521-T                  | Intergenic                | $2 \times 10^{-65}$ | 1.92    | [1.78-2.08] |                          |                              |
|                 | MUC21, C6orf15   | 6p21.33  | rs4947296-C               | Intergenic                | $4 \times 10^{-51}$ | 1.77    | [1.65-1.91] |                          |                              |
|                 | HLA, DRB1, DQA1, DQB1 | 14q31.1 | rs6457617-T               | Intron                    | $7 \times 10^{-33}$ | 1.4     | [1.32-1.48] |                          |                              |
|                 | TSHR             | 2q33.2   | rs12101261-T              | Intergenic                | $7 \times 10^{-24}$ | 1.35    | [1.28-1.43] |                          |                              |
|                 | CD28, CTLA4      | 4p14     | rs1024161-T               | Intergenic                | $2 \times 10^{-17}$ | 1.3     | [1.23-1.38] |                          |                              |
|                 | RHOH, CHRNA9     | 1q23.1   | rs6832151-G               | Intron                    | $1 \times 10^{-13}$ | 1.24    | [1.17-1.31] |                          |                              |
|                 | FCRL3            | 6q27     | rs3761959-A               | Intergenic                | $2 \times 10^{-15}$ | 1.23    | [1.17-1.30] |                          |                              |
|                 | RNASET2, FGFR10P | 6q15     | rs9355610-G               | Intron                    | $7 \times 10^{-10}$ | 1.19    | [1.13-1.26] |                          |                              |
|                 | BACH2, MAP3K7    | 6p21.32  | rs370409-T                | Intron                    | $2 \times 10^{-7}$  | 1.15    | [1.09-1.22] |                          |                              |
|                 | ABO              | 9q34.2   | rs505922-T                | $8 \times 10^{-7}$        | 1.13        | [1.07-1.20] |                          | [109] Nakabayashi K, J Hum Genet 2011 |
|                 | MHC              | 6p21.32  | rs2273017-A               | Japanese/Japanese         | Intron       | $2 \times 10^{-32}$ | 1.53        | [1.40-1.66]              |                              |
|                 | MHC              | 6p22.1   | rs3893464-G               | Intergenic                | $2 \times 10^{-30}$ | 1.53    | [1.39-1.67] |                          |                              |
|                 | MHC              | 6p22.1   | rs4313034-T               | Neargene-5               | $2 \times 10^{-15}$ | 1.67    | [1.47-1.90] |                          |                              |
|                 | MHC              | 6p21.33  | rs3132613-C               | Intergenic                | $1 \times 10^{-15}$ | 1.43    | [1.30-1.57] |                          |                              |
|                 | MHC              | 6p21.33  | rs4248154-C               | Intron                    | $1 \times 10^{-15}$ | 1.38    | [1.27-1.50] |                          |                              |
|                 | MHC              | 6p21.31  | rs4713693-T               | $7 \times 10^{-13}$       | 1.4         | [1.28-1.53] |                          |                              |
|                 | MHC              | 6p21.31  | rs9394159-T               | $4 \times 10^{-12}$       | 1.36        | [1.24-1.48] |                          |                              |
an ongoing immune process. [112, 113]. Chen H, et al. [114, 115] reported common L-selectin or E-selectin variants may be associated with susceptibility to Graves’ disease in Chinese population. Cytokines, a large group of non-enzymatic proteins, participate in the induction and effector phases of all inflammatory and immune responses, and are therefore likely to play a critical role in the development of autoimmune diseases [116]. A series of case-control studies have evaluated the associations of genetic variations of several interleukin family members with Graves’ diseases [117-125]. They reported the genetic variations in interleukin-1, 3, 4, 5, 8, 9, 12, 13, 16 and 21 were related to the Graves’ diseases in well defined Chinese case control designed studies. Another important candidate gene for thyroid diseases is the interferon-induced helicase (IFIH1) gene. IFIH1 also identified as a type 1 diabetes (T1D) susceptible loci [126] and a cause gene by re-sequencing the genomic regions initially identified by GWAS [127]. rs1990760-T was associated with decreased risk of T1D. It was found to be associated with increased risk of Graves’ disease in Caucasians [128]. In vivo study showed that rs1990760-T is associated with anti-dsDNA antibodies and may play a biological impact on the autoimmune disease risk allele within the interferon-α (IFN-α) pathway [129]. However, the rs1990760-T polymorphism is not related to Graves’ disease in Chinese [130] or Japanese population [131].

CONCLUSION

During the past several years, genetic studies of complex diseases have made substantial progression. Hundreds of susceptibility variations have been identified related to the common complex diseases and traits (T2D, obesity, hypertension, cancers, hyperthyroidism, and as well as plasma glucose levels, BMI, A1c, etc). Though the effect of most of the identified loci are moderate, often located in the intergenic or intronic regions, and small discrimination fraction from conventional clinical risk factors, the genetic findings encourage clinicians and investigators to engage much more efforts on further exploration of disease prediction, high-risk population stratification and pathogenesis study. There will be a long journey before applying the GWAS results into personalized medicine. The future studies aimed to translate the GWAS data to clinical interpretation are eagerly needed. The studies for interactions of genetic variations and environmental factors maybe a promising field to utilize the genetic variants. The successful functional and biological studies of the reported susceptibility genes depend on the identification of ‘causal’ locus, indicating rare variants to be more important.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported by the grants from the Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health (1994DP131044), the Sector Funds of Ministry of Health (201002002), the Creative Research Group of Ministry of Education (IRT0932), National Natural Science Foundation of China (81270877) and Canadian Institutes of Health Research (NSFC-CIHR, 30911120493).

REFERENCES

[1] Klein, R.J.; Zeiss, C.; Chew, E.Y.; Tsai, J.Y.; Sackler, R.S.; Haynes, C.; Henning, A.K.; SanGiovanni, J.P.; Mane, S.M.; Mayne, S.T.; Bracken, M.B.; Ferris, F.L.; Ott, J.; Barnstable, C.; Hoh, J. Complement factor H polymorphism in age-related macular degeneration. Science, 2005, 308: 385-389.
[2] Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, G. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care, 2004, 27, 1047–52.
[3] Shaw, J.E.; Sicree, R.A.; Zimmet, P.Z. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract., 2010, 87: 4–14.
[4] Vanderpump, M: Epidemiology of thyroid dysfunction – Hypothyroidism and Hyperthyroidism. www.thyrolink.com/mercerk_serono_thyrolink/en/images/Thyroid-Int-2-2009-WEB-NEU_tcm1553_62515.pdf?Version= (February, 2009).
[5] Davies, T.F.; Larsen, P.R: Thyrototoxicosis. In: Kronenberg, H.M., Melmed, S., Polonsky, K.S., Larsen, R., eds. Williams Textbook of Endocrinology. 11th ed. Philadelphia, Pa: Saunders Elsevier; 2008; chap 11.
[6] Gough, S.C. The genetics of Graves’ disease. Endocrinol Metab Clin North Am, 2000, 29, 255–266.
[7] Simmonds, M.J.; Gough, S.C. Unraveling the genetic complexity of autoimmune thyroid disease: HLA, CTLA-4 and beyond. Clin Exp Immunol., 2004, 136, 1–10.
[8] Horikawa, Y.; Oda, N.; Cox, N.J.; Li, X.; Orho-Melander, M.; Hara, M.; Hinokio, Y.; Lindner, T.H.; MASHIMA, H.; Schwarz, P.E.; DEL Bosque-Plata, L.; Horikawa, Y.; Oda, Y.; Yoshiuchi, I.; Collilla, S.; Polonsky, K.S.; Wei, S.; Concannon, P.; Iwaski, N.; Schulze, J.; Baier, L.J.; Bogardus, C.; Groop, L.; Boerwinkle, E.; Hanis, C.L.; Bell, G.J. Genetic variation in the gene encoding capain-10 is associated with type 2 diabetes mellitus. Nat Genet., 2000, 26, 163-175.
[9] Evans, J.C.; Frayling, T.M.; Cassell, P.G.; Saker, P.J.; Hitman, G.A.; Walker, M.; Levy, J.C.; O’Rahilly, S.; Rao, P.V.; Bennett, A.J.; Jones, E.C.; Menzel, S.; Prestwich, P.; Simecek, N.; Wishart, M.; Dhillon, R.; Fletcher, C.; Millward, A.; Demaine, A.; Wilkin, T.; Horikawa, Y.; Cox, N.J.; Bell, G.I.; Ellard, S.; McCarthy, M.I.; Hattersley, A.T. Studies of association between the gene for calpain-10 and type 2 diabetes mellitus in the United Kingdom. Am J Hum Genet., 2001, 69, 544-552.
[10] Garant, M.J.; Kao, W.H.; Brancati, F.; Corsh, J.; Rami, T.M.; Hanis, C.L.; Boerwinkle, E.; Shuldiner, A.R.; Atherosclerosis Risk in Communities Study. SNP43 of CAPN10 and the risk of type 2 Diabetes in African-Americans: the Atherosclerosis Risk in Communities Study. Diabetes 2002, 51, 231-237.
[11] Takeuchi, M; Okamoto, K; Takagi, T; Ishii, H. Ethnic difference in patients with type 2 diabetes mellitus in inter-East Asian populations: a systematic review and meta-analysis focusing on gene polymorphism. J Diabetes, 2009, 4: 255-62.
[12] Grant, S.F.; Thorleifsson, G.; Reynisdottir, I.; Benediktsson, R.; Manolescu, A.; Sainz, J.; Helgason, A.; Stefansson, H.; Emilsson, V.; Helgadottir, A.; Styrkarsdottir, U.; Magnusson, K.P.; Walters, G.B.; Palsdottir, E.; Jonsson, T.; Gudmundsdottir, T.; Gylfason, A.; Saemundsdottir, J; Wilensky, R.L.; Reilly, M.P.; Rader, D.J.; Birger, V.Y.; Christiansen, C.; Gudmason, V.; Sigurdsson, G.; Thorsteinsson, U.; Gulcher, J.R.; Kong, A; Stefansson, K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet., 2006, 38, 320-3.
[13] Groves, C.J.; Zeggini, E.; Minton, J; Frayling, T.M.; Weedon, M.N.; Rayner, N.W.; Hitman, G.A.; Walker, M.; Wiltshire, S.; Hattersley, A.T.; McCarthy, M.I. 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, 2006, 55, 2640-4.
[14] Zhang, C.; Qi, L.; Hunter, D.J.; Meigs, J.B.; Manson, J.E.; van Diemant, M.; Dhillon, R.; Fletcher, C.; Millward, A.; Demaine, A.; Wilkin, T.; Horikawa, Y.; Cox, N.J.; Bell, G.I.; Ellard, S.; McCarthy, M.I.; Hattersley, A.T. Studies of association between the gene for calpain-10 and type 2 diabetes mellitus in the United Kingdom. Am J Hum Genet., 2001, 69, 544-552.
[15] Cauchi, S.; El Ashchab, Y.; Choquet, H.; Dina, C.; Krempfer, F.; Weitgasser, R.; Nejjar, I.; Patsh, W.; Chikri, M.; Meyre, D.;
Froguel, P. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. *J Mol Med (Berl)*, 2007, 85, 777-82.

[16] Scott, L.J.; Bonnycastle, L.L.; Wiljer, C.J.; Sprau, A.G.; Jackson, A.U.; Narisu, N.; Duren, W.L.; Chines, P.S.; Stringham, H.M.; Erdos, M.R.; Valle, T.T.; Tuomilehto, J.; Bergman, R.N.; Mohlke, K.L.; Collins, F.S.; Boehnke, M. Association of transcription factor 7-like 2 (TCF7L2) variants with type 2 diabetes in a Finnish sample. *Diabetes*, 2006, 55, 2649–53.

[17] Ng, M.C.; Park, K.S.; Oh, B.; Tam, C.H.; Cho, Y.M.; Shin, H.D.; Lam, V.K.; Ma, R.C.; So, W.Y.; Cho, Y.S.; Kim, H.L.; Lee, H.K.; Chan, J.C.; Cho, N.H. 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, 2256-62.

[18] Altshuler, D.; Hirschhorn, J.N.; Klannemark, M.; Lindgren, C.M.; Vohl, M.C.; Nemesh, J.; Lane, C.R.; Schaffner, S.F.; Bolk, S.; Brewer, C.; Tuomi, T.; Gaudet, D.; Hudson, T.J.; Daly, M.; Groop, L.; Land, E.S. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet.*, 2000, 26, 76-80.

[19] Gloyon, A.L.; Weeden, M.N.; Owen, K.R.; Turner, M.J.; Knight, B.A.; Hitman, G.; Walker, M.; Levy, J.C.; Sampson, M.; Halford, S.; McCarthy, M.I.; Hattersley, A.T.; Frayling, T.M. 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.

[20] Stumvoll, M.; Häring, H. The peroxisome proliferator-activated receptor-gamma2 Pro12Ala polymorphism. *Diabetes*, 2002, 51, 2341-7.

[21] Deeb, S.S.; Fajas, L.; Nemoto, M.; Pihlajamaki, J.; Mykkänen, L.; Kuusisto, J.; Laakso, M.; Fujimoto, W.; Auwerx, J. A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet.*, 1998, 20, 284–287.

[22] Zeggini, E.; Weeden, M.N.; Lindgren, C.M.; Frayling, T.M.; Elliott, K.S.; Lange, H.; Timponi, N.J.; Perry, J.R.; Rayner, N.W.; Freathy, R.M.; Barrett, J.C.; Shields, B.; Morris, A.P.; Ellard, S.; Groves, C.J.; Harries, L.W.; Marchini, J.L.; Owen, K.R.; Knight, B.; Cardon, L.R.; Walker, M.; Hitman, G.A.; Morris, A.D.; Doney, A.S.; Wellcome Trust Case Control Consortium (WTCCC); McCarthy, M.I.; Hattersley, A.T. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*, 2007, 316, 1336-41.

[23] 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.

[24] Sladek, R.; Rocheleau, G.; Rung, J.; Dina, C.; Shen, L.; Sigurdsson, G.; Hattersley, A.T.; Vallotton, M.P.; Xiang, T.; Cashy, J.; Suarez, B.K.; van Vierssen, O.; Frigge, M.L.; Ober, C.; Holker, M.H.; Wijmenga, C.; Christiansen, C.; Rader, D.J.; Palmer, C.N.; Rotimi, C.; Chan, J.C.; Pedersen, O.; Tong, P.C.; Ng, M.C.; Hansen, T.; Andersen, G.; Borch-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, E.S.; Pedersen, K.; Kamatani, N.; Kikkawa, R.; Nakamura, Y.; Maedler, K.; SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet.*, 2008, 40, 1098-102.

[25] Scott, L.J.; Mohlke, K.L.; Bonnycastle, L.L.; Wiljer, C.J.; Li, Y.; Duren, W.L.; Erdos, M.R.; Stringham, H.M.; Chines, P.S.; Jackson, A.U.; Prokunina-Olsson, L.; Ding, C.J.; Swift, A.J.; Narisu, N.; Hu, T.; Pruit, R.; Xiao, R.; Li, X.Y.; Connelly, K.N.; Riebow, N.L.; Sprau, A.G.; Tong, M.; White, P.P.; Hetrick, K.N.; Barnhart, M.W.; Bark, C.W.; Goldstein, J.L.; Watkins, L.; Xiang, F.; Saramies, J.; Buchanan, T.A.; Watanabe, R.M.; Valle, T.T.; Kinnunen, L.; Abecasis, G.R.; Pugh, E.W.; Doheny, K.F.; Bergman, R.N.; Tuomilehto, J.; Collins, F.S.; Boehnke, M. A genome-wide association study detects multiple susceptibility variants. *Science*, 2007, 316, 1341-5.

[26] Steinthorsdottir, V.; Thorleifsson, G.; Reynolds, I.; Benediktsdottir, K.; Jakobsdottir, M.; Bjarnason, H.; Ng, M.C.; Hansen, T.; Bagger, Y.; Wilensky, R.L.; Reilly, M.P.; Adeyemo, A.; Chen, Y.; Zhou, J.; Gudnason, V.; Chen, G.; Huang, H.; Lasshle, K.; Doumatey, A.; So, W.Y.; Ma, R.C.; Andersen, G.; Borch-Johnsen, K.; Jorgensen, T.; von Vliet-Ostapchouk, J.V.; Holmer, M.; Wijmenga, C.; Christiansen, C.; Rader, D.J.; Rotimi, C.; Gurney, M.; Chan, J.C.; Pedersen, O.; Siddurss, G.; Gulcher, J.R.; Thorstindottir, U.; Kong, A.; Steffanson, K. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet.*, 2007, 39, 57-60.

[27] Takeuchi, F.; Serizawa, M.; Yamamoto, K.; Fujisawa, T.; Nakashima, E.; Ohnaka, K.; Ikegami, H.; Sugiyama, T.; Katsuya, T.; Miyagishi, M.; Nakashima, N.; Nawata, H.; Nakamura, J.; Kono, T.; Takeyanagi, R.; Kato, N. Confirmation of multiple risk loci and genetic impacts by a genome-wide association study of type 2 diabetes in the Japanese population. *Diabetes*, 2009, 58, 1690-9.

[28] Zeggini, E.; Scott, L.J.; Saxena, R.; Voight, B.F.; Marchini, J.L.; Hu, T.; de Bakker, P.I.; Abecasis, G.R.; Almgren, P.; Anders, G.; Ardlie, K.; Boström, K.; Bergman, R.N.; Bonnycastle, L.L.; Borch-Johnsen, K.; Burt, N.P.; Chen, H.; Chines, P.S.; Daly, M.J.; Deodhar, P.; Ding, C.J.; Doney, A.S.; Duren, W.L.; Elliott, K.S.; Frayling, T.M.; Freathy, R.M.; Grallert, H.; Graur, H.; Grimes, C.J.; Guiducci, C.; Hansen, T.; Herder, C.; Hitman, G.A.; Hughes, T.E.; Isomaa, B.; Jackson, A.U.; Jorgensen, T.; Kong, A.; Kubalanza, K.; Kuruvilla, F.G.; Kiusisto, J.; Langenberg, C.; Lango, H.; Lauritzen, T.; Li, Y.; Lindgren, C.M.; Lysenisko, V.; Marvelle, A.F.; Meisinger, C.; Midtjylland, K.; Mohlke, K.L.; Morken, M.A.; Morris, A.D.; Narisu, N.; Nilsson, P.; Owen, K.R.; Palmer, C.N.; Payne, F.; Perry, J.R.; Perterson, E.; Platou, C.; Prokopenko, I.; Qi, L.; Qin, L.; Rayner, N.W.; Rees, M.; Roix, J.J.; Sandbaek, A.; Shields, B.; Sjögren, M.; Steinthorsdottir, V.; Stringham, H.M.; Swift, A.J.; Thorleifsson, G.; Thorstindottir, U.; Timponi, N.J.; Tuomilehto, J.; Walker, M.; Watanabe, R.M.; Weeden, M.N.; Wiljer, C.J.; Wellcome Trust Case Control Consortium, Illig, T.; Hveem, K.; Hu, F.B.; Laakso, M.; Stefansson, K.; Pedersen, O.; Wareham, N.J.; Barroso, I.; Hattersley, A.T.; Collins, F.S.; Groop, L.; McClellan, M.; Boehnke, M.; Altschuler, D. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet.*, 2008, 40, 203-12.

[29] Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena, R.; Voight, B.F.; Lysenisko, V.; Burt, N.P.; de Bakker, P.I.; Chen, H.; Roix, J.J.; Kathiresan, S.; Hirschhorn, J.N.; Daly, M.J.; Hughes, T.E.; Groop, L.; Altschuler, D.; Almgren, P.; Florez, J.C.; Meyer, J.; Ardlie, K.; Bengtsson, Boström, K.; Isomaa, B.; Lettre, G.; Lindblad, U.; Lyon, H.N.; Melander, O.; Newton-Chen, A. The role of common variants affecting glucose tolerance in the pathogenesis of type 2 diabetes. *Nat Genet.*, 2007, 39, 95-106.
C.; Nilsson, P.; Orho-Melander, M.; Råstam, L.; Spellotes, E.K.; Taskinen, M.R.; Tuomil, T.; Guiducci, C.; Berglund, A.; Carlson, J.; Giangni, L.; Hackett, R.; Hall, L.; Holmkvist, J.; Laurila, E.; Sjögren, M.; Sterner, M.; Surti, A.; Svensson, M.; Svensson, M.; Tsuchiy, R.; Blumenstei, B.; Parkin, D.; Defelice, M.; Barry, R.; Bocker, W.; Camara, J.; Chia, Y.; Aoki, N.; Kato, M.; Maegawa, Handarker, B.; Healy, C.; Nguyen, K.; Gates, C.; Sougnej, G.; Cade, G.; Nizzari, M.; Gabriel, S.B.; Chirn, G.W.; Ma, Q.; Parikh, R.; Richardson, D.; Ricke, D.; Purcell, S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science, 2007, 316, 1331-6.

[33] Yasuda, K.; Miyake, K.; Horikawa, Y.; Hara, K.; Osawa, H.; Fujita, H.; Hirota, Y.; Morii, J.; Jonsson, A.; Sato, Y.; Yamagata, K.; Hinoki, Y.; Wang, H.Y.; Tanahashi, T.; Nakamura, N.; Oka, Y.; Iwasaki, N.; Iwamoto, Y.; Yamada, Y.; Seino, Y.; Maegawa, H.; Kashiwagi, A.; Takeda, J.; Maeda, E.; Shin, H.D.; Cho, Y.M.; Park, K.S.; Lee, H.K.; Ng, M.C.; Ma, R.C.; So, W.Y.; Chan, J.C.; Lyssenko, V.; Tuomi, T.; Nilsson, P.; Group, L.; Kamatani, N.; Sekine, A.; Nakamura, Y.; Yamamoto, K.; Yoshida, T.; Tokunaga, K.; Ikata, M.; Makino, H.; Nanjo, K.; Kadotsu, T.; Kasuga, M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. Nat. Genet., 2008, 40, 1092-7.

[34] Voight, B.F.; Scott, L.J.; Steinthorsdottir, V.; Morris, A.P.; Dina, C.; Welch, R.P.; Zeggini, E.; Huth, C.; Aulchenko, Y.S.; Thorleifsson, G.; McCulloch, L.J.; Altshuler, D.; Kliment, L.N.; Wu, G.; Wu, C.C.; Willer, C.J.; Raychaudhuri, S.; McCarroll, S.A.; Langenberg, C.; Hofmann, O.M.; Dupuis, J.; Qi, L.; Segre, A.V.; van Hoek, M.; Navarro, P.; Ardlie, K.; Balkau, B.; Benediktsson, K. Genome-wide association study of type 2 diabetes implicates a variant at 2q24 associated with susceptibility to type 2 diabetes. PLoS Genet., 2010, 6, e1000847.

[35] Sim, X.; Ong, R.T.; Suo, C.; Tay, W.T.; Liu, J.; Ng, D.P.; Beury, D.; Chan, J.C.; Park, K.S.; Jia, W.; Chuang, L.M.; Chan, J.C.; Maeda, S.; Shibata, Y.; Iwasaki, N.; Iwamoto, Y.; Yamada, Y.; Seino, Y.; Maegawa, H.; Horikoshi, M.; Nakamura, M.; Fujita, H.; Grarup, N.; Cauchi, S.; Collins, F.S.; Gyllensten, U.; Hansen, T.; Florez, J.C.; Frayling, T.M.; Groop, L.; Uitterlinden, A.; Walker, M.; Wareham, N.J.; Watanabe, R.M.; Laakso, M.; Mohlke, K.L.; Morris, A.D.; Palmer, C.N.; Hide, W.A.; Hitman, G.A.; Hofman, A.; Hunter, D.J.; Hveem, K.; Meitinger, T.; Wiggs, J.L.; Samani, N.J.; Ikram, M.A.; Narisu, N.; Nilsson, P.; Owen, K.R.; Payne, F.; Perry, J.R.; Shi, J.; van Duijn, C.M.; Stefansson, K.; Altshuler, D.; Boehnke, M.; Pouta, A.; Prentki, M.; Ribel-Madsen, R.; Ruokonen, M.; Mazur, A.; Meyre, D.; Montpetit, A.; Pisinger, C.; Posner, B.; Hadjadj, S.; Järvelin, M.R.; Laitinen, J.; Lauritzen, T.; Marre, M.; Johnsen, K.; Charpentier, G.; Dina, C.; Durand, E.; Elliott, P.; Cavalcanti-Proença, C.; Bacot, F.; Balkau, B.; Belisle, A.; Borch-Johnsen, K.; Asturias, E.; Bennett, A.J.; Blagieva, R.; Boerwinkle, E.; Bonnycastle, L.L.; van Hoek, M.; Navarro, P.; Ardlie, K.; Balkau, B.; Benediktsson, K.; Chen, C.H.; Hu, F.B.; van Dam, R.M.; Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC); Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) Consortium. GwAS analysis identifies loci for type 2 diabetes and triglyceride levels. Nat Genet., 2008, 40, 638-45.
Imamura, M.; Maeda, S.; Yamauchi, T.; Hara, K.; Yasuda, K.; Morizono, T.; Takahashi, A.; Horikoshi, M.; Nakamura, M.; Fujita, H.; Tsunoda, T.; Kato, M.;ocabu, M.; Iwabu, M.; Shojiya, N.; Oshige, T.; Omori, S.; Iwata, M.; Hirose, H.; Kaku, K.; Ito, C.; Tanaka, Y.; Toke, K.; Kashiwagi, A.; Kawamori, R.; Kasuga, M.; Kamatani, N.; Diabetes Genet Replication and Meta-analysis (DIAGRAM) Consortium, Nakamura, Y.; Kadowaki, T. A single-nucleotide polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with type 2 diabetes in Japanese populations. *Hum Mol Genet.*, 2012, 21: 3042-9.

Huang, J.; Ellinghaus, D.; Franke, A.; Howie, B.; Li, Y. 1000 Genomes-based imputation identifies novel and refined associations for the Wellcome Trust Case Control Consortium phase 1 Data. *Eur J Hum Genet.*, 2012, 20, 801-5.

Cui, B.; Zhu, X.; Xu, M.; Guo, T.; Zhu, D.; Chen, G.; Li, X.; Xu, Y.; Bi, Y.; Chen, G.; Li, X.; Wang, W.; Wang, H.; Huang, W.; Ning, G. A genome-wide association study confirms previously reported loci for type 2 diabetes in Han Chinese. *PLoS One*, 2011, 6, e22253.

Horikoshi, M.; Haru, K.; Ito, C.; Nagai, R.; Froguel, P.; Kadowaki, T. A genetic variant of the transcription factor 7-like 2 gene is associated with risk of type 2 diabetes in the Japanese population. *Diabetologia*, 2007, 50, 747–51.

Chang, Y.C.; Chang, T.J.; Jiang, Y.D.; Kuo, S.S.; Lee, K.C.; Chu, K.C.; Chu, K.C.; Chu, L.M. Association study of the genetic polymorphism of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. *Diabetes*, 2007, 56, 2631–7.

Horikoshi, M.; Han, X.; Zhang, Y.; Zhou, X.H.; Ji, L.N. Exon sequencing and association analysis of polymorphisms in TCF7L2 with type 2 diabetes in a Chinese population. *Diabetologia*, 2008, 51, 1146–52.

Voight, B.F.; Scott, L.J.; Steinthorsdottir, V.; Morris, A.P.; Dina, C.; Welch, R.P.; Zeggini, E.; Huth, C.; Aulchenko, Y.S.; Thorleifsson, G.; McCellough, E.J.; Ferreira, T.; Grallert, H.; Amin, N.; Wu, G.; Willer, C.J.; Raychaudhuri, S.; McCarron, S.; Zeng, L.; Horikoshi, M.; Oostra, B.M.; Shrader, P.; Sigurdsson, G.; Sparsø, T.; Strassburger, K.; Midthjell, K.; Morken, M.A.; Narisu, N.; Nilsson, P.; Owen, K.R.; Polasek, O.; Posthuma, D.; Potter, S.C.; Pouta, A.; Province, M.A.; Willer, C.J.; Raychaudhuri, S.; McCarron, S.A.; Langenberg, C.; Hoffmann, O.M.; Dupuis, J.; Qi, L.; Segré, A.V.; van Hoek, M.; Navarro, P.; Ardile, K.; Balkau, B.; Benedikttson, R.; Bennett, A.J.; Blagova, R.; Boerwinkel, E.; Bonnycastle, L.L.; Bengtsson, M.; Boehnke, M.; Froguel, P.; Kadowaki, T. A single-nucleotide polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with type 2 diabetes in Han Chinese. *Diabetologia*, 2007, 50, 747–51.

Saxena, R.; Gianniny, L.; Burtt, N.P.; Lyssenko, V.; Giuducci, C.; Perry, J.R.; Frayling, T.M.; Groop, L.; Städler, B.; Frayling, T.M.; Illig, T.; Froguel, P.; van Duijn, C.M.; Stefansson, K.; Altshuler, D.; Boehnke, M.; McCarthy, M.I.; Soranzo, N.; Wheeler, E.; Glazer, N.L.; Bouatia-Naji, N.; Mägi, R.; Goodarzi, M.O.; Graessler, J.; Grundy, S.; Gwilliam, R.; Hattersley, A.T.; Hattersley, A.T.; Hivon, E.; An, P.; O'Connell, J.; Luan, J.; Elliott, T.; Elliott, P.; Syddall, H.; Syvänen, A.C.; Tanaka, T.; Tönjes, A.; Silveira, A.; Simpson, L.; Singleton, A.; Smith, N.L.; Sovio, U.; Rolandsson, O.; Sandbaek, A.; Sandhu, M.; Sanna, S.; Sayer, A.A.; Polasek, O.; Posthuma, D.; Potter, S.C.; Pouta, A.; Province, M.; Willer, C.J.; Raychaudhuri, S.; McCarron, S.A.; Langenberg, C.; Hoffmann, O.M.; Dupuis, J.; Qi, L.; Segré, A.V.; van Hoek, M.; Navarro, P.; Ardile, K.; Balkau, B.; Benediktsson, R.; Bennett, A.J.; Blagova, R.; Boerwinkel, E.; Bonnycastle, L.L.; Bengtsson, M.; Boehnke, M.; Froguel, P.; Kadowaki, T. A single-nucleotide polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with type 2 diabetes in Han Chinese. *Diabetologia*, 2007, 50, 747–51.

Saxena, R.; Gianniny, L.; Burtt, N.P.; Lyssenko, V.; Giuducci, C.; Perry, J.R.; Frayling, T.M.; Groop, L.; Städler, B.; Frayling, T.M.; Illig, T.; Froguel, P.; van Duijn, C.M.; Stefansson, K.; Altshuler, D.; Boehnke, M.; McCarthy, M.I.; Soranzo, N.; Wheeler, E.; Glazer, N.L.; Bouatia-Naji, N.; Mägi, R.; Goodarzi, M.O.; Graessler, J.; Grundy, S.; Gwilliam, R.; Hattersley, A.T.; Hattersley, A.T.; Hivon, E.; An, P.; O'Connell, J.; Luan, J.; Elliott, T.; Elliott, P.; Syddall, H.; Syvänen, A.C.; Tanaka, T.; Tönjes, A.; Silveira, A.; Simpson, L.; Singleton, A.; Smith, N.L.; Sovio, U.; Rolandsson, O.; Sandbaek, A.; Sandhu, M.; Sanna, S.; Sayer, A.A.; Polasek, O.; Posthuma, D.; Potter, S.C.; Pouta, A.; Province, M.; Willer, C.J.; Raychaudhuri, S.; McCarron, S.A.; Langenberg, C.; Hoffmann, O.M.; Dupuis, J.; Qi, L.; Segré, A.V.; van Hoek, M.; Navarro, P.; Ardile, K.; Balkau, B.; Benediktsson, R.; Bennett, A.J.; Blagova, R.; Boerwinkel, E.; Bonnycastle, L.L.; Bengtsson, M.; Boehnke, M.; Froguel, P.; Kadowaki, T. A single-nucleotide polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with type 2 diabetes in Han Chinese. *Diabetologia*, 2007, 50, 747–51.
transcription factor 7-like 2 (TCF7L2) gene is associated with reduced insulin secretion in nondiabetic women. Diabetes, 2006, 55, 3630-4.

Loos, R.J.; Franks, P.W.; Francis, R.W.; Barroso, I.; Gribble, F.M.; Savage, D.B. Ong, K.K.; O’Rahilly, S.; Wareham, N.J. TCF7L2 polymorphisms modulate proinsulin levels and beta-cell function in a British Europid population. Diabetes. 2007, 56, 1943-7.

Lyssenko, V.; Lupi, R.; Marchetti, P.; Del Guerra, S.; Orho-Melander, M.; Almgren, P.; Sjögren, M.; Ling, C.; Eriksson, K.F.; Lethagen, A.L.; 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.

Lee, Y.H.; Kang, E.S.; Kim, S.H.; Han, S.J.; Kim, C.H.; Hij, A.; Ahn, C.W.; Cha, B.S.; Nam, M.; Nam, C.M.; Lee, H.C. Association between polymorphisms in SLC30A8, HHEX, CDKNA2/B, 11G2BP2, FTO, WFS1, CDKAL1, KCNQ1 and type 2 diabetes in the Korean population. J Hum Genet. 2008, 53, 991-8.

Xu, M.; Bi, Y.; Yu, Y.; Yu, B.; Huang, Y.; Gu, L.; Wu, Y.; Zhu, X.; Li, M.; Wang, T.; Song, A.; Hou, J.; Li, X.; Ning, G. Combined effects of 19 common variations on type 2 diabetes in Chinese: results from two community-based studies. PLoS One. 2010, 17, e14022.

Chimenti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, Znt8, localized into insulin secretory granules. Diabetes. 2004, 53, 2330-7.

Chimenti, F.; Favier, A.; Seve, M. Znt8, a pancreatic beta-cell-specific zinc transporter. Biomol. 2005, 18, 313-7.

Pound, L.D.; Sarkar, S.A.; Benning, R.K.; Wang, Y.; Suwanchikul, A.; Shladov, M.K.; Printz, R.L.; Oeser, J.K.; Lee, C.E.; Piston, D.W.; McGuinness, O.P.; Hutton, J.C.; Powell, D.R.; O’Brien, R.M. Deletion of the mouse Slc30a8 gene encoding zinc transporter-8 results in impaired insulin secretion. Biochem J., 2009, 421, 371-6.

Nicolson, T.J.; Bellomo, E.A.; Wijeskarana, N.; Loder, M.K.; Baldwin, J.M.; Guilkhandanyan, A.V.; Koshkin, V.; Tarasov, A.I.; Carzaniga, R.; Kronenberger, K.; Tanje, T.K.; da Silva, Xavier, G.; Libert, S.; Rocheford, T.; Schieferman, R.; Stetsuk, V.; Ravassard, P.; Parker, H.; Gribble, F.M.; Reimann, F.; Sladek, R.; Hughes, J.; Johnson, S.J.; Porh, M.; Maserbou, M.; Burcelin, R.; Baldwin, S.A.; Liu, M.; Lara-Lemus, R.; Arvan, P.; Schutt, F.C.; Wheeler, M.B.; Chimenti, F.; Rutter, G.A. Insulin storage and glucose homeostasis in mice null for the granule zinc transporter Znt8 and studies of the type 2 diabetes-associated variants. Diabetes., 2009, 58, 2070-83.

Xiang, J.; Li, X.Y.; Xu, M.; Hong, J.; Huang, Y.; Tan, J.R.; Lu, X.; Dai, M.; Yu, B.; Ning, G. Zinc transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J Clin Endocrinol Metab., 2008, 93, 4107-12.

Boesgaard TW, Zilinskaite J, Vänttinen M, Laakso M, Jansson PA, Xu, M.; Bi, Y.; Xu, Y.; Yu, B.; Huang, Y.; Gu, L.; Wu, Y.; Zhu, X.; Li, M.; Wang, T.; Song, A.; Hou, J.; Li, X.; Ning, G. Combined effects of 19 common variations on type 2 diabetes in Chinese: results from two community-based studies. PLoS One. 2010, 17, e14022.

Chimenti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, Znt8, localized into insulin secretory granules. Diabetes. 2004, 53, 2330-7.

Chimenti, F.; Favier, A.; Seve, M. Znt8, a pancreatic beta-cell-specific zinc transporter. Biomol. 2005, 18, 313-7.

Pound, L.D.; Sarkar, S.A.; Benning, R.K.; Wang, Y.; Suwanchikul, A.; Shladov, M.K.; Printz, R.L.; Oeser, J.K.; Lee, C.E.; Piston, D.W.; McGuinness, O.P.; Hutton, J.C.; Powell, D.R.; O’Brien, R.M. Deletion of the mouse Slc30a8 gene encoding zinc transporter-8 results in impaired insulin secretion. Biochem J., 2009, 421, 371-6.

Nicolson, T.J.; Bellomo, E.A.; Wijeskarana, N.; Loder, M.K.; Baldwin, J.M.; Guilkhandanyan, A.V.; Koshkin, V.; Tarasov, A.I.; Carzaniga, R.; Kronenberger, K.; Tanje, T.K.; da Silva, Xavier, G.; Libert, S.; Rocheford, T.; Schieferman, R.; Stetsuk, V.; Ravassard, P.; Parker, H.; Gribble, F.M.; Reimann, F.; Sladek, R.; Hughes, J.; Johnson, S.J.; Porh, M.; Maserbou, M.; Burcelin, R.; Baldwin, S.A.; Liu, M.; Lara-Lemus, R.; Arvan, P.; Schutt, F.C.; Wheeler, M.B.; Chimenti, F.; Rutter, G.A. Insulin storage and glucose homeostasis in mice null for the granule zinc transporter Znt8 and studies of the type 2 diabetes-associated variants. Diabetes., 2009, 58, 2070-83.

Xiang, J.; Li, X.Y.; Xu, M.; Hong, J.; Huang, Y.; Tan, J.R.; Lu, X.; Dai, M.; Yu, B.; Ning, G. Zinc transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J Clin Endocrinol Metab., 2008, 93, 4107-12.

Boesgaard TW, Zilinskaite J, Vänttinen M, Laakso M, Jansson PA, Xu, M.; Bi, Y.; Xu, Y.; Yu, B.; Huang, Y.; Gu, L.; Wu, Y.; Zhu, X.; Li, M.; Wang, T.; Song, A.; Hou, J.; Li, X.; Ning, G. Combined effects of 19 common variations on type 2 diabetes in Chinese: results from two community-based studies. PLoS One. 2010, 17, e14022.

Chimenti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, Znt8, localized into insulin secretory granules. Diabetes. 2004, 53, 2330-7.

Chimenti, F.; Favier, A.; Seve, M. Znt8, a pancreatic beta-cell-specific zinc transporter. Biomol. 2005, 18, 313-7.

Pound, L.D.; Sarkar, S.A.; Benning, R.K.; Wang, Y.; Suwanchikul, A.; Shladov, M.K.; Printz, R.L.; Oeser, J.K.; Lee, C.E.; Piston, D.W.; McGuinness, O.P.; Hutton, J.C.; Powell, D.R.; O’Brien, R.M. Deletion of the mouse Slc30a8 gene encoding zinc transporter-8 results in impaired insulin secretion. Biochem J., 2009, 421, 371-6.

Nicolson, T.J.; Bellomo, E.A.; Wijeskarana, N.; Loder, M.K.; Baldwin, J.M.; Guilkhandanyan, A.V.; Koshkin, V.; Tarasov, A.I.; Carzaniga, R.; Kronenberger, K.; Tanje, T.K.; da Silva, Xavier, G.; Libert, S.; Rocheford, T.; Schieferman, R.; Stetsuk, V.; Ravassard, P.; Parker, H.; Gribble, F.M.; Reimann, F.; Sladek, R.; Hughes, J.; Johnson, S.J.; Porh, M.; Maserbou, M.; Burcelin, R.; Baldwin, S.A.; Liu, M.; Lara-Lemus, R.; Arvan, P.; Schutt, F.C.; Wheeler, M.B.; Chimenti, F.; Rutter, G.A. Insulin storage and glucose homeostasis in mice null for the granule zinc transporter Znt8 and studies of the type 2 diabetes-associated variants. Diabetes., 2009, 58, 2070-83.

Xiang, J.; Li, X.Y.; Xu, M.; Hong, J.; Huang, Y.; Tan, J.R.; Lu, X.; Dai, M.; Yu, B.; Ning, G. Zinc transporter-8 gene (SLC30A8) is associated with type 2 diabetes in Chinese. J Clin Endocrinol Metab., 2008, 93, 4107-12.

Boesgaard TW, Zilinskaite J, Vänttinen M, Laakso M, Jansson PA, Xu, M.; Bi, Y.; Xu, Y.; Yu, B.; Huang, Y.; Gu, L.; Wu, Y.; Zhu, X.; Li, M.; Wang, T.; Song, A.; Hou, J.; Li, X.; Ning, G. Combined effects of 19 common variations on type 2 diabetes in Chinese: results from two community-based studies. PLoS One. 2010, 17, e14022.

Chimenti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, Znt8, localized into insulin secretory granules. Diabetes. 2004, 53, 2330-7.

Chimenti, F.; Favier, A.; Seve, M. Znt8, a pancreatic beta-cell-specific zinc transporter. Biomol. 2005, 18, 313-7.
with metformin treatment response in type 2 diabetes: a replication and meta-analysis of five cohorts. Diabetologia, 2012, 55, 1971-7.

Kilpelaïnen, T.O.; Qi, L.; Brage, S.; Sharp, S.J.; Sonestedt, E.; Demerath, E.; Ahmad, T.; Mora, S.; Kaakinen, M.; Sandholt, CH.; Holzapfel, C.; Autenrieth, C.S.; Hyppönen, E.; Cauchi, S.; He, M.; Kovanlik; Z.; Kumari, M.; Stančáková, A.; Tan, J.T.; Mangino, M.; Timpson, N.J.; Song, Y.; Zillikens, M.C.; Jablonski, K.A.; Garcia, M.E.; Johansson, S.; Bragg-Gresham, J.L.; Wu, Y.; van Vliet-Oostapchouk, J.V.; Onland-Moret, N.C.; Zimmermann, E.; Rivera, N.V.; Tanaka, T.; Stringham, H.M.; Silbernagel, G.; Kanoni, S.; Feitoza, M.F.; Snitker, S.; Ruiz, J.R.; Metter, J.; Larrad, M.T.; Alatay, M.; Hakonen, M.; Amin, N.; Cavalcanti-Proenca, C.; Gronvall, A.; Hallmans, G.; Jansson, J.O.; Koh, J.; Kähönen, M.; Lutsey, P.L.; Nolan, J.J.; Pala, L.; Pedersen, S.; Perséus, L.; Renström, F.; Scott, R.A.; Shungin, D.; Sovio, U.; Tammelin, T.H.; Rönnemaa, T.; Lakka, T.A.; Uusitupa, M.; Rios, M.S.; Fernucci, L.; Bouchard, C.; Meirhaeghe, A.; Fu, M.; Walker, M.; Borecki, I.B.; Dedoussis, G.V.; Fritsche, A.; Ohlsson, C.; Boehnke, M.; Bandinelli, S.; van Duijn, C.M.; Ebrahim, S.; Lawlor, D.A.; Gudnason, V.; Harris, T.B.; Sørensen, T.I.; Mohlke, K.L.; Hofman, A.; Uitterlinden, A.G.; Tuomilehto, J.; Lehtimäki, T.; Raitakari, O.; Isomaa, B.; Njølstad, P.R.; Florez, J.C.; Liu, S.; Kähönen, M.; Lutsey, P.L.; Nolan, J.J.; Palla, L.; Pedersen, O.; Qi, L.; Chatterjee, N.; Hu, F.B.; Kraft, P. Gene-environment interactions in genome-wide association studies: a comparative study of tests applied to empirical studies of type 2 diabetes. Am. J. Epidemiol., 2012, 175, 191-202.

Qi, L.; Cornellis, M.C.; Zhang, C.; van Dam, R.M.; Hu, F.B. Genetic predisposition, western dietary pattern, and risk of type 2 diabetes in the Nurses’ Health Study and Health Professionals Follow-up Study. Diabetes Care, 2010, 33, 1453–58.

Brix, T.H.; Kyvik, K.O.; Christensen, K.; Hedingøs, L. Evidence for a major role in heredity in Graves’ disease: a population-based study of two Danish twin cohorts. J Clin Endocrinol Metab., 2011, 86, 930-4.

Brix, T.H.; Kyvik, K.O.; Hedingøs, L. What is the evidence of genetic factors in the etiology of Graves’ disease? A brief review. Thyroid, 1998, 8, 727.

Zeitlin, A.A.; Simmonds, M.J.; Gough, S.C. Genetic developments in autoimmune thyroid disease: an evolutionary process. Clin Endocrinol (Oxf), 2008, 68, 671-82.

Schleusener, H.; Schernthaner, G.; Mayr, W.R.; Kotulla, P.; Hofbauer, H.; Götting, G.; Weiss, K.W. HLA-DR3 and HLA-DR5 associated thyrotoxicosis—two different types of toxic diffuse goiter. J Clin Endocrinol Metab., 1983, 56, 781–785.

Weetman, A.P.; Zhang, L.; Webb, S.; Shine, B. Analysis of HLA-DQA1 and HLA-DPB1 alleles in GD by oligonucleotide probing of enzymatically amplified DNA. Clin Endocrinol (Oxf), 1990, 33, 65–71.

Gu, L.Q.; Zhu, W.; Zhao, S.X.; Zhao, L.; Zhang, M.J.; Cui, B.; Song, H.D.; Ning, G.; Zhao, Y.J. Clinical associations of the genetic variants of CTLA-4, Tg, TSHR, PTN22, PTN12 and FCRL3 in patients with Graves' disease. Clin Endocrinol (Oxf), 2010, 72, 248-55.

Blodow, O.I.; Barrett, J.; Simmonds, M.J.; Newby, P.R.; McCabe, C.J.; Bruce, C.K.; Kysela, B.; Carr-Smith, J.D.; Brix, T.; Hunt, P.J.; Wiersinga, W.M.; Hedegøs, L.; Connell, J.; Wass, J.A.; Franklyn, J.A.; Weetman, A.P.; Haward, J.M.; Gough, S.C. Association of the thyroid stimulating hormone receptor gene (TSHR) with Graves’ disease. Hum. Mol. Genet., 2009, 18, 1704–1713.

Hiratani, H.; Bowden, D.W.; Ikekami, S.; Shirasawa, S.; Shimizu, A.; Iwata, Y.; Akamizu, T. Multiple SNPs in intron 7 of thyrotropin receptor are associated with Graves’ disease. J Clin Endocrinol Metab., 2005, 90, 2989–2993.

Velaga, M.R.; Wilson, V.; Jennings, C.E.; Owen, C.J.; Herington, S.; Donaldson, P.T.; Ball, S.G.; James, R.A.; Quinton, R.; Perros, P.H.; Pearce, S.; Wiersinga, W.M.; Siscovick, D.S. The variant codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves’ disease. J Clin Endocrinol Metab., 2004, 89, 5862–5865.

Vaidya, B.; Imrie, H.; Perros, P.; Dickinson, J.; McCarthy, M.J.; Kendall-Taylor, P.; Pearce, S.H. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphism confers susceptibility to thyroid associated orbitopathy. Lancet, 1995, 349, 743–744.

Wellcome Trust Case Control Consortium; Australo-Anglo-Amerian Spondylitis Consortium (TASC), Burton, P.R.; Clayton, D.G.; Cardon, L.R.; Craddock, N.; Deloukas, P.; Duncanson, A.; Kwiatkowski, D.P.; McCarthy, M.I.; Owuahwu, W.H.; Samani, N.J.; Todd, J.A.; Donnelly, P.; Barrett, J.C.; Davey, D.; Easton, D.; Evans, D.M.; Leung, H.T.; Marchini, J.L.; Morris, A.P.; Spencer, C.C.; Tobin, M.D.; Attwood, A.P.; Boorman, J.P.; Cant, B.; Everson, U.; Hussey, J.M.; Jolley, J.D.; Knight, A.S.; Koch, K.; Meech, E.; Nutland, S.; Prowse, C.; Stevens, H.E.; Taylor, N.C.; Walters, G.R.; Walker, N.M.; Watkins, N.A.; Winzer, T.; Jones, R.W.; Ardèche, W.L.; Ring, S.M.; Strachan, D.P.; Pembre, M.; Breen, G.; St Clair, D.; Caesar, S.; Gordon-Smith, K.; Jones, L.; Pearson, C.; Green, F.; Grozeva, D.; Hamshere, M.L.; Holmans, P.A.; Jones, I.R.; Kirov, G.; Moskvina, V.; Nikolov, I.; O’Donovan, M.C.; Owen, J.M.; Collier, D.A.; Elkin, A.; Farmer, A.; Williams, R.; McGuffin, P.; Young, A.H.; Ferrier, I.N.; Ball, S.G.; Balfourm, A.J.; Barrett, J.H.; Bishop, T.D.; Iles, M.M.; Maqbool, A.; Yuldasheva, N.; Hall, A.S.; Braund, P.S.; Dixon, R.J.; Mangino, M.; Stevens, S.; Thompson, J.R.; Bredin, P.; Tremelling, M.; Parkes, M.; Drummond, H.; Lees, C.W.; Nimmor, E.R.;
[125] Gu, X.J.; Cui, B.; Zhao, Z.F.; Chen, H.Y.; Li, X.Y.; Wang, S.; Ning, G.; Zhao, Y.J. Association of the interleukin (IL)-16 gene polymorphisms with Graves’ disease. *Clin Immunol.*, 2008, 127, 298-302.

[126] Smyth, D.J.; Cooper, J.D.; Bailey, R.; Burren, O.; Smink, L.J.; Guja, C.; Ionescu-Tirgoviste, C.; Widmer, B.; Dunger, D.B.; Savage, D.A.; Walker, N.M.; Clayton, D.G.; Todd, J.A. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet.* 2006, 38, 617-9.

[127] Nejentsev, S.; Walker, N.; Riches, D.; Egholm, M.; Todd, J.A. Rare variants of IFIH1, a gene implicated in antiviral responses protect against type 1 diabetes. *Science.* 2009, 324, 387-9.

[128] Sutherland, A.; Davies, J.; Owen, C.J.; Vaikkakara, S.; Walker, C.; Cheetham, T.D.; James, R.A.; Perros, P.; Donaldson, P.T.; Cordell, H.J.; Quinton, R.; Pearce, S.H. Genomic polymorphism at the interferon-induced helicase (IFIH1) locus contributes to Graves’ disease susceptibility. *J Clin Endocrinol Metab.* 2007, 92, 3338-41.

[129] Robinson, T.; Kariuki, S.N.; Franek, B.S.; Kumabe, M.; Kumar, A.A.; Badaracco, M.; Mikolaitis, R.A.; Guerrero, G.; Utset, T.O.; Drevlow, B.E.; Zaacks, L.S.; Grober, J.S.; Cohen, L.M.; Kirou, K.A.; Crow, M.K.; Jolly, M.; Niewold, T.B. Autoimmune disease risk variant of IFIH1 is associated with increased sensitivity to IFN-α and serologic autoimmunity in lupus patients. *J Immunol.* 2011, 187, 1298-303.

[130] Zhao, Z.F.; Cui, B.; Chen, H.Y.; Wang, S.; Li, I.; Gu, X.J.; Qi, L.; Li, X.Y.; Ning, G.; Zhao, Y.J. The A946T polymorphism in the interferon-induced helicase gene does not confer susceptibility to Graves’ disease in Chinese population. *Endocrine.* 2007, 32, 143-7.

[131] Ban, Y.; Tozaki, T.; Taniyama, M.; Nakano, Y.; Ban, Y.; Hirano, T. Genomic polymorphism in the interferon-induced helicase (IFIH1) gene does not confer susceptibility to autoimmune thyroid disease in the Japanese population. *Horm Metab Res.* 2010, 42, 70-2.