Insights into the genetic basis of type 2 diabetes

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ABSTRACT

Type 2 diabetes is one of the most common complex diseases, of which considerable efforts have been made to unravel the pathophysiological mechanisms. Recently, large-scale genome-wide association (GWA) studies have successfully identified genetic loci robustly associated with type 2 diabetes by searching susceptibility variants across the entire genome in an unbiased, hypothesis-free manner. The number of loci has climbed from just three in 2006 to approximately 70 today. For the common type 2 diabetes-associated variants, three features have been noted. First, genetic impacts of individual variants are generally modest; mostly, allelic odds ratios range between 1.06 and 1.20. Second, most of the loci identified to date are not in or near obvious candidate genes, but some are often located in the intergenic regions. Third, although the number of loci is limited, there might be some population specificity in type 2 diabetes association. Although we can estimate a single or a few target genes for individual loci detected in GWA studies by referring to the data for experiments in vitro, biological function remains largely unknown for a substantial part of such target genes. Nevertheless, new biology is arising from GWA study discoveries; for example, genes implicated in β-cell dysfunction are over-represented within type 2 diabetes-associated regions. Toward translational advances, we have just begun to face new challenges – elucidation of multifaceted (i.e., molecular, cellular and physiological) mechanistic insights into disease biology by considering interaction with the environment. The present review summarizes recent advances in the genetics of type 2 diabetes, together with its realistic potential. (J Diabetes Invest, doi: 10.1111/jdi.12067, 2013)

KEY WORDS: Genetics, Plasma glucose, Type 2 diabetes

INTRODUCTION

Genetic, environmental and demographic factors, and their interaction, determine an individual’s risk for type 2 diabetes; its heritability has been estimated as approximately 25%. Despite considerable concerted efforts over the past 15 years, it is only in the past 5 years that substantial progress has been made in identifying genetic variants robustly associated with type 2 diabetes, largely as a result of technological advances. In particular, the advent of genome-wide association (GWA) studies involving several thousands of samples has facilitated this progress. This approach is to search for susceptibility variants across the entire genome in an unbiased, hypothesis-free manner.

The alleles or mutations responsible for rare monogenic forms of diabetes, including maturity onset diabetes of the young (MODY), were relatively easily identified through family-based linkage analyses. These discoveries then led to molecular diagnostics of the diseases with demonstrable prognostic and therapeutic relevance. Although similar approaches have been applied to common forms of type 2 diabetes, the multifactorial nature has rendered the identification of genetic variants an enormous challenge. In consideration of its low penetrance, it was proposed that association analyses in large unrelated sample sets should be more powerful in susceptibility gene discovery for type 2 diabetes than family-based linkage approaches.

The association signal can be detected only if one examines the causal variant itself or a nearby marker with which it is tightly correlated; therefore, researchers were obliged to direct their attention to particular candidate gene variants of interest until the advent of GWA studies. Among a number of candidate genes thus interrogated, common coding variants in PPARG and KCNJ11/ABCC8 were shown to be associated with type 2 diabetes. In 2006, without prior knowledge of biology, TCF7L2 was first discovered to be a susceptibility gene after systematic association analysis across a 10.5-Mb region of previously reported linkage. Subsequently, in 2007, the first wave of GWA studies identified six novel loci in populations of European descent. Successive rounds of GWA studies and meta-analyses have brought the number of confirmed common variants associated with type 2 diabetes to approximately 70, and have also discovered >40 common variants influencing normal physiological variation in continuous glycemic measures (e.g., fasting glucose and insulin) to date.
In the present article, the evidence in favor of a genetic basis for type 2 diabetes, focusing specifically on the DNA sequence variants that have been implicated in risk predisposition and the assumed clinical implications of genomics, are reviewed.

**DISCOVERY OF SUSCEPTIBILITY GENE VARIANTS FOR TYPE 2 DIABETES**

Largely through GWA studies, the number of loci robustly implicated in type 2 diabetes risk; that is, those that have attained a genome-wide significance level \( (P < 5 \times 10^{-8}) \) and also have been repeatedly validated in independent samples, has climbed from just three – PPARG, KCNJ11/ABCC8 and TCF7L2 – in 2006 to approximately 70 today (Table 1).

GWA studies are based on the principle of linkage disequilibrium (LD) at the population level. LD is the phenomenon in which alleles of two different loci (or genes) occur together more often than would be predicted by chance, indicating that the two alleles are physically close on the DNA strand. LD is created by evolutionary forces, such as mutation, drift and selection, and is broken down by recombination. A set of single nucleotide polymorphisms (SNPs) and mutations in strong LD tend to be inherited together by forming haplotypes. On carrying out GWA studies, we normally assay not all SNPs, but a subset of SNPs that can be chosen by considering the LD structure in a particular chromosomal region. If the pattern and strength of LD between the SNPs and mutations in the target region are similar, and the causal variants are commonly present among different populations (or different ethnic groups), the association in question is detectable at the SNP markers across the populations.

For the common type 2 diabetes-associated variants, three features have to be noted. First, genetic impacts of individual variants or loci are generally modest; that is, allelic odds ratios (ORs) for type 2 diabetes are mostly in the range between 1.06 and 1.20, apart from several loci including TCF7L2 (Figure 1). This reflects the necessity of a large sample size in meta-analysis to expose variants of smaller effect and more extreme risk allele frequency. Collectively, the most strongly associated variants at individual loci are estimated to explain approximately 10% of familial aggregation of type 2 diabetes\(^{15}\). Second, most of the variants identified to date are not in or near obvious candidate genes, but some are often located in the intergenic regions. This leads to the difficulty in estimating causal transcript; that is, the transcript responsible for mediating the effect of the associated variants, according to the location of association signals as discussed later. Third, although the number of variants is limited, there might be some population specificity in type 2 diabetes association. This has to be carefully interpreted by considering several possibilities; for example, the lack of power as a result of insufficient sample size and cross-population differences in LD structure\(^{34}\). Although the majority of common variants have a consistent effect on the risk of type 2 diabetes across multiple ethnic groups\(^{35}\), some variants appear to exert more pronounced genetic effects in specific ethnic groups; for example, the association at KLF14 is prominent in Europeans\(^{15,36,37}\), but not in East\(^{20}\) and South\(^{19}\) Asians.

Notably, it has been reported that most of the risk alleles for type 2 diabetes loci share a consistent pattern of decreasing frequencies along human migration from sub-Saharan Africa to East Asia\(^{37}\). Such differential frequencies are hypothesized to be caused by the promotion of energy storage and usage appropriate to environments and inconsistent energy intake.

Along with the GWA meta-analyses in individual populations, ‘transethnic’ meta-analysis is currently being carried out, and will allow for a better chance to show novel susceptibility loci and pathophysiological pathways of type 2 diabetes, and might also facilitate the fine mapping of common causal variants by utilizing ethnic differences in LD structure\(^{38}\).

**OVERLAP OF ASSOCIATION BETWEEN TYPE 2 DIABETES AND GLYCEMIC MEASURES**

GWA studies have also identified a number of genetic variants influencing glycemic measures (Tables S1–S3). When we focused on genome-wide significant \( (P < 5 \times 10^{-8}) \) association signals, we found that they partially overlapped between type 2 diabetes\(^{9,26}\) and the glycemic measure traits – fasting glucose and insulin/homeostatic model assessment (HOMA)-B (a parameter reflecting \( \beta \)-cell function) and glycated hemoglobin (HbA\(_{1c}\)) levels in the non-diabetic population\(^{12,27–32}\) (Figure 2). As has been pointed out\(^{39}\), common variants associated with fasting plasma glucose levels do not necessarily influence the risk of type 2 diabetes and, by contrast, those associated with type 2 diabetes do not necessarily influence normal variation in fasting plasma glucose levels (48%, 11 of 23 loci overlapped), suggesting that a different set of genes influence physiological and pathophysiological variation in glucose homeostasis. Furthermore, from the viewpoint of disease mechanism and classification, of interest is the fact that there is some disparity in the list of associated loci between type 2 diabetes and fasting insulin/HOMA-B (45%, 9 of 20 loci overlapped), and between type 2 diabetes and HbA\(_{1c}\) levels (38%, 5 of 13 loci overlapped). In the latter case, more than half of the detected loci likely influence HbA\(_{1c}\) levels through a non-glycemic pathway, erythrocyte biology (e.g., iron homeostasis\(^{31}\)).

**TRANSITION FROM ASSOCIATION SIGNAL TO CAUSAL MECHANISM**

Most loci associated with type 2 diabetes map to regulatory or intergenic regions of the genome, and in many cases the causal transcript remains undetermined. Surprisingly few of the genome-wide association signals have mapped near strong biological candidates. Nevertheless, at some loci, it is inferred, based on a combination of supportive data; for example, coding variants (in particular, non-synonymous SNPs), nearby biological candidates and cis expression quantitative trait loci (cis-eQTLs), which regulate expression levels of messenger ribonucleic acid. Here, eQTLs that map to the approximate location of their
## Table 1 | List of susceptibility loci for type 2 diabetes with significant evidence for association (P < 5E-8)

| Mapped gene(s)* | Reported gene(s)* | Lead SNP | Region | Pos (GRCh37) | Risk allele | RAF in controls | P-value | Reported study† | OR [95% CI] | First-reported ethnic group |
|----------------|-------------------|----------|--------|--------------|-------------|-----------------|---------|----------------|-------------|---------------------------|
| NOTCH2/ADAM30 | NOTCH2 | rs10923931 | 1p12 | 120517959 | T | 0.11 | 4E-08 | Zeggini et al. | 1.13 [1.08-1.17] | European descent |
| RPL31P13/PROX1 | PROX1 | rs340874 | 1q32.3 | 214159256 | C | 0.54 | 7E-10 | Dupuis et al. | 1.07 [1.05-1.09] | European descent |
| GCKR | GCKR | rs780094 | 2p23.3 | 27741237 | C | 0.60 | 1E-09 | Dupuis et al. | 1.06 [1.04-1.08] | European descent |
| THADA | THADA | rs7578597 | 2p21 | 45732823 | T | 0.90 | 1E-09 | Zeggini et al. | 1.15 [1.10-1.20] | European descent |
| EIF3F/PLC11A | PLC11A | rs243021 | 1p16.1 | 6058481 | A | 0.48 | 3E-15 | Voight et al. | 1.08 [1.06-1.10] | European descent |
| TMEM163 | TMEM163 | rs988541 | 2q23.1 | 135429288 | G | 0.86 | 6E-12 | Tabassum et al. | 1.56 [1.38-1.77] | South Asian |
| RND3/FABP5P10 | RND3 | rs7560163 | 2q23.3 | 151637936 | C | 0.86 | 7E-09 | Palmer et al. | 1.33 [1.19-1.49] | African American |
| ZBED3/ADAM30 | ADAM30 | rs10923931 | 1p12 | 120517959 | T | 0.11 | 4E-08 | Zeggini et al. | 1.13 [1.08-1.17] | European descent |
| GCKR | GCKR | rs780094 | 2p23.3 | 27741237 | C | 0.60 | 1E-09 | Dupuis et al. | 1.07 [1.05-1.09] | European descent |
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| TMEM163 | TMEM163 | rs988541 | 2q23.1 | 135429288 | G | 0.86 | 6E-12 | Tabassum et al. | 1.56 [1.38-1.77] | South Asian |
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| Gene(s)* | Lead SNP | Region | Pos (GRCh37) | Risk allele | RAF in controls | p-value | Reported study† | OR [95% CI] | First-reported ethnic group‡ |
|---------|----------|--------|-------------|-------------|----------------|---------|----------------|-------------|-----------------------------|
| TCF7L2  | TCF7L2   | rs7903146 | 10q25.2     | 114758349   | T              | 0.29    | Perry et al.¹² | 1.58 [1.47-1.68] | European descent           |
| GRK5    | GRK5     | rs10886471 | 10q26.11    | 121149403   | C              | 0.78    | Li et al.¹⁶     | 1.12 [1.08-1.16] | Chinese                     |
| KCNQ1   | KCNQ1    | rs21362   | 11p15.5     | 2691471     | G              | 0.52    | Voight et al.¹⁵ | 1.08 [1.06-1.10] | European descent           |
| KCNQ1   | KCNQ1(OT1)| rs2237895 | 11p15.4     | 2857194     | C              | 0.33    | Tsai et al.¹³   | 1.29 [1.19-1.40] | European/Han Chinese       |
| KCN11/ABCC8 | KCN11   | rs5219    | 11p15.1     | 17406830    | C              | 0.40    | Zeggini et al.³³ | 1.14 [1.10-1.19] | European descent           |
| ARAP1   | ARAP1    | rs1552224 | 11q13.4     | 72433098    | A              | 0.87    | Voight et al.¹⁵ | 1.14 [1.11-1.17] | European descent           |
| RPS3AP2/MTNR1B | MTNR1B | rs1387153 | 11q26.11    | 92673828    | T              | 0.28    | Voight et al.¹⁵ | 0.90 [0.86-0.94] | European descent           |
| KLHDC5  | KLHDC5   | rs10842994| 12p15.5     | 27965150    | C              | 0.80    | Morris et al.²⁴ | 1.10 [1.06-1.13] | European descent           |
| KCNQ1   | KCNQ1    | rs231362  | 11p15.5     | 2691471     | G              | 0.52    | Zeggini et al.³³ | 1.14 [1.10-1.19] | European descent           |
| KCNQ1   | KCNQ1(OT1)| rs2237895 | 11p15.4     | 2857194     | C              | 0.33    | Tsai et al.¹³   | 1.29 [1.19-1.40] | European/ Han Chinese      |
| RAFI    | RAFI     | rs5219    | 11p15.1     | 17406830    | C              | 0.40    | Zeggini et al.³³ | 1.14 [1.10-1.19] | European descent           |

*Mapped and reported genes are arbitrarily denoted according to those shown in A Catalog of Published Genome-Wide Association Studies (http://www.genome.gov/gwastudies/index.dfm?pageid=26525384#searchForm). When >1 studies have reported genome-wide significant association at the relevant loci, we select one for each locus according to: (i) an ethnic group where the association was first reported; and (ii) the largest study in a given ethnic group. At KCNQ1, although the association was first reported in Japanese (ref. 10,11), it is not included in A Catalog of Published Genome-Wide Association Studies and we show a Chinese study (ref. 13) alternatively for reference. On chromosome 3p25.2, although it did not attain a genome-wide significance level in each study, the reproducible association has been shown for a candidate gene, PPARG, rs13081389, which is in linkage disequilibrium (r² = 0.536) with rs1801282 (P12A, PPARG) in HapMap CEU. RAF, risk allele frequency; SNP, single nucleotide polymorphism. At KCNQ1, significant association was also reported in European-descent populations (ref. 15), which is not in linkage disequilibrium with the one-first reported in Japanese (ref. 10,11).
Elements (ENCODE) Consortium40, which will help identify candidates and released to the public by the Encyclopedia of DNA loci for type 2 diabetes (T2D), which have shown significant

technological methods for identifying SNPs that overlap regulatory elements, such as transcription factor binding sites, are required. High-throughput functional assays (e.g., ChIP-seq40) can experimentally detect such sites, which can support particular coding sequence variants as causal. For example, the type 2 diabetes association signal on chromosome 2p23 was shown to derive from a common non-synonymous SNP rs1260326, P446L, in GCKR, which is one of 17 genes mapped to the 420-kb interval of association in tight LD44. In addition to the strong candidacy of GCKR in glucose metabolism, functional characterization in vitro showed that P446L could explain a mutational mechanism for the reported counterintuitive association with increased triglycerides and reduced glucose levels on 2p23.

NEW BIOLOGY ARISING FROM GWA STUDY DISCOVERIES

β-Cell Dysfunction

Regarding the pathogenesis of type 2 diabetes, there has been a long-standing debate over the relative roles of insulin secretory defects and insulin resistance. In this context, of interest is the fact that a large part of the type 2 diabetes-risk loci exert their primary effects on disease risk through reduced insulin secretion rather than increased insulin resistance in the general population15,45. Genes implicated in cell-cycle regulation are overrepresented within type 2 diabetes-associated regions; this is consistent with the notion that control of β-cell mass is a key component of disease risk15.

However, when we look at genetic loci associated with proinsulin levels, there are divergent directions of association between type 2 diabetes risk and proinsulin levels46. Similar to the relationship between type 2 diabetes and fasting plasma glucose39, the loci are partially overlapped between the traits. Among the loci associated with proinsulin, three loci – TCF7L2, C2CD4A and SLC30A8 – were significantly associated with type 2 diabetes in a manner consistent with established epidemiological relationships; that is, higher proinsulin levels are associated with impaired β-cell function, insulin resistance and risk of type 2 diabetes17,48. In contrast, one locus – ARAP1 – showed trait association in a counterintuitive direction. Thus, both disproportionate elevations and reductions in proinsulin can indicate β-cell dysfunction at individual loci46.

Efforts to show that the genes mapping close to susceptibility loci are enriched for particular pathways or processes have not been particularly rewarding so far, apart from a few instances (e.g., cell-cycle regulation)15. This indicates the possibility that type 2 diabetes is highly heterogeneous, and/or existing biological knowledge is as yet insufficient to capture key fundamental aspects of its pathophysiology through database search. Although it is challenging to establish the biological mechanism at each associated locus, a combination of experimental and bioinformatic approaches will help understand the broad

gene-of-origin are referred to as cis-eQTLs. Although eQTLs can be used to identify the downstream targets that are likely to be affected by associations detected in GWA studies, they still rely on genotyping methods, and therefore point to regions of LD rather than to individual SNPs. Accordingly, independent methods for identifying SNPs that overlap regulatory elements, such as transcription factor binding sites, are required. High-throughput functional assays (e.g., ChIP-seq40) can experimentally detect functional chromosomal regions, such as transcription factor binding sites, and the presence of SNPs in these regions can lead to differences in transcription factor binding between individuals41. Recently, the relevant experimental datasets have been generated and released to the public by the Encyclopedia of DNA Elements (ENCODE) Consortium40, which will help identify functional SNPs associated with type 2 diabetes and their potential causal transcript.

Although we can estimate a single or a few target genes for individual loci by referring to the data for experiments in vitro; for example, the ENCODE data, biological function remains largely unknown for a substantial part of such target genes. So far, just 17% (12 of 70 loci) have been proven to show type 2 diabetes-related phenotypes in their knock-out mice experiments in vivo (Table 2). Besides, three target genes – GCK, HNF1B and HNF4A – overlap with causal genes for MODY, where GCK15 and HNF4A knock-out mice show hyperglycemia and glucose intolerance, respectively.

Despite significant enrichment for regulatory (and non-coding) sequence variants in disease-associated regions, there are some cases where substantial statistical and biological evidence can support particular coding sequence variants as causal. For example, the type 2 diabetes association signal on chromosome 2p23 was shown to derive from a common non-synonymous SNP rs1260326, P446L, in GCKR, which is one of 17 genes mapped to the 420-kb interval of association in tight LD44. In addition to the strong candidacy of GCKR in glucose metabolism, functional characterization in vitro showed that P446L could explain a mutational mechanism for the reported counterintuitive association with increased triglycerides and reduced glucose levels on 2p23.

Figure 1 | Risk allele frequencies and effect sizes of known susceptibility loci for type 2 diabetes (T2D), which have shown significant (P ≤ 5 × 10−8) association. Gene names are attached to the loci with odds ratio (OR) ≥ 1.2; they are not necessarily proven to be causal, but represent candidate transcripts on the basis of location and biological plausibility. Although a large part of associated loci were originally identified in populations of European descent, some were exclusively found or first reported in non-European populations, which are differentially colored in the figure.

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processes of disease pathogenesis by integrating a number of loci identified in the unbiased genome-wide approach.

**Epigenetics**

The evidence for familial aggregation of type 2 diabetes comes from a number of epidemiological studies; parental type 2 diabetes has been reported to give rise to an approximately three-fold increase in disease risk in the offspring.\(^49\) The familial aggregation might reflect epigenetic mechanisms, such as the fetal origins hypothesis,\(^50\) in addition to genetic influences and shared family environment. As an approach to addressing this issue, Kong *et al.*\(^51\) examined the impact of parental origin on disease associations in previous GWA studies and identified parental-origin-specific associations with type 2 diabetes at variants located in the known imprinted region on chromosome 11p15. Here, the allele that confers risk when paternally inherited (odds ratio [OR] = 1.41, \(P = 4.3 \times 10^{-9}\)) is protective when maternally transmitted (OR = 0.87, \(P = 0.02\)) and also correlated with decreased methylation of CTCF-binding site at 11p15.\(^51\)

A growing body of data has established that the molecular basis of metabolic programming involves DNA methylation and histone modifications.\(^52\) To date, relatively few studies have explored the epigenetic component to the development of type 2 diabetes, with most of them focusing on the methylation status of selected C-phosphate-G (CpG) sites in candidate genes. Because of the relatively high cost and procedural complexity of epigenetic analysis, as well as tissue differences in methylation profile, there are few convincing results that support the contribution of epigenetics to disease pathogenesis at present. To make the situation intricate, it has been reported that epigenetic effects might, at least in part, be driven by underlying variation in the DNA sequence.\(^53\) That is, methylation levels at a CpG site in the first intron of *FTO*, one of the principal risk loci for obesity and type 2 diabetes, were correlated with a genotype at nearby disease-associated SNPs. This could be simply regarded as a subset of genetic association signals at which the downstream effects are mediated by genotype-dependent changes in local DNA methylation. However, it remains unclear whether methylation by

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**Figure 2** A schematic representation of intertrait difference (or overlapping) for 41 diabetes-related trait associated loci that have been reported in meta-analyses of genome-wide association studies.\(^12\)\(^27\)\(^-\)\(^32\). The traits include fasting plasma glucose (FPG), insulin and its related-traits (homeostasis model assessment of \(\beta\)-cell function (HOMA-B) and HOMA of insulin resistance), and glycated hemoglobin (HbA\(_1c\)). Here, an associated locus is assumed to overlap between the traits when \(P \leq 5 \times 10^{-8}\) was concordantly attained. Underlined are the loci that have shown significant \((P \leq 5 \times 10^{-8})\) association with type 2 diabetes; at three loci with asterisks – *ANK1*, *CDKL1* and *GRB14* – variants associated with individual traits are not in linkage disequilibrium \((r^2 < 0.3)\).
Table 2 | Genome-wide association study-identified positional candidate genes for type 2 diabetes, with supportive phenotypes observed in knock-out mice

| Gene   | MGI ID | Phenotypes observed in knock-out mice                                                                 | Reference (PMID no.)                                                                 | Other associated trait identified via GWA study* |
|--------|--------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------|
| GRB14  | 1355324| Improved glucose tolerance, insulin levels decreased, increased incorporation of glucose into glycogen in the liver and skeletal muscle of males. Both males and females showed a decrease in body size. | Cooney GJ, 2004 EMBO J (14749734)                                                  | Waist-hip ratio                                |
|        |        |                                                                                                      |                                                                                     | Blood pressure                                |
| IRS1   | 99454  | Impaired glucose tolerance, mild insulin and IGF-1 resistance; 50% reductions in body weight at birth and at 4 months-of-age. Homozygotes: lethal. | Araki E, 1994 Nature (7526222)                                                     | Visceral adipose tissue/subcutaneous adipose tissue ratio |
|        |        |                                                                                                      |                                                                                     | Adiponectin levels                             |
| PPARG  | 97747  | Heterozygotes: greater $\beta$-cell proliferation, enhanced leptin secretion, and resistance to high-fat diet-induced adipocyte hypertrophy and insulin resistance. | Kubota N, 1999 Molecular Cell (10549291)                                           | Plasminogen activator inhibitor type 1 levels |
| WFS1   | 1328355| Decreased pancreatic beta cells, impaired glucose tolerance, decreased body weight and abnormal behavior associated with increased sensitivity to stress. | Ishihara H, 2004 Hum Mol Genet (15056606); Riggs AC, 2005 Diabetologia (16215705) | N/A                                             |
| SLC30A8| 2442682| Reduced islet zinc levels, insulin levels decreased and glucose-stimulated insulin secretion decreased. | Lemaire K, 2009 Proc Natl Acad Sci USA (19706465)                                  | Asthma                                          |
| GLIS3  | 2444289| Postnatal lethality associated with neonatal diabetes and polycystic kidney disease.                 | Kang HS, 2009 Mol Cell Biol (19273592); Watanabe N, 2009 FEBS Lett (19481545)    | Type 1 diabetes                                |
| FTO    | 1347093| Body weight decreased, adipose tissue decreased and body fat decreased; metabolism increased, serum lipids increased and serum glucagon increased. | Fischer J, 2009 Nature (19234441)                                                 | Body mass index                                |
|        |        |                                                                                                      |                                                                                     | Waist circumference                            |
|        |        |                                                                                                      |                                                                                     | Osteoarthritis                                 |
|        |        |                                                                                                      |                                                                                     | Menarche                                       |
| MC4R   | 99457  | Hyperglycemia and weight gain.                                                                        | Huszar D, 1997 Cell (9019399)                                                     | Body mass index                                |
|        |        |                                                                                                      |                                                                                     | Waist circumference                            |
|        |        |                                                                                                      |                                                                                     | Osteoarthritis                                 |
| HNF4A  | 109128 | Nullizygous embryos: delayed growth and lethality. Conditional deletion in pancreatic beta cells: hyperinsulinemia and impaired glucose tolerance. | Gupta RK, 2005 J Clin Invest (15761495); Pearson ER, 2007 PLoS Med (17407387) | C-reactive protein                             |
|        |        |                                                                                                      |                                                                                     | Ulcerative colitis                             |
| GCKR   | 1096345| Reduced glucokinase protein levels and activity in the liver and altered glucose homeostasis.        | Farrelly D, 1999 Proc Natl Acad Sci USA (10588736)                                 | Total protein/albumin levels                   |
|        |        |                                                                                                      |                                                                                     | Sex hormone-binding globulin levels            |
|        |        |                                                                                                      |                                                                                     | Phospholipid levels                            |
|        |        |                                                                                                      |                                                                                     | Platelet counts                                |
|        |        |                                                                                                      |                                                                                     | C-reactive protein                             |
|        |        |                                                                                                      |                                                                                     | Crohn's disease                                |
|        |        |                                                                                                      |                                                                                     | Urate levels                                   |
|        |        |                                                                                                      |                                                                                     | Chronic kidney disease                         |
|        |        |                                                                                                      |                                                                                     | N/A                                             |
| GCK    | 1270854| Mild hyperglycemia in heterozygous mice and extreme hyperglycemia and embryonic to postnatal ethality in homozygous mice. | Bali D, 1995 J Biol Chem (7665557)                                               | Body mass index                                |
|        |        |                                                                                                      |                                                                                     | Birth weight                                   |
|        |        |                                                                                                      |                                                                                     | Crohn's disease                                |
| CDKAL1 | 1921765| Conditional deletion in pancreatic beta cells: impaired tRNA Lys modification, reduction of glucose-stimulated proinsulin synthesis. Global deletion: body weight decreased, glucose intolerance manifested after 20 weeks of high-fat diet. | Wei FY, 2011 J Clin Invest (21841312); Okamura T, 2012 PLoS One (23173044)       | Body mass index                                |
|        |        |                                                                                                      |                                                                                     | Birth weight                                   |
|        |        |                                                                                                      |                                                                                     | Crohn's disease                                |

*Phenotype traits, with which genome-wide association (GWA) studies identified significant association at the corresponding gene locus are listed, except for lipid and glucose-related traits. IGF-1, insulin-like growth factor 1; MGI, mouse genome informatics.
Itself constitutes the causal link between the FTO risk allele and type 2 diabetes.54.

### Pleiotropy

GWA studies of type 2 diabetes have provided substantial evidence of pleiotropy; the same variants are associated with multiple traits (Table 3), providing clues to the common biological pathways involved. For example, at ADCYS and CDKAL1, the birth weight-lowering allele was associated with a greater risk of type 2 diabetes55. This is consistent with the fetal insulin hypothesis56, that is, common genetic variation influencing insulin secretion or action, both in prenatal development and adult life, could partly explain epidemiological correlations between lower birth weight and type 2 diabetes. Here, of particular note is the fact that the type 2 diabetes risk allele at CDKAL1 also showed a significant association with coronary heart disease (CHD) risk (OR = 1.07) in the population of European-descent57, and the minor allele A of rs391300 is inversely associated with type 2 diabetes (OR = 0.78) in the Chinese population58; two SNPs near SRR are in LD ($r^2 = 0.552$ in the HapMap population of European ancestry and 0.588 in the HapMap population of East Asian ancestry). At another region on chromosome 9p21 near CDKN2A/B, a significant association has been identified for CHD60, as independent functional variants are likely to exist within this region and could be associated with individual diseases. Apart from these two loci, the results for associations between the individual diabetes-predisposing genetic variants and CHD risk appear to be inconsistent. A few recent studies, however, have shown that, when tested in aggregate using a genetic risk score, the overall genetic predisposition to type 2 diabetes is associated with an increased risk of CHD60-61.

### Table 3 | List of gene variants showing potential pleiotropic effects on type 2 diabetes and other traits

| Trait | Nearby gene(s) | Variant | LD coefficient, $r^2$ (HapMap panel) | Type 2 diabetes-associated SNP* | Effect on the trait | Reported study |
|-------|----------------|---------|--------------------------------------|---------------------------------|---------------------|---------------|
| Adiponectin levels | IRS1 | rs925735 | 0.648 (CEU) (JPT+CHB) | rs7578326 | ↓ | Dastani Z, 2012 PLoS Genet |
| Adiponectin levels | PEPA | rs731839 | 0.345 (CEU) 0.894 (JPT+CHB) | rs3786897 (East Asians) | ↓ | Dastani Z, 2012 PLoS Genet |
| Birthweight | ADCYS | rs9883204 | 0.782 (CEU) (JPT+CHB) | rs11708067 | ↓ | Freathy RM, 2010 Nat Genet |
| Birthweight | CDKAL1 | rs6931514 | 1.000 (CEU) (JPT+CHB) | rs7766070 | ↓ | Horikoshi M, 2012 Nat Genet |
| Height | IGFBP2 | rs720390 | 0.491 (CEU) (JPT+CHB) | rs4402960 | ↑ | Lango Allen H, 2010 Nature |
| Height | JAZF1 | rs1635852 | 1.000 (CEU) (JPT+CHB) | rs849134 | ↑ | Johansson A, 2008 Hum Mol Genet |
| Height | C2CD4A | rs7178424 | 0.422 (CEU) 0.082 (JPT+CHB) | rs7172432 (Japanese) | Unknown | Lango Allen H, 2010 Nature |
| Height | MC4R | rs17782313 | 0.813 (CEU) (JPT+CHB) | rs12970134 | ↑ | Lango Allen H, 2010 Nature |
| Type 1 diabetes | GLIS3 | rs7020673 | 0.902 (CEU) 0.705 (JPT+CHB) | rs7041847 (East Asians) | ↑ | Barrett JC, 2009 Nat Genet |
| Type 1 diabetes | RASGRP1 | rs8035957 | 0.732 (CEU) 0.424 (JPT+CHB) | rs7403531 (Chinese) | Unknown | Grant SF, 2008 Diabetes |
| Multiple sclerosis | HEX | rs9223837 | 0.699 (CEU) (JPT+CHB) | rs5015480 | ↑ | Sawcer S, 2011 Nature |
| Coronary heart disease | SRR/SMG6 | rs216172 | 0.552 (CEU) 0.588 (JPT+CHB) | rs391300 (Chinese) | ↓ | Schunkert H, 2011 Nat Genet |
| Prostate cancer /endometrial cancer | HNF1B | rs4430796 | 1.000 (CEU) (JPT+CHB) | rs4430796 | ↓ | Gudmundsson J, 2007 Nat Genet |
GWA studies have provided evidence for an interrelation between type 2 diabetes and prostate cancer\(^{44}\). Observational studies have consistently shown an inverse association between the two diseases, with meta-analysis risk ratios ranging from 0.84 to 0.91\(^{33,66}\). In good accordance with this, one shared genomic region at \(HNF1B\) has been highlighted in GWA scans\(^{67}\), where the major allele A of rs4430796 is positively associated with prostate cancer (OR = 1.22) and inversely associated with type 2 diabetes risk (OR = 0.91). Although the biological mechanism underlying such paradoxical associations is poorly understood, it is hypothesized that in type 2 diabetes patients, metabolic status might move gradually from hyperinsulinemia to endogenous insulin deficiency, thus blunting oncogenic action of insulin in the prostate\(^{68}\). The GWA results have further indicated a direct association between diabetes risk variants other than \(HNF1B\) and prostate cancer risk plus the lack of significant evidence supporting the potential for a type 2 diabetes phenotype to mediate the genetic effect of \(HNF1B\)^{44}.

**POTENTIAL OF TRANSLATIONAL ADVANCES**

**Missing Heritability**

It has been argued that susceptibility loci identified through GWA studies explain only a small proportion of heritability (approximately 5–10%) for type 2 diabetes. This discrepancy, termed missing heritability\(^{69}\), has been attributed to a number of factors including insufficient survey of rare variants and structural variants, inaccuracy of current heritability estimates (e.g., inflation because of shared family environment), and epigenetics. It remains to be defined whether complex traits are truly affected by thousands of variants with small effect, but recent analysis of GWA study data using a computational technique has suggested that many hundreds of common weakly-associated variants might be sufficient to account for the majority of heritability – approximately 50% of overall trait variance for type 2 diabetes\(^{70}\), in accordance with the assumption of ‘hidden’ heritability\(^{71}\). Along this, given the strong interplay of genetics, epigenetics and environment, partitioning individual propensity to develop type 2 diabetes is not feasible.

**Personalized Medicine**

Successful applications of personalized medicine in the clinical management of diabetes patients are restricted to the rare, monogenic forms of disease. For example, it is known that MODY patients with \(HNF1A\) mutations respond particularly well to sulphonylurea treatment\(^{72}\). Similar efforts have been made for common forms of type 2 diabetes, in two principal areas of personalized medicine – molecular prediction (or diagnosis) and personalized therapy. To provide improved predictive power over conventional risk factors, genetic testing must be sensitive and specific in discriminating subjects who will develop the disease on follow up from those who will not\(^{73}\). In this line, it has been recognized that genetic variants so far identified do not substantially improve the discriminative accuracy of disease prediction based on conventional risk factors\(^{74,75}\). Even genetic models incorporating thousands of additional putative common variants are likely to offer limited improvement\(^{73,76}\). Although some studies have shown that molecular prediction is slightly more effective in certain patient groups, such as the young\(^{74,77}\), the discriminative accuracy still falls short of the clinical utility at the individual level. At the group level, in contrast, risk stratification is achievable to some extent by using a genetic risk score (GRS); this is an integrated summary of genetic risk from all the different variants in the genome that GWA studies have identified as predisposing to the disease. The GRS thus calculated has the capacity to highlight patient groups at the top end of the risk distribution\(^{78,79}\). A higher GRS was shown to be associated with indices of diminished β-cell function and incidence of diabetes during follow up, gaining predictive ability in comparison with clinical characteristics alone\(^{79}\). Furthermore, lifestyle interventions appear to be effective even among individuals at highest genetic risk\(^{78,80}\). Therefore, it is worth testing whether targeting such high-risk groups for an earlier preventative intervention strategy is beneficial.

From the viewpoint of individual therapeutic utility, pharma- macogenetic studies in common forms of type 2 diabetes have not yet achieved remarkable progress, apart from a few successes in the candidate gene approach; for example, positive associations between variation in sulfonylurea response and genotype at the \(ABCC8/KCNJ11\) and \(TCF7L2\) loci\(^{81,82}\). It is assumed that individual loci affecting antidiabetes drug response exert modest effects, and hence large-scale pharma- genetic GWA studies are required to identify novel susceptibility gene variants.

Also, in terms of clinical management, genetics of diabetic microvascular complications – retinopathy, nephropathy and neuropathy – is an issue of great interest. Although a number of suggestive loci have been nominated through candidate gene approach or GWA study\(^{83,84}\), none have attained genome-wide significant association with the disease, partly because of the lack of statistical power. Given the substantial genetic heterogeneity, future large-scale consortium-based studies are warranted.

**PERSPECTIVE**

Remarkable progress has been made in the genetics of type 2 diabetes in the past 5 years, principally through GWA studies. This proceeds with the rapid technological advances in ‘the era of big data’, which will further enable the sequencing of entire genomes in large samples at affordable costs. We expect that a larger list of associated loci can be discovered in the next few years, thanks to unprecedented global collaboration involving different ethnic groups. Under such circumstances, we have just begun to face new challenges – elucidation of multifaceted (i.e., molecular, cellular and physiological) mechanistic insights into disease biology by considering interaction with environment\(^{85}\) – before clinical translation.
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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | List of loci regulating fasting plasma glucose level with suggestive or significant evidence for association (P < 1E-5)
Table S2 | List of loci regulating insulin-related traits with suggestive or significant evidence for association (P < 1E-5)
Table S3 | List of loci regulating glycosylated hemoglobin level with suggestive or significant evidence for association (P < 1E-5)