Introduction
Type 2 diabetes is caused by defective insulin secretion in the presence of insulin resistance. It usually occurs in late adulthood and is associated with high body mass index (BMI). Genome-wide association studies (GWASs) have identified more than 200 genetic variants associated with metabolic traits, including 65 loci associated with type 2 diabetes (Figure 1) [1-17]. This number is increasing as larger meta-analyses of GWASs are performed. For most of the variants the precise gene involved and its biological role in type 2 diabetes is unknown. Nevertheless, some genetic variants have provided interesting insights into the links between metabolic traits and disease. We discuss several examples in this review (Table 1).

Genetic studies highlight the differences between glucose homeostasis in the general population and risk of type 2 diabetes
GWASs have identified 36 variants associated with normal variation in fasting glucose levels [14,18,19]. We might have expected these variants to be associated with type 2 diabetes with effect sizes proportional to their effects on fasting glucose in the normal range, but this relationship is not clear. Several genetic variants have proportionally larger effects on fasting or stimulated glucose in the normal range compared with their effects on type 2 diabetes risk, and vice versa [14,17]. Three variants stand out: those in GCK, MTN1RB and G6PC2, which have the strongest effect on fasting glucose but no effect (G6PC2) or small effects (GCK and MTN1RB) on risk of type 2 diabetes (Figure 2). Arguably the most interesting is the variant at G6PC2. This gene encodes glucose-6-phosphatase that functions in glucose transport and sensing. Variants lying in the intronic region of this gene, but of no obvious function, are associated with fasting glucose and insulin secretion but not type 2 diabetes. The allele associated with increased fasting glucose is also, paradoxically, associated with improved response to an oral glucose challenge [20]. In contrast, TCF7L2 is most strongly associated with type 2 diabetes, but has a relatively limited effect on fasting glucose in the normal range. These findings suggest that there are differences in the genes and mechanisms that influence normal physiological glucose levels compared with the beta cell dysfunction and pathophysiological glucose levels seen in type 2 diabetes.

Insights into the relationship between circadian rhythm and type 2 diabetes
Genetic studies have revealed that polymorphisms in the MTNR1B gene influence the risk of type 2 diabetes and glucose control in the non-diabetic population. MTNR1B encodes one of two distinct receptors through which melatonin exerts its effect [21]. Melatonin is a circulating hormone that regulates circadian rhythm. The MTNR1B receptor is expressed in human islets [22,23]. Increased nocturnal levels of melatonin coincide with decreased insulin levels. There is evidence from animal studies that if the central and peripheral circadian rhythms, including the melatonin pathway, are disrupted, the risk of metabolic disorders and type 2 diabetes is increased [24,25]. The association between MTNR1B genetic variation and glucose control appears to be driven by a primary effect on insulin secretion [23]. The variants in MTNR1B are also associated with alterations to MTNR1B gene expression in human islet samples - the type 2 diabetes risk and
glucose raising allele is associated with increased MTNR1B expression [23]. A large-scale exon sequencing study of the MTNR1B locus in more than 7,000 Europeans revealed 36 very rare variants (minor allele frequency <0.1%) associated with type 2 diabetes risk [26]. Four of these rare variants caused complete loss of melatonin binding and signaling capabilities [26].

Figure 1. Sixty-five loci associated with type 2 diabetes. This figure illustrates effect size, risk mechanism and year of discovery for all 65 loci associated with type 2 diabetes [1-17]. The x axis gives the year that the association was discovered with robust (genome wide) significance. The y axis is the effect size (odds ratio) for type 2 diabetes association. Colors indicate possible disease mechanism. The odds ratios for type 2 diabetes were all obtained from the recent publication by the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium [1].

Table 1. Evidence for links between diabetes and related metabolic traits from genetic studies

| Primary trait | Secondary trait | Loci | Result | Reference(s) |
|---------------|----------------|------|--------|--------------|
| Fasting glucose in the normal range | Type 2 diabetes | GCK and MTNR1B | Variants at these loci have the strongest effects on fasting glucose but relatively small effects on risk of type 2 diabetes | [14,18,20] |
|                  |                 | G6PC2 | Fasting glucose increasing allele is paradoxically associated with improved response to an oral glucose challenge | |
| Circadian rhythm | Insulin secretion | MTNR1B | Variants in the melatonin receptor MTNR1B are associated with increased fasting glucose, impairment of insulin secretion from the pancreatic beta cell, and increased risk of type 2 diabetes | [2,23,26] |
| Inflammatory marker | Obesity and metabolic syndrome phenotypes | CRP | CRP has no causal effect on obesity and development of insulin resistance and type 2 diabetes, suggesting inflammation is not causally linked to obesity | [28,44] |
| BMI | Circulating CRP | FTO | Obesity causally affects the circulating levels of CRP | [28] |
| SHBG levels | Type 2 diabetes | SHBG | Raised circulating SHBG levels reduce the risk of type 2 diabetes | [33,36] |
| Birth weight | Type 2 diabetes | CDKAL1, HHEX, IDE and ADCYS | Genetic variants that influence birth weight also influence type 2 diabetes risk | [40-42] |

BMI, body mass index; CRP, C-reactive protein; SHBG, sex hormone binding globulin.
associated with increased risk. One suggestion is that the increased expression could be the result of the absence of negative feedback regulatory events under conditions of impaired melatonin receptor signaling [26].

**Insights into the relationship between obesity, inflammation and diabetes**

Genetic studies have provided important insights into the relationships between obesity, inflammation and diabetes. Obesity is associated with a multitude of adverse metabolic traits, including insulin resistance, non-alcoholic fatty liver disease, hyperglycemia, hypertension and dyslipidemia. One intriguing association is that between inflammation and obesity, but the causal direction is unknown. GWASs have identified genetic variants associated with obesity, and variants associated with inflammation. Variants in the FTO gene are associated with obesity and variants in the C-reactive protein (CRP) gene are associated with C-reactive protein (CRP) levels - an inflammatory marker synthesized by the liver. FTO associates with multiple metabolic phenotypes to the extent expected based on its association with BMI and the correlations between BMI and secondary metabolic phenotypes [27]. These associations include FTO versus circulating CRP levels [28]. In contrast CRP genetic variants are not associated with obesity [28]. These findings suggest that inflammatory markers, particularly CRP, do not causally influence the risk of obesity. This finding provides evidence that the subclinical inflammatory profile associated with obesity is more likely to be secondary to adiposity rather than causal. The causal effect of obesity on inflammatory markers is likely to be driven by adipocytes that are a key expresser of inflammatory molecules [29-31].

**Insights into the relationship between circulating sex hormone binding globulin levels and type 2 diabetes**

Recent genetic studies have highlighted a possible causal role for lower sex hormone binding globulin (SHBG) levels
and increased risk of type 2 diabetes. This evidence comes from studies of genetic variation in the \textit{SHBG} gene.

\textit{SHBG}, a plasma transport protein that is mainly produced by the liver, binds to sex hormones: estradiol, and with higher affinity to testosterone. It was assumed that \textit{SHBG} plays one role only, which is regulation of free sex hormone bioavailability to target tissues. However, several physiologic roles have been suggested for \textit{SHBG} through its multiple interactions with its receptor; these roles include modification of sex hormone uptake and cell proliferation [32-34]. The multiple interactions between \textit{SHBG} and its receptors in various target tissues suggest that the role is more complex than the simple transport of sex hormones in serum.

A number of observational epidemiological studies have demonstrated associations between type 2 diabetes and androgens (primarily testosterone), estrogens (estradiol) and \textit{SHBG} [34] that cannot be explained by adiposity. It is controversial whether \textit{SHBG} is a cause or consequence of these conditions. The non-genetic evidence that suggests reduced \textit{SHBG} levels increase the risk of type 2 diabetes, and the evidence that points to reverse causation, are summarized in Table 2.

Two Mendelian randomization analyses, using genetic variants at the \textit{SHBG} locus, have provided evidence that raised circulating \textit{SHBG} levels reduce the risk of type 2 diabetes [35,36]. In both studies, the effects of \textit{SHBG} variants on risk of type 2 diabetes were consistent with those predicted by the effect of the SNPs on \textit{SHBG} levels and the correlation between \textit{SHBG} levels and type 2 diabetes.

\begin{table}[h]
\centering
\caption{Evidence of links between \textit{SHBG} and sex hormones and insulin resistance/type 2 diabetes from non-genetic studies}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Study} & \textbf{Primary perturbation} & \textbf{Effect on insulin secretion/resistance} & \textbf{Reference(s)} \\
\hline
Evidence that \textit{SHBG} is upstream of type 2 diabetes & & & \\
Prospective studies & Altered levels of sex hormones & Increased risk of type 2 diabetes & [34] \\
PCOS in women & Elevation in levels of androgens & Increased risk of non-insulin-dependent diabetes mellitus & [45] \\
Randomized controlled trial & Androgen supplementation in men with low testosterone levels & Increased insulin sensitivity & [46] \\
Animal model (male mouse) & Lack of androgen receptor & Insulin resistance & [47] \\
Animal model (female rat) & Treatment with testosterone after oophorectomy & Insulin resistance & [48] \\
\hline
Evidence that \textit{SHBG} is downstream of type 2 diabetes & & & \\
\textit{In vitro} study & Incubation of hepatoblastoma cell line with IGF-I & Decreased \textit{SHBG} levels & [49] \\
Animal model (mouse) and \textit{in vitro} study & Increased fasting glucose & Downregulation of \textit{SHBG} expression & [50] \\
Intervention study & Insulin lowering interventions in non-diabetic men and women (without PCOS) & Increased \textit{SHBG} levels & [51,52] \\
Study of obese women with PCOS & Increase insulin levels & Reduced serum \textit{SHBG} levels & [53] \\
\hline
\end{tabular}
\end{table}

\textit{IGF-1}, insulin-like growth factor I; \textit{PCOS}, polycystic ovarian syndrome; \textit{SHBG}, sex hormone binding globulin.

Insights into the relationship between birth weight and type 2 diabetes

Numerous epidemiological studies have shown that reduced birth weight is associated with impaired glucose tolerance and type 2 diabetes. There are two hypotheses proposed to explain the association between birth weight and type 2 diabetes. (a) The fetal programming hypothesis proposes that poor intra-uterine nutrition will not only cause small, thin babies, but also programs the development of risk factors of disease, such as type 2 diabetes in adults [37,38]. (b) The fetal insulin hypothesis suggests that fetal genetics influencing insulin secretion and action have a direct effect on small, thin babies and their increased risk of type 2 diabetes [39]. Maternal genes such as \textit{GCK} and \textit{TCF7L2} can indirectly, through their effect on intra-uterine glucose levels, influence fetal growth [40,41]. The hypothesis suggests that the glucose raising variants in mothers increase the birth weight of offspring because the fetal pancreas is exposed to more glucose and therefore secretes more insulin. In contrast, the genetic variants at \textit{CDKAL1}, \textit{HHEX/IDE} and \textit{ADCYS} loci are associated with birth weight through fetal genotype independently of maternal genotype [40-43]. Variants at the \textit{CDKAL1}, \textit{HHEX/IDE} and \textit{ADCYS} loci are all associated with insulin secretion and their association with birth weight suggests the mechanism starts in prenatal life. The association of three type 2 diabetes loci, \textit{CDKAL1}, \textit{HHEX/IDE} and \textit{ADCYS}, with birth weight is consistent with the fetal insulin hypothesis. The assessment of the role of the remaining 62 type 2 diabetes loci with birth weight could elucidate whether type 2
diabetes loci in addition to CDKAL1, HHEX/IDE and ADCYS also influence prenatal growth.

Limitations of genetic association studies

The genetic links between type 2 diabetes and metabolic traits have highlighted possible new biological pathways. Nevertheless, genetic association studies have some limitations. One caveat is that the variant discovered by GWASs may not be the actual causal variant but just linked to it on a chromosome (linkage disequilibrium). Indeed, the causal variant could be in a nearby gene or non-genic region. The other limitation is that the variants discovered to be associated with complex traits explain a very small proportion of individual variation in disease risk or trait levels. These small effect sizes have compromised the disease predictive value of common genetic variants. One explanation is that common diseases such as type 2 diabetes are caused not only by many common variants with small effect but also by rare variants with larger effect that would not be detected in a GWAS. With the advent of high-throughput platforms and methods, full sequencing of samples could make it feasible to assess structural variants and rare variants and discover more of the heritable component to type 2 diabetes.

Summary

In summary, we have presented a number of examples of how genetics helps us understand the complex associations between type 2 diabetes and many other metabolic traits, including glucose homeostasis, circadian rhythm, SHBG, inflammation and birth weight.

GWASs, which do not rely on a prior understanding of disease biology, have resulted in remarkable progress in our understanding of the genetic underpinnings of type 2 diabetes in the last 5 years. We anticipate that advances in technology and resources, including very large sample sizes such as the 500,000 individuals available in the UK Biobank, will lead to even more progress in understanding the highly complex genetic and non-genetic risk factors for metabolic diseases.

Abbreviations

BMI, body mass index; CRP, C-reactive protein; GWAS, genome-wide association study; SHBG, sex hormone binding globulin; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

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