REVIEW

Genetics of Type 2 diabetes in Asian Indians

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Practice Points

- The etiopathogenesis of Type 2 diabetes involves the interplay of both genetic and environmental factors.
- Asian Indians have certain unique clinical and biochemical characteristics that are collectively referred to as the 'Asian Indian phenotype'.
- The genetics of Type 2 diabetes can be of two broad groups: genetics of monogenic forms and polygenic forms of diabetes.
- Identification of rarer monogenic forms of diabetes such as maturity-onset diabetes of the young and neonatal diabetes could help plan treatment more accurately.
- Certain genes appear to uniquely predispose Asian Indians to Type 2 diabetes.
- To identify the complex individual susceptible and protective genes, a full understanding of the complex gene–gene and gene–environment interactions is required.

SUMMARY Type 2 diabetes (T2D) is a polygenic disorder with multiple genes located on different chromosomes contributing to its susceptibility. Analysis of the genetic factors is further complicated by the fact that numerous environmental factors interact with genes to produce the disorder. Only a minority of cases of T2D such as maturity-onset diabetes of the young are caused by single gene defects. As Asian Indians have an increased susceptibility to diabetes and have increased insulin resistance, they are a unique population for carrying out genetic studies. Asian Indians develop T2D at lower levels of BMI, one to two decades earlier and have stronger heritability factors compared with Europeans. All these factors point to the role of possible ethnic variations in genetic susceptibility. Recent genetic studies on Asian Indians indicate that certain genes appear to predispose Indians to diabetes while other genes, which afford protection against diabetes and insulin resistance to Caucasians, do not appear to protect Indians. In addition, there are several genes (e.g., *TCF7L2*), which are similar in Asian Indians and in Europeans, that contribute to susceptibility to T2D. Advances in genotyping techniques and the availability of large patient cohorts have made it possible to identify common genetic variants associated with T2D through genome-wide association studies. Recent studies have shown that common genetic variations contribute to T2D risk within populations but do not explain the difference between populations. In this context, the risk allele evaluation of T2D in Asian Indians could help provide better understanding of increased susceptibility to T2D within this ethnic group.

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Type 2 diabetes (T2D) is a complex heterogenous group of conditions characterized by elevated levels of plasma glucose that is caused by impairment in both insulin secretion and insulin action. The etiopathogenesis of T2D involves the interplay of both genetic and environmental factors. There are multiple lines of evidence to support the view that genetic factors are very important in susceptibility to T2D, such as ethnic variation in prevalence of diabetes, concordant rates in twin studies and familial clustering [1–3].

According to the recent projections of the International Diabetes Federation (IDF), India has nearly 51 million Type 2 diabetic subjects and this could reach almost 87 million by the year 2030 [4]. Recent population-based studies in Asian Indians revealed a rising prevalence of diabetes in urban areas of India with figures ranging from 15 to 19% [5,6]. While environmental factors certainly play a major role in the diabetes epidemic, this usually occurs on a background of genetic susceptibility.

Heritability of diabetes among Asian Indians

Studies performed in the 1980s in a group of 135 Asian Indian and 146 European diabetic patients attending a diabetic clinic in the UK showed that 36% of Europeans had a first-degree relative with diabetes compared with 45% of Asian Indians [7]. Another study from our group measured the prevalence of diabetes among the offspring of two T2D parents in India. This study showed that 60% of offspring had diabetes or impaired glucose tolerance [8], which was considerably higher than in the European population [2,9]. In a population-based study Chennai Urban Population Study (CUPS) conducted on 1262 individuals in Chennai (formerly Madras) in southern India, we assessed the influence of family history on prevalence of T2D. The prevalence of diabetes was higher among subjects who had a positive family history of diabetes (18.2%) compared with subjects without a family history of diabetes (10.6%; $p = 0.0015$). Further, the odds ratio of the risk for diabetes among subjects with one diabetic parent was 2.5 and this increased to 6.62 in subjects who had both parents affected by diabetes [10].

Very recently, the heritability of quantitative traits associated with T2D in large multiplex families from south India were estimated [11]. The study revealed strong familial aggregation of quantitative traits that are typically associated with T2D, lending credence to the role of genetic factors in T2D.

It has been recognized that Asian Indians have certain unique clinical and biochemical characteristics that are collectively referred to as the 'Asian Indian phenotype' [12]. Despite a relatively lower prevalence of generalized obesity as measured by BMI, they tend to have larger waist measurements and waist to hip ratios, thus having a greater degree of central obesity. This is associated with a characteristic metabolic profile with higher plasma insulin levels, a greater degree of insulin resistance and a higher prevalence of diabetes. Furthermore, Indians also tend to have excess body fat, in particular, abdominal and truncal adiposity [13]. For any given waist circumference, they also have increased body fat and for any given body fat, they have increased insulin resistance. This clearly indicates that Asian Indians have a predisposition to diabetes, probably caused by their genetics and thus studies on the genetics of T2D in Indians are essential.

Genetic studies in Asian Indians

The genetics of T2D can be considered under two broad groups: genetics of monogenic forms of diabetes, where a single gene is causal in the development of the disease, and genetics of polygenic forms of diabetes, where a number of genes are responsible for the susceptibility of the disease.

■ Monogenic diabetes

Some of the most compelling evidence that inherited variations can cause glycemic dysregulation comes from the clinical and genetic description of monogenic diabetes, which includes maturity-onset diabetes of the young (MODY), insulin resistance syndromes, mitochondrial diabetes and neonatal diabetes. Although rare, these syndromes provide a framework for understanding and investigating the complex genetics of T2D [14].

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young was first described in 1975 as a unique type of noninsulin-dependent autosomal-dominant diabetes characterized by β-cell dysfunction, in thin, young adults (usually <25 years of age) who were not prone to ketoacidosis [15,16]. All patients clinically designated as MODY satisfied the following criteria of Tattersall and Fajans [15]:

- Age at onset of diabetes of <25 years
- Correction of hyperglycemia for a minimum period of 2 years without insulin
- Absence of ketonuria at any time
- Evidence of autosomal dominant inheritance with three-generation transmission of diabetes

This syndrome accounts for approximately 1–2% of diabetes cases worldwide, although MODY has been reported to be responsible for as many as 5% of European diabetic cases [17]. Seven different MODY genes have been identified to date (*HNF4A, GCK, HNF1A, NEUROD1, HNF1B, PDX1* and *INS*), although approximately 30–40% of MODY patients have no identifiable genetic mutation in any of them, possibly due to the presence of other undiscovered gene(s), likely the MODY 'X' [18].

MODY 1 results from mutations in *HNF4A* on chromosome 20, which affects the development and function of human pancreatic β cells [19]. MODY 2 results from mutations in the *GCK* gene on chromosome 7p [20,21] and accounts for approximately 20% of MODY cases. Mutations of *GCK* result in mild, stable, lifelong fasting hyperglycemia. Drug treatment is rarely required [22]. MODY 3 results from mutations in *HNF1A* (*TCF1*), which impairs key steps of glucose transport, metabolism and mitochondrial metabolism [23]. It is the most common MODY subtype, with more than 300 different mutations. Retinopathy and nephropathy are common in MODY 3; however, macrovascular disease is not [19,24]. MODY 4 results from heterozygous mutations in the gene that encodes insulin promoter factor 1 (*IPF1* or *PDX1*), a transcription factor that regulates insulin gene transcription as well as islet and pancreatic development [25]. MODY 5, a more common MODY variant than originally suspected, is unique in that it is associated with renal anomalies. *HNF1B* is highly expressed in the pancreas, liver and kidney. Diabetes results from both hepatic insulin resistance and β-cell loss. *HNF1B* mutations have been associated with renal dysfunction, genitourinary problems, abnormal liver function and hyperuricemia [26]. MODY 6 has been shown to result from mutations in *NEUROD1* (*BETA2*), which is important for pancreatic development and insulin gene transcription. MODY 6 is extremely rare, with only a few cases reported in the literature [27].

Studies on MODY in India

An earlier study reported on the high prevalence of MODY (using the clinical criteria used at that time) in south Indians (4.8%) [28]. The insulin responses in MODY and the β-cell response in the offspring of MODY indicated an increased insulin resistance compared with classical Indian Type 2 diabetic subjects [28]. Recently, our work has revealed important insights into the genetics of MODY in south India. We identified nine novel variants comprising seven mutations (one novel mutation -538G>C at the promoter region and six novel coding region mutations) and two polymorphisms in the *HNF1A* gene. A novel mutation, Arg263His, was identified in a family of 30 individuals. The mutation co-segregated with diabetes in this family and this mutation was not seen in nondiabetic members of the family, thus suggesting that the mutation is involved in the development of MODY [29]. A further three novel MODY 1 mutations have also been identified in the *HNF4A* gene in the same population [30]. Thus, approximately 9% of the clinically diagnosed MODY subjects are MODY 3, while 3% are MODY 1 in south India.

MODY 3 is the common form of MODY worldwide [16]. These patients are of normal BMI, often present with severe hyperglycemia and have microvascular complications. The prevalence of MODY 3 in patients with early-onset T2D varies from 2.5 to 36% [31–33].

■ Polygenic T2D

In contrast to the rarer monogenic forms of diabetes, as described above, the more common T2D is a polygenic disorder. The complex individual susceptible and protective genes are more difficult to identify, given the limited individual impact of a single genetic locus. A full understanding of the complex gene–gene and gene–environment interactions at play in this disease has proven quite challenging thus far.

The susceptibility to complex forms of T2D is associated with frequent polymorphisms that create amino acid variants in exons or influence the expression of genes in the regulatory pathways [34]. Alleles of these polymorphisms are present in both healthy individuals and T2D patients, although with statistically significant differences in the frequencies. The sequence variants are associated with an increase in the risk of developing the disease and are considered susceptibility variants, but not causative factors

that determine the disease. The candidate gene approach focuses on the search for an association between T2D and sequence variants in or near biologically defined candidate genes that have been chosen based on their known physiological function. The importance of these variants or other nearby variants is tested by comparing the frequency in T2D patients and normal glucose-tolerant subjects. A second approach is the genome-wide linkage scan strategy [35], in which regularly spaced markers are traced in families and sibling pairs for segregation with T2D. No prior knowledge of gene or gene effects is necessary, but the genetic locus must have sufficient impact on the disease susceptibility in order to be detectable.

Extending the analysis of genes implicated in monogenic forms of diabetes has proved successful for T2D, as exemplified by the discovery of roles for *HNF4A, HNF1A, PPARG2, KCNJ11, WFS1, GCK, IRS1* and *GLIS3* genes [36]. Common variants of *HNF4A* (MODY 1) have been associated with T2D in both Finnish and Ashkenazi Jewish populations [37,38].

Our studies on the *HNF4A* gene have revealed important insights into the role of its variants with the T2D. Single nucleotide polymorphism (SNP) rs4810424 and SNP rs736823 of the *HNF1A* gene were associated with T2D, whereas the Val255Met and SNP rs1884614 of *HNF1A* gene were shown to be protective. Furthermore, our study of a common polymorphism of the *HNF1A* gene, namely, the Ala98Val, clearly showed that in Asian Indians, the Ala98Val polymorphism of the *HNF1A* gene is associated with MODY and with an earlier age of onset of T2D [39]. This association was also confirmed by another study in north India [40] and is similar to the association of G319S polymorphism in the Oji-Cree population [41].

PC-1 gene

The *PC-1* gene impairs insulin signaling at the insulin receptor level. The K121Q polymorphism of the *ENPP1/PC-1* gene is associated with insulin resistance/atherogenic phenotypes, including earlier onset of T2D and myocardial infarction [42]. The Q121 variant binds and inhibits insulin receptor more strongly than the K121 variant and is associated with insulin resistance, hyperglycemia and other related metabolic abnormalities in the vast majority of studied populations [43–47]. Homozygous carriers of the ENPP1 Q121 variant are characterized by an altered glucose homeostasis. Reduced early-phase insulin secretion and inefficient interplay between insulin secretion and sensitivity, which occur at early ages, are major determinants of this defect [48]. Bacci *et al.* [45] and Prudente *et al.* [49] suggested that the Q121 allele is a gene variant with pleiotropic deleterious effects on several metabolic abnormalities such as insulin resistance, obesity and T2D. A comprehensive meta-analysis showed that Europeans who were homozygous for the Q121 allele had an increased risk of T2D, but this association was mediated by its effect on BMI [50]. Other studies showed that the K121Q *PC-1* polymorphism has no significant impact on insulin sensitivity and is not a critical determinant for either diabetes or obesity [51–53]. Our study in Asian Indians supports the hypothesis that *ENPP1* 121Q predicts genetic susceptibility to T2D in both south Asians and Caucasians [54]. Considering the unique phenotype of Asian Indians with excess abdominal and truncal adiposity it would be of interest to evaluate a genetic variant such as K121Q with obesity and the measures of obesity, whose effect seems to be mediated through BMI.

PPARG gene

One of the main candidate genes implicated in adipogenesis, insulin resistance and T2D is the peroxisome proliferator activated receptor-γ (*PPARG*) gene. It is involved in adipogenesis and in regulation of adipocyte gene expression and glucose metabolism. We carried out another genetic study in collaboration with the Dallas group in the same populations on *PPARG* gene polymorphism. We found the frequencies of the common Pro12Ala polymorphism in south Indians living in Chennai to be 19%, while the frequency in south Asians in Dallas was 18% and for Caucasians in Dallas it was 20%. The Caucasian diabetic subjects had a significantly lower prevalence of PPAR-12Ala when compared with Caucasian nondiabetic subjects (20 vs 9%; $p = 0.006$). However, there were no significant differences between diabetic and nondiabetic subjects with regard to the Pro12Ala polymorphism among the south Asians living in Dallas (20 vs 23%) and the Indians in Chennai (19 vs 19.3%). Although Caucasians carrying *PPARG* Pro12Ala had lower 2-h plasma insulin levels at 2 h of OGTT than the wild-type (Pro/Pro) carriers (76 ± 68 and 54 ± 33 U/ml, respectively; $p = 0.01$), no differences in either fasting or 2-h plasma insulin concentrations were

found between south Asians (Indians) carrying the *PPARG* Pro12Ala polymorphism and those with the wild-type (Pro/Pro) genotype either in Chennai or Dallas. We concluded that despite the frequency of the Ala allele at the *PPARG*-Pro12Ala locus being the same in individuals of south Asian descent, as in Caucasians, this particular polymorphism does not appear to improve insulin sensitivity or decrease risk for T2D in south Asians (Asian Indians) as it does in Caucasians. Our study thus supports the hypothesis that the Pro12Ala polymorphism is protective against diabetes in Caucasians but not in south Asians [55]. However, a recent study by Sanghera *et al.* has demonstrated the protective nature of the Pro12Ala polymorphism against T2D in Asian Indian Sikh population [56]. The difference could be attributable to ethnic-specific differences (e.g., south Indian vs Punjabi sikh) or due to differences in the power of the studies.

Further, PPARγ is a nuclear hormone receptor of a ligand-dependent transcription factor involved in adipogenesis and a molecular target of the insulin sensitizers thiazolidinediones. We addressed the question of whether the three variants (-1279G/A, Pro12Ala and His478His) in the *PPARG* gene are associated with T2D mellitus and its related traits in a south Indian population [57]. The study subjects (1000 T2D mellitus and 1000 normal glucose-tolerant subjects) were chosen randomly from the Chennai Urban Rural Epidemiology Study (CURES), an ongoing population-based study in southern India [58]. The variants were screened by single-stranded conformational variant, direct sequencing and restriction fragment length polymorphism. Linkage disequilibrium was calculated from the estimates of haplotypic frequencies. The -1279G/A, Pro12Ala and His478His variants of the *PPARG* gene were not associated with T2D mellitus. However, the two-loci analyses showed that, in the presence of the Pro/Pro genotype of the Pro12Ala variant, the -1279G/A promoter variant showed increased susceptibility to T2D (odds ratio: 2.092; 95% CI: 1.22–3.59; p = 0.008), whereas in the presence of the 12Ala allele, the -1279G/A variant showed a protective effect against T2D (odds ratio: 0.270; 95% CI: 0.15–0.49; p = 0.0001). The three-loci haplotype analysis showed that the A-Ala-T (-1279G/A-Pro12Ala-His478His) haplotype was associated with a reduced risk of T2D mellitus (p = 0.0001). Although our data indicate that the *PPARG* gene variants independently have no association with T2D mellitus, the two-loci genotype analysis involving -1279G/A and Pro12Ala variants and the three-loci haplotype analysis have shown a significant association with T2D in this south Indian population.

The *PPARG* gene is known to play a significant role in regulating adipose cell differentiation. The Pro12Ala polymorphism has been reported to reduce transactivation activity *in vitro,* which might lead to lower levels of adipose tissue mass accumulation [59,60]. Although there was no association with T2D in our study, we wanted to examine the association of the Pro12Ala polymorphism with adiponectin levels in Asian Indians. We selected 400 diabetic subjects, 200 with the Pro12Pro genotype (100 male and 100 female) and 200 with the Pro12Ala genotype (100 male and 100 female) and 400 age- and sex-matched normal glucose-tolerant subjects with similar genotype profiles from the CURES. Fasting serum adiponectin levels were measured using radioimmunoassay. The Pro12Ala polymorphism was genotyped by PCR–restriction fragment length polymorphism using *BstUI.* All clinical and biochemical parameters were similar in the subjects with the Pro12Pro and Pro12Ala genotypes. There was no significant difference in serum adiponectin values between subjects with the Pro12Pro and Pro12Ala genotypes (males 5.4 vs 5.8 µg/ml, p = 0.546; females 6.9 vs 7.2 µg/ml, p = 0.748). Adiponectin values did not differ among these two genotypes even when categorized based on diabetic status (7.9 vs 7.7 µg/ml for Pro12Pro vs Pro12Ala, respectively, in normal glucose-tolerant subjects, p = 0.994; 4.7 vs 5.4 µg/ml for Pro12Pro vs Pro12Ala, respectively, in diabetic subjects, p = 0.622). We concluded that the Pro12Ala polymorphism of the *PPARG* gene is not associated with serum adiponectin levels in Asian Indians [61].

PGC-1A gene

PGC-1A is a cofactor involved in adaptive thermogenesis, fatty acid oxidation and gluconeogenesis. Dysfunctions of this protein are likely to contribute to the development of obesity and the metabolic syndrome. Franks and Loos [62] showed that the *PGC-1A* sequence variation may interact with physical activity to modify diabetes risk via changes in oxidative energy metabolism. It has been observed that expression of PGC-1A is downregulated in muscles of Type 2 diabetic subjects. In addition, a common polymorphism of the *PGC-1A* gene (Gly482Ser), expressing

reduced PGC-1A activity, has been linked to an increased risk of T2D. These observations suggest that either reduced levels or compromised activity of PGC-1A can be associated with the development of insulin resistance and T2D [63]. In a study on seven *PGC-1A* variants only the Gly482Ser polymorphism was associated with a 1.34 genotype relative risk of T2D [64]. Studies on Thr394Thr, Gly482Ser and +A2962G polymorphisms of the *PGC-1A* gene and their association with T2D in Asian Indians showed that the Thr394Thr (G-A) polymorphism is associated with T2D and also with total, visceral and subcutaneous body fat [65,66]. Another study showed that the Thr394Thr and Gly482Ser variant genotypes provide susceptibility to T2D mellitus in two north Indian population groups [67].

ADIPOQ gene

Adiponectin, encoded by the *ADIPOQ* gene, is one of the adipocyte-expressed proteins that enhances insulin sensitivity and regulates the homeostatic control of glucose, lipid and energy metabolism [68,69]. Genome-wide scans have mapped a susceptibility locus for T2D and obesity/metabolic syndrome to chromosome 3q27, where the *ADIPOQ* gene is located [70–73]. SNPs of the *ADIPOQ* gene have been genotyped in large datasets from various ethnic groups and several SNPs associated with hypoadiponectinemia, obesity and T2D have been identified [74–78]. Two SNPs in the adiponectin gene, a silent T to G substitution in exon 2 (+45T/G) and a G to T substitution in intron 2 (+276G/T), were significantly associated with T2D and adiponectin level in Japanese population, and with insulin resistance in some Caucasian populations (from Italy and Germany) [74,79,80]. In addition, SNP 45 was associated with obesity in a German population [81]. In the proximal promoter region of the *APM1* gene, SNPs -11426A/G and -11391A/-11377G haplotypes predicted associations with fasting plasma glucose, T2D and adiponectin levels [74,82]. Adiponectin has been associated with low diabetes risk. The metabolic effects of adiponectin are mediated by adiponectin receptors 1 (ADIPOR1) and 2 (ADIPOR2). A study on six polymorphisms in *ADIPOR1* and 16 polymorphisms in *ADIPOR2* demonstrated a significant association between *ADIPOR1* haplotypes and diabetes risk [83]. Bouatia-Naji *et al.* [84] reported the associations of the adiponectin gene SNPs -11,377C (odds ratio: 1.23; p = 0.001) and +276T (odds ratio: 1.19; p = 0.006) with both childhood and morbid adult obesity [83]. Guo *et al.* [85] have observed strong linkage evidence for a quantitative trait locus at 3q27, likely distinct from the *APM1* gene, contributes to the variation of plasma adiponectin levels in the Hispanic–American population. Adiponectin is an adipose tissue-specific protein that is decreased in subjects with obesity and T2D. Our study showed for the first time that the +10211T/G polymorphism in the first intron of the adiponectin gene is associated with T2D, obesity and hypoadiponectinemia (odds ratio: 1.28; 95% CI: 1.07–1.54; p = 0.008) in the Asian Indian population [86], thereby suggesting that adiponectin is a very important gene for obesity and T2D. A recent meta-analysis by Gong *et al.* was performed on 10267 T2D patients and 12837 controls [87]. Overall the -11377G allele showed an 8% elevated risk of T2D compared with the -11377C allele (OR: 1.08; 95% CI: 1.01–1.15; p = 0.034), while the -11391A allele showed no significant effect on T2D risk in all subjects (p = 0.240; OR: 1.10; 95% CI: 0.94–1.29) compared with the -11391G allele. In the subgroup analyses by ethnicity, the -11391A allele increased T2D risk in European population (p = 0.046; OR: 1.09; 95% CI: 1.00–1.09), thereby suggesting that the ADIPOQ -11377G allele is a low-penetrant risk factor for developing T2D, but that -11391A is a risk factor only in European Caucasians. Bowden *et al.* used a combination of family-based linkage, whole-exome sequencing, direct sequencing and association methods to identify a rare (1.1%) G45R mutation in the *ADIPOQ* gene [88]. The variant showed a strong linkage signal (logarithm of the odds [to the base 10; LOD] >8.0) and accounted for approximately 17% of the variance in plasma adiponectin levels in Hispanic Americans and 63% of the variance in families carrying the mutation.

TCF7L2 gene

By far the strongest association with T2D is seen for SNPs in the gene encoding for *TCF7L2*. *TCF7L2* encodes for a transcription factor involved in Wnt signaling. Investigators at deCODE Genetics in Iceland first reported a strong association of a common T allele of rs7903146 in the *TCF7L2* gene with an increased risk of T2D in three white populations [89]. These results have subsequently been replicated and confirmed in multiple ethnic groups [90–95]. All of these studies demonstrate robust and convincing statistical evidence

of association with diabetic risk and consistent effect sizes. The effect of the risk allele appears to be additive; one allele confers approximately a 40% risk whereas two copies confer a 80% risk of diabetes. The *TCF7L2* risk allele may result in a defective or poorly expressed protein that leads to decreased insulin secretion and consequent hyperglycemia [14]. Our *TCF7L2* study showed the association of the rs12255372 and rs7903146 polymorphisms of the gene with T2D in southern India. The 'T' allele of both rs12255372 and rs7903146 polymorphisms was associated with T2D. Further, the 'T' allele of these SNPs showed an association with T2D in nonobese subjects. The results of this study add to the rapidly expanding body of evidence that implicates *TCF7L2* as an important risk factor for T2D in multiple ethnic groups including Asian Indians [96].

FTO gene

A recent genome-wide association study (GWAS) for T2D in a UK population revealed a novel locus associated with BMI – the *FTO* gene on chromosome 16 [97]. The representative SNP rs9939609 was confirmed to be associated with elevated BMI after replication in over 38,000 study participants of European ancestry. In addition, adiposity appeared to mediate an association between the *FTO* variant and the risk of T2D [98,99]. Several other studies have also observed associations between *FTO* variants and obesity-related traits in various populations [100,101]. Earlier studies on rs9939609 T/A and rs7193144 C/T variants of intron 1 of the *FTO* gene showed an association with T2D that was independent of BMI in Asian Indians [102,103]. A recent study examining the association of six variants, rs9940128, rs7193144, rs8050136 (intron 1), rs918031, rs1588413 (intron 8) and rs11076023 (3′UTR), across three regulatory regions of the *FTO* gene with obesity and T2D in a south Indian population showed that the rs9940128 A/G, rs1588413 C/T and rs11076023 A/T variants were associated with T2D but not with obesity. The rs8050136 C/A variant was associated with obesity and its association with T2D was also mediated through obesity. The haplotype 'ACCTCT' confers a lower risk of T2D in this south Indian population [104].

Mendelian forms of severe insulin resistance associated with T2D

Insulin resistance is common and plays a central role in the pathogenesis of T2D. Lipodystrophy is a major cause of severe insulin resistance. Monogenic forms of insulin resistance, such as familial partial lipodystrophy, which results from mutations in either *LMNA* (encoding lamin A/C) or *PPARG*, and congenital generalized lipodystrophy, which results from mutations in either *AGPAT2* (encoding 1-acylglycerol-3-phosphate O-acyltransferase) or *BSCL2* (encoding seipin), can display features seen in the common metabolic syndrome. In addition, insulin resistance is seen in disorders associated with insulin receptor mutations, progeria syndromes and in inherited forms of obesity. Although insulin resistance in such rare monogenic syndromes could simply be secondary to fat redistribution and/or central obesity, the products of the causative genes might also produce insulin resistance directly, and might illuminate new causative mechanisms for insulin resistance in such common disorders as T2D mellitus and obesity [105]. Extreme forms of insulin resistance are a rare cause of T2D. Severe insulin resistance typically presents in one of the following ways: disordered glucose metabolism including both diabetes and/or paradoxical hypoglycemia; acanthosis nigricans, a velvety hyperpigmentation of axilliary and flexural skin often associated with skin tags; or hyperandrogenism in girls (hirsutism, oligo-/amenorrhoea and polycystic ovaries) [106].

Mitochondrial diabetes & syndromic forms of diabetes

Mitochondrial diabetes is another rare variant of monogenic diabetes. Since mitochondrial inheritance is exclusively related to maternal transmission, mutations within the maternal genome could explain an excess of maternally related T2D. A few mtDNA mutations strongly associate with diabetes. Maternally inherited diabetes and deafness is caused by the most common mutation the A3243G mutation in the mitochondrial DNA-encoded tRNA (Leu UUR) gene [107]. This mutation is also associated with the MELAS (myopathy, encephalopathy, lactic acidosis and stroke-like episodes) syndrome [107]. Many other rare monogenic forms of diabetes have been studied, which include mutations in the insulin receptor gene and *WFS1* gene (Wolfram syndrome) [108]. McCarthy *et al.* studied the importance of the maternal history of noninsulin-dependent diabetes mellitus (NIDDM) in south Asian patients [109]. None of 142 unrelated subjects with NIDDM were found to have nt3243 MELAS mutation. However, sequencing identified two variants of potential

importance at nt3290 (7/142) in the tRNA (Leu UUR) gene and at nt3316 in the ND1 gene (4/142). Both were found to be statistically significant (p = 0.51). Significance of these variants to the development of NIDDM is not clear.

In summary, various genetic studies using the candidate gene approach have indicated a role for different genes towards the susceptibility of T2D with moderate success.

New genes identified by GWAS for T2D

Our understanding of the role of genetics in T2D was developed through epidemiological studies, studies of candidate genes and genetic linkage in families for decades. While this has provided important insights into some rare monogenic forms of diabetes, understanding the genetics of common T2D remains a major challenge. By examining the entire genome, it is possible to identify, in an unbiased manner, the genetic variation that is associated with specific diseases. Advances in genotyping techniques and the availability of large patient cohorts have made it possible to identify common genetic variants associated with T2D through GWAS. The results of five independent GWA screens for T2D genes have been published [98,99,110–112], and these were followed by five smaller GWAS [113–117]. The five large studies were all conducted using a two-stage strategy consisting of a GWA screen in an initial cohort of unrelated cases and controls followed by replication of the most significant findings in additional sets [95,101]. The number of loci showing consistent evidence of association with T2D and its related phenotypes has grown to 59 [36,118–121]. Results of the first GWAS on non-European populations were published in 2008, using a multistage approach [122,123]. In both studies the *KCNQ1* gene was identified as a T2D susceptibility gene, and the results of these studies also showed that *KCNQ1* is expressed in the pancreas. In addition to these studies, another GWAS in Japanese individuals highlighted the need to extend large-scale association efforts to different populations, such as Asian populations [124]. The association of the *KCNQ1* gene with susceptibilty to T2D was also replicated in other populations, including Chinese and European [119,125]. However, no study has been performed in Asian Indians to date.

In a very recent GWAS of T2D in people of Chinese ethnicity two additional susceptibility genes, *SRR* and *PTPRD*, together with the one known *KCNQ1* gene, were reported [126].

Kong *et al.* have identified a novel association between the SNP rs2334499 at 11p15 and T2D [127]. The allele confers a risk for T2D when paternally inherited but is protective when maternally transmitted. They have identified a differentially methylated CTCF-binding site at 11p15 and demonstrated correlation of rs2334499 with decreased methylation of that site.

Dupuis *et al.* [36] performed meta-analyses of 21 GWAS that covered fasting glucose, fasting insulin and indices of β-cell function (HOMA-B) and insulin resistance (HOMA-IR) in 33 additional cohorts. The study reported new genome-wide significant associations of SNPs with fasting glucose (in or near *ADCY5*, *MADD*, *ADRA2A*, *CRY2*, *FADS1*, *GLIS3*, *SLC2A2*, *PROX1* and *C2CD4B*) and one influencing fasting insulin and HOMA-IR (near *IGF1*). It also demonstrated an association between *ADCY5*, *PROX1*, *GCK*, *GCKR* and *DGKB-TMEM195* and T2D. Saxena *et al.* identified five loci associated with 2-h glucose in *GIPR, VPS13C, ADCY5, GCKR* and *TCF7L2* [120]. *ADCY5* variants are associated with fasting and 2-h glucose levels and with an increased risk of T2D, highlighting the fact that investigation of diabetes-related quantitative traits can lead to identification of additional T2D-associated loci.

In a GWA replication study on nine significant loci previously reported to be associated with T2D in Caucasian populations, four SNPs (*PPARG2* [Pro12Ala], *IGF2BP2, TCF7L2* and *FTO*) were shown to confer a significant association with T2D in Asian Indian Sikhs [101]. This was the first study reporting the role of recently emerging loci in this high-risk population from the south Asian subcontinent. A recent meta-analysis on three GWA scans identified six loci (*NOTCH2, THADA, ADAMTS9, JAZF1, CDC123/CAMKID* and *TSPAN8/LGRS*) highly associated with T2D in Caucasians. Sanghera *et al.* genotyped highly significant variants from each locus in a case–control cohort consisting of 680 T2D cases and 637 normoglycemic controls in Khatri Sikh diabetics of north India [128]. The findings suggested that *CDC123/CAMKID* could be a major risk factor for the development of T2D in Sikhs by affecting β-cell function.

Replicating the recently found genetic association is imperative and informative. A recent study in Indians replicated common variants in eight gene loci, namely the *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A*,

IGF2BP2 and *CDKAL1* genes, and demonstrated an association between these variants and T2D [129].

Very recently we sought to replicate a total of 45 SNPs from 15 genes and 13 unannotated loci identified from recent GWAS T2D subjects, in 926 unrelated T2D and 812 normal glucose-tolerant subjects from southern India. Only six of 45 SNPs studied were replicated in this south Indian population. SNPs rs7756992 (p = 0.007), rs7754840 (p = 0.015) and rs6931514 (p = 0.029) of the *CDKAL1* gene, rs7020996 (p = 0.003) of the *CDKN2A/B* gene, rs7923837 (p = 0.038) of the *HHEX* gene and rs12056034 (p = 0.033) of the *BAZ1B* gene were associated with T2D in our population. Large-scale studies are needed in this population to validate the findings [130].

Conventional and high-throughput technologies have led to the identification of genes that play a role in T2D. The validation and characterization of these genes and gene loci is underway. This should hopefully shed more light on the genetics of T2D in Asian Indians **(Table 1)**.

Genome-wide association study continue to open our eyes to the broad nature of the molecules that might contribute to the pathogenesis of T2D. Different environmental stresses, population differences in activity and different diets clearly cause some genes to manifest as a disease phenotype. The effect of a common gene variant between populations that have very different diets and exercise habits might be expected to be totally different. Our increased understanding of such phenomena will hopefully enable us to see how common variants can alter disease susceptibility, and this is essential to understand the physiologic importance of the genetic associations that are uncovered.

Studies on the genetics of diabetes complications

Type 2 diabetes is characterized by chronic hyperglycemia resulting from insulin resistance and relative insulin insufficiency. Delay in treatment and control will accelerate progression towards the many microvascular and macrovascular complications of T2D, including retinopathy, nephropathy, neuropathy, coronary disease, stroke and peripheral vascular disease. Frank clinical end points of severe consequence from T2D include blindness, kidney failure, amputation, myocardial infarction, stroke and sudden death. Asian patients had more evidence of macro- and microvascular disease and macrovascular complications when compared with Europeans [131].

■ Genetic studies of diabetic retinopathy

Diabetic retinopathy (DR) can be defined as damage to the microvascular system in the retina due to prolonged hyperglycemia [132]. DR is one of the most common and specific complications of diabetes. Three earlier studies from India have confirmed that the prevalence of DR is lower in Indians, ranging from 17.6 to 26.8% [133–135] compared with a prevalence of 33.6% reported in the Liverpool Diabetic Eye Study, UK [136], 29% in diabetic patients included in the Grampian DR screening program with gradable photographs [137] and 55.5% in the Prevalence of Diabetic Eye Disease in Tayside, Scotland (P-DETS) study [138].

The involvement of genetic factors in the pathogenesis of DR has been supported by studies that have demonstrated the familial clustering of DR. Earlier studies performed by Rema *et al.* in a south Indian population showed that siblings of subjects with DR were 3.5-times more likely to develop DR compared with siblings of subjects without DR, suggesting a strong genetic component associated with the development of DR in this population [139]. Various candidate genes have been tested for their association with DR, which have had conflicting reports in various populations. Among many candidate genes that have been found to be associated with retinopathy, the gene encoding RAGE is of particular significance, because RAGE-mediated signaling induces key pathological changes in the microvasculature leading to DR. A functional polymorphism Gly82Ser in exon 3 has been previously implicated in DR, and the Ser allele of this Gly82Ser polymorphism has been shown to be protective in the development of DR in the Asian Indian population [140]. Our own study on the promoter polymorphisms of the *RAGE* gene revealed a modest association with the -374T/A polymorphism in the nonproliferative DR subgroup while no association was found with 429 TC promoter polymorphisms in relation to DR in south Indian Type 2 diabetic subjects [141].

In another study by Kumaramanickavel *et al.* [142], the Z-2 allele of the aldose reductase gene was found to be associated with risk for DR among the Indian population. Kumaramanickavel *et al.* [143] also investigated a promoter microsatellite $(GT)_n$ in the *TNF* gene for association with retinopathy in a self-reported diabetic cohort and found a low-risk allele ($(GT)_9$) and a high-risk allele ($(GT)_{13}$) for DR in this gene. A study conducted on a pentanucleotide repeat polymorphism $(CCTTT)_n$ in the *iNOS*

Table 1. Summary of recent genetic studies in Type 2 diabetes.

Study number	Gene	Other ethnic groups	Asian Indians	Study type
1	*PPARG* (Pro12Ala)	Pro12Ala polymorphism protective in Caucasians [59,64,160,161]	Pro12Ala polymorphism not protective in south Asians [55]	CS
2	*PGC-1α* (Thr394Thr)	'G' allele is associated with relative risk of T2D in a European population [64]	'A' allele is associated with T2D and with body fat in a south Indian population [65,66]	CS
		Not associated with T2D in a Japanese population [162]	Associated with T2D in a north Indian population [67]	CS
3	*PGC-1α* (Gly482Ser)	Associated with relative risk of T2D in a European population [64]	Not associated With T2D [65]	CS
		Associated with the development of insulin resistance and T2D [63]	Associated with T2D in a north Indian population [67]	CS
5	*TCF7L2* (rs7903146)	T allele of rs7903146 associated with an increased risk of T2D [89]	Associated with T2D in Asian Indians [93,95,96]	CS
6	Adiponectin (+45T/G;+276G/T)	Significantly associated with T2D and adiponectin level in Japanese population, and with insulin resistance in some Caucasian populations [74,80,163]	+10211T>G associated with T2D [86]	CS
7	*FTO*	Associated with T2D (adiposity mediated) [98,99]	Associated with T2D and obesity in south Asian Indians [104]	CS
8	*FTO*	Associated with BMI [97,100,101]	Associated with T2D in south Asian Indians [103]	CS
9	*PC-1* (K121Q)	Not associated with T2D in Caucasians in Sweden and Denmark [164,165] Associated with T2D in Caucasians in USA, and in Caucasians in Finland [54,166] Has no significant impact on insulin sensitivity [51] Associated with obesity and increased risk of T2D [43] Associated with insulin resistance/ atherogenic phenotypes [42] Not associated with obesity [167]	Associated with T2D in a south Indian population [54] Not associated with T2D in a north Indian population [168]	CS
10	*CDKAL1*, *CDKN2A/B*, *HHEX* and *BAZ1B*	Associated with T2D in Caucasian populations [98,110–112,169]	Associated with T2D in south Indians [130]	GWAS

CS: Candidate study; GWAS: Genome-wide association study; T2D: Type 2 diabetes.

gene found a moderate association between two low-risk alleles ($[CCTTT]_{13\&17}$) and a high-risk allele ($[CCTTT]_{13}$) and DR [144], while the 27 bp intron 4 VNTR of the *eNOS* gene was not associated with DR in a population-based south Indian cohort [145].

Diabetic retinopathy is the leading cause of vision impairment in working-aged adults and there has been not much GWAS data published on this outcome [146]. A GWAS in a Taiwanese population identified a genetic association for susceptibility to DR in five novel chromosomal regions and the *PLXDC2* and *ARHGAP22* genes, which are implicated in endothelial cell angiogenesis and increased capillary permeability. These findings suggested unsuspected pathways in the pathogenesis of DR [147].

■ Genetic studies of diabetic nephropathy

Diabetic nephropathy (DN) is a kidney disease that occurs as a result of diabetes. Nephropathy is the leading cause of chronic renal failure worldwide and is responsible for renal failure in approximately a third of patients who undergo dialysis. One of the initial markers of this condition is microalbuminuria, which indicates an increased risk of progression to nephropathy as well as an elevated risk of cardiovascular events. The prevalence of DN was 30.3% in chronic renal failure patients. The prevalence of chronic interstitial nephritis and chronic glomerulonephritis was 23 and 17.7%, respectively. The prevalence of nephropathy in India was less (8.9% in Vellore and 5.5% in Chennai) when compared with the prevalence in Asian Indians in the UK (22.3%) [6,47].

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide, and it is estimated that approximately 20% of Type 2 diabetic patients reach end-stage renal disease during their lifetime. Risk factors for overt nephropathy have been found to be poor glycemic control, long duration of diabetes and high systolic blood pressure, while for microalbuminuria smoking and high diastolic blood pressure were additional risk factors [148].

Genetic susceptibility plays an important role in the pathogenesis of DN and multiple genetic approaches, including candidate gene association studies and GWAS are being pursued to identify the susceptibility gene(s) for DN [149–153]. A study conducted in Asian Indians on genes encoding the inflammatory cytokines that might confer susceptibility to DN showed that common variants of inflammatory cytokine genes (*CCL2, CCR5* and *MMP9*) exert a modest effect on risk of DN and a combination of risk alleles confer a substantial increased risk of nephropathy in T2D among Asian Indians [154].

Earlier, we demonstrated that a silent *PPARGC1A* gene polymorphism (Thr394Thr) is associated with T2D in Asian Indians [64], but the Pro12Ala of the *PPARG* gene, which is protective against diabetes in Europeans, was not protective in Asian Indians [55]. This study was extended to investigate the possible association of *PPARG* and *PPARGC1A* gene variants with DN. Out of the six variants selected (-1279G/A, Pro12Ala and His478His of the *PPARG* gene and Thr394Thr, Gly482Ser and +A2962G of the *PPARGC1A* gene), the Gly482Ser polymorphism of the *PPARGC1A* gene was found to be associated with DN in the Asian Indian population. In addition, the study also showed that the *PPARG* gene is not associated with or protective against DN in this ethnic group [155].

Using GWAS data from the GoKinD collection, Pezzolesi *et al.* have reported the genetic associations of *ELMO1* with DN [156]. Earlier studies have shown the strongest associations to be at variants located more than 280 kb apart in introns 17 and 13 [157,158].

Genome-wide association studies on susceptibility variants associated with kidney diseases and measures of kidney function have indentified common variants in the *UMOD* and *PRKAG2* genes that are associated with risk of chronic kidney disease, variants in *CLDN14* with risk of kidney stone disease, and variants in or near *SHROOM3, STC1, LASS2, GCKR, NAT8/ALMS1, TFDP2, DAB2, SLC34A1, VEGFA, FAM122A/PIP5K1B, ATXN2, DACH1, UBE2Q2/FBXO22* and *SLC7A9* that are associated with differences in glomerular filtration rate. Results from GWAS of renal phenotypes aid our understanding of the underlying mechanisms of kidney function and disease [159].

In conclusion, the eventual genetic landscape of T2D and its various complications in Asian Indians will integrate a large number of genes, many with multiple variants and GWAS could shed more light on this.

Conclusion

Advances in genotyping techniques and the availability of large patient cohorts have made it possible to identify common genetic variants associated with T2D through GWAS. A genetic dissection of T2D mellitus in Asian Indians could help our understanding of the disease mechanism and explain the increased susceptibility to T2D mellitus of this ethnic group.

Future perspective

Dissecting the genetics of T2D is a complicated task and in the past 10 years there have been tangible breakthroughs – at least 18 genes that have consistently been shown to increase the risk of T2D have been identified. Although these new findings can be considered only as a starting point, there is little doubt that additional T2D loci and genes will be identified through follow-up of 'hot spots' in existing scans and GWA scans focused on certain ethnic groups and specific clinical or pathophysiological phenotypes of T2D. As the effect of these genetic variants becomes increasingly established, attention needs to be focused on gene–gene and gene–environment interactions. Hopefully this could help in earlier identification of, and possibly better therapies for, T2D.

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