Review Article

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The genetics of diabetes mellitus

V. Radha, K.S. Vimaleswaran, R. Deepa & V. Mohan

Madras Diabetes Research Foundation & M.V. Diabetes Specialities Centre, Chennai, India

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Genes play an important role in the development of diabetes mellitus. Putative susceptibility genes could be the key to the development of diabetes. Type 1 diabetes mellitus is one of the most common chronic diseases of childhood. A combination of genetic and environmental factors is most likely the cause of Type 1 diabetes. The pathogenetic sequence leading to the selective autoimmune destruction of islet b-cells and development of Type 1 diabetes involves genetic factors, environmental factors, immune regulation and chemical mediators. Unlike Type 1 diabetes mellitus, Type 2 diabetes is often considered a polygenic disorder with multiple genes located on different chromosomes being associated with this condition. This is further complicated by numerous environmental factors which also contribute to the clinical manifestation of the disorder in genetically predisposed persons. Only a minority of cases of type 2 diabetes are caused by single gene defects such as maturity onset diabetes of the young (MODY), syndrome of insulin resistance (insulin receptor defect) and maternally inherited diabetes and deafness (mitochondrial gene defect). Although Type 2 diabetes mellitus appears in almost epidemic proportions our knowledge of the mechanism of this disease is limited. More information about insulin secretion and action and the genetic variability of the various factors involved will contribute to better understanding and classification of this group of diseases. This article discusses the results of various genetic studies on diabetes with special reference to Indian population.

Key words Genes - HLA - insulin resistance - PPARγ - type 1 diabetes - type 2 diabetes

The prevalence of diabetes has been rapidly increasing world-wide. Both Type 1 and Type 2 diabetes are known to be multifactorial diseases caused by a combination of genetic (inheritance) and environmental (diet and lifestyle) factors[1,2]. This article will focus on genetic factors associated with both Type 1 and Type 2 diabetes.

Pathophysiology of Type 1 diabetes

Type 1 diabetes is the most severe type of diabetes, requiring daily insulin injections on a life long basis. The etiology of Type 1 diabetes is not well understood. This type of diabetes results from selective destruction of the insulin producing β cells of the pancreatic islets of Langerhans, a process that is immunologically mediated and occurs in genetically susceptible individuals. The islet β-cells are destroyed by an autoimmune response mediated by T-lymphocytes (T cells) that react specifically to one or more β-cell proteins (autoantigens)[3]. The disease process evolves over a period of years during which time there appear a number of immune markers indicating the presence of ongoing β cell damage, accompanied by a progressive decline of β-cell function. The clinical syndrome of Type 1 diabetes mellitus becomes evident when the majority of β-cells have been destroyed and hyperglycaemia supervenes. Several genetic factors have been identified for the disease although environmental factors also play a crucial role[4,5].

Genetics of Type 1 diabetes

Over 20 regions in the human genome are associated with Type 1 diabetes, but most make only a minor contribution overall to the susceptibility to Type 1 diabetes[6,7]. Some of the genes associated with Type 1 diabetes are shown in Table I. The strongest linkage with Type 1 diabetes is shown by the human leucocyte antigen (*HLA*) gene cluster in the major histocompatibility complex (*MHC*) located on chromosome 6p21.

HLA and Type 1 diabetes

HLA antigens are cell-surface glycoproteins that play a crucial role in presenting auto antigen peptide fragments to T lymphocytes and thus initiate an auto immune response[8]. They comprised of two classes, class I and class II, which are encoded by different genes within the HLA region and thus differ fundamentally in structure.

Class I molecules comprise the HLA A, B, C while class II molecules comprise HLA DP, DQ and DR and are coded by their respective genes[9]. The HLA class II molecules are central to the human immune response because they present peptide antigens to T-helper (CD 4 positive) cells. There are two types of class II genes: those encoding α- polypeptides and those encoding β-polypeptides which together form the functional class II α-β heterodimer. This results in a variety of genes

Table I. Susceptibility genes for type 1 diabetes

Locus	Chromosome location	Candidate genes	Markers
IDDM1	6p2l.3	HLA DR/DQ	-
IDDM2	11p15.5 16q22-24	INSULIN VNTR	- D16S3098
IDDM3	15q26		D15S1O7
IDDM4	11q13.3	MDU1, ZFM1, RT6, ICE, LRP5, FADD, CD3	FGF3, D11S1917
IDDM5	6q25	MnSOD	ESR, a046Xa9
IDDM6	18q12-q21	JK (Kidd), ZNF236	D18S487, D18S64
IDDM7	2q31-33	NEUROD	D2S152, D251391
IDDM8	6q25-27	-	D6S281, D6S264, D6S446
IDDM9	3q21-25	-	D3S1303, D10S193
IDDM10	10p11-q11	-	D10S565
IDDM11	14q24.3-q31	ENSA, SEL-1L	D14S67
IDDM12	2q33	CTLA-4	(AT)n 3' UTR, A/G Exon 1
IDDM13	2q34	IGFBP2, IGFBP5, NEUROD, HOXD8	D2Sl37, D2S164, D2S1471
IDDM15	6q21	-	D6S283, D6S434, D6S1580
IDDM17	10q25	-	D10S1750, D10S1773
IDDM18	5q31.1-33.1	IL12B	IL12B

MDU1, Monoclonal Duke University; ZFM1, zinc finger protein; RT6, rat T cell differentiation antigen; ICE, interleukin-1 β converting enzyme; LRP5, low-density lipoprotein receptor related protein; FADD, fas-associated protein with death domain gene; CD3, cluster differentiation factor 3 gene; MnSOD, manganese superoxide dismutase; JK (Kidd), JK kidd blood group gene; (ZNF 236), zinc finger protein 236; ENSA, endosulphine alpha; SEL, 1L suppressor of Lin 12 - like; CTLA, 4, cytotoxic T - lymphocyte associated antigen 4; IGFBP2, insulin like growth factor binding protein 2; IGFBP5, insulin like growth factor binding protein 5; NEUROD, neurogenic differentiation; HOXD8, homeobox D8; IL12B, interleukin 12B

such as *DP a, DP b, DQ a, DQ b, DR a* and *DR b*. Excepting DR α, all the other genes are expressed. The β genes are known to be highly polymorphic[10]. The number of polymorphic alleles range between 18 (HLA-C) to 72 (HLA-DR), which gives several million possible haplotypes. For example, there are several loci at DR β region, such as DRB1, DRB2, DRB3, DRB9 and DRA. A further resolution gives rise to generic level HLA typing. Polymorphisms in the genes encoding specific peptide chains of the HLA molecules may therefore modulate the ability of the β cell derived antigen to trigger an auto immune response against the β cell.

Molecular cloning, sequencing and fine mapping of HLA genes and class II proteins have made it possible to study genetic loci that may explain the strong association of and linkage to Type 1 diabetes[11]. It is speculated that the HLA DQ class II molecules associated with Type 1 diabetes provide antigen presentations that generate T-helper cells that initiate an immune response to specific islet cell autoantigens. This immune response includes the formation of cytotoxic T cells, which kill the insulin producing cells in the islets of Langerhans, and also leads to the formation of autoantibodies.

The combination of susceptibility genes and environmental factors may initiate a disease process that is associated with a formation of an autoimmune response to the insulin-producing cells. This autoimmune reaction is reflected by the presence of antibodies against prominent antigens in the pancreatic β cell. The HLA type of the individual may control the recognition of certain autoantigens. The most important markers for β cell autoimmunity are autoantibodies against insulin, glutamic acid decarboxylase (GAD65) and islet cell antigen-2(IA-2)[12].

Many studies have shown that regardless of ethnic background, Type 1 diabetes is strongly genetically linked and associated with HLA on chromosome 6[11,13]. A recent fine-mapping study of the UK population confirmed that the DRB 1 and DQB1 genes are the major determinants of HLA-encoded susceptibility to Type 1 diabetes[14]. Although disease associations with the DQ genes are generally stronger than with the *DR B1* gene[15] it is clear from recent studies that both loci are important for determining overall disease risk. The HLA-DQ 6 molecule confers strong protection against Type 1 diabetes. This protective effect is dominant over the susceptibility conferred by the DR B1 loci. Any genotype that includes DQ 6 confers a low risk of disease, due to the dominant protective effect of the DQ 6 molecule[16]. The HLA-DPB 1 locus also seems to influence disease risk independent of DR and DQ alleles. The contribution of DPB 1 to disease susceptibility appears to be small, but its role may be more significant among individuals who do not carry the high-risk *DR B1* and DQ 8 genotype[15].

Polymorphisms of the genes encoding the α- and β- chains of the class II molecule could alter the binding of autoantigen peptide within the cleft of the molecule, and thus the efficiency of its presentation to helper T lymphocytes. HLA coded disease susceptibility may be predicted by a combination of seven residues (DR β residues 67 and 86, DQ α-residue 47 and DQ β-residues 9, 26, 57 and 70)[16]. Although these residues do not necessarily have a functional importance in the pathogenesis of diabetes, they may be useful as a marker for predicting disease risk.

The influence on disease susceptibility of a particular HLA molecule is likely to be determined by its three-dimensional structure, which in turn has a significant impact on its function in the immune response. The structural differences between diabetogenic and protective molecules result in differences in antigen peptide selectivity and binding affinity and the stability of the HLA molecule on the cell surface. Different HLA molecules favour distinct peptide binding motifs and may therefore interact differently with a given diabetogenic autoantigen. This mechanism seems to offer protection for certain haplotypes and susceptibility for certain others[17] (Table II). The disease susceptibility conferred by HLA represents the combined effect of several genes within the MHC. At least three major loci are involved (HLA- DRB 1, -DQA 1 and -DQB1), but several other genes may also contribute. The precise identity of these genes remains to be determined.

Table II. HLA markers and Type 1 diabetes

Polymorphic markers on HLA	DRB1	Effect on diabetes susceptibility
DQA1*0102/DQB1*0602	1501	Protective
DQA1*0102/DQB1*0502	1601	Predisposing
DQA1*0103/DQBI*0601	1502	Neutral
DQA1*0501/DQB1*0201	0301	High risk
DQA1*0301/DQBI*0302	0401	High risk
DQA1*0301/DQB1*0302	0402	Predisposing
DQA1*0301/DQBI*0302	0403	Neutral
DQA1*0301/DQB1*0302	0404	Predisposing
DQA1*0301/DQB1*0302	0405	High risk
DQA1*0301/DQB1*0301	0401	Neutral
DQA1*0301/DQB1*0303	0401	Neutral
DQA1*0101/DQB1*0503	1401	Protective
DQA1*0201/DQB1*0303	0701	Protective
DQA1*0401/DQB1*0402	0801	Predisposing

It has been estimated that 60 per cent of the genetic susceptibility to Type 1 diabetes is conferred by HLA, and this type of Type 1 diabetes is labeled as IDDM 1. Several approaches to identify other susceptibility genes have been undertaken. Currently there are more than 20 genes identified as Type 1 diabetes candidate genes (Table I). It is possible that a combination of HLA with other genetic factors may either enhance or decelerate the Type 1 diabetes process[18].

Other genetic markers for Type 1 diabetes

Insulin gene (INS) VNTR regulatory polymorphism: Subjects with allelic variation at the insulin gene (INS) VNTR regulatory polymorphism have been categorized as IDDM2. Two discrete classes have been shown in Caucasians, class I alleles are recessive and induce susceptibility to Type 1 diabetes, while class III are dominant and protective. The class III alleles are hypothesized to silence rather than enhance thymic insulin expression and studies also suggest that class III VNTR-associated INS mRNA is associated with elevated levels of preproinsulin protein which enhances immune tolerance to preproinsulin, a key autoantigen in Type 1 diabetes. However, studies on parental transmission have revealed that the class I allele does not predispose to disease when paternally inherited, suggestive of polymorphic imprinting, but this paternal effect is observed only when the father's untransmitted allele is a class III[19,20].

Locus on chromosome 15q26: Subjects with a susceptibility locus near D15Sl07 on chromosome 15q26 are categorized as IDDM3. A study on 250 families from UK, USA and Canada revealed that families lacking the typical HLA predisposition had evidence for linkage, with sibling pair disease concordance or discordance being strongly affected by allele sharing at the D15S107 locus[21]. Evidence for this association also arises from other studies on 104 Caucasian families and 81 Danish families[22,23]. However, contradictory results were reported in a study on 265 Caucasian families[24].

Cytotoxic T lymphocyte associated-4 (CTLA-4) gene: This gene encodes for IDDM 12. The *CTLA-4* gene is a strong candidate gene for autoimmune diseases since it encodes for a molecule that functions as a key negative regulator of T-cell activation, and the linked markers encompass a region containing an (AT) n microsatellite located in the 3' UTR of the *CTLA-4* gene. The linkage to *CTLA-4* gene is not well understood. It has been speculated that a gene polymorphism involving AT repeat at the C terminus at the 3' end of the gene may affect the stability of CTLA -4 mRNA. The longer the repeat, the less stable the CTLA-4 mRNA. Because CTLA-4 is critical to T-cell apoptosis, it has been speculated that long AT repeats may lead to T-cell survival because the CTLA 4 protein is not formed[25]. A recent multiethnic (US Caucasian, Mexican-American, French, Spanish, Korean, and Chinese) study on 178 simplex and 350 multiplex families, performed a transmission disequilibrium test and suggested a significant association/linkage with three markers within CTLA4 and two immediate flanking markers (D2S72 and D2S105) on each side of CTLA4[26].

Some other prominent candidates are the insulin gene on chromosome 11 the *TCR* genes, immunoglobulin genes, *CD 4* gene and the vitamin D receptor gene. However association studies of these genes have produced conflicting results[27].

Genetic studies on Indian Type 1 diabetic subjects

Studies on HLA in Indian Type 1 diabetic subjects started over two decades ago. Serjeantson *et al*[28] showed that the DR, DQ linkage arrangements in south Indians for DR2, DR4 and DRw6 were different from those commonly seen in Europeans. Kirk *et al*[29] studied Type 1 diabetic subjects from three different centres and showed that HLA-B8 and BF*F were significantly increased and C4*A6 decreased in south Indians. Another study by Hitman *et al*[30] revealed that south Indian Type 1 diabetic subjects had an increased frequency of the Taq 1 DQ beta restriction fragment length polymorphisms designated T2 omega/T6 and of homozygotes for Taq 1 DQ alpha 4.6 kb. The protective effect of "DPA*B" and "DPB*B" has also been shown among eastern Indian Type 1 diabetic subjects[31].

Analysis of MHC class II alleles showed statistically significant increase of DRB1*03011 DQB1*0201, DQA1*0501 and DPB1 *2601 compared to normals[32]. Mehra *et al*[33] reported the haplotype A26-B8-DR3 to be the most common autoimmunity-favouring haplotype in Indians. This association was considered to be unique to Indian autoimmune patients, as it replaces the otherwise most commonly associated Caucasian haplotype Al-B8-DR3 (AH8.1) in this population[33]. Several studies have explored the association of genes with autoimmunity in Indians[34-36]. Collaborative studies are currently in progress on the HLA associations in north and south Indian Type 1 diabetic patients.

Although several genes have been implicated in Type 1 diabetes there is still no clear picture of which genes are specifically linked to this disease. Fine mapping of the intervals identified by the genome screens has not yet determined the identity of the putative susceptibility genes for Type 1 diabetes. However, identification of genetic markers should facilitate early screening of individuals with a family history of Type 1 diabetes, to identify those at high risk of the disease. As environmental factors have a major impact on the risk of Type 1 diabetes, it is vital that genetic and environmental components are studied in tandem. The identification of susceptibility genes and studies of their function could allow insights into the pathophysiology of Type 1 diabetes and ultimately lead to new therapeutic strategies. The molecular mechanisms by which the HLA molecules influence disease risk needs to be elucidated by future studies.

Pathophysiology of Type 2 diabetes

The natural history of Type 2 diabetes has four stages (Fig. 1). The first stage begins at birth, when glucose homeostasis is normal but individuals are at risk for Type 2 diabetes because of genetic polymorphisms (diabetogenic genes). During stage 2, decrease in insulin sensitivity emerges probably as a result of a genetic predisposition and lifestyle (environmental), which are initially compensated for by an increase in β-cell function, so that glucose tolerance remains normal[37], but later both the β-cell function and insulin sensitivity, deteriorate, so that when challenged, as during a glucose tolerance test or a standardized meal, post prandial glucose tolerance becomes abnormal (stage of impaired glucose tolerance). At this point, β-cell function is clearly abnormal, but sufficient to maintain normal fasting plasma glucose concentrations. In stage 3, as a result of further deterioration in β-cell function and increased insulin resistance, fasting plasma glucose can increase due to an increase in basal endogenous glucose production, but the patient is still asymptomatic. Finally in stage 4, as a result of further deterioration in β-cell function, both fasting and postprandial blood glucose levels reach clearly diabetic levels and the patient becomes symptomatic.

The ability of β-cells to adapt to insulin resistance depends on various genetic factors that determine the total β-cell mass, rates of replication and apoptosis of the cells, and the activity of key biochemical components of cells. Environmental factors can probably aggravate the genetic predisposition leading to β-cell failure[38].

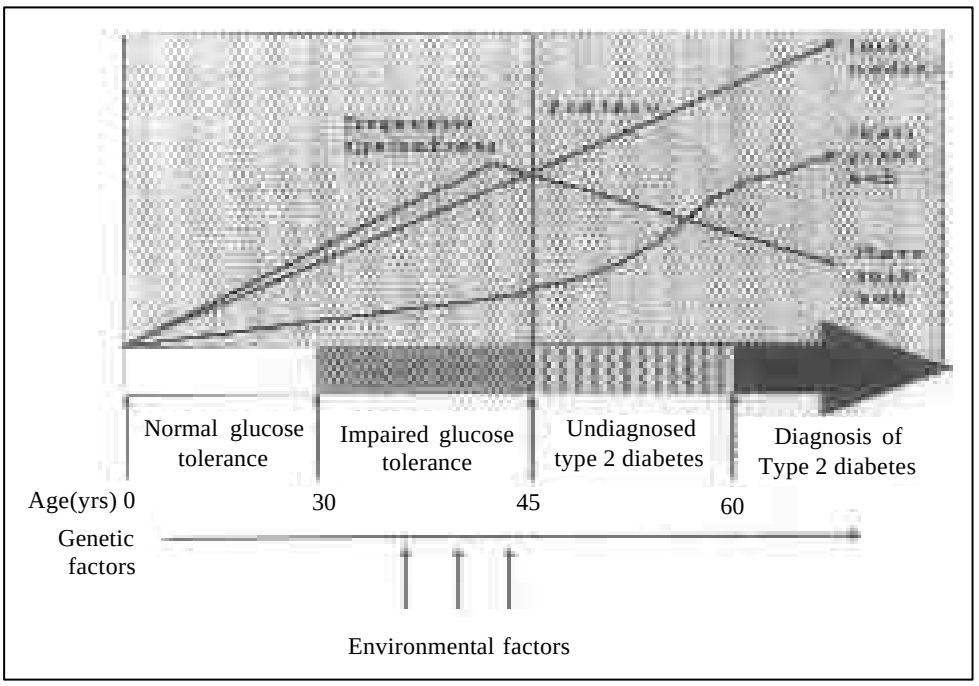

Fig. 1. A model for the natural history of Type 2 diabetes.

Current evidence supports the view that the liver and β-cells are sensitive to insulin and that increased hepatic glucogenesis and β-cell failure are different facets of the same metabolic phenotype. The exact mechanism of β-cell failure however remains controversial and is probably regulated at the gene level[β8-41]. The first phase of insulin secretion occurs in response to an increase in extracellular glucose and ATP and cAMP levels increase. This leads to closure of the ATP-sensitive potassium channels, which causes depolarization of the β-cell membrane and an influx of calcium through the voltage-sensitive calcium channels; the resultant increase in intracellular calcium leads to the movement of insulin-containing granules towards the β-cell membrane, where they merge, incorporate, and melt into the membrane with the release of the granules contents (insulin, proinsulin and C-peptide). The second phase of insulin release involves synthesis of new insulin molecules as well as ATP-dependent mobilization of granules from a storage pool into a rapidly releasable pool. The normal β-cell response to an increase in glucose concentration is dependent on glucose entry into the β-cell and its metabolism, synthesis of insulin and insulin granules, and other proteins necessary for moving the granules towards the β-cell membrane and facilitating their melting into the membrane so that their contents can be released. There is evidence that the integrity of these responses is necessary for maintenance of normal glucose homeostasis.

This complex scheme that maintains normal glucose homeostasis permits interplay of genetic and environmental factors at multiple sites of the metabolic pathway leading to Type 2 diabetes. The common variety of Type 2 diabetes results from a combination of genetic and acquired factors that adversely affect cell function and tissue insulin sensitivity.

Genetics of Type 2 diabetes

Type 2 diabetes shows a clear familial aggregation but it does not segregate in a classical Mendelian fashion. It is polygenic, with different combinations of gene defects. Genetic and environmental factors may affect insulin biosynthesis, insulin secretion and insulin action (Fig. 2). The complex interactions

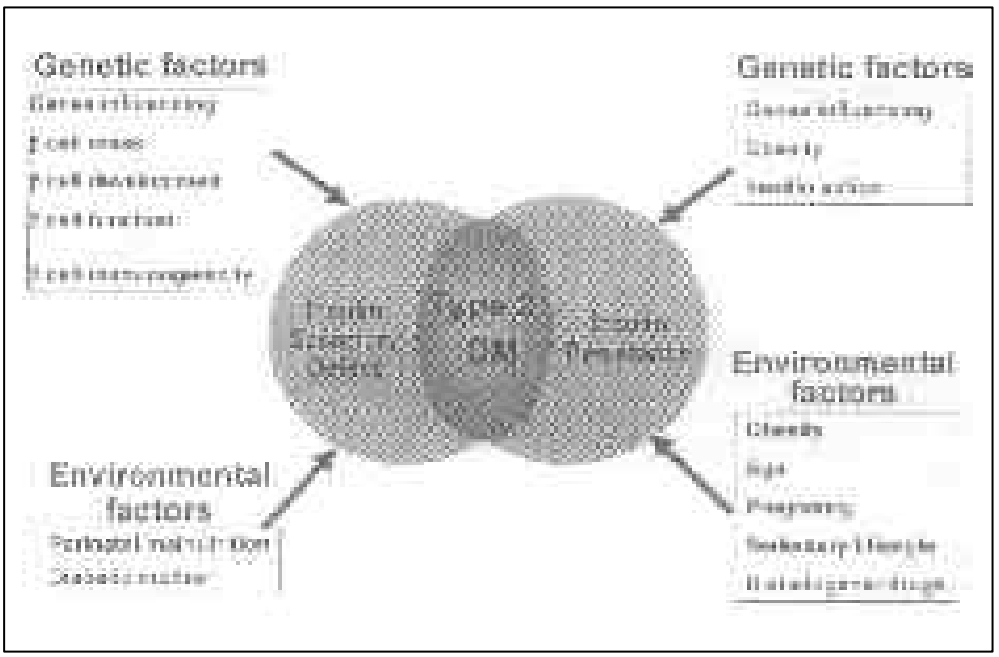

Fig. 2. Genes - environment interaction in Type 2 diabetes.

between genes and the environment complicate the task of identifying any single genetic susceptibility factor for Type 2 diabetes. The maintenance of normal glucose homeostasis depends on a precisely balanced and dynamic interaction between tissue sensitivity to insulin (especially in muscle and liver) and insulin secretion. The molecular circuitry that maintains glucose homeostasis depends on the result of several combined gene defects, or from the simultaneous action of several susceptible alleles, or else from combinations of frequent variants at several loci that may have deleterious effects when predisposing environmental factors are present[42].

It is generally accepted that insulin resistance (IR) precedes the failure of insulin secretion and exacerbates this by imposing an increased secretory burden on the β-cells[43]. However, subtle abnormalities in β-cell function have been demonstrated early in the course of Type 2 diabetes mellitus, and even in first degree relatives of individuals with Type 2 diabetes mellitus - suggesting a possible basis for an inherited component for β-cell failure[44]. A prospective study in Pima Indians showed that the progression from normal to IGT and finally to Type 2 diabetes was accompanied by a progressive decline in β-cell secretory capacity[45]. The mechanisms underlying β-cell failure in Type 2 diabetes however remain elusive.

Type 2 diabetes being an extremely heterogenous disorder, phenotypically, and pathogenetically, is polygenic in nature. This means that multiple genes (polymorphism), each insufficient in themselves, must be present in order to cause diabetes. Such genes might affect β-cell apoptosis, regeneration, glucose sensing, glucose metabolism, ion channels, energy transduction, and other islet proteins necessary for synthesis, packaging, movement and release of secretory granules. Many rare forms of defective glucose metabolism have been shown to be caused by gene defects involving the β-cell and the insulin receptor[46]. Of these the most common and important form is the maturity onset diabetes of the young (MODY).

Maturity onset diabetes of the young: MODY is a monogenic subtype of Type 2 diabetes, characterized by an autosomal dominant inheritance, and an age of onset at 25 yr or younger. Phenotypically, MODY is primarily associated with insulin secretion defects and patients with MODY have normal insulin sensitivity and are in most cases lean[47]. It has been estimated that 2-5 per cent of all patients with Type 2 diabetes may have MODY. Studies by Mohan *et al* showed a high prevalence of MODY in south Indians (4.8%)[48], besides reporting the insulin responses in them[48] and β-cell response in the offspring of patients with MODY[49].

MODY is genetically heterogeneous and at present there are at least 6 different forms, *viz*., MODY1—MODY6. The different forms are caused by mutations in the genes encoding hepatocyte nuclear factor -4α (HNF -4α), glucokinase, hepatocyte nuclear factor -1α (*HNF -1α*), insulin promoter factor (IPF-1), hepatocyte nuclear factor -1β (*HNF -1b*) and *Neuro D*, respectively[50-52]. MODY 1-3 seem to be the most common the world over. All the known MODY genes have also been considered as possible candidates for gene defects in late-onset Type 2 diabetes mellitus.

Candidate genes for Type 2 diabetes

Recent insights into the molecular mechanisms of pancreatic development, insulin signaling, insulin secretion and adipogenesis, and in physiologic changes in these and other pathways thought to contribute to diabetes, have resulted in an explosion in the number of candidate genes for Type 2 diabetes[53,54]. The following are a few potential candidate genes with strong evidence for a susceptibility role.

As discussed earlier, genetic polymorphism at various points that could affect utilization of blood glucose can lead to Type 2 diabetes. Type 2 diabetes being a component of the insulin resistance syndrome, genetic polymorphism associated with the contributory factors of this syndrome like obesity, insulin resistance may also contribute to diabetes. Some of the candidate genes associated with insulin resistance, obesity and insulin secretion are shown in Table III.

Insulin gene & genes associated with insulin secretion: The human insulin gene (*INS*) is located on chromosome 11 p 15.5. It appears that transcription of the insulin gene is the restricting step for insulin synthesis and secretion and transcription is regulated at least in part by the untranscribed sequences immediately upstream (5' flanking sequences) of the transcription start site. The promoter functions in a distinctly cell type-specific fashion. The sequence of the insulin promoter must encode a regulatory signal that only β-cells can read correctly. However, only a small number of diabetics seem to have mutation in this gene[55].

The pancreatic duodenal homeodomain (*PDX 1*) gene is a transcription factor gene that is central in regulating pancreatic development and islet cell function. In the pancreatic islets, PDX 1 functions in concert with additional transcription factors in regulating expression of insulin and additional islet specific genes[56]. Pancreatic and liver tissues share a common expression of several factors, chief among which are the hepatocyte nuclear factor (*HNF*) gene. A number of mutations in this gene is known to cause MODY and Type 2 diabetes[57].

An association has been shown between Type 2 diabetes and variations in β-cell genes including the *SUR/KIR 6.2* genes that encode components of the β-cell K ATP channel, which couple glucose metabolism to membrane depolarization and subsequent insulin release[58].

Genes associated with insulin resistance: One of the main candidate genes that is often implicated in adipogenesis, insulin resistance and Type 2 diabetes is the peroxisome proliferator activated receptor-γ (*PPAR-g*) gene. This is a transcription factor that is involved in adipogenesis and in the regulation of adipocyte gene expression and glucose metabolism. Within a unique domain of *PPAR-γ 2* gene that enhances ligand-independent activation of a prevalent Pro12Ala polymorphism has been identified[59]. The polymorphism in several studies

Table III. Candidate genes for Type 2 diabetes

Genes	Implications
Peroxisome proliferator activated receptor -γ (PPAR-γ)	Obesity & insulin resistance leading to Type 2 diabetes
PPAR-γ coactivator -1 (PGC-I)	
GLUT 4	
Adiponectin	
Resistin	
Leptin	
Uncoupling protein-2 (UCP2)	
lnsulin receptor substrate (IRS)	Insulin signalling and glucose transport
Calpain 10	
Glucose transporter (GLUT)	
	Genes involved in insulin secretion
Insulin	
GLUT2	
SUR	
Kir 6.2	
GCK	

has been shown to be involved in the pathogenesis of obesity and recently, using a family based design to control for population stratification it was reported that Ala -allele of this polymorphism was associated with decreased risk of Type 2 diabetes[60]. Variation in the insulin receptor substrate (*IRS*) gene has been shown to be associated with decreased insulin sensitivity and impairment of insulin stimulated PI3-kinase activity[61]. The glucose transporter (*GLUT*) gene is an attractive candidate since it acts as a sensor to the β-cell and as a major signaling molecule[62]. Recent studies have shown the role of calpain gene in the regulation of both insulin secretion and insulin action[63].

Genes associated with obesity: It has been estimated that 40 to 70 per cent of the variation in obesity-related phenotypes in humans is heritable. Studies on experimental models have shown single-gene mutations to cause obesity. However in humans, obesity seems to be considerably more complex, with gene-environment interaction. Some of the genes which has been of great interest in obesity include adiponectin, resistin and uncoupling protein 2 (*UCP2*).

Genetic variants in the adiponectin gene associated with hypoadiponectinemia may result in insulin resistance and Type 2 diabetes. Genome wide scan on Caucasians on adiponectin gene on chromosome 3q27 revealed a common silent T-G exchange in nucleotide 94 (exon 2) of the adiponectin gene to be associated with increased circulating adiponectin levels. A Japanese study suggested that single nucleotide polymorphisms at positions 45 and 276 in the adiponectin gene to be associated with risk for Type 2 diabetes[64].

Leptin receptor mutations have been identified, which has been associated with hyperglycaemia in

mice. Pro12Ala substitution in the *PPAR-γ* has been associated with leptin levels indicating an interaction between obesity and insulin sensitivity[65]. After a meta analysis of 9 studies on leptin receptor (LEPR) gene and obesity Heo *et al*[66] suggested that certain genotypic effects could be population-specific. However, the study also suggested that there was no statistically compelling evidence that the LEPR alleles were associated with BMI or waist circumference in the overall population[66,67].

Uncoupling protein 2 *(UCP2)* has been implicated in thermogenesis and has been shown to be associated with obesity and Type 2 diabetes. Evidence for UCP association with glucose homeostasis comes from the studies on isolated islet cells. Glucose increased expression of UCP2 in isolated islets while leptin decreased the same[68].

Genetic studies on Indian Type 2 diabetic subjects

Several genetic studies have been performed on Indian Type 2 diabetic subjects in the southern part of India. Initial studies were focused on the islet amyloid polypeptide (*IAPP*), revealed that *IAPP* gene is unlikely to represent a major susceptibility factor for the development of Type 2 diabetes[69]. Following this the glucokinase gene, apolipoprotein D, *GLUT 1*, *GLUT 4* were studied in south Indian Type 2 diabetics[70]. These studies showed that glucokinase acts as a minor gene influencing the development of Type 2 diabetes, and GLUT1 polymorphism may contribute to susceptibility to Type 2 diabetes. A significant difference in genotype distribution of apo D genotypes between diabetic subjects and controls was observed, which was similar to that previously found in Nauruan subjects. This study which also showed no association between diabetes and the GLUT 2 Taq I polymorphism concluded that Apo D might act as a modifying gene for Type 2 diabetes[71].

A study on 10 candidate genes: namely the glucagon receptor, insulin receptor substrate 1, insulin receptor, human beta 3 adrenergic receptor, fatty acid binding protein 2, mitochondrial tRNA [*Leu(UUR)*], sulphonylurea receptor, human uncoupling protein and the glycogen-associated regulatory subunit of protein phosphatase-1 genes suggested that none of them was associated with Type 2 diabetes in south Indians[72]. *Calpain 10* gene showed a positive association with diabetes[73]. Genes associated with obesity like the uncoupling proteins the *UCP2* and *UCP3* were studied in a subgroup of south Indians. This study though showing a lack of association of *UCP2* with Type 2 diabetes, revealed that the *UCP2* Exon 8 variant influenced weight gain by its regulation of leptin[74]. Another study suggested *UCP 3* to be associated with high waist to hip ratio[75].

Do Indians have a stronger genetic predisposition to diabetes?

Various studies on migrant Indians have consistently shown high prevalence of diabetes among Indians compared to the indigenous population[76,77]. This was later confirmed by epidemiological studies in native Indians[78]. Further, the recent projections from the World Health Organization suggest that India has nearly 30 million diabetic subjects, which is 15 per cent of the total diabetes world-wide. This number is projected to increase to 57 million by the year 2025. This epidemic increase in diabetes in India along with various studies on migrant and native Indians clearly indicate that Indians have a predilection to diabetes which could probably due to genetic predisposition.

As diabetes is a component of the insulin resistance syndrome, several studies have tried to compare the prevalence of components of this syndrome in migrant Indians with other ethnic groups. Sharp *et al*[79] and Mohan *et al*[80], showed that insulin resistance and the prevalence of hyperinsulinaemia, a precursor for diabetes are higher in Indians. Though body mass index (BMI) an indicator of obesity, is lower among Indians, the waist to hip ratio for any given BMI was higher among Indians compared to other ethnic groups. Further, for any BMI, Indians also had higher body fat and for any given body fat, Indians had higher insulin resistance compared to other ethnic groups[81]. A very recent study on neonates which compared body weight and insulin resistance of Indians with white Caucasian, supports the intrauterine origin of adiposity, central adiposity, and hyperinsulinemia in

Indians[82]. All these studies suggest that there could be genetic susceptibility to insulin resistance and diabetes.

As discussed earlier genes are triggered by environmental factors. As India is presently facing an epidemiological transition with more urbanization, there is a shift in the economy with more affluent and sedentary life-styles. This has led to a shift in the health burden from communicable diseases to non-communicable diseases, particularly diabetes. Evidence from the influence of urbanization on noncommunicable disease comes from the Chennai Urban Population Study (CUPS) which revealed increased prevalence of all the components of the metabolic syndrome in the middle income group compared to lower income group[83,84]. Studies on genes and diet interaction have revealed that a substantial interaction exists between allelic variants of lipoprotein lipase gene and dietary ingredients[85].

It thus appears that multiple genes are involved in the pathogenesis of Type 2 diabetes, each contributing a small amount to the overall risk, making Type 2 diabetes a truly complex disorder. Our understanding of genetics of the disease gives a better perspective of the biochemical and molecular mechanisms of the disease in general. A total understanding of these aspects of diabetes will help in developing better treatment modalities. However, very little is known about the genes contributing to diabetes and also the gene environment interaction in Indians and large cohort studies on this aspect would help unravel the genetics of Type 2 diabetes in this high risk group.

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Reprint requests : Professor V. Mohan, Director, Madras Diabetes Research Foundation, 4 Conran Smith Road Gopalapuram, Chennai 600086, India
e-mail: mvdsc@vsnl.com