Studies on Genetics of Diabetes in Ethnic Indians
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INTRODUCTION

Genes play a major role in the pathogenesis of type 2 diabetes and this is substantiated by several lines of evidence. First, ethnic variation in prevalence of diabetes itself points to the role of genes in diabetes although environmental factors may well explain this. Secondly, the concordance rate of Type 2 diabetes among identical twins varies between 60-90%. Thirdly, several studies have shown associations between various genes and type 2 diabetes and the intermediate traits that precede diabetes namely insulin resistance and impaired insulin secretion. Finally, recent studies on whole genome scan have implicated numerous regions on many different chromosomes, which show susceptibility to type 2 diabetes. In this chapter we review some of the published studies on genetics of diabetes in Indians.

FAMILIAL AGGREGATION OF DIABETES IN INDANS

Studies conducted 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 the Europeans had a first degree relative with diabetes compared to 45% of Asian Indians. Noteworthy was the finding that nearly 10% of Asians compared to 1% in Europeans had both parents with diabetes. Another study measured the prevalence of diabetes among the offspring of two diabetic parents in India. This study showed that 62% of offspring had diabetes or impaired glucose tolerance. This frequency was considerably higher than the prevalence of diabetes in offspring of Europeans in whom only 25% of the offspring had glucose intolerance. This shows that the “double dose” gene effect is higher in Indians.

In the Chennai Urban Population Study (CUPS) conducted on 1282 individuals in Chennai in southern India, we observed an effect of family history on the prevalence of type 2 diabetes. The prevalence was higher among subjects who had a positive family history of diabetes (18.2%) compared to subjects without (10.6%, p=0.0015). Moreover, 9.3% of subjects with family history of diabetes had impaired glucose tolerance (IGT - a pre-diabetic stage) compared to 5.0% of subjects without a family history (p = 0.016). The overall prevalence of glucose intolerance (diabetes + IGT) among subjects with two diabetic parents was significantly higher (55%) than those who had diabetic parent (22.1%, p=0.005) or those with two non-diabetic parents (15.6%, p<0.0001)

IS INSULIN RESISTANCE ALSO GENETICALLY INHERITED IN INDANS?

Sharp et al and Mohan et al, showed that insulin resistance and the prevalence of hyperinsulinemia, are higher in Indians compared to matched groups of...
Europeans. Though body mass index (BMI) an indicator of obesity was lower among Indians, the waist to hip ratio for any given BMI was higher among Indians compared to other ethnic groups and this is referred to as the "Asian Indian phenotype".  

One factor contributing to insulin resistance is obesity. Asian Indians, however, rarely have marked obesity. Studies in Caucasians reveal that even a moderate degree of obesity can elicit insulin resistance when fat is accumulated predominantly in the intra-abdominal region (visceral fat). Individuals with abnormal fat distribution, characterized by a high waist to hip ratio or a high truncal to peripheral skin fold thickness ratio appear to be predisposed to developing insulin resistance. There is data to suggest that Asian Indians are susceptible to developing truncal obesity, which might account for their propensity to insulin resistance. This tendency is reflected in reports of increased waist to hip ratios and increased truncal skin fold thickness in Asian Indians compared to other populations. This in turn leads to lower insulin sensitivity or increased insulin resistance.

Factors that determine the distribution of body fat are not known; the possibility that abnormal insulin action at the level of adipose tissue could promote the accumulation of truncal fat cannot be excluded. Studies on low birth weight and insulin resistance in Indian neonates have shown that Indian babies have hyperinsulinemia and adiposity even at birth compared to Caucasians. These studies underscore the importance of genetic susceptibility in Indians towards developing diabetes and insulin resistance (Table 1).

STUDIES ON GENES RELATED TO TYPE 1 DIABETES

Studies on HLA in Indian type 1 diabetic subjects started over two decades ago. A study by Serjeantson et al revealed that the DR, DQ linkage arrangements in South Indians to be different for DR2, DR4 and DRW6 from those commonly seen in Europeans. Kirk et al in 1985 studied Type 1 diabetic subjects from three different centres and showed that HLA-B8 and BF*F to be significantly increased and C4*16 to be decreased in South Indians. Another study by Hitman and Mohan 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 (relative risk = 10.6), and of homozygotes for Taq 1 DQ alpha 4.6 kb. The protective effect of "DPA*1" and "DPB*1" has also been shown among Eastern Indian type 1 diabetic subjects.  

Analysis of MHC class II alleles showed statistically significant increase of DRB1*0301 (p < 0.00001), DQB1*0201 (p < 0.007), DQA1*0501 (0.0027) and DPB1*2601 (p < 0.0042) compared to normals. Mehra et al reported the haplotype A26-B8-DR3 to be the most common autoimmunity-favoring haplotype in Indians. This association was considered to be unique to Indian autoimmune patients, as it replaces the otherwise most commonly associated Caucasian haplotype A1-B8-DR3 (AH8,1) in this population. Several studies have explored the association of genes with autoimmunity in Indians. Although many genes have been implicated in type 1 diabetes, no clear cut cause has been proved.

STUDIES ON GENES RELATED TO MODY IN INDIANS

Earlier studies by the senior author reported on the high prevalence of MODY (using the clinical criteria used at that time) in South Indians (4.8%). He also reported on the insulin responses in MODY and the beta-cell response in the offspring of MODY. Recently we studied 73 unrelated young South Indian diabetic subjects with at least one parent diabetic for mutations in hepatocyte nuclear factor 1-α (HNF-1-α). Only 6-8% of South Indian MODY had any mutation in HNF-1-α. Four novel missense mutations, one silent mutation, and promoter mutations were identified in the hepatocyte nuclear factor 1-α. This data demonstrates that MODY3 mutations in South Indians may be different from that observed in Western populations.

Among Europeans, mutations in the hepatocyte nuclear factor-1A (HNF1A) gene are associated with the most common form of maturity-onset diabetes of the young (MODY3). In Asian Indians, type 2 diabetes occurs earlier and often overlaps with MODY, but the genetics of the latter are unknown. In our group we investigated the prevalence of a common polymorphism, the Ala98Val of the HNF1A gene in different types of diabetes in Asian Indians, including MODY and a control group of glucose-tolerant patients and evaluated its role in conferring risk of diabetes in Asian Indians. This study showed that in Asian Indians, the Ala98Val polymorphism of HNF1A gene is associated with MODY and with earlier age at onset of type 2 diabetes. This is the first report on the genetics of MODY from India and also the first showing an association of this polymorphism with MODY and age at onset of type 2 diabetes.
Table 1. Summary of Genetic Studies in Indians

<table>
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<th>Genes Studied</th>
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<tr>
<td>I. Type 1 Diabetes Genes</td>
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<tr>
<td>HLA</td>
<td>Serjeantson et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>DR, DQ linkage arrangements in South Indians to be different for DR2, DR4 and DRW6 from those commonly seen in Europeans</td>
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<td></td>
<td>Kirk et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>HLA-B8 and BF<em>F to be significantly increased and C4</em>A6 to be decreased in South Indians</td>
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<td></td>
<td>Hitman and Mohan&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Increased frequency of the Taq 1 DQ beta restriction fragment length polymorphisms in South Indians</td>
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<td></td>
<td>Mehra et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>The haplotype A26-B8-DR3 to be the most common autoimmunity-favoring haplotype in Indians</td>
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<td>II. MODY Genes</td>
<td>Mohan et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>High prevalence of MODY in South Indians</td>
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<td></td>
<td>Radha et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>MODY3 mutations in South Indians different from that observed in Western populations</td>
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<td></td>
<td>Anuradha et al&lt;sup&gt;45&lt;/sup&gt;</td>
<td>HNF-1 alpha Ala98Val associated with MODY and age at onset of diabetes in South Indians</td>
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<td>III. Type II Diabetes Genes</td>
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<td>1. Genes involved in Insulin secretion</td>
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<td>a. Insulin gene</td>
<td>Sanjeevi et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Increased occurrence of the class 3 allele of the hyper variable region in the 5' region of insulin gene</td>
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<td>b. IAPP gene</td>
<td>Rani et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>No abnormalities in the IAPP gene in South Indians</td>
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<td>c. TCFL2 gene</td>
<td>Chandak et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>rs12255372 and rs7903146 polymorphisms associated with type 2 diabetes</td>
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<td></td>
<td>Bodhini et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>'T' allele of rs12255372 and rs7903146 Polymorphisms associated with type 2 diabetes</td>
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<td>2. Genes associated with insulin resistance</td>
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<td>a. PPARγ gene</td>
<td>Radha et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>&quot;Ala&quot; allele offers no protection against diabetes or insulin resistance in South Asians but protective in Europeans</td>
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<td>b. PC-1 gene</td>
<td>Abate et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>K121Q polymorphism of ENPP1/PC1 gene confers susceptibility to type 2 diabetes</td>
</tr>
<tr>
<td>c. IRS gene</td>
<td>Hitman et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Significant association of Gly 972 Arg polymorphism with type 2 diabetes</td>
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<td>d. IRS2 gene</td>
<td>Bodhini et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>DD genotype of G 1057 D polymorphism susceptible to type 2 diabetes by interacting with obesity</td>
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<td>3. Apolipoprotein D gene</td>
<td>Baker et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Apo D might act as a modifying gene for Type 2 diabetes</td>
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<td>4. Calpain 10 gene</td>
<td>Cassell et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>The haplotype combinations show increased risk of both IFG/IGT, and type 2 diabetes in South Indians</td>
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<td>5. Genes associated with obesity</td>
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<td>a. Uncoupling protein 3 gene</td>
<td>Cassell et al&lt;sup&gt;76,77&lt;/sup&gt;</td>
<td>UCP 3 to be associated with a high waist to hip ratio</td>
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<tr>
<td>b. Uncoupling protein 2 gene</td>
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<tr>
<td>c. PGC-1A gene</td>
<td>Vimalaswaran et al&lt;sup&gt;55&lt;/sup&gt;</td>
<td>UCP2 Exon 8 variant influences weight gain by its regulation of leptin</td>
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<td>IV. FCPD Genes</td>
<td>Witt et al&lt;sup&gt;81&lt;/sup&gt;</td>
<td>The &quot;A&quot; allele of Thr394Thr polymorphism of PGC-1A gene confers 1.6 times higher risk for the development of type 2 diabetes in Asian Indians</td>
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<td>SPINK 1</td>
<td>Bhatia et al&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Mutation associated with FCPD</td>
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<td>Chandak et al&lt;sup&gt;44&lt;/sup&gt;</td>
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<td></td>
<td>Hassan et al&lt;sup&gt;85&lt;/sup&gt;</td>
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STUDIES ON GENES ASSOCIATED WITH INSULIN SECRETION IN INDIANS

Studies on genetics in Indian diabetics have shown increased occurrence of the class 3 allele of the hypervariable region in the 5' region of insulin gene and this was more pronounced in South Indian subjects rather than in Punjabi Sikhs. This study was further expanded and done on a total of 130 subjects inclusive of South Indians and Punjabi Sikhs. Using Polymerase chain reaction and Restriction Fragment length polymorphism (RFLP), a part of the insulin gene was amplified to look for mutation which may be in linkage disequilibrium with Class 3 allele. This analysis included 3' untranslated region of the insulin gene. However, no difference in allelic frequency was observed in the South Indians or Punjabi Sikhs between controls and diabetics. Another study was on Islet Amyloid Polypeptide (IAPP) gene which was studied in 118 South Indians both control and diabetic subjects, by PCR-RFLP method using PvuII enzyme. This study showed no abnormalities in the IAPP gene in South Indians thus negating its contribution in a major way to disease development.

The most exciting and promising gene associated with type 2 diabetes is the TCF7L2 gene. Recently, Grant et al. reported that within a region in linkage to type 2 diabetes on chromosome 10q, a set of single nucleotide polymorphisms (SNPs) and a microsatellite marker in a well-defined linkage disequilibrium block (LD) in the transcription factor 7 -like 2 (TCF7L2) gene were strongly associated with type 2 diabetes in Icelandic subjects. Florez et al. reported that the polymorphisms rs12255372 (G/T) and rs7903146 (C/T) in the TCF7L2 gene were associated with an increased risk of type 2 diabetes in persons with impaired glucose tolerance. Subsequent studies have consistently replicated the association of the TCF7L2 variants with type 2 diabetes including a study from Pune and Hyderabad by Yajnik and Chandak and our own study in a South Indian population where the intrinsic SNP has been shown to be associated with type 2 diabetes. The specific genetic variant which causes the association of TCF7L2 with type 2 diabetes is still unclear. However, its effect on type 2 diabetes risk appears to act at a physiological level through an impairment of insulin secretion. Studies have shown that a per allele additive effect is seen on measures of insulin secretion but not on measures on insulin resistance. Although the exact role of TCF7L2 is still unknown, it appears to act through the WNT signaling pathway. WNT signaling is critical for cell proliferation and for the development of pancreas and islets during embryonic growth. The search for diabetes susceptibility genes on most other chromosomes is ongoing.

STUDIES ON GENES ASSOCIATED WITH INSULIN RESISTANCE IN INDIANS

One of the main candidate genes that is implicated in adipogenesis, insulin resistance and type 2 diabetes is the Peroxisome Proliferator Activated Receptor-γ (PPAR-γ) gene. This is a transcription factor that is involved in adipogenesis and in regulation of adipocyte gene expression and glucose metabolism. Within a unique domain of PPAR-γ 2 gene that enhances ligand-independent activation, a common Pro 12 Ala polymorphism has been identified. The polymorphism has been shown to be associated with obesity. Recently, using a family based design to control for population stratification, it was reported that the Ala allele of this polymorphism was associated with a decreased risk of type 2 diabetes. Recently we have carried out genetic studies on PPARγ gene where we have compared the frequencies of the common Pro 12 Ala polymorphism in South Indians living in Chennai (19%) with South Asians (18%) and Caucasians (20%) living in Dallas/Forth Worth, and found them to be similar. We have shown that the polymorphism does not modulate either the excessive insulin resistance or risk of type 2 Diabetes in our ethnic population.

Another genetic study of ours carried out in the same populations on Plasma Cell glycoprotein PC-1 gene polymorphism K121Q, showed its potential role in the identification of genetic susceptibility to type 2 diabetes. The study evaluated the role of ENPP1 K121Q polymorphism in prediction of type 2 diabetes in three populations that differ in susceptibility to diabetes and environmental exposure. The prevalence of subjects carrying the polymorphic ENPP1 K121Q allele was 25% in the nondiabetic group and 34% in the diabetic group of South Asians living in Chennai (p=0.01). The prevalence in the nondiabetic and diabetic groups was 33 and 45% (p=0.01) for the South Asians living in Dallas and 26 and 39% (p=0.003) for the Caucasians. Our study supports the hypothesis that ENPP1 K121Q predicts genetic susceptibility to type 2 diabetes in both South Asians and Caucasians. Thus, the ENPP1 121Q variant may provide an important genetic marker to identify people at risk and focus treatment strategies for prevention of type 2 diabetes.
A variant 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. A small study with an aim to examine the role of IRS1 missense mutation of codon 972 (Glycine to Arginine) and 513 (Alanine to proline) in South Indian and Finnish population showed similarity in prevalence of these two variants in the two populations studied. A meta analysis of one of the polymorphisms in IRS-1 gene (Gly972 Arg)in four populations comprising of a small South Indian population, Finnish, French and Danish Caucasian population showed a significant association of this polymorphism with type 2 diabetes. 

IRS-2, one of the major substrates of the insulin receptor has a crucial role in insulin signaling and in beta cell development and survival. While several polymorphisms have been identified in the IRS-2 gene, the Gly1057Asp polymorphism (G1057D, rs1805097) is found in various populations with prevalence sufficiently high to modulate a population’s risk for type 2 diabetes. The G1057D polymorphism of IRS2 gene was genotyped in 1193 NGT subjects and 1018 type 2 diabetic subjects. The genotype frequency of the G1057D polymorphism was significantly different between the NGT and type 2 diabetic groups (p=0.0007) in the total study subjects and among the obese subjects (p=0.0007). Logistic regression analysis showed that the DD genotype showed an increased susceptibility to diabetes with an odds ratio (adjusted for age and sex) of 2.19 (95% CI:1.34-3.57, p=0.002) when compared to the GG+GD genotype, among the obese subjects, but not in non obese subjects. In order to explore possible interaction with obesity, logistic regression analysis was performed and the coefficient corresponding to the Interaction parameter (genotype x obesity) was significant (p=0.0001). In conclusion, the DD genotype increases susceptibility to type 2 diabetes by interacting with obesity.

Other genes studied in South Indian type 2 diabetic subjects include Glucokinase and the Glucose transporters, GLUT 1 and GLUT 4. The Glucose Transporter (GLUT) gene is an attractive candidate since it acts as a sensor to the α-cell and as a major signaling molecule. These studies have shown that glucokinase acts as a minor gene influencing the development of type 2 diabetes, and that the GLUT1 polymorphism may contribute to susceptibility to type 2 diabetes.

A significant difference in genotype distribution of Apolipoprotein D genotypes between diabetic subjects (n = 110) and controls (n = 88; p = 0.004) was observed, which was similar to that previously found in the Nauruan subjects. This study also showed no association between diabetes and the GLUT 2 Taq 1 polymorphism and concluded that Apo D might act as a modifying gene for type 2 diabetes.

Recent studies have shown an association of Calpain 10 gene with type 2 diabetes in some populations but not in others. A study on the haplotype combinations of Calpain 10 gene was found to show increased risk of both IFF/IGT, and type 2 diabetes in South Indians. The study reported that the at-risk haplotype combination 112/121 and its intrinsic variants (UCSNP 43, -19, -63) was infrequent in South Indian type 2 diabetics. Our group has undertaken a major study on the genetics of type 2 diabetes and insulin resistance in a large population based study in Chennai.
STUDIES ON GENES ASSOCIATED WITH OBESITY IN INDIANS

Genes associated with obesity like the uncoupling proteins the UCP2 and UCP3 were studied in a subgroup of South Indians. This study showed a lack of association of UCP2 with type 2 diabetes, but UCP2 Exon 8 variant was found to influence weight gain by its regulation of leptin. AAnother study suggested UCP 3 to be associated with a high waist to hip ratio.

A study on the known variants in the 10 candidate genes, such as, the glucagon receptor, insulin receptor substrate 1, insulin receptor, human beta 3 adrenergic receptor, fatty acid binding protein, mitochondrial tRNA (Leu (UUR)), sulfonylurea receptor, human uncoupling protein and the glycogen-associated regulatory subunit of protein phosphatase-1 genes suggested that none of them were associated with type 2 diabetes in South Indians studied at Pondicherry.

STUDIES ON GENES RELATED TO FCPD IN INDIANS

Fibrocalculous Pancreatic Diabetes (FCPD) is a form of diabetes secondary to non-alcoholic chronic pancreatitis of uncertain etiology predominantly seen in tropical developing countries. FCPD is seen in developing countries of the world and is characterized by huge pancreatic stones in association with secondary diabetes.

Our group was the first to suggest a genetic susceptibility to FCPD and in that report we found that FCPD shares common susceptibility genes with both type 1 and type 2 diabetes. Many subsequent studies have looked for genetic abnormalities in all forms of chronic pancreatitis following the discovery of genetic mutations in hereditary pancreatitis. We reported no association between FCPD and the reg gene or the trypsinogen gene. In a previous study on a small cohort of patients with tropical pancreatitis, the frequency of CFTR mutations was lower than in white subjects. However, during the last 2-3 years, a number of independent groups have confirmed an association between SPINK 1 mutations and FCPD.

Pancreatic secretory trypsin inhibitor (PSTI / SPINK 1) is a potent protease inhibitor and thought to be a major protective mechanism preventing inappropriate activation of pancreatic digestive enzyme cascade by inhibiting up to 20% of potential trypsin activity. Mutations of SPINK 1 gene are significantly associated with tropical calcific pancreatitis as demonstrated by Chandak et al. SPINK 1 mutations were also studied in FCPD subjects from Chennai and Dhaka. In the total study group (Bangladeshi and Southern Indian) the N34S variant was present in 33% of 180 subjects with FCPD, 4.4% in non-diabetic subjects and 3.7% in Type 2 diabetes. Bhatia et al. also found a strong association with SPINK 1 trypsin inhibitor mutations and a high prevalence of N34S in FCPD. These results suggest that the N34S variant of SPINK 1 is a susceptible gene for FCPD.

SUMMARY

From the various studies quoted above, it is thus very clear that more studies are needed to look into different regions of the known genes to see if any of them harbor important variants that predispose to disease development in Indians. Such studies would help to unravel the genes associated with diabetes and the gene-environment interactions which make Asian Indians so highly susceptible to diabetes. Diabetes mellitus ultimately results from the interaction of many genetic and environmental factors. There is unlikely to be a single grand unifying theory. As the pathogenesis of the diabetic phenotypes is treated out, genetic undercurrents for one or more of the pathogenetic mechanisms can be identified. In this quest towards reductionism, genetic studies in comparatively homogenous populations such as Pima Indians offer leads, that have been subsequently shown to be universal. Two broad approaches are being applied analysis of candidate genes for sequence variation and genome-wide linkage studies to identify susceptibility genes and to positionally clone them. Positional cloning identifies a disease gene by its occurrence in a chromosomal region that segregates with phenotype. As of now only a few functional variants in biological candidate genes have been identified; these are however, only minor pieces in the multigene puzzle of type 2 diabetes. It is not an easy task, requiring as it does an enormous commitment of time and resources. But it is possible.
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