Family History and Pedigree Charting — A Simple Genetic Tool for Indian Diabetics

Shashank R Joshi, Rakesh M Parikh

GENETICS OF DIABETES

Genetic transmission of diseases has been known since long but the mode of inheritance is no more as simple as previously thought. In the diseases with transmission in Mendelian fashion, risk of offspring being affected can be easily estimated depending on the pattern of transmission whether dominant or recessive and whether it is through sex chromosomes or autosomes. Detailed family history and pedigree charting plays a very important role in exploring pattern of inheritance in such disorders. With the rapid rise of non-communicable diseases like diabetes mellitus (DM), hypertension and coronary artery disease (CAD), role of family history and pedigree charting is relevant for the practicing physicians. Parental influence in development of diabetes mellitus is well known. Genetic susceptibility has been shown to play a role in most of the types of diabetes though the genes involved and pathogeneses are different. For type 1 DM at least 20 different loci including IDDM 1 to IDDM 16 have been demonstrated. There are a few varieties of diabetes for which single gene defect is responsible and are called monogenic diabetes. These include varieties of Maturity Onset Diabetes of Young (MODY), Maternally Inherited Diabetes and Deafness (MIDD), various syndromes of severe insulin resistance etc. Unlike Mendelian disorders, type 2 DM has polygenic inheritance. These polymorphisms may be localized in the coding or regulatory parts of the genes and are present in patients of type 2 DM as well as in healthy populations although with different frequencies. So far genes like calpain 10, PPARγ, KCNJ11, adiponectin, IRS-1 and insulin have been implicated in pathogenesis of type 2 DM. Genomewide linkage studies of presumed polygenic type 2 diabetic populations indicate that loci on chromosomes 1q, 5q, 8p, 10q, 12q and 20q contain susceptibility genes. Mutation analyses of selected candidate susceptibility genes in various populations have also identified the widespread Pro12Ala variant of the PPAR and the common Glu23Lys variant of the ATP-sensitive potassium channel, Kir6.2 (KCNJ11). These variants may contribute significantly to the risk type 2 diabetes conferring insulin resistance of liver, muscle and fat (Pro12Ala) and a relative insulin secretory deficiency (Glu23Lys).

ASIAN INDIAN PHENOTYPE

Asian Indians have always been at high risk of diabetes and CAD. They have a typical phenotype with high percentage body fat at a low BMI, less muscle (sarcopenia) more fat, truncal obesity, classical lipid triad, hypertension and type 2 diabetes compared to Caucasians and a higher risk at low waist circumference (WC). Recently short stature has been implicated as a risk factor for CAD among men and women. Our own group has described a novel parameter – Index of Central Obesity (ICO), which attenuates the effect of stature and validated it for defining metabolic syndrome (MS). Asian Indians have a highly atherogenic lipid profile with high levels of small dense low density lipoproteins. Though in India there is diversity of culture with variety of dietary patterns, most of them are rich in carbohydrates and low in proteins. Though traditionally rural Indians were hard workers, modernisation has affected them as well and most of urban Indians have acquired a sedentary lifestyle. Higher percentage body fat at low BMI, central obesity with low WC, highly atherogenic lipid profile, atherogenic diet and sedentary lifestyle are peculiarities of Indians that predispose them to higher risk of CAD. All these environmental factors add on to the genetic susceptibility of Asian Indians.

ASIAN INDIAN GENOTYPE

Mohan et al have demonstrated that genetic factors are stronger in Indians compared to Europeans. In their cohort nearly 10% of Asian Indian diabetics had family history of diabetes compared to 1% of Europeans. In CUPS study prevalence of glucose intolerance (diabetes + IGT) was significantly higher among subjects with both parents diabetic (55%) compared to those with one parent diabetic (22.1%, p = 0.005) and those with no family history (15.6%, p < 0.0001). Indian patients have been demonstrated to have some peculiarities. Pro12ala polymorphisms in PPARγ genes which are protective against diabetes do not appear to offer protection among Indians. Thr394Thr (G —> A) polymorphism PGC-1
has been strongly associated with diabetes which body fat is not reported in other ethnic groups. Gly1057Asp polymorphism of IRS-2 gene predisposes Indians to diabetes particularly in presence of obesity. Polymorphism in adiponectin gene has also been studied in Indian patients.

**HOW TO FIND GENES INVOLVED?**

There can be two ways of searching for genes involved in diabetes. One is to look at loci encoding proteins likely to be involved in the control of blood sugar homeostasis. The other consists in performing exclusion mapping by systematic searching the genome. Both approaches have been successfully used for identifying MODY genes. A positive linkage between a marker and a trait reflects the fact that the marker and the gene associated with the trait are near one another on the same chromosome and are thus inherited together. Assertion of linkage is based on statistical analysis of the distribution pattern in the kindred of both the trait and the alleles of the marker. An odds ratio (L) of linkage versus non-linkage is calculated, based on the observed data, and the decimal logarithm of L (lodscore) is reported. An L of 3 (an odds ratio of 1,000 to 1) is usually required to assert linkage, and an L of -2 to exclude it. When there is no indication of which gene may be involved in a disease, or when candidate genes have not been localized in the genome, the approach of reverse genetics can be used to identify susceptibility genes in families. Linkage analysis is a powerful tool for detecting susceptibility genes in diseases with a well-defined mode of inheritance. However, in the case of complex diseases such as type 2 DM, the detection of linkage between the trait and a marker can be obscured by several factors. Type 2 DM has an unclear mode of transmission which might be related to its genetic heterogeneity and partial penetrance. Study of animal models suggests that glucose tolerance status in single individual results from interactions of a number of genes.

**CLINICAL RELEVANCE – FAMILY HISTORY AND PEDIGREE CHARTING**

As of now use of genetic analysis is restricted to research. With knowledge of genetic factors involved in a disease, a fair degree of predictions can be made regarding the probability of other family members being affected. Family history also provides clue towards diagnosis of the patient. Vertical transmission of diabetes with diabetes appearing at younger age in each subsequent generation is the typical presentation of MODY and should raise suspicion especially if patient does not have other risk factors for development of diabetes. Risk of developing type 1 DM is 12% for dizygotic twins and 36% for monozygotic twins. Among the siblings the risk is 6%. Risk of developing type 1 DM is 3-4% if mother is type 1 diabetic, 7-8% if father is type 1 diabetic and around 30% if both the parents are patients of type 1 DM.

In this issue of JAPI, Deo et al have reported their findings on pedigree analysis of diabetic patients from Western India. In their cohort 58% cases of Type 2 DM had family history of DM while 14% patients did not have details of family history. 37% of the type 1 diabetic patients gave a history of type 2 DM, significance of which is questionable though similar findings are reported from other studies as well. They also observed decrease in age of onset in the successive generations with both the parents conferring equal risk of inheriting diabetes in offspring as previously reported in Framingham offspring study. The age of onset of diabetes did not show significant correlation with whether one or both the parents were diabetic. Excess of maternal transmission as previously reported in the Korean population and the south Indian population was not observed in this study. In one similar study though extensive familial aggregation of Type 2 diabetes was seen in Indian population, it failed to replicate the evidence for excess maternal transmission. On the contrary paternal influence has been demonstrated to be stronger than maternal influence in the transmission of diabetes. Pedigree charting has been used to put up the hypothesis that migration from rural area to metropolis accelerates the development of metabolic syndrome in next generation. Mohan et al have demonstrated familial clustering of diabetic retinopathy, risk being three times higher in siblings of Type 2 diabetic subjects with diabetic retinopathy. In South Indians, complex models have been shown to provide more satisfactory descriptions on segregation of type 2DM, inadequately described by simple major gene models.

**REFERENCES**


