Genetics of Gestational Diabetes Mellitus – The Indian Perspective

Gestational diabetes mellitus (GDM) represents an interesting and important etiological type of diabetes. Typically, the disease remits after delivery albeit conferring a future risk of diabetes. The unique nature of this disease has sparked an interest in unravelling its cause. Accordingly extensive research into genetics of gestational diabetes has been conducted worldwide.

The studies in GDM have revealed both genetic and epigenetic factors could play a role in GDM. The genetic factors are mostly related to single nucleotide polymorphisms or gene mutations while the epigenetic processed include gene methylation, histone modification as well as microRNAs which can bind to mRNA.[1] The results of these genetic studies indicate that several genes and their variants are associated with GDM. In a large study based upon the Danish National Birth Cohort and the Nurse Health study, Ding *et al.*[2] found eight novel single nucleotide polymorphisms associated with GDM. Some of the notable genes in question were MTNR1B, TCF7L2, HNF1A and SLC30A8). MTR1B had earlier been implicated in a study in Mexican Americans also.[3] IRS-1 gene polymorphisms showed an association with GDM in a study from Rome.[4] A meta-analysis found six polymorphisms of various genes which were associated with GDM. These genes included MTNR1B, TCF7L2, IRS-1, IGF2BP2, and TNF-alpha.[5] Other genes such as GCK), KCNJ11, CDKAL1 also have been found to be associated with GDM.

Certain populations of the world appear to be more at risk for metabolic disorders. South Asians represent one such population. The prevalence of GDM in women of South Asian origin living in the US is greater than Caucasians and other ethnic groups. Further, GDM occurs at a much lower body mass inde (BMI) in the Asian women.[6] Foreign-born Asian women living in Florida were twice as likely to develop GDM as compared to US-born women. This difference persisted even after adjusting for confounders like BMI, age and parity.[7] Further, population estimates of GDM prevalence indicate that the highest prevalence of GDM is seen in Africa and Asia while North America and Europe had the lowest prevalence.[8] Indian women from Punjab had higher prevalence of GDM with lesser insulin resistance as compared to Scandinavian women in one study.[9] The higher prevalence and onset at lower BMI suggests that GDM is a more aggressive disorder and a bigger public health problem for Asian countries as compared to the Western parts of the world. The genetic basis of GDM is accordingly expected to be different.

Of late, increasing research has been conducted in South Asian countries to uncover the genetics of GDM. A study in Korean women implicated FTO gene (rs8050136) in GDM risk apart from other genes.[10] CDKAL1 CDK5 regulatory subunit associated protein 1 like-1 was associated with GDM in Asian populations.[11] Kwak *et al.*[12] found that KCNQ1 gene polymorphisms were associated with GDM in Korean women. A subgroup analysis of the meta-analysis by Wu *et al.*,[5] found that certain polymorphisms of TCF7L2 (rs7903146) and PPARG (rs1801282) were associated with GDM in Asian populations but this was not true for Caucasian women. Lin *et al.*[13] reported that polymorphisms of SLC30A8 (rs13266634) occur only in Asian women with GDM as compared to Caucasian women. In the same study, an FTO polymorphism rs9939609 occurred only in Caucasian women. These data suggest that South Asians may have a different genetic composition which may influence the phenotype of GDM.

India is among the most populous countries in the South Asian region and in view of its young population, faces a high burden of GDM. While the clinical research in GDM in India has been extensive, the genetic research had been lacking. However, in the recent past more and more genetic studies are being reported.

Kanthimathi *et al.*[14] found that variants of HMG20A (rs7178572) and HNF4A (rs4812829) were associated with GDM. A case control study from India found that micro RNA7 was elevated in placental tissue as well as maternal and cord blood in GDM patients. The expression of IRS1, IRS2, and RAF1 was also lower in maternal blood presumably as a consequence of elevated miRNA7.[15] However, single amino acid substitutions of MTHFR and factor V Leiden genes were not associated with GDM in a study from South India.[16] Placental tissues of women with GDM had lower expression of proteins Annexin A5 and apelin.[17] The genes involved require further study. The mutation or insertion deletion of mitochondrial t RNA genes was also associated with GDM in one study from India.[18] Variants of hexokinase domain containing 1 (HKDC1) gene were also found to be associated with GDM. The association of this gene with GDM was reported for the first time in this study.[19] A polymorphism of osteoprotegrin gene T950C may also increase the risk of GDM in Indian women.[20] Calpain 10 gene polymorphisms, which are believed to be involved in insulin secretion and thermogenesis was not associated with GDM.[21]

Polymorphisms of the CDKAL1 gene were associated with GDM in one study from India.[22] Single nucleotide polymorphisms of KCJN11 and GRB14 genes were also associated with GDM.[23]

Some Indian studies have reported differences between the genetic factors in Indian and Caucasian women with GDM. The rs11605924 single nucleotide polymorphism of the CRY2 gene conferred a reduction in GDM risk in Indian women while the same increased the risk in Scandinavian women.[9] In this issue, Ranjan *et al.* found that the rs7903146 (C/T) SNP of the TCF7L2 gene was not associated with either GDM or diabetes in pregnancy.[24] Among the TCF7L2 SNPs associated with GDM, the rs7903146 (C/T) has been documented in multiple Caucasian studies also. According to a meta-analysis, this is the only TCF7L2 SNP which was associated with GDM in Asian women.[25] Whether this indicates that Indian women are genetically distinct from other Asian women in term of GDM risk, is an interesting proposition which merits further study.

The increasing genetic studies from India bode well for the future of research in GDM. The impact of this disease on the health of the mother as well as the baby dictates that every effort should be made to improve our understanding of this disease. Better understanding of the genetics of this disease may open doors which improve the screening, management and prevention of this unique disease.

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