ABSTRACT

TITLE OF THE ABSTRACT : **The study of pregnant women with diabetes and screening for mutations related to panel of ten MODY (maturity onset diabetes of the young) genes and polymorphisms in TCF7L2.**

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KEYWORDS:
Gestational Diabetes
MODY
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Next Generation Sequencing (NGS)
NEUROD1, PDX1

Aims & Objectives:

Gestational diabetes mellitus (GDM) is believed to result when a genetic predisposition is perpetuated by an increase in insulin resistance during pregnancy. However, in the subjects with GDM in our population, little is known about the genetic basis of MODY and its potential clinical significance. Due to an overlap of clinical features with the more common polygenic type 2 diabetes (T2D) and type 1 diabetes (T1D), the differentiation of patients with maturity onset diabetes of the young (MODY) is a diagnostic challenge. Therefore, we aimed to screen pregnant women with diabetes for a comprehensive panel of ten MODY genes utilizing next generation sequencing (NGS). Further, among the T2D diabetogenic genes, the common variants of TCF7L2 have been shown to be associated with T2D in Asian-Indian population. Our aim was also to investigate whether these TCF7L2 variants associated with T2D would also confer risk for gestational diabetes mellitus.

Material and Methods:

We included 50 south Indian women with diabetes complicating their pregnancy to screen for mutations in a comprehensive panel of ten MODY genes [HNF1A, HNF4A, GCK, PDX1, HNF1B,

NEUROD1, KLF11, CEL, PAX4 and INS]. A novel multiplex polymerase chain reaction (PCR) based target enrichment followed by NGS on the Ion Torrent Personal Genome Machine (PGM). The detected rare variants which were of pathogenic significance were confirmed by Sanger sequencing and genotype phenotype correlation was done. Further, in 166 unrelated women (117 women with gestational diabetes mellitus, 49 ethnically matched non-diabetic control subjects) DNA extraction was done using the Gentrapuregene blood method. The primers were validated by Sanger sequencing (3130 genetic analyzer) and genotyped 3 TCF7L2 polymorphisms (rs7903146, rs12255372 and rs4506565) using TaqMan allelic discrimination assay. The data was analysed using SPSS version 16.0.

Results:

Mutations were identified in 16% (8/50) of the subjects screened. There were two mutations in NEUROD1, two in PDX1, one each in HNF1A, GCK, CEL and INS genes. Seven of these mutations were novel. We further proceeded to identify and confirm the presence of these mutations in the relatives of some of these patients and also the neonates. We have found that the odds ratio (OR) of TCF7L2 polymorphisms *rs4506565,* rs7903146, rs12255372 for the occurrence of gestational diabetes when compared with controls were 3.75(C.I=0.75-18.53,*p=0.08*), 1.77 (C.I=0.503-6.263,p=0.37) and 1.40 (C.I=0.24-8.11, P=0.70) respectively.

Conclusions:

Pregnant women of Asian Indian origin harbor a higher frequency of NEUROD1 and PDX1 mutations, a pattern that differs from the western literature. The NGS platform provides an accurate, rapid and cost effective method for parallelized genetic testing for MODY and hence overcomes the inherent limitation of scalability and cost of Sanger sequencing. The TCF7L2 polymorphism *rs4506565* has showed a strong trend towards association with the occurrence of gestational diabetes, when compared to the other two common polymorphisms in TCF7L2 (rs7903146, rs12255372). This is the first preliminary data of TCF7L2 polymorphism associations with gestational diabetes in a south Indian population.