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# Association of Gene Polymorphisms with Psychological Stress in Gestational Diabetes Mellitus

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## Background

Gestational diabetes mellitus is a common pregnancy related metabolic disturbance accounting for about 12% to 18% of all pregnancies [1]. In Pakistan alone the prevalence of GDM is approximately 12% of all pregnancies [2]. GDM has been related with a multitude of factors that include genetic, epigenetic and environmental factors. Furthermore, GDM is associated with both short term and long-term complications and thereby causes a lot of stress to both the mother and the developing fetus. Stress in not only limited to physical stress but also extends to mental and psychological stress to the expecting mother and pregnant females with GDM are four times likely to develop psychological stress [3]. In recent years the role of genetic factors in GDM [1] and psychological and behavioral reactions have started to gain global attention [4]. Genetic studies such as Genome Wide Studies (GWAS) have successfully lead to discoveries of Single-Nucleotide Polymorphisms (SNPs), common genetic variants and new loci that are related to common complex diseases [5]. Such studies along with meta-analysis, case-control analysis and linkage analysis have identified candidate genes in the etiology of both GDM [6] and psychological stress disorders. However genetic studies that link GDM with psychological stress are less well studied. The aim of this review is to understand the association of genetic changes particularly single nucleotide polymorphisms common in females with GDM and pregnancy induced psychological stress.

## Single Nucleotide Polymorphism

Polymorphisms are a form of genetic variation, which refers to the presence of two or more alternative forms of a distinct phenotype. This variation can occur in any morphological, physiological, and behavioral traits and can occur in both coding and non-coding regions of the DNA [7]. Among these genetic variations the Single Nucleotide Polymorphisms (SNP) are of the most common type occurring in about 90% of the observed differences in the genome. Another feature of a polymorphism is that the most abundant allele should be present in the population at a test frequency of 99% or less. Therefore the rare allele will present at a total frequency of at-least 1% [8]. Most SNPs occur in the non-coding regions of the human genome but about 50,000 SNPs have been estimated to occur in the coding region of the DNA called cSNP where they can alter protein structure. These SNPs are an important genetic variation as they can influence morphological, physiological and pathological traits thereby have relevance to disease mechanism [9] as shown in Figure 1. Associations of these SNPs have been linked as risk factors to many diseases including both type 1 and type 2 diabetes mellitus. Establishing an association with the genetics can offer prediction of drug response and possibly develop a genome based diet that is safer to risked individual [10]. Graph: Created using Reactome [11,12] and modified from Wikipedia.

## Single Nucleotide Polymorphisms in Gestational Diabetes Mellitus

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity diagnosed with onset or during pregnancy [13]. It is the most common metabolic disturbance during pregnancy. It is a multifactorial disease with a rising prevalence globally where both environmental and genetic factors play an important role in the pathogenesis of the disease and associated post pregnancy complications [14]. In a systemic review done by Zhang et al. have assessed multiple genes that are associated with GDM. Among these they identified seven genes that are very significantly associated with GDM. These are The minor alleles of Transcription Factor 7 Like 2 (*TCF7L2*), Glucokinase

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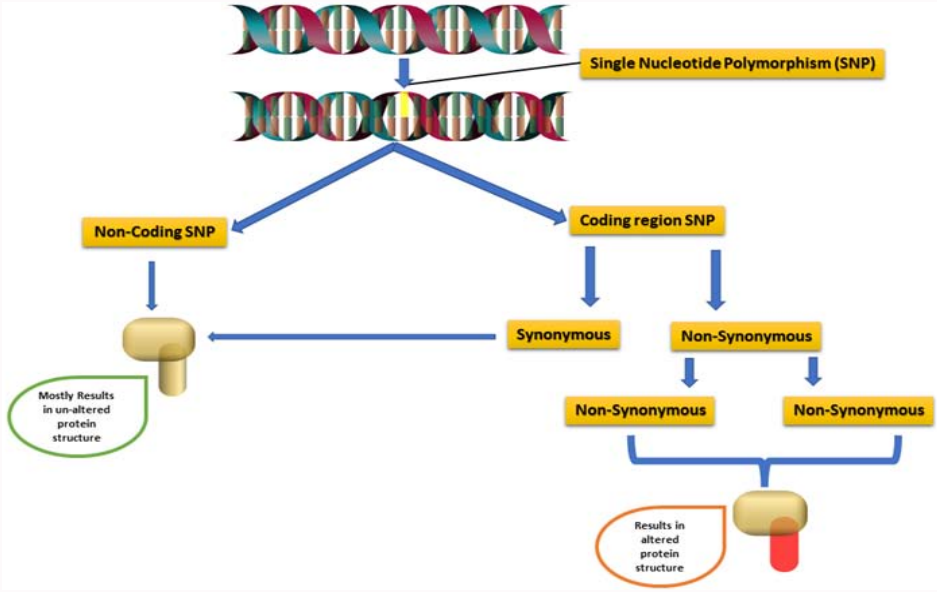


**Figure 1: Single Nucleotide polymorphism:** A single base pair substitution in the DNA (indicated in yellow) can occur in either non coding region or the coding region. The SNPs in the coding region are further sub divided into synonymous or non-synonymous SNPs. The synonymous SNPs and Non-coding SNPs results in un-altered protein structure whereas as non-synonymous SNPs result in altered protein structure which contributes to the pathogenesis of the disease.

(GCK), Potassium Inwardly Rectifying Channel Subfamily J Member 11 (*KCNJ11*), CDK5 Regulatory Subunit Associated Protein 1 Like 1 (*CDKAL1*), Insulin Like Growth Factor 2 MRNA Binding Protein 2 (*IGF2BP2*), Melatonin receptor 1B (*MTNR1B*), and Insulin Receptor Substrate 1 (*IRS1*). Among these *TCF7L2* showed the strongest association with GDM risk [15].

## Single Nucleotide Polymorphisms in Gestational Diabetes Mellitus (GDM) and Psychological Disorders

Gestational Diabetes Mellitus is a pregnancy related metabolic disorder characterized by glucose intolerance that was nonexistent prior to pregnancy [16]. A diagnosis of GDM furthermore increases emotional distress, such as depression, anxiety or stress among women. A study done by Lee et al. [17] showed that prevalence depression, anxiety and stress were 39.9%, 12.5% and 10.6 % respectively [17]. Pregnancy itself being a stressful condition the superimposed GDM along with stress results in further complications that could potentially lead to postpartum depression or diabetes mellitus post pregnancy. Multiple factors come into plays that contribute towards the development of stress and GDM however genetic factors play substantial role in the etiology of both psychological symptoms and GDM. In a recent review done by Yahya et al. [18] they identified about 83 candidate genes that were associated with GDM of which *TCF7L2*, *MTNR1B*, *CDKAL1*, *IRS1*, and *KCNQ1* are the most prevalent [18]. For the purpose of the review, we would only focus on these 5 major genes any overlap of these genes with psychological symptoms.

## Transcription Factor 7 Like 2

Genetic studies have showed *TCF7L2* is found to be the strongest determinant of Type 2 Diabetes Mellitus (T2DM) in the human population. In a review done by Chang et al. encompassing 22 studies 6 out of 8 common SNPs were found to be strongly associated with GDM where rs7903146, rs12255372 and rs790169 had the strongest association [19]. Furthermore *In vivo* studies showed that not only *TCF7L2* is associated with T2DM but is also related to altered behavior of the mice which was seen prior to the development of glucose intolerance [20]. This shows that *TCF7L2* could potentially be associated with stress and GDM however further studies would be needed to make this association.

## The Melatonin Receptor 1B (*MTNR1B*)

The Melatonin Receptor 1B (*MTNR1B*) is a newly identified candidate gene belonging to the class of G protein coupled receptors. Till date human genetic studies have identified many common variants of this gene associated with T2DM and GDM. Among these the polymorphism rs1387153 and rs10830963 was to be highly significant [6,21] later being also found in placental tissues associated with increased risk of GDM [21]. However when rs10830963 polymorphism was assessed for depressive symptoms in T2DM no correlation was found [22] but independently this polymorphism was associated with increased risk of Schizophrenia [23].

## The Cyclin-Dependent Kinase 5 (CDK5) Regulatory Subunit-Associated Protein 1-Like 1 (*CDKAL1*)

The *CDKAL1* is a member of the methylthiotransferase family encoded by *CDKAL1* gene has been implicated in the development of T2DM [24] and GDM particularly the rs7754840 variant [25]. Although this variant was not yet studied with respect to stress development multiple genetic variants of this gene were found to be associated with depressive symptoms with T2DM [26].

## Insulin Receptor Substrate IRS-1

Insulin receptor substrate-1 is an important endogenous substrate of the insulin signaling pathway. Variants of this gene mainly rs1801278 have been shown to be associated with both T2DM and GDM [27,28]. Other variants of this gene particularly rs13411764 and rs3820926 in the upstream region have found to be a risk factor for major depressive disorder [29]. Though not linked via studies as a risk factor for stress in GDM the potential of IRS being involved

in GDM and variants having association with psychological illnesses could possibly serve as a question for future research studies.

## Potassium Voltage-Gated Channel Subfamily Q Member 1 (*KCNQ1*)

The Potassium Voltage-Gated Channel Subfamily Q Member 1 *(KCNQ1)* gene variants rs2237892, rs2237895, rs2283228, rs151290, and rs2074196, have been recently identified as a risk factor for the development of T2DM [30,31]. Among these the variant rs2237892 and rs2237895 were found to be associated with GDM in Chinese and Pakistani population respectively [32,33]. Polymorphisms of this gene in relation to psychiatric disorders are not much studied KCNQ1 variant rs8234 was found to be associated with increased of Schizophrenia [34].

## Studies Showing SNPS in Stress Related to GDM

Currently there are not many studies that have related SNPs associated with stress and GDM. A study done by Lee et al. [35], have shown 14 genes associated with GDM and stress. These are *NPY5R*; *ANO2*; *EPHX2*; *TPH2*; *NRG1*; *LHPP*; *FKBP5*; *SDK2*; *RORA*; *OXTR*; *BDNF*; *HTR2C*; *TEX51*; and *PLEKHG1* which are important candidates for various psychological disorders such as depression, anxiety and stress [35]. In another study by Lin et al the authors investigated that association between gene polymorphisms, environment and psychological stress in GDM. The study included *COMT*, *NPSR1*, *HSP90B1*, *HSP90AA2*, *FKBP5*. Among these genes only *NPSR1* (rs324981) T/T genotype was associated with reduced risk of psychological stress where as the other genes had no significant association [4].

At present only two studies have shown associations of genetic variants with respect to stress and GDM. However, the candidate genes studied were mostly associated predominantly with stress and psychological disorders. This review further tried to link common candidate gene variants predominantly associated with GDM with potential relation to stress and therefore could serve as a basis for further studies.

## Implications of Future Research

There is no any research work conducted in a local setting, highlighting the relationship of stress with GDM in background of genetic mutations. Thus; exploring the genetic profile of pregnant women is of paramount importance. Identifying the epigenetic mechanism of stress and GDM can benefit for sustainable long-term behavioral change measures to address the mental health of pregnant women. Further, the study will help the health providers treat the pregnant woman in a best suited way as well as to determine whether the new born to a woman will be predispose to psychological disorders in the future.

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