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The Role of TCF7L2 Gene Polymorphisms and Epidemiological Factors in the Prevalence of Gestational Diabetes Mellitus in East Godavari, Andhra Pradesh

Surekha Aravalamma Dasari*, Hima Girisha Dasari, Sai Kandula, Sudhakar Godi

Research Scholar Andhra University Visakhapatnam, Medico GSL Hospital Rajahmundry, Diabetologist Kandula Sai Diabetic Care Hospital, Professor of Andhra University Visakhapatnam and Registrar in Nannaya University Rajahmundry.

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KEYWORDS

Gestational Diabetes Mellitus, TCF7L2 gene, rs7901695, rs7903146, genetic polymorphisms, East Godavari, Andhra Pradesh, case-control study, genotyping, real-time PCR.

ABSTRACT:

Aim: This study aims to explore and compare features, rate, risk, susceptibility, and comorbidity of GDM, about the genetic polymorphisms within the TCF7L2 gene (rs7901695 and rs7903146). A cross-sectional study with 300 participants was carried out in East Godavari, Andhra Pradesh, India.

Methods: The study included 150 GDM patients and 150 control subjects. Genomic DNA extraction and real-time polymerase chain reaction (PCR) were used for genotyping the TCF7L2 gene polymorphisms rs7901695 and rs7903146. Statistical analysis was performed using SPSS.

Results: The results indicated that GDM patients had significantly higher BMI, obesity rates, literacy levels, family history of T2DM, and history of previous GDM compared to the control group. Miscarriage rates were also higher in the control group. Diet was not found to significantly influence the odds of GDM, as the study group had more vegetarians. Diagnosis of GDM was most common during the second trimester, highlighting the need for early screening. No significant demographic differences were observed between the groups.

Genetic Analysis: There was no tangible genetic association between TCF7L2 polymorphisms (rs7901695 and rs7903146) and GDM.

Conclusion: GDM is influenced by factors such as weight, obesity, literacy, family history of T2DM, miscarriage history, and previous GDM, with no significant genetic association with TCF7L2 polymorphisms. Future research should focus on population-specific epidemiological trends and genetic markers to improve diagnostic, therapeutic, and management strategies for GDM.

Introduction:

It is widely known that Gestational Diabetes (GDM) can first develop during pregnancy in any trimester. It usually affects pregnant women throughout the second and third trimester. According to the American Diabetes Association (ADA), less than 10% of pregnant women develop gestational diabetes mellitus. Women who are diagnosed with GDM and infants born to such women are at a higher risk of developing type 2 diabetes **(Goyal R, Jialal I.2019)**. Gestational diabetes is also present which is defined as diabetes mellitus first diagnosed during pregnancy and a type of glucose intolerance. Therefore, based on traditional GDM criteria, this condition appears to be diagnosed clinically by risk factors and screening of pregnant women alongside glucose tolerance, which is mild and in most cases subnormal; any symptoms that are being screened also appear to be generated by changes physiological and genetic comparable to those of type 1 or type 2 DM.

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Female candidates who have earlier been diagnosed with GDM are at a higher risk of getting postnatal diabetes or if they get pregnant again **(Thomas A. Buchanan and Anny H. Xiang 2005)**.

Objectives:

This current study aims to categorize and contrast the risks related to GDM and to determine the relationship of TCF7L2 gene polymorphisms, rs7901695, and rs7903146 with GDM.

Materials and methods:

In this evaluation of the knowledge, attitude, and practice regarding Gestational Diabetes Mellitus a case-control study methodology was used with detailed questionnaires (total = 300) distributed on human subjects. This cohort specifically included 150 patients with Gestational Diabetes Mellitus who have provided written informed consent to participate and underwent phenotypic screening and molecular analysis. Criteria for 150 control groups were based on age and sex-matched individuals for Gestational Diabetes Mellitus chosen in random order from the population. The study received approval from the Institutional Ethics Committee of Andhra University (IEC No: 2) to draw blood from people for scientific analysis. 2ml of venous blood samples in the form of fresh whole blood were collected in heparinized tubes in the EDTA vials. The collected blood samples which were with EDTA tubes were spun at 3000 rpm for 3 mins. Subsequently, for each blood sample, the buffy coat was carefully scraped off the inner surface of the tubes and was transferred to a separate microcentrifuge, and the Genomic DNA was isolated from the buffy coat with the Machery Nagel kit (NucleoSpin Blood method). The calculation of the concentration of DNA using a spectrophotometer at the wavelength of 260nm. The obtained DNA quality was analyzed, and with the help of the given concentration of agarose gel, 0.8% (0.8g in 100 ml TEB 1X) until the completion of electrophoresis, and the outcomes were further examined under UV transilluminator. Primers for this study were designed using the WASP allele-specific tool available at http:///bioinfo.biotec.or.th/WASP. Single nucleotide polymorphisms were genotyped using allelic discrimination with a fast 7500 Real-Time PCR System (Roche Light Cycle nano). The set of probes and primers are self-designed primers from Sigma Aldrich and a master mix 2X TB Green Premix Ex Taq was used in the study. All procedures were performed following the instructions. All samples were genotyped twice in the presence of controls. The results of the samples were confirmed using the sequencing method. DNA was amplified as denaturation at 95°C for 5 seconds, annealing at 60°C for 20 sec, and extension at a temperature of 72°C for 20 sec (Data collection) (Cycle number 35). (Table 1) Samples from patients and controls, including molecular analyses of these samples tested epidemiologically were documented and compiled into an SPSS data format for a complete statistical analysis. As far as the details are concerned, the intermediate data analysis was done with SPSS (version 16) and involved simple frequency count and estimation of the basic quantitative characteristics; such as mean ± SD along with Chi-square and t-tests wherever required.

Table 1. Primer sequences

Primer	Sequence	Annealing temperature	Amplicon length (bp)
7903146F	GCTAAGCACTTTTTAGATAC	60^{0C}	247
7903146R	ACTATGTATTGTTGCCAGTC		
7901695F	AATGGTATCATAAAATCTAC	64^{0C}	207
7901695R	TGTGCAAAATGTTCATAGTA		

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Results:

The characteristics of the study population are presented in Table 2.

Table 2. Patient characteristics

CHARACTERISTICS		STUDY GROUP GDM	CONTROLS	t value	P
Age (years)		161.7(±11.2)	139.3(±11.2)	2.412	.008228
Weight (kgs)		181.42(±30.42)	122.77(±28.23)	6.506	.00001*
Obesity		9.92(±2.92) 37.33%	4.5(±2.5) 10.66%	2.340	.01461
Religion	Hindu	14.46(±0.04) 86%	14.53(±0.03) 94%	0.804	.214166
	Muslim	8(±0) 6.66%	8(±0) 3.33%	0.343	.36875
	Christian	9(±0.5) 7.33%	7.4(±1.1) 2.66%	0.438	.33376
Education	Literate	7.57(±0.07)	7.43(±0.07) 97.33%	149	.00001*
	Illiterate	3(±2.5)	8(±2.5) 3.33%	3.767	.00036*
Occupation	Homemaker	13.42(±0.08) 74%	13.58(±0.08) 78%	1.206	.119507
	Employee	11.33(±0.83)24%	9.82(±0.68)19.33%	1.046	.152046
	Business	56.49(±0.49)0.66%	55.5(±0.5) 0%	0.845	.218264
	Farmer	6.42(±0.08)0.66%	6.58(±0.08)2%	-2	.058058
Economic status	Above average	9.5(±0) 6%	9.5(±0) 6%	0	.5
	Average	31.22(±0.22) 90.66%	30.79(±0.21) 90%	0.156	.438551
	Below average	6(±0) 3.33%	6(±0) 4%	0	.5
Area	Urban	22.9(±0.1) 35.33%	23.08(±0.08) 42.66%	0.010	.460027
	Rural	38.12(±0.88) 64.66%	39.62(±0.62) 57.33%	-0.017	.492945
Food habits	Mixed	40.3(±1.2) 86%	42.82(±1.32) 90%	0.740	.232972
	Vegetarian	9.5(±2.5) 14%	5.44(±1.56) 10%	2.812	.004819*
Family history of type 2 diabetes	With	33.64(±4.64)	16(±13)	7.155	.00001*
	Without	86.5(±0)	86.5(±0)	-2.385	.010006
Number of Pregnancies		155.03(±4.53)	145.97(±4.53)	0.782	.43451
Number of Miscarriages		162.7(±12.74)	137.18(±12.2)	4.060	.00006*
Diagnosis in Previous Pregnancy		36(±12) 15.33%		5.095	.00001*
Age of Menarche		165.2(±14.7)	135.8(±14.7)	3.517	.00050*
Age of onset (TRIMESTER)		258.5 (±91.5)		49.22	.00001*
Comorbidities	With	76(±25) 33.33%	26.49(±24.51)	49.50	.00001*
	Without	123(±0) 66.66%	123(±0)	0	.5000
Type of Delivery	Normal	5.5(±0) 2%	5.5(±0) 2%	0	.5000
	C section	13.29(±2.21) 96.66%	18.38(±2.88) 97.33%	-1.548	.12114

p — p value, probability value**;** *–significant values

The investigation also revealed that the study group had a higher average weight and more percentage of them were grossly overweight than the control group. (p-value .00001). As for the results, the study group showed better results in terms of literacy than the control group. This rather surprising result may pinpoint certain socio-economic determinants of GDM rates or care availability that should be further explored. (.00036). Regarding more details about family history, the study group revealed a higher percentage of

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participants with this history than the control group. (.00001) The result shows that a family history of diabetes, a genetic factor, significantly affects the onset of GDM. As was seen in the case of the previous table, the study group had a higher percentage of miscarriages. (p value.00006). The results have also shown a significantly higher percentage prevalence of GDM in women of the study group than that of the control group. (p-value.00001) The following discovery demonstrates the risk that GDM will reoccur in future pregnancies. The study group also had menarche at a later age as compared to the group of females selected as control. (p-value .00050) This difference could be attributed, at least in part to hormonal factors affecting insulin regulation and glucose utilization. The study group had the GDM diagnosis in the pregnancy significantly more in the 2nd trimester. This finding underlines the need for screening and follow-up for GDM as early as possible, especially among women at high risk of developing GDM. (p-value .00001). Thus, the prevalence of comorbidities in the study group was more than in the control group (p-value .00001). The study group also had a higher percentage of people who had a vegetarian diet. (p-value .004819) This result is contrary to popular belief that vegetarians are less likely to develop GDM and should be studied in the presence of possible mediators. The remaining characteristics as regarded as the age, religion, the occupations of the women, their economic status, their place of residence, number of pregnancies, and mode of delivery did not reach any statistically significant differences between the two groups. The distribution of genotypes for SNP rs7903146 in the study group (GDM) shows the presence of a significantly higher number of people with the C/C genotype (60.66%) compared to the control group (66.66%). It was observed that the frequency of the C/T genotype is also equal in this study (24%) and control (25.33%). This study shows that the T/T genotype occurs more frequently in the group under investigation (study group) and is seen in 15.33% of these patients while in the control group, it is seen in only 8%. T allele frequency of the performed study is significantly higher in the group of patients (27.33%) compared to the control group (20.67%). The odds ratio (OR) for the presence of the T allele is 1.2967 with a 95% confidence interval (CI) ranging from 0.8090 to 2.0784, indicating no significant association (p-value = 0.2804). The Hardy-Weinberg equilibrium (HWE) p-value for the study group is 0.0053, suggesting a deviation from HWE.

Table 3. The distribution of genotypes and allele frequency in the study group and the control

SNP	Genotype	STUDY GROUP (GDM)		CONTROLS		OR	95% CI	p-value	HWE p-value
		L	%	L	%				
	C/C	91	60.66	100	66.66				
rs7903146	C/T	36	24	38	25.33		0.809		
TCF7L2	T/T	23	15.33	12	8	1.2967	to	0.2804	0.0053
C > T	%T	27.33		20.67			2.0784		
	T/T	74	49.33	78	52		0.7074 to		
rs7901695	T/C	50	33.33	60	40	1.1126	1.7499	0.6442	0.9226
TCF7L2	C/C	26	17.33	12	8				
T >C	%C	34		28					

SNP– Single Nucleotide Polymorphism; GDM– Gestational Diabetes Mellitus; OR - Odds Ratio; CI – Confidence Interval ; p-value – Probability value ; HWE p – value – Hardy-Weinberg Equilibrium probability of the control group

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SNP rs7903146; SNP rs7901695 and GDM

SNP rs7901695 (TCF7L2 T > C): For SNP rs7901695, the T/T genotype is slightly less frequent in the study group (49.33%) compared to the control group (52%). The T/C genotype is more common in the control group (40%) than in the study group (33.33%). The C/C genotype is more frequent in the study group (17.33%) compared to the control group (8%). The C allele frequency is higher in the study group (34%) than in the control group (28%). The OR for the presence of the C allele is 1.1126 with a 95% CI of 0.7074 to 1.7499, also indicating no significant association (p-value = 0.6442). The HWE p-value for the study group is 0.9226, suggesting the data is in HWE. Genotype distribution is presented in Table 3.

Discussion:

Being overweight and obesity are considered key determinants of GDM. Analyzing the results of the research the authors established that the patients with GDM were more likely to have obesity than women in the control group. This agrees with other studies that establish a correlation between obesity and higher chances of developing insulin resistance as well as GDM **(Hedderson, et.al.2010; Lee, et al. 2018)**. Active prevention of GDM involves weight management through dietary and physical activity interventions due to the link between the two for satisfactory results for pregnant ladies.

Literacy level was determined to be higher in the GDM group than in the control group study. The women with GDM had lower literacy levels and this within itself could influence their capability in managing GDM. Health literacy has been defined as the ability by which people can understand health information and comprehend medical orders and prescriptions **(Berkman, et. al .2011; Lee, et al. 2018)**. Education in health literacy and compliance with health information could have potentially benefited the management of GDM and the incidence that comes with it.

Regarding the past medical history of their first-degree relatives, it was observed that there was a significantly higher number of cases of Type 2 Diabetes in the GDM group. Diabetes mellitus type 2 is categorically influenced by hereditary factors and various studies conducted have established the hereditary factors that are linked with GDM **(Williams, et.al .2004; Lee, et al. 2018)**. Knowledge of the family history of diabetes can be useful in the identification of persons with a predisposition to develop GDM and timely interventions to exclude the possibility of GDM's development.

The strengths of the study are that three medical centers were involved and there was an increased number of miscarriages and past diagnoses of GDM in the GDM group as compared with the control group. It was established that women with a GDM history have increased chances of developing the disease again in subsequent pregnancies; they also have a high likelihood of miscarriages **(Kim, et al. 2007; Lee, et al. 2018).** Hence, because of these observations, there is a need to provide constant care and specific interventions to women with previous GDM who wish to get pregnant again to obtain a better scenario of pregnancy and its course.

Thus, changes in the age of menarche, the age of onset, or the age difference between menarche and onset should be viewed as standard parts of research on mental illness.

The development of GDM and the age of menarche also progressively differed between the groups. Early menarche is also linked to GDM development because Girls who have menarche earlier are exposed to reproductive hormones that affect glucose levels for an even longer time **(He, et al.2010).** Knowledge of such relations is valuable for select populations' risk assessment and age-targeted primary prevention.

Antihypertensive medications for hypertension, lipid profile for dyslipidemia, and hormonal profile including insulin resistance for PCOS were significantly higher in the GDM group. These conditions are closely related to GDM, through factors such as insulin resistance and obesity which are evident in these diseases **(Gyamfi, et al. 2010; Lee, et al. 2018).** Therefore, coupled management of these comorbidities is critical in the management of GDM and its burden as well as improvement of the maternal and fetal outcomes.

A remarkable difference in the choice of diet was also established with females in the vegetarian category. The vegetarian diet has been shown to decrease the occurrence of GDM because of its source of fiber real

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and low glycemic index **(Chen, et al. 2018).** However, more studies are required to know the nutritional factors that give a shield against GDM and to know more about the place of diet in the prevention and treatment of GDM.

The results regarding the alleles and genotypes' distribution of two polymorphic markers SNP rs7903146 and SNP rs7901695 in the group of women with Gestational Diabetes Mellitus and the control group of women without GDM were found to be insignificant. Based on these findings, it can be concluded that these particular SNPs within the TCF7L2 gene are not very relevant to refer to GDM in this study's particular population.

Based on the results of the study, it was proven that SNP rs7903146 and SNP rs7901695 are not risk factor indicators for GDM. The results of the analysis also relate that these genetic variants neither confirm the association with the condition nor endorse any relation with it. This is contrary to the literature that links these SNP's to T2D, as supported by other research works; **(Grant et al., 2006 and Cauchi et al., 2007).** These findings indicate that there is a lack of genetic relationships between the two disease states in this study because although they share some risk factors, GDM has a distinct genetic makeup from T2D.

TCF7L2 is a protein of T cells transcription factor and exists on chromosome 10q25, with a size of 215kb. 9 kB. The Wnt signaling pathway which is involved in the control of cell proliferation and differentiation process is affected by the TCF7L2 gene and, therefore, TCF7L2 is very important in the development of type 2 diabetes **(Prunier, et al. 2004).** The last stage of this process is the binding of TCF/LEF1 transcription factors (T cell factor and Lymphocyte enhancer factor-1) to DNA with the help of β-catenin. Mammalian cells contain four TCF proteins: These are TCF7 (or TCF1), LEF, TCF7L1 (or TCF3), and TCF7L2(or TCF4).

Therefore, polymorphisms of the TCF7L2 gene might influence insulin resistance or the release of glucagon-like peptide 1 **(Cauchi, et al. 2006; Saxena et al. 2006)** conducted a study that showed that variations in the TCF7L2 gene cause susceptibility to type 2 diabetes through effects on insulin release **(Saxena, et al. 2006).** That said, there is disagreement as to exactly how TCF7L2 alters the insulin resistance level, as it works in several signaling pathways that are characteristic of transcription factors.

The polymorphism most related to Gestational Diabetes Mellitus (GDM) is the one that is present in the TCF7L2 gene and is termed rs7903146. The meta-analysis of nine studies in 2013 showed a relation between SNP rs7908146 T allele that has OR 1 for the development of GDM. 44 (95% CI 1.29–1.60, $p < 0.001$). Thus, the results of studies are significantly different when applied to the Caucasian and Asian populations in particular **(Zhang, et al. 2013).**

A 2013 long-term study was conducted on Finnish women with GDM where 69 polymorphisms were analyzed and out of these polymorphisms, a statistically significant correlation with a weak association was observed between the gene polymorphism rs7903146 polymorphism of the TCF7L2 gene and GDM the OR is 1. 30 95% CI 1.03 – 1.64, p 0. 0028 (Houpio, et al. 2013). Several population-based investigations in Sweden also support the association between certain alleles, such as C > T in rs7903146, and diabetes, mainly GDM. For instance, Papadopoulou et al. (2011) took a cross-sectional sample of GDM subjects of 805 patients, borne between 2000 and 2004, and found out that the CT and TT genotype of rs7903146 facilitated 1.6 times [OR 1.63 (95% CI 1.34–1.97), p-value < 0.0001)] and 19[OR 1.90 (95% CI 1.37–2.64), $p < 0.0001$] higher risk for GDM, respectively **(Papadopoulou, et al. 2011).**

Shaat et al. (2007) carried out a study to establish the relationship between the various polymorphisms of type 2 diabetes with the GDM only the polymorphism genetic type rs7903146 was considered significant. The T/T genotype was associated with about twofold increased prevalence of GDM as opposed to the C/C genotype **(Shaat, et al. 2007).** Analyzing data from the HAPO study, the authors Freathy et al. 2010 investigated the effect of rs7903146 on GDM in Caucasian women of Great Britain and Australia to that of Thai women of Asian origin. In the Caucasian group the T allele was 29.2–30.6% and proved to be associated with GDM whereas in the Asian group, the T allele was 4.7% and was not related to hyperglycemia **(Freathy, et al. 2010).**

Vcelak et al. (2012) provided the allele distribution data of 261 Czech women with GDM and that is very

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close to our study. However, the control group's allele distribution was somewhat dissimilar to our finding. Vcelak and others proved that the subjects, who carry the T allele in the position rs7903146, especially women, had 1.4-fold increased GDM incidence (%T = 33.8% vs 26.7%, OR 1.41, 95% CI 1.08-1.84, p = 0·0148). The genotype distribution in women with GDM was: In this study, there was a significant increase of expression of the marker in cases treated with CC 41.5%, CT 49.2% TT 9.3%, compared with the control group CC 54.4%, CT 39.0% TT 6.5%. Indeed, the study did not show an increased prevalence of GDM in TT homozygotes compared to the other study participants (8 TT homozygotes, 1.33 healthy women; OR, 133, 95% CI 070–2.51, p = 0.476) **(Vcelak, et al. 2012).**

Several investigations have right supported that the case-control experiment of polymorphism rs7903146 is not associated with the raising of hazard GDM. For example, Klein et al. (2012) investigated a Caucasian population in Austria and it was identified that the frequency of the T allele was comparable in the GDM group defined by the 2007 IADPSG criteria and in the control group (48.8 % vs. 49.2 %) **(Klein, et al. 2012).** Scientists analyzed the frequencies of the CC, CT, and TT genotypes of rs7903146 Rizk et al. (2011) among Arab people. The authors were able to prove that the differences if any, between the GDM and control groups (39.4%, 50%, and 10.6% vs. 40.6%, 43.8%, and 15.6% respectively) were statistically insignificant with a calculated p-value of = 0. 444 **(Rizk, et al. 2011).**

But research on the other polymorphism that is rs7901695 is limited and the findings are less convincing. Another study conducted in Sweden by Papadopoulou and her colleagues found that the TC genotype for mannose-binding protein can completely increase the risk of GDM with an OR of 1.56; 95% CI (1.28–1.89) p-value < 0. 00001, while the CC genotype increased the risk by a factor of nearly 1.9-fold, increased with OR of 1.87; 95% CI 1.36–2.57, p< 0.0001] **(Papadopoulou, et al. 2014)** explored the association between the SNPs and the risk of GDM among the white and black women in the USA, the study's author indicated that the T allele in the rs7901695 increased GDM thrice among the two groups (OR 1.98, 95% CI 1.31–2.99) **(Stuebe, et al. 2014).**

However, Pagan et al. (2014) carried out a study with 25 healthy women and 45 Caucasian women with GDM and it was identified that there was no positive association between the polymorphism, rs7901695, and the development of GDM (**Pagán, et al. 2014).**

Conclusion:

In comparing the GDM study group to the group that the study uses as a control, significant variations were identified with regards to weight, obesity, literacy, the family history of Type 2 Diabetes, miscarriage history, prior GDM diagnosis, age at menarche, onset age, comorbidities, vegetarian diet. Sophisticated demographic and clinical differences that were observed did not translate into genotype and allele distribution between the GDM study group and the control group for SNPs rs7903146 and rs7901695. The statistics showed that there was no correlation of genetic basis with GDM among the p-values. The observed deviation from HWE in SNP rs7903146 implies that there might be population stratification of other factors that influence the allele distribution in the study population, which enumerates the role of the gene involved in GDM.

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