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RESEARCH ARTICLE

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THE STUDY OF RELATIONSHIP BETWEEN SINGLE NUCLEOTIDE POLYMORPHISM AND GESTATIONALDIABETES MELLITUS AND ITS PREGNANCY OUTCOMES

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Abstract

GDM is a major cause for perinatal morbidity and mortality complications such as shoulder dystocia, macrosomia, hyperbilirubinemia, hypoglycemia, long term type 2 diabetes mellitus, maternal death, Pre-eclampsia. Hence it is one of the most important global health problems tobe addressed. Pregnancy is a physiological state which can significantly alter both the maternaland fetal metabolic processes bringing in an insulin resistance (IR) like state. During Pregnancyinsulin resistance may develop which can lead to increased maternal adiposity, impaired beta cell.

AIM: This study is designed to find the association of SNPs of genes related to Insulin resistance (KCNQ1, IGFBP2) with the biochemical markers of GDM and to correlate this association with the maternal and fetal outcomes in Gestational diabetes mellitus.

MATERIAL AND METHODS: The molecular and biochemical markers was investigated in419 pregnant women (Pregnant women with GDM (group 1-case, n=210), Pregnant women without GDM (group 2-control, n=209). A total of 5ml of venous blood was collected from thepregnant women with

GDM. **REPORTS**: There was association between KCNQ1 gene and IGF2BP2 gene polymorphism in Gestational diabetes mellitus. **CONCLUSION**: which couldidentify at-risk patients in early stages and designing new therapeutics which will thus help in diagnostics, treatment and eventually prevention of this disease further studies are needed to confirm these findings in different functional genes and their associated microRNA and protein expression in pregnant women with GDM.

Keywords: Single nucleotide polymorphism, Gestational diabetes mellitus, Pregnancy outcomes, cardio metabolic risk factors

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (1,2). GDM has a worldwide prevalence of 1-17% and Indian prevalence of 7-18 % (3,4). GDM is a major cause for perinatal morbidity and mortality complications such as shoulder dystocia, macrosomia, hyperbilirubinemia, hypoglycemia, long term type 2 diabetes mellitus, maternal death, Pre-eclampsia (5,6). Hence it is one of the most important global health problems to be addressed. Pregnancy is a physiological state which can significantly alter both the maternal and fetal metabolic processes bringing in an insulin resistance (IR) like state (7). During Pregnancy insulin resistance may develop which can lead to increased maternal adiposity, impaired beta cell (8). In those mothers with pre-existing diabetes, there could be acceleration of the onset of micro / macro-vascular complications (9,10). Even the fetus suffers from malformations if the glycemic status is not maintained with adequate insulin therapy (11). Although pregnancy is characterized by progressive IR, overt GDM develops only in a small percentage of pregnant women. GDM andT2DM share a common pathophysiology background including glucose intolerance, insulin resistance, and insulin secretion (12). Understanding the pathophysiology is important as it guides diagnostic screening and treatment. The insulin resistance of normal pregnancy facilitates provision of metabolic substrates to the fetus and is multi factorial in origin. Recent identification of hepatic and skeletal muscle lipid deposition in Type 2 diabetes demonstrated by novel magnetic resonance spectroscopy techniques, is likely to be the underlying cause of pathological insulin resistance (13). Similar mechanisms almost certainly under gestational diabetes, although further studies are required to prove this. Women who develop gestational diabetes have demonstrable insulin resistance prior to pregnancy that is part of a chronic process of lipid accumulation ultimately lead to type 2 diabetes later in life (12,14). The importance of life style and dietary modification and the rationale behind the use of metformin are thus explained (15,16). Respective risk factors and genetic variants used to determine the risk of developing T2DM might also be associated with the prevalence of GDM.

Our study of genetic information could lead to improved insight into the underlying pathogenic mechanisms and therelationship between Gestational diabetes mellitus and T2DM. Impaired beta cell function, Insulin resistance, and glucose utilization genes related to variants have been suggested to increase the risk of GDM. This study is designed to find the association of SNPs of genes relatedto Insulin resistance (KCNQ1, IGFBP2) with the biochemical markers of GDM and to correlatethis association with the maternal and fetal outcomes in Gestational diabetes mellitus (17,18).

Materials and methods:

The present case-control study was carried out at tertiary health care setup in Puducherry after

obtaining Institute human ethics committee approval and written informed consent form study subjects. The molecular and biochemical markers was investigated in 419 pregnant women (Pregnant women with GDM (group 1-case, n=210), Pregnant women without GDM (group 2-control, n=209). The pregnant women from south India residing in Tamil Nadu and Puducherryin the age group 18-38 years both primi and multigravida at 24-28 weeks of gestation were screened for GDM by DIPSI (Diabetes in Pregnancy study group Indian) criteria. 75g of anhydrous glucose was given to pregnant women irrespective of their fasting state, if after 2hrsblood glucose was ≥140mg/dL then women were diagnosed as GDM. A total of 5ml of venous blood was collected from the pregnant women with GDM. Serum sample was used for biochemical analysis such as lipid profiles, Insulin C-peptide calcium, Mg2+, Fasting glucose, Renal function test and Liver function test, which were analyzed by auto analyzer cobas411. A whole blood (2ml) was collected in EDTA tube for the genetic analysis. Genomic DNA was extracted based on spin column kit method. The DNA samples were stored at -20°C until analysis. The pregnancy outcomes data were obtained from medical record regarding adverse pregnancy outcomes of both the mothers and their infants.

Results

In this study, the anthropometric and clinical characteristics of the study group were compared between pregnant women with GDM and without GDM. The study included 210 pregnant women with GDM and 209 pregnant women without GDM. 27% of the case group were primigravid. The anthropometric measures of both case and control groups were presented in Table.1. There was a significant difference in the diastolic (*P =0.00***) and systolic (*P=0.00***)blood pressure among the case group when compared with the control group. The weeks of gestation (*P=0.10*), height (*P=0.40*) and weight (*P=0.80*) were not significant among the casegroup. 43% of the GDM cases had family history of GDM.

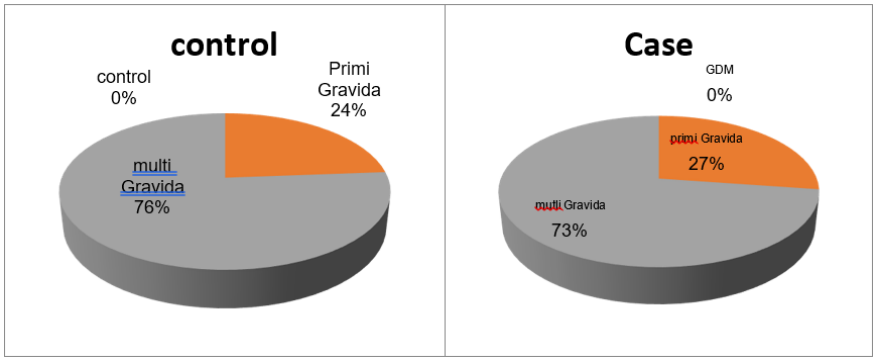

Fig 1: the anthropometric and clinical characteristics of the study group

Table 1: Anthropometric and clinical characteristics in GDM and non-GDM groups

Markers	Control	Case	P value
Weeks of gestation	25.5 ± 2.49	25.9 ± 3.03	0.10
Height	154.1 ±10.89	154. ± 10.89	0.40
Weight	58.9 ± 10.9	58.9 ± 10.92	0.80
Diastolic	110.3 ± 7.74	119.5 ±10.5	0.00**
Systolic	71.7 ±9.03	74.9 ±8.43	0.00**

Liver function tests variables of case and control group were listed in table 9: aspartate transaminase (AST) levels were not statistically significant in pregnant women with GDM groups and non-GDM group. Alkaline phosphatase (ALT) was significant between the study groups (<0.001). Table 3 showed sodium (*P=0.01***) and chloride (*P=0.01***) were statistically significant with GDM group.

Table 2: Comparison of liver function tests in GDM and non-GDM groups

Biochemical markers	Control Mean ± SD	Case Mean ± SD	P Value	Effect size
AST	11.27±2.06	11.33±2.13	0.76	0.02
ALB	2.89±0.70	3.03±0.98	0.11	0.16
ALT	7.65±1.64	9.09±1.94	<0.001**	0.80
Direct Bilirubin	0.05±0.01	0.06±0.02	0.2	0.63
Total Bilirubin	0.41±0.2	0.46±0.3	0.06	0.19

Table 3: Comparison of Electrolytes in GDM and non-GDM group

Biochemical markers	Control Mean ± SD	Case Mean ± SD	P Value	Effect size
Sodium	133.09±8.61	139.66±14.82	0.00**	0.54
Potassium	4.08±1.98	4.29±0.94	0.17	0.13
Chloride	104.98±7.9	111.34±13.8	0.00**	0.56

Table 4: Comparison of Renal function tests in GDM and non-GDM

Biochemical markers	Control Mean ± SD	Case Mean ± SD	P Value	Effect size
Urea	8.51±2.5	10.06±4.2	<0.001**	0.43
Creatinine	0.60±0.19	0.68±0.21	<0.001**	0.39
Uric acid	1.36±0.55	2.97±0.93	<0.001**	2.1

Table 4: shows comparison between renal function tests among both groups. There was significant difference in urea (<0.001), creatinine (<0.001), uric acid (<0.001) levels in pregnantwomen with GDM and non-GDM group.

Single nucleotide polymorphism and Gestational diabetes mellitus

KCNQ1 (rs223789) gene polymorphism was moderately associated with GDM shown (Table 5). CT genotype was found in 55(26%) control cases 37(18%) (ORs =1.6 (95CI% 1.0 – 2.7). There was CT genotype was not associated with GDM.TT genotype was found in 04(2%) control, and cases 07(4%).CC genotype frequency to be found in control 168 (80%) and case 148 (70%).C allele frequency found in control 373(93%), case 351 (89%). T allele frequency was found in control 45(7%) and case 69(11%) There was TT genotype and T allele frequencystrongly associated with Gestational diabetes mellitus (ORs= 1.7)

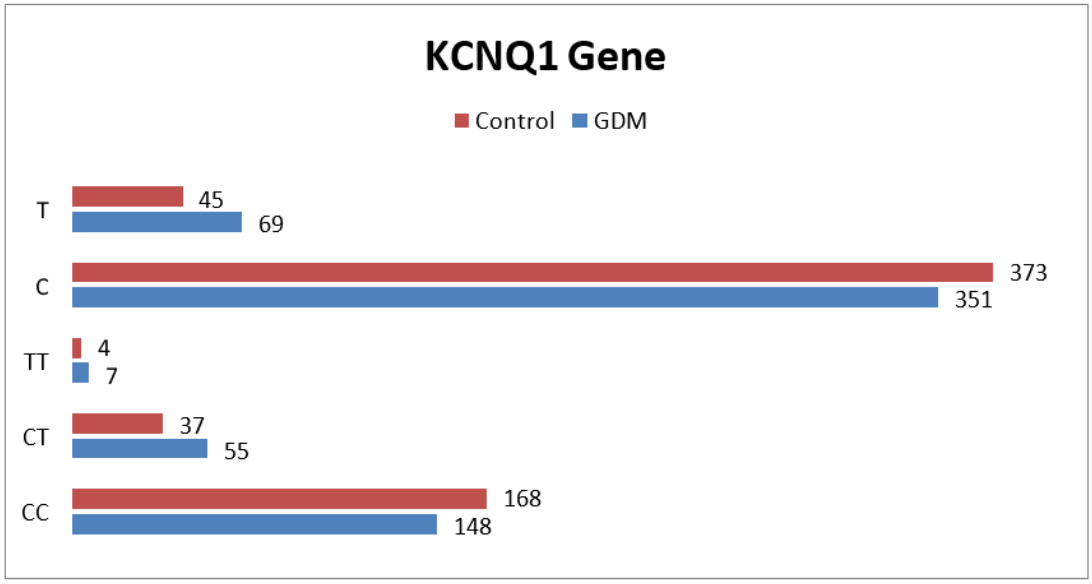

Fig 2: Allele frequency of KCNQ1 gene polymorphism

Table 5: Association of KCNQ1 gene polymorphism in Gestational diabetes mellitus

Genotypes	GDM	Non-GDM	Odds ratio	95%CI	P value
CC	148(70%)	168(80%)	-		-
CT	55(26%)	37(18%)	1.6	1.0 to 2.7	0.02**
TT	07(4%)	04(2%)	1.9	0.5 to 6.9	0.2
CC vs CT + TT	59	41	1.7	1.0 to 2.6	0.01*
C	351(89%)	373(93%)	-	-	-
T	69(11%)	45(7%)	1.7	1.0 to 2.8	0.03*

** 'p' value less than 0.05 is significant, GDM – Gestational diabetes mellitus, CI – ConfidenceInterval*

IGF2BP2 gene polymorphism was strongly associated with Gestational diabetes mellitus (Table 17). GT genotype was found in control 39(19%) and cases 58(28%) (ORs = 1.7 95CI% 1.1 – 2.8). GG genotype frequency was found in control 158(76%) and case 133(62%). TT genotype frequency observed in control 12(6%) and case 19 (10%). G allele variance were found to be in control 355(88%) and case 324(81%). T allele was observed in control 63(12%) and case 96(19%) TT genotype and T allele variance were found to be at higher risk of developing GDM in pregnant women with Gestational diabetes mellitus (ORs=1.6) (Table: 6).

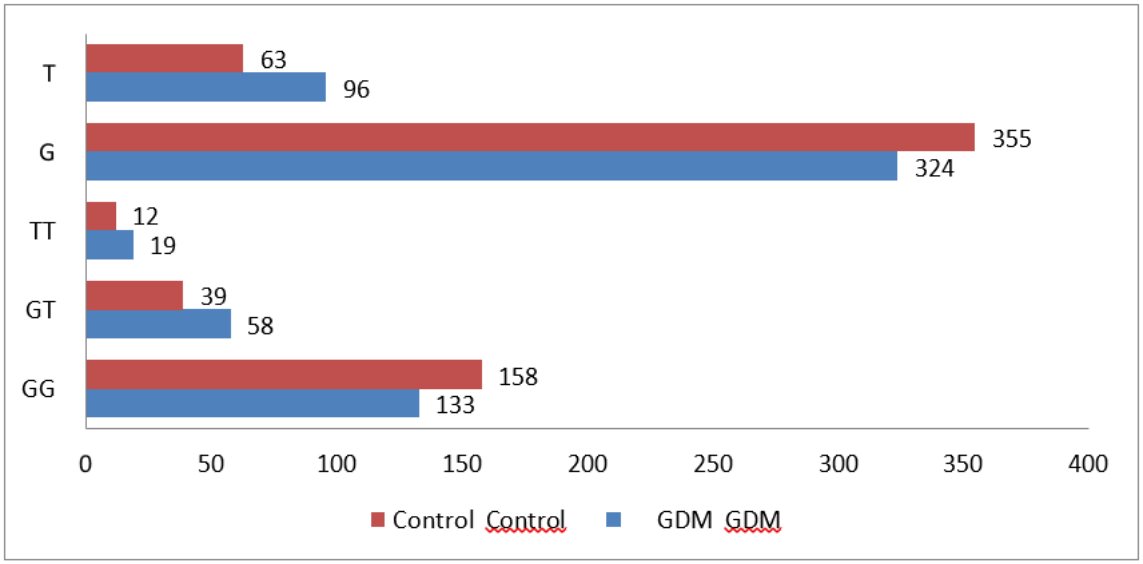

Fig 3: Allele frequency of IGF2BP2 Gene Polymorphism

Table 6: Association of IGF2BP2 gene polymorphism in Gestational diabetes mellitus

Genotypes	GDM	Non-GDM	Odds ratio	95%CI	P value
GG	133 (62%)	158(76%)	1	1	

GT	58(28%)	39(19%)	1.7	1.1 – 2.8	0.01**
TT	19(10%)	12(6%)	1.8	0.8 – 4.0	0.1
GG vs GT+TT	77	51	1.7	1.1 – 2.7	<0.01**
G	324(81%)	355(88%)	1	1	
T	96(19%)	63(12%)	1.6	1.1– 2.6	<0.001*

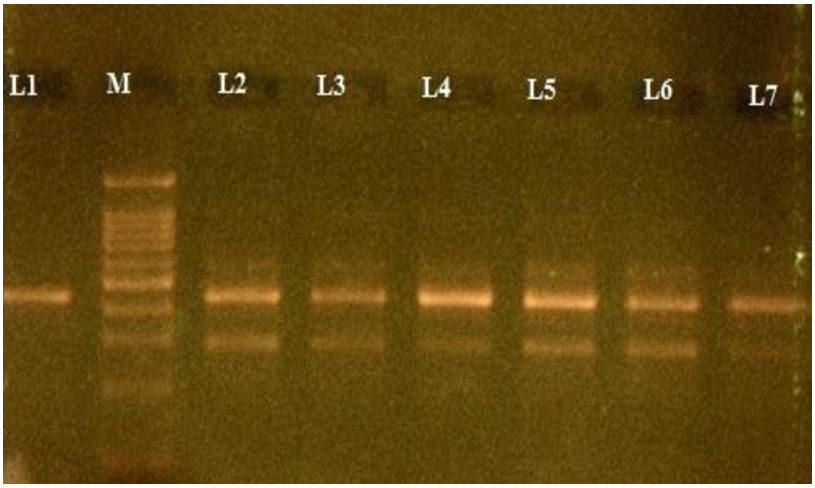

Fig 4: Genotyping result for IGF2BP2(rs4402960)gene : M-Marker (100bp): Ladder 2,Lane 3, Lane 4, Lane 5, Lane 6, Lane 7 G/ G (G-291, T-188bp)

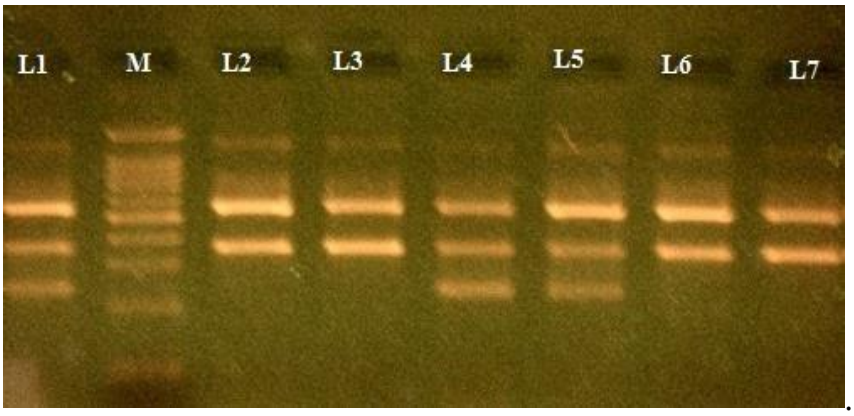

Fig 5:Genotyping result for KCNQ1 Gamma gene (rs1801282): M-Marker (100bp): Ladder 1 G/C (G-235bp, C-355bp), Lane 2,Lane 3 C/C (355bp), Lane 4, Lane 5 G/C, Lane6, Lane 7: C/C genotype

Cardio -metabolic risk factor and Gestational diabetes mellitus:

In this present study we have observed association between cardio metabolic risk factor and genetic

variations in Gestational diabetes mellitus. There was no association between gene polymorphism such as KCNQ1 *(CT, P =0.45, TT=0.37)*, IGF2L2 *(CT, P =0.10*), and cardio metabolic risk factor in GDM.

Table 7: KCNQ1 genotype and cardio metabolic risk factors in GDM

Genotypes	Yes	No	Total	OR (95%CI)	P value
CC	23	125	148	1	
CT	11	44	55	1.36 (0.61 to 3.01)	0.45
TT	02	5	7	2.17 (0.40 to 11.89)	0.37

Table 8: IGF2BP2 gene polymorphism and cardio metabolic risk factor in GDM

Genotype	Yes	No	Total	ORs(95%CI)	P value
GG	21	112	133	1	
GT	15	43	58	1.86 (0.88 to 3.95)	0.10
TT	00	19	19	00	-

OR – Odd's Ratio, CI – Confidence Interval

Our study observed that KCNQ1 gene polymorphism was associated with sleep disturbance (P=0.02*). TT genotype with sleep disturbance (ORs=6.19 95% CI=1.27-30.17 *P=0.02*). CC genotype with sleep disturbance CC genotype is 16, CT genotype is 07 and TT genotype is 03. Therefore, Respiratory syndrome with CC genotype is 4 and TT genotype is 01. There was no association between caesarean section sections (*P=0.28*), macrosomia, pulmonary oedema , Neonatal hypoglycemia (*P=0.22*), hyperbilirubinemia (*P=0.001*), and gestational diabetes mellitus.

Table 9: KCNQ1 gene polymorphism and Gestational diabetes mellitus pregnancy outcomes

Outcomes	Genotype	Yes	No	Total	ORs (CI -95%)	*P value*
Caesarean section	CC CTTT	52 19 01	96 36 06	148 55 07	10.97(0.51 to 1.87) 0.30(0.04 to 2.64)	0.93 0.28
Shoulder dystocia	CC CTTT	00 00 00	148 55 07	148 55 07	1 - -	 -
Macrosomia	CC CTTT	03 00	145 55	148 55	1 -	 -

		00	07	07	-	
Sleep disturbance	CCCTTT	16 07 03	132 48 04	148 55 07	1 1.20(0.47 to 3.10) 6.19(1.27 to 30.17)	0.70 0.02*
Maternal Death	CCCTTT	00 00 00	148 55 07	148 55 07	1 - -	-
Pulmonary oedema	CCCTTT	01 00 00	147 55 07	148 55 07	1 - -	-
Preterm	CCCTTT	24 08 02	124 47 05	148 55 07	1 0.87 (0.36 to 2.0) 2.0 (0.37 to 11.28)	0.7 0.40
Fetal Death	CCCTTT	01 00 00	147 55 07	148 55 07	1 - -	-
Neonatal hyperbilirubinemia	CCCTTT	10 03 00	138 53 07	148 55 07	10.80(0.21to 3.01)	0.71
Neonatal Hypoglycemia	CCCTTT	15 09 01	133 46 06	148 55 07	11.73(0.71 to 4.23) 1.48(0.17 to 13.12)	0.22 0.72
Respiratorysyndrome	CC CTTT	04 00 01	144 55 06	148 55 07	1 - 6.0(0.58 to 62.50)	0.13
APGAR score	CC CTTT	00 00 00	148 55 07	148 55 07	1 - -	-

** 'p' value less than 0.05 is significant, OR – Odd's Ratio, CI – Confidence IntervalApgar score : >3-Poor:1>3-10- normal:2*

Our study observed that IGF2BP2 gene polymorphism was not associated with pregnancy outcomes such as caesarean section (*P=0.96*), sleep disturbance (*P=0.89*), pulmonary oedema, preterm

(*P=0.70*), Neonatal hypoglycemia (*P=0.81*), Respiratory syndrome (*P=0.81*), Neonatal hyperbilirubinemia (*P=0.81*) and Gestational diabetes mellitus. (Table 10)

Table 10: IGF2BP2 gene polymorphism and Gestational diabetes mellitus pregnancy outcomes

Outcomes	**Genotype**	**Yes**	**No**	**total**	**ORs (95 %CI)**	***P value***
Caesarean sections	GG	45	133	133		
	GT	20	58	58	1.02(0.55 to 1.88)	0.96
	TT	07	19	19	1.09 (0.43 to 2.76)	0.85
Shoulder dystocia	GG	00	133	133	1	
	GT	00	58	58	-	-
	TT	00	19	19	-	
Macrosomia	GG	03	130	133	1	
	GT	00	58	58	-	-
	TT	00	19	19	-	
Sleep disturbance	GG	17	116	133		
	GT	07	51	58	0.94(0.37 to 2.40)	0.89
	TT	02	17	19	0.80(0.17 to 3.17)	0.78
Maternal Death	GG	00	133	133	1	
	GT	00	58	58	-	-
	TT	00	19	19	-	
Pulmonary oedema	GG	00	133	133	1	-
	GT	00	58	58	-	
	TT	01	18	19	-	
Preterm	GG	20	113	133	1	
	GT	10	48	58	1.18(0.51 to 2.70)	0.70
	TT	04	15	19	1.51(0.45 to 5.01)	0.50
Fetal Death	GG	01	132	133	1	
	GT	00	58	58	-	-
	TT	00	19	19	-	
Neonatal hyperbilirubinemia	GG	08	125	133	1	
	GTTT	04	54	58	1.16(0.33 to 4.01)	0.81
		01	18	19	0.87(0.10 to 7.35)	0.89

Neonatal	GG	13	120	133	1	
Hypoglycemia	GTTT	08	50	58	1.48(0.58 to 3.78)	0.41
		04	15	19	2.46(0.71 to 8.53)	0.51
Respiratorysyndrome	GG	03	130	133	1	
	GTTT	01	57	58	0.76(0.08 to 7.47)	0.81
		01	18	19	2.41(0.24 to 24.41)	0.45
	GG	00	133	133	1	
APGAR score	GT	00	58	58	-	-
	TT	00	19	19	-	

** 'p' value less than 0.05 is significant, OR – Odd's Ratio, CI – Confidence IntervalApgar score : >3-Poor:1>3-10- normal:2*

Discussion

KCNQ1 gene encodes a voltage-gated potassium channel, KQT-like subfamily, member1 (KCNQ1), KCNQ1 is also expressed in pancreatic islets; KCNQ1 channels may play a role inregulation of insulin secretion. The polymorphism of KCNQ1 (rs2237892) was first observed to be associated with GDM in Korean populations (19,20). In this present study, our report showed that *KCNQ1 (rs2237892)* was significantly associated with Gestational diabetes mellitus (ORs=1.6). Our report showed that pregnant women with TT genotype (ORs=1.9) and T allele variance were found to have more risk of developing Gestational diabetes mellitus. This finding was in accordance with the studies conducted by *Shin et al*.,(ORs=1.25), *Xueyan Zhou et al*.,(*P=0.002*)., *Zhou et al*.,(ORs=1.45)., *Saif Ali et al*.,(41,44,228,229). Our study revealed an odds ratio of 1.9 which was relatively high when compared to others. (The odds ratio for the study conducted by *Chang et al, 1.49,* 1.21 odds ratio for the study conducted by*van vliet* et al., 1.49 for *Ben et al.*)

The *KCNQ1* gene which plays an important role in cardiac action potential is also expressed in pancreatic islets. *Roura et al*., study showed *KCNQ1* gene is associated with levels of TG, HDL-C, and apoA1. In this present study KCNQ1 gene is not associated with cardio metabolicrisk factors (*CT, P=0.45, TT, P=0.37*). KCNQ1 gene was associated with pregnancy outcomesof respiratory sleep disturbance (*TT, P=0.04*). *Novotny et al*., studies was report that KCNQ1 gene polymorphism was indirectly related to Jervell and Lange-Nielsen syndrome. Further studies are needed to prove association of other pregnancy complications (21,22,23).

We have observed association between IGF2BP2 gene polymorphism and Gestational diabetes mellitus. Our report confirmed the positive association between *IGF2BP2* gene polymorphismand GDM (ORs=1.8). This finding was in accordance with *Lebedy et al*., (ORs=1.8), *Zhang L.-F et*

al.,(Chinese population), this result was similar to that observed by a Korean GDM study (OR=1.18, 95%CI=1.01–1.38). This study did not show that didn't show any associationbetween IGF2BP2 gene polymorphism and cardio metabolic risk factors (ORs= 1.86) (GT, *P=0.10*).GG genotype variance is 21, GT variance is 15. *Hoek et al*., showed the association between IGF2BP2 gene polymorphism and fetal birth weight (24,25). We have observed association between IGF2BP2 gene polymorphism and Gestational diabetesmellitus. Our report confirmed the positive association between *IGF2BP2* gene polymorphismand GDM (ORs=1.8).

This finding was in accordance with *Lebedy et al*., (ORs=1.8), *Zhang L.-F et al*., (Chinese population), this result was similar to that observed by a Korean GDM study(OR=1.18, 95%CI=1.01–1.38). this study did not that didn't show any association between IGF2BP2 gene polymorphism and cardio metabolic risk factors (ORs= 1.86) (GT, *P=0.10*).GGgenotype variance is 21, GT variance is 15. *Hoek et al*., showed the association between IGF2BP2 gene polymorphism and fetal birth weight. Several studies observed that IGF2BP2 may be explained by over efficient modulating effects of risk alleles during fetal development.IGF2BP2 gene polymorphism couldn't show any correlation with maternal and fetal outcomes.We have to study about Gene–gene and gene–environment interactions which may further help illustrate the biological basis of complex diseases and provide important clues for personalizedinterventions or clinical therapeutics (26,27).

Conclusion

To conclude there was significant association between the *KCNQ1, IGF2BP,* gene polymorphism and Gestational diabetes mellitus. Since SNPs of *KCNQ1* genes are associated with reduced insulin secretions in GDM, our study assumes relevance in targeting this gene intherapeutic management of GDM by modifying insulin dosage in GDM. GDM and T2DM share a common genetic background including glucose intolerance, insulin resistance, and insulin secretion. It has major cause of perinatal morbidity and mortality, as well as maternal

morbidity. The outcomes of study will help us to develop new therapeutic targets which couldhelp us to manage of GDM as well as its complications such as preeclampsia, hypoglycemia, shoulder dystocia, respiratory distress, hyperbilirubinemia, and low birth weight. We could saythat a proper understanding of genetic background of GDM and hormonal changes during pregnancy which could identify at-risk patients in early stages and designing new therapeutics which will thus help in diagnostics, treatment and eventually prevention of this disease furtherstudies are needed to confirm these findings in different functional genes and their associated microRNA and protein Expression in pregnant women with GDM.

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ABBREVATIONS

1. GDM –Gestational diabetes mellitus
2. KCNQ1 -Potassium voltage-gated channel subfamily Q member 1
3. IGF2BP2 -Insulin-like growth factor 2 mRNA-binding protein 2
4. IR -Insulin Resistance
5. SNPs -Single nucleotide polymorphism
6. AST -Aspartate aminotransferase
7. ALT -alanine aminotransferase