Advances in Bioresearch
Adv. Biores., Vol 14 (4) July 2023: 177-184

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.4.177184

Advances in Bioresearch

ORIGINAL ARTICLE

Association Between Gestational Diabetes Mellitus and Single Nucleotide Polymorphism of rs10830963 in the Melatonin Receptor (MTNR1B) Loci - A Prospective Case-Control Study in South Indian Population

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ABSTRACT
Gestational diabetes mellitus (GDM) is any glucose intolerance with onset or first recognition during pregnancy. A case-control study was performed to analyze the relationship between GDM and Melatonin receptor 1B genetic variability of rs10830963 in the Melatonin receptor 1B (MTNR1B) locus in the case and control population. Melatonin is a hormone secreted into the circulation by the pineal gland. It regulates both seasonal and circadian rhythms. The polymorphisms of MTNR1B are linked with increased fasting plasma glucose levels, impaired insulin production, and the development of type 2 diabetes, supported by solid evidence from genome-wide association studies. Allele frequencies of the Indian control population are not well established as only a few studies were conducted in the Indian population that looked into the association between the MTNR1B gene and GDM. This study evaluated the association between GDM and the single nucleotide polymorphism of rs10830963 in the MTNR1B loci. The MTNR1B polymorphism (rs10830963) analysis in the present study showed G allele as a significant allele in category GDM. In contrast, the control population's allele proportions showed G allele as a minor allele. The inheritance models showed the G allele with a higher odds ratio than the C allele, where the G allele is a possible risk factor for GDM and BMI in our population. SNP analysis in the GDM group showed the SNP rs10830963 CG and GG genotypes as potential risk factors for developing GDM in the study population. In contrast, the control population showed higher frequencies of CC Genotype.
Keywords; *Gestational diabetes mellitus, Melatonin receptor 1B polymorphism, Melatonin, SNP Analysis, Insulin resistance*

Received 11.05.2023 Revised 07.06.2023 Accepted 19.07.2023

How to cite this article:
S. Ammulu, Geena Augustine, Jithesh T K, Rajkumar K.K. Association Between Gestational Diabetes Mellitus and Single Nucleotide Polymorphism of rs10830963 in the Melatonin Receptor (MTNR1B) Loci - A Prospective Case-Control Study in South Indian Population. Adv. Biores. Vol 14 (4) July 2023: 177-184.

INTRODUCTION

Gestational diabetes mellitus is any glucose intolerance that develops or is initially diagnosed during pregnancy [1]. GDM causes a substantial impact on the mother and the infant's pregnancy outcomes. Even though it may have a detrimental influence on the lives of pregnant women, it continues to be a contentious issue with contradictory management and treatment guidelines. The Asian population has a greater-than-normal risk of getting type 2 diabetes. It has been demonstrated that lifestyle changes, namely decreased physical activity and increased sedentary behavior, substantially contribute to the incidence of GDM. According to the Diabetes Atlas Survey, 88 million people in Southeast Asia live with diabetes. This number is anticipated to reach 115 million by 2030 and 153 million by 2045, a 74% increase. Maintaining a healthy weight and diet is crucial, and children born to moms with gestational diabetes have a 1.8-fold greater chance of acquiring type 1 diabetes in adulthood [2]. This will make a substantial contribution toward

attaining the 2045 prediction. GDM is a clinical con dition primarily believed to be caused by a combination of genetic and environmental risk factors, even though its exact etiology and mechanisms remain unknown. Melatonin is a hormone secreted into the circulation by the pineal gland. It regulates both seasonal and circadian rhythms. Islets of the pancreas express the functional melatonin receptor subtype MTNR1B, a member of the melatonin receptor subtype family [1]. The studies demonstrate a link between variations in the MTNR1B gene, hyperglycemia, impaired early phase insulin secretion and beta cell function. The risk genotype predicts the future development of type 2 diabetes. Carriers of the risk genotype exhibit increased expression of MTNR1B in islets. The polymorphisms of MTNR1B, are linked with increased fasting plasma glucose levels, impaired insulin production, and the development of type 2 diabetes, supported by solid evidence from genome-wide association studies. As GDM shares many clinical features with T2DM, there is a high possibility that MTNR1B is associated with increased susceptibility of GDM. There are reports of MTNR1B gene associated with type 2 diabetes, our study specifically focus on GDM mothers and association/involvement of MTNR1B gene variations in the etiology of GDM. Allele frequencies of the Indian control population are not well established as there are only few studies conducted in the Indian population which looked into the association between the MTNR1B gene and GDM. This study aimed to evaluate the association between GDM and the single nucleotide polymorphism of rs10830963 in the Melatonin receptor (MTNR1B) loci [2, 3].

MATERIAL AND METHODS

After obtaining ethical clearance from the institutional ethics committee, a case-control study was performed in the MES Medical College, Perinthalmanna, and Kerala. Pregnant women admitted to the Obstetrics and Gynecology department's labor ward were enrolled in the study, fulfilling the selection criteria.

In the control group were pregnant women of comparable age who have undergone a standard glucose challenge test (GCT) and have not been diagnosed with any other systemic disorders. The GDM screening test was administered as part of routine prenatal screenings in line with the WHO-approved procedure followed by the central laboratory. Pregnant women were monitored at 24–28 weeks for GCT by providing a 50g oral glucose load regardless of the time of day. If the GCT was indicative (≥140mg/dl), gestational diabetes status was confirmed with an oral glucose tolerance test (OGTT). The prenatal patients were given 75g glucose dissolved in approximately 300ml of water in a fasting state. Blood glucose level after 2 hours of oral glucose load was evaluated. The threshold sugar level of >140mg/dl was taken as the cut off for diagnosis and management of gestational diabetes mellitus.

As there were contradictory reports on the prevalence of GDM in the Indian population, the sample size was calculated based on the findings of a pilot study. The case population were 100 in numbers with GDM and the control group, fifty pregnant women of a comparable age who did not have the disease or any other concerns were included in the research. Participants in the case and control populations were presented with in-depth information about the research endeavor and gave their written consent.

The demographic information, the mothers' health status, the number of newborns, and their parameters were extracted from the medical records. These variables included the mother's age, height, weight, systolic and diastolic blood pressure, maternal relations, previous obstetric history, fasting and postprandial blood glucose, and delivery technique. Before the babies were born, 5ml maternal venous blood was taken and preserved for molecular analysis at 4 °C.

The molecular study was performed to analyze the MTNR1B polymorphism (rs10830963- CC: CG: GG), which is said to have an association with the onset of gestational diabetes. The blood samples were collected in EDTA (purple-top) vacutainer to screen the single nucleotide polymorphism. The following molecular techniques were carried out.

Genomic DNA Extraction was carried out using using a Kit method of ORIGIN that was standardized in the Jubilee Centre for Medical Research, Jubilee Mission medical college & Research Institute, Thrissur, Kerala. Quantification of DNA (QUBIT ASSAY) was done using Qubit 2.0 instrument.

Qualitative analysis of DNA using Agarose gel electrophoresis

Agarose gel with a 0.5% concentration for the whole genome was prepared. The agarose-Ethium Bromide mixture was well combined before being poured into a gel boat fastened with combs and placed on a water-leveled platform. It was chosen to let the agarose solution in the gel boat solidify (approximately 20 minutes). Before introducing the gels into the submersible Gel Electrophoresis device, the combs were removed. A 0.5XTBE buffer was then added to the system (pH 7.5). DNA samples were placed beside the DNA itself in the wells to measure the DNA quality. The gel was then put in a 70-volt current for two hours while an experimenter watched with a UV transilluminator.

Amplification-refractory mutation system (ARMS) analysis for genotyping

To determine the genotype of the rs10830963 marker, tetra-primer amplification refractory mutation system analysis was used (tetra-primer ARMS-PCR). On 2% agarose gels, the behavior of the various PCR products was evaluated. The ARMS PCR results were used to identify people with specific genotypes. At least two qualified individuals trained to comprehend genotypes were responsible for supplying phenotypic descriptions. The PCR was done using an Applied Biosystems VeritiTM 96 Thermal Cycler with the best settings.

ARMS-PCR Conditions		
Reaction	Temperature (°C)	Duration
Initial denaturation	95	5 minutes
Denaturation	95	30 seconds
Annealing	56.5	40 seconds
Extension	72	30 seconds
Final extension	72	10 minutes
On hold	4	∞

Statistical analysis

The statistical study was conducted using version 20 of the IBM SPSS software package. The mean and standard deviation are the two methods to express continuous variables. Statistically, the Student's t-test and the Mann-Whitney U test were used to determine how substantially various continuous variables varied between the case and control groups. The case and control ARMS genotyped data were submitted to an exact test to evaluate whether they departed from the Hardy-Weinberg equilibrium. Using several genetic models, the allele frequencies, genotype frequencies, and Hardy-Weinberg equilibrium of the rs10830963 polymorphisms were analyzed, and the SNP association with the response (GDM) was computed (Codominant, Dominant, Recessive, and Over-dominant). For each variable, estimates and confidence intervals with a 95% level of precision were calculated. The web application SNP Stat was used for both genotyping and association study analysis.

RESULTS

Demographic data analysis of GDM cases and controls

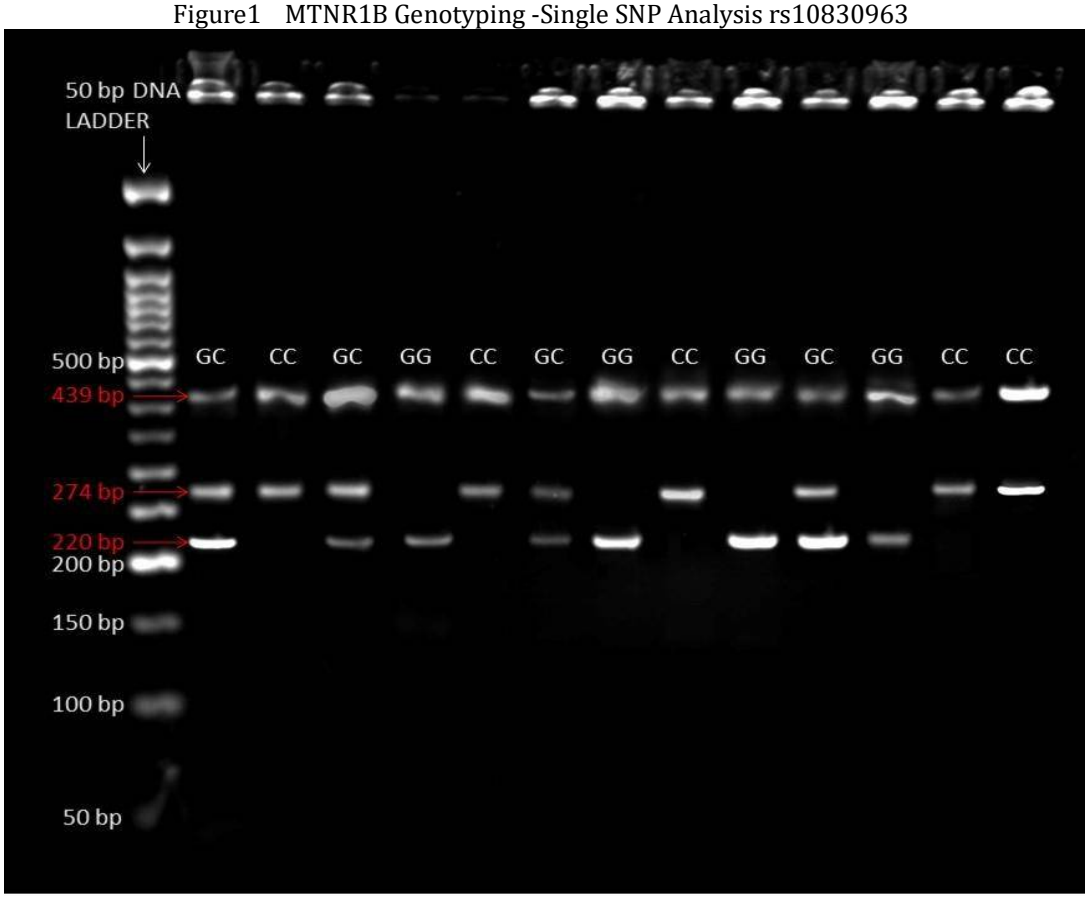
Age, height, weight, systolic and diastolic blood pressure, and other parameters were obtained and analyzed from the medical records (table:-1). The collected data were analyzed, and the findings were compared to those of a control group. A comparative analysis was conducted between the GDM group and the control group regarding the mode of delivery (vaginal vs. cesarean section). The GDM patients had a much greater cesarean section rate than the controls (92 cesarean sections vs. 8 vaginal births) (20 cesarean sections and 30 vaginal deliveries).

Table1 Demographic Variables In GDM Cases And Controls

Variables	**Group**	**N**	**Mean**	**Std. Deviation**	**p-value**
Age (Yrs)	Case	100	29.14	2.57	0.299 NS
	Control	50	28.40	3.57	
Height (cm)	Case	100	152.68	4.60	0.164 NS
	Control	50	153.80	4.66	
Weight (Kg)	Case	100	63.32	5.68	<0.001***
	Control	50	55.28	4.35	
BMI (Kg/m2)	Case	100	27.16	2.08	<0.001***
	Control	50	23.36	1.41	
Systolic BP(mmHg)	Case	100	118.6	4.91	0.229 NS
	Control	50	119.6	4.52	
Diastolic BP (mmHg)	Case	100	78.30	3.78	0.655 NS
	Control	50	78.0	4.04	
Birth weight (Kg)	Case	100	3.14	0.43	0.043*
	Control	50	3.00	0.39	
FBS (mg/dl)	Case	100	95.47	4.24	<0.001***
	Control	50	90.88	7.10	
PPBS(mg/dl)	Case	100	151.32	7.48	<0.001***
	Control	50	121.84	12.96	

Values obtained for GDM cases are compared with controls. Values are represented as mean ± S.D. Level of significance - *** p <0.001, * p <0.05, NS: not significance.

Figure1 MTNR1B Genotyping -Single SNP Analysis rs10830963



The Amplification Refractory Mutation System (ARMS) - PCR Results for The Amplification Refractory Mutation System (ARMS) - PCR Results for rs10830963

Representative Agarose Gel picture of the ARMS PCR results for rs10830963. The outer forward and reverse primer amplify 439 bp PCR product. The inner primers specific for rs10830963 make 274 bp PCR product specific for the C allele and 220bp PCR product specific for the G allele. The amplification of both inner primer products is considered heterozygous GC alleles.

Table :-2 SNP allele frequencies (n=150)

	All subjects		**Category=Control**		**Category=Case (GDM)**	
Allele	**Count**	**Proportion**	**Count**	**Proportion**	**Count**	**Proportion**
C	164	0.6	66	0.66	98	0.49
G	136	0.5	34	0.34	102	0.51

The allele frequencies of the G allele and C allele in all the subjects studied, the Control population and GDM are separately given in the above table as proportions (table :-2).

Table:-3 Genotype frequencies

All subjects			**Category=Control (n=50)**		**Category= Case (GDM) (n=100)**	
Genotype	**Count**	**Proportion**	**Count**	**Proportion**	**Count**	**Proportion**
C/C	44	0.29	21	0.42	23	0.20
C/G	76	0.51	24	0.48	52	0.50
G/G	30	0.20	5	0.1	25	0.30

The genotype frequencies of the C/C, C/G and G/G in all the subjects studied, the Control population, and GDM gave in the above table as proportions (table:-3).

Table:-4 SNP exact test for Hardy-Weinberg equilibrium (n=150)

	CC	CG	GG	C	G	P-value	HWE (Yes/No)
All subjects	44	76	30	164	136	0.87	Yes
Category=Control	21	24	5	66	34	0.76	Yes
Category=GDM	23	52	25	98	102	0.84	Yes

The SNP seems to be in the HWE as the exact test for the study groups do notsignificantly differ (table:-4).

Table:-5 SNP association with response Affected and Unaffected (n=150,crude analysis)

Model	Genotype	Control	Case (GDM)	OR (95% CI)	P-value
Codominant	C/C	21 (42%)	23 (23%)	1	0.016^{NS}
	C/G	24 (48%)	52 (52%)	1.98 (0.92-4.25)	
	G/G	5 (10%)	25 (25%)	4.57 (1.48-14.10)	
Dominant	C/C	21 (42%)	23 (23%)	1	0.018*
	C/G-G/G	29 (58%)	77 (77%)	2.42 (1.17-5.03)	
Recessive	C/C-C/G	45 (90%)	75 (75%)	1	0.023*
	G/G	5 (10%)	25 (25%)	3.00 (1.07-8.39)	
Over dominant	C/C-G/G	26 (52%)	48 (48%)	1	0.6^{NS}
	C/G	24 (48%)	52 (52%)	1.17 (0.59-2.32)	
Log-additive	---	---	---	2.10 (1.24-3.54)	0.0042**

Level of significance - *p<0.05, **p<0.01, NS: not significant

The genotype GG is strongly associated with the test group (GDM) as the OR > 1, and the p-value is p<0.05. The genetic models tested for the association are Codominant, Dominant, Recessive, and over-dominant. The results show that the genotype GG is a risk factor in GDM (table: -5).

Table:-6 SNP association with overweight

Model	Genotype	N	BMI Mean	Difference (95% CI)	p-value
Codominant	C/C	44	25.1	0	0.02*
			(0.33)		
	C/G	76	26.02	0.92 (-0.03 - 1.87)	
			(0.32)		
	G/G	30	26.72	1.62 (0.44 -2.81)	
			(0.45)		
Dominant	C/C	44	25.1	0	0.02*
			(0.33)		
	C/G-G/G	106	26.22	1.12 (0.22 -2.02)	
			(0.26)		
Recessive	C/C-C/G	120	25.68	0	0.05*
			(0.24)		
	G/G	30	26.72	1.04 (0.01 -2.07)	
			(0.45)		
Over dominant	C/C-G/G	74	25.76	0	0.54^{NS}
			(0.28)		
	C/G	76	26.02	0.26 (-0.57 -1.10)	
			(0.32)		

Level of significance - *p<0.05, NS: not significant

The genotype GG is strongly associated with BMI >26 as the OR > 1. The genetic models related to BMI and SNP show that GG genotype isassociated with GDM (table: -6).

DISCUSSION

The demographic baseline descriptive data such as age, height, weight, systolic and diastolic blood pressure, FBG, and PPBG were extracted from the medical records and analyzed before delivery. The records also included systolic and diastolic blood pressure measurements. The mean fasting blood glucose level of GDM patients was 95.47 4.2 mg/dl, whereas the mean FBG level of healthy controls was 90.88 7.0 mg/dl. In cases of GDM, the mean PPBG was 151.32 7.48 mg/dl, whereas it was 121.84 12.9 mg/dl in the control group. Comparing the results of the cases and the controls revealed statistically significant differences (p less than 0.001). Compared to the control group, the incidence of cesarean sections was more significant in the GDM group. The data revealed a statistically significant difference in maternal weight (pvalue 0.001), birth weight (p value 0.05), and BMI (pvalue 0.001). None of the factors reached statistical significance, including age (p-value: 0.299), height (p-value: 0.164), systolic blood pressure (p-value: 0.229), and diastolic blood pressure (p-value: 0.229). (p-value: 0.655). The average age of GDM population was 29.17 years (standard deviation: 2.57), whereas the average age of controls was 28.64 years (standard deviation: 3.57). There was no statistically significant difference between the two groups (table:-1).

Insulin resistance and diabetes are often influenced by excess fat and obesity. Excessive weight gain early in pregnancy may raise the likelihood of developing gestational diabetes, among other possible complications. In response to this, the mother's weight was measured and reported. In this study, the average weight of pregnant women with GDM was 63.32 kg, whereas the average weight of the controls was 55.28 kg. There was a statistically significant difference in the outcomes of the two groups (pvalue 0.001).

The likelihood of getting diabetes and GDM is higher in obese individuals. The case population and the control group's body mass index (BMI) were examined. The BMI of those with type 2 diabetes was determined to be 27.16 kg/m2, while the BMI of those without diabetes was 23.36 kg/m2. The results revealed a statistically significant correlation (p-value 0.001). According to the study results, metabolic risk factors begin to accrue in obese pregnant women early in pregnancy. These risk factors are connected with an increased risk of type 2 diabetes. So, the fact that metabolic problems tend to cluster in obese women during the first trimester of pregnancy may be another way obesity and GDM are linked.

Women with gestational diabetes may be more likely to develop preeclampsia and high blood pressure during pregnancy. Elevated systolic and diastolic blood pressure during pregnancy may cause serious complications that endanger the mother and the unborn child. Consequently, the enrolled research groups' systolic and diastolic blood pressures were determined and reported. Those with GDM had a mean diastolic blood pressure of 78.0 mmHg, whereas those acting as controls had a mean diastolic blood pressure of 78.3 mmHg. The results revealed no statistically significant associations (p-value = 0.655). In the GDM population, the systolic blood pressure was 119.6 4.9 mmHg, while the systolic blood pressure in the control group was 118.6 4.5 mmHg. Comparisons of systolic blood pressure between the two groups indicated no statistically significant differences (p-value: 0.229).

Studies by Shin, D., and Song, W.O., [5, 6] have demonstrated that maternal hypertension is a risk factor for gestational diabetes. However, the current study population did not reveal any statistically significant differences in blood pressure between GDM cases and controls. According to reports, the metabolic alteration of the fetus's prenatal environment in gestational diabetes may lead to high birth weight and subsequent obesity in infants . There was a statistically significant difference in the average birth weight of babies born to mothers with gestational diabetes and those delivered to mothers without gestational diabetes. When maternal glycemic control is impaired, and the maternal serum glucose level is high, the glucose crosses the placenta. The fetal pancreas starts to respond to hyperglycemia and autonomously secrete insulin regardless of glucose stimulation. This combination of hyperinsulinemia (insulin being a primary anabolic hormone) and hyperglycemia (glucose being a major anabolic fuel) can increase the fat and protein stores of the fetus.

MTNR1B genotyping SNP Analysis rs10830963

The MTNR1B polymorphism (rs10830963) analysis revealed that the G allele was significant in the GDM category. However, the proportions of alleles in the control group indicated that the G allele was minor. The findings of our investigation are supported by further research. According to Tarnowski et al., the MTNR1B rs10830963 polymorphism is associated with GDM susceptibility, and women with a more significant proportion of G alleles had an increased risk of developing GDM . Liu Q. et.al. [10] revealed that MTNR1B SNPs are significantly associated with GDM. In the Korean population, two single nucleotide polymorphisms (SNPs) in the melatonin receptor 1B gene, designated rs10830963 and rs1387153, were

shown to be associated with altered levels of fasting plasma glucose and type 2 diabetes. Liu et al. [10] conducted a meta-analysis to determine whether the rs10830963 polymorphism in MTNR1B is associated with an increased risk of GDM [11]. According to the studies, there were significant connections between GDM and the rs10830963 polymorphism in the Chinese population. Using correlation studies and meta-analyses, the melatonin receptor 1B (MTNR1B) single nucleotide polymorphisms (SNPs) rs1387153 and rs10830963 are associated with type 2 diabetes. Numerous studies using the genome-wide association study (GWAS) indicate that inherited variants of critical genes associated with pancreatic islet-cell function, especially MTNR1B, are likely involved in the onset of type 2 diabetes [5-8].

The GWAS (Genome-Wide Association Study) results suggest that the MTNR1B receptor may be implicated in the pathophysiology that leads to type 2 diabetes. MTNR1B inhibits the expression of glucokinase and insulin production in response to glucose. When beta cells express more of MTNR1B, insulin secretion is inhibited. As a direct result, abnormal expression of MTNR1B contributes to the development of GDM. Even though the rs10830963 SNP is located in the intron of the MTNR1B gene, the significant association with GDM shows that the variation plays a crucial function in regulating MTNR1B expression. The MTNR1B rs10830963 polymorphism is linked to a difference in how much the melatonin receptor is expressed on beta cells. The G allele is connected to a higher expression level than the C variant.

The CC genotype frequency was lower in GDM groups than in control groups, making the CG and GG genotype the risk genotypes for GDM patients. In the inheritance models, the G allele was revealed to have a higher odds ratio than the C allele, indicating that the G allele may be a risk factor for GDM and BMI in our population. Analysis of SNPs in the GDM group indicated that the CG and GG genotypes of SNP rs10830963 are likely to be risk factors for developing GDM in the study population. On the other hand, the frequency of the CC genotype was higher in the control population. Having the GG genotype was associated with a higher BMI.

CONCLUSION

The MTNR1B polymorphism (rs10830963) analysis showed G allele as a significant allele in category GDM, where the control population's allele proportions showed G allele as a minor allele. The inheritance models showed the G allele with a higher odds ratio than the C allele, where the G allele is a possible risk factor for GDM and BMI in our population. SNP analysis in the GDM group showed the SNP rs10830963 CG and GG genotypes are possible risk factors to develop GDM in the study population, whereas the control population showed higher frequencies of CC Genotype. Due to this, MTRN1B gene analysis is an essential component of prenatal screening to identify mothers prone to developing gestational diabetes. The present findings can prioritize future research investigating the association of the MTNR1B gene & GDM, and also pregnancy outcomes in a larger sample population.

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