Research Article

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PPARG and SIRT1 Gene Polymorphisms but Not ACE and PPARGC1A Polymorphism are Risk Factors for Gestational Diabetes in the Russian Population

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Abstract

Gestational Diabetes Mellitus (GDM) is the most frequently encountered extra genital pathology of gestation and represents a serious medical and social problem, increasing the incidence of unwanted pregnancy outcomes for both the mother and the fetus. The pathogenesis of GDM is complex and includes risk factors such as age, obesity, and a family history of diabetes. Studies have shown that genetic factors also play a role in the pathogenesis of GDM. The aim of our study was to assess the effect of Single Nucleotide Polymorphisms (SNPs) rs4646994 ACE gene, rs8192678 PPARGC1A gene, rs1801282 PPARG and rs7895833 SIRT1gene gene on the development of GDM in the Russian population.

The study used the genomic DNA derived by phenol-chloroform extraction method from venous blood samples in 272 pregnant women, including DNA samples of 136 pregnant women with GDM and DNA samples of 136 pregnant women with normal glucose tolerance. Genotyping of the selected polymorphisms was performed by real-time PCR with detection by competing TaqMan probes.

A statistically significant association with GDM was found in homozygous carriers of the I allele of the rs4646994 and heterozygous carriers of the G rs7895833 allele in the general inheritance model, heterozygous carriers of the G rs1801282 allele in the general and dominant inheritance models.

The data we obtained point to the need to further investigate the polymorphic loci we selected in a larger patient sample, which will

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enable using this genetic marker in the future as the assessment criterion in the individual outlook of preeclampsia development in GDM pregnant women to take efficient preventive measures to timely remedy and improve the pregnancy outcome.

Keywords: ACE gene; Gestational diabetes mellitus; PPARGC1A gene; PPARG gene; SIRT1 gene; SNP

Background

GDM is a diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes [1]. Hyperglycemia in the mother, not diagnosed at the stage of pregnancy planning and in the first trimester, can have an adverse effect on both the pregnant woman's body and the fetus [2].

Over the past 20 years, the worldwide distribution of gestational diabetes mellitus has increased and prevalence rates vary depending on population characteristics, screening methods and diagnostic criteria from 1 to 28% [3,4]. This indicator is estimated at 4,5% in Russia [5]. It is expected that by 2045 the prevalence of GDM will reach 16% in all regions of the world [6].

GDM is characterized by the relative inability of pancreatic β -cells to adequately respond to the increased need for insulin during pregnancy, which contributes to the development of hyperglycemia of varying degrees [7]. Under conditions of hyperglycemia, glucose freely penetrates into the vascular endothelium and causes functional disorders of its cells [8]. In addition, lipid metabolism may change during pregnancy due to the effects of estrogen and insulin resistance. The development of dyslipidemia also leads to endothelial dysfunction [9].

To date, about 40 genetic loci associated with the synthesis and secretion of insulin, with the transmission of the insulin signal, and regulating carbohydrate and lipid metabolism have been identified [10]. Previous studies have shown that some of the genetic loci that predispose to the development of type 2 diabetes may also predispose to GDM [11,12].

Angiotensin-Converting Enzyme (ACE) plays not only a key role in the regulation of blood pressure, but also participates in the processes of the local renin-angiotensin system in pancreatic tissues, regulating local blood flow and insulin biosynthesis of islet β -cells [13,14]. The gene encoding the angiotensin converting enzyme is located at the 17q23.3 locus on the 17th chromosome on the plus strand of DNA. Of the more than 100 allelic variants of the ACE gene, the most important is the insertion-deletion I/D polymorphism in the 16th intron, which consists in the insertion (I) or loss (D) of the Alu repeat. Deletion of the Alu repeat leads to increased expression of the ACE gene [15]. I/D polymorphism of the ACE gene, according to various studies, increases the risk of such diseases as type 2 diabetes mellitus, diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy [16].

SIRT1 belongs to the family of proteins with deacetylase activity and regulates energy balance, lipid homeostasis, and protects the structure and functions of microvascular endothelium [17,18]. SIRT1 is highly expressed in pancreatic β -cells and has the ability to enhance glucose sensitivity [19]. A decrease in SIRT1 expression is facilitated by increased insulin resistance and an inadequate response of β -cells, followed by an increase in glucose concentration, which may play a key role in the development of vascular dysfunction [20,21]. SIRT1 gene is located in the 10-th chromosome in the q21.3 locus and comprises 11 exons. Previous studies have shown that point mutations in promoters are more common than in coding regions of a gene and can affect its expression [22]. The rs7895833 polymorphism in the SIRT1 gene promoter region is associated with type 2 diabetes and obesity, according to few studies [23,24].

PGC-1a belongs to the family of transcription coactivators and is involved in the regulation of cellular energy metabolism, mitochondrial biogenesis in the vascular endothelium, carbohydrate and lipid metabolism [25-27]. Although the expression of PGC-1a in the pancreas is low compared with tissues such as the heart, skeletal muscle, liver, brown adipose tissue, and brain, it plays an important role in glucose transport in pancreatic β -cells [28]. The PGC-1 α protein is encoded by the PPARGC1A gene, which is mapped to the 4p15 locus. 2 and consists of 24 exons. Among the numerous variations in PPARGC1A gene, of special interest is the substitution the nucleotide A for nucleotide G in position 1444 of the 8-th exon, which causes serine substitution for glycine in position 482 of PGC-1a protein (Gly482Ser polymorphism), which is accompanied by the reduction in PGC1a gene expression [29]. The single nucleotide polymorphism of PPARGC1A (rs8192678) is associated with type 2 diabetes and its complications, relative obesity risk and insulin resistance [30].

Deacetylation of PGC-1 α through the action of SIRT1 increases the activity of PGC-1 α , which leads to the coactivation of several transcription factors, including nuclear receptors such as PPAR γ [31,32].

Peroxisome Proliferator-Activated Receptor- γ (PPAR γ) is a ligand-dependent transcription factor and belongs to the nuclear hormone receptor superfamily. PPAR γ plays an important role in lipid and glucose metabolism and controls endothelial function [33,34]. A moderate amount of PPAR γ is expressed in pancreatic β -cells [35]. El Midaoui et al., (2006) showed that the infusion of insulin and glucose is a factor contributing to the decrease in the level of PPAR γ protein [36]. The PPARG gene is located on the human chromosome locus 3p25 and consists of nine exons. The more common allele (C) of the single nucleotide polymorphism rs1801282 in exon B of the PPARG gene, also known as Pro12Ala, encodes the amino acid "Pro". The Pro to Ala substitution at codon 12 is associated with a decrease in PPAR γ activity, which may be a risk factor for obesity, type 2 diabetes and GDM [37-40].

Identifying additional genetic risk markers for GDM may be useful in early diagnosis and would also allow for earlier prevention and treatment. In this regard, the purpose of this study was to study the relationship between GDM and the selected polymorphisms of the ACE, SIRT1, PPARG, and PPARGC1A genes, which affect the function of pancreatic beta cells and vascular endothelial cells, glucose sensitivity, carbohydrate and lipid metabolism.

Materials and Methods

Research objects

The design of the study and the use of human material were approved by the ethics committee of the Research Institute of General Pathology and Pathophysiology. The study included patients who, in the period from April 2019 to December 2022, were observed and delivered in the Maternity Department of the State Clinical Hospital No. 29 (N.E. Bauman Hospital) of the Healthcare Department of Moscow. All respondents were native Russian speakers of indeterminate ethnicity (due to the ethical standards of the local medical register) and gave written consent to participate in the study. The diagnosis of GDM was established in accordance with the IADPSG recommendations and based on the criteria of the Russian National Consensus clinical guidelines "Gestational diabetes mellitus: diagnosis, treatment, postpartum care" [41,42]. The exclusion criteria were type 1 and type 2 diabetes mellitus, acute and chronic diseases in the acute stage, autoimmune, neuropsychiatric and oncological processes of any localization. The study did not include women with multiple pregnancies, other pregnancy complications, as well as disorders affecting glucose metabolism. QUANTO quantification software (Version 1.2.4, https://bio.tools/QUANTO), which takes into account the frequency of SNPs in the population and the prevalence of the disease [43]. In accordance with the above parameters, a sample size of 136 case-control pairs is required to identify the association between the selected polymorphisms and the risk of GDM. Blood samples were collected from pregnant women with GDM and pregnant women with normal glucose tolerance. All blood samples were obtained by venipuncture after an overnight fast and stored at -20 °C until analysis.

Genomic DNA extraction and Polymerase Chain Reaction (PCR)

DNA was extracted from venous blood with the standard phenol-chloroform extraction method of Maniatis et al., [44]. The blood cell element lysis was conducted with the Kunkel method [45]. The high-molecular DNA was desiccated at ambient temperature and dissolved in TE buffer, and the resulting DNA was stored at -20 °C. All DNA extractions were performed by a single investigator only.

Genotyping polymorphisms rs7895833 of the SIRT1 gene in the promoter region, rs8192678 within the coding region of the PPARG-C1A, rs1801282 of the PPARG gene andrs4646994 of the ACE gene was performed by real-time using the technology of competing TaqMan probes according to the method taken from the literature. All primers and Taq-man probes were synthetically produced by Evrogen LLC, Russia (Table 1).

The reaction mixture for rs7895833, rs8192678, rs1801282 RT-PCR for one 25 μ l sample contained 20 ng DNA, 5 μ l of 5x qP-CRmix-HS, 200 μ M forward primer, 200 μ M reverse primer, 400 μ M each of Taq-man probes.

The reaction mixture for rs4646994 RT-PCR of 25 μ l sample contained 20 ng DNA, 5 μ l of 5x qPCRmix-HS, 100 μ M each of the forward primers, 200 μ M reverse primer, 400 μ M each of Taq-man probes.

Amplification was carried out in the CFX 96 programmable amplifier (Bio-Rad, USA) with the subsequent thermocycling parameters for rs7895833, rs8192678, rs1801282 and rs4646994: initial denaturation for 5 minutes at 95°C; then 40 cycles including

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SNP	Oligonucleotide type and sequences			
	Forward 1: GGAGACCACTCCCATCCTTTC			
	Forward 2: GCCTCAGCCTCCCAAG			
	Revers: ATGTGGCCATCACATTCGTCAGAT			
rs4646994	Taq-Man Probe for D allele:			
	FAM-GCTGCCTATACAGTCACTTTTATGTGGT-RTQ1			
	Taq-Man Probe for I allele:			
	R6G-CCCGCCACTACGCCCGGCTAA-BHQ2			
	Forward: TCCATGCTGTTATGGGTGAAACT			
	Revers: CTTTACCTTGTGATATGTTTGCAGACA			
ma1901292	Taq-Man Probe for reference allele:			
181801282	FAM-TCTCCTATTGACCCAGAAAGCGATTCCTT-BH			
	Taq-Man Probe for alternative allele:			
	HEX-TCTCCTATTGACGCAGAAAGCGATTCCTT-BHQ2			
	Forward: CACTTCGGTCATCCCAGTCAA			
	Revers: TTATCACTTTCATCTTCGCTGTCATC			
ro8102678	Taq-Man Probe for reference allele:			
188192078	FAM-AGACAAGACCGGTGAA-BHQ1			
	Taq-Man Probe for alternative allele:			
	HEX-CAGACAAGACCAGTGAA-BHQ1			
	Forward: TTCTGAAGTAATGAGGTGG			
	Revers: AGGAGACTCTGCCAGAAAT			
ro7805822	Taq-Man Probe for reference allele:			
rs7895833	FAM-CCTACAGGAAATCAACGTAA-BHQ1			
	Taq-Man Probe for alternative allele:			
	HEX-CCTACAGGAAGTCAACGTAA-BHQ1			

rs1801282, rs8192678 and rs7895833.

denaturation at 95°C for 30 seconds, at 60°C for 30 seconds, at 72°C for 30 seconds with subsequent fluorescence pickup. The obtained data was examined using the CFX Manager TM software (Bio-Rad).

To eliminate genotyping errors, 30% of randomly selected samples were re-genotyped and the results obtained were additionally evaluated.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Continuous data were shown as mean \pm standard deviation (\pm SD) if normally distributed. Differences in age between groups were analyzed using Student's t-test. The Hardy–Weinberg equilibrium test was performed using the chi-square test in cases and controls separately for each variant before association analysis. Differences in allele and genotype frequencies between groups were analyzed using Pearson's chi-square test. Logistic regression analysis was used to evaluate associations between SNP genotypes and alleles and GDM risk by calculating Odds Ratios (ORs) and their 95% confidence intervals (CIs). The anticipated risk factor was regarded as significant for pathology if OR adjusted by CI was greater than 1. The level of significance was considered significant at p <= 0.05.

Results

Clinical characteristics

The study used DNA samples from 136 women with GDM (mean age 31.72 ± 4.95 years) and 136 pregnant women with normal glucose tolerance (mean age 31.01 ± 4.83 years). There were no significant differences in the average age indicators (p>0.05).

Association analysis

Analysis of the polymorphic loci rs4646994 of ACE gene, rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene and rs7895833 of the SIRT1 gene made it possible to estimate the frequency of occurrence of alleles and genotypes of the polymorphic loci of the studied genes (Table 2).

The distribution of frequencies of genotypes and alleles of polymorphic loci of the studied genes in the control group corresponded to that expected under the Hardy-Weinberg equilibrium.

The distribution of the rs4646994, rs1801282, rs8192678 and rs7895833 genotypes in the GDM group differed from that expected for HWE. The probable reason for the deviation of the observed genotype frequencies for the three polymorphisms in this group is not the genotyping error, but the association of loci with the disease.

Significant differences in the frequency of alleles and the distribution of genotypes between the studied groups were revealed. The prevalence of allele I and homozygous genotype II rs4646994 in the group of pregnant women with GDM were higher compared to the control group without statistical significance (56.0% vs. 51.8%, p=0.301; 32.4% vs. 27.2%, p=0.353). The frequency of occurrence of the G allele and heterozygous genotype CG rs1801282 in the group of pregnant women with GDM were higher in the group with GDM compared to the control group (22.4% vs. 12.5%, p=0.002; 36.0% vs. 12.5%, p=0.007). The frequency of occurrence of the G allele and the heterozygous genotype AG rs7895833 in the group of pregnant women with GDM were higher than in the control group (31.2% vs. 21.3%, p=0.009; 55.1% vs. 33.8%, p=0.002).

Gene/SNP	Genotypes and alleles	GDM, n=136	Control, n=136
ACE rs4646994	II	74 (54.4%)	37 (27.2%)
	ID	67 (49.3%)	69 (50.7%)
	DD	25 (3.7%)	30 (22.1%)
	I	215 (79.0%)	143 (51.8%)
	D	117 (21%)	129 (48.2%)
PPARG rs1801282	CC	81 (59.6%)	104 (76.5%)
	CG	49 (36.0%)	30 (22.1%)
	GG	6 (4.4%)	2 (2.4%)
	C	211 (77.6%)	238 (87.5%)
	G	61 (22.4%)	34 (12.5%)
PPARGC1A rs8192678	CC CT TT C T	69 (50.7%) 52 (38.2%) 15 (11.1%) 190 (69.9%) 82 (30.1%)	55 (40.4%) 64 (47.1%) 17 (12.5%) 174 (63.9%) 98 (36.1%)
SIRT1 rs7895833	AA	56 (41.2%)	84 (61.8%)
	AG	75 (55.1%)	46 (33.8%)
	GG	5 (3.7%)	6 (4.4%)
	A	187 (68.8%)	214 (78.7%)
	G	85 (31.2%)	58 (21.3%)

Table 2: Distribution of alleles and genotypes of polymorphisms rs4646994 of the ACE gene, rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene and rs7895833 of the SIRT1 gene in pregnant women with GDM.

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Gene/SNP	Model of inheritance	Genotypes	GDM, n=136	Control, n=136	OR (95% of CI)	Р*
ACE rs4646994	Codominant	П	44	37	1.00 0.45-1.47	0.354
		ID	67	69	0.82 0.35-1.39	0.809
		DD	25	30	0.70 0.215-0.807	0.361
	Dominant	II/ID + DD	44/92	37/99	0.465 0.46-1.32	0.3531
	Recessive	II + ID/DD	111/25	106/30	0.80 0.44-1.44	0.4501
	Additive	I	155	113	0.74 0.53-1.05	0.376
		D	117	129	0.84 0.59-1.17	0.299
	Codominant	СС	81	104	0.544 0.103-2.874	0.468
PARG rs1801282		CG	49	30	2.097 1.223-3.596	0.007
		GG	6	2	3.852 0.757-19.590	0.082
	Dominant	CC/CG + GG	81/55	104/32	2.207 1.307-3.726	0.003
	Recessive	CC + CG/GG	130/6	134/2	0.323 0.064-1.631	0.151
	Additive	С	211	238	0.494 0.312-0.782	0.002
		G	61	34	2.024 1.279-3.201	0.002
PPARGC1A rs8192678	Codominant	сс	69	55	0.877 0.404-1.904	0.739
		СТ	52	64	0.658 0.395-1.096	0.107
		TT	15	17	0.750 0.348-1.619	0.463
	Dominant	CC/ CT + TT	69/67	55/81	0.678 0.419-1.095	0.111
	Recessive	CC + CT/ TT	121/15	119/17	1.090 0.526-2.257	0.817
	Additive	С	190	174	0.788 0.552-1.127	0.192
		Т	82	98	1.268 0.887-1.813	0.192

		1			1	
SIRT1 157895833	Codominant	AA	56	84	1.957 0.565-6.776	0.283
		AG	75	46	2.446 1.485-4.028	0.001
		GG	5	6	1.250 0.364-4.294	0.723
	Dominant	AA/AG + GG	56/80	84/52	2.308 1.419-3.752	0.001
	Recessive	AA+AG/GG	131/5	130/6	1.209 0.360-4.061	0.758
		А	187	214	0.596 0.405-0.878	0.009
		Additive	G	85	58	1.677 1.139-2.470

Table 3: Association of genotypes of polymorphisms rs4646994 of the ACE gene, rs1801282 of the PPARG gene, rs8192678 of the PPARGC1A gene and rs7895833 of the SIRT1 gene with preclampsia in pregnant women with GDM.

GDM [52].

Descriptions for table 3: OR - odds ratio, CI - Confidence interval, chi2 - chi-square distribution, P - P Value Definition.

* - P value is greater ≤ 0.05

The analysis of associations established the relationship of polymorphisms rs1801282 of the PPARG gene and rs7895833 of the SIRT1 gene with GDM (Table 3). Thus, heterozygous genotype AG rs7895833 in the general model of inheritance are genetic predisposition factors for this pregnancy complication, increasing the risk of its development by more than 2 times (p=0.001). The heterozygous genotype CG rs1801282 in the common and dominant inheritance patterns increases the risk of developing GDM by 2.1 (p=0.007) and 2,2 (p=0.003) times, respectively. A significant GDM risk association was observed in carriers of the G rs1801282 allele in an additive inheritance model (2.024; p=0.002). The risk of developing GDM increased by 1.6 times in carriers of the A allele of the rs7895833 (p=0.009).

A review of the world literature shows that Gestational Diabetes Mellitus (GDM) is the most frequently encountered extra genital pathology of gestation and represents a serious medical and social problem, increasing the incidence of unwanted pregnancy outcomes for both the mother and the fetus. The study of gene polymorphisms that affect the function of pancreatic beta-cells and vascular endothelial cells, insulin resistance, carbohydrate and lipid metabolism will allow not only early diagnosis, but also earlier preventive and therapeutic measures.

The main goal of this study was to study the relationship between the polymorphic loci allele of the ACE gene, rs7895833 of the SIRT1 gene, rs1801282 of the PPARG gene, and rs8192678 of the PPARG-C1A gene and the risk of developing gestational diabetes mellitus in the Russian population. The study involved 272 patients with GDM (136 women with GDM and 136 pregnant women with normal glucose tolerance). Our results showed that these ACE, PPARG, and SIRT1 gene polymorphisms were associated with the risk of developing GDM. ACE and PPARGC1A gene polymorphism was not associated with gestational diabetes mellitus, which is consistent with the results of previous studies [46-51].

According to experimental and clinical studies, I/D polymorphism of the ACE gene is associated with the risk of developing type 2 diabetes mellitus, diabetic nephropathy, and diabetic retinopathy [16]. The results of the association studies of I/D polymorphism with GDM

The Gly482Ser (rs8192678) polymorphism of the PPARGC1A gene is one of the most studied variants. Research results have shown that the minor allele of this polymorphism is associated with susceptibility to type 2 diabetes, relative risk of obesity, insulin resistance, and decreased beta-cell function [30, 53-55]. Even though the previous studies suggested that GDM and type 2 diabetes share genetic polymorphisms with the same effect size for the same risk alleles, the findings of the studies by Leipold H et al., Shaat N et al., and Franza-

are controversial. Therefore, Dostálová Z et al., Aggarwal P et al.,

Mirfeizi M et al., did not reveal a significant association in the dis-

tribution of genotypes or allele frequency between the control group

and women with gestational diabetes mellitus [49-51]. Whereas Khan

IA et al., (2014) showed in their study that the frequency of the I/D

genotype significantly differs between individuals with and without

The rs1801282 polymorphic variant, also known as Pro12Ala, is associated with obesity, type 2 diabetes, and GDM [37-40]. However, studies have shown conflicting results regarding the role of Pro12Ala in the development of GDM. Anghebem-Oliveira et al., found no relationship between the rs1801282 polymorphism and the risk of developing GDM in the Brazilian population [56]. The results of the study by Ustianowski et al., indicate that PPARG gene polymorphism (rs1801282) is not a significant risk factor for GDM in the Polish population [57]. Lin et al., after analyzing sixteen studies involving 3129 women with GDM and 7168 without it, found that the protective G allele of the rs1801282 polymorphism was associated with a reduced risk of GDM in Asians, especially Chinese, but not South Koreans [58]. Data from meta-analyses of studies of the genetic association of Pro12Ala polymorphism with the risk of developing GDM by Wu et al., and Wang et al., suggest a potential role for the Pro allele in the pathogenesis of GDM in Asian populations, but not in the Caucasian population [39,40].

go M et al., did not reveal any association between the rs8192678 of

the PPARGC1A gene with GDM development risk [56-58].

According to previous studies, the rs7895833 polymorphism in the promoter region of the SIRT1 gene is associated with type 2

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diabetes mellitus and obesity, but no research has focused on its relationship with GDM [23,24]. It should be noted that studies to identify the association of polymorphic variants of the SIRT1 gene with the risk of developing GDM have not been previously conducted. The genetic variant rs7895833 that we have chosen in association with GDM has also not been studied.

In conclusion, the results of this study suggest the PPARG (rs1801282) and SIRT1 (rs7895833) gene polymorphisms are significant risk factors for the development of GDM in the Russian population. The small sample size of the study groups is the key limitation of this study. Nonetheless, the data obtained point to the need to further investigate the polymorphic loci we selected in a larger patient sample, which will enable using this genetic markers in the future as the assessment criterion in the individual outlook of GDM pregnant women to take efficient preventive measures to timely remedy and improve the pregnancy outcome.

Data Availability

The data used to support the findings of this study are included within the article.

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Conflicts of Interest

All authors declared no competing interests.

Source of Support

Departmental sources

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