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HUMAN GENETICS

The Polymorphic Locus rs780093 of the *GCKR* Gene Is Associated with the Risk of Infertility in Endometriosis

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Abstract—In this study, we examine the associations of nine polymorphic loci associated with the level of sex hormone binding globulin (SHBG) with the development of infertility in women with genital endometriosis. The study was conducted on a sample of 395 patients with genital endometriosis (132 women with genital endometriosis and concomitant infertility, 263 women with genital endometriosis without infertility), natives of the Central Black Earth Region of Russia. Genotyping of nine polymorphic loci associated with SHBG levels according to previously conducted genome-wide association studies (GWAS) was performed: rs12150660 *SHBG*, rs10454142 *PPP1R21*, rs780093 *GCKR*, rs17496332 *PRMT6*, rs3779195 *BAIAP2L1*, rs440837 *ZBTB10*, rs7910927 *JMJD1C*, rs4149056 *SLCO1B1*, rs8023580 *NR2F2*. It was found that the genotype *TT* rs780093 *GCKR* is associated with a low risk of infertility in endometriosis (OR = 0.43; $p = 0.017$; $p_{perm} = 0.019$). It has been identified that interlocus interactions rs8023580 *NR2F2*–rs10454142 *PPP1R21*–rs17496332 *PRMT6* are significantly associated with the risk of infertility in genital endometriosis (Wald criterion $WH = 19.15$, $p_{perm} \leq 0.001$). Combinations of genotypes rs8023580-*TT NR2F2*–rs10454142-*TT PPP1R21*–rs17496332-*AA PRMT6* (*beta* = 0.71, $p = 0.042$), rs8023580-*TC NR2F2*–rs10454142-*CC PPP1R21*–rs17496332-*AA PRMT6* (*beta* = 1.55, $p = 0.025$), and rs8023580-*TC NR2F2*–rs10454142-*TT PPP1R21*–rs17496332-*AG PRMT6* (*beta* = 1.92, $p = 0.027$) are risk factors for infertility in genital endometriosis. Thus, the polymorphic locus rs780093 *GCKR* and the interlocus interactions rs8023580 *NR2F2*–rs10454142 *PPP1R21*–rs17496332 *PRMT6* are associated with the risk of infertility in endometriosis.

Keywords: endometriosis, single nucleotide polymorphism (SNP), sex hormone binding globulin, infertility, risk factors

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INTRODUCTION

Endometriosis is a chronic immune-dependent, dyshormonal, genetically determined disease, which is characterized by the presence of tissue similar in its morphological and functional characteristics to the endometrium outside the uterine cavity [1, 2]. This disease has high medical and social significance owing to the severity of clinical manifestations and recurrent course [3]. The variety of symptoms of endometriosis and the presence of asymptomatic forms (in 30% of cases) lead to a significant delay in diagnosis [4]. Delayed diagnosis and the inability to carry out timely treatment can subsequently lead to the development of severe forms of endometriosis, which are often associated with the development of infertility [5]. Infertility is one of the most important (and often the only) clinical manifestations of endometriosis [6]. The risk of developing infertility in women with endometriosis is increased by 4 times; endometriosis-associated infertility occurs in 30–50% of patients [7, 8]. Therefore, early diagnosis of the development of infertility in patients with genital endometriosis is of paramount importance in terms of assessing female fertility.

According to published data, genetic factors play an important role in the development of endometriosis [9–11]. The presented studies (genome-wide, twin, family, associative) allow us to conclude that the contribution of genetic factors to the development of endometriosis is approximately 50% [12, 13]. The majority of polymorphic loci identified in GWAS studies (95% of the 200 SNPs identified (single nucleotide polymorphisms)) associated with the development of endometriosis have not been confirmed in other independent genome-wide studies [13]. The results of the association studies conducted (more than 150 such reviews have been published to date) are ambiguous and contradictory [13, 14]. Thus, despite the extensive work carried out, continuation of molecular genetic studies of genital endometriosis remains relevant.

Endometriosis is a hormone-dependent disease, in the pathogenesis of which sex hormones (estrogens,

progesterone, testosterone) play an important role, the content of active forms of which depends on sex hormone binding globulin (SHBG) [15]. SHBG is a blood plasma glycoprotein synthesized in the liver [16]. The biological significance of SHBG is the binding and transport of sex hormones such as testosterone and estrogens [16]. The concentration of circulating SHBG in the body is 50% dependent on hereditary factors [17]. According to genome-wide studies, a number of GWAS-significant SNPs associated with SHBG levels are known [18, 19]. To date, the role of individual GWAS-significant genetic determinants of SHBG in the formation of genital endometriosis and its combination with infertility has not been studied, which determines the relevance of this work.

The aim of this work is to study the associations of polymorphic loci associated with SHBG levels at the genome-wide significance level (rs12150660 *SHBG*, rs10454142 *PPP1R21*, rs780093 *GCKR*, rs17496332 *PRMT6*, rs3779195 *BAIAP2L1*, rs440837 *ZBTB10*, rs7910927 *JMJD1C*, rs4149056 *SLCO1B1*, rs8023580 *NR2F2*) with the risk of developing infertility in patients with endometriosis.

MATERIALS AND METHODS

The study included 395 patients with genital endometriosis (132 women with genital endometriosis and concomitant infertility, 263 with genital endometriosis without infertility). All women included in the study were Russian, residents of the Central Black Earth Region of the Russian Federation. The sample was formed on the basis of the perinatal center of the Belgorod Regional Clinical Hospital of St. Joasaph [20, 21].

The group of patients included women with an established diagnosis of genital endometriosis (the diagnosis was confirmed as a result of a morphological study after surgical treatment). Study of the level of sex hormones in the serum of patients ($n = 99$) was performed on an Elecsys 2010 analyzer (Hitachi, Japan) on the second or third day of the menstrual cycle with a preserved menstrual cycle or menstrual-like reaction. Blood progesterone levels were assessed on days 20–22 of the cycle. To determine the concentration of hormones, diagnostic kits from Roche were used.

For genetic research, DNA samples isolated from venous blood using the phenol-chloroform extraction method were used [22, 23]. The selection of polymorphic loci for the present study was carried out on the basis of the following criteria [24]: (1) associations of polymorphic loci with SHBG levels established in genome-wide studies (at the level of statistical significance $p \le 5 \times 10^{-8}$); (2) significant regulatory potential (regSNP) and association with expression of genes (eSNP) [25, 26]; (3) population frequency of the minor allele of at least 5%. The regulatory potential of SNPs was assessed *in silico* using the bioinformatics database HaploReg (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). In total, nine polymorphic loci were studied in the work: rs12150660 *SHBG*, rs10454142 *PPP1R21*, rs780093 *GCKR*, rs17496332 *PRMT6*, rs3779195 *BAIAP2L1*, rs440837 *ZBTB10*, rs7910927 *JMJD1C*, rs4149056 *SLCO1B1*, rs8023580 *NR2F2*.

For genotyping of polymorphic loci, the polymerase chain reaction method (real-time PCR, TagMan probe method) and locus-specific reagent kits (synthesized by Test-Gen, Ulyanovsk) were used. PCR was performed on a BioRad CFX96 amplifier (BioRad, United States) [27–29]. Quality control of the study was carried out by repeating genotyping of 5% of the analyzed DNA samples, selected randomly. To assess the associations of SNPs with infertility in genital endometriosis, the program gPLINK (version 1.07, https://zzz.bwh.harvard.edu/plink/, United States) [30, 31] and the logistic regression method with calculations in four genetic-statistical models (allelic, dominant, recessive, and additive) were used. The following parameters were included as covariates: age and body mass index (BMI). The functional effects of locus rs780093 of gene *GCKR*, which showed significant associations with the development of infertility in patients with genital endometriosis, were analyzed in detail *in silico* using bioinformatics resources: HaploReg (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to study epigenetic effects and Blood eQTL Browser (http://www.mulinlab.org/qtlbase/index.html) and GTExportal (https://gtexportal.org/home) to study the relationship to transcription and gene splicing.

To study interlocus interactions associated with the development of infertility in genital endometriosis, the MDR (Multifactor Dimensionality Reduction) method was used in its modification MB-MDR [32]. Two-, three-, and four-locus models were considered. Calculations were performed with covariates in the MB-MDR program (version 2.6, United States) in the R software environment. The most significant models of interlocus interactions associated with endometriosis were selected on the basis of the Bonferroni correction (taking into account the possible number of combinations of the nine studied loci at different levels of interlocus interactions). Further analysis included models of interlocus interactions that met the following criteria: two-locus models—$p < 1.78 \times 10^{-3}$ ($<0.05/28$), three-locus models—$p < 8.92 \times 10^{-4}$ ($<0.05/56$), four-locus models—$p < 7.14 \times 10^{-4}$ ($<0.05/70$). For the most significant SNP × SNP interaction models selected in accordance with the above criteria, associated with the development of infertility in endometriosis, a permutation test was performed (1000 permutations were performed). It was considered statistically significant $p_{perm} \le 0.001$. Individual genotype combinations associated with the risk of developing endometriosis were identified by the MB-MDR method $p < 0.05$.

RESULTS AND DISCUSSION

Clinical and anamnestic characteristics and the results obtained from the study of the hormonal status of patients with genital endometriosis depending on the presence/absence of infertility are presented in Table 1. The average age of women with genital endometriosis and infertility was 34.07 ± 6.55 years, and in patients without infertility, it was 42.77 ± 8.77 years ($p < 0.001$). The body mass index was 24.33 ± 4.68 kg/m^2 among patients with genital endometriosis and infertility and 27.88 ± 5.28 kg/m^2 in the group of women with endometriosis without infertility ($p < 0.0001$). The age of menarche and the duration of menstruation and the menstrual cycle did not differ in the study groups. In the group of patients with genital endometriosis and concomitant infertility, a lower number of pregnancies (3.3 times, $p < 0.0001$), births (4.8 times, $p < 0.0001$), and artificial abortions (4.1 times, $p < 0.0001$) were observed than in the second group. The incidence of ectopic pregnancies was higher in patients with infertility (7.57%) compared to women without infertility (1.9%, $p = 0.010$). Among patients with genital endometriosis and infertility, STDs (sexually transmitted diseases) were 2.7 times more common than in women without infertility ($p = 0.010$). Among gynecological diseases, an increased incidence of uterine leiomyoma (1.57 times) is noted in individuals of the second group. The conducted analysis of concomitant extragenital diseases showed that women in the second group more often have diseases of the cardiovascular (2.8 times, $p = 0.010$), digestive (1.6 times, $p = 0.025$), and urinary (2.4 times, $p = 0.025$) systems compared with women in group 1. In the group of patients with genital endometriosis and infertility, a high number of surgical interventions on the ovaries was observed (cystectomy—25.00%, ovarian resection—17.42%, adnexectomy—6.82%).

The genetic analysis of the observed distribution of genotypes for the nine studied polymorphic variants (rs12150660 *SHBG*, rs10454142 *PPP1R21*, rs780093 *GCKR*, rs3779195 *BAIAP2L1*, rs17496332 *PRMT6*, rs440837 *ZBTB10*, rs7910927 *JMJD1C*, rs4149056 *SLCO1B1*, rs8023580 *NR2F2*) showed its compliance with the expected distribution according to the Hardy–Weinberg law (Table 2).

It has been established that, within the framework of the recessive genetic model, the polymorphic locus rs780093 (*C>T*) *GCKR* is associated with the development of genital endometriosis with infertility. Comparative analysis of patients with genital endometriosis with and without infertility showed differences in the frequencies of genotype *TT* rs780093 (*C>T*) *GCKR*: this genotype is found significantly less frequently (2 times) among patients with infertility (8.59%) compared to patients without infertility (17.58%) and is a protective factor in the development of infertility in women with genital endometriosis (OR = 0.43; 95%CI 0.21–0.86; $p = 0.017$; $p_{perm} = 0.019$) (Table 3).

A three-locus model rs8023580 *NR2F2*–rs10454142 *PPP1R21*–rs17496332 *PRMT6* was established when assessing interlocus interactions associated with the occurrence of infertility, which is significantly associated with development of infertility in genital endometriosis (Wald criterion $WH = 19.15$, $p_{perm} \leq 0.001$). Within the framework of this three-locus model, three combinations of genotypes were identified that serve as risk factors for the development of infertility in genital endometriosis: rs8023580-*TT* *NR2F2*–rs10454142-*TT* *PPP1R21*–rs17496332-*AA* *PRMT6* (*beta* = 0.71, $p = 0.042$), rs8023580-*TC* *NR2F2*–rs10454142-*CC* *PPP1R21*–rs17496332-*AA* *PRMT6* (*beta* = 1.55, $p = 0.025$), rs8023580-*TC* *NR2F2*–rs10454142-*TT* *PPP1R21*–rs17496332-*AG* *PRMT6* (*beta* = 1.92, $p = 0.027$).

A comparative analysis of our results and published data shows the following. According to data from a genome-wide study conducted in 2012 by A.D. Coviello et al., the polymorphic variant rs780093 (*C>T*) of gene *GCKR* (2p23.3) is associated with the content of SHBG in the body [18]. Allelic variant *T* of this polymorphism is associated with a reduced level of SHBG in the body ($\beta = -0.033$, at $p = 2.2 \times 10^{-16}$) [18]. This locus is in linkage disequilibrium with eight SNPs ($r^2 \geqslant 0.8$), half of which (rs1260326, rs780096, rs780095, and rs780094) are localized in the region of histones marking promoters in the liver. Several polymorphic loci strongly linked to rs780093 *GCKR*, according to GWAS studies, are associated with liver enzyme levels: gamma-glutamyltranspeptidase (rs1260326, $p = 1 \times 10^{-48}$, $r^2 = 0.91$, $D' = 0.96$; rs6547692, $p = 5 \times 10^{-35}$, $r^2 = 0.84$, $D' = 0.99$; rs780094, $p = 3 \times 10^{-129}$, $r^2 = 0.98$, $D' = 0.99$) [33–35], alkaline phosphatase (rs1260326, $p = 5 \times 10^{-11}$, $r^2 = 0.91$, $D' = 0.96$; rs780094, $p = 4 \times 10^{-103}$, $r^2 = 0.98$, $D' = 0.99$) [35, 36], aspartate aminotransferase (rs1260326, $p = 5 \times 10^{-20}$, $r^2 = 0.91$, $D' = 0.96$; rs6547692, $p = 2 \times 10^{-17}$, $r^2 = 0.84$, $D' = 0.99$; rs780096, $p = 1 \times 10^{-8}$, $r^2 = 0.88$, $D' = 1.00$; rs780094, $p = 5 \times 10^{-16}$, $r^2 = 0.98$, $D' = 0.99$) [34–38], glucokinases (rs1260326, $p = 2 \times 10^{-16}$, $r^2 = 0.91$, $D' = 0.96$) [39], and alanine aminotransferase (rs6753534, $p = 4 \times 10^{-10}$, $r^2 = 0.86$, $D' = 0.98$) [37]. In addition, genome-wide studies have shown that some of these SNPs highly linked with rs780093 *GCKR* are associated with SHBG levels in the body: rs1260326, $p = 4 \times 10^{-235}$; rs6547692, $p = 2 \times 10^{-10}$; rs780094, $p = 8 \times 10^{-175}$ [19, 35, 40]. It should be noted that the main site of SHBG synthesis is the liver [17].

SHBG is a plasma glycoprotein whose biological significance lies in the binding and transport of sex hormones such as testosterone and estrogens [16]. SHBG is a key protein that, by binding to sex steroids in plasma, transports them into the blood in a metabolically inactive form and also determines the ratio of free and protein-bound fractions of these hormones in

Table 1. Clinical and anamnestic characteristics of patients with genital endometriosis depending on the presence/absence of infertility

Indicators	Infertile patients $n = 132$ $X \pm SD$	Patients without infertility $n = 263$ $X \pm SD$	p, comparison of groups
Age, years	34.07 ± 6.55	42.77 ± 8.77	**<0.0001**
Height, m	1.65 ± 0.06	1.65 ± 0.06	0.885
Weight, kg	56.75 ± 13.91	75.65 ± 13.66	**<0.0001**
BMI, kg/m^2	24.33 ± 4.68	27.88 ± 5.28	**<0.0001**
Menarche and the menstrual cycle			
Age of menarche, years	13.17 ± 1.20	13.4 ± 1.43	0.170
Duration of the menstrual cycle (MC), days	27.61 ± 2.19	27.73 ± 2.33	0.504
Duration of menstruation, days	4.94 ± 1.28	5.2 ± 1.65	0.256
Indicators of reproductive function implementation			
Age at first pregnancy, years	22.11 ± 4.42	21.01 ± 2.33	0.447
Number of pregnancies	1.03 ± 1.31	3.41 ± 2.33	**<0.0001**
Number of births	0.3 ± 0.56	1.45 ± 0.89	**<0.0001**
Number of artificial abortions	0.41 ± 0.81	1.7 ± 1.74	**<0.0001**
Proportion of women with a history of pregnancy, % (n)	50.76 (67)	84.03 (221)	**0.010**
Distribution of women by number of births in anamnesis, % (n):			
one birth	15.90 (21)	29.28 (77)	**<0.0001**
two or more	16.67 (22)	50.19 (132)	
no history of childbirth	67.43 (89)	20.53 (54)	
Proportion of women with a history of abortions and spontaneous miscarriages, % (n)	34.09 (45)	70.72 (186)	**0.010**
Past and concomitant gynecological diseases, % (n)			
Adenomyosis	99.24 (131)	96.58 (254)	0.900
Leiomyoma of the uterus	37.88 (50)	59.69 (157)	**0.010**
Sexually transmitted diseases	46.21 (61)	14.44 (38)	**0.010**
Benign diseases of the cervix	31.06 (41)	28.89 (76)	0.900
Chronic salpingitus and oophoritis	31.06 (41)	30.79 (81)	0.900
Chronic endometritis	9.84 (13)	9.12 (24)	0.900
Abnormal uterine bleeding	3.03 (4)	5.7 (15)	0.900
Associated extragenital diseases, % (n)			
Cardiovascular	15.15 (20)	43.35 (114)	**0.010**
Endocrine	12.12 (16)	12.55 (33)	0.900
Immune system	0.76 (1)	1.14 (3)	0.900
Nervous system	1.52 (2)	5.32 (14)	0.100
Digestive system	17.42 (23)	27.75 (73)	**0.025**
Urinary system	5.30 (7)	12.93 (34)	**0.025**
Respiratory system	2.27 (3)	–	–
Systemic diseases	–	0.76 (2)	–
Surgical treatment performed, % (n)			
Conservative myomectomy	6.82 (9)	5.32 (14)	0.900
Hysteroresectoscopy, RDV	1.52 (2)	0.38 (1)	**0.010**
Hysteroscopy, RDV	49.24 (65)	50.95 (134)	0.900
Cystectomy	25.00 (33)	9.51 (25)	**0.010**

Table 1. (Contd.)

Indicators	Infertile patients $n = 132$ $X \pm SD$			Patients without infertility $n = 263$ $X \pm SD$			p, comparison of groups
Ovarian resection	17.42 (23)			5.32 (14)			**0.010**
Adnexectomy	6.82 (9)			0.76 (2)			**0.010**
Proportion of individuals with a history of ovarian surgery	49.24 (65)			15.59 (41)			**0.010**
Characteristics of hormonal profile, % (n)							
Sex hormones studied	$<N$	N	$>N$	$<N$	N	$>N$	
Estradiol ($n_1 = 80$; $n_2 = 18$)	13.75 (11)	78.75 (63)	7.50 (6)	55.50 (10)	38.95 (7)	5.55 (1)	0.124
Progesterone ($n_1 = 50$; $n_2 = 13$)	68.00 (34)	30.00 (15)	2.00 (1)	69.23 (9)	23.08 (3)	7.69 (1)	0.592
Testosterone ($n_1 = 74$; $n_2 = 19$)	66.21 (49)	29.72 (22)	4.07 (3)	73.68 (14)	26.32 (5)	– (0)	0.296
17-Hydroxyprogesterone ($n_1 = 58$; $n_2 = 8$)	29.31 (17)	68.97 (40)	1.72 (1)	25.00 (2)	62.50 (5)	12.50 (1)	0.070

BMI—body mass index; n_1—the number of patients studied with genital endometriosis and infertility, n_2—the number of studied patients with genital endometriosis without concomitant infertility; $<N$—the hormone level below reference values, N—the hormone level within the reference interval, $>N$—the hormone level above reference values.

Table 2. Distribution indices of SNP genes associated with SHBG levels in patients with endometriosis depending on the presence/absence of infertility

Polymorphic variant	Minor allele frequency	Number of chromosomes studied	Data on the number of genotypes*	Heterozygosity		P_{HWE}
				obs.	expect.	
Patients with endometriosis and infertility ($n = 132$)						
rs17496332 (*A>G*) *PRMT6*	0.344	256	17/54/57	0.422	0.451	0.440
rs780093 (*C>T*) *GCKR*	0.352	256	11/68/49	0.531	0.456	0.081
rs10454142 (*T>C*) *PPP1R21*	0.284	250	12/47/66	0.376	0.407	0.385
rs3779195 (*T>A*) *BAIAP2L1*	0.169	248	1/40/83	0.323	0.281	0.194
rs440837 (*A>G*) *ZBTB10*	0.242	260	8/47/75	0.362	0.367	0.814
rs7910927 (*G>T*) *JMJD1C*	0,470	262	29/65/37	0.496	0.498	1.000
rs4149056 (*T>C*) *SLCO1B1*	0.229	262	7/46/78	0.351	0.353	1,000
rs8023580 (*T>C*) *NR2F2*	0.276	254	7/56/64	0.441	0.399	0.372
rs12150660 (*G>T*) *SHBG*	0.248	262	6/53/72	0.405	0.373	0.481
Patients with endometriosis without infertility ($n = 263$)						
rs17496332 (*A>G*) *PRMT6*	0.382	508	39/116/99	0.457	0.472	0.597
rs780093 (*C>T*) *GCKR*	0.416	502	45/119/87	0.474	0.486	0.698
rs10454142 (*T>C*) *PPP1R21*	0.294	486	22/99/122	0.407	0.415	0.759
rs3779195 (*T>A*) *BAIAP2L1*	0.183	498	6/79/164	0.317	0.299	0.401
rs440837 (*A>G*) *ZBTB10*	0.238	470	19/74/142	0.315	0.363	0.051
rs7910927 (*G>T*) *JMJD1C*	0.464	498	55/121/73	0.486	0.497	0.704
rs4149056 (*T>C*) *SLCO1B1*	0.211	498	12/81/156	0.325	0.333	0.705
rs8023580 (*T>C*) *NR2F2*	0.287	492	16/109/121	0.443	0.409	0.215
rs12150660 (*G>T*) *SHBG*	0.224	508	11/92/151	0.362	0.348	0.592

* Homozygotes (rare allele)/heterozygotes/homozygotes (common allele).

Table 3. The relationship of polymorphic loci associated with the level of SHBG to the risk of infertility in endometriosis (data from a comparative analysis of patients with endometriosis, with and without infertility)

Polymorphic variant	Sample size	Genetic model															
		allelic				additive				dominant				recessive			
		OR	95%CI		P	OR_c	95%CI_c		P_c	OR_c	95%CI_c		R_c	OR_c	95%CI_c		P_c
			L95	U95			$L95_c$	$U95_c$			$L95_c$	$U95_c$			$L95_c$	$U95_c$	
rs17496332 (*A>G*) *PRMT6*	382	0.85	0.62	1.16	0.303	0.74	0.45	1.22	0.238	0.96	0.48	1.91	0.912	0.85	0.62	1.16	0.303
rs780093 (*C>T*) *GCKR*	379	0.76	0.56	1.04	0.084	0.85	0.51	1.41	0.532	0.50	0.23	1.10	0.083	**0.43**	**0.21**	**0.86**	**0.017**
rs10454142 (*T>C*) *PPP1R21*	368	0.95	0.68	1.33	0.772	0.85	0.52	1.39	0.526	0.93	0.40	2.17	0.864	0.95	0.68	1.33	0.772
rs3779195 (*T>A*) *BAIAP2L1*	373	0.91	0.61	1.36	0.653	1.14	0.67	1.92	0.635	0.35	0.04	3.46	0.372	0.91	0.61	1.36	0.653
rs440837 (*A>G*) *ZBTB10*	365	1.02	0.72	1.46	0.903	0.90	0.55	1.48	0.678	0.54	0.20	1.44	0,220	1.02	0.72	1.46	0.903
rs7910927 (*G>T*) *JMJD1C*	380	1.02	0.76	1.38	0.883	1.13	0.66	1.95	0.658	0.90	0.50	1.61	0.718	1.02	0.76	1.38	0.883
rs4149056 (*T>C*) *SLCO1B1*	380	1.11	0.78	1.59	0.564	1.09	0.66	1.81	0.738	1.01	0.33	3.07	0.985	1.11	0.78	1.59	0.564
rs8023580 (*T>C*) *NR2F2*	373	0.95	0.68	1.33	0.752	1.01	0.62	1.65	0.963	0.43	0.14	1.35	0.148	0.95	0.68	1.33	0.752
rs12150660 (*G>T*) *SHBG*	385	1.14	0.80	1.62	0.461	1.27	0.78	2.07	0.329	0.79	0.25	2.48	0.691	1.14	0.80	1.62	0.461

The figures were obtained by adjusting for covariates. OR—odds ratio, 95%CI—95% confidence interval and its lower (L95) and upper (U95) boundaries; *P*—level of statistical significance. Statistically significant results based on the adaptive permutation test are highlighted in bold. Values with subscript k are calculated after adjustment for covariates.

plasma [17]. There is an inverse correlation between circulating SHBG concentrations and free testosterone and estrogen levels in the body: low SHBG levels lead to high testosterone and estrogen levels [41–43]. According to our study, the allele *T* of locus rs780093 (*C>T*) of gene *GCKR* is associated with reduced SHBG levels, and therefore it may be associated with high testosterone concentrations in women with genital endometriosis without associated infertility. On the contrary, the allele *C* of rs780093 of gene *GCKR*, which marks a high level of SHBG (and correspondingly low level of testosterone), is associated with the development of genital endometriosis with infertility. The data we obtained are consistent with the materials published by N. Dinsdale et al. [44] and B. Crespi [45], who put forward the theory that endometriosis occurs because of atypical functioning of the hypothalamic-pituitary axis in the prenatal period, and low levels of prenatal testosterone play a key role in the development of the disease.

The online resources HaploReg (v4.2), Blood eQTL Browser, and GTEx Portal were used to evaluate the regulatory effects and influence on the expression and alternative splicing of the polymorphic locus rs780093 of gene *GCKR*, associated with the risk of infertility in women with genital endometriosis. So, polymorphism rs780093 (*C>T*) *GCKR*, associated with the risk of developing infertility with endometriosis, increases the sensitivity of DNA to transcription factor INSM1 (allelic variant *T*, difference in the "LOD scores" of alleles *T* and *C* of 10.4).

It was found that polymorphic marker rs780093 (*C>T*) *GCKR* is associated with the transcription level of 12 genes (*ZNF512*, *TRIM54*, *SNX17*, *PPM1G*, *NRBP1*, *KRTCAP3*, *GPN1*, *GCKR*, *FNDC4*, *C2orf16*, *ATRAID*, *AC074117.10*) in 18 different organs/tissues, including those significant for endometriosis. At the same time, alternative allele *T* reduces the transcriptional activity of genes *FNDC4* (for reference allele *C*, NES = 0.23; $p = 1.8e^{-13}$), *GCKR* (for reference allele *C*, NES = 0.25; $p = 1.1e^{-10}$), *C2orf16* (for reference allele *C*, NES = 0.14; $p = 0.0000030$), *ATRAID* (for reference allele *C*, NES = 0.076; $p = 0.00011$), and *ZNF512* (for reference allele *C*, NES = 0.097; $p = 0.00033$) in the thyroid gland, as well as the gene *KRTCAP3* in the adrenal glands (for reference allele *C*, NES = 0.46; $p = 1.2e^{-8}$) and blood (for reference allele *C*, NES = 0.18; $p = 4.0e^{-7}$). At the same time, the alternative allele *T* is related to increased expression of three genes in adipose tissue—*NRBP1* (for reference allele *C*, NES = –0.17; $p = 6.4e^{-10}$), *AC074117.10* (for reference allele *C*, NES = –0.11; $p = 0.000046$), and *PPM1G* (for reference allele *C*, NES = –0.069; $p = 0.000062$).

It is known that *GCKR* encodes a protein belonging to the GCKR subfamily of the SIS (Sugar ISomerase) protein family [46]. The gene product is a regulatory protein that inhibits glucokinase in pancreatic and liver islet cells [46]. According to published data, *GCKR* is associated with diseases such as nonalcoholic fatty liver disease and type 2 diabetes mellitus and with the development of metabolic syndrome [47–49]. A 2020 study by G. Frühbeck et al. showed that FNDC4 directly participates in the lipid metabolism of adipocytes, thereby influencing the pathophysiological processes of development of obesity [50]. It was found that plasma FNDC4 was reduced in patients with morbid obesity, and high expression of FNDC4 and its receptor GPR116 was noted in visceral adipose tissue [51]. It is known that obesity can negatively affect fertility, and underweight contributes to the development of amenorrhea, anovulation, or miscarriage [51]. Studies have shown that FNDC4 can cleave and release the bioactive protein sFNDC4, which regulates the sensitivity of peripheral tissues to insulin. The receptor for this protein (ADGRF5) is expressed in the ovaries [50]. Gene *NRBP1*, with the expression of which is associated rs780093 (*C>T*) *GCKR*, suppresses proliferation of breast cancer cells via the Wnt signaling pathway [52].

It has been established that polymorphic locus rs780093 (*C>T*) *GCKR* is associated with sQTL (splicing quantitative trait loci) of six genes (*FNDC4*, *GCKR*, *GPN1*, *IFT172*, *KRTCAP3*, *TRIM54*) in 22 different organs/tissues, including those pathogenetically significant for endometriosis. At the same time, alternative allele *T* marks a reduced level of alternative splicing of transcripts of genes *KRTCAP3* (for reference allele *C*, IntronID:27442440:27442842:clu_51100; NES = 0.28; $p = 3.1e^{-7}$) in the thyroid gland and *FNDC4* (for reference allele *C*, IntronID:27492478:27493389:clu_46625; NES = 0.15; $p = 0.0000024$) in adipose tissue, and is also associated with high levels of alternative splicing of the transcript of gene *IFT172* in the thyroid gland (for the reference allele *C*, IntronID:27461836:27462701:clu_51111; NES = –0.59; $p = 9.9e^{-31}$), pituitary gland (for the reference allele *C*, IntronID:27461836:27462701:clu_45428; NES = –0.71; $p = 7.5e^{-18}$), adipose tissue (for the reference allele *C*, IntronID:27461836:27462701:clu_47932; NES = –0.48; $p = 1.9e^{-17}$), and adrenal glands (for the reference allele *C*, IntronID:27461836:27462701:clu_37939; NES = –0.67; $p = 4.6e^{-13}$).

According to the data of the GWAS conducted, the level of leptin in the body is associated with the polymorphic locus rs780093 *GCKR* ($p = 4 \times 10^{-10}$) [53]. Allelic variant *C* was associated with increased levels of this hormone [53]. Also, polymorphic locus rs1260326 strongly linked to rs780093 *GCKR* ($p = 2 \times 10^{-10}$) is associated with leptin levels according to another genome-wide study [54]. According to published data, recently, adipose tissue has increasingly been considered as a separate endocrine organ [55]. One of the functions of adipose tissue is the synthesis of hormone-like substances—adipokines, which include

leptin [55]. Currently, leptin is considered an endogenous regulator of the functions of the female reproductive system, which affects the functional activity of all links of the hypothalamic-pituitary-gonadal axis [56]. Leptin stimulates the secretion of gonadotropin-releasing hormone (GnRH) by hypothalamic neurons and affects the secretion of LH, FSH, and hCG [47]. An increase in leptin concentration has an inhibitory effect on the ovaries: it suppresses the synthesis of progesterone and estradiol by follicular cells, blocks the stimulating effect of IGF-1 on the production of estradiol and progesterone by the ovaries, and prevents the onset of hCG-stimulated ovulation [57]. It is known that changes in the concentration of leptin in the blood and follicular fluid in women can affect fertility and lead to low IVF efficiency [58]. Thus, the allele *C* of polymorphic locus rs780093 (*C>T*) *GCKR*, associated with increased leptin levels, may contribute to the development of infertility in women with genital endometriosis, and the presence of the allele *T* of rs780093 (*C>T*) *GCKR* will be a protective risk factor for the development of infertility, which is identical to the data we obtained.

Thus, the data indicate an association of genotype *TT* of rs780093 *GCKR* with a reduction in the risk of infertility in women with genital endometriosis in the Central Black Earth Region of Russia. Interlocus interaction rs8023580 *NR2F2*–rs10454142 *PPP1R21*–rs17496332 *PRMT6* significantly is associated with development of infertility in genital endometriosis.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Belgorod State University on January 30, 2024, protocol no. 2.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research ethics committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed voluntary consent was obtained from each of the participants included in the study or their legal representatives.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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