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HUMAN GENETICS

The Polymorphism rs7579411 of the *LHCGR* Gene Is Associated with the Development of Endometrial Hyperplasia

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Abstract—The associations of single nucleotide polymorphisms of the *LHCGR* gene with the formation of endometrial hyperplasia in the Russian population were studied. Genotyping of four loci of the *LHCGR* gene (rs4953616, rs4374421, rs6729809, rs7579411) was performed in 520 patients with endometrial hyperplasia (EH) and 981 women of the control group. A significant contribution to the susceptibility to endometrial hyperplasia of the rs7579411 polymorphism of the *LHCGR* gene has been established. The genotype *C/C* rs7579411 of the *LHCGR* gene is risky for EH (OR = 1.26, $p = 0.05$), whereas the allelic variant *T* rs7579411 of the *LHCGR* gene is a protective factor for EH (OR = 0.79, $p_{perm} = 0.05$). The rs7579411 locus of the *LHCGR* gene has significant epigenetic effects (located in DNA regions marking regulatory sequences (enhancers)) and is associated with the expression of the *STON1-GTF2A1L* gene in organs and tissues (thyroid gland, peripheral blood) involved in the pathophysiology of the disease. At the same time, the allele *T* rs7579411 of the *LHCGR* gene is associated with low transcriptional activity of the *STON1-GTF2A1L* gene ($\beta = -0.25$).

Keywords: endometrial hyperplasia, *LHCGR*, polymorphism, associations

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INTRODUCTION

Hyperplastic processes of the endometrium (HE) are characterized by pathologically altered proliferation (focal or diffuse) of various components of the mucous layer of the uterus (glandular/stromal) with a predominant lesion of the glandular structural elements [1, 2]. The prevalence of HE among different groups of the female population varies widely, and the share of this disease in the structure of gynecological pathology can reach 50% [3, 4]. It is believed that HE without atypia is more often detected in women aged 50 to 54 years, while hyperplasia with atypia is most common in the age group of 60–64 years, while in women under the age of 30 the disease is recorded quite rarely [5, 6]. According to the published data, HE (especially with elements of atypia) is a predisposing factor in the occurrence of endometrial cancer, and an increased risk of malignant transformation is observed in women with endometrial hyperplastic processes aged ≤39 and ≥50 years [7]. There are published data that about 40% of young women with HE undergo surgery, which as a result can cause various reproductive disorders [8].

Among the risk factors for HE, a significant role is given to estrogen-progesterone imbalance, early menarche and late menopause, insulin resistance, inflammation, the presence of comorbid diseases (obesity, diabetes mellitus, hypertension, benign diseases of the pelvic organs), genetic factors, etc. [1, 3, 4, 6, 7, 9–11]. It is important to note that, despite the obvious importance of hereditary factors in the formation of HE [1], the number of genetic studies of this disease not only in our country but throughout the world is very limited [2, 3, 12]; these works are fragmentary, and the results obtained are ambiguous, which determines the relevance of continuing molecular genetic studies of HE.

The purpose of this study is to evaluate associative links of single nucleotide polymorphism of gene *LHCGR* with HE.

MATERIALS AND METHODS

The work was carried out on a sample of 520 patients with HE and 981 women in the control group formed in the Regional Clinical Hospital (Department of Gynecology) under the supervision of the Ethics Commission of the National Research University Belgorod State University. Diagnosis of HE was carried out by certified gynecologists (hysteroscopy was performed with endometrial biopsy and its subsequent morphological examination). The presence of simple HE without atypia was the basis for inclusion in the group of patients. The control group included women without clinical and ultrasound signs of HE (examined

during preventive examinations) [2]. The age characteristics of patients and controls were comparable (41.78 and 40.73 years, respectively, $p > 0.05$). The study group included Russian women born and living in the Central Chernozem region of the Russian Federation [13, 14] who previously agreed to participate in the study.

For genetic studies, we used DNA isolated from blood samples by the conventional (phenol/chloroform) method [15]. Four polymorphic variants of the gene *LHCGR* were selected for genotyping (rs4953616, rs4374421, rs6729809, rs7579411), which are regulatory [16, 17]: according to the bioinformatic database HaploReg [18], these loci are characterized by a significant regulatory potential. Genotyping of the studied polymorphic loci was performed by PCR (TaqMan probe method) [19].

For a comparative assessment of the frequencies of alleles and genotypes between patients with HE and the control group, the χ^2 criterion was used (the Yates correction for continuity was applied) [20]. The calculations were carried out in the STATISTICA software program using 2 × 2 contingency tables. To assess the associative links of single nucleotide polymorphisms (including their haplotypes) with HE, the OR (odds ratio) and 95%CI (95% confidence interval for OR) indicators generally accepted in genetic and epidemiological studies were used [21]. The OR and 95%CI values were obtained by the logistic regression method [22] implemented in the gPLINK program [23]. Three genetic models (additive, recessive, dominant) were used in the calculations [24, 25]. Linkage disequilibrium between analyzed variants of gene *LHCGR* was estimated on the basis of Lewontin's *D*' coefficients and Pearson's r^2 correlation. The block structure was identified using "confidence intervals" at a given level $r^2 > 0.2$ and $D' > 0.8$ in the gPLINK program. Correction for multiple comparisons was carried out by permutational procedures [26] with the calculation of the indicator p_{perm} (the value of $p_{perm} < 0.05$ was taken as statistically significant [27]).

To assess the functional effects of polymorphic variants of the gene *LHCGR* associated with HE, public bioinformatic resources were used [28, 29]: HaploReg (studied epigenetic effects) [18] and GTExportal (studied association with gene transcription) [28], and previously published techniques were used [2, 30, 31].

RESULTS AND DISCUSSION

HWE conformity was revealed for all considered loci of gene *LHCGR* both in the patients with HE and in the control (data are presented in Table 1); the Bonferroni correction for the number of analyzed loci $p_{bonf} > 0.0125$ (0.05/4) was used.

The data obtained in the work (Table 1) indicate the relationship of rs7579411 of gene *LHCGR* with HE. Genotype *C/C* rs7579411 has a "risk" value for HE (OR = 1.26, 95%CI = 1.00–1.59, $p = 0.05$). According to regression analysis, the minor allele *T* rs7579411 exhibits a protective effect during the formation of the disease within the framework of the dominant genetic model (OR = 0.79, 95%CI = 0.63–0.99, $p = 0.05$, $p_{perm} = 0.05$). Significant differences in the frequencies of haplotypes within the identified haploblock rs757941/rs6729809/rs4953616 (the haploblock selection parameters $r^2 > 0.2$, $D' > 0.8$) were not found in the patients with HE or in the control (Table 2).

According to the bioinformatic resource HaploReg, the localization of rs7579411 of gene *LHCGR* has been established in the region of DNA associated with histone proteins (H3K4me1) marking the regulatory sequences of the genome (enhancers) in the culture of neuronal progenitor cells, adipocyte-derived cells, and primary osteoblast cells, as well as in the DNA region interacting with H3K27ac-type histone proteins marking functionally active enhancer sites in a cultured mesoderm cell culture.

At *in silico* estimation of the association of the rs7579411 variant with the level of transcriptional activity of genes in the body carried out using the GTExportal bioinformatic resource, the association of this single nucleotide polymorphism with expression of gene *STON1-GTF2A1L* (Gene ID: 286749) was established in the thyroid gland ($p = 0.0000031$, $FDR \leq 0.05$). However, the allele *T* of this variant (in comparison with its alternative variant *C*) determines lower values of the level of expressive activity of gene *STON1-GTF2A1L*, as evidenced by the negative value of the regression index for this allele ($\beta = -0.25$). At the same time, according to the data presented in HaploReg, rs7579411 of the gene *LHCGR* is associated with the transcriptional activity of the gene *STON1-GTF2A1L* in peripheral blood ($p = 0.00064$).

Thus, the data obtained in this work on the functional effects of the polymorphic locus rs7579411 of the gene *LHCGR*, which determines susceptibility to endometrial hyperplasia, indicate its important epigenetic significance (associated with regulatory sequences of DNA enhancers) and the effect on expression of gene *STON1-GTF2A1L* in the thyroid gland and peripheral blood (allele *T* rs7579411 "protective" for HE determines the low level of transcription).

According to the genetic database GeneCards [32], the gene *LHCGR* is protein-coding and controls the synthesis of receptors for luteinizing hormone (LH)/human chorionic gonadotropin (CG). It should be noted that LH is one of the "key" hormones of the female body that controls the "work" of her reproductive system. Through interaction with these receptors, LH affects the formation of estrogens/androgens in the ovarian follicles, is an ovulation inducer, is involved in the formation of the corpus luteum due to luteinization of granulosa cells, and affects the synthesis of progesterone and other steroid hormones by the

Table 1. Comparative analysis of allele and genotype frequencies of polymorphic loci of gene *LHCGR* in patients with endometrial hyperplasia and in the control group

Loci	Alleles, genotypes	Patients ($n = 520$) abs. (%)	Control ($n = 981$) abs. (%)	OR (95%CI)	p
r4374421	*T*	677 (69.79%)	1300 (68.71%)	1.05 (0.88–1.24)	0.58
	C	293 (30.21%)	592 (31.29%)	0.95 (0.80–1.13)	
	T/*T*	244 (50.31%)	441 (46.62%)	1.16 (0.93–1.45)	0.20
	T/*C*	189 (38.97%)	418 (44.19%)	0.80 (0.64–1.01)	0.07
	C/*C*	52 (10.72%)	87 (9.19%)	1.18 (0.81–1.73)	0.41
	H_o/H_e (P_{HWE})	0.390/0.422 (0.106)	0.442/0.430 (0.449)		
	T/*T* vs. *T*/*C* vs. *C*/*C* (additive model)			0.95 (0.80–1.12)	0.55
	T/*T* vs. *T*/*C* + *C*/*C* (dominant model)			0.86 (0.69–1.07)	0.18
	T/*T* + *T*/*C* vs. *C*/*C* (recessive model)			1.19 (0.82–1.70)	0.36
rs7579411	*C*	587 (57.44%)	1071 (54.98%)	1.10 (0.94–1.29)	0.21
	T	435 (42.56%)	877 (45.02%)	0.90 (0.77–1.06)	
	C/*C*	175 (34.25%)	285 (29.26%)	**1.26 (1.00–1.59)**	**0.05**
	C/*T*	237 (46.38%)	501 (51.44%)	0.82 (0.65–1.02)	0.07
	T/*T*	99 (19.37%)	188 (19.30%)	1.00 (0.76–1.33)	1.00
	H_o/H_e (P_{HWE})	0.464/0.489 (0.241)	0.514/0.495 (0.244)		
	C/*C* vs. *C*/*T* vs. *T*/*T* (additive model)			0.90 (0.77–1.05)	0.19
	C/*C* vs. *C*/*T* + *T*/*T* (dominant model)			**0.79 (0.63–0.99)**	**0.05**
	C/*C* + *C*/*T* vs. *T*/*T* (recessive model)			1.00 (0.77–1.32)	0.97
rs6729809	*T*	713 (69.22%)	1264 (67.67%)	1.07 (0.91–1.27)	0.41
	C	317 (30.78%)	604 (32.33%)	0.93 (0.78–1.10)	
	T/*T*	247 (47.96%)	419 (44.86%)	1.13 (0.91–1.41)	0.28
	T/*C*	219 (42.52%)	426 (45.61%)	0.88 (0.70–1.10)	0.29
	C/*C*	49 (9.52%)	89 (9.53%)	0.99 (0.68–1.46)	1.00
	H_o/H_e (P_{HWE})	0.425/0.426 (1.000)	0.456/0.438 (0.205)		
	T/*T* vs. *T*/*C* vs. *C*/*C* (additive model)			0.93 (0.78–1.09)	0.38
	T/*T* vs. *T*/*C* + *C*/*C* (dominant model)			0.88 (0.71–1.09)	0.26
	T/*T* + *T*/*C* vs. *C*/*C* (recessive model)			0.99 (0.69–1.43)	0.99
r4953616	*T*	742 (72.46%)	1408 (72.06%)	1.02 (0.86–1.21)	0.85
	C	282 (27.54%)	546 (27.94%)	0.98 (0.82–1.16)	
	T/*T*	267 (52.15%)	493 (50.46%)	1.07 (0.86–1.33)	0.57
	T/*C*	208 (40.63%)	422 (43.19%)	0.90 (0.72–1.12)	0.37
	C/*C*	37 (7.22%)	62 (6.35%)	1.15 (0.74–1.79)	0.59
	H_o/H_e (P_{HWE})	0.406/0.399 (0.740)	0.432/0.403 (0.026)		
	T/*T* vs. *T*/*C* vs. *C*/*C* (additive model)			0.98 (0.82–1.16)	0.81
	T/*T* vs. *T*/*C* + *C*/*C* (dominant model)			0.93 (0.75–1.16)	0.54
	T/*T* + *T*/*C* vs. *C*/*C* (recessive model)			1.21 (0.75–1.75)	0.51

OR is the odds ratio indicator, p is the significance level, H_o is the observed heterozygosity, H_e is the expected heterozygosity, and P_{HWE} is the significance level of the deviation from the Hardy–Weinberg law.

Table 2. Distribution of haplotypes of polymorphic loci rs757941–rs6729809–rs4953616 of gene *LHCGR* among patients with endometrial hyperplasia and in the control group

Haplotype	Haplotype frequency		OR	*p*
	sick	the control		
TCC	0.270	0.277	0.94	0.705
TCT	0.036	0.044	0.86	0.288
TTT	0.127	0.131	0.98	0.773
CTT	0.567	0.549	1.05	0.338

The results were obtained by the method of logistic regression, OR is the odds ratio, and *p* is the significance level.

corpus luteum [33]. These LH-mediated processes in the "hypothalamus-pituitary-ovaries" system of a woman are of great pathophysiological significance in the occurrence of HE, since one of the key points in the formation of the disease is hyperestrogenism (absolute or relative) with a lack of progesterone [1, 3, 4].

According to GeneCards [32], the result of the expression of a DNA region in a region of gene *LHCGR* is the formation of a transcript *STON1-GTF2A1L*. A feature of this transcript is that it includes elements of polynucleotide chains transcribed from two genes—*STON1* and *GTF2A1L*—and may be subjected to further alternative splicing. The product of gene *GTF2A1L* is one of the subunits of the main transcription factor TFIIA (it is the "key" factor in the regulation of the transcriptional activity of an overwhelming number of genes). Gene *STON1* controls the synthesis of the stonin 1 protein, which is involved in the mechanisms of "local" cell motility, adhesion, and endocytosis [32]. A number of previous studies have demonstrated the relationship of rs7579411 *LHCGR* (as part of epistatic interactions) to the age of the appearance of the first menstruation (age of menarche) and the growth of women [16] and the risk of developing genital endometriosis [9]. At the same time, the fact that (according to the published data [34]) the allele *T* is associated with late menarche ($\beta = 0.058$), and according to our data, this allelic variant has a protective value for endometrial hyperplasia, which is fully consistent with each other, attracts attention. Also, published data indicate the relationship of single nucleotide polymorphism of genes *LHCGR* and *STON1-GTF2A1L* to polycystic ovaries [35, 36]. A higher expression of these genes in the subcutaneous adipose tissue in women with polycystic ovaries [37] and interethnic differences in transcriptional activity of *STON1-GTF2A1L* were found in white/black women in the age group of 35 years and older with uterine fibroids [38].

The study demonstrated the association of the polymorphic variant rs7579411 of the gene *LHCGR* with HE. Genotype *C/C* has a risk value for HE, while the allelic variant *T* serves as a "protective" factor in the event of a disease. Single nucleotide polymorphism rs7579411 *LHCGR* has significant epigenetic effects (located in the DNA region marking regulatory sequences) and is associated with expression of the gene *STON1-GTF2A1L* in organs and tissues (thyroid gland, peripheral blood) involved in the pathophysiology of the disease. At the same time, the allele *T* associated with low transcriptional activity of the gene *STON1-GTF2A1L*.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in human research comply with the ethical standards of the institutional and/or national research ethics committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Informed consent was obtained from each of the participants included in the study.

REFERENCES

1. Sanderson, P.A., Critchley, H.O.D., Williams, A.R.W., et al., New concepts for an old problem: the diagnosis of endometrial hyperplasia, *Hum. Reprod. Update*, 2017, vol. 23, no. 2, pp. 232—254.
2. Ponomarenko, I., Reshetnikov, E., Polonikov, A., et al., Candidate genes for age at menarche are associated with endometrial hyperplasia, *Gene*, 2020, vol. 757, p. 144933. https://doi.org/10.1016/j.gene.2020.144933
3. Chandra, V., Kim, J.J., Benbrook, D.M., et al., Therapeutic options for management of endometrial hyperplasia, *J. Gynecol. Oncol.*, 2016, vol. 27, no. 1, p. e8. https://doi.org/10.3802/jgo.2016.27.e8
4. Burke, T.W., Tortolero-Luna, G., Malpica, A., et al., Endometrial hyperplasia and endometrial cancer, *Ob-*

stet. Gynecol. Clin. North Am., 1996, vol. 23, no. 2, pp. 411—456.

5. Reed, S.D., Newton, K.M., Clinton, W.L., et al., Incidence of endometrial hyperplasia, *Am. J. Obstet. Gynecol.*, 2009, vol. 200, no. 6, p. 678. e1-6. https://doi.org/10.1016/j.ajog.2009.02.032
6. Rodriguez, A.M., Polychronopoulou, E., Hsu, E., et al., Factors associated with endometrial cancer and hyperplasia among middle-aged and older Hispanics, *Gynecol. Oncol.*, 2021, vol. 160, no. 1, pp. 16—23. https://doi.org/10.1016/j.ygyno.2020.10.033
7. Jeong, J.Y., Hwang, S.O., Lee, B., et al., Risk factors of progression to endometrial cancer in women with endometrial hyperplasia: a retrospective cohort study, *PLoS One*, 2020, vol. 15, no. 12. e0243064. https://doi.org/10.1371/journal.pone.0243064
8. Kadirogullari, P., Atalay, C.R., Ozdemir, O., and Sari, M.E., Prevalence of co-existing endometrial carcinoma in patients with preoperative diagnosis of endometrial hyperplasia, *J. Clin. Diagn. Res.*, 2015, vol. 9, no. 10, pp. QC10—QC14.
9. Ponomarenko, I., Reshetnikov, E., Polonikov, A., et al., Candidate genes for age at menarche are associated with endometriosis, *Reprod. Biomed. Online*, 2020, vol. 41, no. 5, pp. 943—956. https://doi.org/10.1016/j.rbmo.2020.04.016
10. Ponomarenko, I., Reshetnikov, E., Polonikov, A., et al., Candidate genes for age at menarche are associated with uterine leiomyoma, *Front. Genet.*, 2021, vol. 11, p. 512940. https://doi.org/10.3389/fgene.2020.512940
11. Alsudairi, H.N., Alrasheed, A.T., and Dvornyk, V., Estrogens and uterine fibroids: an integrated view, *Res. Results Biomed.*, 2021, vol. 7, no. 2, pp. 156—163. https://doi.org/10.18413/2658-6533-2021-7-2-0-6
12. Demakova, N.A., Molecular and genetic characteristics of patients with hyperplasia and endometric polyps, *Res. Results Biomed.*, 2018, vol. 4, no. 2, pp. 26—39. https://doi.org/10.18413/2313-8955-2018-4-2-0-4
13. Litovkina, O., Nekipelova, E., Dvornyk, V., et al., Genes involved in the regulation of vascular homeostasis determine renal survival rate in patients with chronic glomerulonephritis, *Gene*, 2014, vol. 546, no. 1, pp. 112—116. https://doi.org/10.1016/j.gene.2014.04.020
14. Reshetnikov, E.A., Akulova, L.Y., Dobrodomova, I.S., et al., The insertion-deletion polymorphism of the *ACE* gene is associated with increased blood pressure in women at the end of pregnancy, *J. Renin Angiotensin Aldosterone Syst.*, 2015, vol. 16, no. 3, pp. 623—632. https://doi.org/10.1177/1470320313501217
15. Tikunova, E., Ovtcharova, V., Reshetnikov, E., et al., Genes of tumor necrosis factors and their receptors and the primary open angle glaucoma in the population of Central Russia, *Int. J. Ophthalmol.*, 2017, vol. 10, pp. 1490—1494. https://doi.org/10.18240/ijo.2017.10.02
16. Ponomarenko, I., Reshetnikov, E., Altuchova, O., et al., Association of genetic polymorphisms with age at menarche in Russian women, *Gene*, 2019, vol. 686, pp. 228—236. https://doi.org/10.1016/j.gene.2018.11.042
17. Starikova, D., Ponomarenko, I., Reshetnikov, E., et al., Novel data about association of the functionally significant polymorphisms of the MMP-9 gene with exfoliation glaucoma in the Caucasian population of Central Russia, *Ophthalmic Res.*, 2021, vol. 64, no. 3, pp. 458—464. https://doi.org/10.1159/000512507
18. Ward, L.D. and Kellis, M., HaploReg v4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease, *Nucleic Acids Res.*, 2016, vol. D1, pp. D877—D881.
19. Reshetnikov, E., Zarudskaya, O., Polonikov, A., et al., Genetic markers for inherited thrombophilia are associated with fetal growth retardation in the population of Central Russia, *J. Obstet. Gynaecol. Res.*, 2017, vol. 43, no. 7, pp. 1139—1144. https://doi.org/10.1111/jog.13329
20. Moskalenko, M.I., Milanova, S.N., Ponomarenko, I.V., et al., Study of associations of polymorphism of matrix metalloproteinases genes with the development of arterial hypertension in men, *Kardiologiia*, 2019, vol. 59, no. 7S, pp. 31—39. https://doi.org/10.18087/cardio.2598
21. Reshetnikov, E., Ponomarenko, I., Golovchenko, O., et al., The VNTR polymorphism of the endothelial nitric oxide synthase gene and blood pressure in women at the end of pregnancy, *Taiwan J. Obstet. Gynecol.*, 2019, vol. 58, no. 3, pp. 390—395. https://doi.org/10.1016/j.tjog.2018.11.035
22. Eliseeva, N., Ponomarenko, I., Reshetnikov, E., et al., The haplotype of the CDKN2B-AS1 gene is associated with primary open-angle glaucoma and pseudoexfoliation glaucoma in the Caucasian population of Central Russia, *Ophthalmic Genet.*, 2021, vol. 42, no. 6, pp. 698—705. https://doi.org/10.1080/13816810.2021.1955275
23. Purcell, S., Neale, B., Todd-Brown, K., et al., PLINK: a tool set for whole-genome association and population-based linkage analyses, *Am. J. Hum. Genet.*, 2007, vol. 81, no. 3, pp. 559—575. https://doi.org/10.1086/519795
24. Minyaylo, O., Ponomarenko, I., Reshetnikov, E., et al., Functionally significant polymorphisms of the MMP-9 gene are associated with peptic ulcer disease in the Caucasian population of Central Russia, *Sci. Rep.*, 2021, vol. 11, no. 1, p. 13515. https://doi.org/10.1038/s41598-021-92527-y
25. Eliseeva, N., Ponomarenko, I., Reshetnikov, E., et al., *LOXL1* gene polymorphism candidates for exfoliation glaucoma are also associated with a risk for primary open-angle glaucoma in a Caucasian population from central Russia, *Mol. Vis.*, 2021, vol. 27, pp. 262—269.
26. Che, R., Jack, J.R., Motsinger-Reif, A.A., and Brown, C.C., An adaptive permutation approach for genome-wide association study: evaluation and recommendations for use, *BioData Min.*, 2014, vol. 7, p. 9. https://doi.org/10.1186/1756-0381-7-9
27. Moskalenko, M., Ponomarenko, I., Reshetnikov, E., et al., Polymorphisms of the matrix metalloproteinase genes are associated with essential hypertension in a Caucasian population of Central Russia, *Sci. Rep.*, 2021, vol. 11, no. 1, p. 5224. https://doi.org/10.1038/s41598-021-84645-4

28. GTEx Consortium, The GTEx Consortium atlas of genetic regulatory effects across human tissues, *Science*, 2020, vol. 369, no. 6509, pp. 1318—1330. https://doi.org/10.1126/science.aaz1776

29. Dvornyk, V., Ponomarenko, I., Belyaeva, T., et al., Filaggrin gene polymorphisms are associated with atopic dermatitis in women but not in men in the Caucasian population of Central Russia, *PLoS One*, 2021, vol. 16, no. 12. e0261026. https://doi.org/10.1371/journal.pone.0261026

30. Golovchenko, O., Abramova, M., Ponomarenko, I., et al., Functionally significant polymorphisms of *ESR1* and *PGR* and risk of intrauterine growth restriction in population of Central Russia, *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2020, vol. 253, pp. 52—57. https://doi.org/10.1016/j.ejogrb.2020.07.045

31. Dvornyk, V., Ponomarenko, I., Minyaylo, O., et al., Association of the functionally significant polymorphisms of the MMP9 gene with *H. pylori*-positive gastric ulcer in the Caucasian population of Central Russia, *PLoS One*, 2021, vol. 16, no. 9. e0257060. https://doi.org/10.1371/journal.pone.0257060

32. http://www.genecards.org/.

33. Plant, T.M., The hypothalamo-pituitary-gonadal axis, *J. Endocrinol.*, 2015, vol. 226, no. 2, pp. T41—T54. https://doi.org/10.1530/JOE-15-0113

34. He, C., Kraft, P., Buring, J.E., et al., A large–scale candidate–gene association study of age at menarche and age at natural menopause, *Hum. Genet.*, 2010, vol. 128, pp. 515—527.

35. Chen, Z.J., Zhao, H., He, L., et al., Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3, *Nat. Genet.*, 2011, vol. 43, no. 1, pp. 55—59.

36. Shi, Y., Zhao, H., Shi, Y., et al., Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome, *Nat. Genet.*, 2012, vol. 44, no. 9, pp. 1020—1025.

37. Jones, M.R., Brower, M.A., Xu, N., et al., Systems genetics reveals the functional context of PCOS loci and identifies genetic and molecular mechanisms of disease heterogeneity, *PLoS Genet.*, 2015, vol. 11, no. 8. e1005455

38. Davis, B.J., Risinger, J.I., Chandramouli, G.V.R., et al., Gene expression in uterine leiomyoma from tumors likely to be growing (from black women over 35) and tumors likely to be non-growing (from white women over 35), *PLoS One*, 2013, vol. 8, no. 6. e63909