Full length article

Functionally significant polymorphisms of *ESR1* and *PGR* and risk of intrauterine growth restriction in population of Central Russia

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ABSTRACT

Objective: This study aimed to investigate the role of *ESR1* and *PGR* gene polymorphisms in development of intrauterine growth restriction (IUGR) among Russian women in Central Russia.
Study design: This case–control study recruited a total of 520 women in the third trimester of pregnancy, including 196 IUGR patients and 324 controls. The participants were unrelated women of self-reported Russian ethnicity. Participants were genotyped at 4 functionally significant polymorphisms of the *ESR1* (rs2234693, rs9340799) and the *PGR* (rs484389, rs1042838) genes. The association analysis was performed using logistic regression. Two polymorphisms, which were associated with IUGR, and 26 polymorphisms linked to them ($r^2 \geq 0.6$) were analyzed for their functional significance *in silico*.
Results: Haplotype TG of loci rs2234693-rs9340799 *ESR1* (OR = 1.94, p_{perm} = 0.006) was associated with an increased risk of IUGR. Allele T of rs2234693 decreases expression of *ESR1* in thyroid gland, allele T of rs2234693 and allele G of rs9340799 increase affinity to eight transcription factors (AP-4, HEN1, E2A, LBP-1, RP58, LUN, Ets and Hand). The loci that are linked ($r^2 \geq 0.6$) to the IUGR-associated SNPs, have the *cis*-eQTL value (expression *ESR1* in thyroid gland) and showed their regulatory effects in organs and tissues related to pathogenesis of IUGR.
Conclusion: Haplotype TG defined by polymorphisms rs2234693-rs9340799 of the *ESR1* gene is associated with the development of IUGR in Russian women from Central Russia.

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Introduction

Intrauterine growth restriction (IUGR) is a condition when the rate of fetal growth is lower than expected for the gender and race of the fetus [1,2]. IUGR usually results from innate reduced growth potential or multiple adverse effects on the fetus. The "normal" neonate has birth weight between the 10th and 90th percentile for the given gestational age, race and gender with no sign of growth retardation and malnutrition [1]. An estimated fetal weight or abdominal circumference of less than the 10th centile for the population at a given gestational age was traditionally considered highly suggestive of IUGR [3].

The worldwide prevalence of IUGR is estimated between 5 % and 10 % of all pregnancies [4]. It may strongly affect the newborn's short- and long-term health [5]. For affected infants, the health

complications at delivery may include hypothermia, hyper- or hypoglycemia, persistent pulmonary hypertension, polycythemia, pulmonary hemorrhage, intrapartum asphyxia and stillbirth [1]. Since IUGR often results in preterm birth, various prematurity-associated multisystem diseases, such as impaired cognitive and motor development or/and physical growth may contribute to the intermediate and long-term health complications in IUGR newborns [5]. Moreover, an impaired fetal growth can increase a risk for certain diseases later in life, such as metabolic syndrome, type 2 diabetes mellitus, obesity, dyslipidemia, cardiovascular diseases and others [6,7].

The mechanisms underlying IUGR remain unclear, since there is much heterogeneity of disease etiology. In general, IUGR has been associated with *1)* fetal etiologies, such as genetic abnormalities (chromosomal abnormalities, syndromes,), *2)* maternal factors (persistent hypoxia or undernutrition, vascular disease, and toxins), and *3)* placental etiologies [8,9]. It is thought that 40 % of birth weight is ascribable to genetic factors, whereas the other 60 % is due to fetal environmental contributions [7]. Evidence from variance components analyses and monogenic human models [10] shows

that birth weight variation is influenced both by genotypes inherited by the fetus and by maternal genotypes that influence the intrauterine environment [11].

Maternal genotypes determine maternal phenotypes, which may affect growth of the fetus, such as circulating levels of various metabolic factors (e.g., glucose, hormones, etc.) or/and transfer of these and other nutrients through the placenta. Such maternal environmental effects underlain by maternal genotype may affect fetal growth independently from the effects of respective genetic variants that are inherited by the fetus directly from the mother [12].

This study was aimed to analyze a role of polymorphisms of the ESR1 and PGR genes in the development of IUGR among Russian women from Central Russia.

Material and methods

Study subjects

Between 2013 and 2017, 520 unrelated women in the third trimester of pregnancy were enrolled in the study. The ethical approval was obtained from the Regional Ethics Committee of Belgorod State University. All individuals gave their written informed consent prior to entering the study. The participants were examined in the perinatal center of the Saint Joasaph Belgorod Regional Clinical Hospital.

When recruiting the participants, the following inclusion criteria were applied: Russian ethnicity (self-reported), birthplace in Central Russia [13], and singleton pregnancy. Patients with pre-eclampsia, congenital malformations of internal genitals, anomalies of placental location, uterine fibroids, self-declared non-Russian descent or a birthplace outside of Central Russia, isosensitization of Rh factor or ABO blood group systems were not enrolled. IUGR of varying severity was diagnosed in 196 participants. The diagnosis of IUGR was based on clinical data, growth and weight parameters after the birth and ultrasound fetometry (TOSHIBA XARIO SSA-660A) (as described elsewhere, [14]). Based on the differences between fetometric data and nomograms, three degrees of IUGR were defined: the first corresponded to the reduction of the estimated gestational ages from the standard ones by 2 weeks; the second – by 3–4 weeks; and the third – by more than 4 weeks [15]. The first-degree IUGR was revealed in 105 patients (53.57 %), second-degree in 77 patients (39.28 %) and third-degree in 14 patients (7.14 %). Women without IUGR were controls (324 in total).

DNA isolation and genotyping assay

Approximately 4−5 ml blood sample from each participant was collected in vacutainer tubes (Vacutainer®). DNA was extracted from whole blood by phenol-chloroform method and then checked for quality (as described earlier, [16]).

Based on the significant regulatory potential, in total four SNPs in ESR1 (rs2234693, rs9340799) and PGR (rs484389, rs1042838) genes were selected for the analysis [17]. These SNPs are located in a region of regulatory motifs and have impact on gene expression level (Table 1) (determined using the online tools HaploReg, v4.1 update 05.11.2015, https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php).

Genotyping for all the polymorphisms was done using the MALDI-TOF mass spectrometry iPLEX platform (Agena Bioscience Inc, San Diego, CA). Genotyping blind replicates were included to ensure quality control. The repeatability test for 5 % of randomly selected samples was performed, yielded 100 % reproducibility.

Statistical analysis

Hardy-Weinberg equilibrium was assessed, based on the determined frequencies of genotypes and by using the chi-square test. The logistic regression method was used to analyze associations of the SNPs with IUGR assuming additive (i.e., comparison of all genotypes, e.g., TT vs TC vs CC), recessive (CC vs TC/TT, where C is a minor allele) and dominant (CC/TC vs TT, where C is a minor allele) genetic models with adjustment for covariates (BMI and age at menarche as quantitative variables (value of the trait), and history of medical abortion as qualitative variables (yes/no)) (Table 2). The adaptive permutation test was applied to adjust for multiple comparisons [18]. The PLINK v. 2.050 software (available at http://zzz.bwh.harvard.edu/plink/) was used to perform the association analyses.

Functional SNPs

The genetic variants associated with IUGR and SNPs strongly linked to them were studied for their functional significance (regulatory potential and eQTLs). SNPs in strong linkage disequilibrium (LD) ($r^2 \geq 0.6$) with the IUGR-associated ones were identified using HaploReg (v4.1) (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php). The data of the European population from the 1000 Genomes Project Phase was used to estimate linkage disequilibrium.

The regulatory potential of the candidate SNPs for IUGR was analyzed in silico using HaploReg (v4.1). The affinity between the factor-binding site of the reference (ref) and alternative (alt) alleles of a locus and transcription factors was estimated as a difference between the LOD scores of the alleles: $\Delta LOD = LOD(alt) - LOD(ref)$ [19]. A negative value indicates the increased affinity of this motif by the reference allele, while a positive value suggests the respective increase for the alternative allele.

Table 1

The regulatory potential of the studied SNPs (HaploReg, v4.1, http://archive.broadinstitute.org/mammals/haploreg/haploreg.php). (For interpretation of the references to colour in this table, the reader is referred to the web version of this article.)

chr	pos (hg38)	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	GERP cons	SiPhy cons	DNAse	Motifs changed	Selected eQTL hits	RefSeq genes	dbSNP func annot
6	151842200	rs2234693	T	C	0.57	0.35	0.42	0.4				6 altered motifs		ESR1	intronic
6	151842246	rs9340799	A	G	0.27	0.29	0.18	0.29				Ets,Hand1		ESR1	intronic
11	101039078	rs484389	A	G	0.41	0.3	0.23	0.26				5 altered motifs	2 hits	PGR	3'-UTR
11	101062681	rs1042838	C	A	0.01	0.15	0.01	0.19			HRT	4 altered motifs	2 hits	PGR	missense

Table 2
Phenotypic characteristics of the study participants.

Parameters	IUGR patients, n (%)	Controls, n (%)	p
N	196	324	–
Age, years (min–max)	26.63 ± 4.41 (16.0–41.0)	26.18 ± 4.98 (18.0–41.0)	0.07
BMI, kg/m2	22.69 ± 3.39	23.72 ± 3.61	**0.001**
Age at menarche and menstrual cycle			
Age at menarche, years	12.77 ± 1.10	12.54 ± 1.02	**0.01**
Duration of bleeding menstrual (mean, days)	5.05 ± 0.73	5.03 ± 0.80	0.76
Menstrual cycle length (mean, days)	28.56 ± 1.95	28.32 ± 1.62	0.33
Gynecological pathologies			
History of medical abortion	32.14 (63)	22.53 (73)	**0.02**
History of infertility	1.53 (3)	2.16 (7)	0.86
History of miscarriage (total)	15.82 (31)	13.89 (45)	0.63
Miscarriage in first trimester	10.20 (20)	8.02 (26)	0.49
Pregnancy loss in first trimester	3.06 (6)	3.74 (12)	0.89
Ectopic pregnancy	2.04 (4)	3.09 (10)	0.66
History of disorders of the menstrual cycle	7.14 (14)	8.02 (26)	0.84
History of pelvic inflammatory disease	15.82 (31)	13.89 (45)	0.63
Intrauterine infection during pregnancy	28.06 (55)	25.93 (84)	0.66
Antenatal intrauterine fetal death	1.53 (3)	0 (0)	0.10
Somatic pathologies			
Essential hypertension	27.04 (53)	20.06 (65)	0.08
Arterial hypotension	2.55 (5)	2.47 (8)	1.00
Chronic pyelonephritis	20.92 (41)	14.81 (48)	0.09
Obesity	8.67 (17)	10.49 (34)	0.60
Varicose veins	3.57 (7)	1.54 (5)	0.23
Endocrine disorders	7.65 (15)	6.17 (20)	0.63
Chronic gastroduodenitis	4.08 (8)	2.47 (8)	0.44
Nervous system pathology	0.05 (1)	0 (0)	0.80

GTExportal data (http://www.gtexportal.org/) as of 10.12.2017 (Release V7 updated on 09/05/2017) (dbGaP Accession phs000424. v7.p2) was used to estimate an effect of the IUGR candidate SNPs on gene expression level (cis- and trans-eQTL). The False Discovery Rate (FDR) ≤0.05 was applied to determine significant eQTLs. Linear regression coefficient (β) that indicates a change of the normalized gene expression per a single polymorphic variant was used to estimate effect of an allelic variant on the gene expression.

Results

The phenotypic characteristics of the case and control groups are presented in Table 2. The IUGR patients had lower BMI (p = 0.001,)) higher rates of history of medical abortion (p = 0.02) and later menarche at age (p = 0.01) as compared to the controls (Table 2). Therefore, these factors were applied as covariates in the association analyses.

The data about the studied SNPs are shown in Table 3. All polymorphisms had MAF > 5 % and did not deviate from the HWE (p>0.30). None of the SNPs appeared to be significantly associated with IUGR according to the additive, dominant or recessive models

(Table 4). Haplotype TG defined by rs2234693-rs9340799 of the ESR1 gene (according to the HaploReg (v4.1), the distance between SNPs is 46bp, r^2 = 0.61, Dʹ = 1, LOD > 2) was associated with IUGR (OR = 1.94, p = 0.001, p_{perm} = 0.006) (Table 5).

The results of the HaploReg (v4.1) analysis suggest that the IUGR-associated SNPs (rs2234693 and rs9340799) have a significant regulatory potential (Table 1): they are located in an evolutionarily conserved regions (GERP cons) that have enhancer histone mark (H3K27ac, H3K4me1) in adipose nucleia, and a region of eight regulatory motifs. Allele G of rs2234693 ESR1 decreases affinity to 6 transcription factors - E2A (ΔLOD = −12,0), AP-4 (ΔLOD = −11,9), HEN1 (ΔLOD = −11,9), LUN (ΔLOD = −12,0), LBP-1 (ΔLOD = −1,6), RP58 (ΔLOD = −11,9), and allele G of rs9340799 ESR1 increases affinity to 2 transcription factors - Hand1 (ΔLOD = 11,8) and Ets (ΔLOD = 4,3).

We also studied 26 SNPs, which were linked (r^2≥0.6) to the two IUGR-associated polymorphisms (Supplementary Table 1). Among those, rs2077647 (synonymous) was located in an exon and all the others were located in introns. One SNP (rs2077647) was located in an evolutionarily conserved region. Several genetic markers appeared to have a significant regulatory potential. For example, rs2077647 (linked to rs2234693) has a promoter histone

Table 3
The allele and genotype frequencies of the studied SNPs in the case and control groups.

Chr	SNP	Minor allele	Major allele	Minor allele frequency	Number of the studied chromosomes	Genotype distribution*	Ho	He	P HWE
IUGR patients (n = 196)									
6	rs2234693	T	C	0.510	390	50/99/46	0.508	0.500	0.887
6	rs9340799	G	A	0.410	388	33/93/68	0.479	0.484	0.883
11	rs484389	C	T	0.240	388	11/71/112	0.366	0.365	1.000
11	rs1042838	T	G	0.169	390	3/60/132	0.308	0.281	0.305
control group (n = 324)									
6	rs2234693	T	C	0.484	632	69/168/79	0.532	0.500	0.310
6	rs9340799	G	A	0.388	636	48/151/119	0.475	0.475	1.000
11	rs484389	C	T	0.225	636	19/105/194	0.330	0.349	0.337
11	rs1042838	T	G	0.145	640	7/79/234	0.247	0.248	0.824

Note: * minor allele homozygotes/heterozygotes/major allele homozygotes.

Table 4
Associations of the SNPs of the *ESR1* and *PGR* genes with IUGR.

Chr	SNP	n	Additive model				Dominant model				Recessive model			
			OR	95 %CI		P	OR	95 %CI		P	OR	95 %CI		P
				L95	U95			L95	U95	L95		U95		
6	rs2234693	511	1.12	0.86	1.44	0.407	1.09	0.71	1.64	0.719	1.23	0.82	1.87	0.323
6	rs9340799	512	1.09	0.85	1.42	0.498	1.11	0.76	1.61	0.589	1.15	0.71	1.87	0.565
11	rs484389	512	1.09	0.81	1.46	0.590	1.15	0.80	1.65	0.464	0.95	0.44	2.03	0.887
11	rs1042838	515	1.21	0.85	1.72	0.295	1.30	0.88	1.92	0.188	0.70	0.18	2.73	0.606

All results were obtained after adjustment for covariates.
OR, odds ratio.
95 %CI, 95 % confidence interval.

Table 5
Associations of the haplotypes with IUGR.

Gene	SNPs included	Haplotype	Frequency		OR	P
			IUGR patients (n = 196)	Controls (n = 324)		
ESR1	rs2234693|rs9340799	TG	0.143	0.080	**1.94**	**0.001**
	rs2234693|rs9340799	CG	0.267	0.308	0.87	0.175
	rs2234693|rs9340799	TA	0.368	0.404	0.93	0.332
	rs2234693|rs9340799	CA	0.223	0.208	1.13	0.453
PGR	rs484389|rs1042838	CT	0.162	0.139	1.21	0.300
	rs484389|rs1042838	CG	0.081	0.089	0.90	0.651
	rs484389|rs1042838	TG	0.757	0.772	0.93	0.645

Note: The results were obtained by the logistic regression analysis with adjustment for covariates; OR - odds ratio, p - significance level.

mark in 24 tissues, is located in a DNase-1 hypersensitive region in seven tissues, a region of four regulatory motifs (RP58, LUN-1, Znf143, Zfp410), and a binding region for regulatory protein HAE2F1. Polymorphism rs62442056 (linked to rs9340799) is located in a DNase-1 hypersensitive region in 29 tissues, a region of five regulatory motifs (Foxa, Foxi1, CEBPB, TCF12, HDAC2), and a binding region for three regulatory proteins (TCF12, NRSF, SIN3AK20). Polymorphism rs9479130 linked to two loci (rs2234693 and rs9340799) of the *ESR1* gene (r^2 = 1.00 and r^2 = 0.61, respectively) is associated with IUGR. This SNP is located in a DNAase- hypersensitivity region in 24 tissues, a region of two regulatory motifs (ZBTB33, AP-1), and a binding region for three regulatory proteins (TCF12, NRSF, SIN3AK20). Importantly, the loci that are linked to the IUGR-associated SNPs, showed their regulatory effects in organs and tissues related to pathogenesis of IUGR, *i.e.* ectoderm, mesoderm, and endoderm cultured cells, amnion, placenta, fetal organs (brain, muscle, adrenal gland, *etc.*), adult organs (pancreas, ovaries, muscle tissue, adrenal gland, adipose tissue, various brain regions (angular gyrus, substantia nigra, hippocampus, germinal matrix *etc.*), liver *etc.*) [7].

According to the GTExportal database, variant rs2234693 has the *cis*-eQTL value and may affect expression of *ESR1* in the thyroid glands: allele G of rs2234693 *ESR1* is associated with the higher gene expression (β = 0.13, p = 0.000035, $p_{FDR} \le 0.05$). Also, two IUGR-associated SNPs (rs2234693 and rs9340799) are in strong LD with the other *cis*-eQTL polymorphisms (16 SNPs) affecting *ESR1* expression in the thyroid gland (Supplementary Table 2).

Discussion

In the present study, we report for the first time the associations of two *ESR1* gene polymorphisms with IUGR in Russian women from Central Russia: haplotype TG defined by loci rs2234693-rs9340799 increased a risk for IUGR (OR = 1.94). According to the HaploReg database (v4.1), allele T of rs2234693 and allele G of rs9340799 increase affinity to the transcription factors E2A, AP-4, LBP-1, HEN1, LUN, RP58, Hand and Ets. The rs2234693 and rs9340799 polymorphisms of the *ESR1* gene are located in an evolutionarily conserved regions and have a enhancer histone mark in adipose nucleia. Variant rs2234693 and sixteen polymorphisms linked to rs2234693 and rs9340799 have the *cis*-eQTL significance and may influence the *ESR1* gene expression in the thyroid gland (allele T of rs2234693 decreases the expression of *ESR1*). In addition, the loci that are linked to the IUGR-associated SNPs (26 polymorphisms), showed their various regulatory effects in tissues and organs related to the pathogenesis of IUGR, fetal and adult organs.

The *ESR1* gene (6q25.1-q25.2) encodes an estrogen receptor α, a ligand-activated transcription factor consisting of several domains important for hormone binding, DNA binding and activation of transcription. ESR1 and ESR2 (estrogen receptor β) mediate biological effects of estrogen in target tissues. Growth factors can activate ESR1 in the absence of estrogen. Estrogen signaling plays an important regulatory role in the development and function of the reproductive system [20]. In the mouse and rat, disruption of *ESR1* causes infertility in both females and males [21]. ESR1 is predominantly expressed in the mammary glands, hypothalamus, pituitary, uterus and ovarian theca cells [22]. Estrogen is a principal regulator of the gonadotropin hormone-releasing hormone (GnRH). GnRH neurons in the hypothalamus synthesize the GnRH peptide, which is a key regulator of the cascade of hormonal events that are necessary for normal sexual maturation and reproductive function [23].

During pregnancy, the primary source of steroid hormones (estrogens and progesterone) is placenta. Studies performed *in vivo* suggest that placental steroid hormones may be important in driving the changes in glucose metabolism and insulin sensitivity of the mother during pregnancy (play roles in regulating glucose and insulin homeostasis, appetite regulation and lipid handling) [24].

Estrogen stimulates the activation of the insulin-like growth factor 1 receptor (IGF1R) which triggers the activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway for execution an inhibitory phosphorylation of the glycogen synthase kinase

(GSK-3β). Inactivation of GSK-3β prevents the inhibitory phosphorylation of cyclin D1 and allows for its nuclear translocation [22]. In addition, IGF1R mediates effects of the insulin-like growth factors IGF-1 and IGF-2, thus promoting fetal and neonatal growth, responding to maternal, fetal and placental signals such as oxygen, hormones, and nutrients [6]. IGF-1 controls fetal growth in response to nutrient availability while IGF-2 stimulates differentiation and placental growth [25]. Further, IGFs control hormone secretion, substrate transport and influence fetal growth either directly by affecting placental nutrient uptake and transport or indirectly by influencing maternal substrate availability [25].

Glucose and amino acid uptakes are stimulated by IGF-1, IGF-2, and trophoblasts [26]. Human IUGR was associated with chronic fetal hypoglycemia [7]. The expression levels of *ESR1*, progesterone, and insulin-like growth factor 1 in placenta were shown to influence IUGR and gestational age [27].

Previously, loci rs2234693 and rs9340799 associated with IUGR were also reported as candidate for preeclampsia [28–30], age of menarche [31], precocious puberty [32], height at menarche [33], premature ovarian failure [34], endometriosis [35], breast cancer [36], type II diabetes mellitus [37]. Specifically, Molvarec [28] reported the GG genotype of the rs9340799 was associated with a lower risk of IUGR in patients with severe preeclampsia while the homozygous TA haplotype carriers of *ESR1* rs2234693 and rs9340799 polymorphisms showed an increased risk of severe preeclampsia. According to the present study results, haplotype TG of loci rs2234693-rs9340799 increased a risk for IUGR (OR = 1.94) in patients without preeclampsia. Although the results of the two studies are somewhat inconsistent, they suggest that allele G of the rs9340799 polymorphism may contribute to pregnancy complications. This assumption gains further support from a recent meta-analysis, which showed that the GG genotype of the *ESR1* rs9340799 polymorphism could be a genetic risk factor for severe preeclampsia susceptibility [30].

Conclusion

Haplotype TG defined by loci rs2234693-rs9340799 of the *ESR1* gene was a factor for an increased risk of IUGR (OR = 1.94). Allele T of rs2234693 and allele G of rs9340799 increase affinity to eight transcription factors (LBP-1, AP-4, E2A, HEN1, RP58, LUN, Ets and Hand); allele T of rs2234693 decreases expression of *ESR1* in the thyroid gland. The loci linked to the IUGR-associated SNPs have the *cis*-eQTL value (expression *ESR1* in the thyroid gland) and show their regulatory effects in tissues and organs related to pathogenesis of IUGR. The *ESR1* gene may contribute to the development of IUGR through the estrogen signaling pathway. However, further studies are needed to verify this assumption.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.07.045.

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