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Genes for aryl hydrocarbon receptor signaling are associated with uterine fibroids susceptibility

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Motivation and Aim: Uterine fibroids (UF) are one of the most common benign tumors in females worldwide. UF are associated with a significant impairment of reproductive health and can lead to impaired fertility, pregnancy complications, and adverse obstetric outcomes [1]. In recent years, evidence has emerged indicating that environmental pollutants such as dioxins may be a risk factor for the development of UF [1]. Dioxins contribute to the formation of tumors by affecting cell proliferation and differentiation, and their negative impact on reproductive function is associated with strong toxic effects. These compounds exert their biological and toxicological effects by binding to the aryl hydrocarbon receptor (AhR) [2]. AhR is a ligand-dependent transcription factor that regulates cell differentiation and the induction of xenobiotic biotransformation enzymes. AhR nuclear translocator (ARNT) and AhR repressor (AhRR) regulate AhR function. The ligand-bound AhR moves to the nucleus, where it heterodimerizes with ARNT. The AhR-ARNT heterodimer binds to xenobiotic response elements (XRE) and promotes the activation of target genes involved in the biotransformation of xenobiotics and included in the aryl hydrocarbon receptor signaling pathway. All aryl hydrocarbon receptor signaling pathway genes are expressed in the uterus and are involved in the local response to highly toxic environmental pollutants [3]. A comprehensive analysis of the involvement of polymorphic variants of the aryl hydrocarbon receptor signaling pathway genes in predisposition to UF has not been carried out.

Methods and Algorithms: A total of 1001 unrelated Russian females from Central Russia were examined: 603 patients with UF and 398 healthy females, without clinical and ultrasound signs of uterine fibroids. Written informed consent was obtained from all participants prior to entering the study. The study was approved by the Regional Ethics Committee of Kursk State Medical University. Genotyping of single nucleotide polymorphisms (rs2066853 *AHR*, rs2292596 *AHRR*, rs2228099 *ARNT*, rs1048943 *CYP1A1*, rs762551 *CYP1A2*, rs1056836 *CYP1B1*, rs1800566 *NQO1*) was performed by TaqMan-based PCR on a CFX96 amplifier (Bio-Rad). To analyze the associations of genotypes with the development of UF, we used a log-additive regression model calculated in the SNPStats program (https://www.snpstats.net/start.htm) with an adjustment for age and smoking. To study the regulatory potential of SNPs, the atSNP online resource was used, which assesses the binding ability of transcription factors to DNA regions in the SNP region depending on the carriage of the reference/alternative allele (http://atsnp.biostat.wisc.edu/search). To search for gene ontologies associated with the biological functions of transcription factors, the Gene Ontology tool was used (http://geneontology.org/).

Results: This study showed that rs2228099 *ARNT* (OR = 1.58; 95 %CI = 1.19-2.09; risk allele G) and rs1048943 *CYP1A1* (OR = 0.59; 95 %CI = 0.40-0.91; protective allele G) are associated with development of UF. SNP rs2228099 *ARNT* is characterized by high regulatory potential. According to GTEx Portal data, the risk allele G of rs2228099 *ARNT* has a pronounced cis-eQTL-mediated effect on the expression of *HORMAD1, CERS2, CTSS, ARNT, RP11-54A4.2, SETDB1* genes in adipose subcutaneous, *CTSS, ARNT, RP11-54A4.2, HORMAD1* genes in adipose visceral, *CERS2* gene in uterus, *CTSK, GOLPH3L, HORMAD1, CTSS, SETDB1* genes in whole blood. The risk allele G also creates sites for DNA binding to 8 transcription factors (SMAD3, FOXA1, RREB1, EGR1, HIF1A::ARNT. SMAD, CREB3L1, EGR2), which are jointly involved in the regulation of transforming growth factor beta 2 production (FDR = 0.002), regulation of cytokine production (FDR = 0.014), regulation of vascular endothelial growth factor receptor signaling pathway (FDR = 0.01), positive regulation of vascular endothelial growth factor production (FDR = 0.01), positive regulation of interleukin-1 beta production (FDR = 0.02), response to hypoxia (FDR = 0.002). Protective allele G of SNP rs1048943 *CYP1A1* binds to 20 transcription factors (HOXA2, BSX, NR2C2, CUX2, ATF3, DLX5, NR3C1, HOXB5, HSF, JUN, NKX1-1, SP2, BARX1, DLX2, YY1, PPARA, JUND (var.2), NANOG, PDX1, HOXD3) co-participating in cell differentiation (FDR = 1.55×10-5), steroid hormone mediated signaling pathway (FDR = 0.037), response to steroid hormone (FDR = 0.04). Thus, genetic variants associated with the development of UF have a high regulatory potential and mediate participation in a large number of biological processes involved in the pathogenesis of uterine fibroids.
Conclusion: Thus, for the first time in the world, we have obtained data on the involvement of the genes for the aryl hydrocarbon receptor signaling pathway in the predisposition to UF.
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