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GWAS-significant loci and risk of uterine fibroids in the population of Central Russia

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Motivation and Aim: Uterine fibroids (UF) are common gynecological issue that affects up to 70 % of women of reproductive age [1, 2]. Surgery is currently the main treatment procedure [3]. At the moment, the age of primary diagnosis of uterine fibroids is becoming younger [1, 3]. The disease affects their ability to conceive and have successful pregnancies. Since this condition has a permanent impact on a woman's ability to have children, it's crucial to pay close attention to the factors that increase the risk of UF development. A lot of identified genetic variations associated with UF were identified by GWAS [4, 5]. The aim of this study was to explore the association between GWAS-significant SNPs and the susceptibility to UF in the population of Central Russia.
Methods and Algorithms: DNA samples from 654 UF patients and 401 healthy individuals were analyzed using real-time PCR to detect the rs547025 *SIRT3*, rs2456181 *ZNF346*, rs7907606 *SLK*, *STN1*, rs58415480 *SYNE1*, rs7986407 *FOXO1*, rs72709458 *TERT*, rs117245733 *LINC00598* SNPs, was identified in previous GWASs as UF-linked loci. A log additive regression model was used to assess the associations. Additionally, bioinformatics tools were utilized to investigate the functional effects of the SNPs.
Results: We observed a significant link between the rs547025 *SIRT3* polymorphism and a decreased risk of UF development (OR = 0.64, 95 % CI = 0.47–0.88, P = 0.005). Further investigation using HaploReg v4.2 revealed that rs547025 *SIRT3* resides in the DNA binding region of H3K4me1, with its impact strengthened by H3K27ac, indicating its significant epigenetic regulatory potential in blood. Moreover, rs547025 displays notable cis-eQTL effects, influencing the expression of several genes, including *RIC8A*, *PSMD13*, *BET1L*, *SCGB1C1*, *ODF3*, *IFITM2*, *IFITM1*, *IFITM3*, and *PTDSS2* in blood and adipose tissue. Interestingly, *BET1L* has previously been linked to UF risk, while *IFITM1* is a sensitive marker for endometriosis. These findings offer valuable insights into potential pathways influenced by the *SIRT3* polymorphism in UF development. Additionally, data from the Reproductive System Knowledge Portal indicates a significant association between the rs547025 variant and earlier age at natural menopause, which is recognized as a significant risk factor for UF.
Conclusion: To sum it up, this study was the first to establish the significant association of rs547025 *SIRT3* with the risk of UF in the population of Central Russia. Therefore, this locus can be used as an effective predictive marker of UF development at the preclinical stage as part of predictive medicine.
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References

1. Lou Z., Huang Y., Li S. et al. Global, regional, and national time trends in incidence, prevalence, years lived with disability for uterine fibroids, 1990–2019: an age-period-cohort analysis for the global burden of disease 2019 study. *BMC Public Health*. 2023;23:916. doi 10.1186/s12889-023-15765-x
2. Sliz E., Tyrmi J.S., Rahmioglu N. et al. Evidence of a causal effect of genetic tendency to gain muscle mass on uterine leiomyomata. *Nat Commun*. 2023;14(1):28-35. doi 10.1038/s41467-023-35974-7
3. Karamyan R.A., Ordiyats I.M., Khorolskiy V.A., Asatryan D.R. Uterine fibroids: a look at the problem. *Med Her South Russia*. 2022;13(2):18-25. doi 10.21886/2219-8075-2022-13-2-18-25 (in Russian)
4. Dai Y., Liu X., Zhu Y. et al. Exploring Potential Causal Genes for Uterine Leiomyomas: A Summary Data-Based Mendelian Randomization and FUMA Analysis. *Front Genet.* 2022;13:890007. doi 10.3389/fgene.2022.890007
5. Gallagher C.S., Mäkinen N., Harris H.R. et al. Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. *Nat Commun*. 2019;10(1):48-57. doi 10.1038/s41467-019-12536-4