DOI 10.18699/SBB-2022-253

# Genomics and transcriptomics of preeclampsia

Trifonova E.[1, 2]*, Svarovskaya M.[1, 2], Gabidullina T.[2], Serebrova V.[1], Babovskaya A.[1], Gavrilenko M.[1], Stepanov V.[1]

[1] *Tomsk National Research Medical Center, SB RAS, Tomsk, Russia*

[2] *Siberian State Medical University, Tomsk, Russia*

** ekaterina.trifonova@medgenetics.ru*

**Key words:** preeclampsia, genome-wide analysis of expression profiles, placental tissue, tagSNPs

*Motivation and Aim*: Preeclampsia (PE) is a common pregnancy-specific disorder with unknown etiology. It is the leading cause of maternal and perinatal morbidity and mortality. It is generally accepted that the main pathogenetic mechanisms of PE are associated with impaired placentation processes and reduced remodeling of the myometrial spiral arteries. The study of molecular processes occurring in the placental tissue is considered as the most promising line of research for revealing the pathophysiological mechanisms of PE and the development of prevention and targeted therapy [1, 2]. The aim of our work was to identify placental tissue transcriptome patterns characteristic of women with PE and the physiological pregnancy and to assess the role of polymorphic markers of genes differentially expressed in pathological and normal pregnancy in the structure's of predisposition to PE.

*Methods and Algorithms*: We performed a genome-wide analysis of expression profiles of 24 placental tissue samples from patients with PE and women with physiological pregnancy using microarray technology. To search for differentially expressed genes (DEGs) in the case-control groups, the method of generalized linear models of the limma software package was used. A change in the level of gene expression (FC) by 1.5 times or more was considered significant at an adjusted significance level of $p \leq 0.1$. Functional annotation and functional cluster analysis of DEG groups were performed using the DAVID Web tool. Gene networks were constructed using the STRING 9.0 software.

The sample size for the analysis of DNA variability included more than 1000 women. They were divided into a group of patients with PE ($N = 721$ people) and a control group ($N = 552$ people) according to the course and outcomes of pregnancy. Genotyping of 85 polymorphic markers (tagSNPs) of differentially expressed genes was performed using MALDI-TOF mass spectrometry. To compare the frequencies of alleles and genotypes between the analyzed groups, Pearson's $\chi^2$ test with Yates correction or two-tailed Fisher's exact test was used. To assess associations of SNP genes with the development of a pathological phenotype (PE), the odds ratio (OR) was calculated. The present study was approved by the ethics committee at the Research Institute of Medical Genetics of the Tomsk National Medical Research Center.

*Results*: Sixty three genes are statistically significantly differentially expressed between patients with PE and physiological pregnancy were found. The cluster of DEGs overexpressed in PE included not only known candidate genes previously identified in many genome-wide studies of placental gene expression profiles in preeclampsia (e.g., *LEP, BHLHB2, SIGLEC6, RDH13, BCL6*), but also new potential genes candidates (*CORO2A, SYDE1, PLIN2, CEBPA, HK2, NDRG1, ERRFI1, EFNB1, GFOD2, NCOR2,*

*HMHA1, HERPUD1, KIF2A*), whose association with the development of PE has been established either in single studies or for the first time in the presented work [3].
The functional annotation of DEG indicates a number of biological processes that play an important role in the molecular pathogenesis of PE. These are reactions associated with the immune response, intercellular interaction, regulation of apoptosis, etc. An analysis of the metabolic pathways of DEG indicates a possible involvement in the pathophysiological mechanisms of PE cytotoxicity caused by NK cells, transendothelial migration of leukocytes and signaling pathways mediated by GTPase activators. The network of protein-protein interactions obtained using the STRING database confirms the relationships between genes identified in the study of biological pathways and processes. Analysis of this network identifies the cluster of co-expression genes including the *RAC2, CYBA, TYROBP, HMHA1, ITGB2, LYN*, and *LCP1* genes. In addition, pairs of *LEP*/its receptor *SIGLEC 6*, ephrin and its kinase *LYN* are of particular interest. Integration of DEG functional annotation data and analysis of network interactions of proteins encoded by these genes made it possible to identify a cluster of the most significant DEGs, whose hereditary variability was studied at the genomic level.
The association tagSNPs of 27 genes (*ANKRD37, BHLHE40, CORO2A, GPT2, HK2, INHA, LEP, LHB, NDRG1, PLIN2, PPP1R12C, SASH1, SIGLEC6, SYDE1*, and *ZNF175*) with PE was found. It should be noted that the majority of PE-associated tagSNPs, according to the results of analysis in the online resources HaploReg (v.4.1.) and RegulomeDB (http://compbio.mit.edu/HaploReg; https://regulomedb.org/regulome-search/) were localized at transcription factor binding sites and had a high regulatory potential.
*Conclusion*: We used a new approach to detecting genetic markers of preeclampsia based on a combination of genomic, transcriptomic, and bioinformatic approaches. We have discovered new genetic markers of PE and demonstrated a significant role of regulatory regions of the human genome in predisposition to this pathology. The functional annotation of DEGs demonstrated their overrepresentation in the processes associated with the immune response, intercellular interactions, regulation of apoptosis which probably play a key role in the molecular pathogenesis of PE.
*Acknowledgements*: The study is supported by the Russian Foundation for Basic Research (grant No. 20-34-90128).

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