TOMSK NATIONAL RESEARCH MEDICAL CENTER THE RUSSIAN ACADEMY OF SCIENCES

RESEARCH INSTITUTE OF MEDICAL GENETICS

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Placental transcriptome co-expression analysis reveals key biomarkers and pathways of preeclampsia

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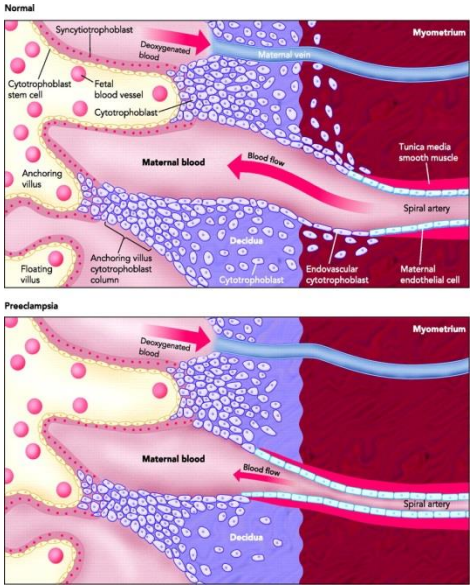

Fig. 1. Abnormal placentation in preeclampsia [from Wang et al., 2009].

Introduction

Preeclampsia (PE) remains a leading cause of maternal/fetal mortality and morbidity associated with gestational hypertension and proteinuria. The underlying mechanism and preventive treatment remain unknown. The pathogenesis of preeclampsia is not fully understood. It is known that preeclampsia originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction (Fig. 1). Due to possible multifactorial causes involved, an increase in “omics” experimental approaches is noted, generating a large amount of information for PE. Therefore, the identification of key genes and pathways is of much importance for clarifying molecular mechanism of PE initiation and progression.

Study goal

The identification of key genes and pathways of preeclampsia by bioinformatics analysis of the placental tissue transcriptomic data.

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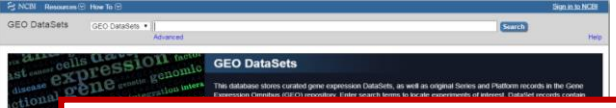


Materials & Methods

Genome-wide expression profiling was performed on placental tissue from PE and normal (n = 47) pregnancies. The examined patients were from the Russian and Yakut populations. Eight original datasets (GSE25906, GSE30186, GSE35574, GSE44711, GSE60438, GSE6573, GSE73374, GSE94643) from patients with PE and normal pregnancy (n = 129) were downloaded from Gene Expression Omnibus and were further integrated and analyzed with our data.

Bioinformatics processing and statistical data analysis were performed in the R software environment using specialized packages of the Bioconductor project.

Gene Set Enrichment Analysis (GSEA) were applied for the identification of pathways in which DEGs significantly enriched. Cytoscape software was for the construction of protein-protein interaction (PPI) network and module analysis to find the hub genes and key pathways. We applied upstream analysis approach implemented in geneXplain platform for detection of upstream transcriptional regulators and their regulatory networks. Finally, weighted correlation network analysis (WGCNA) was conducted to further screen critical gene modules with similar expression pattern.

Results

Subsequently, 4939 DEGs between PE patients and healthy women were identified. Using GSEA we identified the significant role of disturbance of intercellular interactions and regulation of proteins modification in placental tissue during the development of the PE.

WGCNA reveals a similar distribution along the modules detected both in normal and PE conditions. A total of 31 modules were identified as PE related clusters and 34 modules were identified in control group (Fig. 2). Using WGCNA, we found 6 clusters containing 86 genes associated only with PE.

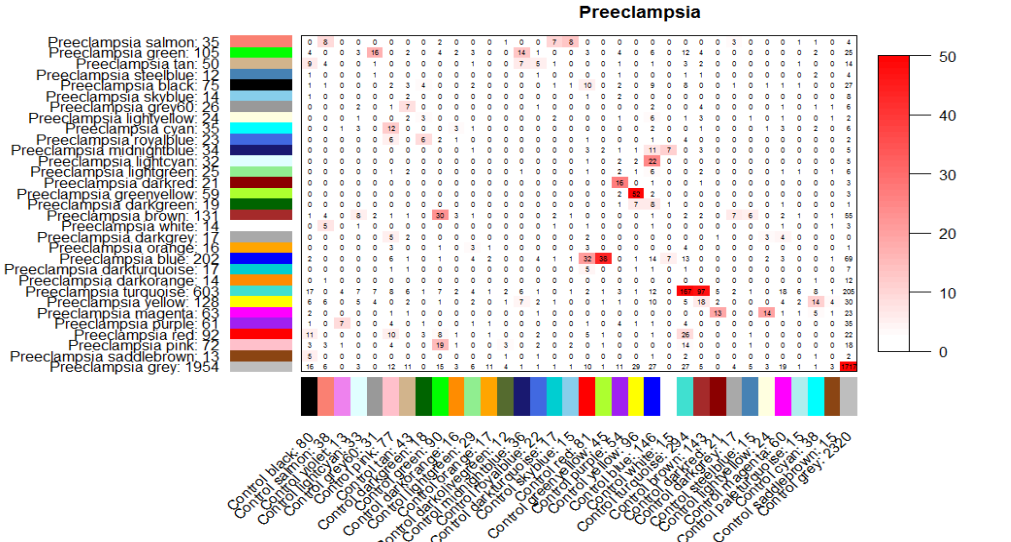
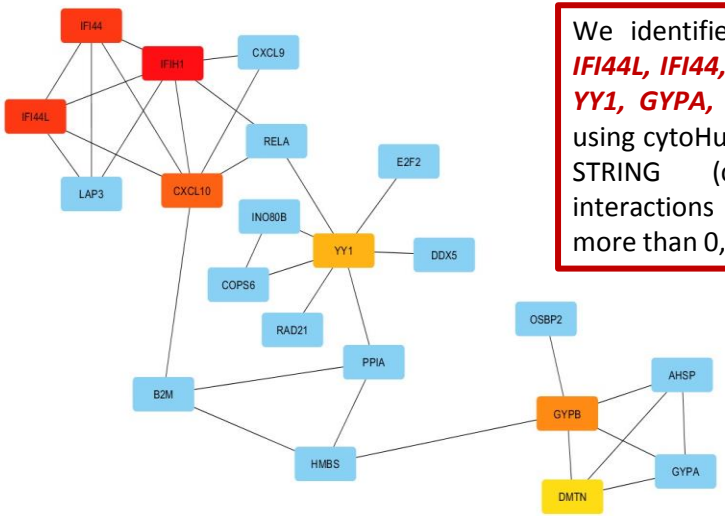
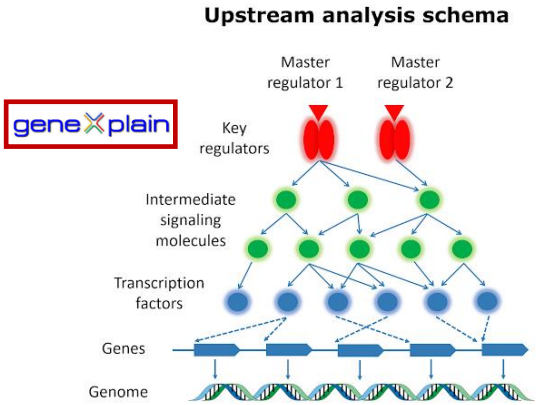


Fig. 2. WGCNA module relationships.



We identified 9 hub genes (***IFIH1, IFI44L, IFI44, CXCL9, CXCL10, RAD21, YY1, GYPA, GYPB***) in these clusters using cytoHubba (MCC, rank < 5) and STRING (combined level of interactions (combined score) is more than 0,7.) (Fig.3 and 4).

Fig. 3. Network of gene interactions associated with PE, reconstructed by Cytoscape 3.7.2 in the plugin cytoHub.



We applied upstream analysis approach implemented in geneXplain platform and identified master regulators (*MAPK3, TP53* and *UBE2D1*) that are new therapeutic targets. These key genes may be potential biomarkers of diagnosis, therapy and prognosis for preeclampsia.

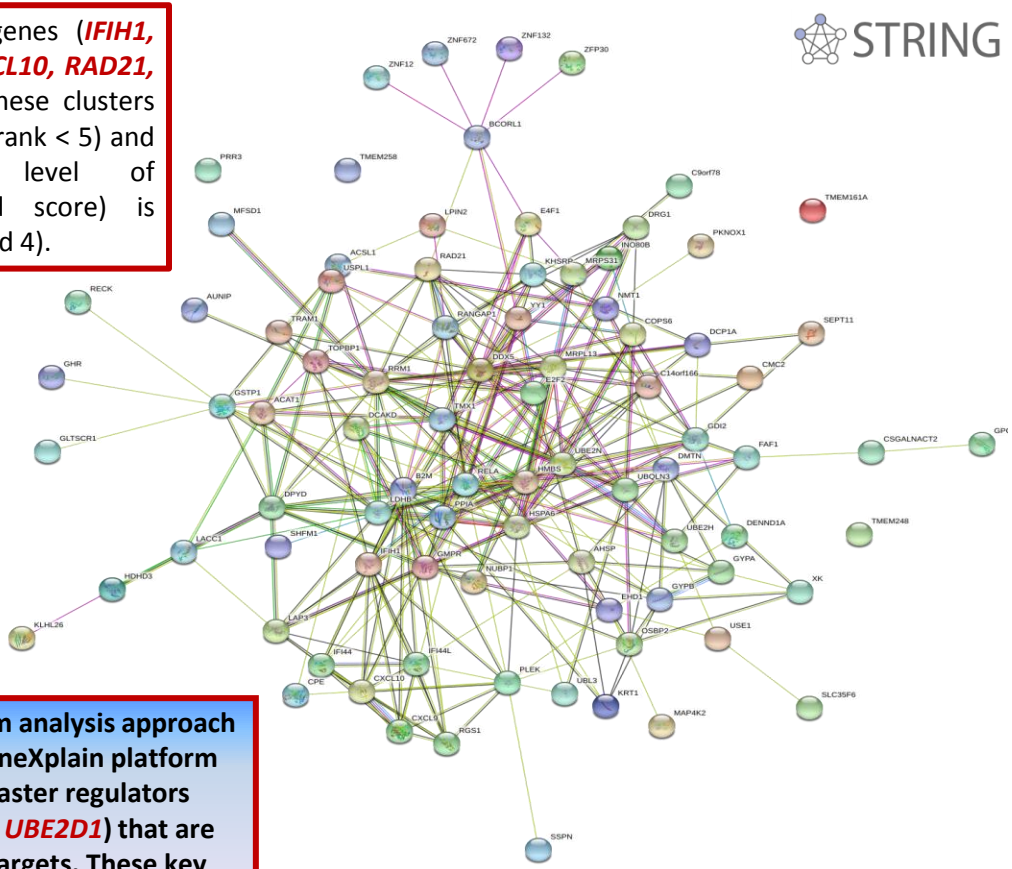


Fig. 4. The protein-protein interaction network from STRING database. The predicted network summarizes the network of predicted associations with other proteins. The network nodes are proteins and the edges signify the predicted functional associations.