DOI 10.18699/SBB-2022-460

In silico determination of the risk haplotype for developing preeclampsia

Karpova N., Dmitrenko O.
Institute of General Pathology and Pathophysiology, Moscow, Russia
** nataliiakarpova.sp@gmail.com*

Key words: FLT1, preeclampsia, risk haplotype, pathology of pregnancy

Motivation and Aim: Preeclampsia (PE) refers to hypertensive disorders during pregnancy, which poses a threat to the life of the mother and fetus. PE complicates about 2–8 % of pregnancies and is diagnosed as a combination of high blood pressure and proteinuria [1]. Trisomy for chr13 is associated with PE, and this chromosome contains the FLT1 gene, polymorphisms in which are also associated with PE (rs4769612-C, rs4769613-C, rs7318880-T). Moreover, the polymorphism of the fetus, rather than the mother, plays an important role [2]. Phupong et al. showed that sFlt1/PlGF is not associated with other pregnancy complications other than PE [3]. Based on these data, we decided to investigate the presence of regulatory regions in polymorphisms and determine the prevalence of the haplotype, which includes risk alleles.
Methods and Algorithms: We used the GWAS catalog and PubMed to identify SNPs in FLT1 associated with preeclampsia in the maternal and child genomes, followed by mapping these SNPs to the human genome in the UCSC genome browser to identify overlapping polymorphisms in regulatory regions [4, 5]. Next, we analyzed the presence of periods in which the enhancer signature is detected in the tissues of the placenta and embryo, using the cCRE details in ENCODE SCREEN [6]. For SNPs in the regulatory region, we selected SNPs with a MAF of 1 % and identified possible haplotypes in European populations.
Results: In the GWAS-catalog, we found 2 polymorphisms in FLT1 associated with preeclampsia: rs4769612-C (p-value 4 x 10-14) and rs7318880-T (p-value 8 x 10-8), with rs4769612 associated with preeclampsia in analysis of the child's genotype, and rs7318880 in the analysis of the mother's genotype. According to the UCSC genome browser (oRegAnno) data, there are 4 regulatory elements in the rs4769612 region: OREG1191996, OREG1658246, OREG1688336, OREG1537828. According to the cCRE details of ENCODE SCREEN, this region contains the putative regulatory element EH38E1663332, the largest distal enhancer signature of which sharply increases at 16 weeks of gestation in the placenta and fetal tissues, which can lead to changes in FLT1 expression. In addition to rs4769612 and rs7318880, the EH38E1663332 region contains 7 more polymorphisms with MAF > 1 %: rs7320190, rs12867370, rs4769613, rs74623647, rs7321138, rs76592233, rs9579193. Of these, only rs7320190 and rs4769613 are mentioned in scientific articles and rs4769612 and rs7318880 in the GWAS database, as well as rs12867370 is associated with the risk of developing schizophrenia in offspring born to mothers with PE [7]. When assessing the prevalence of 4 possible haplotypes, a possible haplotype of the risk of developing preeclampsia was determined, for which the prevalence was 8.25 % (considering the risk alleles of maternal and fetal PE). In addition, this risk haplotype will occur in the homozygous

state with a frequency of 0.68 %, which is close to the prevalence of early-onset preeclampsia rate of 0.38 % [1] (Fig. 1).

RS Number	Position (GRCh37)	Allele Frequencies	Haplotypes			
rs7320190	chr13:29138256	T=0.791, C=0.209	T	T	C	C
rs7318880	chr13:29138285	T=0.539, C=0.461	C	T	T	T
rs12867370	chr13:29138398	G=0.917, A=0.083	G	G	G	A
rs4769612	chr13:29138498	C=0.542, T=0.458	T	C	C	C
rs4769613	chr13:29138609	C=0.544, T=0.456	T	C	C	C
rs74623647	chr13:29138632	G=1.0, T=0.0	G	G	G	G
rs7321138	chr13:29138705	T=0.793, C=0.207	T	T	C	C
rs76592233	chr13:29138761	C=1.0, T=0.0	C	C	C	C
rs9579193	chr13:29138768	G=0.794, A=0.206	G	G	A	A
		Haplotype Count	458	333	124	83
		Haplotype Frequency	0.4553	0.331	0.1233	0.0825

Fig. 1. The prevalence of possible haplotypes, according to the LDhap Tool for polymorphisms rs7320190, rs7318880, rs12867370, rs4769612, rs4769613, rs74623647, rs7321138, rs76592233, rs9579193, calculated for EUR populations (SEU, TSI, FIN, GBR, IBS). Moreover, the risk haplotype occurs at 8.25 % (C_T_A_C_C_G_C_C_A)

Conclusion: As a result, we have *in silico* determined a possible preeclampsia risk haplotype (C_T_A_C_C_G_C_C_A), with a prevalence of 0.68 % for homozygotes, which is comparable to the development of early-onset preeclampsia rate of 0.38 %. The resulting hypothesis will be further tested on clinical samples obtained from mother-child pairs in a case-control study.

Acknowledgements: The study was performed in the framework of the Program for Basic Research of State Academies of Sciences for 2013-2022.

References

1. Lisonkova S., Joseph K.S. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209(6):544.e1-544.e12.
2. Zhao L., Bracken M.B., DeWan A.T. Genome-Wide association study of pre-eclampsia detects novel maternal single nucleotide polymorphisms and copy-number variants in subsets of the hyperglycemia and adverse pregnancy outcome (HAPO) study cohort. *Ann Hum Gene.* 2013;77(4):277-287.
3. Phupong V. et al. Soluble fms-like tyrosine kinase 1 and placental growth factor ratio for predicting preeclampsia in elderly gravida. *Hypertension Pregnancy.* 2020;39(2):139-144.
4. Buniello A. et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* 2019;47(D1):D1005-D1012.
5. Kent W.J. et al. The human genome browser at UCSC. *Genome Res.* 2002;12(6):996-1006.
6. Moore J.E. et al. Expanded encyclopaedias of DNA elements in the human and mouse genomes. *Nature.* 2020;583(7818):699-710.
7. Malaspina D. et al. Short duration of marriage at conception as an independent risk factor for schizophrenia. *Schizophr Res.* 2019;208:190-195.