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In silico determination of changes in transcription factor binding sites for the preeclampsia risk haplotype in the regulatory region of the FLT1 gene

Scientific supervisors:

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MD Budykina T.S.

Introduction

Preeclampsia (PE) is the most common complication of pregnancy that occurs in 3-8% of pregnant women and is among the top five causes of maternal morbidity and mortality, especially with early onset.

PE is characterized by an increase in SBP >140 mm Hg after the 20th week of pregnancy. Art. and/or DBP >90 mmHg Art. associated with proteinuria.

Swedish researchers have shown that the heritability of preeclampsia is estimated at ~ 55%, and the genetic component of both the mother and the fetus contribute to the development of preeclampsia.

It is known that PE sharply increases the expression of the anti-angiogenic protein FLT1, polymorphisms (rs4769612 and rs4769613) in which are associated with pathology in the analysis of the fetal genome.

The aim of this research was identification of the PE risk haplotype near the FLT1 gene and assessment of changes in transcription factor binding sites (TFBS)

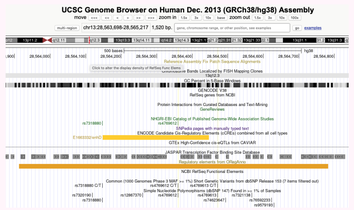
Material and methods

SNPs selection

GWAS Catalog
The NHGRI-EBI Catalog of published genome-wide association studies

PubMed

Search regulatory areas



Revealing enhancer signatures

placenta female embryo 113 days

distal enhancer-like signature

Identification of possible haplotypes

LDhap Tool

Determination TFBS changes

HumanTFDB

Results

SNPs (rs7318880, rs4769612, rs4769613) associated with PE are located in the regulatory region of FLT1 gene, according to the cCREs ENCODE project and oRegAnno. According to the UCSC genome browser (oRegAnno) data, there are 4 regulatory elements overlapped with SNPs: OREG1191996, OREG1658246, OREG1688336, OREG1537828. According to cCRE details at 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 embryonic tissues, which can lead to changes in FLT1 expression

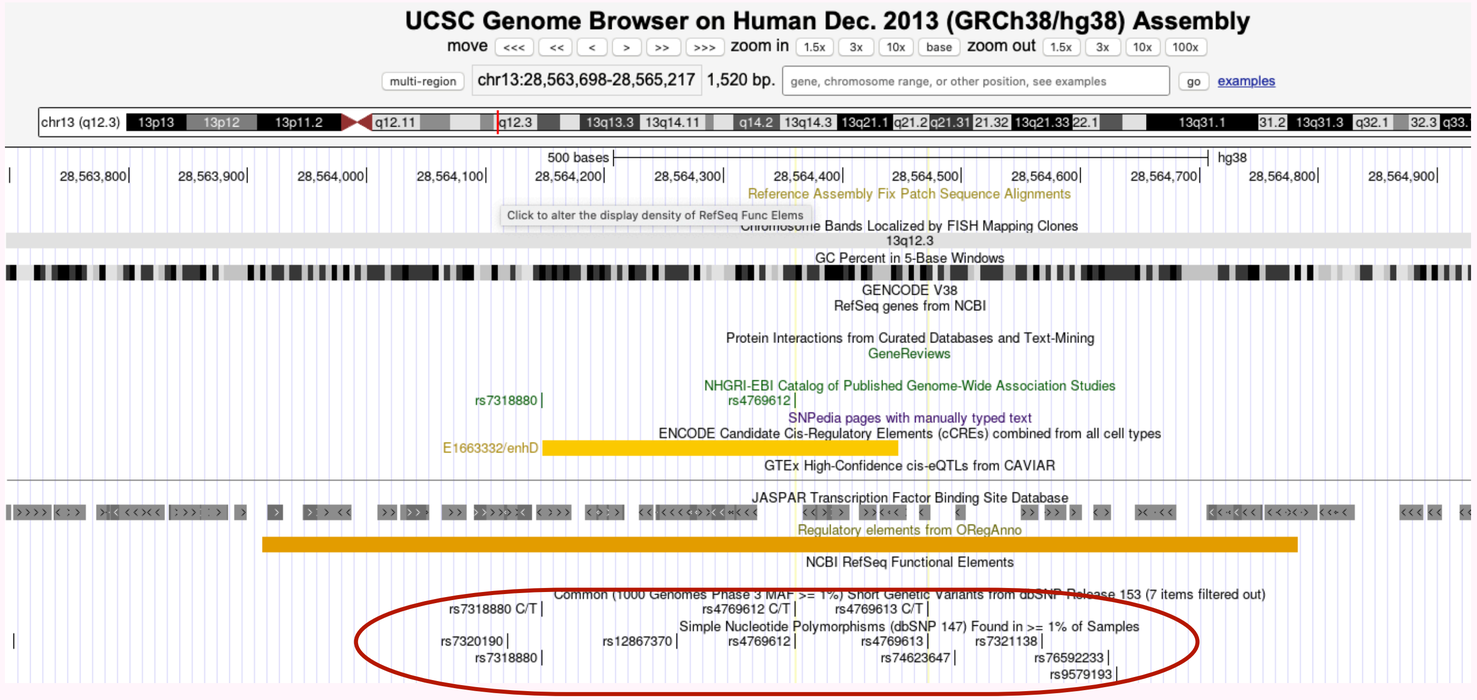


Figure 1. SNPs rs7320190, rs7318880, rs12867370, rs4769612, rs4769613, rs74623647, rs7321138, rs76592233, and rs9579193 overlapped with regulatory elements: OREG1191996, OREG1658246, OREG1688336, OREG1537828 and EH38E1663332, according UCSC genome browser.

Results

As a results we were able to identify a potential preeclampsia risk haplotype (rs7320190-C, rs7318880-T, rs12867370-A, rs4769612-C, rs4769613-C, rs74623647-G, rs7321138-C, rs76592233-C, rs9579193-A), which has a prevalence of 0.68% for homozygotes and a rate of 0.38% for the start of preeclampsia in its early stages (Figure 2).

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

Figure 2. For polymorphisms rs7320190, rs7318880, rs12867370, rs4769612, rs4769613, rs74623647, rs7321138, rs76592233, and rs9579193, the prevalence of potential haplotypes was determined for EUR populations (SEU, TSI, FIN, GBR, IBS). In addition, the risk haplotype (C T A C C G C C A) occurs at 8.25%.

Results

We discovered that the most critical event is the formation of a novel TFBS KAT5, for whose promoter only a DNase signature is seen in the placenta up to day 118 of pregnancy, after which it gains a promoter signature. According to theory, the emergence of a new TFBS can boost FLT1 expression, leading to an imbalance of angiogenic and antiangiogenic factors that is typical of PE (Figure 3).

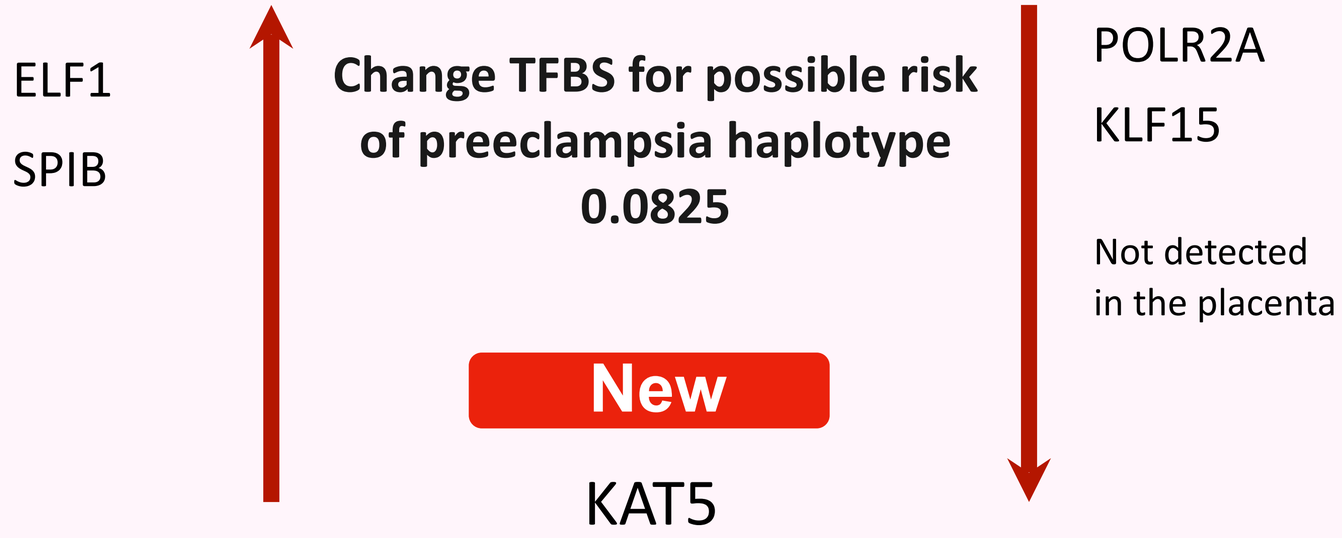


Figure 3. change in 5 TFBS was found in the case of a risk haplotype with a prevalence of 8.025%.

Conclusion

As a results we were able to identify a potential preeclampsia risk haplotype rs7320190-C, rs7318880-T, rs12867370-A, rs4769612-C, rs4769613-C, rs74623647-G, rs7321138-C, rs76592233-C, rs9579193-A), which has a prevalence of 0.68% for homozygotes and a rate of 0.38% for the start of preeclampsia in its early stages.

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Thank you for your attention!

In silico determination of TFBSs changes in possible preeclampsia risk haplotype

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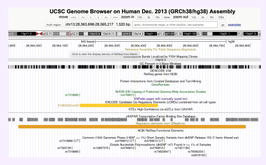

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ELF1

SPIB

Change TFBS for possible risk of preeclampsia haplotype 0.0825

New

KAT5

POLR2A

KLF15

Not detected in the placenta

The KAT5 promoter has only a DNase signature until day 118 of gestation in the placenta, and acquires a promoter signature after day 118.

Figure 2. change in 5 TFBS was found in the case of a risk haplotype with a prevalence of 8.025%.

Author

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