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Evaluation of the regulatory potential of polymorphic variants of complement system genes associated with age-related macular degeneration

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Motivation and Aim: Age-related macular degeneration (AMD) is the most common cause of irreversible and severe visual loss in the elderly population. Genome-wide association studies revealed associations between AMD and variants of alternative complement pathway -associated genes, including the locus ARMS2, whose connection with the complement system has been proven recently. Recently we found that rs10490924 (*ARMS2*), rs800292 (*CFH*) and rs6677604 (*CFH*) polymorphisms are strongly associated with exudative AMD in Russian population and the response to antiangiogenic therapy differed according to the patient's specific rs2285714 (*CFI*) and rs2230199 (*C3*) genotype. This study aimed to assess the functional significance of the rs2285714 (*CFI*), rs10490924 (*ARMS2*), rs2230199 (*C3*), rs800292 (*CFH*), and rs6677604 (*CFH*) polymorphisms by *in silico* analysis.
Methods and Algorithms: To estimate the potential downstream functional effects of the AMD-associated variants, we used the available data of epigenetic effects (HaploReg, RegulomeDB), non-synonymous functional predictions (SNPinfo), expression and alternative splicing quantitative traits (GTEx consortium atlas).
Results: Among the five SNPs studied, 3 loci (rs800292 *CFH*, rs10490924 *ARMS2* and rs2230199 *C3*) cause the replacement of amino acids in the encoded polypeptide. Also, downstream gene variant (rs2285714 *CFI*) and intron variant (rs6677604 *CFH*) were determined. According to the HaploReg database, rs2285714 is located in evolutionarily conserved region, rs2230199—in the promoter histone marks region, and rs6677604 and rs2230199—in the enhancer histone marks region in various tissues. Three SNPs are located in the hypersensitivity region to DNAse-1. All SNPs are located in the DNA regulatory motifs regions. For example, the risk allele of rs2230199 may alteres affinity to transcription factors SP1, VDR, ZBTB7A and E2F3, the rs2285714 influences on affinity to HSF transcription factor. Also the SNPs in strong linkage disequilibrium with studied polymorphisms were determined: from two SNPs for rs2230199 to more than 20 SNPs for rs10490924.
According to the SNPinfo database, polymorphisms rs2230199 C3 and rs2285714 CFI possess the most significant regulatory potential (0.33 and 0.36 respectively). The same SNPs have the highest the RegulomeDB probability scores (0.86, and 0.6). Notably, both SNPs are located in the regions of exonic splicing enhancer (ESE) and exonic splicing silencer (ESS). SNPs that are located at ESE or ESS may disrupt splicing activity and cause alternative splicing. Recently, we have shown a decrease in the level of factor FI, encoded by the CFI gene, in the intraocular fluid, but not in the plasma of patients

carrying the risk rs2285714 genotype. This effect may be partly explained by the effect of rs2285714 on tissue-specific splicing.

According to the GTExportal database, all five AMD risk SNPs are significantly included in the expression quantitative trait loci (eQTL) associated with transcription of 18 target genes. rs10490924 might affect the expression of 3 genes (*HTRA1, PLEKHA1* and *ARMS2*). Also the rs10490924 refers to splicing quantitative trait loci (sQTL) for *PLEKHA1* and *ARMS2* genes. rs2230199 has the cis-eQTL significance potentially affecting the expression of *GPR108* and *CTD-3128G10*.7 genes. rs2285714 has the tissue-specific transcript associations with 4 genes (*CASP6, MCUB, CFI* and *PLA2GA12A*) and is sQTL with strong significance for CFI and PLA2A12A genes. rs6677604 can affect mRNA transcript abundance of 4 genes (*CFHR1, CFHR2, CFHR3, ZBTB41)* in many tissues and organs and refers to sQTL for CFH and CFHR1 genes. rs800292 might affect the expression of 5 genes (*CFH, CFHR1, CFHR3, CFHR4, KCNT2*) and cause sQTL for *CFH, CFHR1, CFHR2* and *F13B* genes.

Conclusion: Using bioinformatic analysis we showed the regulatory potential of SNPs in AMD-associated genes that possessed epigenetic effects and are involved in the control of gene expression and alternative splicing of genes that contribute to AMD pathophysiology. The previously discovered association of SNPs rs2285714 and rs2230199 with response to antiangiogenic therapy in patients with AMD can be explained by the high regulatory potential of these SNPs.

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