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In silico determination of the risk haplotype for developing AMD

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Motivation and Aim: Age-related macular degeneration (AMD) is a multifactorial disease and a prevalent cause of visual impairment in developed countries. Risk factors include environmental components and genetic determinants. 50 % or more of the risk of developing AMD is due to mutations in the region of 2 genes, *CFH* and *ARMS2/HTRA1*. However, the exact mechanisms of pathology development, in particular the role of mutations in the *ARMS2* gene region, remain not fully understood, as well as the functions of the protein [1]. A number of polymorphisms related to ARMS2 associated with the risk of developing AMD were identified in several GWASs at once [2–4]. In this regard, we decided to determine the putative AMD risk haplotype, its prevalence, and compare it with the prevalence of early and late stages of AMD.
Methods and Algorithms: We used the GWAS catalog and PubMed to identify SNPs in *ARMS2* associated with AMD, followed by mapping these SNPs to the human genome in the UCSC genome browser to identify overlapping polymorphisms in genes and regulatory regions [5,6]. We selected SNPs with a MAF of 1 % in the *ARMS2* gene region and identified possible haplotypes in European populations, followed by comparison of the putative risk haplotype with the prevalence of early and late AMD [7].
Results: In the GWAS-catalog, we found 11 polymorphisms in the *ARMS2* region: rs3750846, rs10490924, rs3750847, rs3750848, rs370974631, rs10490923, rs36212732, rs61871744, rs72834437, rs222308 An analysis of the literature made it possible to reduce the number of studied polymorphisms to 5 (rs3750846, rs10490924, rs3750847, rs3750848, rs61871744), since only they are associated with AMD and are located in the region of the gene itself.
When assessing the prevalence of possible haplotypes, a possible AMD risk haplotype was determined, for which the prevalence was 0,1899 or 18,99 % (taking into account the AMD risk alleles, rs10490924-T and rs3750847-T) [8] (Fig. 1).
Conclusion: As a result, we have *in silico* determined a possible AMD risk haplotype: rs61871744-C, rs10490924-T, rs3750848-G, rs3750847-T, rs3750846-C (C_T_G_T_C). Based on the data obtained, it can be assumed that the C_T_G_T_C haplotype in homozygous condition is a risk factor for early AMD, but it remains unclear what triggers the development of the disease. And in the case of heterozygotes, there must be a second risk factor that will increase the detrimental effect of the risk haplotype. The resulting hypothesis will then be tested on clinical samples obtained in a case-control study.

RS Number	Position (GRCh37)	Allele Frequencies	Haplotypes	
rs61871744	chr10:124203787	T=0.808, C=0.192	T	C
rs10490924	chr10:124214448	G=0.805, T=0.195	G	T
rs3750848	chr10:124215315	T=0.805, G=0.195	T	G
rs3750847	chr10:124215421	C=0.805, T=0.195	C	T
rs3750846	chr10:124215565	T=0.805, C=0.195	T	C
		Haplotype Count	808	191
		Haplotype Frequency	0.8032	0.1899

Fig. 1. The prevalence of possible haplotypes, according to the LDhap Tool for polymorphisms rs61871744, rs10490924, rs3750848, rs3750847, rs3750846 of the *ARMS2* gene, in EUR populations (SEU,TSI, FIN, GBR, IBS. Moreover, the risk haplotype occurs with a frequency of 0,1899 (18,99 %). In addition, this risk haplotype will occur in the homozygous state with a frequency of 3,6 % (which is close to the prevalence of early AMD 3,5 % aged 55–59 years) and in the heterozygous state with a frequency of 30,5 % (which is 2 times higher than the prevalence of late AMD at the age of ≥ 85 years) [9]

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