



# **In silico determination of the risk haplotype for developing AMD**

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# Research Objective

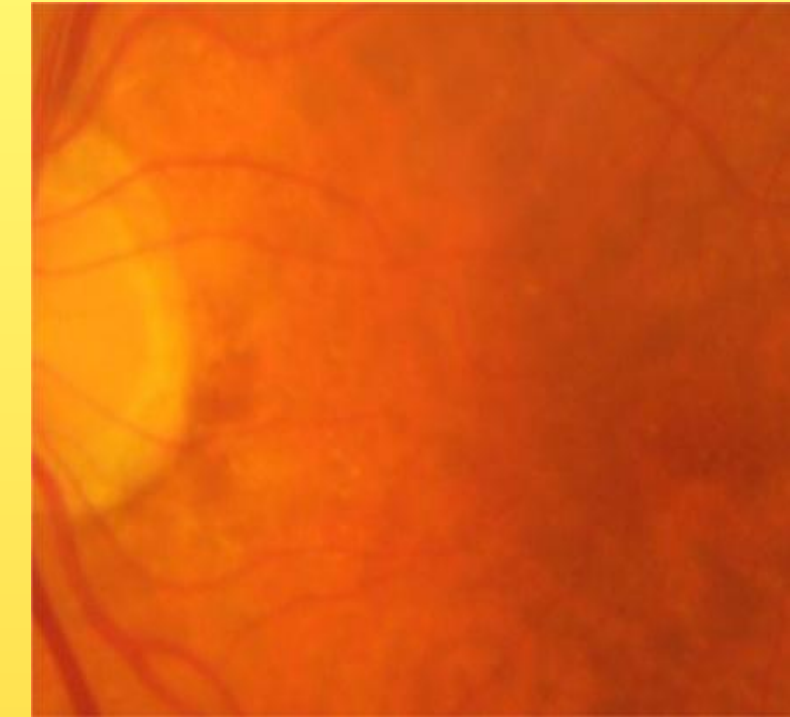
Age-related macular degeneration (AMD) is a multifactorial disease and a prevalent cause of visual impairment in developed countries (Fig. 1-3).

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.

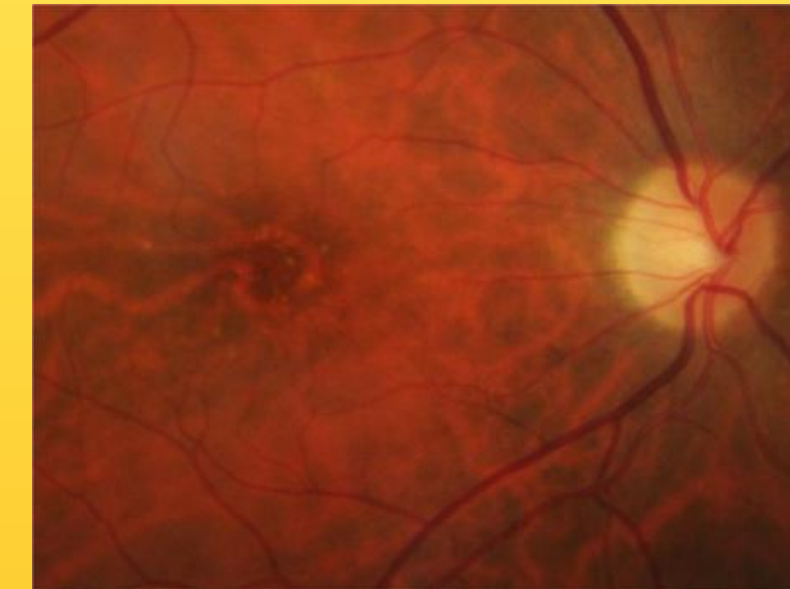
However, the exact mechanisms of pathology development, in particular the role of mutations in the ARMS2 gene region, remain not fully understood, as well as the functions of the protein.

A number of polymorphisms related to ARMS2 associated with the risk of developing AMD were identified in several GWASs at once. 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.

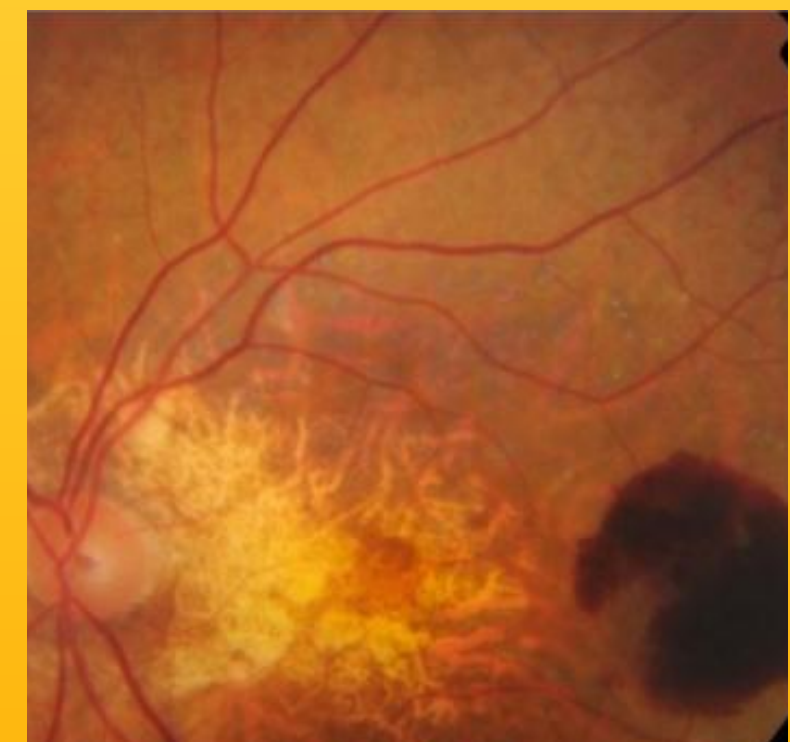
**Figure 1. Fundus photographs of an eye without AMD**



**Figure 2. Fundus photographs of an eye with early AMD**



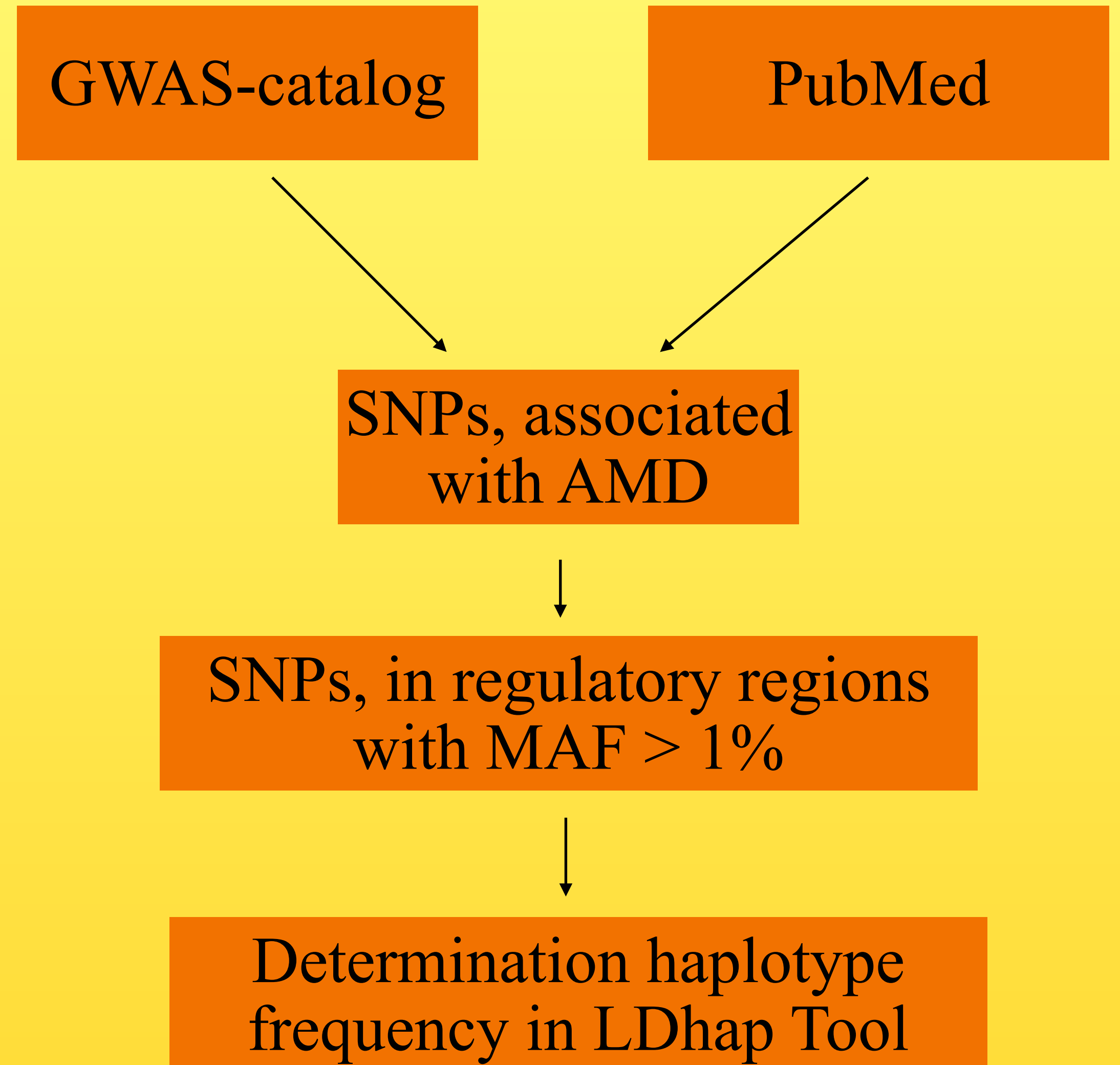
**Figure 3. Fundus photographs of an eye with late AMD**



# Materials and Methods

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.

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.





# 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) (Fig. 4).

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)

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  $\geq 85$  years).

| RS Number                  | Position (GRCh37)               | Allele Frequencies | Haplotypes    |               |
|----------------------------|---------------------------------|--------------------|---------------|---------------|
| rs61871744                 | <a href="#">chr10:124203787</a> | T=0.808, C=0.192   | T             | C             |
| rs10490924                 | <a href="#">chr10:124214448</a> | G=0.805, T=0.195   | G             | T             |
| rs3750848                  | <a href="#">chr10:124215315</a> | T=0.805, G=0.195   | T             | G             |
| rs3750847                  | <a href="#">chr10:124215421</a> | C=0.805, T=0.195   | C             | T             |
| rs3750846                  | <a href="#">chr10:124215565</a> | T=0.805, C=0.195   | T             | C             |
| <b>Haplotype Count</b>     |                                 |                    | <b>808</b>    | <b>191</b>    |
| <b>Haplotype Frequency</b> |                                 |                    | <b>0.8032</b> | <b>0.1899</b> |

**Figure 4.** 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%).

# Conclusion

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.