Complement factor H (CFH)

CFH is a negative regulator of alternative pathway of the complement system which means that in normal conditions, it inhibits the alternative pathway complement system.

It is encoded by a gene localized in 1q23-32 and its dysfunction may lead to excessive inflammation and tissue damage[(10)].

Complement activity is very important for the imune responses against pathogens and dying cells but, over-activation can result in complement-mediated damage to nearby healthy tissue cells.

It is now accepted that CFH gene is an important susceptibility gene, harbouring variants and haplotypes (short DNA sequences containing alleles) associated with increased and reduced risk of AMD.

Six CFH gene variants have been reported in AMD association studies as major genetic factors for developing AMD in Caucasians[(11-15)]: rs1061170, (CFH Y402H); rs3753394; rs800292; rs1061147; rs380390; rs1329428.

However in the Chinese and Japanese populations only three of these CFH SNPs (rs1329498, rs800292 and rs3753394) were associated with risk of AMD[(16,17)].

So it is possible that CFH could play a central role in AMD pathogenesis and that multiple SNPs that alter CFH function might contribute to the development of AMD.

Their importance varies among the race of the population.

In the variant (polymorphism) CFH Y402H of the CFH gene, there is a substitution on the nucleotide in exon 9 (1277) where thymine (T) is changed for cytosine (C) (rs1061170) which is the allele risk.

This change leads to the substitution of the aminoacid in the position 402 in the protein, from tyrosine (Y) to histidine (H).

Homozygote CC or heterozygote TC can account for 50% of AMD cases.

The risk attributable for a disease is the rate of disease among individuals with a given characteristic minus the rate of the disease among indivuals without that characteristic.

The population attributable risk (PAR) in individuals with this polymorphism for developing AMD is 43% to 50%[(11,12,18)].

When compared with those with no risk allele TT, one copy of the Tyr402His polimorphysm (heterozygous for the risk allele TC), increases the risk of AMD by a factor

of 2.2 to 4.6 (these individuals are at least twice and half more likely to develop AMD) and two copies of the risk allele (homozygous for the risk allele CC) increases the risk by a factor of 3.3 to 7.4 in Whites[(19)].

In addition to the common risk haplotype carrying the C allele of CFH Y402H, haplotype analysis of CFH has revealed two common protective haplotypes: homozygous deletions CFHR1 or CFHR3.

The gene cluster of CFH includes other “CFH-related genes“: CFHR1, CFHR2, CFHR3, CFHR4 and CFHR5. This means that the CFH gene resides within the region of complement activation (RCA), which includes also five “CFH–related” genes.

While the function of the CFH related genes is largely unknown, the high degree of sequence similarity between these genes and the suggestion that they arose out of duplication events with CFH, suggest an overlapping function of the CFH-related genes in immune system function and /or regulation.

There is a common and widespread (commonly found in many different populations in the world) deletion within the RCA locus that encompasses the CFHR1 and CFHR3 genes.

However the frequency of homozygous CFHR1 or CFHR3 deletion shows considerable variation between ethnic groups and occurs in 17.3% of African populations, 15.9% of African-American, 6.8% of Hispanic, 4.7% of Caucasian and 2.2% of Chinese cohorts[(20)].

This is in agreement with AMD less frequency among African-Americans compared with Caucasians and Chinese populations.

CFH1 and CFH3 protein may compete with CFH for C3 binding and therefore interfere with normal regulation of the complement system.

Those individuals, who are homozygous for the CFHR1/CFHR3 deletions and, therefore do not express the respective proteins, are highly protected from developing AMD[(20)].

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