HTRA1 (high temperature required factor A-1) SNP and AMD

HTRA1 gene is located on chromosome 10q26.3, extremely close to the locus of the ARMS2 gene (10q26.13) and because of its role in extracellular matrix homeostasis (its extracellular protease activity may favour neovascularization) and in cellular growth or survival (it is an inhibitor of TGF-ß family member[(36)] and it could play a critical role in controlling TGF-ß dependent neuronal survival[(37)] it seems a possible functional candidate gene.

Four significant SNPs have been reported in the promoter and the first exon of HTRA1: G625A (rs11200638); T487C (rs2672598); C102T, A34A (rs1049331); G108T, G36G (rs2293870). However the most well documented, statistically significant AMD associated SNP is rs11200638 (G625A) in the promotor region.

Caucasians, Chinese and Japanese heterozygous for the risk allele (G/A) have a high OR of 1.60-2.61 and Caucasians, Chinese and Japanese homozygous for the risk allele (A/A), 6.56-10.0[(34,35,38-40)].

According to Tam et al.[(40)], there is an increase in population attributable risk (about 5.5 fold increase) by the joint effect of smoking and HTRA1 allele.

This means that smokers homozygous for the risk allele had a substantially higher risk of developing wet AMD than non smokers with the risk allele.

However Deangelis et al[(41)], in 2008 reported no interaction between this SNP and smoking.

In what concerns the studies which relate HRTA1 promoter polymorphisms to risk factors for developing AMD, three problems arise according to Allikmets and Dean[(28)].

The variant encoding the A69S (rs10490924) in ARMS2 and the rs11200638 variant in HTRA1 are almost in complete LD, so it is impossible to assign causality on the basis of allele frequency alone.

10q26 locus doesn’t harbour a wet AMD gene as the authors claimed but a late AMD gene as showned by Weber and colleagues in 2005[(30)].

All subsequent studies have failed to replicate the functional data[(32,42)].

This basically means that, as there is strong linkage disequilibrium (LD) across ARMS2-HTRA1 region, genetic association studies alone are insufficient to distinguish between the two candidates.

It is also necessary not only the characterization of the extent of the variants associated to the disease but also the analysis of their possible functional relevance in the disease process[(42)]. Doing this, Fritsche et al.[(42)] claimed that the functional variant in this locus is the deletion-insertion polymorphism variant 372-815delins54 in the ARMS2 gene.

The deletion removes the polyadenilation signal sequence at position 395-400 exclusively used for the addition of a poly A tract 19 bp downstream.

The insertion introduces a 64 bp AU-rich element, known for its properties to control mRNA decay in many transcripts that encode a wide variety of proteins[(43,45)].

They demonstrated that it is a major risk factor for AMD: individuals carrying a single copy of the risk allele deletion-insertion in ARMS2 gene have a 2.8–fold increased risk compared with an 8.1–fold increased risk in homozigous individuals.

Their work, also revealed that in homozygous for the deletion-insertion variant, expression of ARMS2 is absent.

They localized the ARMS2 protein within the photoreceptor layer namely, to the mitochondria–enriched ellipsoid region of the inner segments and in accordance; they proposed a functional role of ARMS2 in mitochondrial homeostasis.

According to Fritsche et al., this suggests, that this polimorphysm is the sought-after functional variant with relevance in AMD etiology in 10q26 locus.

However, as Fritsche et al. recognize, it is ultimately required formal exclusion of functional consequences for the remaining polymorphisms on the risk haplotype namely, A69S in ARMS2 gene and HTRA1 promoter variant.

The A69S and the InDel are in 100% LD and on the same haplotype and so the effects are not independent to each other[46].

The work of Fritsche and colleagues does not eliminate all other possibilities[28], nobody disputes the role of complement genes in AMD in spite of the functional consequences of the disease associated variants being not known for CFH, CFB/C2 and/or C3.

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