Genetic Mutation Near MMP9 Is Associated With Choroidal Neovascularization In AMD

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Purpose:
There is conflicting evidence whether mutation in MMP9 is associated with exudative AMD. In 2015 the International AMD Genetics Consortium (IAMDGC) found an association of rs142450006 (imputed to be in or near MMP9) specific for exudative AMD but this association was not found with several other SNPs in MMP9 in a Chinese Han population. The purpose of this study was to independently validate whether genetic mutation near MMP9 is associated with exudative AMD.

Methods:
1712 subjects with AMD (672 non-exudative, 1040 exudative) seen at UIowa had blood drawn for this IRB-approved study. To validate the association to those with exudative AMD (compared to non-exudative), re-analysis of the IAMDGC data revealed several SNPs in strong linkage disequilibrium to rs142450006. We developed a real-time PCR assay to efficiently and precisely genotype these 2 SNPs. Firth regression in Plink2 was used to calculate the p-value between those with wet vs dry AMD in our cohort. In addition, we developed a PCR-based assay to amplify the DNA fragment containing the STRP from each patient’s DNA sample. We determined the number of tandem repeats at the MMP9 locus in each patient’s DNA sample using polyacrylamide gel electrophoresis and silver staining.

Results:
We identified three SNPs (rs4810482, rs17576, and rs17577) that encompass the non-redundant set of associated genotypes in the MMP9 locus and genotyped them in our cohort of Iowa AMD patients. All three SNPs are associated with development of exudative AMD (rs4810482, OR 0.83, 95% CI 0.81-0.95, p=0.010; rs17576, OR 0.86, 95% CI 0.75-0.99, p=0.046; and rs17577, OR 0.81, 95% CI 0.67-0.99, p=0.041), and are in linkage disequilibrium (D' > 0.97; R2 from 0.24-0.90) with rs142450006. We also genotyped our cohort of AMD patients from Iowa at rs142450006, the MMP9 polymorphism that was first associated with exudative AMD. We detected a 4bp STRP, (TTTC)n, at the rs142450006 locus that is highly polymorphic and significantly associated with exudative AMD (OR 0.78, 95% CI 0.64-0.95; p=0.016).

Conclusions:
This study is the first to independently confirm and expand an association between the MMP9 locus and exudative AMD, demonstrating a critical role for extracellular matrix abnormalities in choroidal neovascularization development.