Genetic Polymorphisms Associated with Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness in older individuals. AMD is often classified into two clinical categories: non-neovascular AMD (non-neovascular/dry AMD) and neovascular AMD (exudative/wet AMD).

Several studies provide evidence that genetic polymorphisms have been implicated to influence the development and progression of AMD. Moreover, a report regarding a meta-analysis of specific gene polymorphism with AMD becomes popular in the last 5 years. Using online search databases with keywords including “polymorphism”, “age-related macular degeneration”, and “meta-analysis”, I summarized the findings from the latest published meta-analysis1-18 as shown in Figure 1. Moreover, in this short communication additional meta-analysis of TNFα, CCL-2, MMP3, MMP7, MMP9, and TIMP2 were also included19-29.

It was shown that a protective effect of TNFα -863A carrier (A vs C, OR = 0.67, P = 0.007; AA+CA vs CC, OR = 0.58, P = 0.001; CA vs AA+CC, OR = 0.55, P = 0.001; and CA vs AA, OR = 0.54, P = 0.001, Figure 2A-D) and TIMP2 -418C carrier (GC vs CC+GG, OR = 0.54, P = 0.018; and GC vs GG, OR = 0.56, P = 0.046, Figure 2E,F) to the development of AMD. No association was observed in polymorphism of TNFα -1031 T/C, TNFα -308 G/A, TNFα -238 G/A, CCL-2 -2158 A/G, MMP3 -1771 5A/6A, MMP7 -181 A/G, MMP9 -1562 C/T with

Figure 1. Summary of genetic polymorphisms associated with AMD.
AMD (data not shown). Analysis of IL-8/CXCL8 +781C/T polymorphism indicated that the TT genotype is associated with the risk of AMD (in submission). Together with previously published articles, twenty-one genes were analyzed for gene network and gene ontology analysis. Based on gene ontology (GO) analysis, fifty-five clusters were identified, among them regulation of response to stress/external stimuli and immune/inflammatory responses were strongly correlated with AMD (Figure 3). In summary, this report emphasizes that neuroinflammation plays a pivotal role in the development of AMD.

Figure 2. Association of TNFα -863 C/A and TIMP2 -418 G/C polymorphisms with AMD. (A) Allelic model in TNFα -863 C/A; (B) Dominant model in TNFα -863 C/A; (C) Overdominant model in TNFα -863 C/A; (D). Heterozygous model in TNFα -863 C/A; (E) Overdominant model in TIMP2 -418 G/C; (F). Heterozygous model in TIMP2 -418 G/C.
Figure 3. **Gene network analysis.** The size of the node represents the number of connections in this network. This result implies that immune and inflammatory responses as a central mechanism associated with AMD.

**Abbreviations**
- **ABCA1**: ATP binding cassette subfamily A member 1
- **ABCG1**: ATP binding cassette subfamily G member 1
- **ARMS2**: age-related maculopathy susceptibility 2
- **AMD**: age-related macular degeneration
- **C2/3**: complement C2/3
- **CCL2**: C-C motif chemokine ligand 2
- **CETP**: cholesteryl ester transfer protein
- **CFB**: complement factor B
- **CFH**: complement factor H
- **CFI**: complement factor I
CX3CR1: C-X3-C motif chemokine receptor 1
CXCL8/IL-8: C-X-C motif chemokine ligand 8/Interleukin-8
HTRA1: HtrA serine peptidase 1
LIPC: lipase C, hepatic type
LOXL1: lysyl oxidase like 1
LPL: lipoprotein lipase
PEDF: Pigment epithelium-derived factor
MMP2/3/7/9: matrix metallopeptidase 2/3/7/9
SERPING1: serpin family G member 1
SKIV2L: Ski2 like RNA helicase
TIMP2: TIMP metallopeptidase inhibitor 2
TLR1/3/4/6/7/9/10: toll like receptor 1/3/4/6/7/9/10
TNF: tumor necrosis factor
VEGFA: vascular endothelial growth factor A

REFERENCES


