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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 (nonexudative/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-analysis[1-18] as shown in **Figure 1**. Moreover, in this short communication additional meta-analysis of TNFα, CCL-2, MMP3, MMP7, MMP9, and TIMP2 were also included[19-29].

Dry AMD **Wet AMD**

AMD
ABCA1, CFB, CFH, CFI, C2, C3, CX3CR1, LPL, LIPC, SKIV2L, TIMP2, TNFα,TLR3, TLR4, TLR7

ABCG1 ARMS2, CETP HTRA1 IL-8 VEGFA

Not associated with AMD
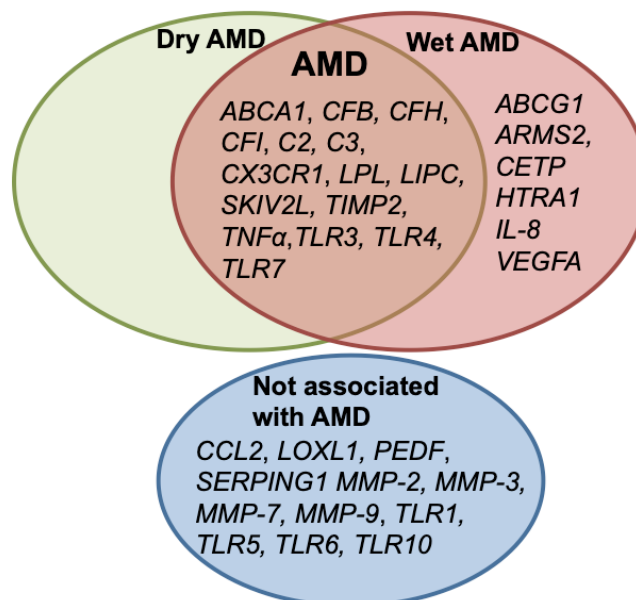*CCL2, LOXL1, PEDF, SERPING1 MMP-2, MMP-3, MMP-7, MMP-9, TLR1, TLR5, TLR6, TLR10*

Figure 1. **Summary of genetic polymorphisms associated with AMD**.

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 CC, 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 TNFa -1031 T/C, TNFa -308 G/A, TNFa -238 G/A, CCL-2 -2158 A/G, MMP3 -1771 5A/6A, MMP7 -181 A/G, MMP9 -1562 C/T with

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.
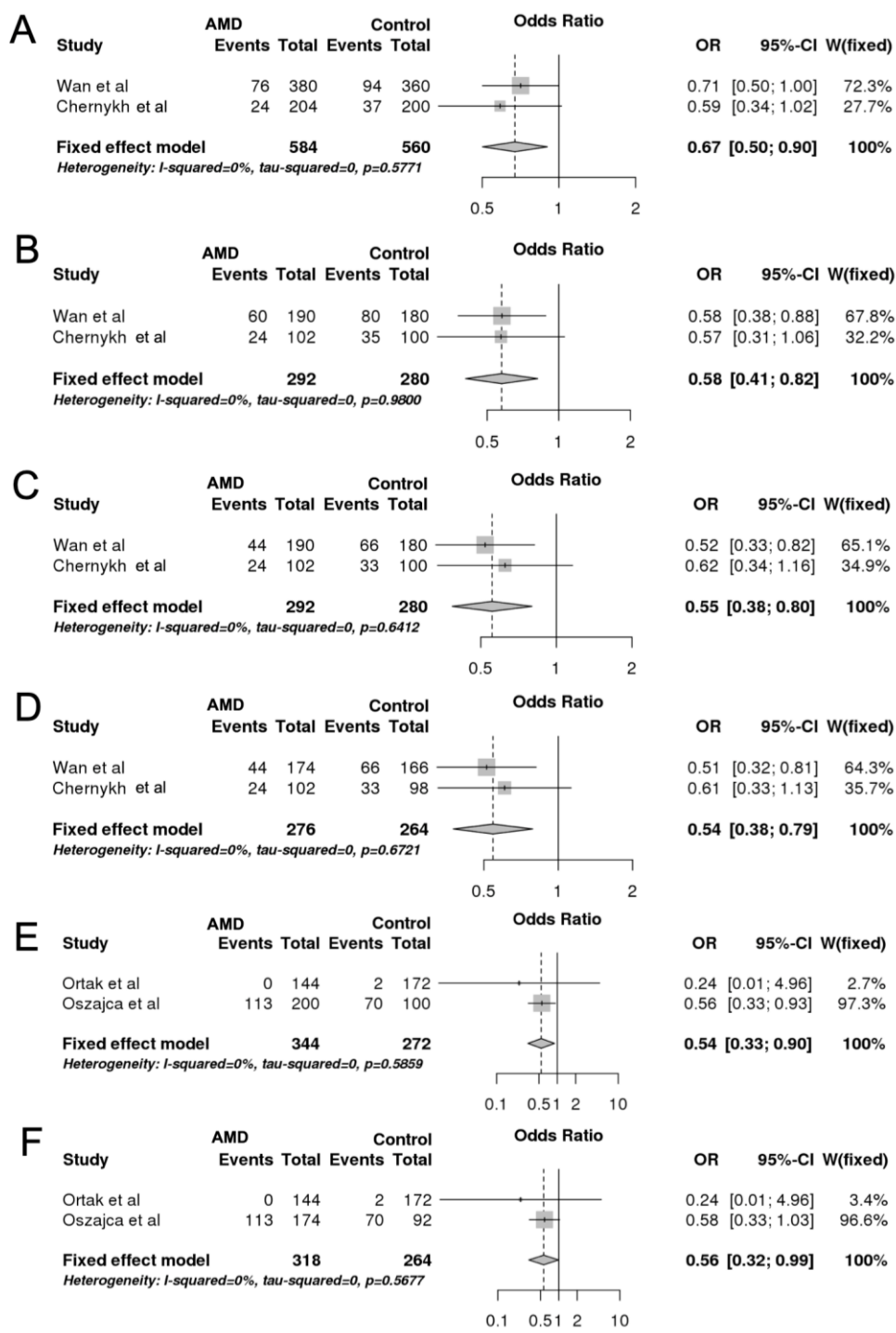

Figure 2. Association of TNFα -863 C/A and TIMP2 -418 G/C polymorphisms with AMD. (A) Allelic model in TNFα -863 C/A; (B) Dominant model in TNFα -863 C/A; (C) Overdominant model in TNFα -863 C/A; (D). Heterozygous model in TNFα -863 C/A; (E) Overdominant model in TIMP2 -418 G/C; (F). Heterozygous model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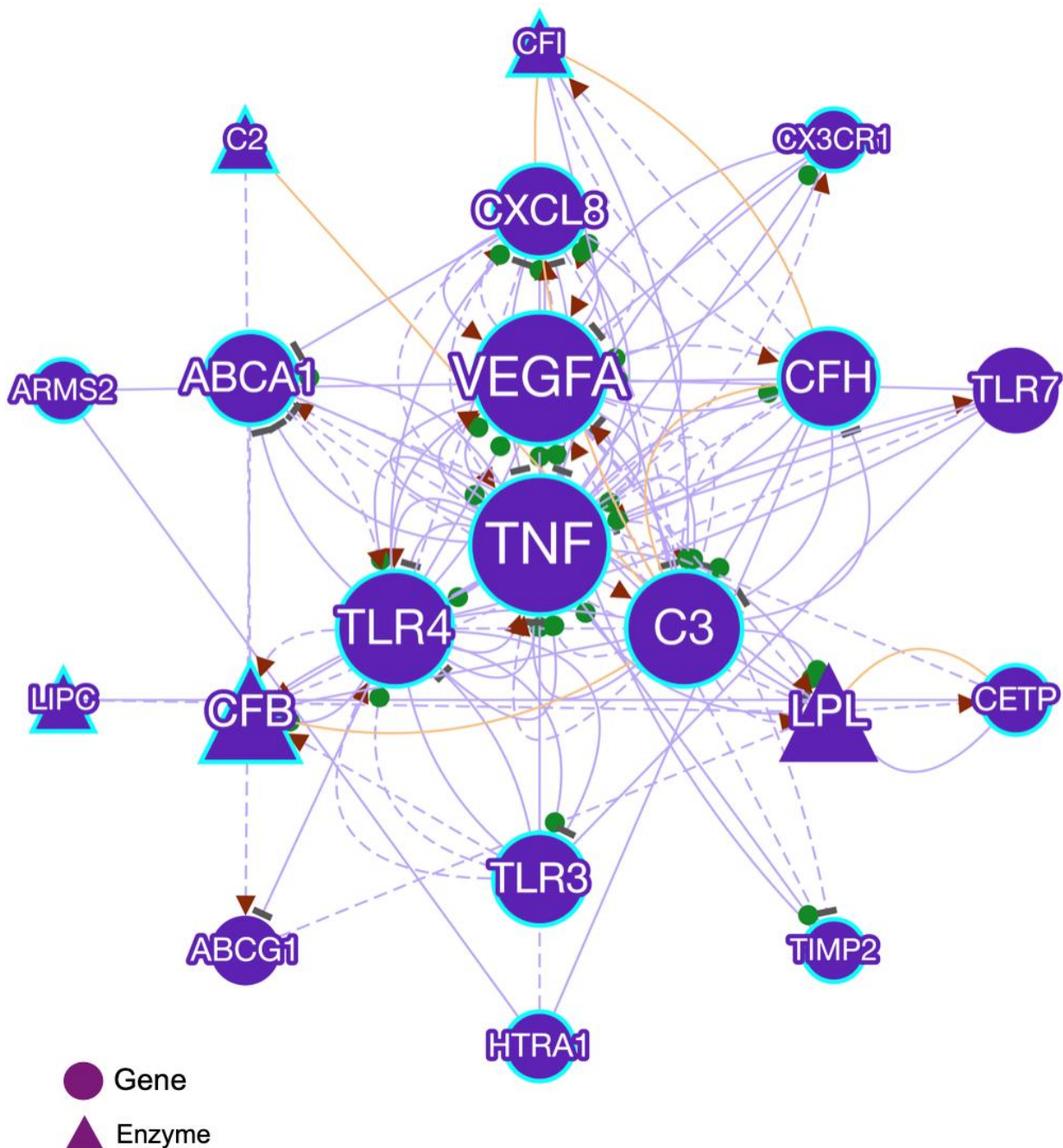
Figure 3. **Gene network analysis**. The size of the node represents the number of connections in this network. This result implies that immune and inflammatory responses as a central mechanism associated with AMD.

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

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