

Age-Related Macular Degeneration, Drug Targets, and DNA Sequence Variation in Genes encoding Lipid-Associated Signaling Pathway Constituents

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Background. Age-related macular degeneration (AMD) is the primary cause of vision loss in elderly people of European ancestry. Biologic plausibility of LCPUFA-retinal disease relationships is supported by: 1) intake-dependent and -modifiable accretion of LCPUFAs to the retina; 2) preferential concentration and localization of LCPUFAs in healthy retinal cells of types manifesting retinal pathology in AMD; and 3) biophysical and biochemical capacity of LCPUFAs to affect processes implicated in AMD pathogenesis. Cholesterol metabolites contribute to chronic inflammatory processes implicated in AMD pathogenesis and progression.

Methods. We analyzed findings from large-scale genotyping projects on the molecular genetics of AMD (17,181 people with AMD + 60,074 elderly AMD-free controls) with data from the 1000 Genomes Project, ENCODE, LIPIDMAPS, and pharmacogenomics databases to identify AMD-associated DNA sequence variants resident in genes encoding proteins involved in lipid synthesis, capture, metabolism, and transport. Public-access gene sets were used with pathway analysis software to make inferences in the context of biochemical systems. P-value for association: $5.0E-3$.

Results. Our findings confirm presence of neovascular AMD-associated DNA sequence variants identified in humans using systems-based analyses on PPAR-RXR and Akt/PI3K signaling constituents. PPAR-RXR pathway genes carrying AMD-associated SNPs included PPARGC1A (rs13106578), NCOA2 (rs17676138), PPARD (rs6902123), and ESRRG (rs1339357). Akt/PI3K pathway genes carrying AMD-associated SNPs included PLCG2 (rs11640294), PIGK (rs1048575), PIK3R1 (rs173702), ITPR2 (rs11048506), INPP5A (rs913196), PIP5K1B (rs3812537). Our findings also provide the first human evidence supporting the role of LCPUFA-related influence of ALOX5 (rs7077173) on pathologic retinal angiogenesis and elucidate a drugable AMD-associated SNP in CETP (rs5882) with the capacity to change protein structure in an evolutionarily conserved domain responsible for binding acyl chains of lipopolysaccharides and neutralizing these molecules on outer membranes of Gram-negative bacteria.

Conclusions. Gene products of PPAR-RXR and Akt/PI3K signaling system constituents, ALOX5, and CETP are: 1) influenced by lipid intake; and, 2) associated with AMD.