Human Plasma Metabolites Associated with Established Age-related Macular Degeneration (AMD) Risk Genes

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Purpose:
Thirty-four loci with more than 7,000 single nucleotide polymorphisms (SNPs) have been linked with age-related macular degeneration (AMD), but how they may contribute to disease development remains elusive. Assessing genetic-metabolite associations (i.e. metabolite quantitative trait loci, mQTL) can provide unique insights into causal mechanisms of AMD. This study aimed to analyze associations between established AMD risk SNPs and plasma metabolites (mQTL) in a cohort of AMD patients and controls.

Methods:
Prospective, cross-sectional, multicenter study (Boston, United States and Coimbra, Portugal). We included subjects with AMD and controls without any vitreoretinal disease (> 50 years old); AMD grading was performed according to the AREDS classification scheme. Fasting blood samples were collected and evaluated with mass spectrometry for metabolomic profiling and Illumina Omni express for SNPs profiling. Analyses of mQTL of endogenous metabolites were conducted using linear regression models adjusted for age, sex, smoking, 10 metabolites principal components (PCs) and 10 SNP PCs. These models were first performed for each cohort and then combined by meta-analysis.

Results:
We included 388 patients with AMD and 98 controls; after quality control, data on 544 plasma metabolites was considered. Meta-analysis identified 66 significant mQTL (p<10^{-5}), correspondent to 9 metabolites and 7 genes. The most significant associations (false discovery rate < 0.05) were seen between SNPs in the LIPC gene and phosphatidylethanolamine metabolites, and SNPs in the ASPM gene and the branched-chain amino acids leucine, isoleucine and valine. Pathway analysis integrating all the metabolites and genes of interest mapped to the glycerophospholipid, as well as to the alanine, aspartate and glutamate metabolite pathways. No common mQTL were found between AMD cases and controls.

Conclusions:
Distinct AMD risk loci are associated with plasma glycerophospholipids and essential branched-chain amino acids. This increases our understanding on the biological relevance of AMD-risk SNPs, offers new potential therapeutic targets and contributes to developing precision medicine for this blinding disease.