

Assessing the Association of Mitochondrial Genetic Variation With Primary Open-Angle Glaucoma Using Gene-Set Analyses

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PURPOSE: Recent studies indicate that mitochondrial proteins may contribute to the pathogenesis of primary open-angle glaucoma (POAG) . In this study, we examined the association between POAG and common variations in gene-encoding mitochondrial proteins.

METHODS: We examined genetic data from 3430 POAG cases and 3108 controls derived from the combination of the GLAUGEN and NEIGHBOR studies. We constructed biological-system coherent mitochondrial nuclear-encoded protein gene-sets by intersecting the MitoCarta database with the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. We examined the mitochondrial gene-sets for association with POAG and with normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) subsets using Pathway Analysis by Randomization Incorporating Structure.

RESULTS: We identified 22 KEGG pathways with significant mitochondrial protein-encoding gene enrichment, belonging to six general biological classes. Among the pathway classes, mitochondrial lipid metabolism was associated with POAG overall ($P = 0.013$) and with NTG ($P = 0.0006$) , and mitochondrial carbohydrate metabolism was associated with NTG ($P = 0.030$) . Examining the individual KEGG pathway mitochondrial gene-sets, fatty acid elongation and synthesis and degradation of ketone bodies, both lipid metabolism pathways, were significantly associated with POAG ($P = 0.005$ and $P = 0.002$, respectively) and NTG ($P = 0.0004$ and $P = 0.0002$, respectively).

CONCLUSIONS: We present an effective approach for assessing the contributions of mitochondrial genetic variation to open-angle glaucoma. Our findings support a role for mitochondria in POAG pathogenesis and specifically point to lipid and carbohydrate metabolism pathways as being important.

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