Genetic and cell type-specific predictors of anterior pathway pathology in multiple sclerosis

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Introduction:

Retinal thinning is common in multiple sclerosis (MS) with pathological studies noting inner retinal atrophy in nearly all people with MS (PwMS). However, genetic contributors to retinal neurodegeneration and their underlying cellular basis are not well understood. We hypothesize genetic factors linked to specific cell types could play a critical role.

Objectives/Aims:

To assess whether genetic variants contribute to retinal and optic nerve pathology in PwMS and quantify function effects of identified variants using single nucleus RNA-seq (snRNA-seq) data from human optic nerve (ON) and retinal tissues as well as a detailed histological characterization of MS ONs.

Methods:

We performed a genome-wide association study of optical coherence tomography (OCT)-derived retinal layer thickness. Individual retinal layers included the ganglion cell/inner plexiform layer, inner nuclear layer, outer nuclear layer, and outer plexiform layer. We performed a multi-trait analysis (via heritability informed power optimization; HIPO) after regressing each OCT phenotype against genetic variants using mixed effects models adjusting for age, sex, and genetic ancestry. We tested for enrichment of variants in specific cell types in ON (n=11) and in retina (n=6) tissues and for colocalization of using results from histological assessment of inflammation, demyelination and axon pathology in ON tissues (n=37) as characterized using immunohistochemistry and multiplex RNA in situ hybridization.

Results:

We included 1561 PwMS (mean age: 42.4y±12.1y, 25% male) in cross-sectional analyses; a subset (n=1163) was included in longitudinal analyses (average follow-up=5.4y±3.6y). Expression of genes associated with longitudinal OCT phenotypes were enriched in subsets of reactive astrocytes, vascular cells, and B cells in ON tissue as well as vascular cells within the retina. We identified genetic variants likely to be contributing to both retinal and ON pathology in PwMS. For example, rs2974846 (in MAPK8IP3) was associated with longitudinal retinal atrophy (HIPO p= 3x10-5) and IL-33 deposition in ON tissues in PwMS (p=3x10-3; colocalization probability P4=96%).

Conclusion:

Results implicate genetic variation in influencing retinal outcomes in PwMS, possibly through involvement of specific cell types associated with MS lesion pathology along the anterior visual pathway. This study suggests novel insights related to the role of astrocytes and vascular cells underlying the genetic contributions to retinal neurodegeneration in PwMS.

Disclosures:

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