

AB024. Phenotypic dissection of myocilin (MYOC)-induced glaucoma reveals that the modifier of glaucoma 1 (MOG1) locus encodes a gene which prevents ocular hypertension

Vincent Raymond^{1,2}, Pascal Belleau^{1,3},
Rose Arseneault¹, Jean-Louis Anctil⁴,
Gilles Côté⁴, Marcel Amyot⁵, Patrick Laplante¹,
Laurent Lamallice¹, Stéphane Dubois¹,
Fahed Elian⁶, Michael A. Walter⁶;
Québec Glaucoma Network⁷

¹CHUL at CHU de Québec - Université Laval, Québec City, QC, Canada; ²Molecular Medicine, Université Laval, Québec City, QC, Canada; ³Cold Spring Harbor Laboratory, NY, USA; ⁴Department of Ophthalmology, Université Laval, Québec City, QC, Canada; ⁵Department of Ophthalmology, Université de Montréal, Montréal, QC, Canada; ⁶Medical Genetics, University of Alberta, Edmonton, AB, Canada; ⁷Ophthalmologists from Province of Québec, Québec, QC, Canada

Correspondence to: Vincent Raymond, MD, PhD. Centre de recherche du CHU de Québec, 2705 boulevard Laurier, Sainte-Foy, QC G1V 4G2, Canada. Email: vincent.raymond@crchul.ulaval.ca.

Background: Pathogenic mechanisms leading to open-angle glaucoma (OAG) are genetically complex. They involve neuroinflammation, elevation of intra-ocular pressures (IOP) and optic nerve hypersensitivity to cellular stresses. We mapped a locus at chromosome 20q13 that contains a modifier gene for glaucoma severity. While searching for its identity, we named this gene modifier of glaucoma 1 (MOG1). The goal of this study is to characterize the mechanism by which MOG1 delays the age of onset of glaucoma when OAG is caused by mutations in the MYOC gene. We hypothesized that MOG1 mechanism may be linked to a specific endophenotype and thus dissected ocular phenotypes present in a large French-Canadian MYOC glaucoma pedigree.

Methods: We studied 375 members of the CA pedigree in which autosomal dominant OAG is caused by the MYOCK423E mutation. In this family, wild-type MOG1 (normal form) delays the age-at-onset (AAO) of glaucoma.

Ocular records of MYOCK423E carriers were reviewed to extract the values of four quantitative traits portraying four endophenotypes: (I) age of maximal intra-ocular pressure (IOP max), (II) IOP progression, (III) rate of optic nerve degeneration and, (IV) AAO defined as the age at which IOP ≥ 22 mmHg or age at which optic disk degeneration was first detected. Endophenotypes were tested for their heritability. A three-stage algorithm was designed to detect double mutants who carry the MYOCK423E mutation and putative MOG1 mutations. Quantitative traits values of double-mutants were then compared.

Results: We found 156 individuals who were heterozygotes (HTZ) for MYOCK423E. One hundred and twenty of these were classified affected as they were OAG or had treatment for ocular hypertension (OHT) with IOP ≥ 22 mmHg. The other 36 HTZ were asymptomatic. Only two endophenotypes, AAO and IOP max, showed significant heritability. OHT was the 1st symptom detected in 99% of the affecteds; it always preceded optic nerve damage. AAO of the affecteds ranged from 7 to 63 years old while rates of optic nerve degeneration did not significantly change between them. When comparing the AAOs of the double mutants (those who are MYOCK423E HTZ + MOG1 mutant) with the median AAOs of their respective neighbors (≤ 1 st cousins) who are MYOCK423E HTZ and MOG1 wild-type (called single mutant as they carry a normal MOG1), we observed that the ages-at-onset of OHT in the double mutants were on average 8 years younger than the median of AAOs in their respective single mutant neighbors.

Conclusions: These findings demonstrate that age-at-onset (AAO) is a reliable endophenotype to use for discovering the effect of putative MOG1 mutations in MYOCK423E carriers. They also show that the wild-type form of MOG1 delays the AAO of myocilin-induced glaucoma by about 8 years. Our study further suggests that wild-type MOG1 acts on intra-ocular pressures (IOP) by counteracting ocular hypertension (OHT) caused by mutant myocilin proteins before the beginning of optic nerve degeneration.

Keywords: Blindness; glaucoma; genetics; modifier; myocilin

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