

AB090. MOG1, the genetic modifier at 20q13, delays the age-at-onset of glaucoma by 8 to 10 years

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Background: Primary open-angle glaucoma (POAG) is a genetically complex disorder caused primarily by gene-gene interactions. To identify these interactions, we studied the CA family, a large French-Canadian pedigree in which the myocilin K423E mutation (MYOCK423E) causes autosomal dominant glaucoma with diagnoses ranging from juvenile-onset OAG (JOAG) to late adult-onset POAG in the heterozygotes (HTZ). To explain this extreme variability, we hypothesized that a second gene, called a modifier, was interacting with MYOC, the primary disease gene. Our goals were (I) to map the modifier on the human genome and; (II) to characterize the symptoms affected genetically by the modifier. These symptoms are called endophenotypes.

Methods: Three hundred seventy-five CA members were studied using four quantitative endophenotypes: age of maximal intra-ocular pressures (IOPmax), IOPs progression, progression of cup to disk ratios and age-at-onset (AAO) defined as age at which ocular hypertension (OHT) was first detected with IOP \geq 22 mmHg. Genome-wide linkage analysis was performed by genotyping 408 genetic markers in 184 CA members. An unbiased pedigree-based algorithm was designed to identify the individuals who were double-mutants, i.e., these individuals carried one MYOCK423E mutation (i.e., they were HTZ, affected or not) and they also carry simultaneously a DNA mutation within the modifier.

Results: Out of the 375 CA family members investigated, 156 were HTZ for the MYOCK423E mutation. 120 HTZ were affected with OAG or OHT with treatment while the remaining 36 HTZ were asymptomatic. AAO ranged from 7 to 63 years old; 4 individuals over 50 years old were still asymptomatic. OHT preceded optic nerve damage in >98% of the HTZ carriers, confirming that AAO reflected the true severity of the disorder. The modifier showed strong inherited effects on 2 of the 4 endophenotypes: AAO and IOPmax. We next mapped with very high confidence the modifier locus for AAO at chromosome 20q13. Saturation genotyping with additional markers refined the locus to a 9 to 10 centimorgan interval, or about 10 million DNA nucleotides, between D20S857 and D20S832. The locus was named modifier of glaucoma 1 (MOG1). When comparing the AAOs of the double mutants versus the median of the AAOs of the MYOCK423E HTZ who carried a wild-type (normal) MOG1 gene and were 1st cousins or closer with the double mutant under investigation, we observed that MOG1 delayed the ages at onset by an average of 8 to 10 years in the double mutants.

Conclusions: The MOG1 locus encodes a DNA element that delays the onset of glaucoma by an average of 8–10 years by hampering the first manifestations of OHT. This research will lead to the development of new therapeutic targets for glaucoma. These treatments should prevent optic nerve damage by maintaining IOPs within the normal range.

Keywords: Blindness; genomics; complex genetic disorder; gene-gene interactions; biostatistics

doi: 10.21037/aes.2018.AB090

Cite this abstract as: Raymond V, Belleau P, Arseneault R, Dubois S, Anctil JL, Côté G, Amyot M, Elian F, Walter MA; Québec Glaucoma Network. MOG1, the genetic modifier at 20q13, delays the age-at-onset of glaucoma by 8 to 10 years. *Ann Eye Sci* 2018;3:AB090.