Lack of Association of Mutations in Optineurin With Disease in Patients With Adult-onset Primary Open-angle Glaucoma

Janey L. Wiggs, MD, PhD; Josette Auguste, BA; R. Rand Allingham, MD; Jason D. Flor, BA; Margaret A. Pericak-Vance, PhD; Kathryn Rogers, BA; Karen R. LaRocque, BA; Felicia L. Graham, MA; Bob Broomer, BA; Elizabeth Del Bono, MPH; Jonathan L. Haines, PhD; Michael Hauser, PhD

Objective: To determine whether mutations in the optineurin gene contribute to susceptibility to adult-onset primary open-angle glaucoma.

Methods: The optineurin gene was screened in 86 probands with adult-onset primary open-angle glaucoma and in 80 age-matched control subjects. Exons 4 and 5, containing the recurrent mutations identified in patients with normal-tension glaucoma, were sequenced in all individuals studied, while the remaining exons were screened for DNA sequence variants with denaturing high-performance liquid chromatography.

Results: The recurrent mutation, Met98Lys, previously found to be associated with an increased risk of disease was found in 8 (9%) of 86 probands. We also found the Met98Lys mutation in 10% of individuals from a control population of similar age, sex, and ethnicity. Consistent segregation of the mutation with the disease was not demonstrated in any of the 8 families. No other DNA changes altering the amino acid structure of the protein were found.

Conclusion: The mutations in the optineurin gene associated with normal-tension glaucoma are not associated with adult-onset primary open-angle glaucoma in this patient population.

Clinical Relevance: Genetic abnormalities that render the optic nerve susceptible to degeneration are excellent candidates for genetic factors that could contribute to adult-onset primary open-angle glaucoma. Mutations in optineurin have been associated with normal-tension glaucoma, but are not associated with disease in patients with adult-onset primary open-angle glaucoma. This result may indicate that normal-tension glaucoma is not necessarily part of the phenotypic spectrum of adult open-angle glaucoma.

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been shown to be expressed in many nonocular tissues, including brain, heart, liver, skeletal muscle, kidney, and pancreas. In the eye, the protein has been detected by reverse transcriptase polymerase chain reaction in human trabecular meshwork, nonpigmented ciliary epithelium, and retina. The protein does not have significant homology to any known protein, but it may participate in the tumor necrosis factor α signaling pathway. Tumor necrosis factor α has been proposed to be one factor that could induce apoptosis in retinal ganglion cells in patients with normal-tension glaucoma and in patients with POAG. It has been speculated that the optineurin protein may function to protect the optic nerve from tumor necrosis factor α–mediated apoptosis, and that the loss of function of this protein may decrease the threshold for ganglion cell apoptosis in patients with glaucoma.

Adult-onset POAG is inherited as a complex disease, suggesting that multiple genes may contribute to the phenotype. One gene, TIGR/Myocilin, has been associated with POAG, and the locations of a number of other genes have been indicated from genetic linkage studies. Genes that predispose to POAG may influence intraocular pressure or optic nerve degeneration or both. As part of a genome scan to identify chromosomal regions harboring POAG susceptibility genes, we have collected data from 86 families with multiple members affected by adult-onset POAG with elevated intraocular pressure and optic nerve degeneration.

METHODS

RESULTS

We have collected DNA and clinical information from 86 families with adult-onset POAG for genetic linkage studies. The optineurin gene was screened for DNA sequence variants in all 86 probands and in 80 controls with similar age, sex, and ethnicity. We found the previously identified disease risk–associated Met98Lys mutation in 8 (9%) of 86 probands and 8 (10%) of 80 controls. We did not find any other DNA sequence variants resulting in a change in amino acid sequence in the probands or controls, including the recurrent disease-associated Glu50Lys mutation in exon 4.

To determine whether the Met98Lys mutation segregated with the disease in the 8 families carrying this DNA sequence change, we sequenced the affected and unaffected members of each family. In these 8 families, we found that this DNA sequence variant was equally distributed between the affected and unaffected individuals, with 14 (36%) of the 39 affected individuals and 9 (69%) of the 13 unaffected individuals heterozygous for the methionine and lysine alleles. Consistent segregation of the mutation with the disease was not demonstrated in any of these 8 families, suggesting that in these families the Met98Lys change is not associated with dis-
Primary open-angle glaucoma is a complex disorder that is likely to be the result of multiple genetic and/or environmental defects. Normal-tension glaucoma may represent a subset of POAG that is characterized by extensive deterioration of the optic nerve in response to normal or even low-normal intraocular pressure. Certain genes that cause the optic nerve to degenerate in the setting of low or normal pressure would be excellent candidates for genes that could potentially contribute to optic nerve degeneration associated with elevated pressure.

In this study, we did not find any of the mutations in optineurin reported to be “disease-causing” in the 86 probands with POAG screened. We did find the “disease-risk–associated” mutation, Met98Lys, in 9% of the probands and in 10% of the control individuals. However, we did not find that the sequence variant segregated with the disease in any of the families in which it was present. Indeed, approximately half of the affected individuals and more than half of the unaffected individuals carried the sequence variant. In a complex disease with multiple genetic causes, a risk-associated gene defect may not segregate perfectly with the disease; however, an overall association of the gene defect with the disease should be evident. Our results would not support a conclusion that the Met98Lys mutation confers a significantly increased risk of disease in adult-onset POAG.

Optineurin has been shown to be associated with disease in families with at least 1 member affected by normal-tension glaucoma. We hypothesized that mutations in optineurin would also contribute to optic nerve degeneration in patients with elevated intraocular pressure. Surprisingly, our results demonstrate that mutations in optineurin are not associated with adult-onset POAG in the patient population we have studied. Possibly defects in other genes that are more commonly associated with optic nerve disease will participate to a larger extent in adult-onset POAG. Alternatively, normal-tension glaucoma may be a genetically distinct disease entity that is not a major component of the phenotypic spectrum of adult-onset POAG.

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Corresponding author and reprints: Janey L. Wiggs, MD, PhD, Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114 (e-mail: janey_wiggs@meei.harvard.edu).

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