



TIGR/MYOCILIN VARIANTS, CLINICAL FINDINGS, AND CONCEPTS CONCERNED WITH GLAUCOMA MECHANISMS

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Background: The recognition of TIGR/Myocilin as a glaucoma gene involved two lines of evidence: (1) stress-related perturbations in the genomic and proteomic profiles in our HTM cell models, and (2) classical genetic linkage studies of juvenile and adult glaucoma families by others. More recent basic gene regulation and protein biosynthetic evaluations from our laboratories have suggested that stress-activated pathways induced by abnormal forms of TIGR/Myocilin need to be considered as a mechanism for glaucoma associated with coding region mutations. In addition, a major variant in TIGR/Myocilin's promoter region known as the mt.1 variant (present in 15-20% of individuals, identified by Nguyen) was recently found associated with a substantial risk for rapid glaucoma progression using both optic disc and visual field measures of disease severity (Polansky, Juster, Spaeth. *Clinical Genetics*, 2003, in Press).

Design: Experimental study

Materials/Methods: Real-time PCR evaluations of gene regulation in our steroid glaucoma model are providing potentially clinically informative leads for new candidate glaucoma genes, some of which have shown an association with Alzheimer's disease: AACT (alpha-1antichymotrypsin), APOD (apolipoprotein D), and SAA1 (serum amyloid A precursor protein). These species show a distinctive regulation, paralleling TIGR/Myocilin in differentiated HTM cells, and have expected roles in homeostatic and/or pathogenic effects. Garchon (Copin et al. *Human Genetics*, 2002) independently reported APOE promoter associations in relation to his group's work on the mt.1 promoter variant of TIGR/Myocilin.

Conclusions: The putative role of promoter variants suggests mechanisms for environmental/genetic interactions in addition to direct effects that could influence the glaucoma phenotype, including effects on glaucoma progression.

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