Discovery and Functional Annotation of SIX6 Variants in Primary Open-Angle Glaucoma

Ulmer Carnes M(1), Liu YP(2), Allingham RR(3), Whigham BT(3), Havens S(3), Garrett ME(1), Qiao C(4); NEIGHBORHOOD Consortium Investigators, Katsanis N(2), Wiggs JL(5), Pasquale LR(6), Ashley-Koch A(7), Oh EC(8), Hauser MA(9)

1 The Center for Human Genetics, Duke University, Durham, North Carolina, United States of America.
2 The Center for Human Disease Modeling, Duke University Medical Center, Durham, North Carolina, United States of America.
3 Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina, United States of America.
4 Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, United States of America; Beijing Tongren Hospital, Beijing Tongren Eye Center, Beijing Ophthalmology & Visual Sciences Key Laboratory, Capital Medical University, Beijing, China.
5 Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, United States of America.
6 Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, United States of America; Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts, United States of America.
7 The Center for Human Genetics, Duke University, Durham, North Carolina, United States of America; Department of Medicine, Duke University Medical Center, Durham, North Carolina, United States of America.
8 The Center for Human Disease Modeling, Duke University Medical Center, Durham, North Carolina, United States of America; Department of Neurology, Duke University Medical Center, Durham, North Carolina, United States of America.
9 The Center for Human Genetics, Duke University, Durham, North Carolina, United States of America; Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina, United States of America; Department of Medicine, Duke University Medical Center, Durham, North Carolina, United States of America.

Glaucoma is a leading cause of blindness worldwide. Primary open-angle glaucoma (POAG) is the most common subtype and is a complex trait with multigenic inheritance. Genome-wide association studies have previously identified a significant association between POAG and the SIX6 locus (rs10483727, odds ratio (OR) =1.32, p=3.87×10^{-11}). SIX6 plays a role in ocular development and has been associated with the morphology of the optic nerve. We sequenced the SIX6 coding and regulatory regions in 262 POAG cases and 256 controls and identified six nonsynonymous coding variants, including five rare and one common variant, Asn141His (rs33912345), which was associated significantly with POAG (OR=1.27, p=4.2×10^{-10}) in the NEIGHBOR/GLAUGEN datasets. These variants were tested in an in vivo Danio rerio (zebrafish) complementation assay to evaluate ocular metrics such as eye size and optic nerve structure. Five variants, found primarily in POAG cases, were hypomorphic or null, while the sixth variant, found only in controls, was benign. One variant in the SIX6 enhancer increased expression of SIX6 and disrupted its regulation. Finally, to our knowledge for the first time, we have identified a clinical feature in POAG patients that appears to be dependent upon SIX6 genotype: patients who are homozygous for the SIX6 risk allele (His141) have a statistically thinner retinal nerve fiber layer than patients homozygous for the SIX6 non-risk allele (Asn141). Our results, in combination with previous SIX6 work, lead us to hypothesize that SIX6 risk variants disrupt the
development of the neural retina, leading to a reduced number of retinal ganglion cells, thereby increasing the risk of glaucoma-associated vision loss.


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