# GLIS1 regulates trabecular meshwork function and intraocular pressure and is associated with glaucoma in humans

K Saidas Nair (# 1) , Chitrangda Srivastava (# 2) , Robert V Brown (# 2) , Swanand Koli (3) , Hélène Choquet (4) , Hong Soon Kang (2) , Yien-Ming Kuo (3) , Sara A Grimm (5) , Caleb Sutherland (2) , Alexandra Badea (6) , G Allan Johnson (6) , Yin Zhao (3) , Jie Yin (4) , Kyoko Okamoto (2) , Graham Clark (7) , Terete Borrás (8) , Gulab Zode (9) , Krishnakumar Kizhatil (7) , Subhabrata Chakrabarti (10) , Simon W M John (7,11) , Eric Jorgenson (12) , Anton M Jetten (13)

1 Department of Ophthalmology and Department of Anatomy, School of Medicine, University of California, San Francisco, San Francisco, CA, USA.
2 Immunity, Inflammation and Disease Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA.
3 Department of Ophthalmology, School of Medicine, University of California, San Francisco, San Francisco, CA, USA.
4 Kaiser Permanente Northern California, Division of Research, Oakland, CA, USA.
5 Integrative Bioinformatics Support Group, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA.
6 Center for In Vivo Microscopy, Department of Radiology, Duke University, Durham, NC, USA.
7 The Jackson Laboratory, Bar Harbor, ME, USA.
8 Department of Ophthalmology, University of North Carolina School of Medicine, Chapel Hill, NC, USA.
9 Department of Pharmacology and Neuroscience, North Texas Eye Research Institute, University of North Texas Health Science Center, Fort Worth, TX, USA.
10 Brien Holden Eye Research Centre, L. V. Prasad Eye Institute, Hyderabad, India.
11 Howard Hughes Medical Institute, Mortimer B. Zuckerman Mind Brain Behavior Institute, Department of Ophthalmology, Columbia University, New York, NY, USA.
12 Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA.
13 Immunity, Inflammation and Disease Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA. jetten@nih.gov.
#Contributed equally.

Chronically elevated intraocular pressure (IOP) is the major risk factor of primary open-angle glaucoma, a leading cause of blindness. Dysfunction of the trabecular meshwork (TM) , which controls the outflow of aqueous humor (AqH) from the anterior chamber, is the major cause of elevated IOP. Here, we demonstrate that mice deficient in the Krüppel-like zinc finger transcriptional factor GLI-similar-1 (GLIS1) develop chronically elevated IOP.

Magnetic resonance imaging and histopathological analysis reveal that deficiency in GLIS1 expression induces progressive degeneration of the TM, leading to inefficient AqH drainage from the anterior chamber and elevated IOP. Transcriptome and cistrome analyses identified several glaucoma- and extracellular matrix-associated genes as direct transcriptional targets of GLIS1. We also identified a significant association between GLIS1 variant rs941125 and glaucoma in humans ($P = 4.73 \times 10\text{-}6$) , further supporting a role for GLIS1 into glaucoma etiology. Our study identifies GLIS1 as a critical regulator of TM function and maintenance, AqH dynamics, and IOP.

Nat Commun. 2021 Aug 12;12(1) :4877. doi: 10.1038/s41467-021-25181-7.

PMID: 34385434 PMCID: PMC8361148 DOI: 10.1038/s41467-021-25181-7