Online supplement 1. Evaluation of pathogenic potential of *FOXC1* and *PITX2* missense mutations

FOXC1				
Mutation	**Grantham score[a]**	**Polyphen**	**SIFT**	**Protein domain**
p.Met109Val	21	Probably damaging	Affects protein function	FHD
p.Ser131Trp	177	Probably damaging	Affects protein function	FHD
p.Lys138Glu	56	Benign	Affects protein function	FHD
PITX2				
Mutation	**Grantham score**	**Polyphen**	**SIFT**	**Protein domain**
p.Phe58Leu	22	Probably damaging	Affects protein function	HD

[a] A Grantham score of more than 60 is considered to be significant.

Online supplement 2. Sequence alignment of the forkhead domain (upper panel) and the homeodomain (lower panel)

Online supplement 3. Comparison of phenotypes of patients carrying the same genotype.

<table>
<tr><th colspan="4">c.286dupG - p.Asp96GlyfsX210</th></tr>
<tr><th colspan="2">Kawase at al., 2001[1]</th><th colspan="2">This study</th></tr>
<tr><td colspan="2">Identified in 15-year old female patient, diagnosed with congenital glaucoma at the age of ten. Other reported features were bilateral posterior embryotoxon, iris hypoplasia, and hypertelorism.</td><td colspan="2">Identified 37-year old female with congenital glaucoma, bilateral posterior embryotoxon and anterior chamber angle abnormalities. Cataract and corneal opacities in the right eye.</td></tr>
<tr><th colspan="4">c.253-11A>G</th></tr>
<tr><th>Semina et al., 1996[2]</th><th>Borges et al., 2002[3]</th><th>Riice et al., 2001[4] and 2009[5]</th><th>This study</th></tr>
<tr><td>Reported in patient with ARM ocular features (not specified), hypodontia, and umbilical hernia.</td><td>Identified in three-generation ARM family with five affected family members, four of which were clinically examined and presented with glaucoma, corneal disease, iris atrophy, and systemic features. Two out of four were found to have anterior synechiae.</td><td>Identified in patient with correctopia in the right eye, bilateral microphthalmic eyes and bilateral hypoplasia of the iris stroma. In addition, in the left eye, iris tissue strands were shown to traverse the trabecular meshwork. The patient also displayed maxillary hypoplasia, hypodontia, and redundant periumbilical skin.</td><td>Identified in 11-year old male proband, his affected sister and mother. The proband displays unilateral posterior embryotoxon, bilateral correctopia, and pigment on the anterior lens capsule. To date, there is no evidence for glaucoma. He has maxillary hypoplasia, hypodontia, and failure of involution of the periumbilical skin. Patient was reported to have short stature.</td></tr>
</table>

References

1. Kawase C, Kawase K, Taniguchi T, et al. Screening for mutations of Axenfeld-Rieger syndrome caused by FOXC1 gene in Japanese patients. *J Glaucoma* 2001;10:477-482.
2. Semina EV, Reiter R, Leysens NJ, et al. Cloning and characterization of a novel bicoid-related homeobox transcription factor gene, RIEG, involved in Rieger syndrome. *Nat Genet* 1996;14:392-399.
3. Borges AS, Susanna R, Jr., Carani JC, et al. Genetic analysis of PITX2 and FOXC1 in Rieger Syndrome patients from Brazil. *J Glaucoma* 2002;11:51-56.
4. Riise R, Storhaug K, Brondum-Nielsen K. Rieger syndrome is associated with PAX6 deletion. *Acta Ophthalmol Scand* 2001;79:201-203.
5. Riise R, D'Haene B, De Baere E, Gronskov K, Brondum-Nielsen K. Rieger syndrome is not associated with PAX6 deletion: a correction to Acta Ophthalmol Scand 2001: 79: 201-203. *Acta Ophthalmol* 2009.