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Childhood Glaucoma Genes and Phenotypes: Focus on *FOXC1* mutations causing anterior segment dysgenesis and hearing loss

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Abstract

Childhood glaucoma is an important cause of blindness world-wide. Eleven genes are currently known to cause inherited forms of glaucoma with onset before age 20. While all the early-onset glaucoma genes cause severe disease, considerable phenotypic variability is observed among mutations carriers. In particular, *FOXC1* genetic variants are associated with a broad range of phenotypes including multiple forms of glaucoma and also systemic abnormalities, especially hearing loss. FOXC1 is a member of the forkhead family of transcription factors and is involved in neural crest development necessary for formation of anterior eye structures and also pharyngeal arches that form the middle ear bones. In this study we review the clinical phenotypes reported for known *FOXC1* mutations and show that mutations in patients with reported ocular anterior segment abnormalities and hearing loss primarily disrupt the critically important forkhead domain. These results suggest that optimal care for patients affected with anterior segment dysgenesis should include screening for *FOXC1* mutations and also testing for hearing loss.

Keywords

Glaucoma; genes; childhood; variable phenotype; hearing loss; anterior segment dysgenesis; FOXC1

Introduction

Glaucoma is a significant cause of blindness in children world-wide (Beck, 2011a; Haddad et al., 2007). Childhood forms of glaucoma are frequently characterized by high intraocular pressure (IOP) resulting from abnormalities of the eye fluid drainage structures (trabecular meshwork), however familial forms of normal-tension glaucoma are also known. High IOP causes irreversible damage to the optic nerve and in elastic pediatric eyes can cause ocular enlargement (buphthalmos) with the associated complications of high myopia, retinal

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detachment and corneal decompensation related to fracture of the corneal basement membranes. As curative therapies for glaucoma do not currently exist, affected children are subject to a lifetime of medical and surgery treatments directed toward lowering elevated intraocular pressure (Zagora et al., 2015; Ben-Zion et al., 2011; Beck et al., 2011b).

The discovery of genes responsible for pediatric glaucoma is an important step toward the development of clinically useful gene-based screening tests and novel and potentially curative genetic therapies. Eleven genes responsible for childhood forms of glaucoma have been identified so far (Table 1). Four genes are now known to cause congenital glaucoma: *CYP1B1* and *LTBP2* causing autosomal recessive disease (Ali et al., 2009; Bejjani et al., 1998; Stoilov et al., 1997) and *TIE2 (TEK)* and *ANGPT1* cause dominantly inherited congenital glaucoma with variable expressivity related to development of Schlemm's canal (Souma et al., 2016; Thomson et al., 2017). Mutations in three genes coding for transcription factors involved in ocular development can cause early-onset glaucoma and anterior segment dysgenesis: *FOXC1* (Axenfeld-Rieger syndrome) (Nishimura et al., 1998), *PITX2* (Rieger Syndrome) (Semina et al., 1996), *PAX6* (Aniridia and Peter's anomaly) (Jordan et al., 1992; Prosser et al., 1998). Recently *CPAMD8* mutations have been identified as a cause of a unique form of autosomal recessive anterior segment dysgenesis that can include congenital cataracts (Cheong et al., 2016; Hollmann et al., 2017). Dominant *MYOC* (myocilin) missense alleles cause juvenile (onset after age 3) glaucoma (Fingert et al., 2002; Wiggs et al., 1998; Stone et al., 1997). Myocilin is an extracellular matrix protein and disease-causing missense alleles induce ER stress from the misfolded protein response (Donegan et al., 2015). Loss of function *MYOC* mutations in mice and humans do not cause glaucoma (Kim et al., 2001; Wiggs et al., 2001). *FOXC1, PITX2* and *PAX6* are regulatory genes that influence development of the ocular anterior segment including structures involved in glaucoma (Fan and Wiggs, 2010). Loss of function dominant alleles cause clinically evident developmental defects that can include glaucoma (Allen et al., 2015). *OPTN* (optineurin) and *TBK1* (tank binding protein 1) cause dominantly inherited early-onset normal tension glaucoma, characterized by profound optic atrophy in the setting of normal IOP (Fingert et al., 2011; Hauser et al., 2006; Rezaie et al., 2002).

Variable phenotypes

Phenotypic variation has been observed in patients with disease caused by childhood glaucoma genes, especially for patients with mutations in *CYP1B1, MYOC, PAX6* and *FOXC1*. Many patients with *CYP1B1* mutations are diagnosed with congenital glaucoma during infancy, however some patients do not show evidence of the disease until later in childhood or even teenage years (López-Garrido et al., 2013; Khan et al., 2011; Suri et al., 2009). Similarly, while many *MYOC* mutations cause disease before age 20, several mutations, including the well-studied Q368X, are known to be responsible for disease in individuals who are not diagnosed with glaucoma until later in life (Nag et al., 2018; Allingham et al., 1998). *PAX6* mutations are classically known to cause aniridia (Prosser et al., 1998) but can also cause autosomal dominant keratitis due to limbal stem cell deficiency (Mirzayans et al., 1995; Li et al., 2015). *FOXC1* mutations can be responsible for disease with onset ranging from birth (Siggs et al., 2019) to adult (Bailey et al., 2016). Additionally our NEIGHBORHOOD consortium has recently identified SNPs in the *FOXC1* 5' UTR that

are significantly associated with adult-onset POAG, suggesting that variable expression of *FOXC1* may contribute to POAG more commonly (Cooke Bailey et al., 2016).

FOXC1 ocular phenotypes

Forkhead transcription factors are a family of proteins that share a highly conserved forkhead DNA-binding domain and are required for regulation of embryogenesis, cell migration, differentiation and fate determination (Golson and Kaestner, 2016). *FOXC1* codes for a member of the forkhead transcription factor family that is required for the migration and specification of the periocular mesenchyme neural-crest derived mesenchymal cells that give rise to important ocular structures related to glaucoma including the stroma of the ciliary body and iris and the trabecular meshwork (Akula et al., 2019).

Both deletions and duplications involving *FOXC1* have been implicated in ocular disease (Lehmann et al., 2000; Nishimura et al., 2001) indicating gene dosage as a critical factor in disease development. *FOXC1* null mice exhibit clinical features of anterior segment dysgenesis including iris hypoplasia, corectopia, and embryotoxon in mice (Kume et al., 1998; Gould et al., 2004).

FOXC1 mutations can cause a broad range of ocular phenotypes: Axenfeld-Rieger syndrome (Nishimura et al., 1998), Peters Anomaly (Honkanen et al., 2003), congenital glaucoma (Siggs et al., 2019), and more recently adult-onset primary open angle glaucoma (Bailey et al., 2016). Frequently *FOXC1* mutations are associated with Axenfeld-Rieger anomaly defined by anterior segment dysgenesis with characteristic posterior embryotoxon, iris hypoplasia, and corectopia (Seifi and Walter, 2018). Axenfeld-Rieger syndrome describes patients with Axenfeld-Rieger anomaly and additional systemic features that may include a flat mid-face due to maxillary hypoplasia and a flat broad nose, teeth abnormalities, redundant umbilical skin and congenital heart defects (Lewis et al., 2017). Many patients with Axenfeld-Rieger anomaly or syndrome will also develop glaucoma, however the severity of the anterior segment dysgenesis does not predict glaucoma risk. Recent studies suggest that patients with truncating *FOXC1* mutations are more likely to be diagnosed with congenital glaucoma (Siggs et al., 2019).

FOXC1 systemic phenotypes

FOXC1 mutation carriers may also exhibit a range of systemic abnormalities. Patients with large-scale deletions or duplications of the 6pter-6p24 region that includes *FOXC1, FOXFQ* and *FOXF2* can present with a syndromic phenotype defined by hearing loss, cardiac abnormalities, short stature, dental abnormalities, facial dysmorphism and hypertelorism (Gould et al., 2004). De Hauwere syndrome describes a subset of the 6pter-6p24 deletion patients that are characterized by Axenfeld-Rieger syndrome, hydrocephalus and hearing loss (Lowry et al., 2007). Dandy-Walker malformation involving the cerebellum has also been described in patients with FOXC1 mutations (Aldinger et al., 2009). FOXC1 is an important component of the signaling pathways necessary for cardiac development and mutations can cause congenital heart disease and abnormal valve formation (Zhu, 2016). Involvement of FOXC1 in the neural crest migration forming the pharyngeal arches and

cardiac neural crest likely underlie these systemic findings in FOXC1 mutation carriers (Kume et al., 2001).

Patients with *FOXC1* point mutations and indels (nonsense, frameshift or missense alleles) also can present with a range of ocular and systemic phenotypes (Table 2). Systemic phenotypes associated with *FOXC1* mutations are similar in range and scope to those identified in patients with large-scale deletions and duplications suggesting that genetic abnormalities involving *FOXC1* are important drivers of the 6pter-6p25 syndromic clinical features.

FOXC1 and Hearing Loss

Patients with large-scale deletions and other copy number variations (CNVs) involving chromosome 6p25 and *FOXC1* frequently are affected with hearing loss in addition to anterior ocular dysgenesis (D'haene et al., 2011; Gould et al., 2004). Although a precise role for FOXC1 in hearing or ear development is not well understood, during development, neural crest cells migrate from the dorsal hindbrain to specific locations in pharyngeal arch (PA) 1 and 2, to form the middle ear bones (malleus, incus and stapes) (Ritter and Martin, 2019). As FOXC1 contributes to neural crest migration in the pharyngeal arches, its possible that *FOXC1* mutations can interfere with this process. Defective FOXC1 can lead to abnormal development and ossification of facial bones (Xu et al., 2018) and *Foxc1*$^{-/-}$ mice have abnormal cranial facial bone development, and failed ossification of the middle ear bones (Inman et al., 2013).

To gain a better understanding of the role of FOXC1 in hearing and deafness we reviewed published reports of *FOXC1* variants and recorded information on hearing and ocular findings (Tables 2 and 3 and Figure 1) by searching PubMed with terms "FOXC1" and "Mutation" or "6p25" or "Ring chromosome 6". We excluded publications that were not in English, did not describe human genetic variants or were not accessible online.

Our review identified 82 different *FOXC1* human mutations (Table 2) and 42 6p25 deletions, duplications or ring chromosomes that include the *FOXC1* genomic region (Table 3). Of the 82 *FOXC1* mutations reported in patients with ocular disease, 17 reported abnormal hearing (Table 2; Figure 1). Fifteen of the 17 mutations found in patients reporting hearing loss either caused a frameshift or premature stop codon in Active Domain 1, leading to the loss of the forkhead domain, or a framshrift, nonsense or missense change located in the forkhead domain itself (Figure 1). Only one mutation within the forkhead domain (Q106RfsX75) reported normal hearing (Kim et al., 2013). Unfortunately, in many cases, there is no mention of the hearing phenotype or the case is reported with "no systemic findings," making it difficult to determine whether or not hearing tests were conducted (Table 2).

Of the 38 reported cases of 6p25 deletions or duplications 20 (53%) have described hearing defects as part of the clinical presentation and 2 of 4 patients with ring chromosome 6 involving the *FOXC1* genomic region also reported hearing loss (Table 3). Nine patients with 6p deletions reported have normal hearing and two patients were reported to have normal auditory brainstem response but no speech (Table 3) suggesting variable expressivity

of the hearing phenotype. Similar to the reports for the *FOXC1* mutations (Table 2) 7 of the 6p25 deletion, duplication or ring chromosome reports did not comment on hearing.

The results of this literature review show that *FOXC1* mutations that cause both anterior segment dysgenesis and hearing loss most likely disrupt the critical forkhead domain. The forkhead domain is necessary for proper FOXC1 nuclear localization and DNA binding, and disruptions to this part of the gene are the most deleterious to protein function (Saleem et al., 2004). There are however, many patients with *FOXC1* mutations involving the forkhead domain that do not report hearing problems. This observation may be due to variable expressivity of the hearing phenotype, or could implicate a second gene or other factors that impact hearing pathogenesis. Alternatively, hearing tests may not have been done or may not have been noted in the report.

Summary

Currently 11 genes are known to cause early-onset glaucoma and variable phenotypes in mutation carriers is frequently observed. In this review we focused on the spectrum of phenotypes found in patients with *FOXC1* mutations with an emphasis on hearing loss. We determined that of the majority of *FOXC1* mutations reported in the literature in patients with anterior segment dysgenesis and hearing loss disrupt the critically important forkhead domain necessary for DNA binding and transcriptional regulation. We also find that approximately 50% of patients reported with 6p25 deletions, duplications or ring chromosomes also report hearing abnormalities. These results overall suggest that *FOXC1* mutations are capable of causing hearing defects and that patients with *FOXC1* mutations should undergo hearing testing.

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References

Akula M, Park JW, West-Mays JA, 2019 Relationship between neural crest cell specification and rare ocular diseases. J Neurosci Res. 97, 7–15. doi: 10.1002/jnr.24245. [PubMed: 29660784]

Aldinger KA, Lehmann OJ, Hudgins L, Chizhikov VV, Bassuk AG, Ades LC, Krantz ID, Dobyns WB, Millen KJ, 2009 FOXC1 is required for normal cerebellar development and is a major contributor to chromosome 6p25.3 Dandy-Walker malformation. Nat Genet. 41, 1037–1042. doi: 10.1038/ng.422. [PubMed: 19668217]

Ali M, McKibbin M, Booth A, Parry DA, Jain P, Riazuddin SA, Hejtmancik JF, Khan SN, Firasat S, Shires M, Gilmour DF, Towns K, Murphy AL, Azmanov D, Tournev I, Cherninkova S, Jafri H, Raashid Y, Toomes C, Craig J, Mackey DA, Kalaydjieva L, Riazuddin S, Inglehearn CF, 2009 Null mutations in LTBP2 cause primary congenital glaucoma. Am J Hum Genet. 84, 664–671. doi: 10.1016/j.ajhg.2009.03.017. [PubMed: 19361779]

Allen KF, Gaier ED, Wiggs JL, 2015 Genetics of Primary Inherited Disorders of the Optic Nerve: Clinical Applications. Cold Spring Harb Perspect Med. 5, a017277. doi: 10.1101/cshperspect.a017277. [PubMed: 26134840]

Allingham RR, Wiggs JL, De La Paz MA, Vollrath D, Tallett DA, Broomer B, Jones KH, Del Bono EA, Kern J, Patterson K, Haines JL, Pericak-Vance MA, 1998 Gln368STOP myocilin mutation in

families with late-onset primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 39, 2288–2295. [PubMed: 9804137]

Anderlid BM, Schoumans J, Hallqvist A, Ståhl Y, Wallin A, Blennow E, Nordenskjöld M, 2003 Cryptic subtelomeric 6p deletion in a girl with congenital malformations and severe language impairment. Eur J Hum Genet. 11, 89–92. [PubMed: 12529712]

Bailey JN, Loomis SJ, Kang JH, Allingham RR, Gharahkhani P, Khor CC, Burdon KP, Aschard H, Chasman DI, Igo RP Jr, Hysi PG, Glastonbury CA, Ashley-Koch A, Brilliant M, Brown AA, Budenz DL, Buil A, Cheng CY, Choi H, Christen WG, Curhan G, De Vivo I, Fingert JH, Foster PJ, Fuchs C, Gaasterland D, Gaasterland T, Hewitt AW, Hu F, Hunter DJ, Khawaja AP, Lee RK, Li Z, Lichter PR, Mackey DA, McGuffin P, Mitchell P, Moroi SE, Perera SA, Pepper KW, Qi Q, Realini T, Richards JE, Ridker PM, Rimm E, Ritch R, Ritchie M, Schuman JS, Scott WK, Singh K, Sit AJ, Song YE, Tamimi RM, Topouzis F, Viswanathan AC, Verma SS, Vollrath D, Wang JJ, Weisschuh N, Wissinger B, Wollstein G, Wong TY, Yaspan BL, Zack DJ, Zhang K, Study EN; ANZRAG Consortium, Weinreb RN, Pericak-Vance MA, Small K, Hammond CJ, Aung, Liu Y, Vithana EN, MacGregor S, Craig JE, Kraft P, Howell G, Hauser MA, Pasquale LR, Haines JL, Wiggs JL, 2016 Genome-wide association analysis identifies TXNRD2, ATXN2 and FOXC1 as susceptibility loci for primary open-angle glaucoma. Nat Genet. 48, 189–194. doi: 10.1038/ng.3482. [PubMed: 26752265]

Beck AD, 2011a Primary congenital glaucoma in the developing world. Ophthalmology. 118, 229–230. doi: 10.1016/j.ophtha.2010.06.015. [PubMed: 21292107]

Beck AD, Lynn MJ, Crandall J, Mobin-Uddin O, 2011b Surgical outcomes with 360-degree suture trabeculotomy in poor-prognosis primary congenital glaucoma and glaucoma associated with congenital anomalies or cataract surgery. J AAPOS. 15, 54–58. doi: 10.1016/j.jaapos.2010.12.002. [PubMed: 21397807]

Bedoyan JK, Lesperance MM, Ackley T, Iyer RK, Innis JW, Misra VK, 2011 A complex 6p25 rearrangement in a child with multiple epiphyseal dysplasia. Am J Med Genet A. 155A, 154–163. doi: 10.1002/ajmg.a.33751. [PubMed: 21204225]

Bejjani BA, Lewis RA, Tomey KF, Anderson KL, Dueker DK, Jabak M, Astle WF, Otterud B, Leppert M, Lupski JR, 1998 Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. Am J Hum Genet. 62, 325–333. [PubMed: 9463332]

Ben-Zion I, Tomkins O, Moore DB, Helveston EM, 2011 Surgical results in the management of advanced primary congenital glaucoma in a rural pediatric population. Ophthalmology. 118, 231–235.e1. doi: 10.1016/j.ophtha.2010.02.027. [PubMed: 20579739]

Carmona S, da Luz Freitas M, Froufe H, Simões MJ, Sampaio MJ, Silva ED, Egas C, 2017 Novel de novo FOXC1 nonsense mutation in an Axenfeld-Rieger syndrome patient. Am J Med Genet A. 173, 1607–1610. doi: 10.1002/ajmg.a.38234. [PubMed: 28432732]

Cella W, de Vasconcellos JP, de Melo MB, Kneipp B, Costa FF, Longui CA, Costa VP, 2006 Structural assessment of PITX2, FOXC1, CYP1B1, and GJA1 genes in patients with Axenfeld-Rieger syndrome with developmental glaucoma, 2006. Invest Ophthalmol Vis Sci. 47, 1803–1809. [PubMed: 16638984]

Cellini E, Disciglio V, Novara F, Barkovich JA, Mencarelli MA, Hayek J, Renieri A, Zuffardi O, Guerrini R, 2012 Periventricular heterotopia with white matter abnormalities associated with 6p25 deletion. Am J Med Genet A. 158A, 1793–1797. doi: 10.1002/ajmg.a.35416. [PubMed: 22678982]

Chakrabarti S, Kaur K, Rao KN, Mandal AK, Kaur I, Parikh RS, Thomas R, 2009 The transcription factor gene FOXC1 exhibits a limited role in primary congenital glaucoma. Invest Ophthalmol Vis Sci. 50, 75–83. doi: 10.1167/iovs.08-2253. [PubMed: 18708620]

Cheong SS, Hentschel L, Davidson AE, Gerrelli D, Davie R, Rizzo R, Pontikos N, Plagnol V, Moore AT, Sowden JC, Michaelides M, Snead M, Tuft SJ, Hardcastle AJ, 2016 Mutations in CPAMD8 Cause a Unique Form of Autosomal-Recessive Anterior Segment Dysgenesis. Am J Hum Genet. 99, 1338–1352. doi: 10.1016/j.ajhg.2016.09.022. [PubMed: 27839872]

Corona-Rivera JR, Corona-Rivera A, Zepeda-Romero LC, Rios-Flores IM, Rivera-Vargas J, Orozco-Vela M, Santana-Bejarano UF, Torres-Anguiano E, Pinto-Cardoso M, David D, Bobadilla-Morales L, 2018 Ring chromosome 6 in a child with anterior segment dysgenesis and review of its overlap

with other FOXC1 deletion phenotypes. Congenit Anom (Kyoto). 2018 9 18. doi: 10.1111/cga.12309.

D'Haene B, Meire F, Claerhout I, Kroes HY, Plomp A, Arens YH, de Ravel T, Casteels I, De Jaegere S, Hooghe S, Wuyts W, van den Ende J, Roulez F, Veenstra-Knol HE, Oldenburg RA, Giltay J, Verheij JB, de Faber JT, Menten B, De Paepe A, Kestelyn P, Leroy BP, De Baere E, 2011 Expanding the spectrum of FOXC1 and PITX2 mutations and copy number changes in patients with anterior segment malformations. Invest Ophthalmol Vis Sci. 52, 324–33. doi: 10.1167/iovs.10-5309. [PubMed: 20881294]

Donegan RK, Hill SE, Freeman DM, Nguyen E, Orwig SD, Turnage KC, Lieberman RL, 2015 Structural basis for misfolding in myocilin-associated glaucoma. Hum Mol Genet. 24, 2111–2124. doi: 10.1093/hmg/ddu730. [PubMed: 25524706]

Du RF, Huang H, Fan LL, Li XP, Xia K, Xiang R, 2016 A Novel Mutation of FOXC1 (R127L) in an Axenfeld-Rieger Syndrome Family with Glaucoma and Multiple Congenital Heart Diseases. Ophthalmic Genet. 37, 111–115. doi: 10.3109/13816810.2014.924016. [PubMed: 24914578]

Fan BJ, Wiggs JL, 2010 Glaucoma: genes, phenotypes, and new directions for therapy. J Clin Invest. 120, 3064–3072. doi: 10.1172/JCI43085. [PubMed: 20811162]

Fetterman CD, Mirzayans F, Walter MA, 2009 Characterization of a novel FOXC1 mutation, P297S, identified in two individuals with anterior segment dysgenesis. Clin Genet. 76, 296–299. doi: 10.1111/j.1399-0004.2009.01210.x. [PubMed: 19793056]

Fingert JH, Robin AL, Stone JL, Roos BR, Davis LK, Scheetz TE, Bennett SR, Wassink TH, Kwon YH, Alward WL, Mullins RF, Sheffield VC, Stone EM, 2011 Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. Hum Mol Genet. 20, 2482–2494. doi: 10.1093/hmg/ddr123. [PubMed: 21447600]

Fingert JH, Stone EM, Sheffield VC, Alward WL, 2002 Myocilin glaucoma. Surv Ophthalmol. 47, 547–561. [PubMed: 12504739]

Fuse N, Takahashi K, Yokokura S, Nishida K, 2007 Novel mutations in the FOXC1 gene in Japanese patients with Axenfeld-Rieger syndrome. Mol Vis. 13, 1005–1009. [PubMed: 17653043]

Golson ML, Kaestner KH, 2016 Fox transcription factors: from development to disease. Development. 143, 4558–4570. [PubMed: 27965437]

Gould DB, Jaafar MS, Addison MK, Munier F, Ritch R, MacDonald IM, Walter MA, 2004 Phenotypic and molecular assessment of seven patients with 6p25 deletion syndrome: relevance to ocular dysgenesis and hearing impairment. BMC Med Genet. 5, 17. [PubMed: 15219231]

Gould DB, Smith RS, John SW, 2004 Anterior segment development relevant to glaucoma. Int J Dev Biol. 48, 1015–1029. [PubMed: 15558492]

Gripp KW, Hopkins E, Jenny K, Thacker D, Salvin J, 2013 Cardiac anomalies in Axenfeld-Rieger syndrome due to a novel FOXC1 mutation. Am J Med Genet A. 161A, 114–119. doi: 10.1002/ajmg.a.35697. [PubMed: 23239455]

Guillén-Navarro E, Wallerstein R, Reich E, Zajac L, Ostrer H, 1997 Robinow syndrome with developmental brain dysplasia. Am J Med Genet. 1997 11 28;73(1):98–9. [PubMed: 9375934]

Haddad MA, Sei M, Sampaio MW, Kara-José N, 2007 Causes of visual impairment in children: a study of 3,210 cases. J Pediatr Ophthalmol Strabismus. 44, 232–240. [PubMed: 17694828]

Hauser MA, Sena DF, Flor J, Walter J, Auguste J, Larocque-Abramson K, Graham F, Delbono E, Haines JL, Pericak-Vance MA, Rand Allingham R, Wiggs JL, 2006 Distribution of optineurin sequence variations in an ethnically diverse population of low-tension glaucoma patients from the United States. J Glaucoma. 15, 358–363. [PubMed: 16988596]

Hollmann AK, Dammann I, Wemheuer WM, Wemheuer WE, Chilla A, Tipold A, Schulz-Schaeffer WJ, Beck J, Schütz E, Brenig B, 2017 Morgagnian cataract resulting from a naturally occurring nonsense mutation elucidates a role of CPAMD8 in mammalian lens development. PLoS One. 12, e0180665. doi: 10.1371/journal.pone.0180665. [PubMed: 28683140]

Honkanen RA, Nishimura DY, Swiderski RE, Bennett SR, Hong S, Kwon YH, Stone EM, Sheffield VC, Alward WL, 2003 A family with Axenfeld-Rieger syndrome and Peters Anomaly caused by a point mutation (Phe112Ser) in the FOXC1 gene. Am J Ophthalmol. 135, 368–375. [PubMed: 12614756]

Inman KE, Purcell P, Kume T, Trainor PA, 2013 Interaction between Foxc1 and Fgf8 during mammalian jaw patterning and in the pathogenesis of syngnathia. PLoS Genet. 9, e1003949. [PubMed: 24385915]

Ito YA, Footz TK, Berry FB, Mirzayans F, Yu M, Khan AO, Walter MA, 2009 Severe molecular defects of a novel FOXC1 W152G mutation result in aniridia. Invest Ophthalmol Vis Sci. 50, 3573–3579. doi: 10.1167/iovs.08-3032. [PubMed: 19279310]

Ito YA, Footz TK, Murphy TC, Courtens W, Walter MA, 2007 Analyses of a novel L130F missense mutation in FOXC1. Arch Ophthalmol. 125, 128–135. [PubMed: 17210863]

Jordan T, Hanson I, Zaletayev D, Hodgson S, Prosser J, Seawright A, Hastie N, van Heyningen V, 1992 The human PAX6 gene is mutated in two patients with aniridia. Nat Genet. 1, 328–332. [PubMed: 1302030]

Kapoor S, Mukherjee SB, Shroff D, Arora R, 2011 Dysmyelination of the cerebral white matter with microdeletion at 6p25. Indian Pediatr. 48, 727–729. [PubMed: 21992905]

Kaur K, Ragge NK, Ragoussis J, 2009 Molecular analysis of FOXC1 in subjects presenting with severe developmental eye anomalies. Mol Vis. 15, 1366–1373. [PubMed: 19626132]

Kawase C, Kawase K, Taniguchi T, Sugiyama K, Yamamoto T, Kitazawa Y, Alward WL, Stone EM, Nishimura DY, Sheffield VC, 2001 Screening for mutations of Axenfeld-Rieger syndrome caused by FOXC1 gene in Japanese patients. J Glaucoma. 10, 477–482. [PubMed: 11740218]

Kelberman D, Islam L, Holder SE, Jacques TS, Calvas P, Hennekam RC, Nischal KK, Sowden JC, 2011 Digenic inheritance of mutations in FOXC1 and PITX2 : correlating transcription factor function and Axenfeld-Rieger disease severity. Hum Mutat. 32, 1144–1152. doi: 10.1002/humu.21550. [PubMed: 21837767]

Khan AO, Al-Abdi L, Mohamed JY, Aldahmesh MA, Alkuraya FS, 2011 Familial juvenile glaucoma with underlying homozygous p.G61E CYP1B1 mutations. J AAPOS. 15, 198–199. doi: 10.1016/j.jaapos.2011.01.156. [PubMed: 21596299]

Kim BS, Savinova OV, Reedy MV, Martin J, Lun Y, Gan L, Smith RS, Tomarev SI, John SW, Johnson RL, 2001 Targeted Disruption of the Myocilin Gene (Myoc) Suggests that Human Glaucoma-Causing Mutations Are Gain of Function. Mol Cell Biol. 21, 7707–7713. [PubMed: 11604506]

Kim GN, Ki CS, Seo SW, Yoo JM, Han YS, Chung IY, Park JM, Kim SJ. A novel forkhead box C1 gene mutation in a Korean family with Axenfeld-Rieger syndrome. Mol Vis. 2013 4 30;19:935–43. [PubMed: 23687430]

Komatireddy S, Chakrabarti S, Mandal AK, Reddy AB, Sampath S, Panicker SG, Balasubramanian D, 2003 Mutation spectrum of FOXC1 and clinical genetic heterogeneity of Axenfeld-Rieger anomaly in India. Mol Vis. 9, 43–48. [PubMed: 12592227]

Kume T, Deng KY, Winfrey V, Gould DB, Walter MA, Hogan BL,1998 The forkhead/winged helix gene Mf1 is disrupted in the pleiotropic mouse mutation congenital hydrocephalus. Cell. 93, 985–996. [PubMed: 9635428]

Kume T, Jiang H, Topczewska JM, Hogan BL, 2001 The murine winged helix transcription factors, Foxc1 and Foxc2, are both required for cardiovascular development and somitogenesis. Genes Dev. 15, 2470–82. [PubMed: 11562355]

Le Caignec C, De Mas P, Vincent MC, Boceno M, Bourrouillou G, Rival JM, David A, 2005 Subtelomeric 6p deletion: clinical, FISH, and array CGH characterization of two cases. Am J Med Genet A. 132A, 175–180. [PubMed: 15578619]

Lehmann OJ, Ebenezer ND, Jordan T, Fox M, Ocaka L, Payne A, Leroy BP, Clark BJ, Hitchings RA, Povey S, Khaw PT, Bhattacharya SS, 2000 Chromosomal duplication involving the forkhead transcription factor gene FOXC1 causes iris hypoplasia and glaucoma. Am J Hum Genet. 67, 1129–1135. [PubMed: 11007653]

Lewis CJ, Hedberg-Buenz A, DeLuca AP, Stone EM, Alward WLM, Fingert JH, 2017 Primary congenital and developmental glaucomas. Hum Mol Genet. 26, R28–R36. doi: 10.1093/hmg/ddx205. [PubMed: 28549150]

Li G, Xu F, Zhu J, Krawczyk M, Zhang Y, Yuan J, Patel S, Wang Y, Lin Y, Zhang M, Cai H, Chen D, Zhang M, Cao G, Yeh E, Lin D, Su Q, Li WW, Sen GL, Afshari N, Chen S, Maas RL, Fu XD, Zhang K, Liu Y, Ouyang H, 2015 Transcription Factor PAX6 (Paired Box 6) Controls Limbal

Stem Cell Lineage in Development and Disease. J Biol Chem. 290, 20448–20454. doi: 10.1074/jbc.M115.662940. [PubMed: 26045558]

Lin RJ, Cherry AM, Chen KC, Lyons M, Hoyme HE, Hudgins L, 2005 Terminal deletion of 6p results in a recognizable phenotype. Am J Med Genet A. 136, 162–168. [PubMed: 15940702]

Linhares ND, Svartman M, Rodrigues TC, Rosenberg C, Valadares ER, 2015 Subtelomeric 6p25 deletion/duplication: Report of a patient with new clinical findings and genotype-phenotype correlations. Eur J Med Genet. 58, 310–318. doi: 10.1016/j.ejmg.2015.02.011. [PubMed: 25817395]

López-Garrido MP, Medina-Trillo C, Morales-Fernandez L, Garcia-Feijoo J, Martínez-de-la-Casa JM, García-Antón M, Escribano J, 2013 Null CYP1B1 genotypes in primary congenital and nondominant juvenile glaucoma. Ophthalmology. 120, 716–723. doi: 10.1016/j.ophtha.2012.09.016. [PubMed: 23218183]

Lowry RB, Gould DB, Walter MA, Savage PR, 2007 Absence of PITX2, BARX1, and FOXC1 mutations in De Hauwere syndrome (Axenfeld-Rieger anomaly, hydrocephaly, hearing loss): a 25-year follow up. Am J Med Genet A. 143A, 1227–1230. [PubMed: 17486624]

Maclean K, Smith J, St Heaps L, Chia N, Williams R, Peters GB, Onikul E, McCrossin T, Lehmann OJ, Adès LC, 2005 Axenfeld-Rieger malformation and distinctive facial features: Clues to a recognizable 6p25 microdeletion syndrome. Am J Med Genet A. 132A, 381–385. [PubMed: 15654696]

Martinez-Glez V, Lorda-Sanchez I, Ramirez JM, Ruiz-Barnes P, Rodriguez de Alba M, Diego-Alvarez D, Ramos C, Searby CC, Nishimura DY, Ayuso C, 2007 Clinical presentation of a variant of Axenfeld-Rieger syndrome associated with subtelomeric 6p deletion. Eur J Med Genet. 50, 120–127. [PubMed: 17157569]

Mears AJ, Jordan T, Mirzayans F, Dubois S, Kume T, Parlee M, Ritch R, Koop B, Kuo WL, Collins C, Marshall J, Gould DB, Pearce W, Carlsson P, Enerback S, Morissette J, Bhattacharya S, Hogan B, Raymond V, Walter MA, 1998 Mutations of the forkhead/winged-helix gene, FKHL7, in patients with Axenfeld-Rieger anomaly. Am J Hum Genet. 63, 1316–1328. [PubMed: 9792859]

Medina-Trillo C, Aroca-Aguilar JD, Méndez-Hernández CD, Morales L, García-Antón M, García-Feijoo J, Escribano J, 2016 Rare FOXC1 variants in congenital glaucoma: identification of translation regulatory sequences. Eur J Hum Genet. 24, 672–680. doi: 10.1038/ejhg.2015.169. [PubMed: 26220699]

Micheal S, Siddiqui SN, Zafar SN, Villanueva-Mendoza C, Cortés-González V, Khan MI, den Hollander AI, 2016 A Novel Homozygous Mutation in FOXC1 Causes Axenfeld Rieger Syndrome with Congenital Glaucoma. PLoS One. 11, e0160016. doi: 10.1371/journal.pone.0160016. [PubMed: 27463523]

Mirzayans F, Gould DB, Héon E, Billingsley GD, Cheung JC, Mears AJ, Walter MA, 2000 Axenfeld-Rieger syndrome resulting from mutation of the FKHL7 gene on chromosome 6p25. Eur J Hum Genet. 8, 71–74. [PubMed: 10713890]

Mirzayans F, Pearce WG, MacDonald IM, Walter MA, 1995 Mutation of the PAX6 gene in patients with autosomal dominant keratitis. Am J Hum Genet. 57, 539–548. [PubMed: 7668281]

Mortemousque B, Amati-Bonneau P, Couture F, Graffan R, Dubois S, Colin J, Bonneau D, Morissette J, Lacombe D, Raymond V, 2004 Axenfeld-Rieger anomaly: a novel mutation in the forkhead box C1 (FOXC1) gene in a 4-generation family. Arch Ophthalmol. 122, 1527–1533. [PubMed: 15477465]

Murphy TC, Saleem RA, Footz T, Ritch R, McGillivray B, Walter MA, 2004 The wing 2 region of the FOXC1 forkhead domain is necessary for normal DNA-binding and transactivation functions. Invest Ophthalmol Vis Sci. 45, 2531–2538. [PubMed: 15277473]

Nag A, Lu H, Arno M, Iglesias AI, Bonnemaijer P, Broer L, Uitterlinden AG, Klaver CC, van Duijn C, Hysi PG, Hammond CJ, 2017 Evaluation of the Myocilin Mutation Gln368Stop Demonstrates Reduced Penetrance for Glaucoma in European Populations. Ophthalmology. 124, 547–553. doi: 10.1016/j.ophtha.2016.11.018. [PubMed: 28038983]

Nakane T, Kousuke N, Sonoko H, Yuko K, Sato H, Kubota T, Sugita K, 2013 6p subtelomere deletion with congenital glaucoma, severe mental retardation, and growth impairment. Pediatr Int. 55, 376–381. doi: 10.1111/j.1442-200X.2012.03729.x. [PubMed: 23782370]

Nishimura DY, Searby CC, Alward WL, Walton D, Craig JE, Mackey DA, Kawase K, Kanis AB, Patil SR, Stone EM, Sheffield VC, 2001 A spectrum of FOXC1 mutations suggests gene dosage as a mechanism for developmental defects of the anterior chamber of the eye. Am J Hum Genet. 68, 364–372. [PubMed: 11170889]

Nishimura DY, Swiderski RE, Alward WL, Searby CC, Patil SR, Bennet SR, Kanis AB, Gastier JM, Stone EM, Sheffield VC, 1998 The forkhead transcription factor gene FKHL7 is responsible for glaucoma phenotypes which map to 6p25. Nat Genet. 19, 140–147. [PubMed: 9620769]

Ovaert C, Busa T, Faure E, Missirian C, Philip N, Paoli F, Milh M, Mace L, Zaffran S, 2017 FOXC1 haploinsufficiency due to 6p25 deletion in a patient with rapidly progressing aortic valve disease. Am J Med Genet A. 173, 2489–2493. doi: 10.1002/ajmg.a.38331. [PubMed: 28657660]

Pace NP, Maggouta F, Twigden M, Borg I, 2017 Molecular cytogenetic characterisation of a novel de novo ring chromosome 6 involving a terminal 6p deletion and terminal 6q duplication in the different arms of the same chromosome. Mol Cytogenet. 10, 9. doi: 10.1186/s13039-017-0311-y. [PubMed: 28344652]

Panicker SG, Sampath S, Mandal AK, Reddy AB, Ahmed N, Hasnain SE, 2002 Novel mutation in FOXC1 wing region causing Axenfeld-Rieger anomaly. Invest Ophthalmol Vis Sci. 43, 3613–3616. [PubMed: 12454026]

Piccione M, Antona R, Salzano E, Cavani S, Malacarne M, Morreale Bubella R, Pierluigi M, Viaggi CD, Corsello G, 2012 Array-CGH and clinical characterization in a patient with subtelomeric 6p deletion without ocular dysgenesis. Am J Med Genet A. 2012 1;158A(1):150–4. doi: 10.1002/ajmg.a.34308. [PubMed: 22105932]

Prosser J, van Heyningen V, 1998 PAX6 mutations reviewed. Hum Mutat. 11, 93–108. [PubMed: 9482572]

Reis LM, Tyler RC, Volkmann Kloss BA, Schilter KF, Levin AV, Lowry RB, Zwijnenburg PJ, Stroh E, Broeckel U, Murray JC, Semina EV, 2012 PITX2 and FOXC1 spectrum of mutations in ocular syndromes. Eur J Hum Genet. 20, 1224–1233. doi: 10.1038/ejhg.2012.80. [PubMed: 22569110]

Reis LM, Tyler RC, Weh E, Hendee KE, Schilter KF, Phillips JA 3rd, Sequeira S, Schinzel A, Semina EV, 2016 Whole exome sequencing identifies multiple diagnoses in congenital glaucoma with systemic anomalies. Clin Genet. 90, 378–382. doi: 10.1111/cge.12816 [PubMed: 27272408]

Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, Héon E, Krupin T, Ritch R, Kreutzer D, Crick RP, Sarfarazi M, 2002 Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science. 295, 1077–1079. [PubMed: 11834836]

Ritter KE, Martin DM, 2019 Neural crest contributions to the ear: Implications for congenital hearing disorders. Hear Res. 376,22–32. doi: 10.1016/j.heares.2018.11.005. [PubMed: 30455064]

Sadagopan KA, Liu GT, Capasso JE, Wuthisiri W, Keep RB, Levin AV, 2015 Anirdia-like phenotype caused by 6p25 dosage aberrations. Am J Med Genet A. 167A, 524–528. doi: 10.1002/ajmg.a.36890. [PubMed: 25691405]

Saleem RA, Banerjee-Basu S, Murphy TC, Baxevanis A, Walter MA, 2004 Essential structural and functional determinants within the forkhead domain of FOXC1. Nucleic Acids Res. 32,4182–4193. [PubMed: 15299087]

Saleem RA, Murphy TC, Liebmann JM, Walter MA, 2003. Identification and analysis of a novel mutation in the FOXC1 forkhead domain. Invest Ophthalmol Vis Sci. 2003 11;44(11):4608–12. [PubMed: 14578375]

Seifi M, Walter MA, 2018 Axenfeld-Rieger syndrome. Clin Genet. 93, 1123–1130. doi: 10.1111/cge.13148. Epub 2018 1 25. [PubMed: 28972279]

Semina EV, Reiter R, Leysens NJ, Alward WL, Small KW, Datson NA, Siegel-Bartelt J, Bierke-Nelson D, Bitoun P, Zabel BU, Carey JC, Murray JC, 1996 Cloning and characterization of a novel bicoid-related homeobox transcription factor gene, RIEG, involved in Rieger syndrome. Nat Genet. 14, 392–399. [PubMed: 8944018]

Siggs OM, Souzeau E, Pasutto F, Dubowsky A, Smith JEH, Taranath D, Pater J, Rait JL, Narita A, Mauri L, Del Longo A, Reis A, Chappell A, Kearns LS, Staffieri SE, Elder JE, Ruddle JB, Hewitt AW, Burdon KP, Mackey DA, Craig JE, 2019 Prevalence of FOXC1 Variants in Individuals With a Suspected Diagnosis of Primary Congenital Glaucoma. JAMA Ophthalmol. doi: 10.1001/jamaophthalmol.2018.5646.

Souma T, Tompson SW, Thomson BR, Siggs OM, Kizhatil K, Yamaguchi S, Feng L, Limviphuvadh V, Whisenhunt KN, Maurer-Stroh S, Yanovitch TL, Kalaydjieva L, Azmanov DN, Finzi S, Mauri L, Javadiyan S, Souzeau E, Zhou T, Hewitt AW, Kloss B, Burdon KP, Mackey DA, Allen KF, Ruddle JB, Lim SH, Rozen S, Tran-Viet KN, Liu X, John S, Wiggs JL, Pasutto F, Craig JE, Jin J, Quaggin SE, Young TL, 2016 Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity. J Clin Invest. 126, 2575–2587. doi: 10.1172/JCI85830. [PubMed: 27270174]

Souzeau E, Siggs OM, Zhou T, Galanopoulos A, Hodson T, Taranath D, Mills RA, Landers J, Pater J, Smith JE, Elder JE, Rait JL, Giles P, Phakey V, Staffieri SE, Kearns LS, Dubowsky A, Mackey DA, Hewitt AW, Ruddle JB, Burdon KP, Craig JE, 2017 Glaucoma spectrum and age-related prevalence of individuals with FOXC1 and PITX2 variants. Eur J Hum Genet. 25,1290. doi: 10.1038/ejhg.2017.147.

Stoilov I, Akarsu AN, Sarfarazi M, 1997 Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. Hum Mol Genet. 6, 641–647. [PubMed: 9097971]

Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL, Nishimura D, Clark AF, Nystuen A, Nichols BE, Mackey DA, Ritch R, Kalenak JW, Craven ER, Sheffield VC, 1997 Identification of a gene that causes primary open angle glaucoma. Science 275, 668–670. [PubMed: 9005853]

Suri F, Yazdani S, Narooie-Nejhad M, Zargar SJ, Paylakhi SH, Zeinali S, Pakravan M, Elahi E, 2009 Variable expressivity and high penetrance of CYP1B1 mutations associated with primary congenital glaucoma. Ophthalmology. 116, 2101–2109. doi: 10.1016/j.ophtha.2009.04.045. [PubMed: 19744731]

Suzuki K, Nakamura M, Amano E, Mokuno K, Shirai S, Terasaki H, 2006 Case of chromosome 6p25 terminal deletion associated with Axenfeld-Rieger syndrome and persistent hyperplastic primary vitreous. Am J Med Genet A. 140, 503–508. [PubMed: 16470791]

Suzuki T, Takahashi K, Kuwahara S, Wada Y, Abe T, Tamai M, 2001 A novel (Pro79Thr) mutation in the FKHL7 gene in a Japanese family with Axenfeld-Rieger syndrome. Am J Ophthalmol. 32, 572–575.

Swiderski RE, Reiter RS, Nishimura DY, Alward WL, Kalenak JW, Searby CS, Stone EM, Sheffield VC, Lin JJ, 1999 Expression of the Mf1 gene in developing mouse hearts: implication in the development of human congenital heart defects. Dev Dyn. 216, 16–27. [PubMed: 10474162]

Thomson BR, Souma T, Tompson SW, Onay T, Kizhatil K, Siggs OM, Feng L, Whisenhunt KN, Yanovitch TL, Kalaydjieva L, Azmanov DN, Finzi S, Tanna CE, Hewitt AW, Mackey DA, Bradfield YS, Souzeau E, Javadiyan S, Wiggs JL, Pasutto F, Liu X, John SW, Craig JE, Jin J, Young TL, Quaggin SE, 2017 Angiopoietin-1 is required for Schlemm's canal development in mice and humans. J Clin Invest. 127, 4421–4436. doi: 10.1172/JCI95545 [PubMed: 29106382]

Tonoki H, Harada N, Shimokawa O, Yosozumi A, Monzaki K, Satoh K, Kosaki R, Sato A, Matsumoto N, Iizuka S, 2011 Axenfeld-Rieger anomaly and Axenfeld-Rieger syndrome: clinical, molecular-cytogenetic, and DNA array analyses of three patients with chromosomal defects at 6p25. Am J Med Genet A. 155A, 2925–2932. doi: 10.1002/ajmg.a.33858. [PubMed: 22009788]

Vernon HJ, Bytyci Telegrafi A, Batista D, Owegi M, Leigh R, 2013 6p25 microdeletion: white matter abnormalities in an adult patient. Am J Med Genet A. 161A, 1686–1689. doi: 10.1002/ajmg.a.35937. [PubMed: 23686687]

Weegerink NJ, Swinnen FK, Vanakker OM, Casselman JW, Dhooge IJ, 2016 Phenotype of a Belgian Family With 6p25 Deletion Syndrome. Ann Otol Rhinol Laryngol. 2016 9;125(9):734–45. doi: 10.1177/0003489416650687. [PubMed: 27242366]

Weisschuh N, Dressler P, Schuettauf F, Wolf C, Wissinger B, Gramer E, 2006 Novel mutations of FOXC1 and PITX2 in patients with Axenfeld-Rieger malformations. Invest Ophthalmol Vis Sci. 47, 3846–3852. [PubMed: 16936096]

Weisschuh N, Wolf C, Wissinger B, Gramer E, 2008 A novel mutation in the FOXC1 gene in a family with Axenfeld-Rieger syndrome and Peters' anomaly. Clin Genet. 74, 476–480. doi: 10.1111/j.1399-0004.2008.01025.x. [PubMed: 18498376]

Wiggs JL, Allingham RR, Vollrath D, Jones KH, De La Paz M, Kern J, Patterson K, Babb VL, Del Bono EA, Broomer BW, Pericak-Vance MA, Haines JL, 1998 Prevalence of mutations in TIGR/Myocilin in patients with adult and juvenile primary open-angle glaucoma.Am J Hum Genet. 63, 1549–1552. [PubMed: 9792882]

Wiggs JL, Vollrath D, 2001 Molecular and clinical evaluation of a patient hemizygous for TIGR/MYOC. Arch Ophthalmol. 119, 1674–1678. [PubMed: 11709019]

Xu P, Balczerski B, Ciozda A, Louie K, Oralova V, Huysseune A, Crump JG, 2018 Fox proteins are modular competency factors for facial cartilage and tooth specification. Development. 26, 145(12). pii: dev165498. doi: 10.1242/dev.165498.

Yang HJ, Lee YK, Joo CK, Moon JI, Mok JW, Park MH, 2015 A Family with Axenfeld-Rieger Syndrome: Report of the Clinical and Genetic Findings. Korean J Ophthalmol. 29, 249–255. doi: 10.3341/kjo.2015.29.4.249. [PubMed: 26240509]

Zagora SL, Funnell CL, Martin FJ, Smith JE, Hing S, Billson FA, Veillard AS, Jamieson RV, Grigg JR, 2015 Primary congenital glaucoma outcomes: lessons from 23 years of follow-up. Am J Ophthalmol. 2015 159, 788–796. doi: 10.1016/j.ajo.2015.01.019.

Zhang HZ, Li P, Wang D, Huff S, Nimmakayalu M, Qumsiyeh M, Pober BR, 2004 FOXC1 gene deletion is associated with eye anomalies in ring chromosome 6. Am J Med Genet A. 124A, 280–287. [PubMed: 14708101]

Zhang R, Chen X, Li P, Lu X, Liu Y, Li Y, Zhang L, Xu M, Cram DS, 2016 Molecular characterization of a novel ring 6 chromosome using next generation sequencing. Mol Cytogenet. 9, 33. doi: 10.1186/s13039-016-0245-9. [PubMed: 27103944]

Zhu H, 2016 Forkhead box transcription factors in embryonic heart development and congenital heart disease. Life Sci. 144,194–201. doi: 10.1016/j.lfs.2015.12.001. [PubMed: 26656470]

Highlights

- Eleven genes responsible for childhood forms of glaucoma are currently known.
- Variable clinical features can be observed in patients with mutations in childhood glaucoma genes.
- *FOXC1* mutations can cause ocular and systemic disease.
- *FOXC1* mutations causing ocular disease and hearing loss are primarily located in the forkhead domain.

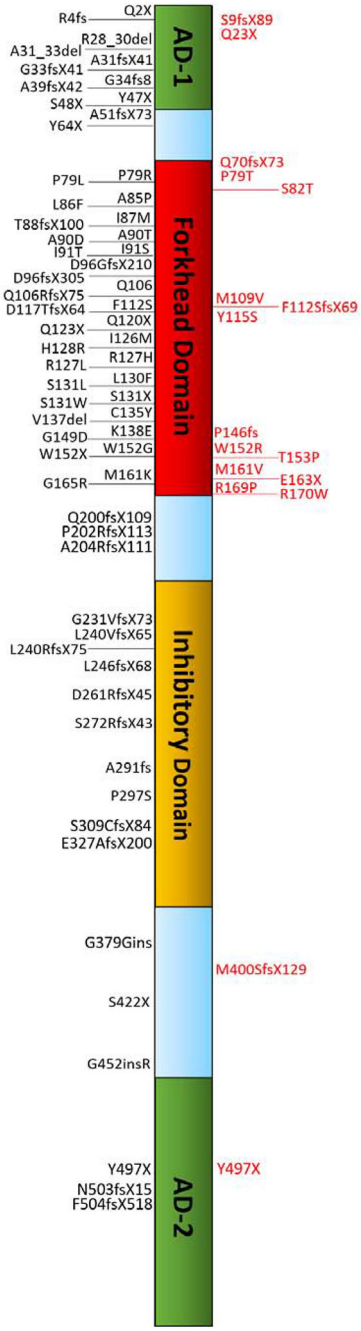

Figure 1. Gene location of *FOXC1* mutations.

The location of the mutations listed in Table 2 are shown. Variants shown in red font are reported in patients with hearing loss. Abbreviations: AD1, Active Domain 1; AD2, Active Domain 2.

Table 1.

Childhood glaucoma genes and phenotypes

Gene	Protein	Inheritance	Phenotypes
CYP1B1	Cytochrome P450 1B1	AR	Congenital and juvenile glaucoma
LTBP2	Latent transforming growth factor binding protein 2	AR	Congenital glaucoma
CPAMD8	C3 and PZP like alpha-2-macroglobulin domain containing 8	AR	Anterior segment dysgenesis
PITX2	Paired like homeodomain 2	AD	Anterior segment dysgenesis and classic Reiger syndrome
FOXC1	Forkhead box C1	AD	Congenital glaucoma, anterior segment dysgenesis, Axenfeld-Rieger syndrome, juvenile open angle glaucoma
PAX6	Paired box 6	AD	Aniridia, corneal keratitis, Peter's anomaly
MYOC	Myocilin	AD	Juvenile open angle glaucoma, adult-onset open angle glaucoma
TIE2 (TEK)	TEK receptor tyrosine kinase	AD	Congenital glaucoma with variable expressivity
ANGPT1	Angiopoietin 1	AD	Congenital glaucoma
OPTN	Optineurin	AD	Normal tension glaucoma
TBK1	TANK binding kinase 1	AD	Normal tension glaucoma

Abbreviations: AD, Autosomal dominant; AR, Autosomal recessive.

Table 2.

FOXC1 mutations and ocular and hearing phenotypes

Protein variant	Protein domain	cDNA variant	Hearing Phenotype	Ocular Phenotype	Reference
Q2X	Active 1	c.4C>T	NR	ARA	Komatireddy et al., 2003
R4fs	Active 1	c.12delC	NR	Glaucoma	Chakrabarti et al., 2009
S9fsX89	Active 1	c.26–47ins	Deafness	Iris hypoplasia, corectopia	Kawase et al., 2001
Q23X	Active 1	c.67C>T	Hearing loss	ARA, glaucoma	Mirzayans et al., 2001
R28_30del	Active 1	c.81_89del9	NR	Glaucoma	Chakrabarti et al., 2009
A31_33del	Active 1	c.92_100del9	NR	Glaucoma	Kaur et al., 2009
A31fsX41	Active 1	c.93_102del10	No systemic findings	ARA, glaucoma	Michael et al., 2016
A31fsX41	Active 1	c.93_102del10	No systemic findings	ARA, glaucoma	Mears et al., 1998
G33fsX41	Active 1	c.99_108del10	NR	ARA	Nishimura et al., 2001
G34fsX8	Active 1	c.100_109del10	NR	PE, glaucoma	Souzeau et al., 2017
A39fsX42	Active 1	c.116_123del8	NR	ARA	Nishimura et al., 2001
Y47X	Active 1	c.141C>G	NR	Glaucoma	Medina-Trillo et al., 2015
S48X	Active 1	c.143C>A	No systemic findings	PE, corectopia	Weisschuh et al., 2006
A51fsX73	Active 1	c.153_163del11	NR	ARA, glaucoma	Nishimura et al., 1998
Y64X	After Active 1	c.192C>G	NR	ARA, glaucoma	Carmona et al., 2017
Q70fsX73	Forkhead	c.210delG	Hearing loss	ARA, glaucoma	Swiderski RE et al. 1999
P79T	Forkhead	c.235C>A	Hearing loss	ARA, glaucoma	Suzuki T et al., 2001
P79R	Forkhead	c.236C>G	NR	Iris hypoplasia, glaucoma	Weisschuh et al., 2006
P79L	Forkhead	c.236C>T	NR	ARA	Saleem et al., 2003
P79L	Forkhead	c.236C>T	NR	ARA	Nishimura et al., 1998
S82T	Forkhead	c.245G>C	Hearing loss	ARA, glaucoma	Mears et al., 1998
A85P	Forkhead	c.253G>C	NR	ARA, glaucoma	Fuse et al., 2007
L86F	Forkhead	c.256C>T	NR	ARA, glaucoma	Saleem et al., 2003
I87M	Forkhead	c.261C>G	No systemic findings	ARA, glaucoma	Mears et al., 1998
T88fsX100	Forkhead	c.262_265insC	NR	ARA	Nishimura et al., 2001
A90T	Forkhead	c.268G>A	No systemic findings	PE, glaucoma	Souzeau et al., 2017
A90D	Forkhead	c.269C>A	NR	Glaucoma	Siggs et al., 2019
I91S	Forkhead	c.272T>G	NR	ARA, glaucoma	Kawase et al., 2001
I91T	Forkhead	c.272T>C	NR	ARA	Mortemousque et al.,2004
D96GfsX210	Forkhead	c.286dupG	NR	PE, glaucoma	D'Haene et al., 2011
D96fsX305	Forkhead	c.286insG	NR	ARA, glaucoma	Kawase et al., 2001
Q106X	Forkhead	c.316C>T	NR	ARA, glaucoma	D'Haene et al., 2011
Q106X	Forkhead	c.316C>T	NR	ARA, glaucoma	Souzeau et al., 2017
Q106RfsX75	Forkhead	c.317delA	Normal hearing	ARA, glaucoma	Kim et al., 2013
M109V	Forkhead	c.325A>G	Hearing loss	Corectopia	D'Haene et al., 2011

Protein variant	Protein domain	cDNA variant	Hearing Phenotype	Ocular Phenotype	Reference
F112SfsX69	Forkhead	c.335del	Hearing Loss	ARA, glaucoma	D'Haene et al., 2011
F112S	Forkhead	c.335T>C	NR	ARA, glaucoma	Nishimura et al., 1998
F112S	Forkhead	c.335T>C	NR	ARA, glaucoma	Honkanen et al., 2003
Y115S	Forkhead	c.339T>C	Middle-ear deafness	ARA, glaucoma	Weisschuh et al., 2006
D117TfsX64	Forkhead	c.349delG	NR	ARA, glaucoma	Siggs et al., 2019
Q120X	Forkhead	c.358C>T	NR	ARA, glaucoma	Weisschuh et al., 2008
Q123X	Forkhead	c.367C>T	NR	ARA, glaucoma	Komatireddy et al., 2003
I126M	Forkhead	c.378C>G	NR	ARA, glaucoma	Nishimura et al., 1998
H128R	Forkhead	c.378A>G	NR	Glaucoma	Chakrabarti et al., 2009
R127H	Forkhead	c.380G>A	NR	ARA, glaucoma	Kawase et al., 2001
R127L	Forkhead	c.380T>G	NR	ARA, glaucoma	Du et al., 2016
L130F	Forkhead	c.388C>T	NR	ARA, glaucoma	Ito et al., 2007
S131L	Forkhead	c.392C>T	NR	ARA, glaucoma	Nishimura et al., 1998
S131X	Forkhead	c.392C>A	NR	Glaucoma	D'Haene et al., 2011
S131W	Forkhead	c.392C>G	NR	ARA	D'Haene et al., 2011
C135Y	Forkhead	c.402G>A	NR	Glaucoma	Chakrabarti et al., 2009
V137del	Forkhead	c.409_411del	NR	PE, glaucoma	Siggs et al., 2019
K138E	Forkhead	c.412A>G	NR	PE, glaucoma	D'Haene et al., 2011
P146fs	Forkhead	c.437_453del17	Hearing loss	ARA, glaucoma	Fuse et al., 2007
G149D	Forkhead	c.446G>A	NR	ARA, glaucoma	Weisschuh et al., 2006
W152R	Forkhead	c.454T>C	Mild deafness	ARA, glaucoma	Michael et al., 2016
W152G	Forkhead	c.454T>G	NR	Glaucoma	Ito et al., 2009
W152X	Forkhead	c.456G>A	NR	ARA, glaucoma	Cella et al., 2006
T153P	Forkhead	c.457A>C	Hearing loss	PE, glaucoma	Siggs et al., 2019
M161V	Forkhead	c.481A>G	Middle-ear deafness	ARA, glaucoma	Weisschuh et al., 2006
M161K	Forkhead	c.482T>A	NR	ARA, glaucoma	Panicker et al., 2002
M161K	Forkhead	c.482T>A	NR	ARA, glaucoma	Komatireddy et al., 2003
E163X	Forkhead	c.487G>T	Hearing Loss	Glaucoma	Siggs et al., 2019
G165R	Forkhead	c.494G>C	NR	ARA, glaucoma	Murphy et al., 2004
R169P	Forkhead	c.506G>C	Hearing loss	ARA	Murphy et al., 2004
R170W	Forkhead	c.508C>T	Hearing Loss	ARA, glaucoma	Gripp et al., 2013
Q200fsX109	After Forkhead	c.599_617del19	NR	ARA	Souzeau et al., 2017
P202RfsX113	After Forkhead	c.605delC	NR	ARA, glaucoma	D'Haene et al., 2011
A204RfsX111	After Forkhead	c.609delC	NR	ARA, glaucoma	Kelberman et al., 2011
I223PfsX87	Inhibitory	c.666_681del16	NR	PE glaucoma	Souzeau et al., 2017
G231VfsX73	Inhibitory	c.692_696del5	NR	ARA, glaucoma	D'Haene et al., 2011
L240VfsX65	Inhibitory	c.718_719delCT	No systemic findings	ARA, glaucoma	Cella et al., 2006
L240VfsX65	Inhibitory	c.718_719delCT	NR	Glaucoma	Siggs et al., 2019

Protein variant	Protein domain	cDNA variant	Hearing Phenotype	Ocular Phenotype	Reference
L240RfsX75	Inhibitory	c.719delT	+	Glaucoma	Hariri et al.,2018
L246fsX68	Inhibitory	c.738delG	NR	Iris atrophy, glaucoma	Weisschuh et al., 2006
D261RfsX45	Inhibitory	c.780dup	NR	NR	D'Haene et al., 2011
S272RfsX43	Inhibitory	c.816_817delinsG	NR	NR	D'Haene et al., 2011
A291fs	Inhibitory	c.853dup25	NR	Glaucoma	Chakrabarti et al., 2009
P297S	Inhibitory	c.889C>T	NR	Glaucoma	Fetterman et al., 2009
P297S	Inhibitory	c.889C>T	NR	Glaucoma	Medina-Trillo et al., 2016
S309CfsX84	Inhibitory	c.925_949del25	NR	Glaucoma	Souzeau et al., 2017
E327AfsX200	Inhibitory	c.980_981del	NR	NR	D'Haene et al., 2011
G379Gins	After Inhibitory	c.1142_1144insGGC	No systemic findings	Iris atrophy, glaucoma	Yang et al., 2015
M400SfsX129	After inhibitory	c.1193_1196dup	Congenital deafness	Iris atrophy, glaucoma	Reis et al., 2016
S422X	After Inhibitory	c.1265C>A	NR	ARA, glaucoma	Souzeau et al., 2017
G452insR	After Inhibitory	c.1362_1364insCGG	No systemic findings	Iris atrophy, glaucoma	Yang et al., 2015
Y497X	Active 2	c.1491C>G	NR	Glaucoma	D'Haene et al., 2011
Y497X	Active 2	c.1491C>G	Hearing Loss	PE, glaucoma	Souzeau et al., 2017
N503fsX15	Active 2	c.1511delT	NR	ARA, glaucoma	Weisschuh et al., 2006
F504fsX518	Active 2	c.1512delG	NR	ARA	Nishimura et al., 2001

Abbreviations: ARA, Axenfeld-Rieger anomaly; PE, Posterior embryotoxon; NR = Not reported.

Table 3.

Chromosome 6p25 abnormalities and ocular and hearing phenotypes

6p25 Variant	Hearing Phenotype	Ocular Phenotype	Reference
.084 Mb deletion	NR	PE, iris atrophy, glaucoma	D'Haene et al, 2011
0.98 Mb deletion	Hearing loss	ARA, glaucoma	Reis et al, 2012
1.10 Mb deletion	Hearing loss	ARA, glaucoma	Reis et al, 2012
1.3 Mb deletion	Hearing loss	ARA	Reis et al, 2012
1.3 Mb deletion	Hearing Loss	Congenital glaucoma	Siggs et al., 2019
1.4 Mb deletion	NR	Normal Ophthalmic exam	Ovaert et al., 2017
1.5 Mb deletion	Normal hearing	Axenfeld-Rieger syndrome, congenital glaucoma	Reis et al, 2012
1.5 Mb deletion	NR	PE, iris atrophy, glaucoma	Sadagopan et al., 2015
2.1 Mb deletion	Conductive hearing defect	Anterior segment dysgenesis	Anderlid et al, 2003
2.1 Mb deletion	Abnormal auditory brainstem response	Congenital glaucoma	Nakane et al., 2013
2.21 MB deletion	Hearing loss	Myopia	Bedoyan et al, 2011
2.54 Mb deletion	Hearing Loss	ARA	Vernon et al., 2013
2.6 Mb deletion	Middle ear malformations and hearing loss	Iris hypoplasia, glaucoma	D'Haene et al, 2011
2.6 Mb duplication	NR	PE, iris atrophy, glaucoma	Sadagopan et al., 2015
2.7 Mb deletion	Sensorineural deafness	PE, iris atrophy, glaucoma	Martinez-Glez et al., 2007
3.4 Mb deletion	Hearing loss	Glaucoma	Weegerink et al, 2016
3.4 Mb deletion	Hearing loss	Glaucoma	Weegerink et al, 2016
3.4 Mb deletion	Hearing loss	PE	Weegerink et al, 2016
3.4 Mb deletion	Middle ear hearing loss	PE, glaucoma	D'Haene et al, 2011
3.9 Mb deletion	Normal hearing	Strabismus	Cellini et al, 2012
34 kb deletion	Hearing loss	PE, glaucoma	D'Haene et al, 2011
4.7 Mb deletion	Hearing loss	ARA	D'Haene et al, 2011
4.8 Mb deletion	Conductive hearing loss	PE, iris atrophy	Le Caignec et al., 2005
5.06 Mb deletion and 1 Mb duplication	Hearing loss	Corectopia	Linhares et al, 2015
5.4 kb deletion	NR	PE	D'Haene et al, 2011
5.5 Mb deletion	Hearing loss	PE, corneal opacity	Le Caignec et al., 2005
6 Mb deletion	Normal auditory brainstem response, but no speech	Normal Ophthalmic exam	Piccione et al., 2012
6.6 Mb deletion	Normal hearing	ARA, glaucoma	Tonoki et al, 2011
6p25 microdeletion	Sensorineural deafness	ARA	Kapoor et al, 2011
6p25-6p22 deletion	NR	ARA	Suzuki et al., 2006
6p25-6pter deletion	Normal hearing	ARA	Maclean et al, 2005
6p25-6pter deletion	Normal hearing	PE, glaucoma	Tonoki et al, 2011
6p25-6pter deletion	Normal hearing	Axenfeld-Rieger syndrome, congenital glaucoma	Reis et al, 2012
6p25-6pter deletion	Hearing loss	ARA, glaucoma	Gould et al, 2004

6p25 Variant	Hearing Phenotype	Ocular Phenotype	Reference
6p25-6pter deletion	Normal hearing	ARA	Gould et al, 2004
6pter deletion	Normal hearing	PE	Lin et al, 2005
6p25 to 6pter deletion	Hearing loss	ARA	Lin et al, 2005
6pter microdeletion	Normal hearing	Anterior segment dysgenesis	Guillen-Navarro et al, 1997
Ring chromosome 6, 6 Mb deletion on 6p	Hearing loss	Peter's anomaly, glaucoma	Zhang et al, 2004
Ring chromosome 6, 1.8 Mb distal 6p deletion	Hearing loss	Ocular features not recorded	Pace et al., 2017
Ring chromosome 6, 6p deletion	Normal auditory brainstem response, but no speech	PE, iris atrophy, glaucoma	Corona-Rivera et al., 2018
Ring chromosome 6, 6p25.2 deletion 1.78 Mb	NR	Anterior segment dysgenesis, microphthalmia	Zhang et al., 2016

Abbreviations: ARA, Axenfeld-Rieger anomaly; PE, Posterior embryotoxon; NR, Not reported.