Comparison of Anterior Segment Abnormalities in Individuals With *FOXC1* and *PITX2* Variants

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Purpose: Axenfeld–Rieger syndrome encompasses a group of developmental disorders affecting the anterior chamber structures of the eye, with associated systemic features in some cases. This study aims to compare the difference in anterior segment phenotypes such as those involving the cornea, iris, lens, and anterior chamber angle between cases with disease-causing sequence variations in *FOXC1* and *PITX2*.

Methods: This cross-sectional study involved 61 individuals, from 32 families with pathogenic *FOXC1* or *PITX2* variants, who were registered with the Australian and New Zealand Registry of Advanced Glaucoma.

Results: The median age of the cohort was 39 years at the time of last assessment (range 3–85 years; females, 54%). Thirty-two patients had pathogenic variants in the *FOXC1* gene, and 29 patients had pathogenic variants in the *PITX2* gene. Corneal abnormalities were more common in individuals with *FOXC1* variants (18/36, 50%) than those with *PITX2* variants (4/25, 16%; $P = 0.007$). Iris abnormalities such as hypoplasia ($P = 0.008$) and pseudopolycoria ($P = 0.001$) were more common in individuals with *PITX2* variants than those with *FOXC1* variants. Glaucoma was present in 72% of participants. Corneal decompensation was positively associated with corneal abnormalities ($P < 0.001$), glaucoma surgery ($P = 0.025$), and cataract surgery ($P = 0.002$).

Conclusions: Corneal abnormalities were more common in individuals with *FOXC1* than in those with *PITX2* variants and were often associated with early onset glaucoma. These findings highlight that patients with *FOXC1* variations require close follow-up and monitoring throughout infancy and into adulthood.

Key Words: anterior segment dysgenesis, corneal anomalies, glaucoma, megalocornea, corneal decompensation, *FOXC1*, *PITX2*

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Axenfeld–Rieger syndrome (ARS, MIM 180500) is a developmental disorder that affects the structures of the anterior segment of the eye, including the cornea, iris, anterior chamber angle, and lens, and in some cases has associated systemic features.[2] ARS includes the disorders such as Axenfeld anomaly, Axenfeld syndrome, Rieger anomaly, and Rieger syndrome. Because these 4 disorders have overlapping ocular and systemic manifestations and result from variants in the same genes, they are considered to be part of a clinical spectrum. ARS is typically inherited as an autosomal dominant disorder showing phenotypic and genetic heterogeneity, with sequence variants (SVs) or copy number variation in the *FOXC1* (MIM 601090) and *PITX2* genes (MIM 601542) accounting for 40% to 70% of the cases.[3–5] *FOXC1* is a member of the fork-head/winged-helix family of transcription factors and is expressed in human tissues, including the eye, brain, and kidney.[6] *PITX2* is a member of the family of homeobox genes and is expressed in teeth, abdominal organs, brain, heart, and kidneys.[7]

ARS is associated with both ocular and systemic manifestations.[8] Ocular features are the main manifestation of ARS and include posterior embryotoxon, iris stromal

hypoplasia, corectopia, pseudopolycoria, and iris processes.[9] Posterior embryotoxon is frequently seen in ARS but has been reported to occur as a very mild manifestation in up to 8 to 12% of the normal population.[10,11] Glaucoma is the most serious ocular consequence of ARS and develops in up to 50% of the patients.[1,12,13] ARS-associated glaucoma is believed to occur because of reduced facility of aqueous outflow caused by maldevelopment of the trabecular meshwork and Schlemm canal.[14] In addition to glaucoma, amblyopia and strabismus have also been reported.[15] Systemic manifestations of ARS include craniofacial abnormalities (hypertelorism, telecanthus, maxillary hypoplasia, and prognathism),[6] dental abnormalities (microdontia, hypodontia, and oligodontia),[16,17] cardiac defects (mitral and tricuspid valve disease, atrial septal defects, and tetralogy of Fallot),[18–20] skeletal abnormalities (short stature, club feet, and joint abnormalities),[21] hearing loss,[8] redundant periumbilical skin, umbilical hernia, anal stenosis, and hypospadias.[22] Variants in *FOXC1* are more commonly associated with isolated ocular abnormalities, but some reports have described associated heart or hearing defects.[13,22] Variants in *PITX2* have been shown to be associated with ocular, dental, and umbilical abnormalities.[22] Corneal abnormalities are commonly reported in Peter anomaly (corneal opacity, iridocorneal synechiae, and an absence of Descemet membrane and corneal endothelium) but are not a common manifestation in ARS. This study aimed to compare detailed anterior segment phenotypes in individuals with ARS caused by *FOXC1* and *PITX2* variants.

MATERIALS AND METHODS

This was a retrospective cross-sectional study. The participants for this study were recruited from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG), as previously described.[23] ANZRAG is a unique genetic repository that aims to determine the genetic basis of childhood glaucoma, in addition to studying the more prevalent forms of adult onset glaucoma. Individuals with ARS and their family members with *FOXC1* and *PITX2* pathogenic SVs or copy number variation were included in this study. Individuals with ARS were recruited in the ANZRAG regardless of their glaucoma status. Family members of individuals with ARS were invited to participate in this study, and every effort was made by registry staff and ophthalmologists to characterize a genotype and phenotype for those family members. Participants with ARS-associated variants in genes, other than *FOXC1* and *PITX2*, were excluded. Data collected from the ANZRAG or from medical records directly included age, sex, ethnicity, gene variant, age at diagnosis of glaucoma, ocular manifestations, systemic manifestations, and ocular treatment (laser, glaucoma surgery, corneal graft, and cataract surgery). SVs and copy number variants (CNVs) identified were confirmed in National Association of Testing Authorities–accredited laboratories, and the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for variant interpretation were used to assess pathogenicity.[24] CNVs have been assessed by different methods, including

SNP array, multiplex ligation-dependent probe amplification and/or karyotype. Variants and CNVs classified as pathogenic, likely pathogenic, and of uncertain significance (but that have evidence toward pathogenicity) were included (see Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/ICO/B380). In our study, advanced glaucoma was defined as visual field loss of at least 2 of 4 central fixation squares having a pattern standard deviation of 0.5% on a reliable Humphrey 24-2 field or a mean deviation of −15 dB in the worse eye. Nonadvanced glaucoma was defined by glaucomatous visual field defects with corresponding optic disc rim thinning and an enlarged cup-to-disc ratio (CDR) (≥0.7) or CDR asymmetry (≥0.2) between the 2 eyes. Ocular hypertension was defined by an intraocular pressure (IOP) > 21 mm Hg. Megalocornea was defined as corneal diameter >13 mm in the horizontal meridian.[25] Corneal abnormality was defined as any corneal lesions present at birth or within 4 years of birth and includes megalocornea, microcornea, corneal opacity, corneal edema, and Haab striae. Corneal decompensation was defined as corneal edema after treatment in a previously normal cornea. We defined early-onset glaucoma as glaucoma developing before the age of 3 years and late-onset glaucoma as glaucoma developing after the age of 3 years. This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee, and all participants provided informed consent. This study adhered to the tenets of the Declaration of Helsinki.

Descriptive statistics of demography and clinical characteristics were performed by using the SPSS software (IBM SPSS Statistics 25, Chicago, IL). The mean and standard deviation were calculated for participants' age at last examination, age at diagnosis of ARS, and age at diagnosis of glaucoma. χ^2 and Fisher exact tests were used to determine the association between the categorical variables. Although all statistical analyses were exploratory in nature, a Bonferroni multiple comparison correction was applied where multiple tests were made. A *P* value of <0.05 was considered as significant.

RESULTS

A total of 61 individuals from 32 families with ARS-associated *FOXC1* or *PITX2* variants were included in this study. The median age of the cohort at last examination was 27 years (range 1–84 years), and 53% were female (Table 1). Most of the participants were of self-reported European ancestry (92%, n = 56). More than half of the participants (59%, n = 36) showed variation in the *FOXC1* gene. The common corneal abnormalities seen in this cohort were megalocornea (13%), Haab striae (10%), congenital corneal opacity (13%), and corneal edema (12%) (Fig. 1). The median central corneal thickness (CCT) in individuals with *FOXC1* variants was 525 (interquartile range, 509–555 μm), and the median CCT in individuals with *PITX2* variants was 541 (interquartile range, 516–602 μm). Interfamilial and intrafamilial variabilities are commonly reported with variants in these genes which support ocular and systemic anomalies being different within family members. The prevalence of megalocornea was significantly higher in individuals with *FOXC1* variants (8/36, 22%) than in

TABLE 1. Sociodemographic and Clinical Characteristics of the Study Population

Variable	n = 61
Age at last examination (yr, n (%))	
<50	50 (82)
Median age, IQR	27 (13–47)
Sex, n (%)	
Male	29 (48)
Ethnicity, n (%)	
White population	56 (92)
Gene variant, n (%)	
FOXC1	36 (59)
PITX2	25 (41)
Age at diagnosis of ASD (yr)	
Median, IQR	12 (0–47)
Age at diagnosis of glaucoma (yr)	
Median, IQR	13 (1–26)

ASD, anterior segment dysgenesis; IQR, interquartile range.

those with *PITX2* variants (0/25, 0%; exact $P = 0.010$) (Table 2). Corneal abnormalities were seen in 36% of the participants (n = 22) and were significantly more common in individuals with *FOXC1* variants (18/36, 50%) than in those with *PITX2* variants (4/25, 16%; $P = 0.007$) (Table 2). The prevalence of Haab striae was 10% (n = 6) and significantly more common in individuals with *FOXC1* variants (6/36, 17%) than in those with *PITX2* variants (0/25, 0%; exact $P = 0.035$). More than half of all participants had posterior embryotoxon. The most common iris abnormalities seen in the cohort were iris stromal hypoplasia, iris processes, and corectopia. The prevalence of pseudopolycoria was 16% (n = 10), and this condition was significantly more common in individuals with *PITX2* variants (9/25, 36%) than in those with *FOXC1* variants (1/36, 3%; $P = 0.001$). The prevalence of iris stromal hypoplasia was 48% (n = 29) and was significantly more common in individuals with *PITX2* variants (17/25, 68%) compared with those *FOXC1* variants (12/36, 33%; $P = 0.008$). The prevalence of cataract was not different between participants with *FOXC1* or *PITX2* variants (22% vs. 16%, respectively, exact $P = 0.548$). Cataract reported in the participants were mostly acquired after an intervention, namely, surgery (n = 8). However, the prevalence of cataract was not significantly different between individuals who had surgical intervention and those without surgical interventions (27% vs. 11%, $P = 0.134$). Twelve individuals had cataract surgery, 7 unilateral and 5 bilateral. However, the prevalence of cataract was 20% and was significantly more common in individuals with corneal abnormalities (9/22, 41%) than in individuals with no corneal abnormalities (3/39, 8%; $P = 0.002$).

Glaucoma was present in 72% (44/61) of participants with 56% (34/61) requiring surgical treatment. The median age at diagnosis of glaucoma was 13 years (range, 0–71 years). There was no significant difference in the prevalence of glaucoma between individuals with *FOXC1* and those with *PITX2* variants (Table 2). However, the median age at diagnosis of glaucoma for *FOXC1* was 4 years (range, 0–71 years), whereas the median age at diagnosis of glaucoma for

PITX2 was 17 years (range, 3–48 years). Early-onset glaucoma was significantly more common in individuals with corneal abnormalities (11/19, 58%) than in individuals without corneal abnormalities (6/25, 24%; $P = 0.022$). Early-onset glaucoma was significantly more common in individuals with megalocornea (6/8, 75%) than in individuals with no megalocornea (11/36, 31%; exact $P = 0.028$). However, the prevalence of Haab striae was not significantly different between individuals with early-onset glaucoma compared with late onset glaucoma (50% vs. 37%, respectively, exact $P = 0.426$). The most commonly performed glaucoma surgeries were trabeculectomy (51%), glaucoma drainage implants (15%), and goniotomy (3%). Thirty-one individuals had trabeculectomy surgery, 21 unilateral and 9 bilateral. Nine individuals had glaucoma tube implant surgery, 8 unilateral and 1 bilateral. Two individuals had bilateral goniotomy, 7 individuals had both trabeculectomy and tube implant surgeries, and 1 individual had both goniotomy and trabeculectomy.

Corneal decompensation was seen in 30% of the individuals and was more common in eyes with corneal abnormalities (13/22, 59%) than in eyes without corneal abnormalities (5/39, 13%, $P < 0.001$). The prevalence of corneal decompensation was not different between individuals with *FOXC1* and those with *PITX2* variants (28% vs. 32%, respectively, $P = 0.722$). The incidence of corneal decompensation was significantly higher in participants who had undergone glaucoma surgery (14/34, 41%) than in individuals who had not undergone glaucoma surgery (4/27, 15%; $P = 0.025$). Corneal decompensation was significantly higher in participants who had undergone cataract surgery (8/12, 67%) than in those without cataract surgery (10/49, 20%; $P = 0.002$). Corneal grafts were more common in patients with corneal abnormalities (5/22, 23%) than in patients without corneal abnormalities (1/39, 3%, exact $P = 0.020$). The systemic features are summarized in Table 3. The Bonferroni correction was applied for multiple comparison corrections. After adjusting for multiple comparisons ($p_{correction} = 0.05/25 = 0.002$), dental abnormalities, redundant periumbilical skin, umbilical hernia, and pseudopolycoria remained statistically significant with a $p_{correction} = 0.025$." Each of the variables has a corrected value of 0.025. Comparison of the clinical features between SV and CNV did not show any significance.

DISCUSSION

This study characterizes the detailed corneal phenotypes of individuals with ARS-associated *FOXC1* and *PITX2* variants. Within the spectrum of anterior segment dysgenesis, corneal abnormalities such as congenital corneal opacities, microcornea, and iridocorneal adhesions are common in Peter anomaly but are uncommon in ARS.[26] Posterior embryotoxon is the only peripheral corneal change that has been frequently reported in ARS; the absence of megalocornea and congenital corneal opacity are often useful criteria to distinguish ARS from other anterior segment disorders.[6] Others have previously reported that ARS is not associated with corneal abnormalities,[6] whereas Fuchs dystrophy/cornea guttatae can
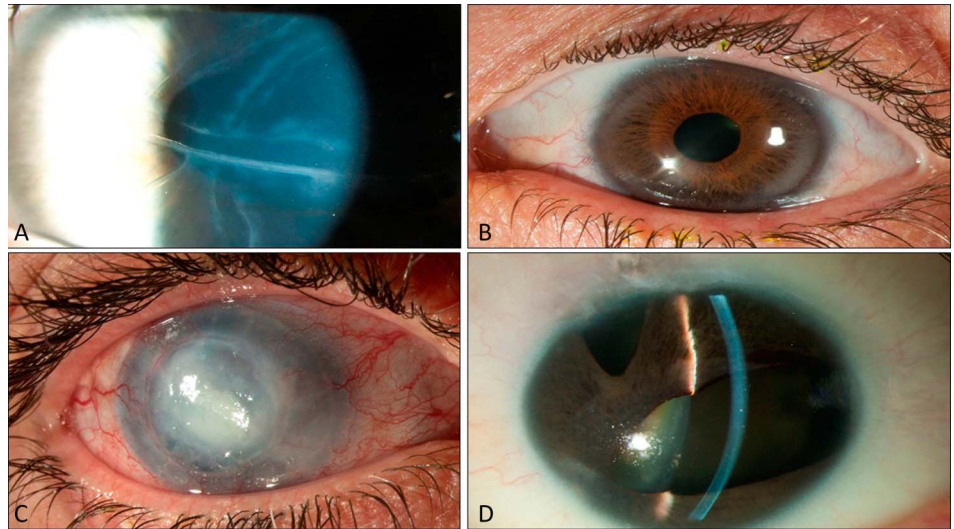
FIGURE 1. Clinical features of Axenfeld–Rieger syndrome: ocular changes, Haab striae (A), endothelial haze (B), corneal edema (C), corectopia, and polycoria (D).

coexist in individuals with ARS-associated *PITX2* variants.[27] In this study, we further extended the phenotypic characterization to assess differences in corneal findings and management in *FOXC1* and *PITX2* carriers. We reported that more than one-third of individuals had corneal abnormalities, with megalocornea the most common. Moreover, we found that corneal abnormalities were more common in individuals with *FOXC1* variants than in those with *PITX2* variants, with only 16% of individuals with *PITX2* variants having corneal abnormalities compared with 50% of those with *FOXC1* variants. We identified that iris abnormalities, including iris stromal hypoplasia and pseudopolycoria, were more common in people with *PITX2* than *FOXC1* variants. Corectopia has been reported to be common in *PITX2* variants,[28] but our study is the first to show that iris hypoplasia and pseudopolycoria were common in individuals with *PITX2* variants. The absence of pseudopolycoria in individuals with *FOXC1* variants is consistent with previous smaller case series.[29,30]

Early-onset glaucoma in individuals with *FOXC1* variants is consistent with previous studies.[28,31] *FOXC1* has been recently identified as a primary open-angle glaucoma susceptibility locus and an essential regulator of lymphangiogenesis,[32] and this could explain the increased prevalence of glaucoma and lower age at diagnosis in the *FOXC1* carriers. *FOXC1* and *PITX2* are developmental genes that are critical for normal corneal development,[33] and variants involving these genes can result in reduced CCT.[34] In our study, the median CCT in individuals with *FOXC1* and *PITX2* was slightly below that of normal population. Studies have shown that corneal abnormalities such as megalocornea, keratoconus, pellucid marginal degeneration, Fuchs endothelial dystrophy, and posterior polymorphous dystrophy can be associated with glaucoma.[35–38] The mechanism of glaucoma development in these corneal conditions is multifactorial and includes oxidative stress, abnormal scleral biomechanical properties, and maldevelopment of angle structures. In ARS, glaucoma development is mostly attributed to the maldevelopment of the angle structures.[14] Glaucoma can also cause corneal changes such as megalocornea, Haab striae,

corneal edema, and reduced endothelial cell count. In our study, most of the individuals with megalocornea had an early-onset glaucoma suggesting that the increased corneal diameter may be attributed to the increased IOP. Endothelial cell loss has been reported in primary open-angle glaucoma, primary angle-closure glaucoma, and secondary glaucoma and is attributed to increased IOP, antiglaucoma medications, and incisional glaucoma surgery.[35] In addition, in our study, corneal decompensation was seen commonly in participants with glaucoma and in those who had undergone glaucoma and cataract surgeries.

ARS has a significant impact on vision because of disruption of the visual axis and can be associated with glaucoma, cataracts, and corneal decompensation. Our findings show that corneal abnormalities were more common in individuals with *FOXC1* variants than in those with *PITX2* variants, and individuals with corneal abnormalities were more likely to require corneal transplantation for corneal decompensation. Moreover, ARS-associated *FOXC1* variant carriers with glaucoma were diagnosed at a younger age and were more likely to require glaucoma procedures and corneal grafts than *PITX2* carriers. Therefore, individuals with *FOXC1* variants require close follow-up and monitoring throughout infancy and into adulthood. Raised IOP, glaucoma surgery, cataract surgery, and corneal grafting are all associated with endothelial cell loss.[39–41] Therefore, individuals with *FOXC1* variants should have endothelial cell density (ECD) assessment by using specular microscopy.

ARS is generally diagnosed by ophthalmologists, and the diagnosis is primarily clinical. Phenotypic and genotypic heterogeneity and overlap of clinical presentations can make diagnosing ARS very challenging, especially in young children who may require an examination under anesthesia to assess angle abnormalities. ARS can present with subtle iris and corneal features and sometimes can be misdiagnosed as primary congenital glaucoma[42] or primary open-angle glaucoma[31] when ARS ocular features are subtle. Although some would argue that the presence of posterior embryotoxon is essential to make a diagnosis of ARS, our study showed

TABLE 2. Univariate Analyses for Associated Ocular Features of Axenfeld–Rieger Syndrome (N = 61)

Variables	Total Prevalence n (%)	*FOXC1*, n (%)	*PITX2*, n (%)	*P**
Corneal abnormality				
Yes	22 (36)	18 (50)	4 (16)	0.007
Corneal decompensation				
Yes	18 (30)	10 (28)	8 (32)	0.722
Megalocornea				
Yes	8 (13)	8 (22)	0 (0)	0.010
Congenital corneal opacity				
Yes	8 (13)	4 (11)	4 (16)	0.426
Corneal edema				
Yes	7 (12)	5 (14)	2 (8)	0.390
Haab striae				
Yes	6 (10)	6 (17)	0 (0)	0.035
Corectopia				
Yes	29 (48)	15 (42)	14 (56)	0.270
Pseudopolycoria				
Yes	10 (16)	1 (3)	9 (36)	0.001
Ectropion uvea				
Yes	5 (8)	4 (11)	1 (4)	0.311
Posterior embryotoxon				
Yes	38 (62)	23 (64)	15 (60)	0.758
Iris hypoplasia				
Yes	29 (48)	12 (33)	17 (68)	0.008
Peripheral anterior synechiae				
Yes	29 (48)	14 (39)	15 (60)	0.104
Iris processes				
Yes	16 (26)	11 (31)	5 (20)	0.324
Cataract				
Yes	12 (20)	8 (22)	4 (16)	0.548
Glaucoma				
Yes	44 (72)	27 (75)	17 (68)	0.549

χ^2 and Fisher exact tests were used to determine the association between the categorical variables. A *P* value of <0.05 was considered as significant.

*Pearson χ^2 test/Fisher exact test.

that posterior embryotoxon was not always identified with *FOXC1* and *PITX2* developmental abnormalities. As a result, genotype–phenotype correlations and the presence of systemic features can assist clinicians in making a correct diagnosis and disease classification. In this study, systemic features were present in more than half of the patients with *FOXC1* variants, but in all individuals with *PITX2* variants, and this has been reported on an overlapping set of ANZRAG patients in the past.[31,43] It has been previously reported that while the systemic features are variably expressed between both genes, the ocular features are believed to be similar between both genes. Tumer et al, Strungaru et al, and D'Haene et al previously reported phenotypic differences between the *FOXC1* and *PITX2* variants, both associated with ARS.[6,22,28] Patients with ARS have a 50% to 60% lifetime risk of developing glaucoma, which can occur anytime during

infancy, childhood, early adulthood, or middle age.[44] Therefore, patients with ARS should be examined annually for the changes in IOP and the optic nerve head. Patients with ARS with corneal abnormalities and those who have undergone surgical interventions are at risk of developing corneal decompensation. Cataract in ARS could either be developmental or acquired after intervention such as glaucoma drainage surgery. Therefore, these patients should be followed regularly with repeated corneal ECD, corneal morphology, and assessment for cataract.

There were some limitations in this study. Because it was a retrospective cross-sectional study, collection of data relied on information provided by ophthalmologists to the ANZRAG or on their record in medical notes when available, and some of the data such as age at diagnosis of ARS and age at diagnosis of glaucoma were missing. However, variables with a large component of missing data were not included in the final analysis. All the participants were drawn from the ANZRAG, and although the registry includes participants with ARS irrespective of their glaucoma status, the recruitment may have introduced bias toward glaucoma. Furthermore, this study may have been underpowered to detect some potentially significant findings because of the small sample size, multiple features examined, and the stringency of the Bonferroni multiple measures correction. This is expected in a

TABLE 3. Univariate Analyses for Associated Systemic Features of Axenfeld–Rieger Syndrome (N = 61)

Variables	Prevalence, n (%)	FOXC1, n (%)	PITX2, n (%)	*P**
Dental abnormalities				
Yes	28 (46)	5 (15)	23 (100)	<0.001
Redundant umbilical skin				
Yes	17 (28)	2 (6)	15 (88)	<0.001
Umbilical hernia				
Yes	10 (16)	1 (3)	9 (56)	<0.001
Hearing loss				
Yes	14 (23)	13 (39)	1 (6)	0.010
Heart defects				
Yes	12 (20)	10 (30)	2 (11)	0.103
Hydrocephalus				
Yes	3 (5)	3 (10)	0 (0)	0.262
Learning abnormality				
Yes	10 (16)	8 (24)	2 (11)	0.259
Short stature				
Yes	6 (10)	3 (9)	1 (6)	0.295
Gastrointestinal abnormalities				
Yes	11 (18)	0 (0)	8 (42)	0.005

χ^2 and Fisher exact tests were used to determine the association between the categorical variables. A *P* value of <0.05 was considered as significant.

Outie is defined as an umbilical tip protruding past the periumbilical skin. Umbilical hernia is a defect in the abdominal wall caused by failure of umbilical ring closure which causes the abdominal contents to protrude out. Redundant umbilical skin is excessive skin surrounding the umbilicus.

*Pearson χ^2/Fisher exact test.

rare disease such as ARS. However, all statistical tests were exploratory in nature, and further studies with a larger sample size should be performed to support our findings. Although there are 3 types of ARS, our study was limited to types 1 and 3 because no gene associated with type 2 ARS has been identified. However, variations in the *FOXC1* and *PITX2* account for 40 to 70% of the cases. Another limitation was that our study did not report the corneal ECD between the *FOXC1* and *PITX2* variants because our attempt to collect this information has been complicated by the small sample size, age of participants, availability of equipment, and the integrity of the cornea which has prevented clear imaging. However, future research should aim to investigate the corneal ECD in these individuals. To conclude, this study compared the anterior segment phenotypes of individuals with ARS-associated pathogenic *FOXC1* and *PITX2* gene variants. Our findings show that 36% of affected individuals had corneal abnormalities and that *FOXC1* variants were significantly more associated with corneal abnormalities compared with *PITX2* variants. The prevalence of cataracts was significantly higher in individuals with corneal abnormalities. Corneal decompensation was positively associated with corneal abnormalities, glaucoma surgeries, and cataract surgeries. These findings have important implications for assisting clinicians in managing patients with ARS.

ACKNOWLEDGMENTS

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