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Neuroimaging Findings in Axenfeld-Rieger Syndrome: A Case Series

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ABSTRACT

SUMMARY: Axenfeld-Rieger syndrome is an autosomal dominant condition associated with multisystemic features including developmental anomalies of the anterior segment of the eye. Single nucleotide and copy number variants in the paired-like homeodomain transcription factor 2 (*PITX2*) and forkhead box C1 (*FOXC1*) genes are associated with Axenfeld-Rieger syndrome as well as other CNS malformations. We determined the association between Axenfeld-Rieger syndrome and specific brain MR imaging neuroradiologic anomalies in cases with or without a genetic diagnosis. This case series included 8 individuals with pathogenic variants in *FOXC1*; 2, in *PITX2*; and 2 without a genetic diagnosis. The most common observation was vertebrobasilar artery dolichoectasia, with 46% prevalence. Other prevalent abnormalities included WM hyperintensities, cerebellar hypoplasia, and ventriculomegaly. Vertebrobasilar artery dolichoectasia and absent/hypoplastic olfactory bulbs were reported in >50% of individuals with *FOXC1* variants compared with 0% of *PITX2* variants. Notwithstanding the small sample size, neuroimaging abnormalities were more prevalent in individuals with *FOXC1* variants compared those with *PITX2* variants.

ABBREVIATION: ARS = Axenfeld-Rieger syndrome

A xenfeld-Rieger syndrome (ARS) is an autosomal dominant genetic condition associated with multisystemic features. It is characterized primarily by ocular features that result from developmental anomalies of the anterior segment of the eye, including posterior embryotoxon (a thickened and anteriorly displaced Schwalbe ring), iris hypoplasia, corectopia (displaced pupil), pseudopolycoria (additional pupillary opening), and iridocorneal adhesions.^{1,2} The developmental anomalies of the structures allowing drainage of the aqueous humor lead to an increased risk of secondary glaucoma. Commonly reported systemic features include facial dysmorphism; dental, umbilical, cardiovascular,

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and endocrinological anomalies; hearing impairment; and developmental delay.^{2,3}

ARS has been associated with variants in the paired-like homeodomain transcription factor 2 (*PITX2*) and forkhead box C1 (*FOXC1*) genes.⁴⁻⁶ *PITX2* belongs to the homeobox gene family and is fundamental to the embryonic development of several tissues, including an essential role in left-right patterning.^{7,8} *FOXC1* encodes a forkhead family transcription factor and is also involved in embryonic development.^{9,10} Pathogenic and likely pathogenic variants in *FOXC1* and *PITX2* have been reported in ~40% of individuals with a clinical diagnosis of ARS,^{11,12} with unique ocular and systemic phenotypes associated with each gene.¹³⁻¹⁶

Variants in both *FOXC1* and *PITX2* have also been associated with a range of CNS malformations, including hydrocephalus,¹⁶⁻¹⁸ classic commissural agenesis (corpus callosum agenesis),¹⁷⁻¹⁹ and cerebellar malformations (Dandy-Walker phenotype,²⁰ mega cisterna magna, and cerebellar vermis hypoplasia).^{18,21,22} More recently, cerebral small-vessel disease has been reported in individuals with *FOXC1* or *PITX2* variants, with the presence of WM hyperintensities, dilated perivascular spaces, and lacunar infarcts on MR imaging.^{23,24}

Here, using a series of ARS cases with accompanying MR imaging of the brain, we systematically determined the association between ARS and specific neuroradiologic anomalies in cases with or without a genomic diagnosis.

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Table 1: Cohort demographics^a

| | All | FOXC1 Variant | PITX2 Variant | No Genetic Diagnosis |
|--|-----------------|-----------------|-----------------|----------------------|
| Prevalence in overall cohort (No.) (%) | NA | 8 (61.5) | 2 (16.7) | 2 (16.7) |
| Sex, female (No.) (%) | 9 (75) | 6 (75.0) | 2 (100) | 1 (50) |
| European ancestry (No.) (%) | 100 (100) | 8 (100) | 2 (100) | 2 (100) |
| Age (yr) | | | | |
| Mean | 37.3 (SD, 21.1) | 29.2 (SD, 16.1) | 51.8 (SD, 3.04) | 10.6 (SD, 14.6) |
| Range | 8–73 | 8–49 | 48–54 | 0–31 |

Note:-NA indicates not applicable.

^a Both sex and ancestry were self-reported.

Table 2: Mean globe parameters

| Parameter | All (n = 12) | FOXC1 Variant (n = 8) | PITX2 Variant (n = 2) | No Genetic Diagnosis (n = 2) | General Population ^{27,28} |
|--------------------------------------|--------------|--------------------------|--------------------------|---------------------------------|--|
| Anterior-posterior diameter of globe | 22.1 | 22.4 | 24.0 | 20.1 | 24.2 |
| Transverse diameter of globe | 22.9 | 23.5 | 24.0 | 20.7 | 24.2 |
| Anterior chamber depth | 2.37 | 2.62 | 1.89 | 1.51 | 2.62 |

MATERIALS AND METHODS

Subjects, Genetic Testing, and Neuroimaging

The study was conducted in accordance with the revised Declaration of Helsinki. Ethics approval was obtained from the Southern Adelaide Clinical Research Ethics Committee, and all participants or their caregivers provided written informed consent. Individuals with a clinical diagnosis of ARS were drawn from the Australian and New Zealand Registry of Advanced Glaucoma as previously described.²⁵ *FOXC1* and *PITX2* genetic testing was performed in a National Association of Testing Authorities–accredited laboratory by Sanger sequencing or multiplex ligation-dependent probe amplification as previously described.^{16,26} Brain MRIs were assessed by 2 pediatric neuroradiologists (A.T. and P.H.) blinded to the genetic results of each participant.

RESULTS

Twelve individuals with ARS were included. The mean age at evaluation was 37.3 (SD, 21.2) years (range, 2 months–73 years), 77% (10/13) were female, and all were of European ancestry (Table 1). Eight individuals had heterozygous pathogenic or likely pathogenic variants in *FOXC1* (including 7 with sequence variants and 1 with a full gene deletion), 2 had heterozygous pathogenic or likely pathogenic variants in *PITX2*, and 2 had no genetic diagnosis despite testing.

Globe and Optic Chiasm

Mean globe parameters are outlined in Table 2 and are compared with ocular biometry from the general population.^{27,28} A thin optic chiasm was reported in 42% (5/12) of the cohort. Both individuals with *PITX2* variants had optic chiasm thinning, whereas only 38% (3/8) of those with *FOXC1* variants had a thin optic chiasm (Fig 1A and Table 3).

Cortex

myelination (n = 1). Prominent perivascular spaces were noted in 3 individuals. Four patients had corpus callosal thinning. Three individuals had colpocephaly/ventriculomegaly, and another had a ventriculoperitoneal shunt. Other corpus callosal abnormalities included thickening of the splenium (n = 1) and genu (n = 1). The prevalence of prominent perivascular spaces in the *FOXC1* variant group was 38% (3/8). Corpus callosum thinning was observed in 38% (3/8) of *FOXC1* variants (Fig 1*B*). Thirty-eight percent (3/8) of individuals with *FOXC1* variants had ventriculomegaly or a ventriculoperitoneal shunt in situ, whereas none (0/2) of the *PITX2* variant group had a ventricular abnormality.

Cerebellum

Hemispheric or global cerebellar hypoplasia was reported in 42% (5/12) of subjects (Fig 1*C*). Superior vermian hypoplasia was identified in 1 patient, and inferior vermis hypoplasia, in another. Other cerebellar findings included tonsillar ectopia (defined as inferior tonsillar location 3–5mm below the plane of foramen magnum) (n = 1) and mega cisterna magna (defined as distance from the posterior aspect of the cerebellar vermis to the inside of the occipital bone of >10 mm) (n = 1) (Fig 1*C*). One of the 2 individuals with *PITX2* variants had superior vermis hypoplasia, and 38% (3/8) of the *FOXC1* variant group had global or hemispheric cerebellar hypoplasia.

Brainstem

An oblong pons was observed in 3 patients. Three subjects had brainstem indentation secondary to tortuous vertebral arteries. Another individual had medullary elongation. Brainstem indentation secondary to tortuous vertebral arteries was observed in 38% (3/8) of individuals with *FOXC1* variants. No brainstem abnormalities were reported in the *PITX2* variant group.

Vessels

Twenty-five percent (3/12) of individuals had circle of Willis abnormalities on MRA. Vertebrobasilar artery dolichoectasia was reported in 6 patients (Fig 1*D*). Four of these 6 individuals also had anterior circulation dolichoectasia. All 3 patients with circle

of Willis abnormalities on MRA had *FOXC1* variants, accounting for 38% of this group. Most (75%) of the *FOXC1* variant group had vertebrobasilar artery dolichoectasia. Of these patients, two-thirds also had anterior circulation dolichoectasia.

Other Findings

Absent or hypoplastic olfactory bulbs were reported in 50% (6/12) of subjects (Fig 1*E*). Other findings included cochlear nerve



FIGURE. A, A 49-year-old woman with a PITX2 mutation had superior vermian volume loss on the TI-weighted sagittal image (AI) and optic chiasm thinning on the T2-weighted coronal image (A2). B, A 2-month-old girl with an unsolved mutation had inferior vermian hypoplasia and a widened tegmentovermian angle on the TI-weighted sagittal image (BI) and malrotated hippocampi on the T2-weighted coronal image (B2). C, A 43-year-old man with a FOXCI mutation had mega cisterna magna and an ectatic basilar artery and a hypoplastic left cerebellar hemisphere on the T2-weighted axial image (CI) and hypoplastic olfactory bulbs on the T2-weighted coronal image (C2). D, A 46-year-old man with a FOXCI mutation had a tortuous basilar artery and an ectatic cavernous segment of the left ICA on axial TOF angiography (DI); a short mesencephalon with loss of the normal relationship among the mesencephalon, pons, and medulla; loss of volume in the superior vermis and ectatic basilar artery; and flow void seen end-on on the T2-weighted sagittal image (D2). E, A 41-year-old woman with a FOXC1 mutation had a tortuous basilar artery flow void on the T2-weighted axial image (EI), a short mesencephalon with loss of the normal relationship among the mesencephalon, pons, and medulla, and bowing of the corpus callosum secondary to ventriculomegaly on the TI-weighted sagittal image (E2). F, A 3-month-old boy with an unsolved mutation had absent olfactory bulbs on the T2-weighted coronal image. G, A 31-yearold woman with an unsolved mutation had a thickened splenium and tonsillar ectopia on the TIweighted sagittal image.

hypoplasia (n = 1), a widened opercula (n = 1), hippocampal malrotation (n = 1), and bilateral absent posterior semicircular canals (n = 1). Absent or hypoplastic olfactory bulbs were reported in 63% (5/8) of subjects with *FOXC1* variants but in none (0/2) of the subjects with *PITX2* variants. Except for 1 subject with right unicoronal craniosynostosis, most of the cohort did not have craniofacial dysmorphism. The pituitary gland and hypothalamus were normal across the cohort. There was no abnormality of the

> deep gray nuclei. No dental abnormalities were observed.

DISCUSSION

This case series reviewed the neuroradiologic features of 12 individuals diagnosed with ARS, comprising 8 individuals with FOXC1 variants, 2 with PITX2 variants, and 2 with unsolved genetic defects. No single anatomic abnormality was observed in most individuals. The most common observation was vertebrobasilar artery dolichoectasia (50% prevalence), which was associated with anterior circulation dolichoectasia in most cases. Other prevalent abnormalities included WM hyperintensities (42%), hemispheric or global cerebellar hypoplasia (42%), corpus callosal thinning (33%), and ventriculomegaly (25%). Optic chiasm thinning was observed in both members of the PITX2 variant group and in 38% of the FOXC1 variant group. Vertebrobasilar artery dolichoectasia was reported in 75% of individuals with FOXC1 variants compared with 0% of individuals with PITX2 variants. Similarly, while 63% of individuals with FOXC1 variants had absent or hypoplastic olfactory bulbs, they were not observed in any of the individuals with PITX2 variants. Circle of Willis abnormalities on MRA and ventricular abnormalities both had a prevalence of 38% in the FOXC1 group compared with 0% in the PITX2 group.

Table 3: Prevalence of neuroradiologic anomalies^a

| (N (%)) | All | FOXC1 | PITX2 | No Genetic Diagnosis |
|---|-------------|------------|------------|----------------------|
| Thin optic chiasm | 5/12 (41.7) | 3/8 (37.5) | 2/2 (100) | 0/2 (0.0) |
| Nonspecific WM hyperintensities | 5/12 (41.7) | 4/8 (50.0) | 1/2 (50.0) | 0/2 (0.0) |
| Corpus callosal thinning | 4/12 (33.3) | 3/8 (37.5) | 0/2 (0.0) | 1/2 (50.0) |
| Ventriculomegaly or ventriculoperitoneal shunt | 4/12 (33.3) | 3/8 (37.5) | 0/2 (0.0) | 0/2 (0.0) |
| Hemispheric or global cerebellar hypoplasia | 5/12 (41.7) | 3/8 (37.5) | 1/2 (50.0) | 0/2 (0.0) |
| Oblong pons | 3/12 (25.0) | 2/8 (25.0) | 0/2 (0.0) | 1/2 (50.0) |
| Brainstem indentation secondary to tortuous vessels | 3/12 (25.0) | 3/8 (37.5) | 0/2 (0.0) | 0/2 (0.0) |
| Circle of Willis abnormalities | 3/12 (25.0) | 3/8 (37.5) | 0/2 (0.0) | 0/2 (0.0) |
| Vertebrobasilar artery dolichoectasia | 6/12 (50.0) | 6/8 (75.0) | 0/2 (0.0) | 0/2 (0.0) |
| Absent/hypoplastic olfactory bulb | 6/12 (50.0) | 5/8 (62.5) | 0/2 (0.0) | 1/2 (50.0) |

^a Data are (No.) (%).

Mean globe parameters were smaller in the cohort without a genetic diagnosis. Although we acknowledge the very small sample size, this group might have an underlying genetic etiology that also impacts globe development, though this remains to be validated. No individuals with *FOXC1* or *PITX2* variants had craniofacial dysmorphism or abnormalities of the hypothalamus, pituitary, deep gray nuclei, or dentition.

The specific endocrinologic manifestations of ARS have not been comprehensively reported in the literature. Santini et al²⁹ have described a patient with growth hormone deficiency associated with ARS. Notably, growth hormone deficiency is a prevalent feature among individuals with septo-optic dysplasia,³⁰ which, like ARS, often involves olfactory bulb–tract hypoplasia.³¹

While there have been several isolated ARS neuroimaging case studies reported,³²⁻³⁴ to our knowledge, there is only 1 case series (Reis et al³⁵) that characterized the genetic and phenotypic features of an ARS cohort comprising 128 individuals with *FOXC1* or *PITX2* variants, including 18 with neuroimaging. The authors observed WM hyperintensities in 94% of *FOXC1* variants and 50% of *PITX2* variants³⁵ (compared with 50% for both *FOXC1* and *PITX2* variant groups in our study). Seventy-one percent of individuals with *FOXC1* variants had colpocephaly/ventriculomegaly (compared with 25% in our study). Reis et al also reported a 31% prevalence of arachnoid cysts in the *FOXC1* variant group, which was not assessed in our case series. Most interesting, the same study observed no correlation between the extent of neuroimaging anomalies and the presence or severity of cognitive impairment in patients with *FOXC1* variants.

Due to the nature of the imaging technique used in this study (MR imaging of the brain), we were not able to reliably detect extracerebral abnormalities such as craniofacial dysmorphism and dental anomalies, which are more sensitively detected by physical examination and specific dental imaging modalities such as orthopantomogram. Reis et al³⁵ reported classic dental anomalies such as hypodontia/oligodontia and microdontia in 91% of individuals with PITX2 variants, with similar anomalies reported in 100% (23/23) of an Australian PITX2 cohort¹⁶ drawn from the same registry as the current study. In contrast, these classic dental anomalies were considerably less common among the FOXC1 group, who had a tendency to present with more atypical anomalies such as enamel hypoplasia/frequent caries (16%) or dental crowding (16%).³⁵ In a similar vein, while craniofacial dysmorphism was not observed on MR imaging of the brain in any of the individuals included in our case series, features such as thin upper lip and maxillary hypoplasia were reported in 78% of individuals with FOXC1 variants and 93% of individuals with PITX2 variants in 1 previous study,³⁵ and in another study (which included all cases described here), hypertelorism/telecanthus and low-set ears were found to be more prevalent in those with FOXC1 variants compared with those with PITX2 variants.¹⁵

This case series was limited by its small cohort size (n = 12), particularly with respect to the *PITX2* variant group (n = 2), which like other ARS case series precluded statistical comparisons.³³

CONCLUSIONS

This study is novel in its description of the relative prevalence of neuroimaging findings among patients with *FOXC1* and *PITX2*

variants, and overall, we observed that the *FOXC1* variant group had a higher prevalence of most (70%) neuroimaging abnormalities assessed (Table 3). The most common observation was vertebrobasilar artery dolichoectasia, which was reported in 75% of individuals with *FOXC1* variants compared with 0% of individuals with *PITX2* variants.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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