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Review article

Axenfeld-Rieger syndrome: A systematic review examining genetic, neurological, and neurovascular associations to inform screening

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ABSTRACT

Axenfeld-Rieger Syndrome (ARS) is comprised of a group of autosomal dominant disorders that are each characterized by anterior segment abnormalities of the eye. Mutations in the transcription factors *FOXC1* or *PITX2* are the most well-studied genetic manifestations of this syndrome.

Due to the rarity this syndrome, ARS-associated neurological manifestations have not been well characterized. The purpose of this systematic review is to characterize and describe ARS neurologic manifestations that affect the cerebral vasculature and their early and late sequelae.

PRISMA guidelines were followed; studies meeting inclusion criteria were analyzed for study design, evidence level, number of patients, patient age, whether the patients were related, genotype, ocular findings, and nervous system findings, specifically neurostructural and neurovascular manifestations.

63 studies met inclusion criteria, 60 (95%) were case studies or case series. The *FOXC1* gene was most commonly found, followed by *COL4A1*, then *PITX2*. The most commonly described structural neurological findings were white matter abnormalities in 26 (41.3%) of studies, followed by Dandy-Walker Complex 12 (19%), and agenesis of the corpus callosum 11 (17%). Neurovascular findings were examined in 6 (9%) of studies, identifying stroke, cerebral small vessel disease (CSVD), tortuosity/dolichoectasia of arteries, among others, with no mention of moyamoya.

This is the first systematic review investigating the genetic, neurological, and neurovascular associations with ARS. Structural neurological manifestations were common, yet often benign, perhaps limiting the utility of MRI screening. Neurovascular abnormalities, specifically stroke and CSVD, were identified in this population. Stroke risk was present in the presence and absence of

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cardiac comorbidities. These findings suggest a relationship between ARS and neurovascular findings; however, larger scale studies are necessary inform therapeutic decisions.

1. Introduction

Axenfeld-Rieger Syndrome (ARS) is a group of autosomal dominant disorders characterized by ocular, neurological, and systemic developmental abnormalities. ARS has a global prevalence of one in 50,000 and has been observed broadly across ethnic backgrounds [1]. Previously known as four separate conditions– Axenfeld anomaly (AA), Rieger anomaly (RA), Axenfeld syndrome (AS), and Rieger syndrome (RS)– these syndromes have since been combined due to extensive phenotypic and genotypic overlap [1,2].

While about 60% of ARS is secondary to an unknown genetic mutation, ARS has been highly linked with the genes forkhead box protein C1 (*FOXC1*; 6p25) and pituitary homeobox 2 (*PITX2*; 4q25), transcription factors that regulate ocular, neurological, craniofacial, and cardiovascular development [3–5]. Both PITX2 and FOXC1 are involved in embryogenesis. PITX2 functions as a transcription regulator during embryogenesis and in the development of the tissues of the anterior segment. FOXC1 is suggested to have a key role in cardiac, renal, ocular, and cerebral morphogenesis.

Though the syndrome is primarily a disorder of the anterior segment of the eye, it is frequently found to include abnormalities in other systems as well. Characteristically these patients exhibit craniofacial dysmorphisms of the midface which includes hypertelorism, telecanthus, maxillary hypoplasia, flattening of the midface, prominent forehead, and a flat nasal bridge. Many also have dental abnormalities including small crowns. The neurological manifestations of ARS tend to include sella anomalies, hydrocephalus, and white matter changes [2,6]. Though not as extensively studied, neurovascular anomalies have been shown to include cerebral small vessel disease (CSVD) and cerebrovascular accidents [4,6].

Patients with ARS are diagnosed through a combination of clinical evaluation, routine examinations, and investigations such as genetic testing or imaging studies. Frequently, the ocular manifestations of ARS are the first anomalies detected through routine eye examinations or in patients exhibiting symptoms of corectopia, glaucoma, or iris hypoplasia [7]. Dental and craniofacial anomalies may be identified in routine dental visits or in the workup of hypodontia or mid-face hypoplasia [8]. Hearing loss, a common feature of ARS due to otosclerosis, may be noted during routine hearing screenings or with clinical changes in auditory function [9]. The clinical diagnosis of ARS involves a comprehensive evaluation of the patient's ocular and systemic manifestations along with a thorough family history analysis.

Given that the structural neurological and neurovascular findings in ARS are poorly defined in the literature, and the impact these associations may have on management of ARS is unknown, a systematic review was conducted to examine the genetic underpinnings, structural neurological manifestations, and neurovascular associations of ARS to better inform care for these patients.

2. Methods

A systematic review was conducted to identify genetic, neurostructural, and neurovascular findings associated with Axenfeld-Rieger syndrome (ARS) to better inform clinical decision-making about screening and management in this patient population. The search protocol, including research question, inclusion, and exclusion criteria, was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

2.1. Search strategy

A comprehensive literature search in English-text performed on March 26, 2022 retrieved articles from PubMed, Embase, and Scopus, with no date restrictions. Concept categories were searched, and results were combined using the appropriate Boolean operators. The concepts searched included: Axenfeld-Rieger syndrome, genetic mutations associated with ARS (identified by brief literature search of ARS), neurological conditions, and neurovascular anomalies– including stroke and moyamoya.

2.2. Selection criteria

Articles were screened by title and abstract for relevance by two authors; duplicate articles were removed, and conflicts resolved by discussion. Remaining articles were screened by full text. Inclusion criteria included: patients with ARS or confirmed mutations in either *FOXC1* or *PITX2* and a neurological defect; available in English; full-text availability. Patients with only *FOXC1* or *PITX2* mutations but no ocular phenotype were still included if they had a neurologic defect because these mutations are known to cause ARS with near complete penetrance [5]. ARS was defined as some combination of posterior embryotoxon, corectopia, pseudopolycoria, iris hypoplasia, and iridocorneal adhesions. Exclusion criteria included: abstracts; full text not available; not available in English-text; not otherwise meeting inclusion criteria. Epilepsy, sensorineural hearing loss, and neuropsychiatric conditions without structural intracranial radiographic abnormalities were excluded. Conflicts about article eligibility after full-text review were resolved by discussion between the two authors.

2.3. Data extraction

Data was extracted from all included articles and comprised of first author, publication year, study design, number of eligible patients, age range of patient(s), whether patients were related, genotype involved (if available), ocular findings relevant to ARS, neurological variables, and neurovascular associations if specified. Age range was defined as the age at diagnosis of the first neurological or relevant ocular phenotype. Ocular phenotypes recorded were only those related to ARS.

2.4. Variables

Structural neurological findings were defined as radiographic abnormalities identified by cranial imaging and detailed in the included studies. These were found to include several categories: white matter abnormalities, agenesis of the corpus callosum, hydrocephalus, Dandy-Walker Complex: including Dandy-Walker malformation, mega cisterna magna, cystic cisterna magna, posterior fossa cyst, and cerebellar vermis hypoplasia, among others. Neurovascular manifestations were further explored due to association with stroke. The manifestations explored included hemorrhage, an arteriovenous malformation (AVM), tortuosity/dolichoectasia of arteries, and CSVD. Of note, Moyamoya was not mentioned in any of the screened articles.

2.5. Statistical analysis

No meta-analysis was performed due to heterogeneity of studies and data reported, precluding pooling. Data is reported descriptively with the number or frequency of studies which report findings examined.

2.6. Quality assessment

Quality of evidence from each article was rated based on study design using a grading system extrapolated from Shadish et al. (Table 1) [10].

3. Results

3.1. Search results

63 articles were included in the study (Fig. 1). Data extracted from all included articles is detailed in Table 2.

3.2. Study characteristics

Of the 63 articles included, none were randomized controlled trials. Sixty (95.2%) were case reports or series, two genome-wide association studies (GWAS) (3.2%), and two case control studies (3.2%). Overall quality ratings were low, with 61 (96.8%) of the studies receiving a D or E quality ranking.

3.3. Genetic associations in ARS

Genetic information was available in 49 (77.8%) studies. *FOXC1* was the most frequently identified gene (67.3%), followed by the gene, collagen type IV alpha 1 (*COL4A1*) (14.3%), and *PITX2* (10.2%) (Table 3). Out of the total number of patients, *PITX2* was the most prevalent (98.2%). Of note, out of the five studies that identified patients with *PITX2* mutations, three studies exclusively focused on this gene [11–13], whereas two studies identified *PITX2* along with the analyses of other genes, including *FOXC1, ZFHX3*, and *HDAC9* [4,14]. *FOXC1* was the most commonly mutated gene in patients with white matter abnormalities (69.2%), followed by

Table 1
Evidence level and quality of study design.

Grade	Design
AA	Systematic review or meta-analysis of randomized trials
A	Systematic review or meta-analysis of non-randomized controlled Randomized trial or cluster randomized trial
B	Systematic review or meta-analysis of controlled studies without a pretest or uncontrolled study with a pretest Non-randomized trial Controlled before-after study Retrospective or prospective cohort study Interrupted time series
C	Systematic review or meta-analysis of cross-sectional studies Non-controlled before-after study
D	Cross-sectional study
E	Case studies, case reports, traditional literature reviews, theoretical papers

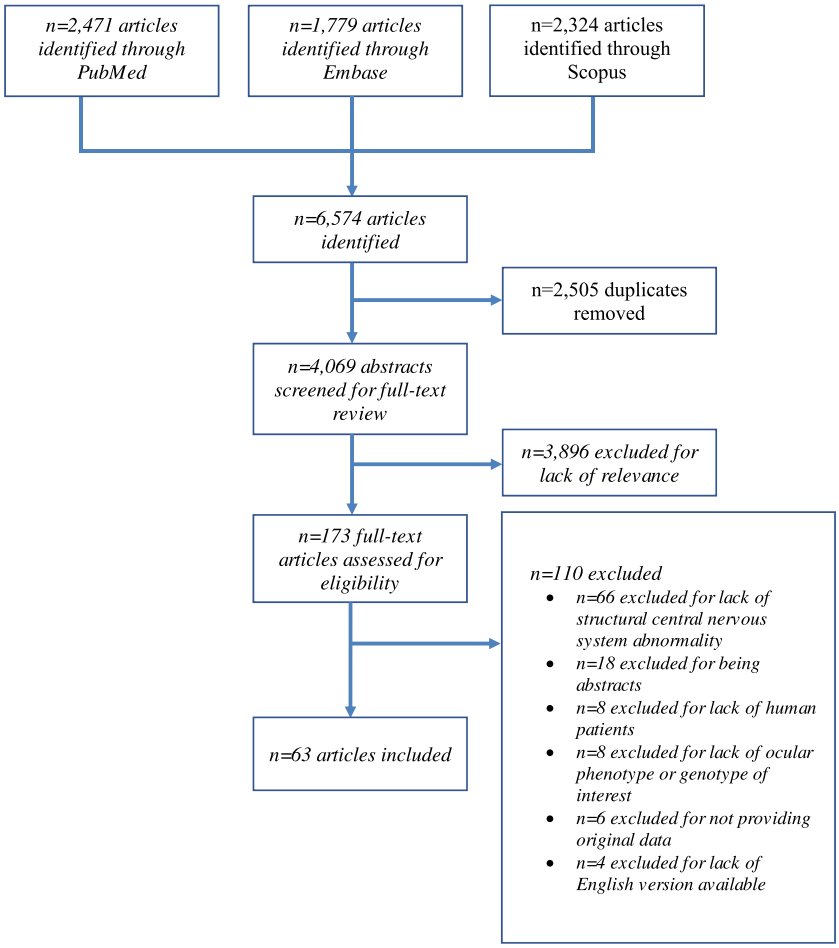

Fig. 1. PRISMA flow diagram demonstrates search results and yield of included articles.

COL4A1 (26.9%). *PITX2* was most commonly identified in those with stroke (50.0%) (Table 2).

3.4. Neurological manifestations

The most common structural neurological finding was white matter abnormalities– including white matter hyperintensities, leukoencephalopathy, and periventricular white matter lesions– reported in 26 (41.3%) papers. Dandy-Walker Complex (19.0%)– including findings of Dandy-Walker malformation, mega cisterna magna, cystic cisterna magna, posterior fossa cyst, and cerebellar vermis hypoplasia– was the second most commonly reported abnormality in 12 (19.0%) papers. Ventriculomegaly was reported in 11 (17.5%) papers, with a diagnosis of hydrocephalus in nine (14.3%) (Table 4).

3.5. Neurovascular associations

Given the known role of FOXC1 in vascular development [70], we examined all studies for neurovascular associations. Stroke was the most prevalent neurovascular disease manifestation, found in four papers (6.3%). The large number of patients in the studies reporting stroke strengthens the evidence for an association of *FOXC1* and *PITX2* with stroke risk [4,11,14]. One *COL4A1* mutated patient also had a hemorrhagic stroke and microhemorrhages [47]. The next most prevalent neurovascular anomaly included three cases of intracranial vascular dolichoectasia (4.8%) [31,47]. Other neurovascular anomalies included eighteen patients with cerebral small vessel disease (CSVD), one arteriovenous malformation (AVM), and one report of thickened small-caliber blood vessels with disrupted basement membranes [4,43,47]. Of note, moyamoya was not specifically reported in any of these studies (Table 5).

4. Discussion

This systematic review was conducted to better characterize the connection between ARS and its genetic, neurological, and neurovascular manifestations, in the hopes of better understanding ARS. This study identifies areas where further study should be

Table 2
Summary of all studies included in the review.

Author	Publication Year	Design	Evidence Level	N	Age[a]	Genetic Findings[b]	Neurological Findings[c]	Ocular Findings
Adkins et al. [55]	1979	Case report	E	1	14 m	Not reported	Aprosencephaly	Rieger anomaly
Aldinger et al. [15]	2009	Case series	D	21	Not reported	*FOXC1*	Dandy-Walker, cerebellar vermis hypoplasia, mega-cisterna magna, white matter hyperintensities, partial agenesis of the corpus callosum	Anterior segment dysgenesis
Ali et al. [51]	2018	Case report	E	1	3 d	*FGFR*	Partial agenesis of the corpus callosum	Axenfeld's anomaly
Avasarala et al. [16]	2018	Case report	E	2	20 y	*FOXC1*	White matter hyperintensities	None
Awan et al. [56]	1977	Case report	E	1	19 y	Not reported	Tilted optic disc, inferiorly displaced macula, dysversion and hypoplasia of optic disc	Rieger's anomaly
Balasubramanian et al. [17]	2012	Case report	E	1	5 y	*FOXC1*	White matter tigroid pattern, polymicrogyria, hypoplasia of the cerebellum, corpus callosum, and brainstem	Posterior embryotoxon, iris adhesions to cornea
Barkana et al. [57]	2012	Case report	E	2	3 y	Not reported	Subcortical white matter lesions	Posterior embryotoxon
Beby et al. [18]	2012	Case report	E	1	26 y	*FOXC1*	Dandy-Walker, optic disc coloboma	Posterior embryotoxon, corectopia
Bellenguez et al. [14]	2012	GWAS	D	9520	Not reported	*PITX2*	Stroke	None
Bozza et al. [19]	2013	Case report	E	2	6 y	*FOXC1*	Increase of R peri-frontal subarachnoid space, shallow sulci	None
Breningstall et al. [20]	2017	Case report	E	1	27 m	*FOXC1*	White matter hyperintensities, ventriculomegaly	Posterior embryotoxon, iris adhesions to cornea
Caluseriu et al. [21]	2006	Case report	E	1	36 y	*FOXC1*	Subcortical atrophy, periventricular white matter attenuation	Posterior embryotoxon, iris atrophy
Cellini et al. [22]	2012	Case report	E	2	8–25 y	*FOXC1*	White matter hyperintensities, supratentorial atrophy, mega-cisterna magna, cerebellar hypoplasia	None
Cok et al. [58]	2005	Case report	E	1	6 y	Not reported	Suprasellar arachnoid cyst	Axenfeld Rieger
Corona-Rivera et al. [23]	2018	Case report	E	1	3 m	*FOXC1*	Mild frontal lobe atrophy, colpocephaly	Posterior embryotoxon, corectopia, iris hypoplasia
Coupry et al. [3]	2010	Case report	E	2	8–58 y	*COL4A1*	Periventricular leukoencephalopathy	Posterior embryotoxon
Davies et al. [24]	1999	Case report	E	2	9–20 y	*FOXC1*	Hydrocephalus, died of intracranial HTN, macrocephaly, cerebral atrophy	Coloboma
Delahaye et al. [25]	2012	Case series	D	5	Prenatal (18w gestation) –27 y	*FOXC1*	Vermis hypoplasia, white matter hyperintensities, mega-cisterna magna	Schwalbe's Ring, corectopia Axenfeld anomaly
DeScipio et al. [26]	2005	Case series	D	5	27w–10 y	*FOXC1*	Posterior fossa cyst, polymicroglia, Dandy-Walker	Posterior embryotoxon
Eid et al. [27]	2020	Case report	E	1	9 m	*FOXC1*	Leukoencephalopathy, cavum septum pellucidum, polymicrogyria, occipital pachygyria	None
Fan et al. [28]	2020	Case report	E	2	24–53 y	*FOXC1*	White matter hyperintensities, basal ganglia calcifications	Posterior embryotoxon
French et al. [4]	2014	Case series, GWAS	D	18	1 y	*FOXC1* & *PITX2*	Cerebral small vessel disease (white matter hyperintensities, dilated perivascular spaces, lacunar infarcts)	None

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Table 2 (*continued*)

Author	Publication Year	Design	Evidence Level	N	Age[a]	Genetic Findings[b]	Neurological Findings[c]	Ocular Findings
Gould et al. [29]	2004	Case report	E	4	Not reported	*FOXC1*	Dandy-Walker, agenesis of the corpus callosum and brainstem	Rieger anomaly
Idrees et al. [13]	2006	Case series	D	3	16–64 y	*PITX2*	Enlarged cisterna magna, flattened sella turcica	Posterior embryotoxon, corectopia
Kapoor et al. [76]	2011	Case report	E	1	6 y	*FOXC1*	Demyelination of subcortical and periventricular white matter	Posterior embryotoxon, corectopia
Kearns et al. [31]	2019	Case series	E	2	6–11 y	*FOXC1*	Enlarged perivascular spaces, white matter hyperintensities, shortened corpus callosum, short vermis, mega cisterna magna, arterial tortuosity, dolichoectasia of vertebrobasilar system, enlargement of occipital horns of lateral ventricles	None
Kerrigan et al. [69]	2007	Case report	E	1	8.6 y	*FOXC1*	Microcephaly at birth, hypothalamic hamartoma	None
Kleinmann et al. [59]	1981	Case series	D	7	2w– 41 + y	Not reported	Enlarged sella	Rieger's anomaly
Koçak-Midillioglu et al. [77]	2003	Case report	E	1	Birth	Not reported	Indistinctness of margins of optic disc, elevated optic nerve head surface, yellow-pink disc, optic nerve drusen	Axenfeld Rieger
Kumar et al. [32]	2017	Case report	E	1	8 y	*FOXC1*	Leukoencephalopathy	Axenfeld Rieger
Levin et al. [33]	1986	Case report	E	1	5w	*FOXC1*	Hydrocephalus	Axenfeld Rieger
Linhares et al. [34]	2015	Case report	E	1	12 y	*FOXC1*	Diffuse leukopathy, CSF fistula (CSF rhinorrhea)	Corectopia
Lopes et al. [35]	2019	Case report	E	1	Not reported	*FOXC1*	White matter hyperintensities, intracranial calcifications	Posterior embryotoxon
Lowry et al. [68]	2007	Case report	E	1	23 y	Normal for *FOXC1, PITX2, & BARX1*	De Hauwere syndrome (Axenfeld Rieger, hydrocephalus, hearing loss)	
Maclean et al. [36]	2005	Case report	E	1	22 m	*FOXC1*	Hydrocephalus; hypoplasia of the cerebellum, brainstem, and corpus callosum	Axenfeld Rieger
Martinez-glez et al. [37]	2006	Case report	E	1	22 y	*FOXC1*	Hydrocephalus	None
McCann et al. [52]	2005	Case report	E	1	3w	*FGFR*	Scaphocephaly, Chiari I	Axenfeld Rieger
Megighian et al. [62]	2003	Case report	E	1	32 y	Not reported	Dysmorphism of the acoustic channels	Bilateral dysgenesis of the iris
Meuwissen et al. [46]	2015	Case series	D	24	Not reported	*COL4A1*	Periventricular leukomalacia	Posterior embryotoxon
Moog et al. [61]	1998	Case report	E	2	35–39 y	Not reported	Hydrocephalus, leptomeningeal calcifications	Axenfeld Rieger
Nandeesh et al. [47]	2020	Case report	E	1	18 y	*COL4A1*	Leukoencephalopathy, microhemorrhagic lesions, hemorrhagic stroke, porencephalic cyst, right vertebral dolichoectasia	Axenfeld Rieger
Nastasi et al. [63]	2018	Case report	E	1	1w	Not reported	Occipital-cervical meningocele, ventriculomegaly	Posterior embryotoxon
Nielsen et al. [54]	1984	Case report	E	1	4 m	*21q22.2* Monosomy	Cerebral atrophy	Posterior embryotoxon
Pace et al. [38]	2017	Case report	E	1	49 y	*FOXC1*	Microcephaly	None
Puklin et al. [64]	1981	Case report	E	1	6w	Not reported	Elevated optic discs with blurred margins and slight pallor	Axenfeld anomaly
Reis et al. [53]	2011	Case series	D	1	6 y	*BMP4*	Macrocephaly	Rieger anomaly

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Table 2 (*continued*)

Author	Publication Year	Design	Evidence Level	N	Age[a]	Genetic Findings[b]	Neurological Findings[c]	Ocular Findings
Rodahl et al. [48]	2013	Case series	D	45	Birth–90 y	*COL4A1*	Cerebral hemorrhages, leukoencephaly, calcifications, ventriculomegaly, cerebellar atrophy	Iris hypoplasia, posterior embryotoxon, corectopia, peripheral anterior synechiae
Saffari et al. [39]	2020	Case report	E	2	Adolescent	*FOXC1* & *COL4A1*	White matter hyperintensities	Axenfeld Rieger
Schumann et al. [40]	2016	Case control	C	4	Prenatal	*FOXC1*	Dandy-Walker, ventriculomegaly	None
Shah et al. [50]	2012	Case report	E	1	Birth	*COL4A1*	Periventricular white matter change, progressive microcephaly	Anterior segment dysgenesis
Shields et al. [2]	1983	Case series	D	5	15–50 y	Not reported	Empty sella, parasellar arachnoid cyst	Posterior embryotoxon Corectopia
Sibon et al. [49]	2007	Case report	E	5	8–58 y	*COL4A1*	Leukoencephalopathy	Axenfeld Rieger
Steinsapir et al. [65]	1990	Case report	E	1	Birth	Not reported	Brachycephalic skull, spina Bifida occulta	Rieger's anomaly
Titheradge et al. [12]	2014	Case report	E	4	4–40 y	*PITX2*	Microcephaly, optic nerve drusen	Posterior embryotoxon, peripheral anterior synechiae
Van Bever et al. [67]	2007	Case report	E	1	Birth	Normal for *PAX6, FOXC1, PITX2,* & *MYNC*	Microcephaly, occipito-temporal hematoma	Iris adhesions to cornea
Van Daele et al. [66]	1996	Case report	E	1	Birth	Not reported	Enlarged frontal and temporoparietal subarachnoid spaces	Axenfeld anomaly
Van Der Knaap et al. [41]	2006	Case report	E	3	1–2 y	*FOXC1*	White matter hyperintensities, white matter tigroid pattern	Posterior embryotoxon
Vernon et al. [42]	2013	Case report	E	1	41 y	*FOXC1*	Leukoencephalopathy	Axenfeld Rieger
Whitehead et al. [6]	2013	Case report	E	1	19 m	Not reported	Deep periventricular white lesions, pineal and pars intermedia cysts	Axenfeld Rieger
Wu et al. [43]	2020	Case series	D	11	Not reported	*FOXC1*	AVM	Axenfeld Rieger
Yararbas et al. [44]	2019	Case report	E	1	2.5 y	*FOXC1*	Cystic cisterna magna, macrocephaly, ventricular dilatation	None
Zhang et al. [45]	2004	Case report	E	1	Birth	*FOXC1*	Cortical atrophy, cerebellar hypoplasia, brachycephaly, microcephaly	None
Zhao et al. [11]	2022	Case control	C	977	$\bar{x} = 64$ y	*PITX2*	Stroke	None

[a] d = days, w = weeks, m = months, y = years.
[b] FOXC1 = forkhead box protein C1, COL4A1 = collagen type IV alpha 1, PITX2 = pituitary homeobox 2, FGFR = fibroblast growth factor receptor, BMP4 = bone morphogenetic protein 4.
[c] HTN = hypertension, CSF = cerebrospinal fluid, AVM = arteriovenous malformation.

directed to inform screening and clinical decision making for these patients.

4.1. *Implications of genetic findings*

In addition to *FOXC1* and *PITX2,* we found that *COL4A1* was associated with ARS and neurological findings. *FOXC1* has a well-established role in ocular development defined by its prevalence in ARS, but its known role in cardiovascular development implicates a role in structural neurologic and neurovascular development as well, which was corroborated in the current study [5]. We found more reports of neurological abnormalities with *COL4A*1 than *PITX2*. *PITX2* was less frequently encountered in the current review, perhaps because this gene is typically associated with eye, dental, and umbilical abnormalities rather than neurological ones [5]. However, *COL4A1* was discovered to be frequently involved in the neurological manifestations of ARS, implicated in leukoencephalopathy and small vessel vascular disease [47,49]. Literature suggests that *COL4A1* tends to be highly pathogenic, associated with porencephaly, perinatal hemorrhage, and epilepsy, among other cardiac and renal anomalies [46,47]. Genetic testing in an

Table 3
Genetic findings associated with AR.

Gene[a]	N (%) of studies[b]	N (%) of total patients[b]	Abnormality	N (%)	Studies
FOXC1 (6p25)	33 (67.3)	100 (0.9)	Deletion	18 (54.5)	[4,11,15–45]
			Missense Mutation	4 (12.1)	
			Ring Chromosome	4 (12.1)	
			Unbalanced Translocation	2 (6.0)	
			Duplication	2 (6.0)	
			Monosomy	1 (3.0)	
			Unknown	2 (6.0)	
COL4A1 (13q34)	7 (14.3)	83 (0.8)	Missense Mutation	6 (85.7)	[3,39,46–50]
			Unknown	1 (14.3)	
PITX2 (4q25)	5 (10.2)	10,504 (98.2)	Missense mutation Deletion/microdeletion	3 (60)	[4,11–14]
				2 (40)	
FGFR (8p11)	2 (4.1)	2 (.02)	Missense mutation	1 (50)	[51,52]
			Unbalanced Translocation	1 (50)	
BMP4 (14q22)	1 (2.0)	5 (.05)	Loss of function (Missense, Nonsense, Frameshift)		[53]
21q22.2	1 (2.0)	1 (.01)	Partial Monosomy		[54]

[a] FOXC1 = forkhead box protein C1, COL4A1 = collagen type IV alpha 1, PITX2 = pituitary homeobox 2, FGFR = fibroblast growth factor receptor, BMP4 = bone morphogenetic protein 4.
[b] The total number of studies and patients in this table is out of those that included genetic data, which excludes 14 studies [2,6,46,55–66] without data and 2 studies [67,68] with no genetic abnormalities noted.

Table 4
Neurological findings.

Structural Neurological Finding	Number of Papers	Associated Genes (number of occurrences)[a]	Studies
White Matter Abnormalities (Including white matter hyperintensities, leukoencephalopathy, periventricular white matter lesions on cranial imaging)	26	6p25/*FOXC1*(18), *COL4A1* (7), 5p15 (1), 17q25(1), *PITX2* (1), 7q33-q36 (1)	[3,4,6,15–17,20–22,25,27, 28,30–32,34–36,39,41,42, 46–50,57]
Dandy-Walker Complex	12	6p25/*FOXC1*(9), 5p15(1), 15q26(1), *PITX2*(1)	[13,15,17,18,22,25,26,29, 31,40,41,44]
Agenesis/Hypoplasia of The Corpus Callosum	11	6p25/*FOXC1*(9), 4p16-p15(1), Xp22 (2), 5p15(1)	[15,17,22,24,25,29,31,36, 40,45,51]
Ventriculomegaly (W/O Explicit Mention of Hydrocephalus)	11	6p25/*FOXC1*(8), 17q25(1), 15q26 (1), 6q27(1), *COL4A1*(1)	[20,23,25,26,31,40,41,44, 45,48,63]
Hydrocephalus	9	6p25/*FOXC1* (6)	[24,26,29,33,36,37,61,66, 68]
Optic Disc/Nerve Abnormality (Not Secondary to Glaucoma)	7	6p25/*FOXC1*(3), 17q25(1), *PITX2*(1)	[12,20,26,45,56,60,64]
Microcephaly	6	6p25/*FOXC1*(3), *COL4A1*(2), *PITX2* (1)	[12,38,45,50,67,69]
Brain Atrophy	6	6p25/*FOXC1*(4), 21q22(1), *COL4A1* (1)	[21,23,24,45,48,54]
Macrocephaly/Enlarged Subarachnoid Spaces	5	6p25/*FOXC1*(3), 15q26(1), *BMP4*(1)	[19,24,44,53,66]
Synostosis	5	6p25/*FOXC1*(1), *FGFR2*(1), 6p24(1)	[6,24,45,52,65]
Stroke	4	6p25/*FOXC1*(1), *COL4A1*(1), *PITX2* (2)	[4,11,14,47]
Gyral Abnormalities	4	6p25/*FOXC1*(4), 5p15(1), 7q33-q36 (1)	[17,19,26,27]
Calcifications	4	6p25/*FOXC1*(2), *COL4A1*(1)	[28,35,48,61]
Skull Variations	4	*PITX2*(1)	[6,13,59,62]
Intracranial Hemorrhage/Microhemorrhage	3	*COL4A1* (3)	[3,47,48]
Brainstem Agenesis/Hypoplasia	3	6p25/*FOXC1*(3), 5p15(1)	[17,29,36]
Dilated Virchow-Robin Spaces	3	6p25/*FOXC1*(3)	[4,22,31]
Aprosencephaly/Porencephaly	2	*COL4A1*(1)	[47,55]
Suprasellar/Parasellar Arachnoid Cyst	2	Not reported	[2,58]
Cerebellar Hypoplasia	2	6p25/*FOXC1*(2)	[36,45]
Other Neurovascular Findings	3	6p25/*FOXC1*(2), *COL4A1*(1)	[31,43,47]
Other	14	See Table 2	[2,4,15,22,27,28,34,42,45, 47,52,63,65,69]

[a] FOXC1 = forkhead box protein C1, COL4A1 = collagen type IV alpha 1, PITX2 = pituitary homeobox 2, FGFR = fibroblast growth factor receptor, BMP4 = bone morphogenetic protein 4.

Table 5
Neurovascular findings.

Abnormality	Author	Brief Description of Study[a]
Stroke	Bellenguez et al. [14]	GWAS of ischemic stroke with 3548 affected patients and 5972 controls. Replicated association between cardioembolic stroke and variants close to PITX2.
	French et al. [4]	GWAS of 9361 patients with FOXC1 mutation found 18 patients with cerebral small vessel disease (CSVD), defined as white matter hyperintensities, dilated perivascular spaces, microbleeds, and lacunar infarcts. Case series found 9 PITX2-attributable ARS patients had white matter hyperintensities and CSVD, independent of atrial fibrillation or other cardiac abnormalities.
	Nandeesh et al. [47]	Case study of 18yo girl with COL4A1 and bilateral Axenfeld Rieger who had hemorrhagic stroke, microhemorrhages, right vertebral dolichoectasia, periventricular white matter changes, and a porencephalic cyst. On histology, found thickening of small-caliber blood vessels and disruption of basement membrane. No cardiac abnormalities.
	Zhao et al. [11]	GWAS of 476 stroke patients and 501 controls found single nucleotide polymorphisms in PITX2 were associated with increased stroke risk.
Other Neurovascular Findings	Kearns et al. [31]	Case series of 2 siblings with 6p25 deletion had intracranial vascular dolichoectasia, which were not thought to be associated until this study. No cardiac abnormalities.
	Wu et al. [43]	Case series of 11 patients with FOXC1 mutations found AVM in one patient with Axenfeld Rieger anomaly. No cardiac abnormalities.

[a] GWAS = genome-wide association studies, PITX2 = pituitary homeobox 2, FOXC1 = forkhead box protein C1, CSVD = cerebral small vessel disease, ARS = Axenfeld Rieger Syndrome, COL4A1 = Collagen type IV alpha 1, AVM = arteriovenous malformation.

ARS patient may be warranted for the identification of implicated genes, confirming diagnosis, identifying potential therapeutic targets in implicated pathways, and stratifying disease pathogenicity to inform screening and prevention measures in the future.

4.2. Implications of neurological findings

The most common ARS associated neurological finding was white matter abnormalities, followed by Dandy-Walker Complex, agenesis of the corpus callosum, ventriculomegaly, and hydrocephalus, among other neurological conditions. In ARS patients that have Dandy-Walker Complex and agenesis of the corpus callosum, a neurology consultation would be appropriate as these findings are associated with neurodevelopmental delay [34,51]. Most of the structural ARS-associated neurological anomalies described were nonspecific findings and considered to be non-intervenable. However, a few studies identified ARS-associated hydrocephalus and craniosynostosis, which if present, could have indications for surgical intervention. Therefore, it is important that physicians diagnosing and evaluating patients with ARS have a firm understanding of the signs and symptoms of such neurologic conditions. However, given the limited data, no definitive association could be identified; therefore, no imaging recommendations could be made for patients presenting with ARS, unless specific symptoms warrant further evaluation.

4.3. Implications of neurovascular findings

ARS-associated neurovascular findings included ischemic and hemorrhagic stroke, CSVD, tortuosity/dolichoectasia of arteries, and arteriovenous malformation (AVM). The association with stroke and other neurovascular abnormalities was independent of cardiac abnormalities in all but the PITX2-associated studies; however, one of the three studies discussing PITX2 and stroke found an increased stroke risk independent of atrial fibrillation, suggesting there is a cerebrovascular component of the PITX2-related stroke risk as well [4]. As a result, measures for detection and prevention of neurovascular disease may be warranted and primary stroke prevention measures may be of importance for consultation and management in at-risk patients. Dolichoectasia of arteries and arteriovenous malformation (AVM) were identified in a few studies, however, were too rare to make can definitive connections between ARS and warrant screening for these abnormalities alone. Nonetheless, in the presence of clinical symptoms, suspicion for potentially morbid neurovascular findings should be higher and screening pursued. Ultimately, recommendations should continue to be made on a patient-by-patient basis, keeping in mind their possible predisposition for stroke and other neurovascular anomalies. It is necessary that larger-scale, prospective, multicentered studies be done to quantify rates of findings, identify associated risk, and better define the disease process in ARS to inform management and treatment.

4.4. Future directions

Several genes associated with ARS in addition to the neurological and neurovascular findings seen in ARS have been identified, however no definitive connections can be made to inform screening and management of the ARS population. Several areas of future study were identified which could lead to a better understanding of the disease pathogenesis and potential management.

While the *FOXC1* and *PITX2* genes have been well-characterized, *COL4A1* is lesser known in relation to this syndrome. *COL4A1* has been associated with anterior segment dysgenesis but is not classically connected to ARS. This gene was studied in the context of case reports and case series, thus further investigation into the role of *COL4A1* in ARS, such as through GWAS, may be warranted. *COL4A1* autosomal dominant mutations are known to cause a spectrum of neurological conditions including epilepsy and cerebrovascular disease. Both focal and generalized epilepsy have been described, but genotype-phenotype correlations have not been established [71].

In *COL4A1*-associated cerebrovascular disease, onset occurs from fetal timing onward with reports ranging from small-vessel disease to fatal intracranial hemorrhage [46,71–75]. The above has overlap with neurological findings that occur with ARS as identified in the literature.

The true frequency or prevalence with which ARS associated structural neurological findings occur remains unknown. Knowing these metrics could be helpful in informing screening, referrals and consultations with collaborating services, and treatment decisions over time. Specifically, such with additional knowledge, treatment decisions affecting management are informed, such as screening and surveillance imaging or therapies for modifying stroke risk. This review was limited to ARS associated structural neurological abnormalities to evaluate support for neuroradiographic imaging and intracranial screening. The broader understanding of neurological sequela of ARS was not in the scope of this study, and thus synthesis of the understanding of non-structural neurological findings, such as epilepsy and psychiatric conditions, and structural abnormalities in other organ systems were deferred. Future directions would entail further investigation into ARS in both non-structural neurological conditions and other systemic abnormalities, contributing to the holistic care of these patients with anticipated healthcare needs over their lifetime. Neurovascular manifestations of ARS were found to be common, especially stroke and CVSD, which were corroborated by multiple groups and larger population studies. This finding suggests a future role of primary stroke prevention in ARS patients.

4.5. Limitations

This systematic review has several additional limitations. Only published studies were included, putting results at risk for publication bias. Results may overestimate the number of positive and significant study results. The quality of evidence was low. There were no randomized trials, prospective or retrospective cohort studies. This phenomenon limits the quality of evidence from which our conclusions are derived. Many of the included studies were case reports or case series, limiting the generalizability of the conclusions. Additionally, articles were limited to the English language; therefore, studies not written in English or not yet translated were not included and may have excluded findings in non-English speaking regions. Lastly, meta-analysis was not possible from the existing data and thus not conducted as part of this systematic review.

5. Conclusion

This study is the first systematic review investigating the genetic underpinnings, neurological manifestations, and neurovascular associations of Axenfeld-Rieger Syndrome (ARS). *FOXC1, COL4A1,* and *PITX2* genes were most frequent in this population. Intracranial radiographic findings included white matter abnormalities and Dandy-Walker Complex. Neurovascular findings were identified, with cerebral small vessel disease and ischemia being the most common. The risk of stroke in ARS is described both in the absence and presence of cardiac comorbidities. The presence of neurological and neurovascular abnormalities in this population may warrant further investigation in these patients, should clinical concern arise, as potential surveillance or treatment paradigms may prove to be helpful.

Ethics approval and consent to participate

No ethics approval or consent to participate was required in this study, as the patient information used was from already published sources.

Availability of data and material

Due to the nature of the research, there was no primary data collected. Materials were obtained from searches of PubMed, Scopus, and Embase.

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Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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