Supplemental Note: Clinical details of all individuals with ARS included in this study.

Individual 1 (ES_11983) is a 12-year-old female with *FOXC1*-related ARS, caused by a heterozygous 3.15 Mb terminal deletion 6pter-p25.2 (6:203433-3140745) involving the entire *FOXC1*. She presented at birth with bilateral cloudy corneas, initially diagnosed as Peters anomaly but later revised to Axenfeld-Rieger anomaly. Specifically, she has a temporal iridocorneal adhesion and shallow anterior chamber in the right eye and bilateral posterior embryotoxon with adhesions and moderate central corneal haze in the left. Visual acuity is 20/50 OD and 20/70 OS with a moderate hyperopia in the left eye (+0.50 OD; +4.00 OS). IOP is normal with no evidence of glaucoma. Non-ocular anomalies include mild hypotonia in early life with normal intelligence, somewhat loose joints, dental crowding, and minor hearing loss. Brain MRI showed a cavum velum interpositum, possibly contributing to headaches. She also has a history of periodic fevers and rash of unknown origin, now resolved, and decreased immune function.

Individual 2 (ES_12489) is a 17-year-old male with *FOXC1*-related ARS, caused by a heterozygous nonsense variant c.477C>G p.(Tyr159*) (XX). He has bilateral ARA with congenital glaucoma diagnosed at 13 days of age based on elevated IOP and optic nerve cupping requiring surgery at 3 months of age and continued use of drops. Eye exam showed bilateral posterior embryotoxon with multiple processes and a Haab's striae in the left eye. Visual acuity is 20/25 OD and 20/40 OS with mild hyperopia (+1.00 OD and +2.50 OS). Non-ocular anomalies include soft teeth with frequent cavities, skeletal anomalies (pectus carinatum, easily broken bones, and ankle anomaly requiring surgical correction), punctate white matter anomalies on Brain MRI with high intelligence, postural orthostatic tachycardia syndrome (POTS) and dysautonomia, and small build as a child with a delayed growth spurt.

Individual 3 (ES_12490), a younger sibling of Individual 2 (ES_12489), is a 14-year-old female with the same nonsense variant in *FOXC1*. She has bilateral ARA with congenital glaucoma diagnosed at 12 days of age based on elevated IOP and optic nerve cupping but treated with drops only (begun at 2 years of age); she has had two surgeries for strabismus. Eye exam

noted vertical Haab's striae in both corneas, posterior embryotoxon with processes from the iris insertion. Visual acuity is 20/30 OD and 70 OS with low hyperopia on the right and low astigmatism on the left. Non-ocular anomalies include small teeth with frequent cavities, mispositioned heart, extensive white matter anomalies on Brain MRI with math disability poor impulse control but advanced empathy, delayed puberty, possible decreased bladder sensation, and POTS with dysautonomia.

Individual 4 (ES_11974) is a 27-year-old male with *PITX2*-related ARS caused by a heterozygous frameshift variant c.515del p.(Gln172Argfs*36). He has bilateral ARA with corectopia in the left eye and severe iris atrophy in the right. Glaucoma was diagnosed in the right eye at 7-8 years of age and in the left eye at 14 years of age based on elevated IOP and optic nerve cupping . He underwent numerous glaucoma surgeries as well as cataract extraction and prosthetic iris implantation in the right eye, but this eye ultimately underwent enucleation. Non-ocular anomalies include microdontia as well as hypodontia/oligodontia, umbilical hernia with redundant periumbilical skin, Meckel diverticulum, Wolf-Parkinson-White syndrome, and double-jointed thumbs.

Individual 5 (ES_12355) is a 38-year-old male with *PITX2*-related ARS caused by a heterozygous frameshift variant c.515del p.(Gln172Argfs*36). He has bilateral ARA with severe iris hypoplasia in both eyes, glaucoma diagnosed in his 20s based on elevated IOP and optic nerve cupping requiring surgery in his left eye only at 31 years of age and right corneal guttata. Visual acuity is 20/200 OD and 20/63 OS with high myopia (-9.00 and -6.50). Non-ocular anomalies were milder than typical for *PITX2*: teeth were mildly small (with room for wisdom teeth) but normal in number and shape, normal umbilical region but small abdominal hernia two inches above the belly button, and history of lower intestinal irritation.

Individual 6 (ES_12481) is a 14-year-old male with *PITX2*-related ARS caused by a heterozygous nonsense variant c.223C>T p.(Gln75*). He has bilateral ARA with severe iris hypoplasia in the right eye and recent diagnosis of cataract in the right eye; mild ptosis is also

noted in the right eye. Glaucoma was diagnosed at 13 years of age with elevated IOP (no info on presence/absence of optic nerve cupping) treated with surgery required in the right eye only at 13 and drops continued in both eyes. Visual acuity is 20/150 OD and 20/40 OS, with high myopia (-14 and -11.75). Non-ocular anomalies include microdontia and hypodontia/oligodontia, umbilical hernia with redundant periumbilical skin, and short umbilical cord (10 inches).

Individual 7 (ES_12482) is a 52-year-old female with *PITX2*-related ARS caused by a heterozygous missense variant affecting the homeodomain c.296T>C p.(Phe99Ser). She has bilateral ARA with severe corectopia on the left, bilateral glaucoma diagnosed at 45 years with elevated IOP (no info on presence/absence of optic nerve cupping) treated with drops only and bilateral cataract diagnosed at 49 years. Visual acuity is 20/20 OD and CF OS. Non-ocular anomalies include microdontia and hypodontia/oligodontia, umbilical hernia with redundant periumbilical skin, and short stature.

Individual 8 (ES_12483), the daughter of ES_12482, is an 18-year-old female with the same missense variant in *PITX2*. She has bilateral ARA with glaucoma diagnosed at 10 years of age (no clinical details available) requiring surgery in the left eye only that led to hypotension; the left eye also underwent surgery for an anterior subcapsular cataract and corneal transplant. Eye exam identified microcornea and cataract in the right eye and iridocorneal adhesion, corectopia, and IOL in the left. She was born prematurely (25 weeks) and has bilateral laser scars from treatment of retinopathy of prematurity. Last measured visual acuity was 20/60 OD and 20/600 OS (but was during hypotensive episode) with high myopia. Non-ocular anomalies include microdontia and hypodontia/oligodontia, short stature, and umbilical hernia with redundant periumbilical skin.

Individual 9 (ES_12486) is a 45-year-old female with *PITX2*-related ARS caused by a novel heterozygous nonsense variant c.211_212del p.(Asp71*). She has bilateral ARA with glaucoma diagnosed in the right eye at 8 years old with documented optic nerve cupping (no info on intraocular pressure). Right eye has more significant iris atrophy and polycoria. She has

bilateral cataracts (right removed at 23 years) and underwent two corneal transplants in the right eye. Visual acuity is 20/250 OD and 20/24 OS with high myopia (-6.00 OS). Non-ocular anomalies include microdontia and oligodontia, redundant periumbilical skin, ulcerative colitis (18 years) and reports difficulty learning to read but normal intelligence.

Individual 10 (ES_12516) is a 44-year-old female with *PITX2*-related ARS caused by a novel heterozygous missense variant c.385A>C p.(Thr129Pro) in the homeodomain. She has bilateral ARA with severe corectopia and glaucoma diagnosed in her 30s with elevated IOP (no info on presence/absence of optic nerve cupping) treated with drops only. High myopia is present (-7.00 OD and -8.00 OS). Non-ocular anomalies include oligodontia and shallow roots in other teeth, 1937and redundant periumbilical skin.

Individual 11 (ES_12526) is a 22-year-old female with *PITX2*-related ARS caused by a heterozygous missense variant c.431G>C p.(Arg144Pro) in the homeodomain. She has bilateral ARA with severe corectopia on the right and severe iris hypoplasia on the left with lenticular opacities as well as bilateral iridocorneal adhesions; glaucoma was diagnosed at 4-5 years of age based on elevated intraocular pressure without evidence of optic nerve cupping and required surgery and continued drops. Visual acuity is 20/200 OU. Non-ocular anomalies include hypodontia, omphalocele with redundant periumbilical skin, and Meckel diverticulum.

Individual 12 (ES_12541) is a 13-year-old male with *PITX2*-related ARS caused by a novel heterozygous missense variant c.287G>C p.(Arg96Pro) in the homeodomain. He has bilateral ARA with severe corectopia and microcornea along with right severe iris hypoplasia and polycoria, early stages of glaucoma noted at 11 years based on elevated intraocular pressure without evidence of optic nerve cupping, and history of strabismus surgery. Visual acuity is 20/80 OD and 20/40 OS with myopia (-3.00 OU). Non-ocular anomalies include oligodontia, redundant periumbilical skin, hypotonia and gross motor delay with normal intelligence but difficulty with emotional regulation, constipation and history of eating issues as a child, and joint hypermobility.

Individual 13 (ES_12570) is a 38-year-old White female with *PITX2*-related ARS caused by a complex genomic rearrangement. She has bilateral ARA with mild left iris hypoplasia and corectopia and right polycoria. She had glaucoma surgery at 14 years in the right eye due to elevated IOP and optic nerve cupping. Visual acuity is 20/25 OD and 20/40 OS. Non-ocular anomalies include redundant periumbilical skin surgically corrected in infancy as well as oligodontia and microdontia.

Table S1: Genetic data.

Gene	Variant	CADD (1.6)	REVEL	gnomADv4 Eur	Individual 1 ES_11983	Individual 2 ES_12489	Individual 3 ES_12490	Individual 4 ES_11974	Individual 5 ES_12355	Individual 6 ES_12481	Individual 7 ES_12482	Individual 8 ES_12483	Individual 9 ES_12486	Individual 10 ES_12516	Individual 11 ES_12526	Individual 12 ES_12541	Individual 13 ES_12570
Axenfeld-Rieger Syndrome alleles																	
FOXC1	3.15 Mb deletion 6pter-p25.2	-	-	-	HET	-	-	-	-	-	-	-	-	-	-	-	-
FOXC1	c.477C>G p.(Tyr159*)	36	-	-	-	HET	HET	-	-	-	-	-	-	-	-	-	-
PITX2	c.515del p.(Gln172Argfs*36)	-	-	-	-	-	-	HET	-	-	-	-	-	-	-	-	-
PITX2	c.663del p.(Asn222Thrfs*6)	-	-	-	-	-	-	-	HET	-	-	-	-	-	-	-	-
PITX2	c.223C>T p.(Gln75*)	41	-	-	-	-	-	-	-	HET	-	-	-	-	-	-	-
PITX2	c.296T>C p.(Phe99Ser)	32	0.951	-	-	-	-	-	-	-	HET	HET	-	-	-	-	-
PITX2	c.211_212del p.(Asp71*)	-	-	-	-	-	-	-	-	-	-	-	HET	-	-	-	-
PITX2	c.385A>C p.(Thr129Pro)	32	0.978	-	-	-	-	-	-	-	-	-	-	HET	-	-	-
PITX2	c.431G>C p.(Arg144Pro)	32	0.88	-	-	-	-	-	-	-	-	-	-	-	HET	-	-
PITX2	c.287G>C p.(Arg96Pro)	32	0.953	-	-	-	-	-	-	-	-	-	-	-	-	HET	-
PITX2	genomic rearrangement	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	HET
Foveal hypoplasia alleles																	
TYR	c.575C>A p.(Ser192Tyr)	24	0.355	0.367 (80073 hom)	HOM	HET	HET	HOM	HET	-	HET	HET	-	HET	HET	HET	HOM
TYR	C.1205G>A p.(Arg402Gln)	29	0.695	0.294 (51519 hom)	-	HOM	HOM	-	HET	HOM	-	-	HOM	-	HET	-	-
OCA2	c.1465A>G p.Asn489Asp	26.6	0.853	0.00088 (1038/1180032; 2 hom)	-	-	-	HET	-	-	-	-	-	-	-	-	-
OCA2	c.1966C>G p.Leu656Val	24	0.355	0.0000270 (30/1111878; 0 hom)	-	-	-	-	-	-	-	-	-	-	-	-	HET

Transcripts IDs: *TYR* (NM_000327.5), *OCA2* (NM_000275.2), *FOXC1* (NM_001453.3), *PITX2* (NM_000325.6)

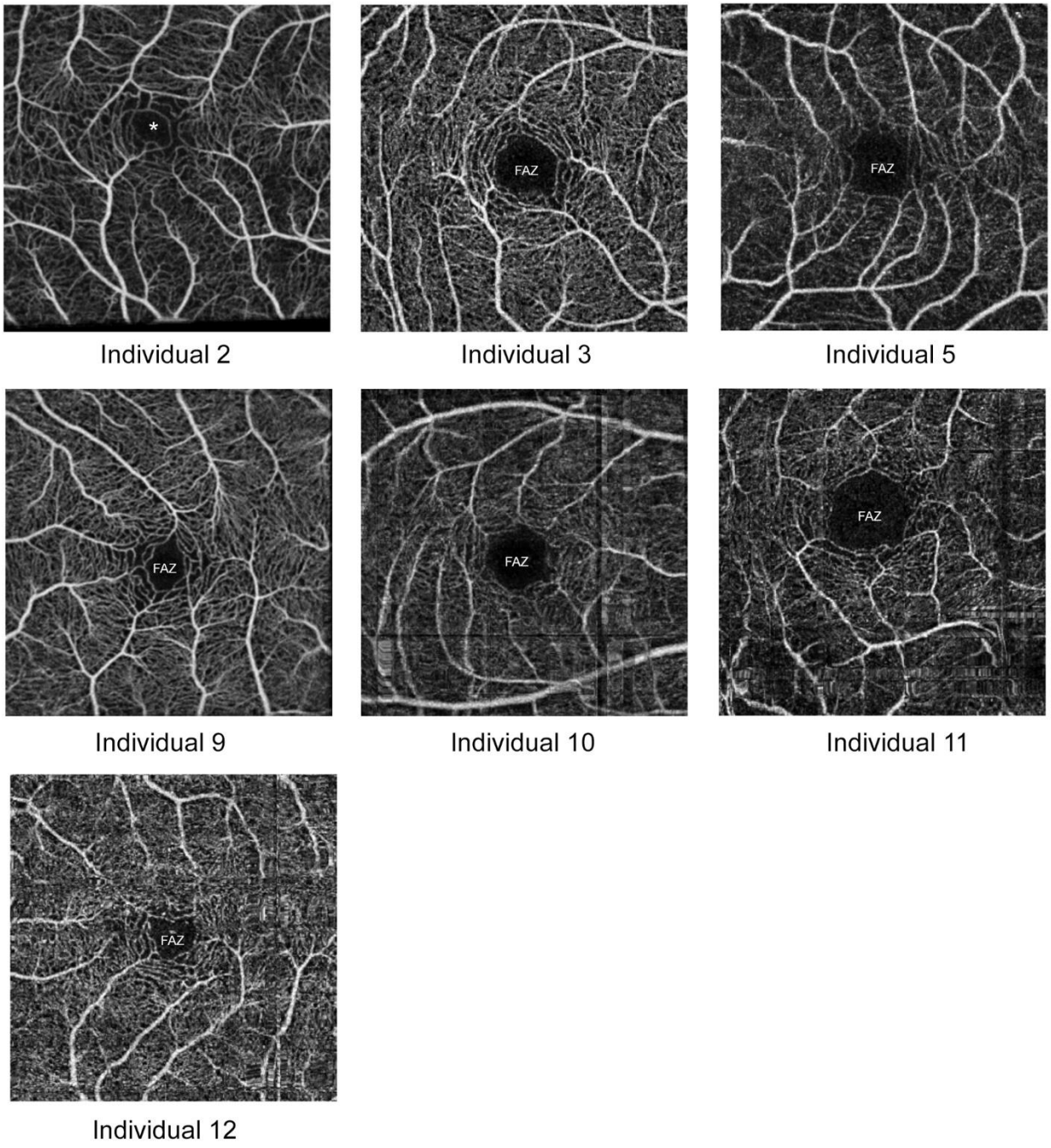

Figure S1: OCT-Angiography data. OCT-angiography images for individuals not included in Figure 5. Images are a nominal 3 x 3 mm size and were correctly scaled when computing foveal avascular zone (FAZ) area as described in the text. Individual 2 (without foveal hypoplasia) also had a fragmented FAZ (asterisk).