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RESEARCH REPORT



Ophthalmic findings in patients with arterial tortuosity syndrome and carriers: A case series

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ABSTRACT

Introduction: Arterial tortuosity syndrome (ATS) is a rare autosomal recessive disease hallmarked by tortuosity, stenosis, and aneurysm development of large- and medium-sized arteries. Mutations in *SLC2A10*, a gene that encodes the facilitative glucose transporter GLUT10, cause ATS. Several case reports have noted associated ophthalmic findings such as keratoconus, keratoglobus, and myopia without detailed descriptions or standardized examinations. We report the ophthalmic findings in a cohort of compound heterozygous ATS patients and heterozygous carriers of *SLC2A10* mutations.

Methods: Five ATS patients and three carriers were identified through an ATS specialty clinic at the Arkansas Children's Hospital in Little Rock, Arkansas. Patients underwent complete eye examinations, including corneal pachymetry, topography, and optical coherence tomography when indicated.

Results: All five patients with ATS had myopia and thin corneas with an average central corneal thickness of 426 μm , and three had corneal ectasia, two with early keratoconus and one with keratoglobus and deep stromal corneal opacities. One patient had bilateral high irregular astigmatism, and one had unilateral high regular astigmatism. All carriers had myopia, one had corneal thinning, and one developed keratectasia in one eye many years after laser-assisted *in situ* keratomileusis (LASIK) surgery.

Conclusion: We document a spectrum of ophthalmic manifestations of ATS with universal findings of myopia, corneal thinning, and a propensity for corneal ectasia leading to keratoconus or keratoglobus. Heterozygous carriers may develop keratectasia after corneal refractive surgery. Our data support regular eye examinations for all patients carrying *SLC2A10* mutations with follow-up tailored to clinical findings.

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Arterial tortuosity syndrome; corneal thinning; keratectasia; keratoconus; keratoglobus; *SLC2A10* mutation

Introduction

Arterial tortuosity syndrome (ATS; OMIM#208050) is a rare autosomal recessive connective tissue disorder caused by mutations in *SLC2A10*, a gene that encodes the facilitative glucose transporter GLUT10. The defect results in severe fragmentation of elastin, affecting all connective tissues, but mainly the vasculature.^{1–3} Individuals with ATS may show vascular elongation, tortuosity, and stenosis and are at risk for aneurysm formation and dissection of large- and medium-sized arteries. Additional connective tissue features may be identified in the skeleton, skin, and other elastic soft tissues.^{1,2,4–17} Incidentally reported ophthalmic findings in patients with ATS include myopia, keratoconus, or keratoglobus^{1,2,10,12,18,19} (Table 1). However, detailed ophthalmologic findings such as corneal thickness, corneal topography, and refraction of ATS patients have not been documented. We report a series of detailed ophthalmologic findings for one adult and four pediatric patients diagnosed with ATS, as well as one adult and two children carrying monoallelic defects in *SLC2A10*.

Materials and methods

Five ATS patients and three carriers were identified through an ATS specialty clinic at the Arkansas Children's Hospital in Little Rock, AR. This clinic was established in cooperation with "A Twist of Fate," a non-profit organization promoting research and clinical care for individuals with ATS. Seven of these individuals presented to the Jones Eye Institute at the University of Arkansas for Medical Sciences for eye exams as part of this clinic. One adult carrier was examined elsewhere. All patients underwent standardized, complete ophthalmologic examinations by a cornea specialist, including vision testing, refraction, motility testing, visual field testing, intraocular pressure (IOP) assessment, slit-lamp examination (SLE), dilated fundusoscopic examination (DFE), corneal pachymetry, topography (Atlas, Zeiss), and optical coherence tomography (OCT; Cirrus 5000 HD-OCT, Zeiss; Spectralis OCT, Heidelberg) when indicated. Patients and families were counseled, and recommendations for follow-up were provided.

Table 1. Previously reported ophthalmic manifestations.

Author	Ophthalmic manifestations
Franceschini et al. ¹⁰	One patient with keratoconus
Couke, et al. ²	One patient with keratoconus
Gardella, et al. ¹²	One patient with myopia and two with keratoconus
Callewaert, et al. ¹	Six patients with myopia and three with either keratoconus or keratoglobus
Hasler et al. ¹⁹	One patient with myopia, keratoglobus, corneal thinning/ectasia, cataract, and deep stromal corneal opacities
Ritelli, et al. ¹⁸	One patient with both myopia and keratoconus

The confidentiality and anonymity of all patients were maintained, and all testing was performed as applicable to the care of the patients assessed. IRB approval (# 24252) was obtained in accordance with the Declaration of Helsinki for the study of these individuals, and informed consent was obtained for the publication of all information acquired through patient examination and disclosure relevant to this study.

Results

The molecular data and ophthalmologic findings are represented in Table 2.

Case 1

An 8-year-old boy was diagnosed with ATS at age 2, when he was found to have severe bilateral pulmonary artery stenosis and pulmonary hypertension, vascular tortuosity, and an intracranial aneurysm. He harbors the compound heterozygous mutations c.394C>T/c.800delC (p.R132W/p.S268Qfs*12) in *SLC2A10*. He was subsequently found to have thin corneas and corneal topography concerning for early keratoconus at another eye clinic. His mother reported that he typically stood close to the television while playing video games, but vision otherwise seemed normal. A review of his prior examination records revealed a cycloplegic refraction of +1.50 + 1.00 × 115 right eye (OD) (20/20) and +1.50 + 1.00 × 0 left eye (OS) (20/25), less than 4 years earlier. On our examination, visual acuity was 20/50 OD and 20/40 OS with manifest refraction (MR) of -3.00 + 4.00 × 110 OD and -1.50 + 2.50 × 051 OS. IOP was 6 mmHg and 8 mmHg in the right and left eyes, respectively (iCare). Pupils, motility, and confrontational visual fields (CVF) were normal. SLE demonstrated bilateral diffuse corneal thinning, steepening, and nearly diffuse posterior lamellar stromal opacification of both corneas sparing a small crescent-shaped gutter nasally in both eyes (OU) (Figure 1A and B). DFE was unremarkable. Ultrasonic corneal pachymetry revealed central corneal thickness (CCT) values of 384 μm and 358 μm in right and left eyes, respectively. Corneal topography demonstrated superonasal steepening, high irregular astigmatism, and mean toric keratometry values (TKM) of 34.14 and 36.38 diopters for the right and left eyes, respectively (Figure 2A and B). Slit-lamp photographs (Figure 1A and B) and anterior segment OCT (Spectralis, Heidelberg, Figure 3A and B) were obtained to document the extensive nature of the posterior corneal opacities. The patient was diagnosed with progressive myopia and astigmatism, keratoglobus and deep stromal corneal opacities. Follow-up

with a cornea specialist to monitor changes in topography and corneal thickness was recommended.

Case 2

A 20-year-old man was diagnosed with ATS around age 13, upon discovery of a tortuous aorta and major blood vessels, bilateral pulmonary artery stenosis, loose skin, and joint hypermobility. He harbors the c.313C>T/c.1333delG (p.R105C/p.G445Efs*40) mutations in *SLC2A10*. He wears spectacles for myopia. MR was -4.00 + 5.25 × 162 OD and -3.00 + 1.75 × 032 OS with best-corrected distance visual acuity (BCDVA) of 20/20 OU. IOP (Tonopen, Reichert) was 5 mmHg OD and 4 mmHg OS, with normal pupils, motility, and CVF. SLE was notable for downward slanting palpebral fissures, floppy upper and lower eyelids, and a normal corneal exam. DFE was unremarkable. Ultrasonic corneal pachymetry revealed CCT values of 463 μm OD and 472 μm OS. Corneal topography demonstrated regular astigmatism OU, which was high in the right eye, and TKM values of 44.26 and 43.73 in the right and left eyes, respectively (Figure 2C and D).

Case 3

A 5-year-old girl harboring the *SLC2A10* c.727C>A/c.314G>A (p.Q243K/p.R105H) mutations was diagnosed with ATS at the age of three when she was evaluated for a heart murmur with echocardiography showing tortuosity of all major arteries. She had a history of failing school eye examinations and running into household objects. Her uncorrected distance visual acuity (UCDVA) was 20/100 OU with auto refraction of -1.25 sph OD and -0.50 + 0.50 × 064 OS. Tonometry (iCare) was 10 mmHg OU and pupils, motility, and CVF were normal. SLE was only notable for corneal thinning. DFE was unremarkable. Ultrasonic CCT values were 468 μm OD and 467 μm OS. Corneal topography (Atlas, Zeiss) demonstrated central and inferior steepening OU with TKM values of 46.7 and 47.13, in the right and left eyes, respectively (Figure 2E and F). Her exam was consistent with early keratoconus, and follow-up with a cornea specialist or pediatric ophthalmologist was recommended.

Case 4

A 7-year-old girl was diagnosed with ATS following the detection of aortic tortuosity and an atrial septal defect. *SLC2A10* gene analysis revealed the c.848C>A/c.1334delG (p.A283D/p.G445Efs*40) mutations. BCDVA was 20/25 OU with MR of -2.75 +0.25 × 020 OD and -3.25 +0.50 × 180 OS.

Table 2. Summary of findings.

Case	1	2	3	4	5	6	7	8
ATS/carrier	ATS	ATS	ATS	ATS	ATS	Carrier	Carrier	Carrier
Mutation	c.394C>T/c.800delC (p.R132W/p.S268Qfs*12)	c.313C>T/c.1333delG (p.R105C/p.G445Efs*40)	c.727 C>A/ c.314G>A (p.Q243K/p.R105H)	c.848C>A/c.1334delG (p.A283D/p.G445Efs*40)	c.394C>T/c.4+5G>A (p.R132W/?)	c.394C>T/WT (p.R132W/WT)	c.314G>A/WT (p.R105H/WT)	c.727 C>A/WT (p.Q243K/WT)
Systemic findings	Vascular tortuosity, pulmonary artery stenosis, valvular heart disease, joint hypermobility, dental crowding, inguinal hernia, pectus excavatum, elongated face with down-sloping palpebral fissures	Vascular tortuosity, pulmonary artery stenosis, valvular heart disease, joint hypermobility, dental crowding, inguinal hernia, pectus excavatum, elongated face with down-sloping palpebral fissures	Vascular tortuosity, poor feeding, reflux, dysautonomia, poor muscle tone, motor delay	Vascular tortuosity, scoliosis, atrial septal defect, inguinal hernia, poor feeding, elongated face with down-sloping palpebral fissures	Vascular tortuosity, delayed gastric emptying, pes planus, joint hypermobility, skin hyperelasticity, hiatal hernia, elongated face with down-sloping palpebral fissures	Recurrent ear infections, asthma	Autistic spectrum disorder, pectus excavatum, scoliosis	Venous thrombosis during pregnancy, joint hypermobility, scoliosis
SE (OD/OS)	-1.00/-0.25	-1.38/-2.13	-1.25/-0.25	-2.63/-3.00	-5.38/-4.88	-1.75/-2.25	-1.75/-2.13	-0.38/+0.13
CCT (OD/OS)	384/358	463/472	468/467	407/412*	422/415	506/512	608/609	533/549
TKM (OD/OS)	34.14/36.38	44.26/43.73	46.7/47.13	45.52/45.21	49.27/49.08	46.69/46.7	44.11/44.41	48.21/43.29
Keratocasia	✓		✓		✓			✓
Keratoconus	✓							
Keratoglobus	✓							
Corneal opacity								

SE: spherical equivalent refraction (diopters), CCT: ultrasonic central corneal thickness (μm) (OCT*), TKM: mean toric keratometry (diopters).

Tonometry (iCare) was 12 mmHg OD and 10 mmHg OS, with normal pupils, motility, and CVF. SLE revealed bilateral downward slanting palpebral fissures and corneal thinning. She had a normal DFE. OCT (Cirrus HD-OCT, Zeiss) demonstrated a CCT of 407 μm and 412 μm in the right and left eyes, respectively. Corneal topography (Atlas, Zeiss) demonstrated central steepening OD and supero-temporal steepening OS with TKM values of 45.52 OD and 45.21 OS (Figure 2G and H). Her exam was consistent with corneal thinning.

Case 5

A 7-year-old girl, carrying the *SLC2A10* mutations c.394C>T/ c.4+5G>A (p.R132W/?), was diagnosed with ATS at birth after developing pulmonary hypertension, and the discovery of arterial tortuosity. She had a past ocular history of myopia with astigmatism, corneal thinning, and possible keratoconus. Her mother stated that due to difficulty seeing the board in school, she was recently fitted for new glasses. BCDVA was 20/25 OD and 20/25 OS with a MR of $-5.50 +0.25 \times 095$ OD and $-5.50 +1.25 \times 075$ OS. Tonometry (Tonopen, Reichert) was 12 mmHg OU. She had normal pupils, motility, and CVF. SLE was notable for bilateral central corneal steepening. DFE was unremarkable. By ultrasonic pachymetry, CCT was 422 μm OD and 415 μm OS. Corneal topography (Atlas, Zeiss) demonstrated central and inferior steepening with TKM values of 49.27 and 49.08 diopters in the right and left eyes, respectively (Figure 2I and J). Her examination was consistent with mild keratoconus, and follow-up with a cornea specialist was recommended.

Case 6

This 11-year-old girl is the sister of the girl described in case 5. She carries a monoallelic mutation in the *SLC2A10* gene c.394C>T/WT (p.R132W/WT). Past medical history (PMH) was notable for ear infections and asthma. She had been followed as a glaucoma suspect because of optic nerve cupping. BCDVA was 20/20 OU with a MR of -1.75 sph and $-2.50 +0.50 \times 090$ in the right and left eyes, respectively. Tonometry (Tonopen, Reichert) was 17 mmHg OU. She had normal pupils, motility, and CVF. SLE was unremarkable, and DFE was only notable for cup to disc ratios of 0.6 OU. Ultrasonic corneal pachymetry demonstrated a CCT of 506 μm OD and 512 μm OS. Corneal topography (Atlas, Zeiss) demonstrated normal corneal curvature and TKM values of 46.69 and 46.70 diopters in the right and left eyes, respectively.

Case 7

This 15-year-old boy has a monoallelic mutation in *SLC2A10* c.314G>A/WT (p.R105H/WT). PMH was significant for autistic spectrum disorder, pectus excavatum, and mild scoliosis. He had a history of myopia for which he sometimes wore glasses but he had no other ocular complaints. MR was -1.75 sph and $-2.50 +0.75 \times 014$, in right and left eyes, respectively, and BCDVA was 20/20 OU. Pupils, motility, CVF testing, and tonometry were normal, as were the SLE

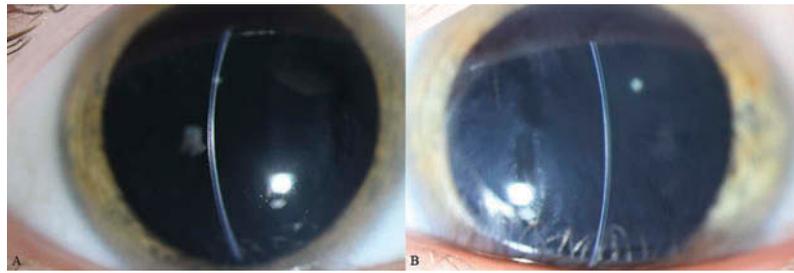


Figure 1. Slit-lamp photographs of case 1 which demonstrate deep corneal stromal opacification in both eyes (A: right eye, B: left eye).

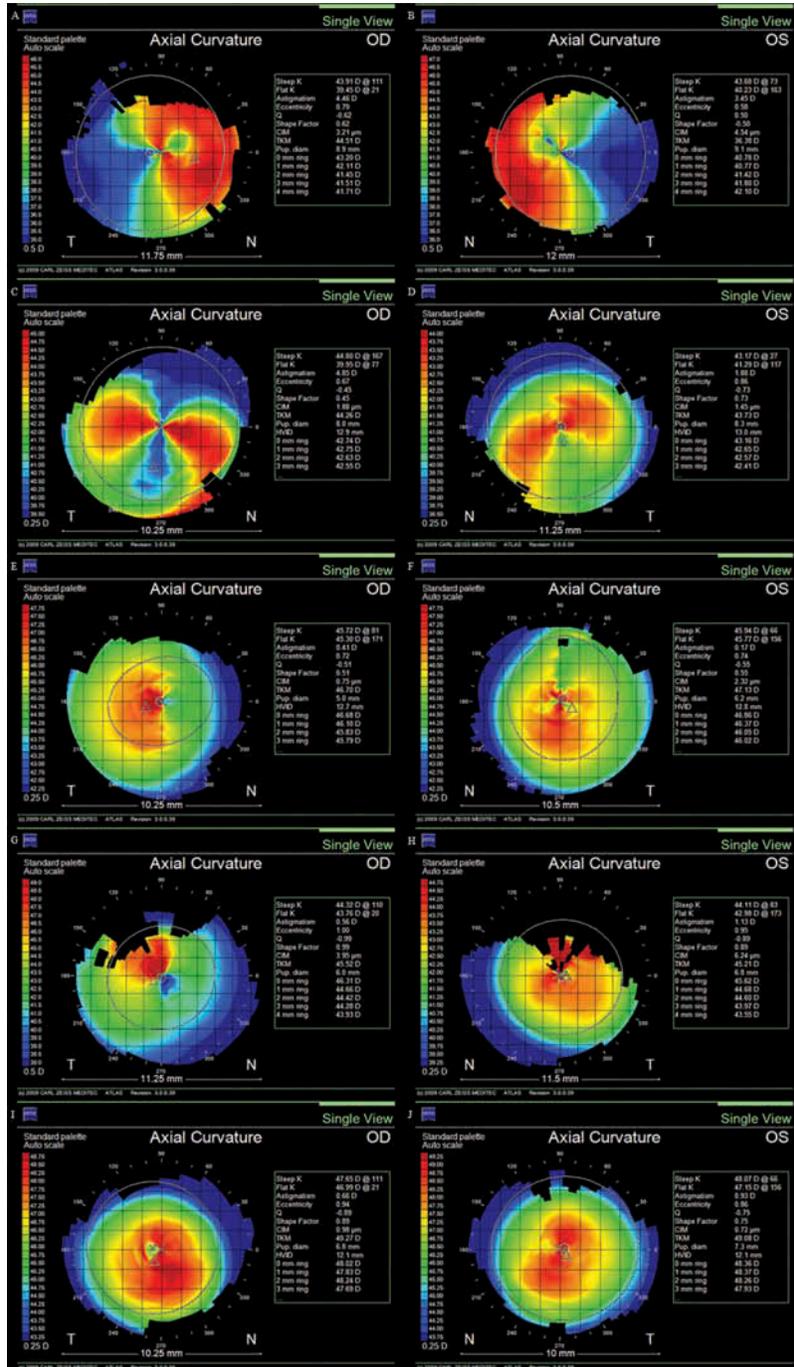


Figure 2. Corneal Topography (Atlas, Zeiss). Case 1 is represented in figures A and B, which demonstrate abnormal nasal steepening, temporal flattening, and irregular astigmatism in OU. Case 2 is represented in figures C and D, which demonstrate high regular astigmatism OD. Case 3 is represented in figures E and F, which demonstrate moderate central steepening with TKM values of 46.7 and 47.13. Case 4 is represented in figures G and H, which demonstrate mild central steepening. Case 5 is represented in figures I and J, which demonstrate moderate central steepening and TKM values of 49.27 and 49.08. Right eye (OD), left eye (OS), corneal irregularity measurement (CIM), mean toric keratometry (TKM), horizontal visible iris diameter (HVID).

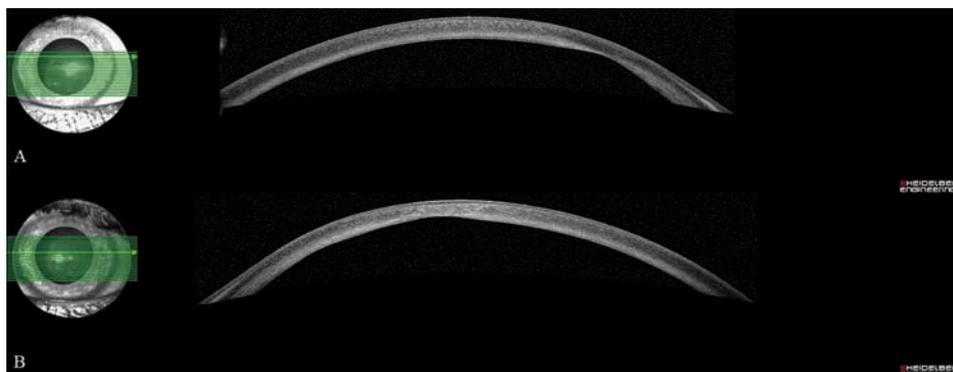


Figure 3. Anterior segment optical coherence tomography (Spectralis, Heidelberg) of case 1 demonstrating corneal thinning, focal posterior corneal steepening, and deep stromal opacification of both eyes (A: right eye, B: left eye).

and DFE. Ultrasonic corneal pachymetry demonstrated CCT of 608 μ m OD and 609 μ m OS. Corneal topography (Atlas, Zeiss) demonstrated normal corneal curvature bilaterally.

Case 8

A 35-year-old female (mother of patient 3) carries the monoallelic *SLC2A10* mutation c.727 C>A/WT (p.Q243K/WT). She had a history of bilateral LASIK for myopia 16 years earlier with subjectively excellent uncorrected distance vision for many years. She now complained of deterioration of vision in the right eye over several months. Ophthalmologic examination showed UCDVA of 20/400 OD and 20/20 OS. BCDVA was 20/40 OD and 20/20 OS with MR of $-2.50 +4.25 \times 160$ and plano $+0.25 \times 047$, in the right and left eyes, respectively. Ultrasonic corneal pachymetry demonstrated CCT of 533 μ m OD and 549 μ m OS. Keratometry was 45.00/47.75@156 OD and 42.75/43.75@093 OS. Topography (Atlas, Zeiss) confirmed the presence of astigmatism in the right eye with TKM values of 48.21 and 43.29 diopters in the right and left eyes, respectively. This patient was diagnosed with keratectasia OD after LASIK surgery, in spite of normal corneal thickness. Pre-operative records were not available for review. She was referred for corneal collagen cross-linking (CXL).

Discussion

Arterial tortuosity syndrome is a rare autosomal recessive connective tissue disorder.^{1,13,17,20} In ATS, GLUT10 deficiency is thought to increase TGF- β signaling which causes elastin fragmentation and poor cellular differentiation.^{3,21} The deficiency results in stenosis, aneurysms, and dissection of large- and medium-sized vessels.²² In addition, skin laxity, inguinal hernias, joint laxity, and skeletal overgrowth reflect generalized connective tissue involvement as seen in most inherited elastinopathies.^{1,2,4-17} Some case reports have mentioned ocular involvement including myopia, keratoconus, and keratoglobus (Table 1), but these reports lack complete and well-documented ophthalmologic examinations and references to ocular pathology were often made based on historical information alone.^{1,2,10,12,18}

We have prospectively confirmed ocular involvement in ATS, finding myopia and thin corneas in all of the patients in this cohort, with three out of five patients having keratoconus or keratoglobus. Irregular astigmatism and deep stromal corneal opacities may be associated. Furthermore, we document that carriers with a monoallelic *SLC2A10* defect may also manifest corneal thinning and are at risk to develop keratectasia after laser vision correction, despite normal CCT. Until now, no phenotypic consequences were described for carriers of monoallelic *SLC2A10* mutations. Some clinical manifestations noted in carriers at the ATS specialty clinic urge us to investigate a possible ophthalmic phenotype for carriers as well and may illustrate the importance of deep phenotyping in specialty clinics for rare disorders. Currently, no genotype-phenotype correlations among ATS patients can be derived. Although two different mutations of the *SLC2A10* gene were shared by more than one individual in our group (Table 2), it has been noted that many mutations in the *SLC2A10* gene are recurrent due to founder effects.¹

It is striking that a disease primarily affecting elastin may have manifestations in the cornea, a tissue structure mainly composed of perpendicularly organized collagen fibers and attendant proteoglycans. However, recent work suggests far greater complexity in corneal tissue with over 3250 unique Swiss-prot annotated proteins in the human cornea.^{23,24} Immunostaining has demonstrated the presence of tangentially arranged collagen and elastin fibers at Schwalbe's line,²⁵ and it has been proposed that this arrangement is necessary to resist tension and maintain the shape of the prolate cornea.^{26,27} Elastin seems to have a key functional role in maintaining the proper elasticity of the corneal stroma and decreased expression and activity of lysyl oxidase (LOX), a critical enzyme for collagen and elastin cross-linking, has been shown in keratectasia.²⁸⁻³⁰ Recent research on Marfan's syndrome, a related elastinopathy mainly characterized by progressive aortic root dilatation, ectopia lentis, and skeletal overgrowth, has implicated both increased TGF β bioavailability and low levels of LOX in association with progressive vascular abnormalities due to mutations in genes encoding the elastic fiber protein fibrillin-1.³¹ Although unconfirmed in ATS, similar deficiencies may ultimately be connected to the pathophysiologic and genetic basis of this disorder and its associated corneal thinning and ectasia.

Based on our findings, we recommend annual eye examinations including vision testing, refraction, corneal topography, pachymetry, and detailed slit-lamp examination for all ATS patients and carriers. Care plans should be individualized given the clinical findings, and caution is warranted for refractive surgery in patients and carriers. Consideration should be given to CXL in cases of progressive corneal ectasia. Although it is only recently approved in the United States for adults with keratoconus, further studies of its safety and efficacy in younger patients are also warranted. CXL in patients with severe corneal thinning (< 400 μm) may pose an increased risk of endothelial damage.¹⁹ Because corneal thinning is common if not ubiquitous in patients with ATS, it is critical to identify progressive corneal ectasia as soon as possible to safely treat their ocular disease and minimize future ophthalmic morbidity. Further grouping of patients in specialty clinics is needed to evaluate the incidence, severity, and rate of progression of the ocular findings in ATS patients and carriers.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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