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Association of Variants in *TMEM45A* With Keratoglobus

Chen Weiner, MSc; Idan Hecht, MD; Alina Kotlyar, BSc; Nadav Shoshany, MD; David Zadok, MD; Uri Elbaz, MD; Fani Segev, MD; Anat Maytal, MD; Yafit Hachmo, PhD; Carine Michiels, PhD; Olivier De Backer, PhD; Noam Shomron, PhD; Adi Einan Lifshitz, MD; Eran Pras, MD

+ Supplemental content

IMPORTANCE Keratoglobus is a rare corneal disorder characterized by generalized thinning and globular protrusion of the cornea. Affected individuals typically have significantly decreased vision and are at risk of corneal perforation. The genetic basis and inheritance pattern of isolated congenital keratoglobus are currently unknown.

OBJECTIVE To identify the genetic basis of isolated congenital keratoglobus.

DESIGN, SETTING, AND PARTICIPANTS This case series and molecular analysis studied 3 unrelated nonconsanguineous families with keratoglobus at a medical center in Israel. Data were collected from June 2019 to March 2021 and analyzed in March 2021.

EXPOSURES Whole-exome sequencing and direct Sanger sequencing, expression analysis by real-time polymerase chain reaction, splice-site variant analysis, immunohistochemical staining, and histological evaluation of a knockout mouse model.

MAIN OUTCOMES AND MEASURE Molecular characteristics associated with keratoglobus.

RESULTS Four pediatric patients (3 male) from 3 families had clinical findings consistent with keratoglobus. These included globular protrusion, corneal thinning more prominent at the periphery, and high astigmatism. Truncating and splice site variants were identified in the *TMEM45A* gene, which fully segregate with the disorder. All affected individuals were homozygous or compound heterozygous for variants in the *TMEM45A* gene, while unaffected family members were heterozygous carriers. Expression analysis in healthy controls showed that *TMEM45A* was expressed 23 times higher in the human cornea compared with peripheral blood. Immunohistochemical staining of the *TMEM45A* protein in normal corneas confirmed its expression in the corneal stroma and epithelium. A *TMEM45A* knockout mouse model showed structural features consistent with keratoglobus.

CONCLUSIONS AND RELEVANCE Expression of *TMEM45A* has been previously shown to result in upregulation of extracellular matrix components and fibrosis. These results suggest that isolated congenital keratoglobus is an autosomal recessively inherited disorder associated with variants in the *TMEM45A* gene.

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Author Affiliations: Matlow's Ophthalmogenetic Laboratory, Department of Ophthalmology, Shamir Medical Center, Zerifin, Israel (Weiner, Kotlyar, Shoshany, Pras); Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Weiner, Hecht, Elbaz, Segev, Maytal, Shomron, Lifshitz, Pras); Department of Ophthalmology, Shamir Medical Center, Zerifin, Israel (Hecht, Shoshany, Lifshitz, Pras); Department of Ophthalmology, Shaare Zedek Medical Center Affiliated with the Hebrew University—Hadassah School of Medicine, Jerusalem, Israel (Zadok); Department of Ophthalmology, Rabin Medical Center, Schneider Hospital, Petah Tikva, Israel (Elbaz); Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel (Segev); Department of Ophthalmology, Meir Medical Center, Kfar Saba, Israel (Maytal); Research and Development unit, Shamir Medical Center, Zerifin, Israel (Hachmo); URBC-NARILIS, University of Namur, Namur, Belgium (Michiels); URPhyM-NARILIS, University of Namur, Namur, Belgium (De Backer).

Corresponding Author: Idan Hecht, MD, Department of Ophthalmology, Shamir Medical Center, Be'er Ya'akov, 70300, Israel (idan.hecht@gmail.com).

Keratoglobus is a rare corneal thinning disorder characterized by generalized thinning and globular protrusion of the cornea. It is a subset of the corneal ectasia group of disorders, which are characterized by corneal thinning, protrusion, and scarring. It affects the entire cornea, causing severe thinning especially at the periphery, unlike keratoconus where thinning is usually central or paracentral or pellucid marginal degeneration where the cornea is mostly attenuated at inferior sectors.¹ Affected individuals typically have significantly decreased vision due to irregular astigmatism and steep keratometric values. Acute hydrops is frequently seen along with an increased risk of corneal perforation either spontaneously or following minimal trauma.^{2,3}

Keratoglobus is considered a congenital disorder; however, there have been reports of acquired forms.^{4,5} Congeni-

tal keratoglobus can be isolated or associated with systemic connective tissue disorders such as Ehlers-Danlos syndrome, Marfan syndrome, Rubinstein-Taybi syndrome, and brittle cornea syndrome.⁶⁻¹² For isolated keratoglobus, an autosomal recessive pattern of inheritance has been suggested, yet the exact genetic basis of the condition remains unknown.³

Management of keratoglobus consists of protective eyewear, and early reports indicate that corneal cross-linking may also be effective.¹³ Identifying the genetic basis of keratoglobus could allow earlier screening, diagnosis, and treatment, in addition to providing insights into genetic counseling and a basis for future therapeutic approaches.

Methods

The study and informed consent procedures were approved by the institutional review board at Shamir Medical Center and followed the tenets of the Declaration of Helsinki.¹⁴ Informed written consent was obtained from all the participants involved in the study. Participants were not offered any compensation or incentives to participate. The approval of the local ethic committee of the University of Namur, Belgium, was obtained for all the experiments involving mice in this study, which were performed according to the European legislation. Data were collected from June 2019 to March 2021 and analyzed in March 2021.

Clinical evaluation included slitlamp biomicroscopy (Haag Streit International) and intraocular pressure measurement (Goldmann applanation tonometry; Haag Streit International). Corneal topographic and pachymetric maps were obtained using the TMS-5 (Tomey Corporation) and the Oculus Pentacam (Oculus). Biometric measurements were obtained using the Zeiss IOL Master 700 (Carl Zeiss Meditec) and anterior segment optical coherence tomography with the Spectralis OCT (Heidelberg Engineering).

Molecular analysis was performed at the Matlow's Ophthalmic-Genetic Laboratory, Shamir Medical Center in Be'er Ya'akov, Israel. Genomic DNA and RNA were extracted from whole blood using standard protocols. The disorder was assumed to have an autosomal recessive mode of inheritance, associated with rare variants (minor allelic frequency <0.01). Whole-exome sequencing was performed on DNA samples of 2 affected siblings and their mother from family 1 by a commercial company (Psomagen) using the Illumina NovaSeq platform, version 6 (Agilent SureSelect) (mean coverage was about 149 reads). The Genomic Intelligence platform (Variantix) was used for bioinformatic analysis and prioritization of variants.¹⁵ Filtration process of identified variants took into consideration the association of the gene with disorders of the cornea and/or connective tissue diseases, predicted pathogenicity, and rarity and concordance with autosomal recessive inheritance mode. For direct Sanger sequencing of the candidate gene *TMEM45A*, primers were designed using Primer 3, version 4.1.0 to cover the gene (ENST00000403410) coding region (CCDS87113), and sequencing was carried out at a commercial sequencing service (Macrogen Europe) using the ABI BigDye Terminator version 3.1 Cycle sequencing kit (Applied Biosystems) in a Mastercycler pro 384 sequencer (Eppendorf). A primer list is provided in the eTable in the [Supplement](#). Human corneal tissue was obtained from human cadaver donors that did not meet the criteria for clinical use. Corneal tissue was harvested in Shamir Medical Center, preserved in Optisol, and kept in a temperature of 4 to 8 °C until processing up to 2 weeks later. Complementary DNA was synthesized using a high-capacity complementary DNA reverse-transcription kit (Applied Biosystems) for gene expression analysis on quantitative polymerase chain reaction (PCR) and for gel electrophoresis analysis of abnormal splicing in the presence of the c.637-1G>T variant.

Key Points

Question What is the genetic basis of isolated congenital keratoglobus?

Findings In this case series, among 3 unrelated families, variants in the *TMEM45A* gene were found to fully segregate with the disease. Expression analysis of *TMEM45A* indicated high expression in the human cornea, and histologic staining of the *TMEM45A* protein confirmed its expression in the corneal stroma and epithelium; *TMEM45A* knockout mice were associated with structural features consistent with keratoglobus.

Meaning Isolated congenital keratoglobus is an autosomal recessively inherited disorder associated with variants in the *TMEM45A* gene; these results may contribute to earlier screening and diagnosis, genetic counseling, and could provide a basis for future therapeutic approaches.

The cornea was preserved in Optisol until horizontally sectioned 2 to 3 μm thick and embedded in paraffin or stained in hematoxylin-eosin. Following standard processing, primary antibody specifically binding human *TMEM45A* (NBP2-49355, 1:50; Novus Biologicals) was applied and incubated overnight. Specific antibodies for Vimentin (347M-16, 1:50; Dako) were also applied and incubated. Secondary antibody Alexa Fluor 647 (A-21245, 1:50) was conjugated against *TMEM45A*, and Alexa Fluor 488 (ab150117, 1:100) was conjugated against vimentin.

A *TMEM45A* knockout mouse model was used to evaluate the consequences of *TMEM45A* deficiency on corneal development. Generation of *TMEM45A* knockout mice was described elsewhere.¹⁶ Briefly, the International Mouse Phenotyping Consortium *TMEM45A*^{tm1a(KOMP)Mbp} knockout first allele was introduced into the mouse genome by recombination in 14Tg2a ES cells. Mice carrying this allele were crossed with PGK-Cre transgenic mice to obtain animals with deleted *TMEM45A* exons 3 and 4 (allele *TMEM45A*^{tm1b(KOMP)Mbp}). Homozygous, heterozygous, and wild-type mice were obtained by intercrossing *TMEM45A*^{tm1b(KOMP)Mbp} heterozygous animals. Genotyping of animals was performed by PCR using DNA extracted from tails. All mice used in this work have a mixed 129/Ola and C57BL/6 genetic background.

These mice develop normally and display no obvious phenotype; however, no analysis of a possible ocular phenotype was performed.¹⁶ Human and mouse *TMEM45A* orthologs show a 65% of amino acid identity. Ten *TMEM45A* knockout mice (study group), 8 wild-type mice, and 3 heterozygous mice (control group), were bred and examined at age 1 to 2 months. Genotyping of the animals was performed by PCR using DNA extracted from ear punch biopsies. Tissue was sent by express delivery from Namur, Belgium, to Matlow's Ophthalmic-Genetic Laboratory in Israel using a dedicated delivery service. The samples were transported in a temperature kept between 15 and 25 °C, after which they were kept in 4 to 8 °C until processing. Clinical examination of the cornea and histological analysis (using hematoxylin-eosin and Periodic acid-Schiff stains) was done for both groups. Clinical evaluation included high-resolution and high-magnification imagery of the

Table. Clinical and Molecular Characteristics of Families 1, 2, and 3

Family	Patient No./sex/age (decade)	Relation to proband	Variant	Zygosity ^a	Affected
1	I-1/F/sixth	Father	c.154C>T	1/2	Not affected
1	I-2/M/sixth	Mother	c.154C>T	1/2	Not affected
1	II-1/M/first	Brother	c.154C>T	2/2	Affected
1	II-2/F/second	Proband	c.154C>T	2/2	Affected
1	II-3/M/second	Brother	c.154C>T	1/2	Not affected
2	I-1/F/fifth	Father	NA	NA	Not affected
2	I-2/M/fifth	Mother	NA	NA	Not affected
2	II-1/M/first	Proband	c.154C>T	2/2	Affected
3	I-1/F/fifth	Father	c.154C>T	1/2	Not affected
3	I-2/M/fourth	Mother	c.637-1G>T	1/2	Not affected
3	II-1/M/second	Proband	c.154C>T + c.637-1G>T	2/2	Affected

^a Zygosity 1, wild type; zygosity 2, variant.

eyes of the live mice. Images were sent blinded (ie, unlabeled by group) and evaluated independently by 3 experienced ophthalmologists including 1 corneal specialist (E.P., N.S., and A.E.L.) for clinical signs consistent with keratoglobus including globular protrusion, overall shape, corneal scarring and opacities, and depth of the anterior chamber.

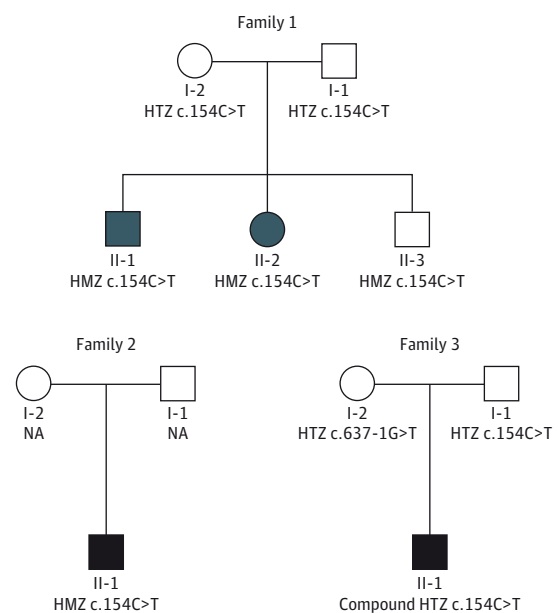
Results

Clinical Findings

We identified 4 patients from 3 families with isolated congenital keratoglobus (Table). Family 1 has a nonconsanguineous Ashkenazi Jewish pedigree (Figure 1). Two siblings (patients II-1 and II-2 from family 1) have been diagnosed with congenital keratoglobus. Patient II-2 from family 1, a 13-year-old girl, with normal development, no dysmorphic features, or easy bruising, was first diagnosed at age 4 years. Her ocular examination demonstrated hypermetropia with high astigmatism in both eyes, thin corneas, and irregular corneal opacifications. Visual acuity was 20/80 OD and 20/100 OS. Corneal topographic and pachymetric maps (eFigure 1 in the Supplement) of both eyes revealed the classic finding of diffuse thinning, more marked in the peripheral cornea with maximal steepening in the nasal corneas (corneal curvature of more than 51 diopters in the anterior sagittal curvature map). At the thinnest point, the corneal thickness was 244 μ m and 286 μ m in the right and left eyes, respectively. During follow-up, she experienced spontaneous hydrops in the right eye. The rest of her ocular examination, including intraocular pressure and endothelial cell counts, were normal. Tympanometry and audiometry tests as well as echocardiography results were normal. Patient II-1 from family 1, her younger brother, also had keratoglobus. He had similar corneal thinning and opacifications in the absence of any systemic findings, dysmorphic features, or developmental delays. Although their father had been diagnosed with Gilbert syndrome, both parents were otherwise healthy with no ocular or systemic illness. The older sibling (patient II-3 from family 1) had alopecia areata but was otherwise healthy without evidence of ocular abnormalities.

Independently, we identified a second nonconsanguineous family (family 2) of Ashkenazi descent. Both parents were

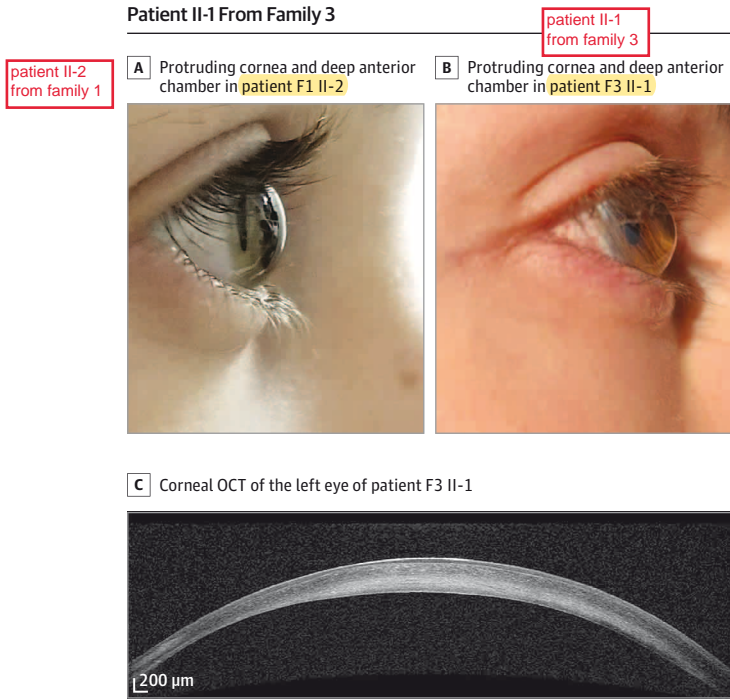
Figure 1. Pedigrees of Families 1, 2, and 3



c.154C>T indicates *TMEM45A* gene variant c.154C>T; p.Arg52* rs201699180. c.637-1G>T indicates *TMEM45A* gene variant c.637-1G>T rs766210908. HTZ indicates heterozygous; HMZ, homozygous; NA, not available.

healthy without evidence of ocular abnormalities. Patient II-1 from family 2, a boy, had normal development and was otherwise healthy with isolated congenital keratoglobus. His ocular examination revealed bilateral high corneal astigmatism and thin corneas. His glasses best-corrected visual acuity was 20/50 OD and 20/40 OS. Corneal topographic and pachymetric maps of both eyes demonstrated diffuse thinning of up to 398 μ m with steepening of up to 49.9 diopters in the left eye and up to 384 μ m with steepening of up to 52.6 diopters in the right eye. His ocular examination disclosed thinning and diffuse opacifications in the anterior stroma, more prominent in the corneal periphery. The rest of the ocular examination, including intraocular pressure and endothelial cell counts, were normal.

Figure 2. Clinical and OCT Images of Patient II-2 From Family 1 and Patient II-1 From Family 3



Clinical photographs of patient II-2 from family 1 (A) and patient II-1 from family 3 (B). Visible in both is a protruding cornea and deep anterior chamber. C, Corneal optical coherence tomographic (OCT) image of the left eye of patient II-1 from family 3. Notice significant thinning at the peripheral nasal aspect of the cornea.

Family 3 is of mixed Jewish origin with no known consanguinity. The mother is of Persian and Turkish origin and the father is of Ashkenazi descent. Both were healthy without evidence of ocular abnormalities. Their son (patient II-1 from family 3), a 15-year-old boy with isolated congenital keratoglobus, was first diagnosed at age 5 years. His examination was positive for high myopia with high astigmatism in both eyes and thin corneas. His visual acuity was 20/40 OU. Corneal topographic and pachymetric maps of both eyes (eFigure 1 in the Supplement) demonstrated diffuse thinning with steepening of up to 66.9 diopters. At the thinnest point, corneal thickness was 184 μm and 252 μm in the right and left eyes, respectively. Anterior segment optical coherence tomography is shown in Figure 2. The rest of his ocular examination, including intraocular pressure, was normal and he is otherwise healthy.

Molecular Findings

To investigate the molecular characteristics of the disease in family 1, we conducted whole-exome sequencing of samples from the mother (patient I-2 from family 1) and both affected siblings (patients II-1 and II-2 from family 1). Whole-exome sequencing yielded 16 102 point variants, none of which appeared in genes with previous association with corneal or connective tissue diseases. Considering concordance with the presumed mode of inheritance, minor allele frequency less than 0.01, and expected deleteriousness of the variant, narrowed down the count to only 1 variant. Using Sanger sequenc-

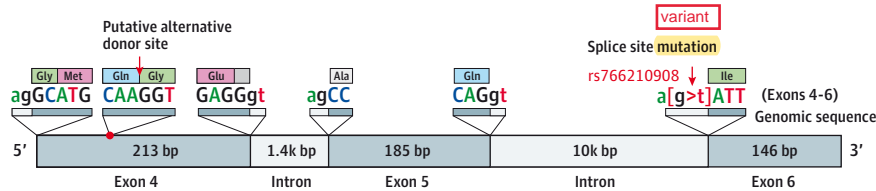
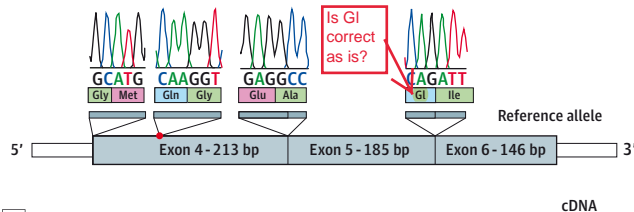
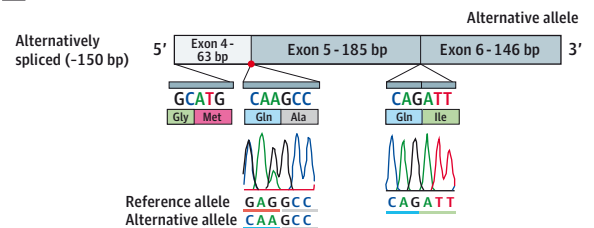
ing, we confirmed segregation for a *TMEM45A* variant in all members of family 1 (including the father [patient I-1 from family 1] and the unaffected sibling [patient II-3 from family 1]). These results confirmed that both parents were heterozygous carriers of a truncating variant c.154C>T (NM_001363876; c.154C>T; p.Arg52* rs201699180) in the *TMEM45A* gene. Affected siblings in family 1 (II-1 and II-2) were homozygous to the same variant and the unaffected sibling in family 1 (II-3) was a heterozygous carrier (Figure 1). This rare variant (minor allele frequency range, 0.00025-0.00008) is predicted to cause a premature stop codon at amino acid 52 (of 291 in the wild-type protein). Pathogenic variants in other genes previously associated with keratoglobus, including brittle cornea syndrome (*ZNF469*, MIM 612078; *PRDM5*, MIM 614161), Ehlers-Danlos syndrome (*COL5A1*, MIM 130000; *COL5A2*, MIM 130010), Rubinstein-Taybi syndrome (*CREBBP*, MIM 180849; *EP300*, MIM 613684), and Marfan syndrome (*FBN1*, MIM 154700), were ruled out.

Following identification of the variant in family 1, direct sequencing of the *TMEM45A* gene was carried out in the other families (families 2 and 3). The affected individual in family 2 (patient II-1) was found homozygous to the same truncating variant (c.154C>T, rs201699180). Samples from the parents were unavailable for analysis. In family 3, affected individual II-1 was found heterozygous for the same truncating variant (c.154C>T, rs201699180), alongside a single base exchange at position c.637-1G>T (NM_001363876, rs766210908, both not reported in ClinVar) at intron 5 acceptor site. This rare change (minor allele frequency range, 0.000004-0.000008) is located within the canonical splice acceptor site and is predicted to result in its loss because of the requirement for an evolutionary conserved AG sequence at the 3' splice site (Human Splicing Finder and NNSPLICE 0.9).^{17,18} His father (patient I-1 from family 3) was found to be a heterozygous carrier of the nonsense truncating variant (c.154C>T, rs201699180), while the mother (patient I-2 from family 3) was a heterozygous carrier for the acceptor splice site variant (c.637-1G>T, rs766210908).

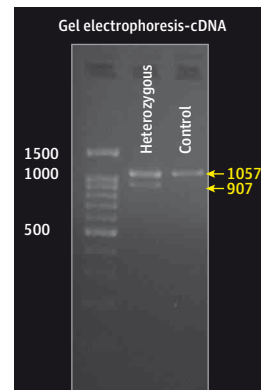
Analysis of the Splice Site Variant c.637-1G>T rs766210908

To analyze the consequence of the variant c.637-1G>T (rs766210908) at the canonical acceptor site, we amplified a segment of *TMEM45A* complementary DNA by PCR using primers located in exon 3 (forward) and exon 7 (reverse) (primer set 1, eTable in the Supplement and Figure 3). Gel electrophoresis of the PCR products showed that in addition to the expected 1057 base-pairs product, a smaller fragment estimated at 907 base pairs was seen in patient I-2 from family 3, alongside the full 1057 base-pair sequence found in the healthy control (Figure 3D). Sequencing the gene coding region, we found that the alteration in the acceptor site introduces abnormal splicing from a potential donor site located in exon 4, resulting in a shorter transcript by 150 base pairs (from 213 base pairs in the reference allele to 63 base pairs in the alternative allele; Figure 3). This alteration reduces the overall *TMEM45A* protein length by 17% (from 291 amino acids to 241) and is predicted to affect transmembrane and small extracellular and cytoplasmic sections of the protein, presumably leading to its

Figure 3. Analysis of the Splice Site Variant c.637-1G>T

A Genomic sequence, *TMEM45A* exons 4-6B cDNA sequence, *TMEM45A* exons 4-6, reference alleleC cDNA sequence, *TMEM45A* exons 4-6, alternative allele

D Gel electrophoresis of cDNA fragments obtained by PCR



A, Splice site variant (rs766210908) position is shown. A putative alternative donor site within exon 4 is marked with a red dot. B, Note the length of exon 4 is 213 base pairs (bp). C, Exon 4 length is significantly reduced to 63 bp, presumably owing to alternative splicing. (D) Gel electrophoresis of complementary DNA (cDNA) fragments obtained by polymerase chain reaction (PCR) from RNA of a heterozygous carrier and an unaffected control. The heterozygous sample shows a dual band with a shorter 907 bp fragment alongside the full 1057 bp sequence found in the control sample. The difference in size corresponds to the decreased length of the alternatively splice exon 4 shown in panel C. Ala indicates alanine; Gln, glutamine; Glu, glutamic acid; Gly, glycine; Ile, isoleucine; Met, methionine.

loss of function. The influence of this variant on the predicted protein structure is illustrated in eFigure 2 in the Supplement.

TMEM45A Expression Analysis in the Human Cornea

Given that this gene has not been previously described to be expressed in the eye or associated with any ocular diseases, we proceeded to evaluate its expression within the cornea. As corneal tissue from affected individuals was unavailable, we analyzed the expression of *TMEM45A* in healthy human cadaver corneas. Using quantitative PCR, we confirmed that *TMEM45A* is expressed in the human cornea, with messenger RNA levels 23 times higher compared with peripheral blood (eFigure 3 in the Supplement).

Immunohistochemical Staining of TMEM45A Protein in the Human Cornea

We hypothesized, based on the pathophysiology of keratoglobus, which is thought to involve the corneal stroma, that the *TMEM45A* gene is also involved with corneal stromal integrity.³ Immunohistochemical staining of *TMEM45A* protein in normal human corneas showed expression in corneal epithelium and stroma, localized to the cytoplasm (Figure 4). Interestingly, protein expression was evident in the stroma, with staining in a small percentage of stromal keratocytes, also located cytoplasmically (Figure 4).

TMEM45A Knockout Mouse Model Analysis

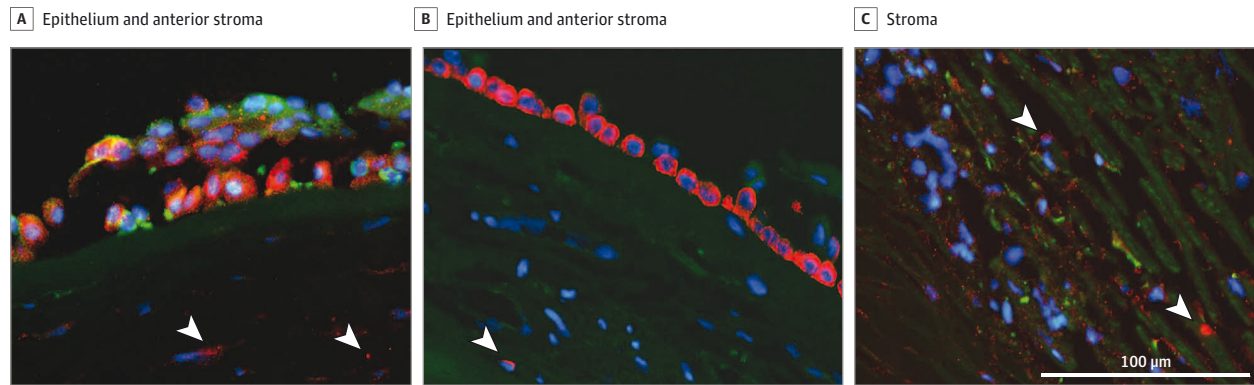
A model of mice deficient for *TMEM45A* has been previously described.¹⁶ These mice develop normally, are fertile, and do

not display any obvious abnormal phenotype. We investigated the corneal phenotype of these mice. Gross appearance of the eye was similar in wild-type and *TMEM45A* knockout mice. However, histological examination showed a consistently thinner stroma in *TMEM45A* knockout mice (eFigure 3 in the Supplement). Stromal thickness was 40 to 50 μ m in the central cornea of the *TMEM45A* knockout mice compared with 80 to 90 μ m in the wild type. No stromal disruption was observed in the anterior stroma and the epithelial and endothelial layers of the cornea appeared normal (eFigure 4 in the Supplement).

Discussion

We showed that homozygous and compound heterozygous truncating and splice variants in the *TMEM45A* gene (MIM 616928) fully segregate with isolated congenital keratoglobus among 3 unrelated nonconsanguineous families. Expression analysis of *TMEM45A* revealed high expression in the human cornea, and histologic staining of the *TMEM45A* protein in normal corneas showed its presence in the corneal epithelium and stroma. *TMEM45A* knockout mice showed corneal thinning consistent with keratoglobus. Taken together, these results confirm that isolated congenital keratoglobus may be a heritable recessive defect resulting from loss of function variants in *TMEM45A*.

The *TMEM45A* gene (also called *DERP7*, *DNAPTP4*, or *FLJ10134*) has been primarily studied as an upregulated marker in various cancers and as an actor of keratinization.¹⁹⁻²¹ It be-

Figure 4. Immunohistochemical Staining of the *TMEM45A* Protein in Healthy Human Corneas

A and B, Healthy human corneal epithelium and anterior stroma with staining for DAPI (nuclear counterstain, 4',6'-diamidino-2-phenylindole, blue), Vimentin (green, Alexa Fluor 488), and *TMEM45A* protein (red, Alexa Fluor 647). C, Healthy human corneal stroma similarly stained for *TMEM45A* (red), Vimentin

(green), and DAPI (blue). Arrowheads indicate *TMEM45A* staining adjacent to stromal keratocytes. Notice the staining for *TMEM45A* in the corneal epithelium adjacent to the nucleus and in the corneal stroma localized to stromal keratocytes.

longs to the *TMEM* family, encoding uncharacterized predicted transmembrane proteins. Their subcellular localization and functions remain mostly unknown, with most available information coming from transcriptomic studies or bioinformatics predictive tools.¹⁹ Animal models show that expression of *TMEM45A* results in upregulation of extracellular matrix components and fibrosis.²² This protein is also overexpressed in many cancers.^{20,21} Taken as a whole, it seems that *TMEM45A* is involved with extracellular structural and fibrotic processes as well as in keratinization. In keratoglobus, several aspects suggest a pathophysiologic association with extracellular matrix components in the corneal stroma. These include the characteristic ectatic clinical nature of thinning and protrusion, the association of keratoglobus with connective tissue disorders, and the typical histopathologic findings, which include stromal thinning and disruption of the collagen-rich Bowman layer, the anterior part of the corneal stroma.^{3,23,24} Taken together, the preliminary evidence on the functions of *TMEM45A* appear to coincide with the current evidence on keratoglobus pathophysiology.

We observed that the corneal stroma of *TMEM45A* knockout mice was about 2 times thinner than that of wild-type mice.²⁵ It should be noted that several elements must be taken into account when using mouse models in the context of keratoglobus. First is that human and mouse *TMEM45A* orthologs encode proteins sharing only 65% of amino acids identity. Second, there is a significant difference between the anterior stroma in humans and mice.²⁵ Finally, we looked at mice that were only 1 to 2 months old. Although congenital keratoglobus in humans can be evident at an early age, progression with age is often seen, a course that might also occur in mice, limiting signs of the disease to those evident at an early age.

The *TMEM45A*-containing chromosomal locus (3p14-q13) has previously been associated with another related corneal ectatic disorder, autosomal dominant keratoconus.²⁶ A 2004 report on a large Italian pedigree with autosomal dominant keratoconus mapped the locus to the one containing *TMEM45A* (3p14-q13).²⁶ Several genes within this locus were examined and did not show pathogenic variants; however, *TMEM45A* was not one of them. None of the other loci and genes associated with keratoconus are in proximity with *TMEM45A*, apart from this locus. It would be interesting to look for variants in *TMEM45A* in sporadic or familial cases of keratoconus.

Limitations

This study has several limitations. First, only 4 individuals with keratoglobus from 3 unrelated families were available for testing owing to the rare nature of the disorder. Second, corneal tissue of affected individuals was unavailable. Third, topographic and pachymetric maps of mice corneas were unavailable. Finally, 2 healthy individuals from family 2 were not available for genetic analysis and their molecular details could not be determined.

Conclusions

To conclude, keratoglobus is a rare corneal ectatic disorder whose genetic basis and inheritance pattern were previously unknown. We identified variants of the gene *TMEM45A* that fully segregate with isolated congenital keratoglobus. These results may contribute to earlier screening and diagnosis in genetic counseling and could provide a basis for future therapeutic approaches.

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responsibility for the integrity of the data and the accuracy of the data analysis. Mr Weiner and Dr Hecht contributed equally.

Concept and design: Weiner, Kotlyar, Shoshany,

Segev, Maytal, De Backer, Shomron, Pras.
Acquisition, analysis, or interpretation of data: Weiner, Hecht, Kotlyar, Shoshany, Zadok, Elbaz, Segev, Hachmo, Michiels, De Backer, Shomron, Einan-Lifshitz, Pras.
Drafting of the manuscript: Weiner, Hecht, Kotlyar, Hachmo, De Backer, Pras.
Critical revision of the manuscript for important intellectual content: Weiner, Kotlyar, Shoshany, Zadok, Elbaz, Segev, Maytal, Hachmo, Michiels, Shomron, Einan-Lifshitz, Pras.
Statistical analysis: Weiner, Kotlyar, Pras.
Administrative, technical, or material support: Weiner, Hecht, Kotlyar, Elbaz, Segev, Hachmo, Michiels, Pras.
Supervision: Weiner, Kotlyar, Zadok, Elbaz, Segev, De Backer, Shomron, Einan-Lifshitz, Pras.

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