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Corneal Decompensation in Recessive Cornea Plana

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***Purpose*: To report corneal decompensation in 3 patients with recessive cornea plana. *Methods*: Retrospective case series. *Results*: An adult and two children (all unrelated) with clinical recessive cornea plana had gradual decrease in vision. Ophthalmic examination revealed corneal decompensation (stromal thickening and haze without epithelial changes) in the 3 patients. Diagnostic DNA sequencing revealed homozygosity for a novel splice (c.995-2A>G) in the adult and 2 previously reported *KERA* mutations in the 2 children (c.1033delC[p.C343A*Fs*X] and c.945C>T[p.R313X]). *Conclusions*: The phenotype of recessive cornea plana can rarely include corneal decompensation. There are likely modifying factors that can lead to endothelial cell dysfunction in the setting of homozygous *KERA* mutation.**

Keywords KERA; cornea plana; endothelial cell; corneal decompensation

INTRODUCTION

Recessive cornea plana (On-line Mendelian Inheritance in Man [MIM] #217300) is a bilateral anterior segment abnormality caused by homozygous mutation in *KERA* (MIM *603288).[1] The distinct phenotype includes small flat corneas, variable deep corneal opacities, limbal haze, variable iris abnormality, and high hyperopia with or without associated accommodative esotropia.[1–6] Rarely, corneal ectasia and hydrops have been documented.[7,8] We document the occurrence of another infrequent finding—corneal decompensation—in 3 unrelated patients (one adult and two children) with genetically confirmed recessive cornea plana.

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REPORT OF CASES

Institutional review board approval was granted for this project by the relevant institutions.

Patient 1

A 45-year-old female complained of gradual decreased vision over the prior 2 months. She had a history of "small eyes" since birth. There was no recent history of trauma. Of her 5 siblings, one sister and one brother had the same "small eyes"; both were currently functioning well with glasses and were unwilling to be examined.

Visual acuity with her +11.00 diopter spectacles was 20/40 in the right eye and 2/200 in the left eye. There was no strabismus. Measured intraocular pressure by applanation tonometry was 15 mm Hg in the right eye and 19 mm Hg in the left eye. Slit-lamp examination was significant bilaterally for flat small cornea, indistinct limbus, horizontal corneal ovalization, and dense arcus

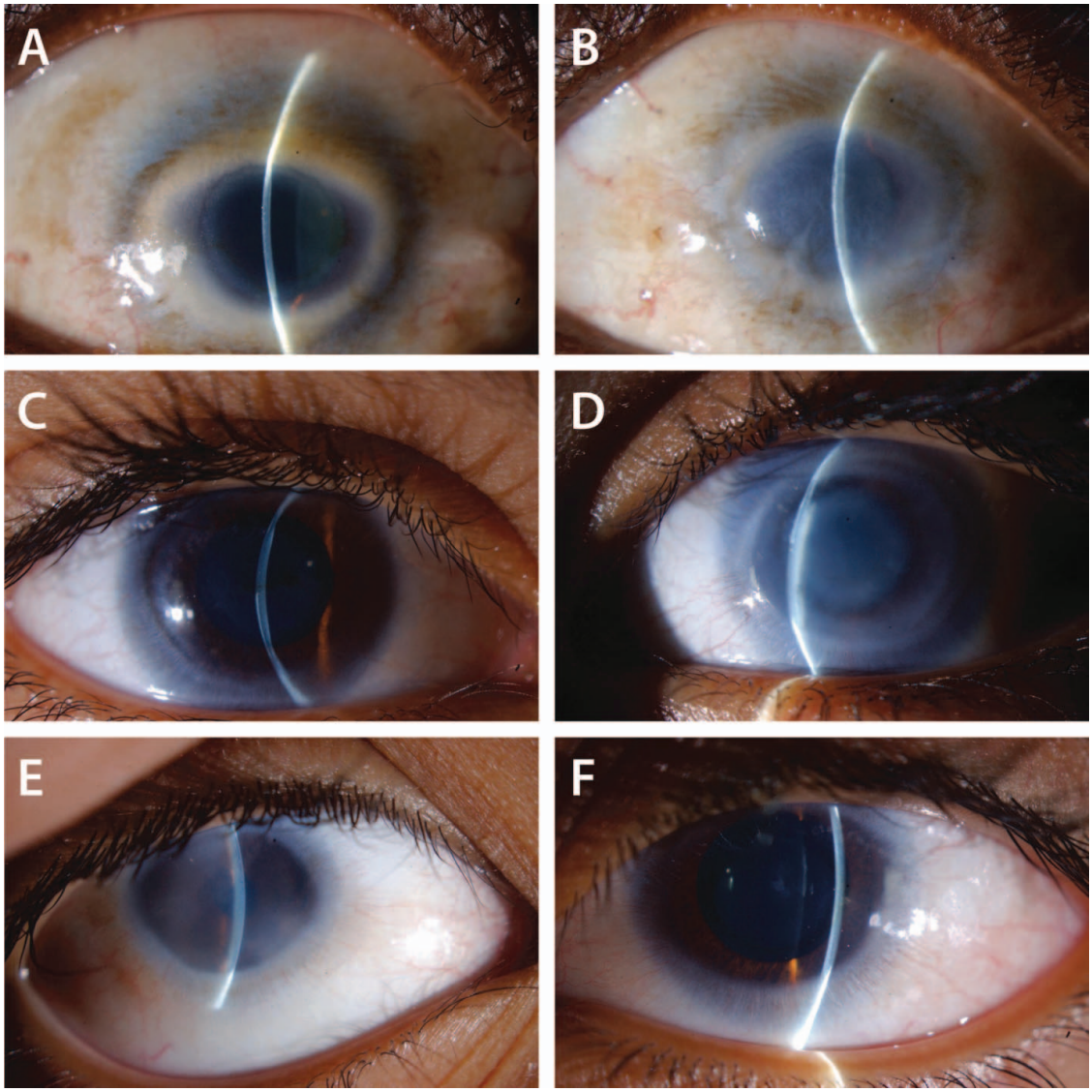

FIG. 1. (A, B): Both right (A) and left (B) corneas of the adult (patient #1) are small, flat, have indistinct limbus, demonstrate horizontal ovalization, and have prominent arcus senilis. In addition, there is obvious corneal decompensation in the left eye (B) with stromal thickening and haze but without epithelial changes. (C, D): Both right (C) and left (D) corneas of the child (patient #2) are small, flat, and have an indistinct limbus. In the right cornea (C) there is a mild paracentral horizontal subepithelial scarring, a feature sometimes found in recessive cornea plana. In addition, there is mild stromal thickening associated with some Descemet folds (not pictured well). In the left cornea (D), the corneal decompensation and haze is obvious. (E, F): Both the right (E) and left (F) cornea of the child (patient #3) are small, flat, and have indistinct limbus. In the right eye (E) the cornea is smaller, demonstrates horizontal ovalization, has a relatively miotic pupil despite cyclopentolate 1% application, and is decompensating (with stromal thickening and haze but without epithelial changes). In the left eye (F) the cornea is clear and the pupil is well dilated following cyclopentolate 1%.

senilis. There was corneal decompensation (thickening and haze without epithelial changes) in the left eye (Figure 1A, B). Specular microscopy revealed an endothelial cell count of 1554 per millimeter squared for the right eye but could not be done for the left eye because of haze.

By ultrasound pachymetry (CORNEO-GAGE PLUS, Sonogage Inc., Cleveland, OH, USA) central corneal thickness was 439 microns in the right eye and 640 microns in the left eye. Cycloplegic refraction (cyclopentolate 1%) was consistent with her current glasses for the right eye but could not be done for

the left eye. Fundus exam was unremarkable (by indirect ophthalmoscopy in the right eye and B-scan ultrasonography in the left eye). Diagnostic *KERA* sequencing (by previously described methods[3,5]) revealed homozygosity for a novel splice site mutation predicted to affect splicing of exon 3 (c.995-2A>G, GenBank accession number AF063301).

Patient 2

An 8-year-old boy with known recessive cornea plana (homozygous c.1033delC(p.C343A*fs*X) *KERA* mutation, by previously described methods[3,5]) and no family history of the condition complained of gradual decreased vision over the previous month. There was no recent history of trauma. Two years prior his vision was 20/40 in either eye with his +7.50 diopter spectacles and he had an esotropia of 10 prism-diopters at distance and 18 prism-diopters at near with his spectacles.

Best-corrected vision upon examination was 20/40 in the right eye and 20/400 in the left eye. The esotropia was stable. Applanation tonometry was 17 mm Hg in the right eye and 19 mm Hg in the left eye.

In addition to findings of cornea plana (small flat cornea with indistinct limbus), slit-lamp examination was significant for corneal edema greater in the left eye than the right eye with significant corneal decompensation (stomal edema and haze without epithelial changes) in the left eye (Figure 1C, D). Specular microscopy revealed an endothelial cell count of 1892 per millimeter squared for the left eye but could not be done for the right eye because of haze.

By the Pentacam Scheimpflug system (PENTACAM HR, Oculus Inc., Lynnwood, WA, USA), central corneal thickness was 530 microns in the right eye (with estimated average keratometry of 34.5 diopters) and 1736 microns in the left eye (with estimated average keratometry of 25 diopters). Cycloplegic refraction (cyclopentolate 1%) was consistent with his current glasses for the right eye but could not be done for the left eye. Fundus exam was unremarkable (by indirect ophthalmoscopy in the right eye and B-scan ultrasonography in the left eye).

Patient 3

An 8-year-old boy with known recessive cornea plana (homozygous c.945C>T(p.R313X) nonsense *KERA* mutation, by previously described methods[3,5]) and a family history of 4 affected siblings (3 of whom are older and none of whom suffered from corneal decompensation) complained of gradual decreased vision over the previous several months. Two years prior his vision was 20/60 in either eye with his +6.00 diopter spectacles.

Best-corrected vision upon examination was 20/200 in the right eye and 20/50 in the left eye. There was no strabismus. Applanation tonometry was 23 mm Hg in the right eye and 19 mm Hg in the left eye. In addition to findings of cornea plana (small flat cornea with indistinct limbus, horizontal ovalization in the right eye, poorly reactive pupil in the right eye), slit-lamp examination was significant for corneal decompensation (stromal edema and haze without epithelial changes) in the right eye (Figure 1E, F). Specular microscopy was difficult and could not be done for the right eye because of haze but seemed to reveal an endothelial cell count of approximately 2400 per millimeter squared in the left eye.

The Pentacam Scheimpflug system (PENTACAM HR, Oculus Inc., Lynnwood, WA, USA) was unable to measure corneal readings from either eye. By ultrasound pachymetry (CORNEOGAGE PLUS, Sonogage Inc., Cleveland, OH, USA) central corneal thickness was 831 microns in the right eye and 544 microns in the left eye. Cycloplegic refraction (cyclopentolate 1%) could not be done for the right eye because of haze but was consistent with his current glasses in the left eye. Fundus exam was unremarkable (by B-scan ultrasonography in the right eye and indirect ophthalmoscopy in the left eye).

DISCUSSION

We document corneal decompensation in 3 unrelated patients—an adult and two children—who are homozygous for one novel and two previously reported *KERA* mutations, respectively. The fact that the corneal decompensation occurred in 3 unrelated patients, 2 of whom are children, suggests that it is a rare feature of phenotype rather than a chance occurrence. Because the corneal decompensation occurred in the settings of a novel splice mutation and 2 previously reported different mutations, the finding is not specific to a particular mutation. Previous studies also support the idea that there is no specific genotype-phenotype correlation for recessive *KERA* mutation; for the 7 previously reported homozygous *KERA* mutations, the reported phenotypes were relatively homogeneous.[1–7]

KERA encodes keratocan, an evolutionarily conserved 352 amino acid small leucine-rich proteoglycan.[9–11] The small leucine-rich proteoglycans are a family of highly conserved extracellular matrix proteoglycans with core proteins comprised mostly of leucine-rich repeats (LRRs).[10] The total number of LRRs in keratocan depends on the criteria used to define subdomains; an Internet-based consortium currently defines 12 LRRs.[12]

These LRRs are flanked by clusters of cysteine, a sulfur-containing amino acid that allows for disulfide bonds and maintenance of three-dimensional conformation.[10] All reported *KERA* mutations to date affect LRR structure/conformation. Mainly expressed in the cornea and showing high conservation among mammals, keratocan plays a role in corneal stromal fibrillogenesis (e.g., fiber diameter and spacing) and thus is important for the unique refractive and transparent properties of the cornea.[9,11]

Kera knockout mice reveal disorganized and large diameter corneal fibers, thin corneal stoma, narrow anterior chamber angles, and no evidence of systemic abnormality.[11] In patients with recessive *KERA* mutation, mutated keratocan in the corneal matrix of the developing embryo presumably cannot bind to collagen fibrils, thus disrupting the modulating effect keratocan has on the development of normal corneal structure. There is

no known affect of *KERA* mutation on endothelial cell function; however, endothelial cell counts have not been specifically studied in prior reports of recessive cornea plana.[1–8]

The mechanism for corneal decompensation in these 3 unrelated cornea plana patients is unclear. There are likely modifying factors that can lead to endothelial cell dysfunction in the setting of homozygous *KERA* mutation.

DECLARATION OF INTEREST

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

REFERENCES

1. Pellegata NS, Dieguez-Lucena JL, Joensuu T, et al. Mutations in KERA, encoding keratocan, cause cornea plana. *Nature Genet.* 2000;25:91–95.
2. Lehmann OJ, El-Ashry MF, Ebenezer N, et al. A novel keratocan mutation causing autosomal recessive cornea plana. *Invest Ophthalmol Vis Sci.* 2001;42(13):3118–14.
3. Khan A, Al-Saif A, Kambouris M. A novel KERA mutation associated with autosomal recessive cornea plana. *Ophthalmic Genet.* 2004;25:147–52. Erratum in: *Ophthalmic Genet.* 2004;25:289. *Ophthalmic Genet.* 2005;26:195.
4. Ebenezer ND, Patel CB, Hariprasad SM, et al. Clinical and molecular characterization of a family with autosomal recessive cornea plana. *Arch Ophthalmol.* 2005;123:1248–1253.
5. Khan AO, Aldahmesh M, Meyer B. Recessive cornea plana in the Kingdom of Saudi Arabia. *Ophthalmology.* 2006;113:1773–1778.
6. Liskova P, Hysi PG, Williams D, Ainsworth JR, et al. Study of p.N247S KERA mutation in a British family with cornea plana. *Mol Vis.* 2007;13:1339–1347.
7. Khan AO, Aldahmesh M, Al-Saif A, Meyer B. Pellucid marginal degeneration coexistent with cornea plana in one member of a family exhibiting a novel KERA mutation. *Br J Ophthalmol.* 2005;89:1538–1540.
8. Khan AO, Aldahmesh M, Meyer B. Corneal ectasia and hydrops in a patient with autosomal recessive cornea plana. *Ophthalmic Genet.* 2006;27:99–101.
9. Tasheva ES, Funderburgh JL, Funderburgh ML, et al. Structure and sequence of the gene encoding human keratocan. *DNA Seq.* 1999;10:67–74.
10. Iozzo RV. The biology of the small leucine-rich proteoglycans. *J Biol Chem.* 1999;274:18843–18846.
11. Liu CY, Birk DE, Hassell JR, et al. Keratocan-deficient mice display alterations in corneal structure. *J Biol Chem.* 2003; 13(278):21672–21677.
12. niProt Consortium. The Universal Protein Resource (UniProt). *Nucleic Acids Res.* 2007;35D,193–197.