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# Coexistence of Meesmann Corneal Dystrophy and a Pseudo-Unilateral Lattice Corneal Dystrophy in a Patient With a Novel Pathogenic Variant in the Keratin K3 Gene: A Case Report

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**Purpose:** This study aims to clinically and genetically report a case of coexisting Meesmann corneal dystrophy (MECD) and pseudo-unilateral lattice corneal dystrophy (LCD).

**Methods:** Clinical characterization was supported by a complete ophthalmological evaluation, including visual acuity measurement and slit-lamp examination. Molecular diagnosis was performed by whole-exome sequencing analyzing the gelsolin, keratin K3 (*KRT3*), keratin K12, and transforming growth factor-beta–induced genes.

**Results:** A 57-year-old woman presented with recurrent corneal erosions over 17 years and visual impairment in both eyes. Ophthalmological evaluation revealed multiple central tiny cysts in the epithelium of both eyes and lattice linear lesions only in the right cornea. In both eyes, a corneal posterior crocodile shagreen degeneration could also be observed. These findings were compatible with a MECD and a unilateral LCD. Molecular analysis identified the novel heterozygous nucleotide substitution c.1492G>A (amino acid change p.Glu498Lys) in the *KRT3* gene, in cosegregation with the MECD familial phenotype. However, no genetic evidence supported the unique LCD phenotype observed in the patient.

**Conclusions:** To the best of our knowledge, this is the first report of a pseudo-unilateral LCD in a patient with coexistent MECD. Moreover, the genetic analysis showed a novel mutation in the previously MECD-associated gene *KRT3*.

**Key Words:** gene mutation, *KRT3*, Meesmann dystrophy, unilateral lattice corneal dystrophy

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Meesmann corneal dystrophy (MECD) is a rare disorder involving the corneal epithelium, characterized by the presence of numerous small, round intraepithelial microcysts diffusely distributed in the interpalpebral zone and extending to the limbus.[1] Although some individuals can be asymptomatic, MECD is normally associated with recurrent corneal erosions, which cause glare, photophobia, foreign-body sensation, lacrimation, contact lens intolerance, and deterioration in visual acuity secondary to subepithelial scarring.[2] This pathology is linked to mutations in the cornea-specific keratins K3 and K12 genes [*KRT3* (MECD2, OMIM #618767) and *KRT12* (MECD1, OMIM #122100), respectively] and is inherited as an autosomal dominant trait with variable expression.[2–4] Keratins are intermediate filament proteins that form a dense fibrous scaffold within the cytoplasm of epithelial cells. Specifically, *KRT3* encodes for the type II intermediate filament, and its alteration is expected to negatively affect the K3/K12 heterodimer complex, causing an abnormal fragility of epithelial cells. To date, a total of 4 different disease-causing mutations have been identified in *KRT3*, all of them associated with MECD.[5]

On the other hand, lattice corneal dystrophy (LCD) is an inherited form of linear stromal amyloidosis, characterized by thin branching refractile lines and/or subepithelial, whitish, ovoid dots that usually appear by the end of the first decade.[1] The symptoms frequently include recurrent corneal erosions and visual impairment. Reported cases of LCD have exhibited an autosomal dominant inheritance pattern and have been associated with missense mutations in the transforming growth factor-beta–induced (*TGFBI*) and gelsolin (*GSN*) genes.[1,5]

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Herein, we present the clinical and molecular study of a Spanish patient carrying a novel *KRT3* mutation with coexistent familial MECD and a pseudo-unilateral LCD, as the first reported case with this combined corneal phenotype.

## MATERIAL AND METHODS

The patient was identified on consultation at the Institut de Microcirurgia Ocular (IMO) (Barcelona, Spain). Clinical diagnosis was established based on standard ophthalmic evaluations, including best-corrected visual acuity and corneal examination performed with a BX 900 slit-lamp (Haag-Streit, Köniz, Switzerland). Total serum protein, serum protein profile, and immunoelectrophoresis were also performed by an accredited external laboratory (Laboratorio Echevarne, Spain). Molecular analysis was performed by whole-exome sequencing on the patient's DNA, obtained from a peripheral blood sample. Libraries were designed and constructed using the SureSelect V6 technology (Agilent), and generated amplicons were genotyped with the HiSeq 4000 (Illumina). The obtained FASTQ raw data files were analyzed using the GeneSystems online platform (Sistemas Genómicos, Paterna, Spain), aligning sequences against the reference genome GRCh38/hg38. A total of 4 different genes (*GSN*, *KRT3*, *KRT12*, and *TGFBI*), previously related to the MECD or LCD phenotypes (PubMed databases), were considered for the genetic analysis. The detected variants were filtered based on the deleterious potential and the minor allele frequency (≤0.0001) from the following open databases: 1000 Genomes, ExAC, GO ESP, TOPMed, and EVS. The pathogenicity of the substitutions was evaluated using several in silico predictors (SIFT, PolyPhen2, LRT, Mutation Taster, Mutation Assessor, FATHMM, MetaSVM, LoFtool, Fathmm-MKL, PROVEAN, M-CAP, Condel, PhastCons, and PhyloP). All the obtained variants were further confirmed by Sanger sequencing. For the cosegregation analysis, Sanger sequencing was also performed on the DNA from the patient's father, collected from a saliva sample, using primers located in the *KRT3* exon 7 (NM_057088.2) (GAGGAATGTTCCCTGACTTTAAG and TGGGCACTGGTTGCATACGTGC). All procedures were in accordance with the Declaration of Helsinki. Ethics approval was received from the IMO Ethics Committee. Informed consent for publication was obtained.

## RESULTS

A 57-year-old woman of Spanish origin attended to IMO with painful irritation and gradual loss of visual acuity in both eyes (OU). The patient's ocular history was significant for photophobia since childhood and recurrent corneal erosions over 17 years. The best-corrected visual acuity was 20/400 in the right eye (OD) and 20/30 in the left eye (OS). Slit-lamp examination revealed multiple central tiny cysts in the epithelium of both eyes and lattice lesions only in the right cornea, consisting on linear fine branching opacities in the anterior corneal stroma. The OD also presented subepithelial and anterior stromal fibrosis located in the inferior part of the cornea. A corneal posterior crocodile shagreen degeneration in the OU could also be observed. These findings were compatible with a MECD and a unilateral LCD (Fig. 1A). Total serum protein, serum protein profile, and immunoelectrophoresis were performed to discard clinically silent paraproteinemia or other hematologic dyscrasias.[6] The obtained serological results were within normal limits (Supplemental Digital Content 1, http://links.lww.com/ICO/B140). As for the family history, her father was diagnosed with MECD, but no lattice lines were observed, whereas the mother and the sister did not present any corneal alterations, according to ophthalmic examinations (Fig. 1B).

To identify the molecular cause of the diseases, whole-exome sequencing was performed on the patient's DNA. Four different genes (*GSN*, *KRT3*, *KRT12*, and *TGFBI*) were analyzed, considering autosomal dominant as the most probable inheritance pattern according to the family history and the reported cases. Only the heterozygous nucleotide variant c.1492G>A (amino acid change p.Glu498Lys) in the *KRT3*

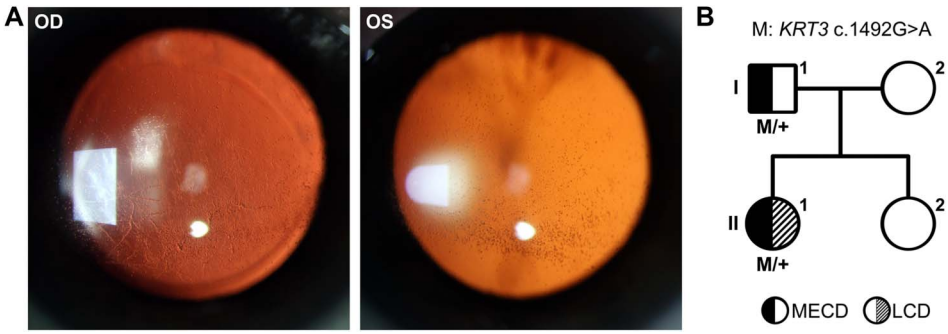


**FIGURE 1.** A, Slit-lamp retroillumination images obtained from the right and the left eye (OD and OS, respectively) of the patient show multiple tiny epithelial microcysts, which extend to the limbus and are most numerous in the interpalpebral area with the clear surrounding epithelium. Moreover, central subepithelial scarring and multiple lattice lines in a spider-like branching pattern confined to the anterior-midstroma are also observed in the OD (left panel). B, The pedigree of the patient (individual II:1) shows the cosegregation analysis of the variant c.1492G>A in the *KRT3* gene with the MECD phenotype. (The full color version of this figure is available at www.corneajrnl.com.)

gene was identified as a putative candidate mutation, which was further confirmed by Sanger sequencing. All the in silico pathogenicity predictors indicated that this variant presents a deleterious effect, while the PhastCons and PhyloP programs determined that the change affects highly conserved nucleotide and amino acid positions. The mutation was not found in an in-house cohort of 137 control individuals and neither in the human polymorphism (dbSNP) and mutational databases (HGMD and Uniprot). In addition, Sanger sequencing performed on the DNA from the patient's father, also affected by MECD, identified the same heterozygous mutation, further confirming the cosegregation of the c.1492G>A variant in *KRT3* with the familial MECD phenotype (Fig. 1B).

## DISCUSSION

The present work reports, for the first time, a case of pseudo-unilateral LCD in a patient with coexistent familial MECD. The molecular screening of all genes previously associated with these 2 phenotypes revealed a novel missense pathogenic variant in *KRT3* (c.1492G>A, p.Glu498Lys), correlating with the morphological and clinical MECD findings. In this regard, a similar missense mutation altering the same amino acid residue (c.1493A>T, p.Glu498Val) had already been reported in a family with MECD.[3] These findings reinforce the identified *KRT3* variant c.1492G>A as the molecular cause of the MECD in our family, which is also inherited in an autosomal dominant pattern.

Concerning the unique pseudo-unilateral LCD in the patient, it is worth mentioning that corneal dystrophies—including LCD—are generally bilateral and symmetric disorders, although some unilateral or markedly asymmetric cases have also been reported.[7,8] Although lattice-like changes can occasionally be caused by recurrent epithelial trauma secondary to MECD,[9,10] or as a result of a paraproteinemic keratopathy,[6] the normal serological findings and the classic LCD lesions noted in the OD of the patient suggested that this may be a unique unilateral variant of the disease. However, the hematological follow-up of the patient should be considered to ensure that the lattice phenotype does not manifest before systemic involvement. Regarding the genetic diagnosis, the screening of *GSN* and *TGFBI* did not reveal any pathogenic mutation in our patient. Therefore, the observed corneal phenotype is a pseudo-unilateral LCD because of the lack of supporting genetic evidences, although several authors had also reported the absence of molecular cause in patients clinically diagnosed with LCD.[11,12] In this respect, it is important to highlight that the lattice lines observed in the patient did not appear to be axially distributed. This feature, in addition to the unilateral nature of the lattice lines and the absence in the father, all argues against an inherited corneal dystrophy. In any case, the identified *KRT3* mutation c.1492G>A does not appear to be correlated with this unique LCD phenotype because the father also harbors the same mutation but yet does not exhibit the disease. Thus, the current clinical data cannot clarify whether the present combined corneal phenotype is a manifestation of common pathogenic mechanisms or adjacent genetic defects, or only a coincidental association between 2 rare diseases, as previously reported in other similar occurrences,[13] and further functional analyses should be performed.

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