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Epithelial Recurrent Erosion Dystrophy Secondary to the *COL17A1* c.3156C>T Mutation in a Non-Caucasian Family

Farnoosh Vahedi, B.S., **Doug D. Chung, Ph.D.**, **Katherine M. Gee, B.S.**, **Pichaya Chuephanich, M.D.**, and **Anthony J. Aldave, M.D.**

Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Abstract

Purpose—To report the identification of the collagen, type XVII, alpha 1 (*COL17A1*) c.3156C>T mutation associated with epithelial recurrent erosion dystrophy (ERED) in a Thai family.

Methods—Slit lamp examination was performed to determine affected status of each member of a Thai family with multiple members demonstrating scattered Bowman layer opacities. After genomic DNA was isolated from saliva, PCR amplification and Sanger sequencing were performed to screen *COL17A1* and exons 4 and 12 of the transforming growth factor β-induced gene (*TGFBI*).

Results—The 67-year-old proband and her four siblings were examined by slit-lamp biomicroscopy, which identified bilateral subepithelial opacities in the proband and in one of the four siblings. In both the proband and affected sister, screening of the *COL17A1* gene identified a heterozygous c.3156C>T synonymous mutation that has been previously demonstrated to introduce a cryptic splice donor site, likely leading to aberrant splicing of *COL17A1*. This mutation was not identified in the unaffected siblings and no mutations were identified in exons 4 or 12 of the *TGFBI* gene in any of the screened family members.

Conclusion—ERED associated with a *COL17A1* mutation has been previously reported in only six families, all Caucasian. The identification of the c.3156C>T mutation, previously identified in five of these six families, in the Thai family we report indicates conservation of the genetic basis of ERED across different races and underscores the importance of ophthalmologists around the globe being familiar with ERED, which has only recently become a recognized corneal dystrophy.

Keywords

epithelial recurrent erosion dystrophy; collagen; type XVII; alpha I; *COL17A1*

INTRODUCTION

Epithelial recurrent erosion dystrophy (ERED; Online Mendelian Inheritance in Man [OMIM] 122400) is an autosomal dominant disorder that is characterized by recurrent

Correspondence: Anthony J. Aldave, M.D., Professor of Ophthalmology, Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095-7003, Tele: 310.206.7202; Fax: 310.794.7906; aldave@jsei.ucla.edu.

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corneal epithelial erosions secondary to impaired epithelial adherence. Developing in childhood, the recurrent corneal erosions lead to subepithelial scarring and fibrosis, which may be mistaken for dystrophic deposits.[1, 2] By 30 to 40 years of age, the severity and frequency of corneal erosions decrease, although the resultant epithelial irregularity leads to impaired vision.[3] Given clinicians' unfamiliarity with ERED and the absence of dystrophic corneal opacities in affected individuals, the majority of affected individuals are either misdiagnosed or not given a specific diagnosis.

While more than a dozen families have been clinically diagnosed with ERED,[2-11] *COL17A1* mutations have been identified in only six families to date: one American family originally reported by Yee and colleagues that we subsequently reported with the c.3156C>T mutation;[9] a Swedish family reported by Jonsson and colleagues with the c.2816C>T mutation;[10] two families from New Zealand, one from the United Kingdom, and one from Tasmania, Australia reported by Oliver and colleagues, all with the c.3156C>T mutation.[11] We report the identification of the *COL17A1* c.3156C>T mutation in a Thai family affected with ERED, representing the seventh pedigree confirmed to have ERED, and the first non-Caucasian family.

MATERIALS AND METHODS

Ethics statement

Researchers followed the guidelines set by the Declaration of Helsinki in the treatment of the subjects reported in this study. Written informed consent was obtained from all participants of the study in accordance with the regulations provided by the Institutional Review Board at the University of California at Los Angeles (UCLA IRB#11-000020).

Patient enrollment and DNA collection

After informed written consent was obtained, slip-lamp biomicroscopy was performed on the proband and enrolled family members to identify clinical features characteristic of ERED.[9,12] Saliva samples were collected from each enrolled individual using the Oragene Saliva Collection Kit (DNA Genotek, Inc., Ottawa, Canada) and genomic DNA was isolated using the Oragene prepIT-L2P Kit (DNA Genotek, Inc.).

PCR and Sanger sequencing

Using previously published primers and PCR conditions, the region of *COL17A1* containing the c.3156C>T variant was screened in each of the enrolled family members.[9] PCR products were sequenced by Sanger sequencing and were compared to the *COL17A1* reference sequence NG_007069.1. To exclude Reis–Bücklers corneal dystrophy (RBCD) and Thiel-Behnke corneal dystrophy (TBCD), exons 4 and 12 of *TGFBI* were also screened using previously reported primers and PCR conditions.[13] PCR sequences were compared to the *TGFBI* reference sequence NG_012646.1.

RESULTS

Clinical characteristics

The proband, a 67-year-old Thai woman (Figure 1, III-1), presented with a four-decade history of recurrent ocular discomfort and progressive decrease in vision in both eyes. Corrected distance visual acuity measured 20/70 OD and 20/100 OS. Slit-lamp examination revealed bilateral, scattered grey-white subepithelial nodules, primarily involving the central 8 mm of each cornea, and diffuse subepithelial scarring (Figure 2). The proband's 62-year-old sister (Figure 1, III-3) reported a 10-year history of recurrent ocular discomfort and mild decrease in vision in each eye, and underwent a phototherapeutic keratectomy in the left eye 1 year prior to presentation. Corrected distance visual acuity measured 20/25 OD and 20/30 OS. Slit-lamp examination revealed bilateral, patchy grey-white subepithelial scarring, more in the right eye than the left, with a few grey-white subepithelial nodules in the right eye (Figure 2). The proband's three other siblings (Figure 1, III-2, III-4, III-5) denied a history of symptoms consistent with recurrent corneal erosions and decreased vision. Slit lamp examination of each demonstrated bilaterally clear corneas. The proband's father and paternal grandfather, both deceased, also had a history of decreased vision since early adulthood. Ocular examination records were not available for either.

TGFBI and *COL17A1* screening

Given the history of recurrent corneal erosions associated with bilateral, axially-distributed subepithelial opacification in the proband and her sister, a *TGFBI* dystrophy, such as RBCD and TBCD, and ERED were suspected. Therefore, DNA was collected from the proband, as well as her affected and unaffected siblings, for screening of *TGFBI* and *COL17A1*. Screening of *TGFBI* exons 4 and 12 in the proband did not identify any sequence variants. Screening of *COL17A1* exon 46 identified the previously reported c.3156T>C mutation in the heterozygous state in the proband and her affected sister, but not in any of their unaffected siblings (Figure 1) .

DISCUSSION

Three different corneal dystrophies, Franceschetti corneal dystrophy (FRCD), Dystrophia Smolandiensis (DS), and Dystrophia Helsinglandica (DH), all of which are characterized by the development of erosions in the first decade of life followed by progressive subepithelial fibrosis, have been grouped together by the International Committee for Classification of Corneal Dystrophies (IC3D) as ERED.[14] While the genetic basis of these three corneal dystrophies remains unknown, the similarity of the clinical phenotype of these dystrophies to that observed in ERED associated with a *COL17A1* mutation indicates that these dystrophies likely share the same common genetic basis as the more recently reported families with ERED[9-11].

ERED is likely a more common clinical entity than the small number of families reported with the dominantly inherited disorder would suggest. Given clinician unfamiliarity with the disorder and the same dominant inheritance pattern, similar clinical course and phenotypic features as RBCD and TBCD, affected individuals are likely misdiagnosed with a *TGFBI*

dystrophy. An example of this is the family diagnosed with presumed Thiel-Behnke corneal dystrophy that was mapped to chromosome 10q23-q24, in which we subsequently identified the c.3156C>T synonymous mutation in *COL17A1*, leading to the reclassification of this family as having ERED[9]. In addition, the diagnosis of ERED may be more challenging to make given that it is not associated with dystrophic deposit formation in a characteristic, recognizable pattern. Instead, the corneal opacification that develops is secondary to a variable scarring response following recurrent corneal erosion formation, which may differ significantly between affected individuals.

These diagnostic challenges underscore the utility of molecular genetic analysis in the accurate diagnosis of corneal dystrophies with overlapping and variable clinical features. The fact that only two pathogenic *COL17A1* mutations have been identified in the seven families screened to date indicates a conservation of mutations, as observed for the TGFBI dystrophies, that facilitates diagnostic genetic testing. However, for molecular genetic analysis to be successfully incorporated into clinical practice, clinicians must understand in which clinical scenarios it may effectively differentiate between two or more suspected corneal dystrophies, as well as between dystrophic and non-dystrophic corneal disorders. As this requires a familiarity with the less common inherited corneal disorders, such as ERED, we report only the seventh family with ERED associated with a mutation in *COL17A1* (the sixth associated with the c.3156C>T synonymous mutation) and the first non-Caucasian family with ERED. We hope that this report will encourage clinicians to incorporate molecular genetic analysis in their practices and to expand our understanding of the genetic basis of ERED by reporting additional families with previously identified and novel mutations. We also encourage the investigators who have reported families affected with FRCD, DS and DH to screen *COL17A1* in these families to determine if a common genetic basis exists for all of the dystrophies that have been categorized as ERED.

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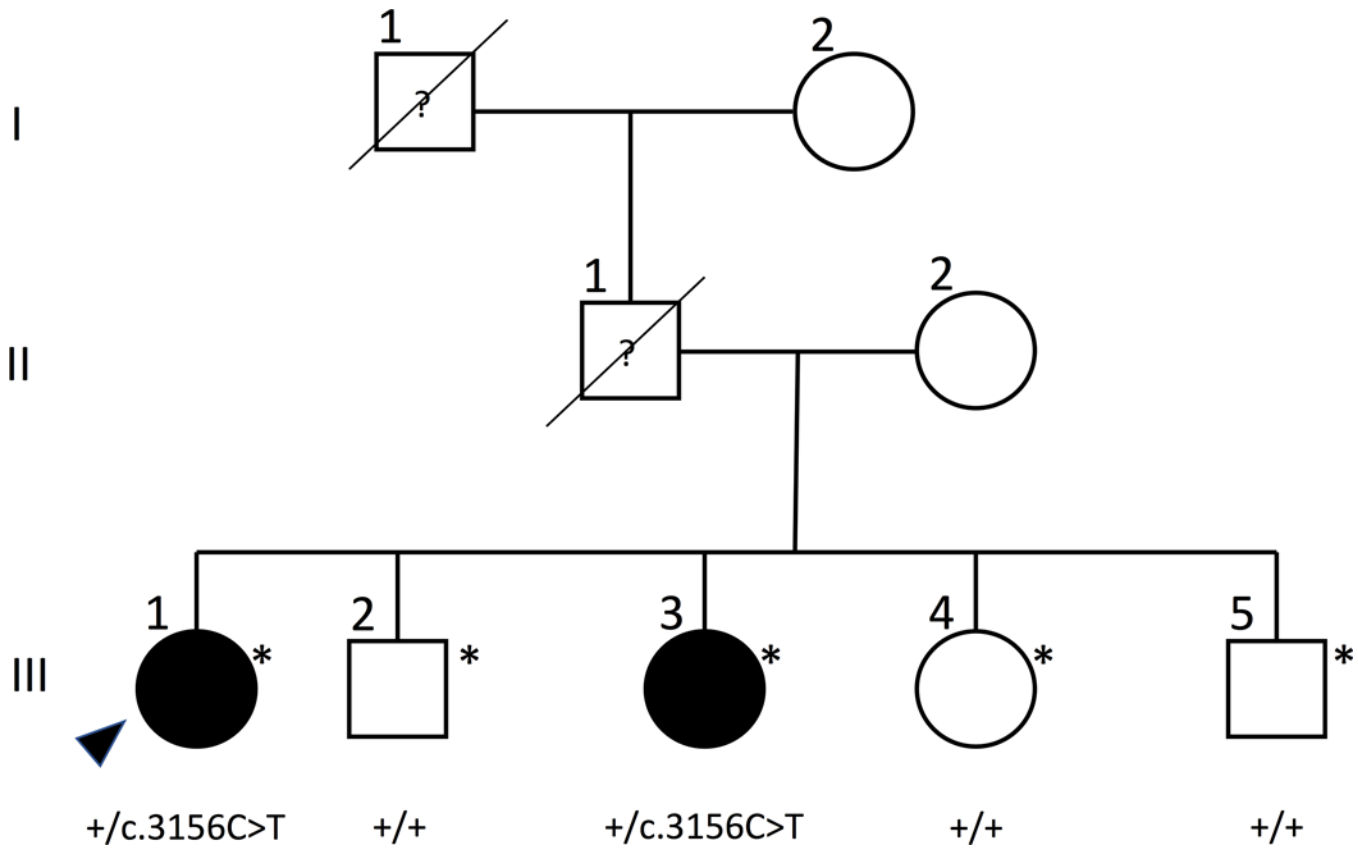

Figure 1. Pedigree of Thai family with epithelial recurrent erosion dystrophy

Females are represented by circles, males by squares. Affected individuals are shown with filled symbols and unaffected are shown with open symbols. Individuals with an unknown affected status are shown with a question mark. The arrowhead indicates the proband. An asterisks indicates individuals who underwent screening for the *COL17A1* c.3156T>C mutation, the results of which are demonstrated beneath the symbol for each individual.

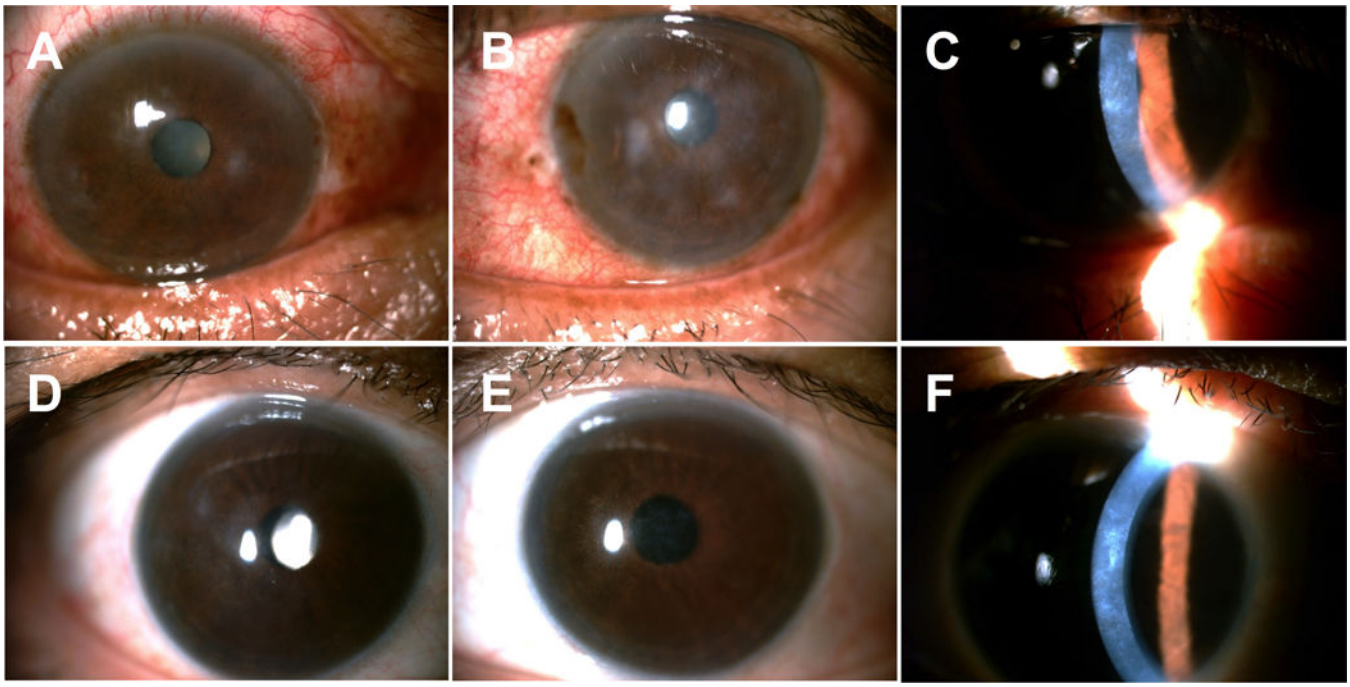

Figure 2. Clinical features of epithelial recurrent erosion dystrophy

67-year-old proband (Figure 1, III-1) demonstrating bilateral, scattered grey-white subepithelial nodules and diffuse subepithelial scarring in the right (A) and left (B and C) eyes. 62-years-old sister of the proband (Figure 1, III-3) demonstrating bilateral, patchy grey-white subepithelial scarring, more in the right eye (D and F) than the left eye (E).