Corneal Thinning Phenotypes—An Alternative Perspective

We were very interested to read of a second mutation in the seed region of miR-184 resulting in EDICT syndrome. We were unsure after reading the paper, however, of how the corneal findings should be classified and of the statement that the family “does not demonstrate a keratoconus phenotype.” Keratoconus, the commonest disorder of corneal thinning and steepening, has been linked with VSX1 and SOD1 in single studies and up to 14 different genetic loci. It has a variable phenotype, and while few would dispute the diagnosis in classic cases with central corneal thinning, identifying variants such as forme fruste disease (where a cone may not be present) may be more challenging. A less common disorder of corneal thinning is keratoglobus, in which the thinning is global and often most pronounced in the periphery. Iris hypoplasia with keratoglobus has been described. Similarly, the occurrence of keratoglobus with a corneal endothelial disease, posterior polymorphous corneal dystrophy, has also been recognized. Histopathologic studies of advanced keratoconus are very similar to those of keratoglobus. Biochemical analyses also reveal that a decreased expression of α1 proteinase inhibitor and upregulation of transcription factor Sp1 are common to both. Disorders of retinal development (as found in 4 of 10 EDICT patients) can also co-segregate with corneal ectasia; CRB1 mutations causing Leber congenital amaurosis (LCA) have been associated with both keratoconus and keratoglobus.

We wonder if the reported corneal phenotype in EDICT syndrome should fall within the keratoconus/globus spectrum and, as such, should be considered a candidate gene for these as well as other “cornea plus” syndromes?

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Author Response: Corneal Thinning Phenotypes—An Alternative Perspective

The authors thank Giasin et al. for their interest in our paper and appreciate the opportunity to respond to their comments. We recently identified a mutation in the seed region of miR-184 as causal in EDICT, a syndrome of the anterior segment characterized by endothelial dystrophy, iris hypoplasia, congenital cataract, and stromal thinning, which was first described by our group 10 years ago. The same mutation was also identified by Hughes et al. as the causal variant in what they described as keratoconus with cataract. Giasin et al. raised the question of whether the corneal phenotype in EDICT syndrome should be classified within the keratoconus/keratoglobus spectrum.

The corneal phenotype that we observed in individuals affected by EDICT syndrome is unlike keratoconus or keratoglobus. The corneal thinning in EDICT is uniform, without the increased central thinning of keratoconus or increased peripheral thinning of keratoglobus. Corneal steepening is likewise uniform, diffuse, and nonectatic, without a cone or a globular contour. Furthermore, histopathology in EDICT syndrome is inconsistent with keratoconus and keratoglobus. Histologic examinations of both keratoconus and keratoglobus corneas have revealed disruption of Bowman’s layer and Descemet’s membrane, two findings that have not been identified in EDICT syndrome. The histopathology of EDICT also includes several features that are not present in keratoconus or keratoglobus, such as polymorphic vacuoles within keratocytes and within and between collagen lamellae in the stroma, along with intracellular and extracellular lipid deposition in the stroma and in Bowman’s layer. In addition, we observed prominent nodular protrusions of Descemet’s membrane, resembling Fuchs’ corneal dystrophy, and small-diameter cytokeratin-positive filaments in the endothelium with overlapping of endothelial cells, characteristic of posterior polymorphous corneal dystrophy. The EDICT corneal phenotype represents a unique combination of pathologic features, and attempts to ascribe a few of these characteristics to a previously defined clinical disease should be resisted.

Giasin et al. also proposed that miR-184 should be considered a candidate gene for other “cornea plus” syndromes. After identifying the +577>T>C variant of miR-184 as causal in EDICT syndrome, we sequenced miR-184 in two different cohorts with anterior segment disease: 285 unrelated individuals with Fuchs’ corneal dystrophy and 63 unrelated individuals with previously unlinked familial congenital cataract (Riazuddin SA, unpublished data, 2011). No variations in the mature miR-184 sequence were identified in these groups. Although it is possible that other mutations in miR-184, particularly if occurring outside the seed region, could cause a less severe “cornea plus” syndrome, such a mutation has yet to be identified.

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