

## The relationship between corneal subbasal nerve density and corneal sensitivity in patients with Fuchs endothelial corneal dystrophy

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**Purpose:** The aim of this study was to investigate the association between alterations in corneal subbasal nerve plexus and tactile corneal sensitivity in patients with Fuchs' endothelial corneal dystrophy (FECD). **Methods:** This retrospective, cross-sectional study included 24 (10 M/14 F) patients with FECD and 25 age- and sex-matched (10 M/15 F) healthy subjects as controls. Subjects with FECD were classified as having early (grades 1 and 2) and late (grades 3 and 4) disease. All subjects underwent central corneal tactile sensitivity measurements with the Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) and subbasal nerve density evaluation using *in vivo* confocal microscopy (IVCM). Association between corneal nerve plexus density and corneal sensitivity alterations were evaluated using the Mann-Whitney *U* test and the Spearman correlation test. **Results:** Compared to healthy subjects (mean age = 60.4 ± 7.5 years), patients with FECD (mean age = 60.6 ± 8.0 years) had worse central corneal sensitivity scores (5.9 ± 0.1 cm vs. 4.2 ± 0.8 cm;  $P < 0.001$ ), reduced corneal nerve fibers (3.4 ± 1.3 nerves/frame vs. 5.0 ± 0.9 nerves/frame;  $P < 0.001$ ) and lower corneal subbasal nerve plexus densities (2229.4 ± 364.3  $\mu\text{m}/\text{mm}^2$  vs. 1901.6 ± 486.8  $\mu\text{m}/\text{mm}^2$ ;  $P = 0.050$ ). Patients with late stage FECD demonstrated lower subbasal nerve densities as compared to those with early disease (2204.3 ± 313.1  $\mu\text{m}/\text{mm}^2$  (range = 1523–2552  $\mu\text{m}/\text{mm}^2$ ); 1397.1 ± 227.4  $\mu\text{m}/\text{mm}^2$  (range = 1120–1834  $\mu\text{m}/\text{mm}^2$ );  $P < 0.001$ ). In the FECD group, subbasal nerve density was found to be directly correlated with corneal sensitivity scores ( $r = 0.457$ ,  $P = 0.025$ ). **Conclusion:** Progressive loss of the corneal subbasal nerve plexus appears to be a consistent feature of FECD. Reduction of the corneal nerve plexus parallels the decrease in corneal sensitivity in this patient population.

**Key words:** Corneal nerves, corneal sensitivity, Fuchs' endothelial corneal dystrophy, *in vivo* confocal microscopy

Fuchs' endothelial corneal dystrophy (FECD) is a bilateral, slowly progressive, genetically heterogenous disorder of the corneal endothelial cells, associated with thickening of the Descemet's membrane and formation of guttate, initially described by Ernst Fuchs in 1910.<sup>[1-3]</sup> Currently, it is the leading indication for corneal transplantation in the United States.<sup>[4]</sup> Progressive endothelial cell loss, secondary to focal accumulation of abnormal collagen, results in corneal edema and visual compromise.<sup>[5,6]</sup> The initial clinical findings usually present in the fourth decade of life. Patients at the early stages of FECD are usually asymptomatic and typically do not require a corneal transplantation until after seventh decade of life.<sup>[7]</sup> Progression is initially characterized by an increase in the size and number of guttae, which can eventually become confluent and affect the peripheral cornea.<sup>[5,6]</sup> Although corneal endothelium is thought to primarily affected, previous reports have shown that all corneal layers may be involved in the course of the disease.<sup>[5,6]</sup>

Corneal subbasal nerve plexus is a dense network of neural tissue located between the basal epithelium and the Bowman's

layer, and provides protective and trophic functions for the epithelium through the sustained release of trophic factors.<sup>[8,9]</sup> This complex neural network is best visualized by *in vivo* confocal microscopy (IVCM) allowing both quantitative and qualitative evaluation of its normal architecture and its disease states.<sup>[10]</sup> Using IVCM, reduction of subbasal nerve density has been shown in FECD and this observation is thought to be responsible for the decrease in corneal sensitivity.<sup>[11-13]</sup> Although inflammation, bullae formation and subepithelial fibrosis have been suggested as the underlying reasons for the loss of nerve fibers, no definitive cause-effect has been established for the loss of the nerve layer in corneas with FECD.<sup>[11,14-16]</sup>

Recently, Aggarwal *et al.*<sup>[17]</sup> demonstrated quantitative reduction of subbasal corneal nerves in both early and late stage FECD with accompanying loss in corneal sensitivity.<sup>[17]</sup> To the best of our knowledge, this is the first study to investigate the relationship between corneal sensitivity and subbasal nerve density in the setting of FECD. Thus, the current study was undertaken to investigate relationship between

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corneal subbasal nerve alterations and corneal sensitivities in patients with FECD in a quantitative manner in an unrelated population. The hypothesis of the study was that corneal sensitivity loss would be associated with corneal subbasal nerve plexus damage in patients with FECD.

## Methods

This was a retrospective, cross-sectional study conducted in a single tertiary referral academic center. The study was approved by the Institutional Review Board (GO 20/300, 2020/07-03) and adhered to the tenets of the Declaration of Helsinki. The study cohort consisted of adult patients who were diagnosed with FECD [range = 45–76 years] based on clinical and confocal microscopic findings. The diagnosis of FECD was established upon detection of characteristic slit-lamp biomicroscopic corneal findings including guttate. Age- and sex- matched healthy subjects were involved as controls. Individuals with dry eye syndrome, diabetes or any other ocular or neurological disorder were not included in the control group. All patients underwent a detailed ophthalmic examination consisting of best-corrected visual acuity (BCVA) assessments with Snellen chart, slit-lamp biomicroscopy, dilated fundus examination, the Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) and IVCN (Confoscan 4, Nidek, Japan). Central corneal sensitivity was measured with the Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France) as previously described.<sup>[17,18]</sup> Patients with other ocular surface disease, including dry eye disease based on abnormal Schirmer's test, tear break-up time, corneal and conjunctival staining were excluded. Patients with a history of ocular surgery, except cataract surgery, inflammatory and infectious eye diseases, glaucoma, contact lens use, and diabetes based on ocular history, clinical signs and symptoms were also excluded. One eye per patient was included for data analysis. The eye with the more severe clinical manifestation of disease was included to avoid selection bias as patients who had bilateral FECD may have had different stages of disease in their eyes. Detailed slit-lamp examination was performed by a cornea specialist (SK). Diagnosis was established with slit lamp biomicroscopy and IVCN. Earliest characteristics of FECD on slit-lamp biomicroscopy to diagnose a case of FECD were the appearance of corneal guttae observed in central cornea in the absence of stromal edema.<sup>[6]</sup> Clinical grading of FECD was assessed at the slit-lamp and IVCN as follows: Grade 1: Presence of non-confluent guttae; grade 2: Presence of any area of confluent guttae, but without edema or clinical thickening; grade 3: Presence of confluent guttae with edema or clinical thickening; and grade 4: Presence of edema associated with whitening or haze, together with corneal guttae.<sup>[6,18,19]</sup> We categorized early stage FECD as grade 1 and 2 and late stage FECD as grade 3 and 4 as put forward in previous studies.<sup>[17,19]</sup>

Tactile corneal nerve sensitivities were measured with the Cochet-Bonnet esthesiometer by gently touching corneal surface with a retractable 6-cm long monofilament nylon thread. Upon a negative response, the thread was shortened by 1.0 cm until a positive response was achieved; thereafter, it was elongated by 0.5 cm to verify the specific value.<sup>[18]</sup>

IVCN was used to measure the number of long and short nerve fibers, corneal subbasal nerve density, and nerve tortuosity.<sup>[20]</sup> The non-contact mode of Confoscan 4 attached to a non-contact 20 × lens on the central corneas of all subjects was utilized to obtain nerve measurements. The average subbasal nerve density in three images was calculated using the Neuron J software (<http://www.imagescience.org/meijering/software/neuronj/>). The number of long and short nerve fibers was calculated per

frame. Subbasal nerve, tortuosity, number of long and short nerve fiber measurements were performed by an observer masked to the underlying diagnosis of the study subjects. Subbasal nerve tortuosity was evaluated in 4 grades, with grade 1 representing perfectly straight nerves and grade 4 representing grossly tortuous nerves with significant convolutions throughout their course.<sup>[21]</sup>

## Statistical analysis

One eye per patient was included for statistical analyses. Statistical analyses were performed with the IBM SPSS for Windows Version 23.0. Numerical variables were summarized as mean ± standard deviation or median [25<sup>th</sup>–75<sup>th</sup> percentile]. Categorical variables were given as frequencies and percentages. Categorical variables were compared by Chi square test. Normality of the continuous variables was evaluated by Kolmogorov Smirnov test. Homogeneity of variances was tested by Levene test. Differences between the groups according to continuous variables were determined by independent samples *t* test or Mann-Whitney *U* test as appropriate. Kruskal-Wallis test was used to compare more than two independent groups. *Post hoc* comparisons were done by the Dunn test. Relation between continuous variables was determined by Spearman correlation coefficient. A value of  $P \leq 0.05$  was considered as significant.

## Results

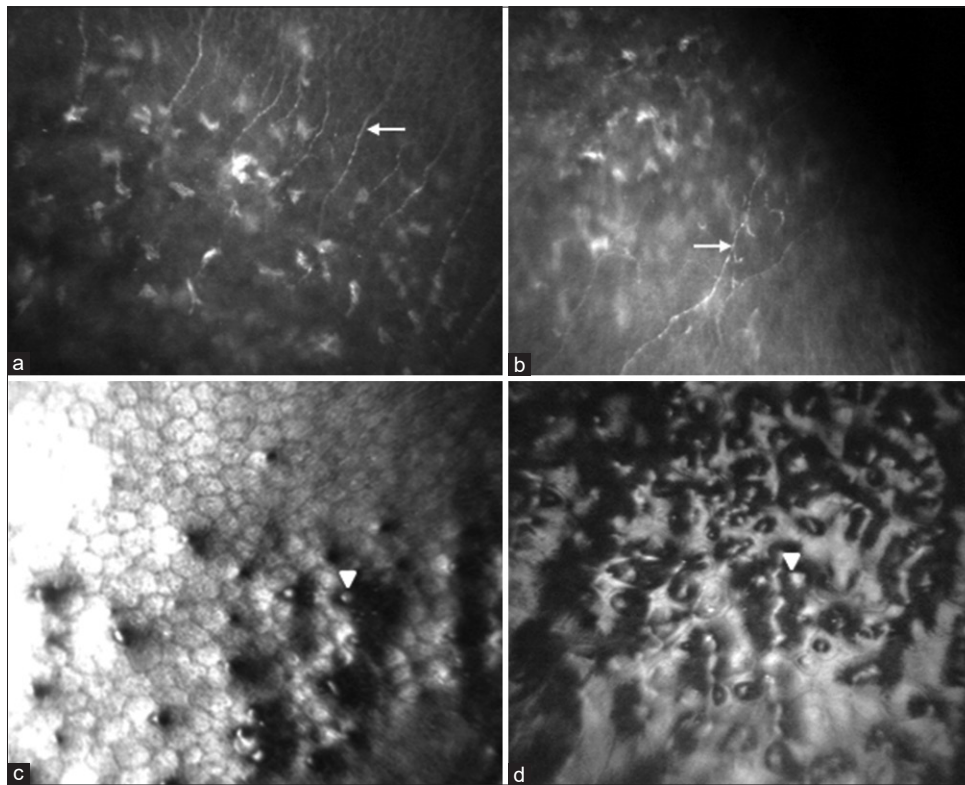
Twenty-four eyes of 24 patients (10 M/14 F) with FECD [mean age = 60.6 ± 8.0 years (range = 45–76 years)] and 25 eyes of 25 (10 M/15 F) healthy control patients [mean age = 60.4 ± 7.5 years (range = 44–65 years)] were included in the study. There was no significant difference in either the mean age ( $P = 0.935$ ) or gender ratios ( $P = 0.136$ ) between the study and the control groups [Table 1]. The cohort included 10 (41.7%) eyes with grade 1, 5 (20.8%) with grade 2, 5 (20.8%) with grade 3 FECD and four (16.7%) with grade 4 FECD (grade 4). Patients with FECD had worse central corneal sensitivity scores as compared to those of healthy controls (5.9 ± 0.1 cm vs. 4.2 ± 0.8 cm;  $P < 0.001$ ). All parameters for the subbasal nerve plexus densities appeared to be reduced in the FECD group as compared to those of controls [Table 2]. In addition, patients with FECD had evidence of attenuated and less tortuous nerves as compared to those of healthy controls [Table 2, Fig. 1]. The corneal sensitivity scores of patients with FECD was found to be correlated with the corneal subbasal nerve plexus densities ( $r = 0.457$ ,  $P = 0.025$ ) and subbasal nerve tortuosity scores ( $r = 0.442$ ,  $P = 0.031$ ) [Fig. 2].

Both early ( $n = 15$ ; 62.5%) and late ( $n = 9$ ; 37.5%) stage FECD showed significant reductions in corneal subbasal nerve density (2204.3 ± 313.1 μm/mm<sup>2</sup> (range = 1523–2552 μm/mm<sup>2</sup>) for early disease; 1397.1 ± 227.4 μm/mm<sup>2</sup> (range = 1120–1834 μm/mm<sup>2</sup>) for late disease as compared to controls (2229.4 ± 364.3 μm/mm<sup>2</sup> (range = 1849–2850 μm/mm<sup>2</sup>), and when compared within themselves (early vs. late stage FECD;  $P < 0.001$ ). The difference between corneal sensitivity scores did not reach the level of statistical significance in patient with early vs. late disease (4.5 ± 0.9 cm vs. 3.7 ± 0.3 cm;  $P = 0.064$ ).

No inflammatory foci of inflammation were noted surrounding the subbasal nerve plexus of patients at any grade of FECD.

## Discussion

Kaufman *et al.*<sup>[22]</sup> published the initial confocal microscopic report in the cornea of a patient with advanced FECD in 1993,<sup>[22]</sup> describing irregular and enlarged endothelial cells, together



**Figure 1:** *In vivo* confocal microscopic images of the subbasal nerve plexus and endothelial cell layer in patients with FECD. Subbasal nerve plexus (a) and endothelial cell layer (c) of an early stage FECD subject. Subbasal nerve plexus (b) and endothelial cell layer (d) of a late stage FECD subject. Subbasal nerve plexus is depicted with arrows in 1B, showing thinning, decreasing and less tortuous nerves of a patient with FECD. Endothelial cell layer reveals decreased endothelial cell density, and guttae (arrow head) in the endothelium (c and d)

**Table 1: Demographics of patients diagnosed with Fuchs' endothelial corneal dystrophy**

	FECD group (n=24)	Control group (n=25)	P
Age (years) [mean±SD] (range)	60.6±8.0 (45-76)	60.4±7.5 (44-65)	0.935
Gender (Male/Female)	10/14	10/15	0.136
Visual acuity (logMAR)	0.5±0.7 (0.7-0.4)	0.1±1.0 (0.1-1.0)	<0.001*

FECD: Fuchs' endothelial corneal dystrophy, logMAR: Logarithm of the minimum angle of resolution, \*Denotes statistical significance

**Table 2: Comparison of subbasal corneal nerve parameters and central tactile corneal sensitivities of patients with Fuchs endothelial corneal dystrophy and those of healthy control subjects**

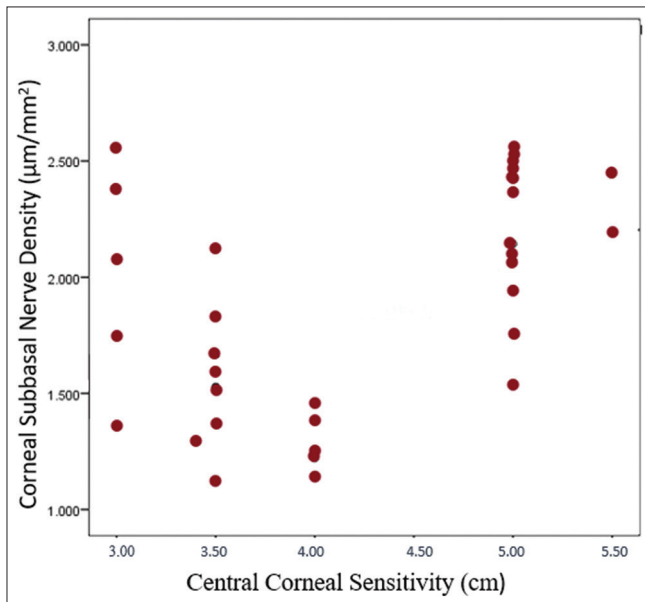
Parameters	FECD (n=24) mean±SD (range)	Control (n=25) mean±SD (range)	P
Central corneal sensitivity (cm)	4.2±0.8 (1-6)	5.9±0.1 (5-6)	<0.001*
Number of long nerve fibers (nerves/frame)	3.4±1.3 (1-5)	5.0±0.9 (3-7)	<0.001*
Number of short nerve fibers (nerves/frame)	3.5±1.2 (1-5)	5.1±1.4 (3-8)	<0.001*
Subbasal nerve density (µm/mm <sup>2</sup> )	1901.6±486.8 (1120-2552)	2229.4±364.3 (1849-2850)	0.050*
Subbasal nerve tortuosity (grade)	1.7±0.8 (1-3)	3.8±0.5 (2-4)	<0.001*

FECD: Fuchs' endothelial corneal dystrophy. \*Denotes statistical significance

with disrupted epithelial layer and hazy stroma.<sup>[22]</sup> Mustonen *et al.*<sup>[23]</sup> subsequently reported the confocal microscopic findings in a cohort of patients diagnosed with FECD, who noted absence of nerves in patients with FECD.<sup>[23]</sup> Further confocal microscopic studies have further demonstrated structural alterations in all corneal layers,<sup>[11,18,23-26]</sup> including subbasal nerve loss,<sup>[17,18,24,26]</sup> reduction of keratocyte density<sup>[27,28]</sup> and subepithelial haze,<sup>[29]</sup> confirming that pathological changes in FECD are not limited to the endothelium alone.<sup>[23]</sup>

In the current study, we were able to demonstrate that loss of the corneal subbasal nerves was accompanied by decrease in corneal tactile sensitivity. Corneal subbasal nerve plexus alterations were present even at the early stages of FECD, being more pronounced in later stages of the disease. Overall, our findings suggest that attenuation and loss of corneal subbasal nerves are an integral part of the degenerative process which defines FECD. It appears that these neural alterations exist even without any evidence of inflammatory or fibrotic changes.





**Figure 2:** The relationship between central corneal sensitivity and corneal subbasal nerve densities of patients diagnosed with FECD

From a clinical standpoint, our findings would help increase awareness with respect to the co-existing corneal neuropathy associated with FECD that may not be readily appreciated by general ophthalmologists and residents-in-training. In turn, we anticipate that this awareness would translate into improved overall patient care for those patients with FECD who may exhibit delayed corneal healing after developing keratopathy and/or epithelial defects. Overall, our results contribute to the understanding of this progressive disorder by providing quantitative evidence of subbasal nerve damage together with co-existing reductions in corneal sensitivity that correlate with neural tissue loss. Our findings appear to be in agreement with those of Aggarwal *et al.*<sup>[17]</sup> in which the authors demonstrated quantitative loss of the corneal subbasal nerve plexus in patients with FECD that was correlated with reduction in corneal mechanical sensitivity in an unrelated population. Similarly, the findings of Schrems-Hoesl *et al.*<sup>[26]</sup> also demonstrated significant reductions in corneal subbasal nerves in patients with FECD, even at the early stages of the disease.<sup>[26]</sup> Corneal subbasal nerve loss were found to be more pronounced in corneas with more advanced disease in a cohort of 30 patients at different stages of FECD.<sup>[18]</sup> Based on our results, as well as those by others,<sup>[17,18,23,26]</sup> it appears that the degenerative process affecting the endothelial cell layer also involves the corneal subbasal nerve plexus early on in the disease.

Qualitative analysis of the corneal images in the current study revealed the presence of thin, attenuated subbasal nerves with straightened out and fragmented appearance in the corneas of patients with FECD [Fig. 1a and b]. A previous study by Ahuja *et al.*<sup>[11]</sup> detected fine and sparse subbasal nerve morphology together with nerve fragmentation in the corneas of patients with FECD undergoing keratoplasty.<sup>[11]</sup> The type of keratoplasty is important for FECD. Corneal sensitivity is decreased in FECD compared to normal after penetrating keratoplasty more than endothelial keratoplasty.<sup>[11]</sup> In addition, the authors of that study were only able to visualize the subbasal nerves in 60% of 42 eyes with FECD.<sup>[11]</sup> Overall, our findings, together with those of Ahuja *et al.*<sup>[11]</sup> are suggestive of a slowly progressive degenerative process in the subbasal plexus, with gradual attenuation and structural

disintegration of the subbasal nerves with resultant loss in corneal sensitivity. Together, these findings lend support to the neurodegenerative origin of FECD involving both the endothelial cells of neural crest cell origin as well as the subbasal nerve plexus.<sup>[30]</sup>

In the current study, reduction in the corneal subbasal nerve tortuosity was found to have a mild-moderate strength of correlation with tactile corneal sensitivity ( $r = 0.442$   $P = 0.031$ ). Similar to our results, Aggarwal *et al.*<sup>[17]</sup> also detected a mild but significant correlation between the subbasal nerve plexus density and corneal sensitivity ( $r = 0.32$   $P = 0.045$ ) in patients with FECD.<sup>[17]</sup> The finding that corneal sensitivity correlates only mildly with subbasal nerve density in our study as well as the study by Aggarwal *et al.*<sup>[17]</sup> is intriguing; it is possible that certain portions of the subbasal nerve plexus may be dysfunctional prior to its eventual demise in this disorder.<sup>[17]</sup> It may also be that the functional nerve units in the basal epithelial area that are responsible for tactile sensitivity, cannot be imaged with confocal microscopy.<sup>[31]</sup> Finally, functional neural loss may occur at the synaptic or nuclear level rather than in the peripheral subbasal nerve fiber bundles and thus cannot be appreciated with IVCM.<sup>[32]</sup>

Although the underlying mechanism of subbasal nerve attenuation as well as reduction in function of the subbasal corneal nerve plexus with increasing severity of FECD is not known so far, the condition likely represents a form of neurodegenerative disorder with a genetic basis. A strong genetic component has been suggested for FECD as a positive family history is present in approximately 50% of patients.<sup>[3]</sup> It is associated with mutations or single-nucleotide polymorphisms (SNPs) of several (>15) different genes that are responsible for different aspects of cellular function.<sup>[3]</sup> Among the genes currently implicated in the pathogenesis of FECD, TCF-4 and COL8A2 have central roles in apoptotic pathways, SLC4A11 and LOXHD1 have plasma membrane functions, the AGBL1 gene is involved in microtubule assembly and others such as PITX2 have more central functions in cell development and tissue differentiation.<sup>[3]</sup> It is likely that malfunction or inactivation of the protein genes acting or pro-apoptotic pathway and in neutralizing oxidative stress cause degeneration in both the endothelial and the neural tissue in the corneas of patients with FECD. Thus, patients with FECD who have certain mutations or SNPs may be more vulnerable to developing neural damage in their corneas. Thus, future studies that take into consideration the underlying mutations or SNPs, may be extremely helpful in undertaking whether a subset of patients with FECD are at higher risk for subbasal nerve loss and reduction in corneal sensitivity.

Our results should be interpreted in the light of its potential limitations. The major limitation of the current study is its retrospective design; prospective collection of data can provide for more standardized acquisition of study outcome measures. The study sample size was relatively limited ( $n = 24$  for the FECD group). Compiling a cohort of patients with ocular FECD is challenging as reflected by low number of patients in similar studies.<sup>[17,18]</sup> Contact esthesiometry is not an absolute measure of corneal sensitivity, as it only measures the mechanoreceptor function. Finally, the genetic profiles of the patients had not been elucidated for any one of the patients in our cohort.

## Conclusion

In conclusion, the results of our study provide further evidence of corneal subbasal nerve loss and reduced corneal sensitivity

in patients with FECD. Neural degeneration, in the form of subbasal nerve plexus loss, appears to be a fundamental component of the degenerative process which defines this disorder and can propagate even without any evidence of overt inflammation. It would be prudent to assume that the various genetic mutations which underlie this disorder have a bearing on the corneal subbasal nerve plexus alterations and the resultant loss of corneal sensitivity. Future prospective studies on FECD taking into consideration the underlying genetic mutations or SNPs would be instrumental in understanding the pathophysiology of alterations that occur at the endothelial cell and the subbasal nerve layers of corneas with FECD.

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#### Conflicts of interest

There are no conflicts of interest.

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