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Fuchs endothelial cornea dystrophy: a review of the genetics behind disease development

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Abstract

Fuchs dystrophy represents the most common form of endothelial dystrophy and is a significant cause of visual impairment. The cause of Fuchs dystrophy is a complicated combination of both genetic and environmental factors. Understanding the underlying causes of the disease can potentially lead to new medical treatments preventing loss of vision.

Introduction

A dystrophy has previously been defined as “the process and consequence of hereditary affections of specific cells in one or more tissues that initially had normal function.”¹ In regards to the cornea, dystrophies are traditionally defined as the groups of disorders that are typically bilateral, symmetric, and progressive but without environmental or systemic factors.² The problem with this definition is that as scientific knowledge expands, exceptions to each aspect of the definition are noted. As such, the International Committee for Classification of Corneal Dystrophies (IC3D) classification system was created to incorporate many aspects of the traditional definitions of corneal dystrophies with new genetic, clinical, and pathologic information. Each dystrophy is placed into a category numbered 1, 2, 3, or 4, depending on the level of evidence supporting the existence of a given dystrophy. The most defined dystrophies, those with a solid clinical phenotype in which a gene has been identified and mutations are known, belong to category 1 and the least defined, those where neither clinical nor genetic information is convincing, belong to category 4.²⁻³

Fuchs’ corneal endothelial dystrophy (FECD) is the most common form of corneal dystrophy affecting the innermost layer of the cornea, the endothelium (Figure 1). FECD was first described in 1910 by Ernst Fuchs as a “dystrophia epithelialis corneae” though the endothelium was found to be the cause shortly thereafter.⁴⁻⁵ Histological studies later described the thickening of Descemet’s membrane and the excrescences known as guttae.⁶⁻⁷ It is characterized by progressive corneal endothelial cell loss, morphological changes in the size and shape of remaining cells, and a concomitant formation of guttae (Figure 1). As endothelial cells decrease in number there is an inversely proportional increase in guttae until a threshold is passed and the remaining cells no longer have the capacity to maintain

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the cornea's necessary state of relative dehydration.⁸⁻¹⁰ Consequently, there is edema which leads to corneal clouding and decreased vision. The IC3D system classifies early-onset FECD as category 1 as it is well defined both clinically and genetically. Late-onset FECD is either category 2 with a well-defined clinical syndrome and evidence of genetic loci, if not specific gene, or category 3 with a well-defined clinical phenotype but no genetic basis has been defined.²⁻³ Regardless of type, FECD generally progresses through four clinically-defined stages that span a course of two-to-three decades.¹¹⁻¹³ The stages are: Stage 1 in which the patient is asymptomatic though microscopy shows non-confluent guttae; Stage 2 in which the guttae coalesce with corresponding loss of endothelial cells and increased pleomorphism and polymegathism; Stage 3 in which corneal edema is seen as there is now a compromise in endothelial pump function; and Stage 4 in which the chronic edema has caused corneal opacity and scarring leading to severely compromised vision and pain. There seem to be regional differences in the prevalence of the disease, ranging from 3.8-11% of patients over age 40.¹⁴⁻¹⁶ Currently, though medical therapy offers some symptomatic relief, the only definitive treatment to restore lost vision is corneal transplantation in the form of penetrating keratoplasty or Descemet's stripping endothelial keratoplasty, making FECD one of the most common indications for corneal transplant in the United States.¹⁷⁻¹⁸

Early-onset FECD

A rare early-onset form of FECD starts in the first decade of life and progresses through the second and third decades and is characterized by a thickened Descemet's membrane at birth and corneal decompensation by the 3rd to 4th decade.¹⁹⁻²¹ Several different multi-generational families have been studied and an autosomal dominant (AD) pattern of inheritance has been consistently seen. As would be expected by an AD trait following Mendelian inheritance, there is no sex predilection.¹⁹⁻²² With the advent of more advanced genetic studies, two mutations in the Col8A2 gene have been described in these populations.^{20, 23} The Col8A2 gene, located on chromosome 1p34.3-p32, encodes the $\alpha 2$ polypeptide of collagen type VIII which constitutes an important part of Descemet's membrane and is secreted by the endothelium. There are two isoforms, $\alpha 1$ and $\alpha 2$, which interact with each other to establish the highly ordered, three-dimensional collagen lattice.²⁴ Notably, both mutations have also been described in another endothelial dystrophy, posterior polymorphous dystrophy (PPMD) patients.^{10, 20, 23} In early-onset, FECD, both mutations give rise to a distinct phenotype characterized by small, round guttae associated with cell centers instead of sharply peaked guttae found between cells as is seen in late-onset FECD. Patients with these mutations (Gln455Lys and Leu450Trp) commonly develop severe symptoms by the time they are young adults.^{20, 23} Both mutations affect the triple helical domain of $\alpha 2$ collagen VIII which could significantly alter the tertiary structure of the protein, disrupting the collagen lattice in Descemet's membrane.²⁵ Further, as collagen type VIII has been found to be involved in terminal cellular differentiation of vascular endothelium, an aberrant basement membrane might impair corneal endothelial terminal differentiation. Recently, a transgenic knock-in mouse, carrying both mutations in collagen VIII, *Col8a2*^{Q455K/Q455K}, was described by Jun *et al.* and was shown to replicate the clinical phenotype seen in the patients with early-onset FECD.²⁶ The mouse shows loss of corneal endothelial cells at an early age with formation of central guttae which supports the

hypothesis that ColVIIIa mutations are necessary and sufficient for the development of early-onset FECD. Further, this transgenic line may represent an ideal model for testing new interventions for treatment of both early- and possibly late-onset disease.²⁶

Late-onset FECD (categories 2 and 3)

Late-onset FECD is significantly more common than its early-onset counterpart and represents the vast majority of patients with this diagnosis. This form of the disease generally expresses itself in the fifth decade of life and progresses over the next two to three decades. Late-onset FECD appears to be autosomal-dominantly transmitted with incomplete penetrance though only approximately 50% of cases show family clustering.^{14, 20, 27} Late-onset FECD is more genetically heterogeneous than its early-onset counterpart and probably represents several different genetic diseases with the same phenotypic endpoint. There are large pedigrees that show FECD transmitting in an autosomal dominant fashion, though the specific genes have not been fully elucidated. FCD1, the first genetic locus identified for late-onset FCD, was found in 2006 as a 26.4-Mb interval extending from the 13p telomere to 13q12.13 and spanning over 40 known genes.²⁷ The FCD1 kindred exhibited Mendelian inheritance with high penetrance. FCD2 is found on chromosome 18 at 18q21.2-q21.3 and covers at least 28 known genes and is the most common locus found to date, though it appears that there may be several different independent mutations and there were no phenotypic differences reported when FCD2 patients were compared to non-familial cases.²⁸ The FCD3 locus, on chromosome 5q33.1-q35.2, spans 97 known genes and has a milder phenotype.²⁹ In contrast, FCD4, on chromosome 9p24.1e22.1 leads to a more severe form of FECD.³⁰

Some more defined genetic causes of late-onset FECD have been described in some families. Five loss-of-function mutations in the TCF8 gene (on chromosome 10) were found to be sufficient, though not necessary for the development of late-onset FECD.³⁰⁻³¹ One of these mutations was inherited in a large family and represents the first mutation to be associated with familial late-onset FECD.³⁰ TCF8 mutations have also been demonstrated in PPMD, however the mutations found in this disease are all either nonsense or truncating suggesting that PPMD and FECD represent a spectrum of disease and the more severe mutation causes an earlier, more severe phenotype.^{30, 32-33} The precise role of the TCF8 gene is not completely clear. It is known to encode the ZEB1 protein, which belongs to the zinc-finger transcription factor family and has both gene repressive and enhancing activities.³⁴ TCF8 expression has been found in corneal endothelium playing an important role in epithelial mesenchymal transition, by repressing E-cadherin expression, as well as other areas of development, and ZEB1 binding sites are found in the promoter regions of various collagen genes.^{31, 33, 35-39} More recently, mutation in the gene for LOXHD1, on chromosome 18, was found in one pedigree of familial late-onset FECD. LOXHD1 is a protein, found in the plasma membrane, which dysfunction of is known to cause progressive autosomal recessive non-syndromic hearing loss. FECD-causing mutations of LOXHD1 lead to over expression in the cornea. High levels of the protein lead to the formation of aggregates which have been hypothesized to be cytotoxic, leading to endothelial cell loss and consequently FECD.⁴⁰

TCF4 and E2-2 protein

The TCF4 gene and its protein represent a new exciting area in the study of the genetics of FECD and merit particular discussion. Alterations in this gene were first described by Baratz *et al.*, in 2010.⁴¹ This group examined FECD patients, without a family history of the disease. A spectrum of disease severity was studied as well as age/sex-matched controls. Genomewide-association studies were performed to identify single-nucleotide polymorphisms (SNP) that were associated with FECD and several were found to be located in the intronic portions of the TCF4 gene. The individual haplotypes that were most strongly associated with FECD had a prevalence of 11% to 17% among case subjects and 1% to 4% among control subjects suggesting that uncommon haplotypes had a large effect on the risk of developing FECD. The group used four genotyped SNPs that were independently associated with FECD across the TCF4 locus to construct a risk model which showed 76-78% accuracy. The prevalence of the described risk haplotypes is low (a few to several percent), but the presence of these haplotypes confers a high risk of FECD. The group hypothesized that intronic variations lead to decreased expression of the protein, rather than complete loss-of-function which is known to result in a very severe phenotype of mental retardation, seizures, and episodic hyperventilation.⁴¹ These studies were validated by Li *et al.* (2011) and Kuot *et al.* (2012), who found that the presence of the same SNPs conferred 2.5-4 times the risk of development of FECD than that for non-carriers.⁴²⁻⁴³ They also discuss that this allelic variation is essentially non-existent in African, East Asian, and South American populations but more prevalent in European, Middle Eastern, and Southern Asian populations which nicely correlates with respective disease prevalences in these populations.⁴²⁻⁴³ Perhaps more intriguing is the study from Wieben *et al.*⁴⁴ They also examined the E2-2 gene in late-onset FECD but from a different perspective. An earlier study found an unstable tri-nucleotide repeat within the third intron of TCF4 in approximately 3% of the population (European).⁴⁵ The data from Wieben *et al.*, indicate that the expansion of the TGC repeat within the TCF4 gene is found in a very high proportion of patients with FECD—over 79% of the 66 samples tested with 6 samples showing expansion in both copies of the gene.⁴⁴ Only 2 control patients (out of 54) showed expansion with more than 50 repeats. Overall, the study suggests that the presence of >50 TCG repeats in intron 3 of the TCF4 gene has 79% sensitivity and a 96% specificity for FECD. It should be noted that for this relatively small study, patients with severe cases of FECD were studied which may have skewed their results. The mechanism by which the intronic expansion cause toxicity is not known, but the authors hypothesize that given the correlation between FECD and oxidative stress, the area of guanine-rich repeats may make this gene particularly susceptible to oxidative damage thereby causing dysfunction.⁴⁴ The TCF4 gene encodes the E2-2 protein, which belongs to the family of class I basic helix-loop-helix (bHLH) transcription factors, and is able to either repress or activate gene expression by binding to E-boxes in target promoters.⁴⁶⁻⁴⁸ Although the TCF4 gene is located on chromosome 18q21, haplotype analyses suggest that SNPs in this gene are likely independent of FCD2.⁴⁹⁻⁵⁰ One gene that the E2-2 protein is known to up-regulate is TCF8 which itself has been found to be mutated in some forms of late-onset FECD. Given that TCF4 is involved in TCF8 regulation and that the two genes' biological functions are similar, it has been suggested that their mutations act within the same pathway, leading to a high risk of FECD development.^{42, 49-50}

Conclusion

Fuchs endothelial corneal dystrophy remains a significant cause of vision loss and impairment and is the most common dystrophic reason for keratoplasty. Treatment of FECD has advanced considerably in the last decade with the advent of Descemet's Stripping Endothelial Keratoplasty allowing for decreased recovery time, improved visual outcomes, and decreased long-term complications compared with traditional penetrating keratoplasty.⁵¹ Despite this improvement, treatment of the disease ultimately requires surgery. If we continue to expand our understanding of the pathogenesis of this complex disorder including the interaction of genetics and environment, new treatment and preventive interventions may be discovered. Beyond the disease itself, FECD may represent a relatively common finding to further our understanding of SNPs and trinucleotide repeat disorders and may impact treatment of rarer more devastating diseases.

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Figure 1.

A. Specular microscopy of the corneal endothelium from a normal patient. B. Confocal microscopy of the corneal endothelium of a normal patient. C. Specular microscopy of the corneal endothelium from patient with FECD. D. Confocal microscopy of the corneal endothelium of a patient with FECD. Black areas (arrows), which are more obvious on specular microscopy, represent corneal guttae that are scattered in between corneal endothelial cells, disrupting a normally continuous layer of hexagonally shaped cells in the patient with FECD.