Published in final edited form as:
*Cornea*. 2014 January ; 33(1): 96–98. doi:10.1097/ICO.0000000000000018.

# Fuchs Endothelial Corneal Dystrophy in Patients with Myotonic Dystrophy: A Case Series

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## Abstract

**Purpose—**To report four cases of Fuchs endothelial corneal dystrophy (FECD) in patients with an established diagnosis of myotonic dystrophy (DM) and suggest a mechanism for their association based on the known molecular genetics and potential pathophysiological parallels of DM and FECD.

**Methods—**We reviewed all available medical records and pathology slides for the four reported cases from the Department of Ophthalmology at Oregon Health & Science University's Casey Eye Institute as well as Devers Eye Institute at Legacy Good Samaritan Medical Center in Portland, OR.

**Results—**Four patients were found to have myotonic dystrophy as well as bilateral corneal guttae, consistent with the diagnosis of FECD. All of the identified patients were female and between the ages of 34–63, and two of the patients were related (mother and daughter). The corneal specimens from two of the four patients who had undergone corneal transplant were pathologically confirmed to be consistent with FECD.

**Conclusion—**To our knowledge, FECD has not been previously reported in association with DM. Because both diseases are somewhat prevalent in the U.S., it is possible that their coexistence is merely a coincidence in these patients. However, recent studies into the pathogenesis of each disease have shown more parallels between FECD and DM, suggesting the possibility of a non-coincidental association. Potential mutual pathogenic mechanisms may involve altered protein expression causing deregulation of ion homeostasis, an unstable intronic trinucleotide repeat expansion, or activation of the unfolded protein response and oxidative stress pathways.

### Keywords

Fuchs endothelial corneal dystrophy; myotonic dystrophy

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Conflict of Interest Disclosures: None

## Introduction

Myotonic dystrophy (DM) is an autosomal dominant, multisystem disorder that is the most common inherited muscle disease in adults, with a prevalence of 1:8000 in most populations.[1] Patients with DM are often seen by ophthalmologists for the associated ocular defects, most prominently the multicolored iridescent ("Christmas tree") cataracts that are commonly the first manifestation of their phenotype. The congenital type 1 form (DM1) results from expansion of an unstable CTG trinucleotide repeat in the 3' noncoding region of the myotonic dystrophy protein kinase (DMPK) gene, located on chromosome 19q13.3.[2] Extensive genetic research into the molecular pathogenesis of DM has resulted in it becoming the prototypical disease for RNA gain-of-function toxicity. The widely accepted pathogenic mechanism asserts that toxic RNAs deregulate alternative splicing in a few developmentally regulated genes that affect multiple tissues, but recent studies have revealed a far more complex pathophysiology, with changes in gene expression and translation efficiency, production of antisense transcripts, non-conventional translation, and micro-RNA deregulation.[3]

Fuchs endothelial corneal dystrophy (FECD) is a common hereditary disease of the corneal endothelium, with a prevalence of approximately 4% in people over age 40.[4] It is typically inherited in an autosomal dominant fashion, with causal genes and additional associated genetic loci having been identified.[5] A recent study of FECD patients also isolated an unstable trinucleotide repeat sequence in the transcription factor 4 (TCF4) gene whose expansion was found to be a strong predictor of disease risk and may play a pathogenic role.[6] FECD is characterized by clinical findings including loss of corneal endothelium, stromal edema, and thickened Descemet membrane with focal excrescences (guttae).[7] The pathophysiology of FECD is secondary to the loss and dysfunction of corneal endothelial cells and subsequent inability to maintain dehydration of the corneal stroma.

While FECD has been associated with a variety of anterior segment disorders and has been described in diseases caused by mitochondrial DNA genetic mutations, it has not been previously reported in connection with DM. Additionally, DM has not formerly been linked to corneal dystrophies, though corneal lesions and keratitis due to the blepharoptosis associated with muscle weakness have long been observed.[8] Here, we report a series of four cases of FECD in patients with an established diagnosis of DM.

## Methods

The cases are from the Department of Ophthalmology at Oregon Health & Science University's Casey Eye Institute as well as Devers Eye Institute at Legacy Good Samaritan Medical Center in Portland, OR. All available medical records and pathology slides were reviewed for each of the cases. Available literature was reviewed on the pathophysiology, clinical presentation, and genetic basis of DM and FECD.

## Results

Four patients were found to have myotonic dystrophy as well as bilateral corneal guttae, consistent with the diagnosis of FECD (Table 1). All of the identified patients were female and between the ages of 34–63, consistent with the most typical presentation of FECD (women around the fourth or fifth decade of life).[7] Two of the patients (3 and 4, Table 1) were related (mother and daughter). Two of the four had undergone corneal transplant because of their FECD, one with a penetrating keratoplasty on one eye (PKP) and the other a Descemet stripping endothelial keratoplasty (DSEK) on both eyes. All of these corneal

specimens were pathologically confirmed to be consistent with FECD. Three of the four had visually significant cataracts that had been removed.

## Discussion

Ocular manifestations of DM have long been known to ophthalmologists, but to our knowledge FECD has not been previously reported in association with the disease. A few clinical reports have described thicker corneas in patients with DM, though a follow-up study determined no abnormalities in endothelial cell number or appearance.[9,10] Given the somewhat common prevalence of both DM and FECD in the U.S. population, it is possible that the coexistence of the two conditions is merely a coincidence in these reported patients. However, as the polygenetic etiology and complex pathophysiology of FECD have become better understood, more parallels arise between FECD and DM that suggest the possibility of a non-coincidental association between the two diseases.

The noncoding trinucleotide repeats causing DM1 may alter the promoter of the adjacent SIX5 gene centromeric to DMPK, which is homologous to the Drosophila *sine oculis* gene and is crucial to proper development of the eye.[1] SIX5 is expressed throughout the adult human corneal epithelium and endothelium, lens and ciliary body epithelium, and the retina and sclera.[1] Mice deficient in SIX5 develop cataracts but not abnormalities of skeletal muscle function.[11] Due to the role of the endothelial $Na^+/K^+$ ATPase in maintaining deturgescence of the cornea, the fact that SIX5 is a transcription factor influencing the expression of the $\alpha_1$ subunit of the ATPase provides a link between DM and FECD.[1] Its altered expression may lead to deregulated ion homeostasis within the cornea as well as within the lens, giving a clinical and pathologic picture consistent with FECD.

Similar to DM1, the unstable TCG repeat recently found in TCF4 is located in a noncoding region (third intron) of the gene, so it may cause the FECD phenotype via a toxic RNA-mediated mechanism as well.[6] TCF4 encodes the E2-2 protein of the class I basic helix-loop-helix (bHLH) transcription factors, and expression of adjacent genes and downstream proteins may be affected by altered interactions with normal or abnormal transcripts. Although the full significance of the TCF4 intronic trinucleotide repeat in FECD has yet to be elucidated, the relationship between the noncoding repeats in both FECD and DM may hint at an analogous genetic and molecular etiology that justifies a clinical correlation between the two diseases.

Of note, Patient 3 from Table 1 reported that none of her relatives in the generation above her has either MD or FECD, but her three children have MD, and two of them have confirmed FECD as well (the third has not had an eye exam to her knowledge). It is therefore possible that the variable expressivity of myotonic dystrophy gives a similar picture in certain patients such as the four reported here. This observation may also be due to the phenomenon of anticipation, which has been documented in DM1 pedigrees as well as in many other trinucleotide repeat disorders.[12] Further investigation into the number of repeats in DM patients with concurrent FECD may provide some answers regarding whether or not there is a threshold repeat length for disease association.

Another potential shared mechanism of disease causation involves the apoptotic pathway, possibly resulting from oxidative and endoplasmic reticulum (ER) stress. Recent findings have highlighted a potential central role of the oxidative stress and unfolded protein response (UPR) pathways in the pathogenesis of FECD.[13,14] Since upregulation of markers in these same pathways have been demonstrated in DM1 muscle cells, these results may be consistent with a joint pathway in the progression to the FECD and DM phenotypes in different tissues.[15,16]

Though many recent advances have expanded our understanding of the pathophysiology and genetic basis for FECD and DM, the exact molecular mechanisms remain elusive. This report of four cases of FECD in patients with a known diagnosis of DM may suggest a non-coincidental mutual pathogenic mechanism that merits additional investigation. Not only will identification of any putative interrelated pathways common to both diseases provide further insights into the pathogenesis of each disease individually, it may also translate into new opportunities for therapeutic development.

## Acknowledgments

**Funding:** This work was generously supported by grants from the J. Willard and Alice S. Marriott Foundation, Edward Colburn, Lorraine Collins, Richard Dianich, Mary Finegan, Barbara Freeman, Stanley Friedler, MD, Diane Kemker, Jean Mattison, Lee Silverman, and Norman Tunkel, PhD (all to ASJ) and Research to Prevent Blindness (to Casey Eye Institute).

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**Table 1**

Clinical and Pathologic Ocular Findings in 4 Adult Patients with Fuchs Endothelial Corneal Dystrophy (FECD) and Myotonic Dystrophy (DM)

| Patient Age | Patient Sex | Lens | Corneal Pathology | Clinical Diagnosis & Procedures |
|---|---|---|---|---|
| 42 | Female | Pseudophakia OU | Thickened Descemet membrane, guttae, attenuated endothelium with 1–3 endothelial cell nuclei per hpf | FECD OU, DM<br>PKP OS |
| 34 | Female | Cataract OD<br>Pseudophakia OS | N/A | FECD OU, DM |
| 63 | Female | Pseudophakia OU | Thickened Descemet membrane, guttae, 3–5 endothelial cells per hpf OS and 5–7 OD | FECD OU, DM<br>DSEK OU |
| 34 | Female | No cataract | N/A | FECD OU, DM |

OU: both eyes; OD: right eye; OS: left eye; hpf: high powered field; PKP: penetrating keratoplasty; DSEK: Descement stripping endothelial keratoplasty