Fuchs’ Endothelial Corneal Dystrophy and RNA Foci in Patients With Myotonic Dystrophy

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Citation: Mootha VV, Hansen B, Rong Z, et al. Fuchs’ endothelial corneal dystrophy (FECD) is an autosomal dominant trait with genetic heterogeneity.11 Rare heterozygous mutations in COL8A2, type VIII, alpha 2 gene (COL8A2, MIM 120252) cause an early-onset corneal endothelial dystrophy.12 Other genes including solute carrier family 4, sodium borate transporter, member 11 (SLC4A11, MIM 610206), transcription factor 8 (TCF8, MIM 189909), lipoxygenase homology domains 1 (LOXHD1, MIM 613267), and ATP/GTP binding protein-like 1 (AGBL1, MIM 615523) collectively account for a small fraction of adult-onset FECD cases.13–20 Genome-wide association studies of adult-onset FECD have implicated transcription factor 4 (TCF4, MIM 602272) and more recently KN motif–and ankyrin repeat domain–containing protein 4 (KANK4, MIM 614612), laminin gamma-1 (LAMC1, MIM 150290), and Na+, K+ transporting ATPase, beta-1 polypeptide (ATP1B1, MIM 182350), with the TCF4 locus noted to have a predominant effect.21,22

CTG triplet repeat expansions in the third intron of TCF4 (CTG18.1 locus) are the most common genetic cause of adult-onset FECD cases in the United States23,24. TCF4 is a conserved class I basic helix-loop-helix (bHLH) transcription factor that binds to the canonical Ebox promoter sequences of target genes. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.
The CTG18.1 locus was discovered in 1997 by the repeat expansion detection assay, with expanded alleles of greater than 37 CTG repeats found to be unstable and present in 3% of subjects in Caucasian pedigrees. \(^{27}\) TCF4 expansions of greater than 30 CTG repeats confer significant risk for the development of FECD with an odds ratio (OR) of 32.3 in greater than 40 CTG repeats confer significant risk for the disease. \(^{33,34}\) Association of MBNL1 with mutant RNA associates with the splicing factor muscleblind-like 1 (MBNL1) in nuclear foci that can be visualized by fluorescent in situ hybridization. \(^{35,36}\) The expanded DM1 repeat RNA associates with the splicing factor muscleblind-like 1 (MBNL1) in nuclear foci that can be visualized by fluorescent in situ hybridization (FISH) and that are a molecular hallmark for disease. \(^{35,34}\) Association of MBNL1 with mutant RNA affects the cellular pool of free MBNL1 and triggers missplicing of some MBNL1 target genes in affected brain, muscle, and heart tissues. \(^{34}\) Accumulation of expanded CUG repeat RNA nuclear foci\(^\dagger\) with colocalization with MBNL1 and missplicing of target genes\(^\dagger\) has been recently reported in endothelial cells of FECD subjects with the TCF4 repeat expansion.

Genes. \(^{25,26}\) The CTG18.1 locus was discovered in 1997 by the repeat expansion detection assay, with expanded alleles of greater than 37 CTG repeats found to be unstable and present in 3% of subjects in Caucasian pedigrees. \(^{27}\) TCF4 expansions of greater than 30 CTG repeats confer significant risk for the development of FECD with an odds ratio (OR) of 32.3 in whites. \(^{21}\) The expanded allele was shown to cosegregate with complete penetrance in 52% of 29 white FECD families and with incomplete penetrance in an additional 10% of these families. \(^{24}\) Transethnic studies have been performed in Singapore-Chinese, Indian, and Japanese documenting the association of the triplet repeat expansion with FECD in nonwhite populations. \(^{26-30}\)

Myotonic dystrophy type 1 (DM1) is a paradigm for genetic disorders caused by CTG expansions. In DM1, the expansion is within the 3' untranslated region (UTR) of the dystrophin myotonia protein kinase gene. \(^{31,32}\) The expanded DM1 repeat RNA associates with the splicing factor muscleblind-like 1 (MBNL1) in nuclear foci that can be visualized by fluorescent in situ hybridization (FISH) and that are a molecular hallmark for disease. \(^{35,34}\) Association of MBNL1 with mutant RNA affects the cellular pool of free MBNL1 and triggers missplicing of some MBNL1 target genes in affected brain, muscle, and heart tissues. \(^{34}\) Accumulation of expanded CUG repeat RNA nuclear foci\(^\dagger\) with colocalization with MBNL1 and missplicing of target genes\(^\dagger\) has been recently reported in endothelial cells of FECD subjects with the TCF4 repeat expansion.

Gatgey et al.\(^37\) reported FECD in four DM1 subjects including a mother–daughter pair. No molecular studies were performed and because these are both common disorders, it can be concluded that additional studies were warranted. In this study, we explored the association between DM1 and FECD. We detected the presence of nuclear RNA-MBNL1 foci in endothelial cells from an organ donor whose corneas were found to be unsuitable for transplantation for the findings of FECD. Surprised that the donor did not harbor a TCF4 expansion, we hypothesized correctly that the subject harbored a CTG repeat expansion in the 3' UTR of the DMPK gene and subsequently confirmed a clinical diagnosis of DM1. Additionally, we tested the hypothesis that DM1 patients are at risk for FECD and determined prevalence of TCF4 and DMPK triplet repeat expansions in a University of Texas Southwestern (UTSW) FECD cohort.

### METHODS

#### Subjects

The study was approved by the UTSW Institutional Review Board (IRB) and conducted in adherence to the tenets of the Declaration of Helsinki.

We obtained corneas from a 54-year-old white male organ donor with “muscular dystrophy” who had succumbed to a cardiac arrest from the eye bank at UT Transplant Services. Certified eye bank technicians had examined the corneas using Cellchek EB-10 specular microscopy (Koanal Medical, Irvine, CA, USA) and detected FECD findings of confluent endothelial guttae and decreased endothelial cell density, and therefore found them to be unsuitable for transplantation. Additional control tissues were also obtained from the eye bank.

To test the hypothesis that patients with DM1 are at risk for FECD, we examined 13 consecutive unrelated patients with an established diagnosis of DM1 over the age of 40 (mean = 54.8, standard deviation [SD] = 10.3) from the UTSW Neuromuscular Cardiomyopathy Clinic (Table 1). Clinical genetic testing results for DM1 were obtained where available. All DM1 subjects were white. All subjects underwent an eye examination including slit-lamp microscopy by a cornea fellowship-trained ophthalmologist (VVM). Inclusion criterion for FECD was the presence of slit-lamp examination findings of grade 2 or higher on the modified Krachmer FECD grading scale: grade 0: no central guttae; grade 1: up to 12 scattered central guttae; grade 2: ≥12 scattered central guttae; grade 3: 1- to 2-mm confluent central guttae; grade 4: 2-5 mm of confluent central guttae; grade 5: >5-mm confluent central guttae without stromal edema; grade 6: >5-mm confluent central guttae with stromal edema. \(^{13}\) Specular microscopy of the corneal endothelium was performed by certified ophthalmic technicians using a Konan SL Specular Microscope (Konan Medical). The endothelial cell density and morphology parameters were calculated by the center method using the microscope’s automated software. We obtained central corneal thickness

### Table 1. Demographic Information and Microscopy Results of DM1 Patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>TCF4 Alleles</th>
<th>DMPK Alleles</th>
<th>FECD Status</th>
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<tr>
<td>VVM683†</td>
<td>52</td>
<td>F</td>
<td>2</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>19</td>
<td>20</td>
<td>5, &gt;100</td>
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<tr>
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<td>F</td>
<td>3</td>
<td>3</td>
<td>571</td>
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<td>36</td>
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<td>36</td>
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<tr>
<td>VVM691</td>
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<td>578</td>
<td>3185</td>
<td>3205</td>
<td>35</td>
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<td>VVM692</td>
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<td>1</td>
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<td>1</td>
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<tr>
<td>VVM697</td>
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<td>M</td>
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<td>1</td>
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<td>537</td>
<td>2967</td>
<td>2817</td>
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<td>69</td>
<td>16, 19</td>
<td>14, &gt;100</td>
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<td>M</td>
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<td>593</td>
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<td>38</td>
<td>56</td>
<td>54</td>
<td>16, 39</td>
<td>5, &gt;100</td>
<td>N</td>
</tr>
</tbody>
</table>

CCT, central corneal thickness based on ultrasound pachymetry; CV, coefficient of variation of endothelial cell size; F, female; M, male; NA, not available; N, no; Y, yes.

† Inclusion criterion for FECD is Krachmer grade of 2 or greater in the more severely affected eye by slit-lamp microscopy.

‡ This subject harbored both DMPK and TCF4 triplet repeat expansions. Southern blot analysis of expanded DMPK alleles presented where available.
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### Table 2. A Comparison* of FECD and Non-FECD Subjects Among DM1 Patients†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FECD</th>
<th>Non-FECD</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1 (16.7)</td>
<td>6 (85.7)</td>
<td>2.9 x 10⁻²</td>
</tr>
<tr>
<td>F</td>
<td>5 (83.3)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>57.4 (10.0)</td>
<td>52.1 (10.0)</td>
<td>3.7 x 10⁻¹</td>
</tr>
<tr>
<td>Krachmer grade, mean (SD)</td>
<td>3.1 (1.0)</td>
<td>0.7 (0.5)</td>
<td>1.7 x 10⁻⁴</td>
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<tr>
<td>CCT, mean (SD), µm</td>
<td>586.1 (17.7)</td>
<td>589.6 (27.3)</td>
<td>7.0 x 10⁻¹</td>
</tr>
<tr>
<td>Cell density, mean (SD), %/mm²</td>
<td>2066.5 (275.4)</td>
<td>3059.6 (478.6)</td>
<td>7.8 x 10⁻³</td>
</tr>
<tr>
<td>CV, mean (SD)</td>
<td>34.7 (2.7)</td>
<td>32.1 (5.2)</td>
<td>1.3 x 10⁻¹</td>
</tr>
<tr>
<td>Hexagonal cells % (SD)</td>
<td>55.5 (8.1)</td>
<td>62.4 (6.6)</td>
<td>3.9 x 10⁻²</td>
</tr>
</tbody>
</table>

* Both eyes of each subject were used for comparison.  † Ultrasound pachymetry and specular microscopy were not performed on subject VVM685.  ‡ Fisher’s exact test was performed when comparing sex distribution, and 2-sample t-test was performed when comparing other variables.

(CCT) measurements using a Corneo-gage Plus ultrasonic pachymeter (Sonomed, New Hyde Park, NY, USA). The average of three separate measurements was used as the CCT.

Then, we screened a cohort of 317 FECD probands recruited at a cornea referral practice at UT Southwestern for the prevalence of the DMPK and TCF4 triplet repeat expansions. All subjects had undergone an eye examination including slit-lamp biomicroscopy by a cornea fellowship-trained ophthalmologist (VVM) and were found to have slit-lamp examination findings of grade 2 or higher on the modified Krachmer FECD grading scale. The triplet repeat expansions in DMPK and TCF4 were genotyped using a combination of short-tandem repeat (STR) and triplet repeat-primed polymerase chain reaction (TP-PCR) assays.

### FISH

Corneal endothelial cells from an organ donor with FECD were examined for the presence of expanded CUG repeat RNA foci. FISH with chemically synthesized CAG₆CA₅ Texas red-labeled 2-O-methyl RNA 20-mers probe (8 µM at 20 ng/µl) (Integrated DNA Technologies, Coralville, IA, USA) and staining with 4’,6-diamidino-2-phenylindole, H-1500 DAPI (Vector Labs, Burlingame, CA, USA) of endothelial cells from this subject and controls were performed as we previously reported. Cells were imaged at ×60 magnification using a Wildfeild Deltavision pDv fluorescence microscope (GE Healthcare, Chicago, IL, USA). Images were processed using ImageJ software (https://imagej.nih.gov/ij/). Fifteen representative images were analyzed to derive percentage of cells with RNA foci. After performing the FISH assay, we stained the cells with anti-MBNL1 antibody as previously described.

### Genotyping of DMPK and TCF4 Triplet Repeat Polymorphisms

DNA from the organ donor corneal tissue was extracted with Trizol reagent (Life Technologies, Carlsbad, CA, USA) per the manufacturer’s protocol. Genomic DNA was extracted from leukocytes of peripheral blood samples from each study subject using Autogen Flexigene (Qiagen, Valencia, CA, USA).

We genotyped the TCF4 CTG18.1 triplet repeat polymorphism using a combination of STR analysis and TP-PCR assay and examined the amplicons with the ABI 3730XL DNA analyzer (Applied Biosystems, Foster City, CA, USA) as previously reported. We genotyped the CTG triplet repeat locus at the 3' UTR of DMPK with STR analysis and TP-PCR using locus-specific primers (Supplementary Table 1).

### RESULTS

Abundant discrete, punctate nuclear RNA foci were identified in 85% of the endothelial cells examined from the subject (16-1348) with FECD and muscular dystrophy (Fig. 1A). Nuclear RNA foci were detected in 61% of the endothelial cells from the subject (16-3407) with FECD and TCF4 triplet repeat expansion included as a positive control (Fig. 1A). Additionally, we demonstrated colocalization of the splicing factor MBNL1 with the nuclear RNA foci (Fig. 1B) in the subject (16-1348) with FECD and muscular dystrophy.

Genotyping results indicated that the subject (16-1348) did not have a TCF4 triplet expansion but rather had homozygous alleles with 12 CTG repeats at the CTG18.1 locus (Supplementary Fig. S1). A certified eye bank technician contacted the family of the organ donor for additional past medical history indicating that the subject (16-1348) had been made 12 years prior at the age of 42. The subject’s medical diagnosis was confirmed with clinical genetic testing which showed evidence of a trinucleotide repeat expansion in the myotonic dystrophy alleles using Southern blot analysis. The CTG repeat numbers of the two DMPK alleles were 10 and approximately 300, respectively.

Then, we examined 13 consecutive unrelated patients with an established diagnosis of DM1 for findings of FECD. Our genotyping results confirmed that all DM1 patients had DMPK triplet repeat expansions; one DM1 subject harbored both DMPK and TCF4 triplet repeat expansions (Table 1). We observed that 6 out of 13 (46%) of the DM1 subjects had slit-lamp examination findings of grade 2 or higher on the modified Krachmer FECD grading scale, which is significantly higher than the 4% prevalence of FECD in the US population over the age 40 (P value = 5.5 x 10⁻⁶). The female DM1 subjects were more likely to be affected with FECD than their male counterparts (P value = 2.9 x 10⁻²; Table 2), compatible with the known female bias for FECD. There was no significant

### Table 3. Demographic Information of FECD Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without TCF4 Expansion</th>
<th>With TCF4 Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>20 (21.1)</td>
<td>80 (36.0)</td>
</tr>
<tr>
<td>F</td>
<td>75 (78.9)</td>
<td>139 (62.6)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>71 (75.3)</td>
<td>204 (95.8)</td>
</tr>
<tr>
<td>Other†</td>
<td>3 (3.2)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.9 (9.6)</td>
<td>69.6 (10.1)</td>
</tr>
</tbody>
</table>

* There are a few missing values in some variables.  † Fisher’s exact test was performed when comparing sex and ethnicity distribution, and 2-sample t-test was performed when comparing other variables.  ‡ Including Asian, Hispanic, and mixed ancestry.
difference between the two groups in terms of age and CCT (Table 2). Specular microscopy confirmed the presence of guttae in all FECD subjects diagnosed by slit-lamp examination (Fig. 2). Based on specular microscopy, the eyes of FECD subjects had a lower endothelial cell density (P value = 7.8 × 10⁻³) and lower percentage of hexagonal cells (P value = 3.9 × 10⁻²) compared to the eyes of non-FECD subjects, which is compatible with the increased cellular senescence seen in FECD.

Next, we examined prevalence of the TCF4 and DMPK triplet repeat polymorphisms in the UTSW FECD cohort and found that 222 of 317 (70%) probands harbored TCF4 expansions. As we had previously reported, the subjects with the TCF4 triplet repeat expansion had a greater clinical severity of disease in comparison to their counterparts without the expansion (Table 3). Out of 95 FECD subjects who did not harbor an expansion in TCF4, only 1 subject was identified with a DMPK triplet repeat expansion with alleles of 15 and 71 CTG repeats (Supplementary Fig. S2). She had undergone cataract surgery and corneal transplantation in both eyes for Krachmer grade 6 severity of FECD. Review of her past medical history revealed no prior clinical diagnosis of myotonic dystrophy. Nearly all DM1 subjects develop a cataract. Patients with comorbid FECD should be counseled that they are at increased risk of corneal edema that may require corneal transplantation at the time of or after their cataract surgery.

We found a subject in our UTSW FECD cohort with a DMPK expansion without a prior clinical diagnosis of DM1. Individuals with small DMPK expansions have a mild DM1 phenotype. They may be asymptomatic except for cataracts and lead active lives with normal life spans.

Our observations confirm that TCF4 triplet repeat expansions are the predominant cause of FECD. DMPK1 triplet repeat expansions, however, can also contribute to the overall genetic burden of this disease and provide a different molecular and clinical perspective on the pathogenesis of
Several genetic diseases are caused by CTG expansions, and the link between molecular mechanism and disease is best characterized for DM1. As a result, DM1 offers insights that may prove valuable for FECD, where we are in the early stages of understanding mechanism and therapeutic development.

DM1 and FECD, however, are not identical diseases even though they both originate from noncoding CTG expansions. The \textit{DMPK} expansion in DM1 results in a multiorgan disease that involves various tissues in the eye including lens, retina, and corneal endothelium. In contrast, the \textit{TCF4} repeat expansion appears to affect the corneal endothelium without any clinically apparent sequelae to other ocular tissues or bodily organs. We speculate that differences in triplet repeat length and/or tissue specific factors define the phenotypic spectrum of these two triplet repeat expansions.

We report here that mutant expansions in \textit{DMPK} and \textit{TCF4} share important similarities, including (1) nuclear foci that contain expanded CUG repeats, (2) association of foci with MBNL1 protein, and (3) an ability to cause FECD. These results suggest that the triplet expansions in both \textit{DMPK} and \textit{TCF4} may cause the same corneal endothelial tissue phenotype of FECD through shared molecular mechanisms that are triggered by toxic gain-of-function RNA. These findings provide a new window on the molecular pathogenesis of FECD and suggest that the DM1 paradigm can be used to facilitate therapeutic development.

**Acknowledgments**

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**References**


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