Relationship Between Fuchs Endothelial Corneal Dystrophy Severity and Glaucoma and/or Ocular Hypertension

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Objective: To investigate whether Fuchs endothelial corneal dystrophy (FECD) severity is associated with glaucoma and/or ocular hypertension (G/OHTN).

Methods: A subset of eyes (n=1610) from the FECD Genetics Multi-Center Study were examined to estimate the association between FECD severity (grades 0-6 based on guttae confluence) and G/OHTN. Logistic regression models that accounted for the correlation between eyes and adjusted for age, sex, central corneal thickness, intraocular pressure, presence of diabetes, and time of day of the initial evaluation were fit.

Results: A total of 107 eyes (6.6%) had G/OHTN based on the study definition. The prevalence of G/OHTN in the control group was 6.0%. The prevalence was lower on the study definition. The prevalence of G/OHTN was higher in index cases and family members with a grade of 4 through 6 (11.2% and 8.5%, respectively). Adjusting for covariates, eyes with a grade of 4 through 6 were more likely to have concurrent G/OHTN than eyes with no FECD (index cases vs controls: odds ratio [OR]=2.10, P=.04; affected vs unaffected family members: OR=7.06, P=.07). Age (OR=1.06 per 1-year increase, P<.001) and intraocular pressure (OR=1.15 per 1–mm Hg increase, P<.001) were also associated with an increased prevalence of G/OHTN. Sex, diabetes, time of day of evaluation, and central corneal thickness were not associated with the prevalence of G/OHTN (P=.15).

Conclusions: Glaucoma and/or ocular hypertension occurs more often in eyes with severe FECD compared with unaffected eyes. Therefore, it may be beneficial to monitor for the development of glaucoma in these patients.


FUCHS ENDOTHELIAL CORNEAL DYSTROPHY

Fuchs endothelial corneal dystrophy (FECD) is a common ocular condition with a prevalence of approximately 4% in the United States. It can result in vision loss through progressive stages of endothelial dysfunction and corneal edema. Prior studies have demonstrated the close association of acute primary angle-closure glaucoma attack may result in changes to the corneal structure with the loss of endothelial cells and degeneration. In a retrospective analysis, Loewenstein et al suggested an association between the development of FECD and glaucoma through a common genetic link.

In this study, we performed a secondary analysis from the FECD Genetics Multi-Center Study of 1610 eyes from 969 individuals with varying degrees of FECD to investigate the relationship between FECD severity and the prevalence of glaucoma and/or ocular hypertension (G/OHTN).

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STUDY POPULATION

Subjects were selected from the FECD Genetics Multi-Center Study cohort. Families with FECD traits, unrelated FECD cases, and control subjects were recruited in that study to iden-
identify genetic risk factors for FECD. Demographic information and ocular and systemic medical histories were obtained through a standardized questionnaire administered to the patient. Each eye was examined separately for inclusion in the study. The control subjects were described previously and included pseudophakic eyes with surgery dates at least 1 year from the time of enrollment. Exclusion criteria for this study included those eyes that (1) had undergone penetrating or endothelial keratoplasty; (2) had cataract surgery within 1 year of the study examination; (3) had a history of blunt, penetrating, or perforating trauma; or (4) had evidence of another corneal endothelial dystrophy. The diagnosis of G/OHTN for each eye was established subjectively through a physician-guided, patient-completed survey as well as by identifying a history of previous glaucoma surgical and/or laser procedures or current use of ocular hypertensive medications. Subject age, time of examination, sex, and presence of diabetes were also recorded. Cornea-fellowship trained ophthalmologists examined eyes for evidence of FECD signs, obtained intraocular pressure (IOP) measurements by applanation tonometry, and recorded the time of the measurement.

FECD GRADE AND CENTRAL CORNEAL THICKNESS DETERMINATION

The degree of FECD was graded according to a modified semi-quantitative 7-point severity scale based on guttae confluence as previously described. The FECD grades were as follows: 0, no guttae; 1, 1 to 12 central or paracentral nonconfluent guttae; 2, more than 12 central or paracentral nonconfluent guttae; 3, 1 to 2 mm of confluent central or paracentral guttae; 4, more than 2 to 5 mm of confluent central or paracentral guttae; 5, more than 5 mm of confluent central or paracentral guttae; and 6, more than 5 mm of confluent central or paracentral guttae with stromal and/or epithelial edema. Central corneal thickness (CCT) was measured 3 times using an ultrasonic pachymeter that had been internally calibrated. Pachymeters were used from the following manufacturers: Accutome, Bausch & Lomb Surgical, DGH Technology, KMI Surgical, Eye Technology, Inc, Haag-Streit, Sonogage, Sonomed, and Tomey. Each instrument internally calibrates and takes repeated measurements to determine the thickness ultrasonically. Given the difficulty in defining the exact center of the cornea, 3 separate readings were obtained immediately after each other and the mean of these measurements was used as the CCT.

STATISTICAL ANALYSIS

Study groups were defined by a combination of FECD grade and how the subjects were sampled, resulting in 6 defined groups. Subjects identified for the study due to the presence of FECD were broken into 2 groups (index cases): those with an FECD grade of 1 through 3 and those with an FECD grade of 4 through 6. Subjects identified for the study due to a family relation of an index case were broken into 3 groups: those with no FECD (an FECD grade of 0 [unaffected family member]), those with mild or moderate FECD (FECD grade 1-3), and those with severe FECD (FECD grade 4-6). Finally, unrelated and unaffected control subjects with an FECD grade of 0 were independently recruited.

Based on eye-level data, univariate and multivariable logistic regression models were used to estimate the odds ratios (ORs) of G/OHTN among the levels of various covariates. Because some subjects contributed 2 eyes to the analyses, the eye-level data were not independent. Although a generalized estimating equations approach is a standard method for modeling correlated data within the same subject, some study groups had a 0% prevalence of G/OHTN; thus, a generalized estimating equations approach could not be used because it resulted in a complete separation of data points. One solution to this problem is the method for penalized maximum likelihood estimation by Firth. However, because this approach is applicable only to independent data, multiple outputation was used to repeatedly sample from the clustered data to produce independent data sets. It fits a logistic regression model with Firth’s approach to each data set, and then aggregate the results. Note that although multiple outputation does allow for computation of ORs and P values, it does not allow for computation of confidence intervals and so none are given. For consistency, all models (including those that did not have complete separation) used this approach.

RESULTS

A total of 1610 eyes from the 969 subjects were analyzed in this study. Of the 1610 eyes, 107 (6.6%) carried a diagnosis of G/OHTN based on the patient-physician completed survey (Table 1). The prevalence of G/OHTN in the control group was 6.0%. Index cases with an FECD grade of 1 through 3 and family members with an FECD grade of 0 or 1 through 3 had lower observed prevalences (0.0%, 0.0%, and 2.1%, respectively), whereas those with an FECD grade of 4 through 6 had higher observed prevalences (11.2% for index cases and 8.5% for affected family members) (Table 2). Among those with-

| Table 1. Baseline Characteristics at the Subject and Eye Levels |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Variable Value |
| Subjects (n = 969) | Age, mean (SD), y | 66.4 (12.2) |
| Subjects (n = 969) | Male, No. (%) | 336 (34.7) |
| Subjects (n = 969) | Diabetes, No. (%) | 105 (10.8) |
| Eyes (n = 1610) | IOP, mean (SD), mm Hg | 15.5 (3.2) |
| FECD Genetics Multi-Center Study Group, No. (%) | Controls | 551 (34.2) |
| FECD Genetics Multi-Center Study Group, No. (%) | Unaffected family members | 121 (7.5) |
| FECD Genetics Multi-Center Study Group, No. (%) | Index cases | 0/121 |
| FECD Genetics Multi-Center Study Group, No. (%) | FECD grade 1-3 | 16 (1.0) |
| FECD Genetics Multi-Center Study Group, No. (%) | FECD grade 4-6 | 276 (17.1) |
| FECD Genetics Multi-Center Study Group, No. (%) | Affected family members | 187 (11.6) |
| FECD Genetics Multi-Center Study Group, No. (%) | FECD grade 1-3 | 459 (28.5) |
| FECD Genetics Multi-Center Study Group, No. (%) | FECD grade 4-6 | 107 (6.6) |

Abbreviations: CCT, central corneal thickness; FECD, Fuchs endothelial corneal dystrophy; G/OHTN, glaucoma and/or ocular hypertension; IOP, intraocular pressure.

| Table 2. Prevalence of Glaucoma and/or Ocular Hypertension by Study Group |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Study Group | FECD Grade, No./Total No. (%) |
| Controls | 33/551 (6.0) |
| Unaffected family members | 0/121 |
| Index cases | 0/16 |
| Affected family members | 4/187 (2.1) |

Abbreviations: FECD, Fuchs endothelial corneal dystrophy; G/OHTN, glaucoma and/or ocular hypertension; IOP, intraocular pressure.
out FECD, unaffected family members were found to have decreased odds of G/OHTN relative to control subjects (OR = 0.11, P = .02), but this result did not hold up in multivariable analysis (OR = 0.23, P = .21). Index cases with severe FECD were found to have increased odds of G/OHTN relative to control subjects (univariate OR = 1.82, P = .05; multivariable OR = 2.10, P = .04), but those with mild to moderate FECD were not found to be different from control subjects. Similarly, affected family members with severe FECD were found to have increased odds of G/OHTN relative to unaffected family members (univariate OR = 12.14, P = .01; multivariable OR = 7.06, P = .07), but no such difference was found for those with mild FECD. No difference in the prevalence of G/OHTN was found between index cases and affected family members for either mild to moderate or severe FECD. Among the other covariates of interest, age and IOP were found to be positively associated with G/OHTN (Table 3 and Table 4).

To our knowledge, this study is the largest of its kind to report an association between the degree of FECD (based on the extent of guttae and presence of corneal edema) and G/OHTN established historically. In our study, we found evidence that index cases and affected family members with severe FECD (grade 4-6) had a higher prevalence of G/OHTN relative to control subjects or unaffected family members. To strengthen the validity of the study and eliminate confounding effects that could elevate IOP, patients were excluded if they had prior keratoplasty, cataract surgery within 1 year of the study examination, or history of trauma. Additionally, subjects were excluded if they had evidence of other corneal endothelial dystrophies besides FECD to better identify a relationship between FECD and G/OHTN. Eyes from both patients with FECD and control subjects consisted of both phakic and pseudophakic conditions.

### Table 3. Univariate Associations Between Each Covariate and the Prevalence of Glaucoma and/or Ocular Hypertension

<table>
<thead>
<tr>
<th>Comparative</th>
<th>Effect Estimated</th>
<th>Raw Prevalence, No./Total No. (%)</th>
<th>Model Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected family members</td>
<td>Controls</td>
<td>0/121, 33/551 (6.0)</td>
<td>OR = 0.11, P = .02</td>
</tr>
<tr>
<td>Index cases</td>
<td>FECD grade 1-3</td>
<td>Affected family members, FECD grade 1-3</td>
<td>0/16, 4/187 (2.1)</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Affected family members, FECD grade 4-6</td>
<td>31/276 (11.2), 39/459 (8.5)</td>
<td>OR = 1.42, P = .24</td>
</tr>
<tr>
<td>FECD grade 1-3</td>
<td>Controls</td>
<td>0/16, 33/551 (6.0)</td>
<td>OR = 0.49, P = .59</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Controls</td>
<td>31/276 (11.2), 33/551 (6.0)</td>
<td>OR = 1.82, P = .05</td>
</tr>
<tr>
<td>Affected family members</td>
<td>FECD grade 1-3</td>
<td>Unaffected family members</td>
<td>4/187 (2.1), 0/121</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Unaffected family members</td>
<td>39/459 (8.5), 0/121</td>
<td>OR = 12.14, P = .01</td>
</tr>
<tr>
<td>1-y increase in age</td>
<td>Male</td>
<td>Female</td>
<td>29/541 (5.4), 78/1069 (7.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No diabetes</td>
<td>9/171 (5.3), 98/1439 (6.8)</td>
<td>OR = 0.80, P = .59</td>
</tr>
<tr>
<td>Grade time in PM</td>
<td>Grade time in AM</td>
<td>57/739 (7.7), 45/757 (5.9)</td>
<td>OR = 1.39, P = .19</td>
</tr>
<tr>
<td>1-µm increase in CCT</td>
<td>1–mm Hg increase in IOP</td>
<td>1.00, P = .30</td>
<td>1.11, P = .004</td>
</tr>
</tbody>
</table>

### Table 4. Multivariable Associations Between Each Covariate and the Prevalence of Glaucoma and/or Ocular Hypertension

<table>
<thead>
<tr>
<th>Comparative</th>
<th>Effect Estimated</th>
<th>Model Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected family members</td>
<td>Controls</td>
<td>OR = 0.23, P = .21</td>
</tr>
<tr>
<td>Index cases</td>
<td>FECD grade 1-3</td>
<td>Affected family members, FECD grade 1-3</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Affected family members, FECD grade 4-6</td>
<td>OR = 1.28, P = .45</td>
</tr>
<tr>
<td>FECD grade 1-3</td>
<td>Controls</td>
<td>OR = 0.38, P = .46</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Controls</td>
<td>OR = 2.10, P = .04</td>
</tr>
<tr>
<td>Affected family members</td>
<td>FECD grade 1-3</td>
<td>Unaffected family members</td>
</tr>
<tr>
<td>FECD grade 4-6</td>
<td>Unaffected family members</td>
<td>OR = 7.06, P = .07</td>
</tr>
<tr>
<td>1-y increase in age</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No diabetes</td>
<td>OR = 0.66, P = .15</td>
</tr>
<tr>
<td>Grade time in PM</td>
<td>Grade time in AM</td>
<td>OR = 0.56, P = .19</td>
</tr>
<tr>
<td>1-µm increase in CCT</td>
<td>1–mm Hg increase in IOP</td>
<td>OR = 1.43, P = .17</td>
</tr>
<tr>
<td>1-µm Hg increase in IOP</td>
<td>1.00, P = .41</td>
<td>1.15, P &lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; FECD, Fuchs endothelial corneal dystrophy; IOP, intraocular pressure; OR, odds ratio.
eyes. Pseudophakic eyes were treated as control eyes as long as they did not show evidence of guttae on corneal examination and if they had undergone their cataract surgery more than a year from the time of study enrollment. If the subject had undergone cataract surgery within a year from the time of study enrollment, they were excluded from the study regardless of their FECD status. While we are able to report an association between the 2 diseases, it becomes difficult in establishing causality. Pitts and Jay identified FECD with axial hypermetropia and shallow anterior chamber depths through biometry analyses. Brunette et al and Shousha et al noticed a change in posterior corneal curvature with thickening into the anterior chamber angle in patients with FECD, possibly contributing to elevated IOPs.

The results of our study may conflict with those of other studies. Krachmer et al performed a similar study involving 64 families, with each individual graded with varying degrees of FECD. In their analysis, only 1 of 71 subjects (1.4%) with corneal edema had open-angle glaucoma with documented visual field loss. A major limitation of their study, however, is the relatively small sample size of patients with FECD. In another retrospective analysis of 430 eyes, Ali et al found no significant risk of open-angle glaucoma in patients with corneal endothelial dystrophy; however, they did note a higher incidence of ocular hypertension and secondary glaucoma in patients with corneal endothelial dystrophy undergoing corneal transplantation. Given the high association we found between severe FECD and G/OHTN in index cases and affected family members, a genetic link initially postulated by Loewenstein et al between the 2 processes may be plausible.

As shown in Table 3 and Table 4, older age and higher IOPs were also associated with G/OHTN. Both results are well supported in the literature. With increasing age, FECD severity may likewise also advance. Because study group comparisons between less and more severe FECD showed increased odds of G/OHTN after adjusting for age, our analysis suggests that age alone is not enough to explain the relationship between FECD severity and the prevalence of G/OHTN. A significant association between diabetes and G/OHTN was not found (univariate OR=0.80, P=0.59; multivariable OR=0.56, P=0.19). Various clinical and population-based studies have been performed to identify a link between the 2 diseases, although the results vary. Additionally, time of day of the examination did not bear a significant relationship to G/OHTN in univariate and multivariable analysis (univariate OR=1.39, P=0.19; multivariable OR=1.43, P=0.17). Studies have demonstrated a diurnal relationship with IOPs, but this association is not universal among all patients with glaucoma. For instance, while some individuals have peak IOPs in the morning, others may have peak IOPs in the afternoon. In our study, IOP was measured only once and at varying times of the day; thus, it is possible that some of our patients may have had higher recorded IOPs in the morning and others in the afternoon, resulting in variability and preventing a significant association between time of day and G/OHTN.

We did not find an association between higher CCT and G/OHTN. Other studies such as the Ocular Hypertension Treatment Study found that lower CCT measurements were positive risk factors for the development of glaucoma, while higher CCT measurements tended to result in falsely elevated IOP readings and a lower prevalence of glaucoma. Patients in this latter group had thicker, healthy corneas. On the other hand, patients with severe FECD tend to have higher CCT measurements due to corneal edema. Diagnosing G/OHTN in patients with severe FECD should not be done based solely on CCT and IOP measurements. Eyes with thicker CCT measurements due to corneal edema should be treated differently than eyes such as those examined in the Ocular Hypertension Treatment Study. As demonstrated in prior studies, the IOP readings by applanation in patients with corneal edema may be inaccurate. Thus, it is more important to identify glaucoma in such patients by other means such as visual field testing and optic nerve analysis.

Our study had several limitations. This was a post hoc analysis of the previously reported FECD Genetics Multi-Center Study, a study conducted to identify genetic factors of FECD. Because the data collected for the FECD Genetics Multi-Center Study were not collected to address this study, this may have resulted in residual confounding as data on all possible confounding factors of the association between FECD and G/OHTN were not obtained. For instance, subjects were denoted as having glaucoma through a physician-guided, subject-completed questionnaire rather than the traditionally defined “optic neuropathy associated with progressive loss of peripheral vision.” The questionnaire asked subjects whether they were diagnosed as having glaucoma, whether they were currently receiving medications to treat glaucoma, and whether they received any form of laser or surgical treatment for their glaucoma. The diagnoses of glaucoma and ocular hypertension were combined for this study owing to the variability in responses from the subject-completed survey. For example, many subjects identified themselves as having glaucoma because they were using glaucoma-treating eyedrops; however, the use of topical glaucoma medications alone cannot be used to diagnose a patient as having glaucoma as patients with ocular hypertension have similar needs for the medications.

We also did not have access to the subject’s visual field testing or optic nerve analyses. Clinical optic nerve findings such as the presence of disc hemorrhages, nerve fiber layer loss, and increased cupping as well as optical coherence tomographic and visual field changes have been shown to be useful diagnostic modalities for assessing progression of glaucoma. Access to such information would have been useful in determining a more conclusive association between FECD severity and G/OHTN. Furthermore, we could not accurately establish which form of glaucoma (ie, primary or secondary open angle vs narrow angle) each subject had. While the survey asked subjects which form of glaucoma they were diagnosed as having, the question was open-ended and was often left unanswered by the subject. A prospective study evaluating patients with FECD in combination with glaucoma-related diagnostic testing will be useful in addressing this issue.

Despite these study limitations, given the large sample size and strong correlation in our study, an association between severe FECD and G/OHTN was found. Thus,
while monitoring FECD progression, particularly with moderate to advanced disease, periodic glaucoma assessments should also be considered. More detailed studies including gonioscopy, subjective visual field testing, and objective optical coherence tomographic readings of such patients may be prudent in further understanding the 2 processes and their genetic relationship.


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