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INSIDE THIS ISSUE

Disease expression and familial transmission in Fuchs' endothelial dystrophy

Fuchs' endothelial corneal dystrophy (FECD) is a highly prevalent, bilateral, late-onset heritable disorder that affects the corneal endothelium. FECD is also the most common trinucleotide repeat expansion disorder."Many patients with FECD harbor an intronic cytosine-thymine-guanine, or CTG, trinucleotide repeat expansion in the transcription factor 4 gene on chromosome 18 — also termed CTG18.1 expansion. CTG repeat lengths are typically 12 to 30 repeats long. Repeat lengths greater than 40 are pathogenic, causing FECD," says Keith H. Baratz, M.D., a consultant in Ophthalmology at Mayo Clinic in Rochester, Minnesota.

Dr. Baratz and fellow researchers collaborated to describe the clinical and genetic variables in a large cohort of unrelated subjects with and without FECD, as well as in a cohort of families affected by FECD with and without CTG18.1 expansion. The researchers also sought to characterize the modes of inheritance of FECD, intergenerational CTG18.1 expansion length stability, phenotypic penetrance and sex differences. Their findings were published in *Investigative Ophthalmology & Visual Science* in 2021.

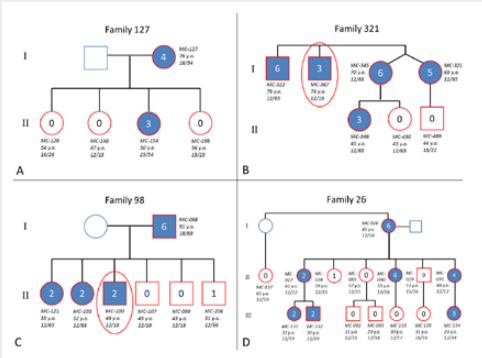

Figure. Representative pedigrees of families affected by FECD listing subject ID, age at time of examination and repeat length in both alleles. (A) Family demonstrating autosomal dominant inheritance of CTG18.1. (B-D) Families positive for CTG18.1 expansion demonstrating autosomal dominant inheritance, incomplete penetrance and variable expression. Families 321 and 98 both had a family member (within red oval) who did not inherit CTG18.1 expansion but still had FECD. Blue outline, not examined; red outline, examined; blue shading, affected by FECD (Krachmer grade 2 to 6); unshaded, no FECD (Krachmer grade 0 to 1). Image reprinted with permission from *Investigative Ophthalmology & Visual Science.*

The cohort

From June 1, 2007, through Aug. 1, 2019, clinician-investigators recruited 1,000 subjects, including patients with FECD and their family members and patients 50 years or older without FECD who served as control subjects. Subjects who initially sought ophthalmic care for FECD were defined as probands.

The clinical hallmark of FECD is excrescence of Descemet's membrane (guttae). FECD cases were defined as subjects having excrescence with a Krachmer grade of 2 or more (more than 12 scattered, nonconfluent guttae). Controls were defined as subjects having excrescence with a Krachmer grade 0 (no guttae) or grade 1 (12 or fewer scattered, nonconfluent guttae). Grades 2 to 4 were defined as mild FECD, and grades 5 to 6 were defined as severe FECD. There were 546 unrelated cases of FECD (67.6% female) and 235 controls (63.8% female) in the cohort.

Researchers compared descriptive statistics between affected and unaffected subjects with FECD (Figure) and between father and mother transmission, reporting the following:

- CTG18.1 expansion (repeats greater than 40 CTG trinucleotides) was observed in 424 (77.7%) cases and 18 (7.7%) controls ($P = 2.48 \times 10^{-44}$).
- CTG18.1 expansion was associated with FECD severity ($P = 5.62 \times 10^{-7}$).
- The family arm included 331 members from 112 families affected by FECD; 87 families showed CTG18.1 expansion.
- Autosomal dominant inheritance with variable expression of FECD was observed regardless of expansion status.
- FECD penetrance of CTG18.1 expansion increased with age, but even in the oldest age quartile (64 to 91 years) penetrance was incomplete at 86%.
- Instability of the repeat length, which is common in other repeat expansion


Keith H. Baratz, M.D.

diseases such as Huntington's disease and myotonic dystrophy, was assessed in 62 parent-offspring transmissions of CTG18.1 expansion. Forty-eight (77.4%) subjects showed minimal instability in CTG18.1 repeat length of 10 or fewer; eight (12.9%) had a change of 50 or more repeats, including five large expansions (approximately 1,000 to 2,000 repeats) that contracted.

"Very surprisingly, among 44 offspring who did not inherit the CTG18.1 expansion allele, eight (18.2%) still exhibited FECD," says Dr. Baratz.

The effect of sex, CTG18.1 expansion status and CTG18.1 repeat length on FECD severity was also assessed, with the following results:

- After age adjustment, sex was not associated with FECD severity (P = 0.69). Compared with mild FECD cases, severe FECD cases were more often positive for CTG18.1 expansion and had on average greater CTG18.1 repeat length.
- After age and sex adjustment, CTG18.1 expansion status remained significantly associated with FECD severity ($P = 5.62 \times 10^{-7}$).
- Severe FECD was also associated with CTG18.1 repeat length among all FECD cases ($P = 8.8 \times 10^{-4}$), but FECD severity was not associated with CTG18.1 repeat length when examining only FECD cases with CTG18.1 expansion (P = 0.33).

Dr. Baratz notes: "Results of this large-cohort study confirm the presence of CTG18.1 expansion in a large proportion of FECD cases, at least in this predominantly white U.S. patient group. This finding contrasts with findings by us and others that CTG repeat expansion accounts for a minority of cases in other racial and ethnic groups, and the primary cause of FECD in other populations remains an important question.

"Novel findings include the assessment of phenotypic penetrance of CTG18.1 expansion, the lack of a clear pattern of intergenerational contraction or expansion of CTG18.1 expansion, and the surprisingly common occurrence of the FECD phenotype in family members who do not harbor the CTG18.1 expansion but are part of families with CTG18.1 expansion. These observations highlight the complex relationship between FECD and the repeat expansion and emphasize the gaps in knowledge regarding other genetic and environmental factors influencing the penetrance and expression of FECD."

For more information

Xu TT, et al. Disease expression and familial transmission of Fuchs endothelial corneal dystrophy with and without CTG18.1 expansion. *Investigative Ophthalmology & Visual Science*. 2021;62:17.

Study supports the use of plaque imaging in the evaluation of patients with acute retinal artery occlusion


Muhammad (M. Tariq) T. Bhatti, M.D.

Central retinal artery occlusion and branch retinal artery occlusion (collectively referred to as retinal artery occlusion or RAO) are analogous to an acute stroke of the brain or heart — and may be a harbinger of a central nervous system stroke. RAO commonly occurs as a result of an embolic event in the context of carotid artery plaque. Various features of carotid plaque increase the risk for ischemic cerebral events, including ulceration, inflammation, neovascularization and degree of stenosis.

"Recently, plaque imaging with various sequences on high-resolution magnetic resonance vessel wall imaging has enabled detection of intraplaque hemorrhage (IPH), which been associated with an acceleration in plaque progression and an increased risk of plaque rupture. Intraplaque hemorrhage has also been shown to be predictive of future cerebral ischemic events," says Muhammad (M. Tariq) T. Bhatti, M.D., a neuro-ophthalmologist at Mayo Clinic in Rochester, Minnesota. "However, whether such an association between carotid IPH and RAO exists remains unknown. If it does exist, it would emphasize the importance of examining for the presence of IPH on high-resolution magnetic resonance angiography (HR-MRA) of the cervical carotid arteries in the setting of acute retinal ischemia."

Dr. Bhatti and his fellow researchers in Radiology, Neurology and Neurosurgery sought to test whether that association does exist. Their study was published in the *Journal of Neuro-Ophthalmology* in 2021.

The team requested medical and imaging records of all patients who underwent neck MRA with plaque imaging that included high-resolution vessel wall imaging with magnetization prepared-rapid gradient echo sequences at Mayo Clinic between 2015 and 2020.

From the 643-member cohort, 14 patients were identified who had ophthalmologically confirmed RAO and HR-MRA plaque imaging of the neck performed within six weeks after an acute retinal ischemic event.

For comparison, 211 patients who had neck MRA with magnetization prepared-rapid gradient echo sequences performed but did not have a history

of a cerebral ischemic event were identified and used as controls.

Data collected included demographic information such as patient age, sex and body mass index from the medical records of included patients. The researchers also noted the presence of comorbid conditions and collected values of laboratory studies. Dr. Bhatti notes: "There was a higher prevalence of males in the RAO group (78.6%) as compared with the control group (40.8%). Otherwise, there were no statistically significant differences in the prevalence of comorbidities or mean laboratory values between groups."

A relatively new technology, carotid vessel wall imaging was performed on all participants on a 3-tesla magnetic resonance imaging scanner with a 16-channel head-neck-spine coil. Information collected included:

- Presence of plaque in the carotid arteries
- Presence of IPH (with laterality relative to RAO)
- Degree of carotid stenosis

A single carotid artery was selected from control patients for use in comparing the presence of IPH and the mean degree of stenosis between controls and the RAO group.

Study findings

Of the patients with RAO, five (35.7%) had imaging evidence of ipsilateral IPH. Seven of 211 (3.3%) patients in the control group had evidence of ipsilateral IPH.

Of the five patients with RAO and ipsilateral IPH, only one (20.0%) was found to have ipsilateral carotid stenosis greater than 70%. Carotid IPH was the only variable that was independently associated with RAO (odds ratio 12.6, 95% confidence interval = 2.2-73.6, P = 0.005).

The mean degree of ipsilateral carotid stenosis in all patients with RAO was 26.7% ± 29.9%, compared with 8.8% ± 22.4% in randomly selected carotid arteries in control patients (P = 0.005).

In arteries with IPH, there was no difference in the mean degree of carotid artery stenosis between the RAO and the control groups (44.8% ± 29.5% versus 55.0% ± 32.1%, P = 0.51).

One patient of five with IPH (20.0%) in the RAO group was found to have ipsilateral carotid artery stenosis greater than 70% compared with three of seven patients (42.9%) with IPH in the control group.

"Our study has three primary findings," says Dr. Bhatti. "First, we found that patients with RAO had a statistically significant higher prevalence of IPH (as seen on HR-MRA carotid plaque imaging within six weeks of the event) as compared with asymptomatic control subjects. Second, the presence of IPH was independently associated with ipsilateral RAO. And third, we observed that a low percentage (20%) of patients with RAO were found to have IPH in the setting of greater than 70% carotid stenosis.

"These findings support the use of plaque imaging in the diagnostic evaluation of patients with acute retinal ischemic events, and emphasize that detecting and managing carotid artery disease is not just based on the traditional thinking that more than 70% stenosis is clinically significant and requires surgical intervention."

For more information

Larson AS, et al. The frequency of carotid intraplaque hemorrhage on vessel wall imaging in patients with retinal artery occlusion: A cross-sectional prevalence study. *Journal of Neuro-Ophthalmology*. In press.

Genomic sequencing shows promise in elucidating genetic causes of strabismus

Strabismus, a common disorder of ocular alignment, affects 3% to 5% of children in the United States, yet the etiology of childhood strabismus is poorly understood. Risk factors for ocular misalignment among a minority of children include premature birth, maternal tobacco exposure, and developmental or neurological disorders. How prominent the role of genetics might be in the development of the most prevalent forms of childhood strabismus, however, is currently unknown.

To investigate candidate genes associated with familial strabismus and propose a theory of their interaction in familial strabismus associated with early neurodevelopment, a research team including Brian G. Mohney, M.D., a consultant in Ophthalmology at Mayo Clinic in Rochester, Minnesota, used exome sequencing analysis to identify possible risk variants of familial strabismus.


Brian G. Mohney, M.D.

"Recent advances in next-generation sequencing technologies have allowed the identification of disease-causing genes," says Dr. Mohney. "Whole-exome sequencing, or WES, is a well-established technology for identifying variants within the coding regions, or exons, of known genes. WES provides an opportunity to identify causal genes in Mendelian and complex genetic disorders with high sensitivity and specificity. Familial studies using WES have revealed rare variants associated with strabismus or genetic syndromes with strabismus."

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In their study, published in *Genes* (Basel) in 2021, the research team used WES to detect single nucleotide variants (SNVs) and insertions-deletions (indels) within a cohort of families with two or more members affected with comitant strabismus.

Researchers prospectively recruited children with familial strabismus, defined as having two or more family members with horizontal, comitant strabismus. The proband and available family members were examined for their visual acuity; angle of deviation at distance (3 meters) and at near (1/3 meter) measured with the prism and alternate cover test; stereopsis; and cycloplegic refraction. Affected members with strabismus were defined as having a horizontal, comitant misalignment of 10 or more prism diopters at either distance or near in the primary position. Nonaffected individuals were defined as having orthophoria and normal stereopsis.

Among the 98 participants initially recruited, 87 participants remained for downstream analysis: Researchers evaluated 18 families — comprising 53 patients diagnosed with strabismus and 34 unaffected family members — using WES, with a 53.6X average sequence read depth and 88.5% average call rate.

Data set results included a total of 320,470 unique SNVs (approximately 120,299 SNVs per individual) and 51,072 unique indels (approximately 18,607 indels per individual). Of these results, 84,376 SNVs and 3,050 indels were located in protein-coding sequences, while 236,094 SNVs and 48,022 indels were found in noncoding sequences.

To identify candidate genes for causing strabismus, the researchers defined causal variants by the following criteria:

- Occurring rarely in the general population
- Resulting in either a loss of function (including nonsense, frameshift and canonical splicing site change) or missense
- Missense variants predicted to be deleterious by either the scale-invariant feature transform or PolyPhen2 algorithm
- Observed in genes with the probability of being loss of function intolerant (score 0.9 or greater)
- Characterized in the developmental process

To assess credible risk variants associated with familial strabismus, researchers prioritized risk variants segregated in multiple family members or occurring in multiple families, possibly suggesting their role in familial strabismus."From 18 families with horizontal and comitant strabismus, we identified 60 candidate variants, including three loss-of-function and 57 missense variants in 58 genes. Two genes had multiple variants," says Dr. Mohney.

Prioritization of the most credible risk variants showed clear segregation in family members affected by strabismus."We found risk variants in four genes — FAT3, KCNH2, CELSR1 and TTYH1 — in five families, suggesting their role in development of familial strabismus," says Dr. Mohney.

Several families in the study had different clinical phenotypes even though they had the same genetic variation, supporting the possibility that the type of strabismus can be affected not only by the role of genetic variation in the expression of strabismus but also by the developmental process, the time of ocular misalignment occurrence or environmental factors.

"Next-generation genome sequencing approaches hold great promise in identifying rare variants associated with the disorder and elucidating the genetic causes of strabismus," says Dr. Mohney."Despite our small-sample study, we were able to identify four genes with causative associations with strabismus. We also observed genetic heterogeneity in strabismus cases with risk genes occurring in several neurodevelopmental disorders. These results add to the increasing evidence for genetic heterogeneity within familial comitant strabismus."

For more information

An JY, et al. Identification of possible risk variants of familial strabismus using exome sequencing analysis. *Genes* (Basel). 2021;12:75.

Education Opportunities

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