HHS Public Access

Author manuscript

*Cornea*. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

*Cornea*. 2021 December 01; 40(12): 1567–1570. doi:10.1097/ICO.0000000000002689.

# Relationship of Body Mass Index with Fuchs' Endothelial Corneal Dystrophy Severity and TCF4 CTG18.1 Trinucleotide Repeat Expansion

**Bhumi B. Kinariwala, MD**[1], **Timothy T. Xu, BS**[2], **Keith H. Baratz, MD**[3], **Ross A. Aleff, BS**[4], **Sanjay V. Patel, MD, FRCOphth**[3], **Leo J. Maguire, MD**[3], **Michael P. Fautsch, PhD**[3], **Eric D. Wieben, PhD**[4], **Amy E. Millen, PhD**[5], **Sangita P. Patel, MD, PhD**[1,6]

[1]Ross Eye Institute, Department of Ophthalmology, Jacobs School of Medicine and Biomedical Sciences, State University at Buffalo, Buffalo, New York, USA

[2]Alix School of Medicine, Mayo Clinic, Rochester, Minnesota, USA

[3]Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, USA

[4]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota, USA

[5]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA

[6]Research and Ophthalmology Services, Veterans Administration of Western New York Healthcare System, Buffalo, NY, USA

## Abstract

**Purpose.—**To investigate the association of body mass index (BMI) with Fuchs' endothelial corneal dystrophy (FECD) severity and *TCF4* CTG18.1 expansion.

**Methods.—**343 patients with FECD were enrolled from the Mayo Clinic. FECD severity was graded by slit lamp biomicroscopy. BMI values were obtained from the electronic medical records. DNA extracted from leukocytes was analyzed for CTG18.1 expansion length, with ≥40 repeats considered expanded. Wilcoxon signed rank tests were used to compare FECD grade and CTG18.1 expansion length in patients by BMI (< 25, ≥ 25 to < 30 and ≥ 30 kg/m$^2$). FECD grade was regressed on age, sex, BMI, and CTG18.1 expansion and separately, BMI on CTG18.1 expansion. Models were investigated for effect modification by age and sex with an interaction term of $p<0.05$ considered statistically significant.

**Results.—**When examining the association between BMI and FECD, there was a significant interaction between BMI and sex (p for interaction=0.004). When controlling for age and CTG18.1 expansion, a positive association was observed between BMI and FECD grade in women, but not in men. Additionally, BMI was not associated with CTG18.1 expansion when controlling for age and sex.

Correspondence to: Sangita P. Patel, MD, PhD, Ross Eye Institute, 1176 Main Street, Buffalo, NY 14209, USA, Tel: 716-862-6577, sppatel@buffalo.edu.

**Conclusion.—**BMI was positively associated with FECD severity among women but not men. There was no significant association between BMI and CTG18.1 expansion. These findings suggest that increased BMI is potentially a modifiable risk factor for FECD disease progression among women.

### Keywords

Fuchs' endothelial dystrophy; cornea; body mass index; trinucleotide repeat expansion; risk factors

## INTRODUCTION

Fuchs' endothelial corneal dystrophy (FECD) is a progressive, bilateral disorder, characterized by guttae on Descemet's membrane, dysfunction and death of corneal endothelial cells, corneal edema, and loss of vision over time. Both genetic and environmental factors play roles in the manifestation of FECD. The common late-onset form of FECD is associated with an intronic trinucleotide repeat expansion in the CTG18.1 locus in the *TCF4* gene. CTG18.1 expansion with repeat length > 50 is found in 79% of Caucasians with FECD.[1] Other risk factors for FECD include age, smoking and female sex.[2–5]

Anthropomorphic factors have inconsistently been associated with FECD, either showing no association[2] or an inverse association[5] between weight or body mass index (BMI) and presence of guttae. We have observed a significantly lower self-reported weight and BMI at age 18 in women with FECD compared to without FECD in a clinical sample.[6] It is possible that BMI could be associated with FECD through an influence of CTG18.1 expansion on BMI. Among patients with the trinucleotide repeat expansion disorder spinocerebellar ataxia type 3, increased repeat length was associated with low BMI and increased disease severity.[7–9] For the current study, we examined whether associations between BMI and FECD grade, and CTG18.1 expansion and BMI exist in our cohort of FECD patients.

## MATERIALS AND METHODS

Protocols were approved by the Mayo Clinic Institutional Review Board. Study participants with FECD were recruited at Mayo Clinic (Rochester, Minnesota, USA; June 2007 through August 2019) and provided written consent. FECD severity was assessed by clinician investigators (KHB, LJM, SVP) via slit-lamp biomicroscopy and was graded using the modified Krachmer grading system: grade 1 (≤12 central guttae) through grade 6 (confluent guttae with edema) with grade ≥2 (>12 central guttae) considered diagnostic of FECD.[10] Eyes with corneal transplantation for FECD were considered grade 6. DNA was extracted from peripheral blood leukocytes to determine *TCF4* CTG18.1 expansion length using direct sequencing and short tandem repeat assay of PCR-amplified DNA. For samples with only one repeat length identified, Southern blotting was performed to differentiate bi-allelic CTG18.1 lengths of the same size versus the presence of a large CTG18.1 expansion. Linked electronic medical records were searched for height and weight closest to the date of study recruitment (median interval =3 months) in order to calculate BMI ($kg/m^2$). Patients were

excluded if BMI, FECD grade of both eyes and repeat length of both alleles were not available or if a family member (proband) was already included in the study.

Unpaired t-tests and the Wilcoxon signed rank test (when variables were highly skewed) were performed to compare the mean age, BMI, and FECD grade (grade of the worse eye), by CTG18.1 defined as <40 repeats and CTG18.1 expansions ≥40 repeats based upon the longer allele. Unpaired ANOVAs and the Wilcoxon signed rank test were performed to compare mean age, BMI, FECD grade, and mean CTG18.1 length by BMI category defined as BMI < 25, ≥25 to <30 (overweight) and ≥ 30 (obese) $kg/m^2$. The BMI category of underweight (<18.5) was not analyzed independently as only one participant in this dataset had an underweight BMI. We assessed the association between FECD grade and the following risk factors: age, sex, BMI, and CTG18.1 expansion, using linear regression. We also examined the association between BMI and CTG18.1 expansion, adjusted for age and sex, using linear regression. Models were investigated for effect modification by age and sex with an interaction term of $p<0.05$ considered statistically significant.

## RESULTS

There were no statistically significant differences in percent of participants with CTG18.1 expansions, CTG18.1 expansion length, or FECD grade by BMI category in all participants or in women when used as an independent cohort. In men, there was a greater proportion of those with CTG18.1 expansion and higher BMIs (Table 1). There was a significant difference observed between FECD grade and CTG18.1 expansion with a lower median grade in those with no expansion compared to those with an expansion (Table 2). There were no statistically significant differences in BMI by CTG18.1 expansion group.

In a multivariable model predicting FECD grade with all participants, only CTG18.1 expansion, when controlling for age, sex, and BMI, was significantly associated with FECD grade (Table 3). The adjusted mean FECD grade was higher in those with CTG18.1 expansion compared to those without the expansion.

Next, we examined whether the associations between BMI and FECD and between CTG18.1 expansion and BMI varied by age or sex. We found a significant interaction between age (continuous) and CTG18.1 expansion (p for interaction=0.04) in the model examining FECD grade as an outcome, suggesting a stronger association with genetic risk in those with younger ages (Table 3). A significant interaction was also observed between sex and BMI (continuous) in the model examining FECD grade as an outcome (p for interaction=0.004). BMI was positively associated with FECD grade in women but not men.

In a multivariable model, analysis of the association between CTG18.1 expansion and BMI (continuous) controlling for age and sex (Table 3) found no association. The association between CTG18.1 length and BMI in those with CTG18.1 expansion (≥40) and without (<40) was also null (data not shown).

## DISCUSSION

Our study objective was to investigate the association of BMI with both FECD severity and CTG18.1 expansion. We did not find an association between CTG18.1 expansion and BMI. We did, however, find a significant positive association between BMI and FECD grade in women, but not men where a negative association did not reach statistical significance. This suggests that BMI in FECD is not dictated by *TCF4* genetics but could be a potential modifiable risk factor for severe FECD, particularly for women, although our study does not determine causation. Differences in risk factors between men and women may be partly responsible for the known differences in FECD prevalence between men and women.

Research in spinocerebellar ataxia type 3, a trinucleotide repeat disorder in the *ATXN3* gene, shows an association between low BMI, severe disease, and increased repeat length.[7–9] The trinucleotide repeat in spinocerebellar ataxia type 3 differs from that of FECD because it falls within a coding region (compared to the intronic repeat of FECD) and results in translation of polyglutamine expansions with toxic properties. Several polyglutamine diseases have shown an association with BMI.[11] However, from our data, it is likely that a relationship between BMI and FECD is independent of *TCF4* CTG18.1 expansion.

In this study, we observed more severe FECD in those with higher compared to lower BMIs in women but not men. In a separate study involving a different FECD cohort containing participants with and without guttae, we found lower self-reported BMI at age 18 in women but not men with guttae, similar to data from other reports.[6] The differences in these associations may be due to the different populations studied, and the lack of a control population without guttae in the current study. Fully elucidating these differences in associations between BMI and FECD will require further investigation into additional study cohorts. Based on the current data, higher BMI may have adverse physiologic effects on FECD pathophysiology in women similar to the systemic effects of obesity in many diseases. Another possibility is the role of estrogen metabolism. Higher endogenous estrogen levels seen with higher BMI, may promote toxicity of estrogen metabolites in the corneal endothelium.[12]

There are several limitations to this study. First, as mentioned above, the FECD grade of study participants was skewed towards higher grades, thus these data may not accurately reflect the spectrum of FECD disease severity. FECD grade may also appear higher due to analysis of the worse-eye grade from each participant, although analysis by better-eye grade did not change the significant data trends. Second, smoking is a known risk factor for FECD, but we did not have smoking history data for adjustment. Third, we only had BMI data close to the time of enrollment which may not accurately reflect the potential effect of fluctuating BMI throughout adulthood.

In summary, *TCF4* CTG18.1 expansion status is not related to BMI. BMI is associated with FECD grade independent of genetic risk in women, making it a potential sex-related modifiable risk factor for FECD, with causation yet to be determined.

## Acknowledgments

Conflicts of Interest and Source of Funding: This work was funded by Office of the Director and National Eye Institute, National Institutes of Health to SPP (K08EY029007), MPF (EY26490) and KHB (EY25071) and the Robert R. Waller Career Development Award, Mayo Clinic (KHB). This material is the result of work supported with resources and the use of facilities at the VA Western New York Healthcare System. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. SPP, BBK, TTX, KHB, RAA, LJM, MPF, EDW and AEM report no commercial relationships disclosures. SVP is a consultant to GlaxoSmithKline, Senju Pharmaceuticals, and Santen Inc.

## REFERENCES

1. Wieben ED, Aleff RA, Tosakulwong N, et al. A common trinucleotide repeat expansion within the transcription factor 4 (TCF4, E2–2) gene predicts Fuchs corneal dystrophy. PloS One. 20;7(11):e49083. [PubMed: 23185296]
2. Higa A, Sakai H, Sawaguchi S, et al. Prevalence of and risk factors for cornea guttata in a population-based study in a southwestern island of Japan: the Kumejima study. Arch Ophthalmol. 2011;129(3):332–336. [PubMed: 21402991]
3. Kitagawa K, Kojima M, Sasaki H, et al. Prevalence of primary cornea guttata and morphology of corneal endothelium in aging Japanese and Singaporean subjects. Ophthalmic Res. 2002;34(3):135–138. [PubMed: 12097795]
4. Zhang X, Igo RP Jr., Fondran J, et al. Association of smoking and other risk factors with Fuchs' endothelial corneal dystrophy severity and corneal thickness. Invest Ophthalmol Vis Sci. 2013;54(8):5829–5835. [PubMed: 23882692]
5. Zoega GM, Fujisawa A, Sasaki H, et al. Prevalence and risk factors for cornea guttata in the Reykjavik Eye Study. Ophthalmology. 2006;113(4):565–569. [PubMed: 16581419]
6. Patel SP, Plotke B, Sima A, et al. Prevalence of and risk factors for Fuchs endothelial corneal dystrophy (FECD). Investigative Ophthalmology & Visual Science. 60(9), 3832.
7. Diallo A, Jacobi H, Schmitz-Hubsch T, et al. Body mass index decline is related to spinocerebellar ataxia disease progression. Mov Disord Clin Pract. 2017;4(5):689–697. [PubMed: 30363449]
8. Saute JA, Silva AC, Souza GN, et al. Body mass index is inversely correlated with the expanded CAG repeat length in SCA3/MJD patients. Cerebellum. 2012;11(3):771–774. [PubMed: 22090366]
9. Yang JS, Chen PP, Lin MT, et al. Association between body mass index and disease severity in Chinese spinocerebellar ataxia type 3 patients. Cerebellum. 2018;17(4):494–498. [PubMed: 29476441]
10. Repp DJ, Hodge DO, Baratz KH, et al. Fuchs' endothelial corneal dystrophy: subjective grading versus objective grading based on the central-to-peripheral thickness ratio. Ophthalmology. 2013;120(4):687–694. [PubMed: 23369486]
11. Gardiner SL, de Mutsert R, Trompet S, et al. Repeat length variations in polyglutamine disease-associated genes affect body mass index. Int J Obes (Lond). 2019;43(3):440–449. [PubMed: 30120431]
12. Liu C, Miyajima T, Melangath G, et al. Ultraviolet A light induces DNA damage and estrogen-DNA adducts in Fuchs endothelial corneal dystrophy causing females to be more affected. Proc Natl Acad Sci U S A. 2020;117(1):573–583. [PubMed: 31852820]

**Table 1:**

Relationship between BMI and variables including age, FECD grade, and CTG18.1 length

| | | Body Mass Index (BMI) (kg/m$^2$) | | | |
|---|---|---|---|---|---|
| | | **< 25** | **≥25 to <30** | **≥ 30** | **P*** |
| **Total** | **Sample size** | 90 | 121 | 132 | |
| | **Age (years), mean (SD)** | 69.5 (11.6) | 69.9 (10.6) | 69.0 (8.3) | 0.75 |
| | **BMI (kg/m$^2$), mean (SD)** | 22.9 (1.7) | 27.4 (1.5) | 35.7 (5.4) | **<0.001** |
| | **CTG18.1 expansion (% ≥ 40 repeats)** | 71% | 83% | 80% | 0.12 |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 46.7 (25.7–53.5) | 49.0 (42.0–57.2) | 49.0 (37.8–55.0) | 0.13 |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 6.0 (4.0–6.0) | 6.0 (5.0–6.0) | 6.0 (5.0–6.0) | 0.52 |
| **Men** | **Sample size** | 32 | 39 | 43 | |
| | **Age (years), mean (SD)** | 67.8 (11.3) | 71.9 (9.3) | 68.5 (7.8) | 0.13 |
| | **BMI (kg/m$^2$), mean (SD)** | 23.4 (1.2) | 27.3 (1.5) | 35.2 (5.5) | **<0.001** |
| | **CTG18.1 expansion (% ≥ 40 repeats)** | 69% | 92% | 84% | **0.03** |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 44.6 (24.7–55.0) | 51.0 (45.5–57.3) | 50.5 (40.0–57.7) | 0.24 |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 6.0 (4.5–6.0) | 6.0 (4.0–6.0) | 6.0 (4.0–6.0) | 0.79 |
| **Women** | **Sample size** | 58 | 82 | 89 | |
| | **Age (years), mean (SD)** | 70.4 (11.7) | 68.9 (11.0) | 69.2 (8.6) | 0.68 |
| | **BMI (kg/m$^2$), mean (SD)** | 22.5 (1.8) | 27.5 (1.5) | 35.9 (5.4) | **<0.001** |
| | **CTG18.1 expansion (% ≥ 40 repeats)** | 72% | 78% | 78% | 0.71 |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 46.9 (25.7–53.5) | 48.8 (38.0–56.5) | 48.5 (35.3–53.7) | 0.44 |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 6.0 (4.0–6.0) | 6.0 (5.0–6.0) | 6.0 (5.0–6.0) | 0.17 |

*P-values are reported from t-tests for age and BMI, for the Wilcoxon rank sum test for CTG18.1 length and FECD grade, and for chi-squares for CTG18.1 (% ≥ 40).

*Cornea*. Author manuscript; available in PMC 2022 December 01.

**Table 2:**

Relationship between CTG18.1 expansion and Variables Including Age, BMI, FECD Grade, and CTG18.1 Length

| | | CTG18.1 (< 40) | CTG18.1exp (≥40) | P* |
|---|---|---|---|---|
| **Total** | **Sample size** | 74 | 269 | |
| | **Age (years), mean (SD)** | 70.1 (11.0) | 69.3 (9.8) | 0.55 |
| | **BMI (kg/m$^2$), mean (SD)** | 29.1 (6.8) | 29.5 (6.2) | 0.67 |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 16.4 (15.0–20.0) | 51.0 (46.3–57.5) | **<0.001** |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 5.0 (3.0–6.0) | 6.0 (5.0–6.0) | **<0.001** |
| **Men** | **Sample size** | 20 | 94 | |
| | **Age (years), mean (SD)** | 71.6 (9.7) | 69.0 (9.4) | 0.28 |
| | **BMI (kg/m$^2$), mean (SD)** | 27.9 (6.0) | 29.4 (6.1) | 0.32 |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 16.9 (14.5–19.2) | 51.8 (47.0–58.0) | **<0.001** |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 3.5 (2.75–6.0) | 6.0 (5.0–6.0) | **0.002** |
| **Women** | **Sample size** | 54 | 175 | |
| | **Age (years), mean (SD)** | 69.5 (11.5) | 69.4 (10.0) | 0.94 |
| | **BMI (kg/m$^2$), mean (SD)** | 29.6 (7.1) | 29.5 (6.3) | 0.96 |
| | **CTG18.1 length, median (25$^{th}$–75$^{th}$ percentile)** | 15.8 (15.0–21.0) | 50.7 (46.0–57.0) | **<0.001** |
| | **FECD (grade, worse eye), median (25$^{th}$–75$^{th}$ percentile)** | 6.0 (3.0–6.0) | 6.0 (5.0–6.0) | **0.001** |

*P-values are reported from t-tests for age and BMI, and the Wilcoxon rank sum test for CTG18.1 length and FECD grade.

*Cornea*. Author manuscript; available in PMC 2022 December 01.

**Table 3:**

Multivariable regression analyses for associations of risk factors with worse eye FECD grade and Body Mass Index

| **Model for predictors of worse eye FECD grade** | | |
|---|---|---|
| **Predictor** | **Beta-coefficient (SE)** | **P** |
| Age (years)* | 0.008 (0.007) | 0.23 |
| Sex† | 0.23 (0.15) | 0.12 |
| BMI (kg/m$^2$)* | 0.01 (0.01) | 0.26 |
| CTG18.1† | 0.87 (0.17) | **<0.001** |
| | **Analysis in <69 years** | |
| Sex† | 0.37 (0.20) | 0.07 |
| BMI (kg/m$^2$)* | −0.002 (0.01) | 0.88 |
| CTG18.1† | 1.51 (0.24) | **<0.001** |
| | **Analysis in ≥69 years** | |
| Sex† | 0.14 (0.21) | 0.51 |
| BMI (kg/m$^2$)* | 0.02 (0.02) | 0.22 |
| CTG18.1† | 0.45 (0.23) | 0.05 |
| | **Analysis in Women** | |
| Age (years)* | 0.004 (0.008) | 0.61 |
| BMI (kg/m$^2$)* | 0.03 (0.01) | **0.01** |
| CTG18.1† | 0.72 (0.20) | **<0.001** |
| | **Analysis in Men** | |
| Age (years)* | 0.02 (0.02) | 0.13 |
| BMI (kg/m$^2$)* | −0.04 (0.02) | 0.06 |
| CTG18.1† | 1.33 (0.31) | **<0.001** |
| **Model for predictors of BMI** | | |
| **Predictor** | **Beta-coefficient (SE)** | **P** |
| Age (years)* | −0.05 (0.03) | 0.18 |
| Sex† | 0.38 (0.73) | 0.60 |
| CTG18.1† | 0.35 (0.84) | 0.68 |

*Age and BMI entered in model as a continuous variable

†Beta coefficient is for women with men as the referent group; Beta-coefficient is for CTG18.1 expansion ≥40 with the referent group as CTG18.1 length <40