




## ORIGINAL ARTICLE

# Phenotype and genotype of concurrent keratoconus and Fuchs endothelial corneal dystrophy

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## Abstract

**Purpose:** To characterise the phenotype and genotype of concurrent keratoconus and Fuchs endothelial corneal dystrophy (KC+FECD).

**Methods:** We recruited 20 patients with concurrent KC+FECD for a retrospective observational case series from the United Kingdom and the Czech Republic. We compared eight parameters of corneal shape (Pentacam, Oculus) with two groups of age-matched controls who had either isolated keratoconus (KC) or isolated FECD. We genotyped probands for an intronic triplet *TCF4* repeat expansion (CTG18.1) and the *ZEB1* variant c.1920G >T p.(Gln640His).

**Results:** The median age at diagnosis of patients with KC+FECD was 54 (interquartile range 46 to 66) years, with no evidence of KC progression (median follow-up 84 months, range 12 to 120 months). The mean (standard deviation (SD)) of the minimum corneal thickness, 493 (62.7)  $\mu\text{m}$ , was greater than eyes with KC, 458 (51.1)  $\mu\text{m}$ , but less than eyes with FECD, 590 (55.6)  $\mu\text{m}$ . Seven other parameters of corneal shape were more like KC than FECD. Seven (35%) probands with KC+FECD had a *TCF4* repeat expansion of  $\geq 50$  compared to five controls with isolated FECD. The average of the largest *TCF4* expansion in cases with KC+FECD (46 repeats, SD 36 repeats) was similar to the age-matched controls with isolated FECD (36 repeats, SD 28 repeats;  $p = 0.299$ ). No patient with KC+FECD harboured the *ZEB1* variant.

**Conclusions:** The KC+FECD phenotype is consistent with KC but with superimposed stromal swelling from endothelial disease. The proportion of cases with a *TCF4* expansion is similar in concurrent KC+FECD and age-matched controls with isolated FECD.

## KEYWORDS

cornea, CTG18.1, Fuchs endothelial corneal dystrophy, keratoconus, *TCF4*

## 1 | INTRODUCTION

Keratoconus (KC) is characterised by thinning and ectasia of the cornea that leads to irregular myopic astigmatism and reduced vision. The onset is usually in childhood or early adulthood, with progression at a variable rate until stabilisation in most cases by 35 years (Gomes et al., 2015; Tur et al., 2017). It is a common cause of visual disability in young people with a prevalence as high as 1.2% in some populations (Chan et al., 2021;

Davidson et al., 2014). Previously, 10% to 15% of patients required corneal transplantation (Gordon et al., 2006; Kennedy et al., 1986; Pearson et al., 2000), although this figure will likely reduce following the widespread introduction of corneal crosslinking (CXL) (Godefrooij et al., 2016; Sandvik et al., 2015). The aetiology of KC is complex. A recent genome-wide association study (GWAS) comprising 4669 cases reported 36 genetic loci that have implicated both dysregulation of corneal collagen matrix integrity and cell differentiation pathways

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as disease-causing mechanisms (Hardcastle et al., 2021). Environmental factors, such as eye rubbing, atopy and prone sleep position, are also likely to play a role in accelerating disease progression in susceptible individuals (Rabinowitz et al., 2021; Song et al., 2022). KC is not thought to be associated with primary corneal endothelial disease (Mylona et al., 2020).

Fuchs endothelial corneal dystrophy (FECD) is also a common age-related cause of visual deterioration. A key feature is the presence of corneal guttae that can be associated with corneal swelling and visual loss in advanced disease (Laing et al., 1981; Repp et al., 2013). In a white population >55 years of age, the prevalence of guttae was estimated to be 10.2% (Zoega et al., 2006), and their presence can be associated with a reduced corneal endothelial cell density (Zoega et al., 2013). However, not all patients with isolated guttae progress to visual loss, and it is unlikely that all cases with guttae have a shared genetic mechanism. Up to 80% of patients who have FECD, and are of white European descent, harbour at least one expanded copy ( $\geq 50$  repeats) of a CTG trinucleotide repeat (termed CTG18.1), situated within a non-coding intronic region of the *TCF4* gene (Fautsch et al., 2020; Zarouchlioti et al., 2018). Other rare reported genetic causes for FECD include heterozygous variants in *COL8A2*, *ZEB1* and *SLC4A11*, but the vast majority of CTG18.1 expansion-negative cases remain genetically unsolved (Fautsch et al., 2020).

More than 60 cases of concurrent KC+FECD have been reported (Mylona et al., 2020). However, it is unclear whether the occurrence of the two conditions in the same individual is the result of a chance event or if there is a shared aetiology. To evaluate this further we have compared the phenotype of 20 individuals with concurrent KC+FECD with the same number of eyes of age-matched patients with isolated keratoconus or isolated FECD. We have also investigated the cases with concurrent KC+FECD for potential genetic associations.

## 2 | METHODS

### 2.1 | Patient examination

The institutional review boards of the Moorfields Eye Hospital and General University Hospital in Prague approved the study (13/LO/1084 and 2/19 GACR), which conformed to the principles of the Declaration of Helsinki. We identified individuals with concurrent KC+FECD as part of a prospective study of inherited corneal disease. Family members were not examined. We compared the keratometry of these cases with two sets of age-matched controls, who had either isolated KC or isolated FECD. Clinical examination included the Snellen best-corrected visual acuity (BCVA), slit-lamp biomicroscopy and corneal Scheimpflug tomography (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany). Following pupil dilation, the fundus was examined at the slit lamp with indirect ophthalmoscopy. The diagnosis of KC was based on a combination of asymmetric anterior corneal curvature, asymmetric corneal thinning and elevation of the posterior corneal surface (Belin Ambrosio Deviation

Display, Pentacam, Oculus) (Hashemi et al., 2016). The diagnosis of FECD was based on the presence of multiple corneal guttae. Eyes with concurrent KC+FECD fulfilled both sets of criteria. We graded the severity of the KC with the topographical keratoconus classification system (TKC) (Herber et al., 2021). The presence of guttae was classified into four grades according to the number of guttae and the presence of corneal oedema (Krachmer et al., 1978). Six eyes of patients with concurrent KC+FECD who had a PK before recruitment and the unaffected eye of one case with unilateral guttae were excluded. We processed five corneas from eyes that had a PK following enrolment to the study for standard light microscopy with haematoxylin and eosin and periodic acid Schiff stains.

To compare the keratometric phenotypes, we selected a scan of the worst affected eye of the 20 cases with concurrent KC+FECD taken at their first visit and before they had cataract surgery or keratoplasty. We compared these with two control groups: one eye selected from an age-matched control patient with isolated KC and one eye selected from an age-matched control patient with isolated FECD. Although we matched the control groups for gender where possible, we could not match controls for ethnicity or the severity of their disease. However, as a group, the severity of isolated KC was similar to the study eyes, with a modal TKC grade of 2 (range 2 to 4), although the modal grade of isolated FECD of 4 (range 3 to 4) was higher than in the study eyes. Only scans with an adequate quality score (QS) were included. For each eye, we selected eight keratometric parameters that we considered most likely to indicate a deviation of corneal shape from normal. These were the minimum corneal thickness (min CT), the maximum anterior keratometry (Kmax), the elevation of the front surface at the thinnest location (F.Ele.Th), the elevation of the back surface at the thinnest location (B.Ele.Th), the deviation of the front elevation difference map (Df), the deviation of the back elevation difference map (Db), the percentage thickness deviation (increase or decrease) from the central cornea at the 4 mm zone (% progress 4) on the corneal thickness spatial profile (CTSP) and the percentage deviation at the 6 mm (% progress 6) on the CTSP.

### 2.2 | Molecular genetic analysis

We extracted DNA using Gentra Puregene™ Blood Kit (Qiagen, Hilden, Germany) or Oragene Saliva Kit (Oragene OG-300, DNA Genotek, Canada) according to the manufacturer's instructions. We confirmed the CTG18.1 repeat expansion status using published methods (Fautsch et al., 2020; Mootha et al., 2014; Zarouchlioti et al., 2018). We defined a CTG18.1 expansion-positive allele as  $\geq 50$  CTG repeats. We also compared the number of CTG repeats in the longest allele in the cases with concurrent KC+FECD with the controls with isolated FECD. The presence of a single rare variant in *ZEB1*, c.1920G >T p.(Gln640His), minor allele frequency 0.00001063 (gnomAD V2.2.2) previously associated with concurrent KC+FECD (Lechner et al., 2013; Mazzotta

et al., 2014), was screened by Sanger sequencing in accordance with our previously published methods (Evans et al., 2015).

We summarised continuous variables using means and standard deviation (SD) if approximately normally distributed (assessed by visual inspection of the histogram), or medians and interquartile ranges (IQR) if we observed evidence of non-normality. We compared the characteristics of patients with concurrent KC+FECD against those with isolated KC or isolated FECD using paired t-tests or the signed rank test for normal and non-normal data, respectively, except for the comparison of TC4 expansion where we used an unpaired t-test with equal variances. We did not adjust for multiple testing because this was an exploratory (first of its kind) analysis. We performed statistical analysis using Stata SE 17.0 for Windows.  $p$ -values  $<0.05$  were considered significant, and all tests were two tailed.

### 3 | RESULTS

We included 20 patients with concurrent KC+FECD (Table 1). Fifteen were white, four were black, one was south Asian and eight (40%) were female. The median (IQR) age at diagnosis with concurrent KC+FECD was 54 (46 to 66) years, although the age of diagnosis of the KC component was less at 24.5 (22 to 32.5) years. One proband reported a family history of FECD, and a different proband reported a family history of KC. The demographics of the control patients with isolated KC or isolated FECD are shown in Table 2.

#### 3.1 | Ocular phenotypes

The most frequent TKC score of the 33 unoperated eyes with concurrent KC+FECD was 2 (range 1 to 4), and the modal FECD grade was 2 (range 1 to 3). There was no significant association between the TKC score and the severity of the FECD (Chi-square gamma 0.010,  $p = 0.964$ ). The median follow-up was 84 months (range 12 to 120 months) with no evidence of KC progression; the values for the minimum corneal thickness (min CT) (mean and standard deviation (SD)) were 497.4 (90.9)  $\mu\text{m}$  (range 318 to 723  $\mu\text{m}$ ) at the first visit compared to 519.9 (74.0)  $\mu\text{m}$  (range 402 to 645  $\mu\text{m}$ ) at the last visit ( $p = 0.109$ , paired t-test). At the end of the study period, 15 (37.5%) eyes had a keratoplasty (six before recruitment), nine eyes had a PK and 6 had an endothelial keratoplasty (four had a Descemet membrane endothelial keratoplasty [DMEK] and two a Descemet stripping endothelial keratoplasty [DSEK]). However, we could not confirm whether there had been a deterioration of endothelial function in eyes with concurrent KC+FECD during the study period. Histology of five PK samples confirmed that guttae were present in cases both with and without a CTG18.1 expansion (Figure 1). In more advanced cases, there was also stromal thinning and breaks in Bowman's layer.

Paired comparisons between the keratometry values of eyes with concurrent KC+FECD, eyes with isolated KC and eyes with isolated FECD are shown in Table 3.

For paired comparisons, isolated KC is statistically significantly different from concurrent KC+FECD in all parameters, and isolated FECD is also statistically significantly different from concurrent KC+FECD in all parameters ( $p < 0.0001$ ). However, the data values for concurrent KC+FECD are closer to the data for isolated KC than for isolated FECD.

#### 3.2 | Genotyping

CTG18.1 genotyping identified seven (35%) patients with concurrent KC+FECD who had at least one expanded CTG18.1 allele of  $\geq 50$  repeats compared to five of the controls with isolated FECD. The average of the largest *TCF4* expansion in cases with concurrent KC+FECD (46 repeats, standard deviation (SD) 36 repeats) was similar to the 20 controls with isolated FECD (36 repeats, SD 28;  $p = 0.299$ ). We did not identify the *ZEB1* variant c.1920G >T p.(Gln640His) in any of the cases with concurrent KC+FECD.

### 4 | DISCUSSION

In this case series, we report the clinical phenotype and CTG18.1 genotype of 20 individuals with concurrent KC+FECD. We have also compared the keratometry of these cases with scans of age-matched eyes with isolated KC and age-matched eyes with isolated FECD. We show that concurrent KC+FECD was diagnosed at a later median age than is typical for isolated KC, with no evidence of progression of the features of KC during follow-up. However, it is possible that progressive corneal thinning could be masked by an increase in stromal swelling from deteriorating endothelial cell function over time (Gupta et al., 2017; Jurkunas & Azar, 2006; Ramos et al., 2012). Comparison between the three disease groups shows that the average pachymetry of cases with concurrent KC+FECD is intermediate between the cases with isolated KC and the cases with isolated FECD, which supports the concept that in concurrent KC+FECD, the effect of KC and FECD on pachymetry have opposing effects. The reduction in pachymetry that can follow endothelial keratoplasty also suggests that compromised endothelial cell function is a feature of concurrent KC+FECD (Gupta et al., 2017; Jurkunas & Azar, 2006). The increase in the anterior corneal curvature (Kmax) and the elevation of the posterior corneal surface in cases with concurrent KC+FECD, which are not major features of isolated FECD, also suggest a phenotype that is like KC.

A CTG18.1 expansion, defined as  $\geq 50$ , is present in up to 80% of cases of FECD from Europe and North America (Fautsch et al., 2020), with an expanded CTG18.1 allele conferring  $>76$ -fold risk for FECD (Zarouchlioti et al., 2018). The relatively young average age of our cohorts with concurrent KC+FECD and isolated FECD may explain why the proportion with an expansion length of  $\geq 50$  is less than in these case series, with an alternate aetiology for the guttae in the majority. It is also noteworthy that a single

TABLE 1 Demographic data of 20 individuals with concurrent keratoconus and Fuchs endothelial corneal dystrophy (KC+FECD).

Case	Age (years)/sex	Ethnicity	Age of diagnosis (years) (KC, FECD)	BCVA (Snellen)		TKC grade		Guttae grade <sup>a</sup>		Corneal surgery		Other ocular findings	CTG18.1 allele length
				RE	LE	RE	LE	RE	LE	RE	LE		
UK1	69/M	White	43, 60	6/9	6/18	1	3–4	2	2	Nil	Nil	Nil	18/70
UK2	44/F	Black	26, 27	6/15	6/9	2–3	0	2	2	Nil	Nil	Nil	12/18
UK3	48/M	Black	39, 38	6/18	6/12	2	2	3	2	DSEK	Nil	Nil	15/28
UK4	73/M	White	56, 64	6/9	6/12	1	3	2	2	Nil	ARM	ARM	12/83
UK5	61/F	Black	48, 48	6/18	6/9	1	3	3	3	Nil	Nil	Nil	15/18
UK6	60/M	South Asian	50, 51	6/12	6/12	3	3	2	3	Nil	DMEK	Nil	12/125
UK7	58/F	Black	54, 54	6/24	6/60	1	2–3	3	3	DSEK	DMEK	DR	16/16
UK8	74/M	White	UA, UA	6/18	HM	1–2	UA	3	UA	DMEK	PK	Glaucoma	15/85
UK9	38/F	White	UA, UA	6/12	6/12	3	3	UA	1	PK	Nil	Glaucoma	18/90
UK10	54/M	White	UA, UA	6/9	6/60	2	3	UA	UA	PK	Nil	Amblyopia	15/27
CR1	54/M	White	51, 51	6/9.5	6/9.5	2	0	1	1	Nil	Nil	Nil	27/97
CR2	63/F	White	47, 53	6/12	6/6	2	2	2	2	Nil	Nil	Floppy eyelid	12/23
CR3	54/F	White	UA, UA	6/18	6/12	2	UA	2	UA	PK	PK	Nil	12/26
CR4	54/M	White	49, 54	6/6	6/12	1	2–3	2	2	Nil	Nil	Nil	12/18
CR5	42/M	White	UA, UA	6/12	6/12	3–4	UA	2	UA	PK	PK	Nil	18/29
CR6	74/M	White	68, 75	6/7.5	6/12	0	2–3	1	2	Nil	Ni	Nil	16/26
CR7	38/F	White	30, 35	6/12	6/7.5	2	2	1	1	Nil	Nil	Nil	12/12
CR8	35/M	White	UA, UA	6/60	6/12	3–4	2	2	2	Nil	Nil	Nil	18/23
CR9	75/M	White	UA, UA	6/60	6/60	UA	2–3	UA	3	PK	DMEK	Nil	23/91
CR10	48/F	White	21, 46	6/15	6/15	1–2	UA	1	UA	Nil	PK	Nil	15/24

Note: CTG18.1 alleles  $\geq 50$  repeats are defined as expanded.

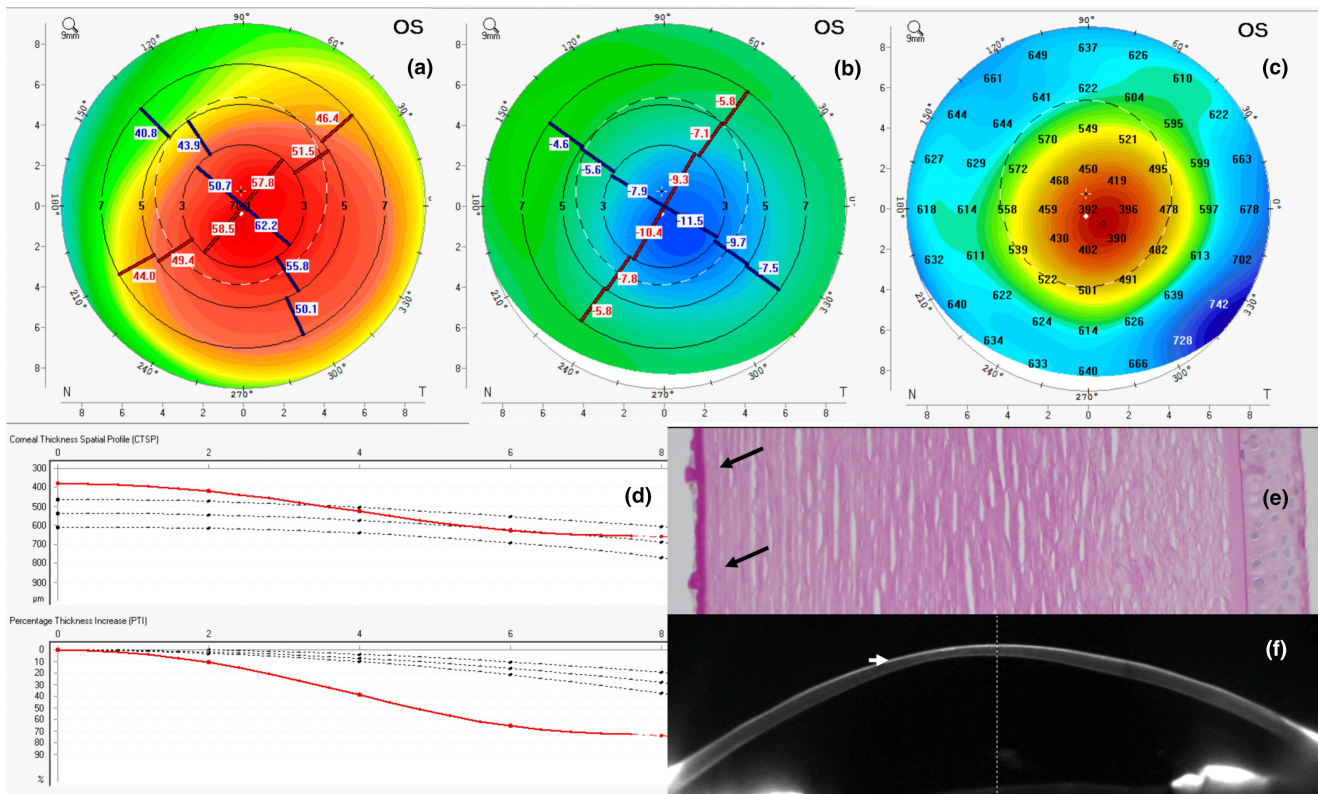
Abbreviations: ARMD, age-related macular degeneration; BCVA, best corrected visual acuity; CR, Czech Republic; DR, diabetic retinopathy; DSEK, Descemet stripping endothelial keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; F, female; FECD, Fuchs endothelial corneal dystrophy; HM, hand movement; KC, keratoconus; LE, left eye; M, male; PK, penetrating keratoplasty; RE, right eye; TKC, topographical keratoconus classification; UA, unavailable; UK, United Kingdom.

<sup>a</sup>Krachmer et al., 1978.

**TABLE 2** Demographics of the three groups of patients ( $n = 20$  for each group).

		Isolated KC	Concurrent KC+FECD	Isolated FECD
Age (years)	Median (IQR)	55 (44 to 65)	54 (46 to 66)	54.5 (45 to 67)
Gender ( $n$ )	Female	10	8	12
	Male	10	12	8
Ethnicity ( $n$ )	White	16	15	14
	Black	3	4	3
	Asian	1	1	3

Abbreviations: FECD, Fuchs endothelial corneal dystrophy; IQR, interquartile range; KC, keratoconus; n, number.



**FIGURE 1** Images of the left eye of a 54-year-old man (UK10) with concurrent keratoconus and Fuchs endothelial corneal dystrophy. Sagittal scans of the anterior (a) and posterior (b) corneal surfaces. Regional corneal pachymetry is shown in (c). The corneal thickness sagittal profiles are shown as absolute values (top) and percentage values (bottom), with marked thinning from the 6 mm zone towards the centre of the pupil (d). Histology of penetrating keratoplasty in the right eye shows thinning, but no other abnormality of the stroma, and an intact Bowman layer with normal epithelial thickness (e). However, there are guttae (arrows) and a reduced endothelial cell density (periodic acid Schiff stain, objective x20). Scheimpflug image of the anterior segment taken before surgery showing thinning of the central cornea and a layer of abnormal reflectivity of the anterior stroma (arrow) (f).

rare *ZEB1* variant c.1920G>T, previously identified in two unrelated probands with concurrent KC+FECD, was absent in all of our cases (Lechner et al., 2013; Mazzotta et al., 2014). Interestingly, a recent keratoconus GWAS identified two distinct loci, encompassing *PIDD1/SLC25A22* (rs7117921,  $p = 1.09 \times 10^{-26}$ ) and *ATP1B1* (rs1200108,  $p = 4.52 \times 10^{-10}$ ) (Hardcastle et al., 2021), that have previously been shown to confer susceptibility to FECD (Afshari et al., 2017). It is thus possible that common pathological variants could be associated with both KC and FECD and hence may underlie disease in cases presenting with dual pathologies. Further genomic association studies are required to explore other potential shared aetiologies of these distinct conditions. However, as both KC and FECD are common disorders, it is also plausible that their occurrence in the same individual is a chance association (Mylona et al., 2020).

The preferred surgical management of concurrent KC+FECD has altered with the widespread introduction of endothelial keratoplasty (Vira et al., 2014). Although an endothelial keratoplasty is the procedure of choice for isolated FECD (Lee et al., 2009), an endothelial keratoplasty for concurrent KC+FECD will only treat the component of stromal oedema. It will not eliminate irregular astigmatism associated with KC, which may require continued rigid contact lens wear for visual correction. Also, when there is concurrent KC+FECD, there may be biometry error and unexpected hyperopia following intraocular lens implantation (Alnawaiseh et al., 2016; Ham et al., 2011; Watson et al., 2014). Finally, strategies to determine whether cataract extraction should be performed alone or in combination with an endothelial keratoplasty, based on the central corneal thickness before surgery, do not apply if there is corneal thinning from associated KC (Jurkunas & Azar, 2006;

**TABLE 3** Summary data comparing concurrent keratoconus (KC) and Fuchs endothelial corneal dystrophy (FECD) (column B) against isolated KC (column A) and isolated FECD (column C) ( $n = 20$  for each group).

Parameter	A isolated KC	B concurrent KC and FECD	C isolated FECD
Min CT ( $\mu$ ) <sup>a</sup>	458.3 (51.1)	493.4 (62.7)	590.2 (56.6)
Kmax (D) <sup>a</sup>	53 (5.4)	56 (6.4)	44.7 (1.9)
F.Ele.Th <sup>a</sup>	19.7 (10.7)	22.6 (14.2)	-0.2 (6.2)
B.Ele.Th <sup>a</sup>	47 (25.2)	54 (24.8)	10.6 (7.4)
Df <sup>b</sup>	5.2 (4, 15))	10 (6.2, 12.5)	-0.4 (-1.0, 0.1)
Db <sup>b</sup>	5.2 (3.3, 10.1)	7.3 (4.5, 11.5)	0.02 (-0.6, 0.9)
% progress 4 <sup>b</sup>	14 (12, 19.5)	16.5 (11, 21)	6.5 (6, 7)
% progress 6 <sup>b</sup>	28 (23, 35.5)	29 (19, 30)	14 (11.5, 15)

Note: For paired comparisons, KC is statistically significantly different from concurrent KC+FECD in all parameters, and FECD is also statistically significantly different from concurrent KC+FECD in all parameters ( $p < 0.0001$ ). However, the data values for concurrent KC+FECD are closer to the data for isolated KC than for isolated FECD.

Abbreviations: B.Ele.Th, elevation of the back surface at the thinnest location; D, dioptre; Df, deviation of front elevation difference map; Db, deviation of back elevation difference map; F.Ele.Th, elevation of the front surface at the thinnest location; FECD, Fuchs endothelial corneal dystrophy; KC, keratoconus; Kmax, maximum anterior keratometry; min CT, minimum corneal thickness; % progress 4, percentage thickness spatial deviation (increase or decrease) from central cornea at 4 mm zone on corneal thickness spatial profile (CTSP); % progress 6, percentage deviation at 6 mm on CTSP.

<sup>a</sup>Mean and standard deviation.

<sup>b</sup>Median and interquartile range (IQR).

Seitzman et al., 2005). Interestingly, it has been reported that after DMEK for FECD, the corneal central corneal thickness may be thinner than normal—suggesting that FECD has an inherently thinner cornea (Arnalich-Montiel et al., 2019). A DALK procedure, which is an alternative procedure for KC (Liu et al., 2015), would only be successful for concurrent KC+FECD if the endothelial disease was minimal. A PK, which addresses both stromal thinning and endothelial disease, remains a valid alternative.

The limitations of this study include inherent uncertainty about the case definition of FECD, or whether there is a threshold value for the number or density of guttae that distinguish isolated guttae from FECD. Secondly, an alternative explanation for the co-occurrence of KC and FECD is that the corneal guttae are pseudo-guttae induced by contact lens wear or the abnormal ocular surface of KC (Nakashima et al., 2007; Waring 3rd et al., 1982). A lower endothelial cell density and increased coefficient of variation of cell size, but not the presence of guttae, have also been documented in advanced KC compared to eyes with early disease (Goebels et al., 2018). Hypoxic stress secondary to contact lenses is known to cause polymegathism and water-filled vacuoles accumulating in corneal endothelial cells, which gives a guttae-like appearance on the posterior cornea (Moshirfar et al., 2019) although they are transient and do not involve Descemet membrane. However, in our series, some patients had not worn contact lenses, and histological confirmation of guttae was available in five cases. Thirdly, the three groups in our study were not matched for the severity of their KC or FECD; patients with FECD are usually only referred for consideration for surgery when there is visual loss from corneal oedema, and emphasis on cases with advanced FECD may have exaggerated the difference in minimum CT between eyes with isolated FECD and eyes with concurrent KC+FECD. When comparing keratometry, we selected parameters that we considered best represent corneal shape, although other parameters could have been used. We did not use the Belin ABCD to categorise

the severity of KC because this incorporates visual acuity, which could be affected by the presence of corneal swelling. Finally, electron microscopy was not available to further characterise differences between concurrent KC+FECD, isolated KC or isolated FECD, or between cases with or without a CTG18.1 repeat expansion.

In conclusion, we have further defined the phenotype of concurrent KC+FECD. A comparison of keratometry values between groups supports the concept that in concurrent KC+FECD, there is a balance between pathological processes with opposing effects. Corneal swelling induced by FECD may lead to an underestimation of the severity of KC, which can become manifest following the resolution of stromal oedema after endothelial keratoplasty. It is unclear whether the co-occurrence is a random association, or if the two conditions share a common disease pathway (Gurnani et al., 2021). KC is a genetically complex disease with many loci of collectively small effect, while FECD is very different with one locus (TCF4), which explains a high proportion of risk (Zarouchlioti et al., 2018). However, a large GWAS has identified potentially shared genetic causes for KC and FECD (Hardcastle et al., 2021), and further genomic association studies will be required to explore whether there are other shared genetic aetiologies of these clinically distinct conditions.

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