Posterior corneal vesicles are not associated with the genetic variants that cause posterior polymorphous corneal dystrophy

[1,2]Petra Liskova PhD

[3]Nathaniel J. Hafford-Tear MSc

[2]Pavlina Skalicka PhD

[1,4]Frantisek Malinka MSc

[1]Jana Jedlickova MSc

[1]Ľubica Ďuďáková PhD

[3]Nikolas Pontikos PhD

[3]Alice E Davidson PhD

[3,5]Stephen Tuft MD FRCOphth

[1]Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Ke Karlovu 2, Prague 128 08, Czech Republic
[2]Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Unemocnice 2, Prague 128 08, Czech Republic
[3]UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK
[4]Department of Computer Science, Czech Technical University in Prague, Karlovo Náměstí 13, 121 35 Prague, Czech Republic
[5]Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK

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Corresponding author: Professor Stephen Tuft

Email: s.tuft@ucl.ac.uk

Tel: 0044 207 253 2411

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Abstract

Purpose: Posterior corneal vesicles (PCVs) have clinical features that are similar to posterior polymorphous corneal dystrophy (PPCD). To help determine if there is a shared genetic basis, we screened 38 individuals with PCVs for changes in the three genes identified as causative for PPCD.

Methods: We prospectively recruited patients for this study. We examined all individuals clinically, with their first-degree relatives when available. We used a combination of Sanger and exome sequencing to screen regulatory regions of *OVOL2* and *GRHL2,* and the entire *ZEB1* coding sequence.

Results: The median age at examination was 38.7 years (range 4.7 to 84.0 years), 20 (53%) were male and in 18 (47%) the PCVs were unilateral. Most individuals were discharged to optometric review, but five had follow-up for a median of 12 years (range 5-13 years) with no evidence of progression. In cases with unilateral PCVs there was statistically significant evidence that the change in the affected eye was associated with a lower endothelial cell density (P = 0.0003), greater central corneal thickness (P = 0.0277) and a steeper mean keratometry (P = 0.0034), but not with a higher keratometric astigmatism or a reduced LogMAR visual acuity. First degree relatives of 13 individuals were available for examination and in 3 (23%) PCVs were identified. No possibly pathogenic variants were identified in the PPCD-associated genes screened.

Conclusion: We found no evidence that PCVs share the same genetic background as PPCD. In contrast to PPCD, we confirm that PCVs is a mild, non-progressive condition with no requirement for long-term review. However, subsequent cataract surgery can lead to corneal oedema.

Introduction

Posterior polymorphous corneal dystrophy (PPCD) is a rare, autosomal dominant and genetically heterogeneous disorder characterized by corneal endothelial and Descemet membrane disease.(Cibis et al. 1977; Krachmer 1985) There are three principal corneal signs, categorized as focal vesicles, Descemet membrane bands, and diffuse endothelial abnormalities.(Cibis et al. 1977; Waring et al. 1978; Laganowski et al. 1991) It is bilateral and associated features can include iridocorneal adhesions, corectopia, pupillary ectropion, and secondary glaucoma. An estimated 40% of cases, depending on the underlying molecular genetic cause, develop corneal oedema that may require corneal transplantation.(Cibis et al. 1977; Raber et al. 2011; Aldave et al. 2013; Liskova et al. 2013) Variants in three genes have been identified as causative for PPCD; *ZEB1* (OMIM *189909),(Krafchak et al. 2005) *OVOL2* (OMIM *616441),(Davidson et al. 2016) and *GRHL2* (OMIM *608576),(Liskova et al. 2018) all mutually regulated and involved in epithelial to mesenchymal transition (EMT) and mesenchymal to epithelial transition (MET).(Kitazawa et al. 2016; Liskova et al. 2018) Despite an early report that associated PPCD with variants in *COL8A2*,(Biswas et al. 2001) this finding has not been replicated and there is currently not enough evidence that polymorphisms in this gene are causative of PPCD.(Aldave et al. 2013)

Posterior corneal vesicles (PCVs) were first described as isolated focal lesions (vesicles) and linear bands (snail track or rail track lines) of the posterior corneal surface. It was thought that PCVs were distinct from PPCD because the signs of PCVs were usually unilateral, with normal vision, no iris abnormalities, and with no evidence they were an inherited condition.(Pardos et al. 1981) It was subsequently reported that a phenotype consistent with PCVs could be familial,(Malbran 1972; Levenson et al. 1973; Cibis et al. 1977; Krachmer 1985) It is now usual to distinguish PCVs from PPCD,(Noguchi et al. 2018) although there can be shared features and in some recent reports PCVs are still included as a feature of PPCD.(Patel et al. 2005; Vincent et al. 2009; Weiss et al. 2015; Fung et al.

2021) The histology of PPCD has been well characterized as an abnormally thickened Descemet layer with multilayering of the corneal endothelium and expression of cellular markers normally associated with epithelium,(Henriquez et al. 1984; Jirsova et al. 2007) but to the best of our knowledge the histology of PCVs has not been described.

In this study we clinically examined a cohort of individuals with PCVs and screened them for variants in the *ZEB1, OVOL2,* and *GRHL2* regions known to be associated with PPCD to explore whether PCVs could be attributed to shared genetic cause.

Methods

Patient Examination and Recruitment

The study followed the tenets of the Declaration of Helsinki and was approved by the local research ethics committee (references 13/LO/1084 and 964/15 S-IV). Individuals with clinical signs of PCVs were recruited at Moorfields Eye Hospital in the UK or the General University Hospital in the Czech Republic. First degree relatives were invited to participate if they were available, but a systematic examination of all pedigrees was not possible. A diagnosis of PCVs was made at slit-lamp microscopy by an experienced corneal specialist (ST, PL). The diagnosis of PCVs was based on slit-lamp examination and defined as an eye with endothelial change but without PPCD-associated clinical features such as peripheral synechiae, glaucoma, iris atrophy, and corneal edema. Patients were excluded if there was a preceding history of trauma or intraocular surgery. Examination included best-corrected visual acuity (BCVA) converted to LogMAR, anterior chamber depth (IOLMaster V.5, Carl Zeiss Meditec AG, Jena, Germany), keratometry and central corneal thickness by Scheimpflug tomography (Pentacam Oculus, Wetzlar, Germany) and corneal endothelial cell density (Noncon ROBO or Pachy SP-9000, Konan Medical Inc., Tokyo, Japan). For the purposes of this paper, and to prevent confusion regarding nomenclature, linear lesions are called rail tracks.(Weiss et al. 2015) In unilateral cases that had not had subsequent intraocular surgery the corneal parameters of affected and unaffected eyes were compared.

As the data appeared to be symmetrically distributed, we used the paired t-test (Microsoft, Washington, USA).

Molecular genetic analysis

Non-coding regulatory regions of *OVOL2* (chr20:18,038,262-18,038,959; hg19) and *GRHL2* (chr8:102,505,052-102,505,656; hg19), previously identified to harbour PPCD associated variants, were screened by bi-directional Sanger sequencing in accordance with previously published methods.(Evans et al. 2015; Davidson et al. 2016; Liskova et al. 2018) All coding exons and intron/exon boundaries of *ZEB1* (NM_030751.6) were analyzed by exome sequencing or by Sanger sequencing, as previously described.(Dudakova et al. 2019) Briefly, exome libraries generated using SureSelect Human All Exome V6 capture kit (Agilent, Santa Clara, California) were sequenced on HiSeq4000 (Illumina San Diego, California). Reads were aligned to the GRCh37/hg19 human reference sequence with NovoAlign V3.02.08 and Variant calling was performed with Genome Analysis Tool Kit (GATK) HaplotypeCaller (version 4.0.1.2).(McKenna et al. 2010) Details of primers are available upon request.

Results

We included 38 individuals (20 males) with PCVs of which 19 (50%) had unilateral changes (Supplementary Table 1). The median age at first examination was 37.5 years (range 4.7 to 84.0 years). The morphology of the corneal changes was grouped as primarily vesicles, rail tracks, or complex when there were elements of both vesicles and rail track. Twenty-seven (47%) of 57 affected eyes had vesicles, 18 (32%) had rail track and 12 (21%) had a complex morphology. Representative clinical signs are shown in Figure 1. Most individuals were discharged to optometric review after one clinic visit, but five individuals had follow-up for a median of 12 years (range 5-13 years) without intraocular surgery, with no evidence of progression of the corneal changes in either eye. Three eyes had cataract surgery following their diagnosis of PCVs; in two of these eyes the cornea decompensated, with one treated

with a Descemet membrane endothelial keratoplasty. Unfortunately, the ECDs had not been recorded prior to surgery. One individual was under review without treatment for ocular hypertension, and one for suspected normal tension glaucoma. First degree relatives of 13 individuals were available for examination and in 3 (23%) families there was at least one relative who also had PCVs. When we compared CCT, ECD and mean keratometry in unilateral cases that had not had cataract surgery there was evidence of a statistically significant difference between the affected and unaffected eyes, although keratometric astigmatism and visual acuity was similar between eyes (Table 2).

Sequencing of mutational hotspots in *OVOL2*, *GRHL2* and the coding sequence and intron/exon boundaries of *ZEB1* did not identify any previously reported PPCD-associated variants or any variants with a minor allele frequency (MAF) ≤ 0.02% as per gnomAD (version 3.1.1) that could be considered to have a potential phenotypical effect.(Dudakova et al. 2021)

Discussion

Posterior corneal vesicles (PCVs) have a characteristic appearance at slit lamp biomicroscopy with vesicular, or linear changes. But in bilateral cases it may be impossible to distinguish with certainty these clinical signs from PPCD. The lesions are thought to be congenital and individuals with PCVs are usually asymptomatic, typically with lesions first identified at routine optometric review. They can present as single or multiple vesicular lesions at the level of Descemet membrane, typically with a surrounding zone of grey haze, or as paired parallel bands with scalloped borders (also termed snail track or rail track lesions). There is no data on prevalence of PCVs. It is not known if vesicles and linear lesions have a separate aetiology, but most authors consider them to a spectrum of a single disease entity.(Harada et al. 1990; Laganowski et al. 1991; Patel et al. 2005; Watanabe et al. 2010; Shiraishi et al. 2016; Noguchi et al. 2018) Although the changes are not progressive,(Harada et al. 1990; Watanabe et al. 2010; Shiraishi et al. 2016; Fung et al.

2021) they can be associated with a reduced endothelial cell density that, in the absence of further surgically-induced endothelial cell loss, does not progress to corneal oedema.(Harada et al. 1990; Patel et al. 2005; Watanabe et al. 2010; Shiraishi et al. 2016; Noguchi et al. 2018) Specular microscopy or in vivo confocal microscopy does not show features suggestive of the multilayering or epithelial transformation that is characteristic of PPCD.(Cibis & Tripathi 1982; Henriquez et al. 1984; Shiraishi et al. 2016) In some unilateral cases, if the lesion is in the central cornea, there may be reduced vision and mild amblyopia compared to the unaffected eye, but with no other ocular abnormalities.(Noguchi et al. 2018)

The relationship between PCVs and PPCD is unclear. Pardos et al examined 30 family members of 6 individuals with unilateral PCVs and, because none of the relatives was affected, they suggested that it is not a genetic disease.(Pardos et al. 1981) In contrast, there have been subsequent reports of small pedigrees with PCVs with multiple affected individuals, as well as pedigrees that have both PCVs and diffuse PPCD, which suggests that there may be a genetic basis for PCVs.(Malbran 1972; Levenson et al. 1973; Cibis et al. 1977; Krachmer 1985) Therefore, to further explore if there is a shared pathogenesis, we screened a cohort of individuals who had clinical signs of PCVs for the variants reported in the three genes associated with PPCD (*ZEB1*, *OVOL2*, and *GRHL2*). Our results show that all 38 individuals in this cohort were negative for previously reported PPCD-associated variants. However, although the pathogenesis of PCVs is likely to be distinct from PPCD, it is feasible that the phenotype is due PPCD-associated variants arising somatically within the affected tissue. The only way to explore this hypothesis further would be to analyse genomic DNA-derived directly from the affected corneal endothelial tissue.

We are aware of one similar study in which 11 probands with a clinical diagnosis reported to be PPCD were screened for variants in *ZEB1*; One individual had a pathogenic variant in *ZEB1* but the remainder were negative.(Vincent et al. 2009) In that study it is likely that the inclusion of individuals with PCVs contributed to their low estimate of the prevalence of a

ZEB1 mutation as a cause for PPCD, which they quoted as 9% compared to the 25-45% reported in previous studies.(Krafchak et al. 2005; Aldave et al. 2007; Liskova et al. 2007) Although we also did not systematically recruit relatives to our study, we identified three individuals who had a first degree relative with PCVs. This finding may be the result of chance, an inherited mechanism, or there may be a shared environmental risk in some families. Recruiting larger families would help define transmission and could identify alternative genetic causes of disease. With available data, the possible explanations for our findings are that PCVs is a variant of PPCD with some shared features, even though the genetic mechanism has not been identified; extensive genomic investigations would be needed to further investigate this hypothesis. Alternatively, PCVs may be a phenocopy of PPCD that is not attributable to genetic causes.

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Supplementary Table 1

Clinical characteristics of 38 individuals with posterior corneal vesicles

Table 2

Comparison of data from the affected and unaffected eyes of individuals with unilateral posterior corneal vesicles. Cases that had prior intraocular surgery were excluded.

Figure 1

Representative corneal images of individuals with posterior corneal vesicles recruited to this study. A) Linear pattern of vesicles viewed in retroillumination. B) Complex morphology of rail track (superiorly) and scattered vesicles and lines on Descemet membrane (inferiorly), viewed in diffuse oblique illumination. There is a diffuse grey haze surrounding the lesions with focal opacities (arrow). C) Meandering pattern of fused vesicles. The bilateral changes were first noted at age 9 years, with normal vision and no change over 4 years of follow-up. D) Mother of individual in (C) with one small unilateral vesicle (arrow). E) Complex pattern of linear and circular lesions of Descemet membrane. F) Specular microscopic image of vesicles across the lower part of the image. The endothelial cells at the top of the image are enlarged with an irregular shape but appear otherwise normal. G) Specular image of the contralateral eye to (F) with no clinically apparent vesicles. H) Confocal microscopic image of vesicles with enlarged endothelial cells peripheral to the lesions. I) Anterior segment

ocular coherence tomography demonstrating focal elevation of Descemet membrane (arrow) corresponding to a linear lesion seen on slit lamp microscopy.