# Coincidental occurrence of Schnyder corneal dystrophy and posterior polymorphous corneal dystrophy type 3

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**ABSTRACT**

**Purpose:** To report the simultaneous occurrence of two rare corneal dystrophies.

**Methods:** Case report of a 30-year-old male with a family history of posterior polymorphous corneal dystrophy type 3 (PPCD3) was invited for ophthalmic examination. Sanger sequencing of the coding regions and intron/exon boundaries of disease-associated genes, *ZEB1* and *UBIAD1* was performed.

**Results:** The clinical findings suggested co-occurrence of PPCD3 and Schnyder corneal dystrophy (SCD) in the proband. This dual diagnosis was supported by genetic findings. He was identified to carry a previously reported heterozygous nonsense mutation in *ZEB1*; c.2157C>G, p.(Tyr719*), and a novel heterozygous missense mutation in *UBIAD1*; c.569T>C; p.(Ile190Thr). The mother of the proband only carried the c.2157C>G in *ZEB1* and slit-lamp examination of her corneas showed endothelial lesions characteristic of PPCD3. The sister of the proband carried the c.569T>C in *UBIAD1* and had corneal crystal deposition in her anterior stroma consistent with the diagnosis of SCD.

**Conclusion**: This case illustrates the coincidental occurrence of two rare and genetically distinct corneal dystrophies in a single patient. Furthermore, it highlights the need to perform comprehensive phenotyping in combination with appropriate genetic diagnostic testing to achieve an accurate diagnosis.

Corneal dystrophies comprise a group of rare phenotypically and genetically heterogeneous disorders. To date, mutations in 14 distinct genes have been reported to cause monogenic corneal dystrophies.[1-4]

Schnyder corneal dystrophy (SCD; OMIM # 121800) is an autosomal dominant disease affecting the corneal stroma. Clinical findings include corneal crystals, stromal haze and arcus.[5,6] In some patients hyperlipidemia is present.[1] Posterior polymorphous corneal dystrophy (PPCD) is also an autosomal dominant disease manifesting predominantly as vesicles, bands and opacities at the level of the corneal endothelium and Descemet membrane.[1] Three genes *OVOL2*, *ZEB1* and *GRHL2* are known to be implicated in pathogenesis; PPCD type 1 (MIM #122000), type 3 (MIM #609141) and type 4 (MIM #618031), respectively.[1-3]

**Case Report**

The study was approved by institutional Ethical committee of the General University Hospital in Prague (reference no. 151/11 S-IV) and adhered to the Helsinki Declaration. Informed consent was signed by the participants prior to the investigation being initiated. A 30-year-old male was invited for clinical ophthalmic review because of family history of PPCD3. His great-aunt had previously been shown to carry a heterozygous *ZEB1* nonsense mutation; c.2157C>G, p.(Tyr719*) (Figure 1E).[7]

The patient reported bad vision in both eyes since childhood with no improvement upon spectacle correction. His best corrected visual acuity was 0.6 in the right eye and 0.9 in the left eye (Snellen charts). Due to a family history of PPCD3 the presence of corneal endothelial disease was expected. Slit-lamp examination revealed however not only mild

changes of the posterior corneal layers but also stromal crystals in both eyes and partial arcus in the right eye (Figure 1A, B, C, D) consistent with the diagnosis of SCD.

The patient was also found to have a borderline total cholesterol level (5.08 mmol/l, reference 2.9-5.0 mmol/l) and a slightly increased LDL-cholesterol level (3.17 mmol/l, reference 1.2-3.0 mmol/l).

Direct sequencing confirmed the presence of the previously reported *ZEB1* nonsense mutation in the heterozygous state (Figure 1E).[7] Screening of the *UBIAD1* gene identified a further novel heterozygous missense variant in the *UBIAD1* gene; c.569T>C; p.(Ile190Thr). This variant is predicted to be pathogenic by PROVEAN, MutationTaster, MutPred2 and SIFT and absent from 141,456 unrelated individuals reported in gnomAD (Supplementary Table 1).

Clinical examination of the asymptomatic mother aged 53 years revealed bilateral opacities of the posterior corneal surface characteristic of PPCD3 (Supplementary Figure 1A,B). BCVA was 1.0 bilaterally. The sister of the proband aged 29 years was also asymptomatic. Her BCVA was 0.9 and 1.0 in the right and left eye, respectively. Discrete paracentral anterior stromal crystals and incipient arcus lipoides formation in the right eye were found to be consistent with a diagnosis of SCD (Supplementary Figure 1C,D). The mother was identified to carry the same *ZEB1* nonsense mutation as her son p.(Tyr719*). The diagnosis of SCD in the sister was supported by the presence of the same heterozygous *UBIAD1* missense mutation as in her brother; p.(Ile190Thr) (Figure 1E). As the mother of the proband did not carry the *UBIAD1* variant it was likely inherited from the sibling's father.

## Discussion

In this report we present a patient coincidentally affected by two distinct and rare corneal disorders, SCD and PPCD3. Both diagnoses are supported by molecular genetic investigation leading to the identification of heterozygous pathogenic variants in *ZEB1* and *UBIAD1*. To the best or our knowledge this is the first report of the distinct and rare monogenic corneal dystrophies occurring in the same individual.

Including this study, in the Czech population SCD has an estimated prevalence of at least 1 in 1,500,000,[5,6] and PPCD3 of at least 1 in 340,000 (unpublished data).[7-10] The coincidental occurrence of these two rare and genetically distinct corneal dystrophies presenting in a single patient is therefore extremely low $5.1 \times 10^{11}$.

Our case highlights the importance of considering a full family history in combination with accurate phenotyping information to guide the use of appropriate genetic diagnostic testing. We also expand the spectrum of disease-causing mutations associated with SCD.

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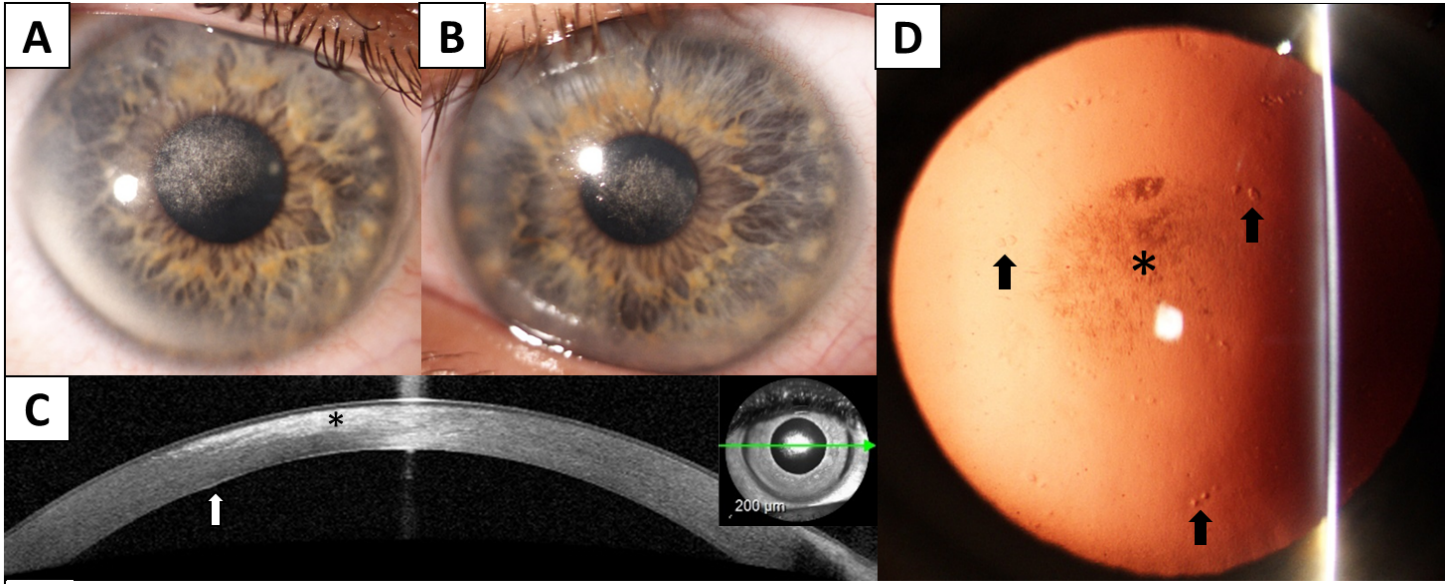
**Figure 1. Results of genetic testing and corneal findings in an individual affected simultaneously with posterior polymorphous corneal dystrophy type 3 (PPCD3) and Schnyder corneal dystrophy (SCD).** (A) Right and (B) left corneal photograph under direct illumination, note bilateral crystalline deposits and partial arcus lipoides in the right eye. (C) Spectral-domain optical coherence imaging in the right eye showing stromal opacification due to crystals, very mild increased reflexivity and unevenness of the posterior corneal surface (arrow). (D) Right cornea in retroillumination. Lesions typical for PPCD3 are marked with arrows, corneal deposits characteristic for SCD are indicated by asterisk. (E) Pedigree of the family showing mutational status of the tested subjects and sequence chromatograms of the mutations detected in *ZEB1* (reference sequence NM_030751.5) and *UBIAD1* (NM_013319.2).

**Supplementary Material** provides *in silico* analysis of novel *UBIAD1* variant and phenotypical data on first degree relatives of the proband.

**Supplementary Table 1:** *In silico* analysis of the effect of novel c.569T>C in *UBIAD1* variant identified in the current study.

**Supplementary Figure 1:** Anterior segment findings in first degree relatives with two distinct corneal dystrophies.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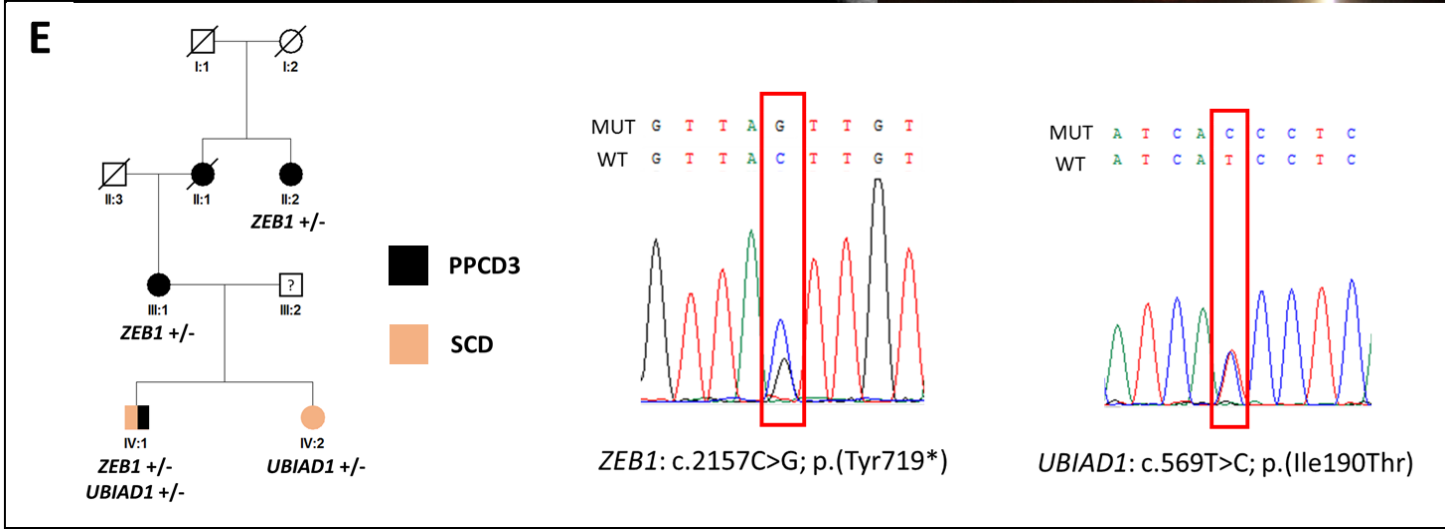
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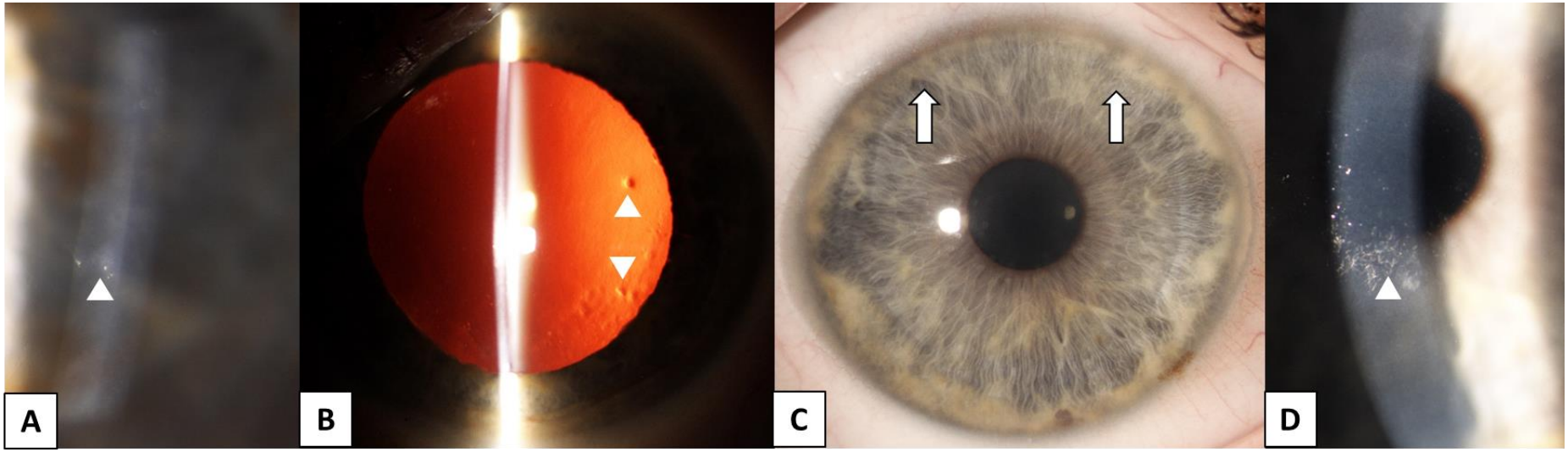
I:1
I:2
II:3
II:1
II:2
ZEB1 +/-
III:1
ZEB1 +/-
III:2
?
PPCD3
SCD
IV:1
ZEB1 +/-
UBIAD1 +/-
IV:2
UBIAD1 +/-
MUT G T T A G T T G T
WT G T T A C T T G T
ZEB1: c.2157C>G; p.(Tyr719*)
MUT A T C A C C C T C
WT A T C A T C C T C
UBIAD1: c.569T>C; p.(Ile190Thr)

**Supplementary Table 1:** *In silico* analysis of the effect of novel c.569T>C in *UBIAD1* variant identified in the current study.

| | PROVEAN[1] | PolyPhen2[2] | MutationTaster[3] | MutPred2[4] | SIFT[5] |
|---|---|---|---|---|---|
| c.569T>C p.(Ile190Thr) | **Deleterious** | **Possibly damaging** | **Disease causing** | **Damaging** | **Damaging** |

Using MutPred an overall probability score > 0.5 was considered as probably disease causing and a score > 0.75 was considered as disease causing. NM_032034.3 and; NP_114423.1 were used as reference sequences.




**Supplementary Figure 1:** Anterior segment findings in first degree relatives with two distinct corneal dystrophies.

A) Slit-beam view of the left cornea of individual III:1 (mother of the proband) and B) in retroillumination, arrowheads indicate posterior opacity typical for posterior polymorphous corneal dystrophy (type 3). C) Anterior segment photographs of the right eye of individual IV:2 (sister of the proband) showing incipient arcus lipoides (arrows) D) Wider slit-beam view of the right cornea highlighting the presence of pericentrally located corneal crystals characteristic of Schnyder corneal dystrophy (arrowhead).

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