Case report of a *PRDM5* linked brittle cornea syndrome type 2 in association with a novel *SLC6A5* mutation

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A 3-year-old girl presenting with blue sclera, hyperlaxity and developmental dysplasia of hip was found to have bilateral corneal thinning with astigmatism and keratoconus. By clinical exome sequencing, a frameshift mutation c.713_716 del TTTG p.(Val238Alafs*35) in *PRDM5* gene causing brittle cornea syndrome 2 and a novel frameshift mutation c.401dup p.(Ser135Glufs*53) in *SLC6A5* gene causing Hyperekplexia 3 were identified. No features of hyperekplexia were identified in proband. The novel homozygous mutation of *SLC6A5* gene in the proband was presently asymptomatic but they were apprised of the possibility of developing neurological symptoms in the later years.

Key words: Blue sclera, Brittle cornea syndrome, hyperekplexia, keratoconus

Brittle cornea syndrome (BCS), a rare autosomal recessive connective tissue disorder with extreme corneal thinning (220-450 microns) and fragility.[1,2] Other ocular features include blue sclera, corneal astigmatism, high myopia, keratoconus, keratoglobus and retinal detachment.[3] Systemic features are hearing defects, joint hypermobility, skin hyperelasticity, kyphoscoliosis and dental abnormalities.[4] Mutation in *ZNF469* (MIM: 612078) cause BCS type 1 and mutations in the *PRDM5*(MIM: 614161) cause BCS type 2.[1,3] Mutations in *PRDM5* produces abnormal fibrillar collagen affecting corneal integrity and alterations in retinal capillaries and Bruch's membrane.[5] Type 1 BCS has wrinkled skin involving palms and soles with scarring, molluscoid pseudotumors, and chestnut-coloured hair.[6,7] Whereas, in Type 2 the skin is soft with easy bruisabilty.[8] We found a mutation in the *PRDM5* in association with S*LC6A5* gene mutation while investigating a child with the bilateral blue sclera and corneal thinning. The *SLC6A5* gene encodes for a presynaptic glycine transporter,[9] and is known to cause hyperekplexia type 3, a neurological syndrome presenting either early or late. *PRDM5* gene mutation causing BCS has not been reported previously from India. A combination of these two recessive conditions has not been reported earlier in the world.

Access this article online	
Quick Response Code:	Website: www.ijo.in
	DOI: 10.4103/ijo.IJO_325_20

Case Report

We report a 3-year-old Indian girl, born to parents of second-degree consanguineous marriage. At birth, she had an Ortolani positive left hip instability and α angles on both sides were 59° which subsequently became 67° at 3 months. She also had blue sclera [Fig. 1]. Pedigree analysis showed no family history of ocular or any other genetic disorders.

At 3 years, due to her eye colour, she was re-examined to rule out collagen disorders. She was found to have hyperlaxity of joints showing 5/5 of Ruth Wynn Davies criteria. Her head circumference was 49 cm, height 94cm (between 50thand 75th centile), lower segment 46 cm and upper segment 48 cm; upper to lower segment ratio (US/LS) 1.04 (normal US/LS is 1.3 at 3 years of age), weight 13 kg (25th-50th centile), arm span 84 cm, and her hips were located. Her systemic and neurological examination was normal. Radiographs showed no fractures or spinal abnormality. Features of Ehler-Danlos, Osteogenesis imperfecta and Marfan syndrome were absent.

Her best corrected visual acuity (BCVA) using Kay pictures was 6/24, with -3.00 × 20^0 improving to 6/19 in the right eye (OD- oculus dextrus) and 6/48 with -3.00/-3.00 × 160^0 improving to 6/24 in the left eye (OS-oculus sinister). Ocular examination showed bilateral diffuse bluish discolouration of sclera. Slit lamp examination showed bilateral thin cornea. Rest of the ocular examination was normal.

Anterior segment optical coherence tomography (OCT-Topcon) showed bilateral thin cornea [Fig. 2]. Central corneal thickness measured using Nidek Optical Biometer

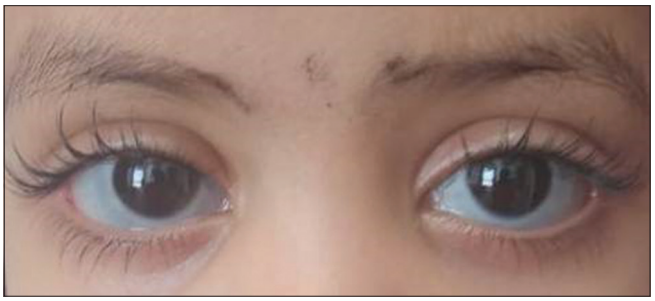

Figure 1: Face photograph showing blue sclera

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Received: 22-Feb-2020 Revision: 19-May-2020
Accepted: 10-Jul-2020 Published: 26-Oct-2020

Cite this article as: Selina A, John D, Loganathan L, Madhuri V. Case report of a *PRDM5* linked brittle cornea syndrome type 2 in association with a novel *SLC6A5* mutation. Indian J Ophthalmol 2020;68:2545-7.

was 266 μm in OD and 310 μm in OS. Corneal tomographic modelling system (TMS-Tomey) showed features suggestive of keratoconus in both eyes [Fig. 3].

Child was diagnosed to have bilateral thin cornea and sclera, with myopic astigmatism OD and compound myopic astigmatism OS with features of keratoconus in corneal tomography. These features combined with blue sclerae, hip dysplasia, hyperlaxity and absence of fractures suggested Brittle Cornea syndrome Type 2.

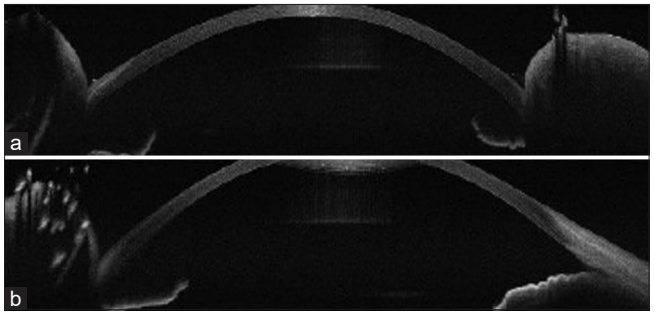

Figure 2: Optical coherence tomography (OCT-Topcon) showing bilateral thin cornea. (a- left eye, b-right eye)

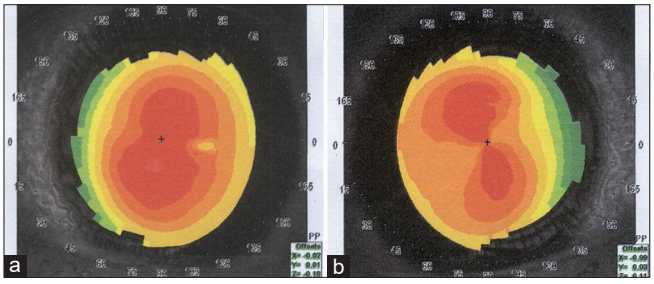

Figure 3: Corneal tomographic modelling system (TMS- Tomey) showed a keratometry reading of SKI 51.53 @1220/SK2 47.33 with a cylinder of 4.20 in OD and SK1 53.38@790/SK2 49.57 with a cylinder of 3.71 in OS with features suggestive of keratoconus in both eyes. (a- left eye, b-right eye)

An informed consent for genetic analysis was obtained, blood samples collected from the child, brother and parents and pedigree analysis was done. Clinical exome sequencing (CES) was performed by CENTOGENE AG (Rostock, Germany) using Illumina platform. A novel combination of *PRDM5* mutation with *SLC6A5* mutation was found.

Validation was done by Sanger sequencing for proband, brother and parent samples in-house to find the inheritance pattern. A homozygous frameshift variant NM_018699.3: c. 713_716 del TTTG p.(Val238Alafs*35) was identified in exon 6 of *PRDM5* gene resulting in premature termination codon. Parents and brother were heterozygous for the same mutation [Fig. 4]. A novel homozygous frameshift variant NM_004211.3: c.401dup p.(Ser135Glufs*53) was identified in exon 2 of *SLC6A5* in the proband and the brother, both parents being heterozygous [Fig. 4].

In view of the genetic diagnosis and ophthalmologic findings, the child was prescribed spectacles for refractive error. Parents were counselled regarding the chances of ocular rupture from trivial trauma and protective glasses were given. The family was provided with an information sheet on the phenotypic effects of *SLC6A5* mutation and the possibility of developing neurological symptoms in the fourth or fifth-decade requiring medication at that time.

Discussion

Molecular analysis of our patient identified a known homozygous frameshift variant in the *PRDM5* gene and a novel homozygous frameshift variant in *SLC6A5* gene. This novel c.401 dup p.(Ser135Glufs*53) variant of *SLC6A5* gene creates a shift in the reading frame starting at codon 135 and the new reading frame ends in a stop codon 52 positions downstream. These two genetic mutations cause BCS type 2 and Hyperekplexia type 3 respectively. BCS has been previously reported in families from the Middle East, China and Pakistan.[2,8,10-12] This particular PRDM5 mutation has been reported earlier.[8]

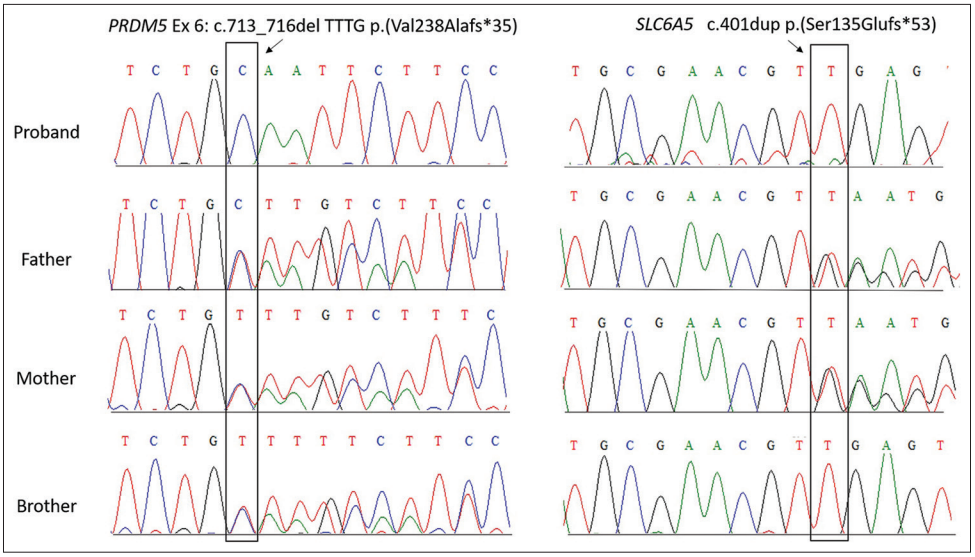

Figure 4: Proband showing homozygous c.713_716 del TTTG p. (Val238Alafs*35) mutation in exon 6 of *PRDM5;* Parents and brother were heterozygous. Proband and brother showing homozygous c.401dup p. (Ser135Glufs*53) in exon 2 of*SLC6A5* gene

The pathological variants are responsible for extracellular matrix development, collagen deposition, and collagen fibril assembly which determines the corneal thickness and its integrity. It also affects the development of retinal microvasculature and Bruch's membrane.[5] However, these abnormal retinal microvascular changes are evident only on immunohistochemistry.[13]

Hyperekplexia type 3 has been reported in families from Canada, Australia, USA, UK and Netherlands.[9,14] This child presented with features of minor developmental dysplasia of the hip, hyperlaxity with blue sclera, thin cornea, myopic astigmatism and keratoconus. BCS has been reported in association with Ehler-Danlos, osteogenesis imperfecta and Marfan syndrome.[2] The *SLC6A5* gene codes for an inhibitory neurotransmitter in the brain, spinal cord and retina causing minor and major forms of hyperekplexia.[15] There was no documentation of increased tone, startle reflex and neonatal apnoea in early infancy, or clumsiness and repeated falls in early childhood which are early manifestations.[14] Her sibling was homozygous for the *SLC6A5* gene mutation and asymptomatic.

Conclusion

In conclusion, we report a Brittle Cornea syndrome due to a *PRDM5* mutation unreported from India earlier. In addition, it is combined with hyperekplexia due to *SLC6A5* mutation. This combination has not been reported in the world earlier.

Acknowledgement

We thank the patient and their families for their participation in this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

This work was supported by the Department of Biotechnology, Government of India. Grant number BT/IN/SWEDEN/09/VM/2017. Indian council of Medical Research.Grant number:54/9/2015-HUM-BMS.

Conflicts of interest

There are no conflicts of interest.

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