Letter to the Editor

A novel mutation in PRDM5 in brittle cornea syndrome

To the Editor:

Brittle cornea syndrome (BCS) (MIM229200) is an autosomal recessive disorder characterized by abnormally fragile cornea that can easily rupture. It was debated whether BCS is a distinct disorder or a subtype of Ehler-Danlos syndrome (EDS VI specifically) (1). However, the demonstration of normal lysylpyridinoline to total hydroxylysylpyridinoline (typically abnormal in EDS VI) provided an early clue and the finding of ZNF469 mutations in BCS proved that BCS is indeed a distinct disorder albeit with overlapping phenotype (1–3). In this communication, we report the results of the molecular characterization of a BCS patient which led to the identification of a new genetic lesion.

Patient 1 is a 2-year-old Saudi girl with blue sclerae and keratoconus. Her parents are healthy first cousins and she has a healthy brother. Her development has been appropriate and her past medical history was negative for fractures or delayed healing. She had normal growth parameters, Stickler-like flat face, blue sclerae and Beighton score of 4 (Fig. 1). Skin displayed normal elasticity. Skeletal survey and hearing test were normal. Six months later, she sustained a trivial trauma to the right eye which resulted in corneal rupture necessitating surgical repair.

The diagnosis of BCS was made and patient was recruited under King Faisal Specialist Hospital and Research Centre (KFSHRC) Institution Review Board-approved protocol with written informed consent. ZNF469 was sequenced but no pathogenic mutations were identified. Autozygosity mapping as described before using Affymetrix Axiom platform and autoSNPa further ruled out ZNF469 (4). We hypothesized that BCS in this patient is caused by a homozygous mutation in another gene that resides in one of the runs of homozygosity (ROH) revealed by autozygosity mapping (Table S1). Therefore, we performed exome sequencing and only considered the novel coding (synonymous changes were excluded) and splice variants that overlap with this patient’s ROH which narrowed the search to two novel homozygous variants. By excluding the missense variant in BCO2 (NM_031938:exon10:c.1385G>A:p.G462D) due to

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Fig. 1. (a) and (b) Clinical photographs of index patient. Note the intense blue discoloration of the sclera and the remarkably flat stickler-like facies. (c) Algorithm used to filter the exome data. (d) Schematic of PRDM5 with the mutation indicated in red (upper panel) and the RT-PCR experiment showing failure of detection of exon 1 in the patient (lower panel).
low conservation score on PolyPhen we were left with a single mutation in the PRDM5 (NM_018699.2) c.93+2T>C (Fig. 1). This mutation abolishes the natural splice donor site of exon 1 as confirmed by RT-PCR from blood (Fig. 1). Both parents were heterozygous for this change and the unaffected brother was homozygous wild-type. Furthermore, in the course of this study, another group identified PRDM5 mutations in consanguineous Pakistani families with BCS using autozygosity mapping (5).

PRDM is a family of 17 genes in humans that encode transcriptional regulators affecting a wide array of cellular events particularly growth and may act as tumor suppressors (6). PRDM16 regulates murine cleft morphogenesis but no developmental role has been assigned to any PRDM in humans until the very recent identification of germline mutations in PRDM5 in patients with BCS (5, 7). Our study demonstrates that PRDM5 is indeed a second locus for BCS. Although there is no evidence of tumors in our patient or those reported recently, it is probably prudent to closely monitor these patients since PRDM5 is silenced in human breast, cervical, ovarian, and liver cancers by hypermethylation (8). It will also be of interest to monitor heterozygote carriers in the extended family for potential inflation of cancer risk.

In summary, we show that PRDM5 is a bona fide BCS locus. Our study also demonstrates the power of combining exome and autozygosity analysis as a tool to identify novel genetic causes of recessive disorders even in simplex cases.

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