Two novel variants and follow-up findings in four children with Bloom syndrome from two families

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List of key features

Bloom syndrome
BLM
Intrauterine growth restriction
Abnormal skin pigmentation
Cancer predisposition
Immunodeficiency

Introduction

Bloom syndrome (OMIM 210900) is a rare autosomal recessive severe intrauterine onset growth retardation (IUGR) syndrome characterized by craniofacial dysmorphism with a long-narrow face and prominent ears and nose, sun-sensitive skin lesions of the face and cancer predisposition. Postnatal growth deficiency, microcephaly, micrognathia, hypo and/or hyperpigmentation, immunodeficiency, insulin resistance, and in some patients developmental delay have been also reported (Flanagan and Cunniff, 2019). Bloom syndrome is caused by biallelic, loss-of-function mutations in the BLM gene which encodes the ATP-dependent DNA helicase RecQ that is involved in DNA replication and repair. Absent or nonfunctional BLM protein results in chromosome instability, excessive homologous recombination and increased frequency of sister chromatid exchange and is responsible for cancer predisposition. Patients with BS, therefore, have a high risk of developing almost all types of cancers at an earlier age and it is the most common cause of death (Kaneko & Kondo, 2004; Seif *et al.*, 2011).

Here, we present the follow-up findings and two novel variants in four children with Bloom syndrome.

Case reports

We present three patients from the same family and one patient from a second family. The histories are summarized briefly below and the clinical and molecular findings of the patients were summarized in Table 1.

Family 1

The first patient was a boy born to first-cousin parents. He had three healthy siblings. Patients 2 and 3 were sisters born to first-cousin, healthy parents who were third cousins once removed to patient 1 (Fig. 1a).

Patient 1 was a boy born at 40 weeks of gestation with IUGR. Birth weight was 2000 g. He had microcephaly, a long-narrow face, prominent ears and nose, micrognathia and both cafe au lait patches and hypopigmented lesions on his skin. He did not have any evidence of a sun-sensitive erythematous rash on his face. (Table 1, Fig. 1b,c). He started talking at the age of 4. Learning disability and IQ of 82 were detected at the age of 8. An anterior mediastinal mass was detected on his chest X-ray and he was diagnosed with non-Hodgkin lymphoma at the age of 18. His final height is –4.68 SDS.

Patient 2 was a girl born at the 40th week of gestation with IUGR. Birth weight was 1700 g. Her physical examination revealed microcephaly, a long-narrow face without any sun-sensitive erythematous rash, cafe au lait patches, a sacral dimple and a proximally located thumb (Fig. 1d–f). Her development was normal. However, IgG deficiency and recurrent infections were detected during follow-up.

Patient 3 was a 20-month-old girl who was the younger sibling of patient 2. She was born at the 40th week of gestation with IUGR and weighed 1520 g. Her dysmorphic facial findings were similar to her sister (Fig. 1g). She also had suffered from recurrent infections including bronchitis. Her biochemical tests revealed IgG deficiency. Her speech was delayed.

Family 2

Patient 4 was born at term with IUGR to first-cousin parents (Fig. 2a). Her birth weight was 1460 g. Her physical examination at 11 years and eight months revealed microcephaly, long-narrow face, hypoplastic alae nasi, multiple cafe au lait patches and a surgically corrected right congenital pes equinovarus together with a sandal gap (Fig. 2b–e). She did not have any sun-sensitive erythematous rash on the face. She received growth hormone treatment for about 4 years but gave up the treatment because of poor response to growth hormone injections.

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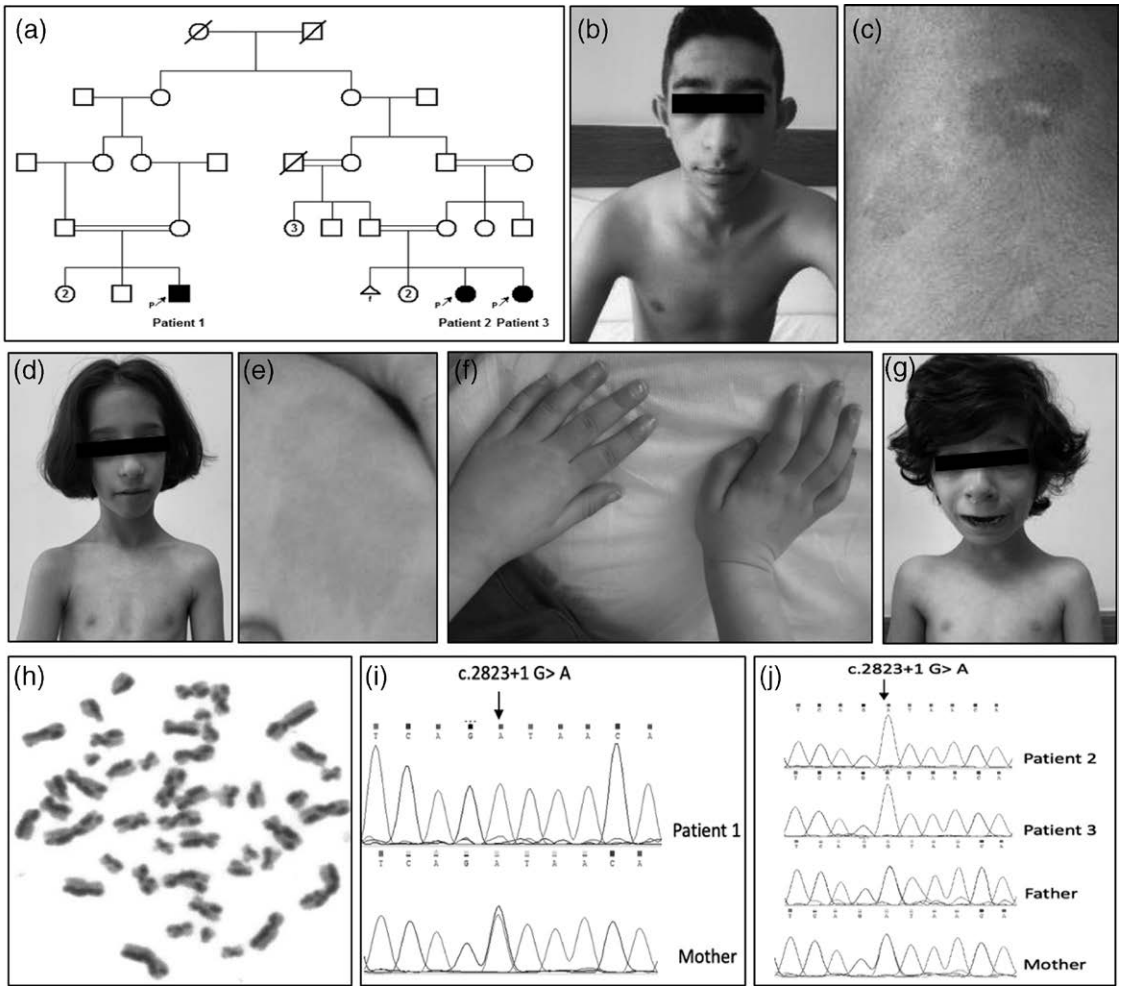
Table 1 Clinical and molecular findings of the patients with Bloom syndrome

	Family 1			Family 2
Features	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Men	Women	Women	Women
Age (first examination)	4 months old	11 months old	20 months old	11 years 8 months old
Age (current)	18 years 7 months old	7 years 7 months old	4 years 10 months old	17 years old
Weight at birth (g) (SDS)	2000 (−3.78)	1700 (−4.49)	1520 (−5.16)	1460 (−5.64)
Height (cm) (SDS)				
At birth	44 (−3.19)	45 (−2.39)	45 (−2.39)	NA
At first examination	56.5 (−2.88)	62 (−4.09)	67 (−4.79)	126 (−3.71)
Current	142 (−4.68)	110 (−2.81)	89 (−4.23)	134 (−4.9)
HC cm (SDS)				
At birth	NA	33 (−1.23)	28.5 (−4.51)	NA
At first examination	36 (−4.6)	38.5 (−5.18)	40 (−5.48)	46.5 (−4.99)
Current	49 (−6.42)	46 (−3.91)	42 (−5.87)	49 (−5.38)
Skin findings				
Cafe au lait spots	+	+	+	+
Hypo/hyperpigmented lesions	+	+	+	+
Acanthosis nigricans	−	−	−	+
Craniofacial findings				
Long-narrow face	+	+	+	+
Wide forehead	+	+	+	+
High palate	+	+	+	−
Prominent ears and nose	+	−	−	+
Micrognathia	+	−	+	−
Telangiectatic facial rash	−	−	−	−
Skeletal findings				
Proximally located thumb	+	+	+	−
Small hands	+	+	+	+
Clinodactyly	−	−	Bilateral	−
Sacral dimple	−	+	+	−
Pes equinovarus and sandal gap	−	−	−	+
Mental development	Speech delay Mild learning disability DQ:82	Normal	Speech delay	Normal
Endocrine disorders				
Hypothyroidism	+	−	+	+
Hyperinsulinism	−	−	−	+
Hypogenitalism	−	−	−	+
Immunological disorders				
Decreased IgA	+	−	−	−
Decreased IgG	−	+	+	−
Recurrent infections	−	+	+	+
Asthma	−	−	−	+
Malignancy	non-Hodgkin Lymphoma at 17 years of age	−	−	−
Other findings	Mild hearing loss Inguinal hernia	−	Mild hearing loss	Truncal obesity Small ovaries
Sister chromatid exchange	NA	Increased	NA	Increased
Biallelic variant in *BLM* gene (NM_000057)		c.2823+1G>A		c.3533delA (p.Thr1179LeufsTer3)
ACMG classification		Pathogenic PVS1, PM2, PP3		Pathogenic PVS1, PM2, PP3

HC, head circumference; Ig, immunoglobulin; SDS, SD score.

Fig. 1



Family pedigree of Family 1 (a). Patient 1 at the age of 17 showing his clinical features including long-narrow face, prominent ears and nose, micrognathia and microcephaly (b), cafe au lait patches and hypopigmented lesions (c). Patient 2 at the age of 7. Note long-narrow face, wide forehead, and microcephaly (d)), large cafe au lait patches (e), proximally located thumbs (f). Patient 3 at the age of 4. Note long face, micrognathia and microcephaly (g). Sister chromatid exchange test result of patient 2 showing increased frequency of SCE (h). Genetic sequencing chromatograms demonstrating that the patient 1 was homozygous and his mother was heterozygous for c.2823+1 G>A *BLM* gene variant (i). Genetic sequencing chromatograms revealing both patients 2 and 3 were homozygous whereas both parents were heterozygous for the c.2823+1 G>A *BLM* gene variant (j).

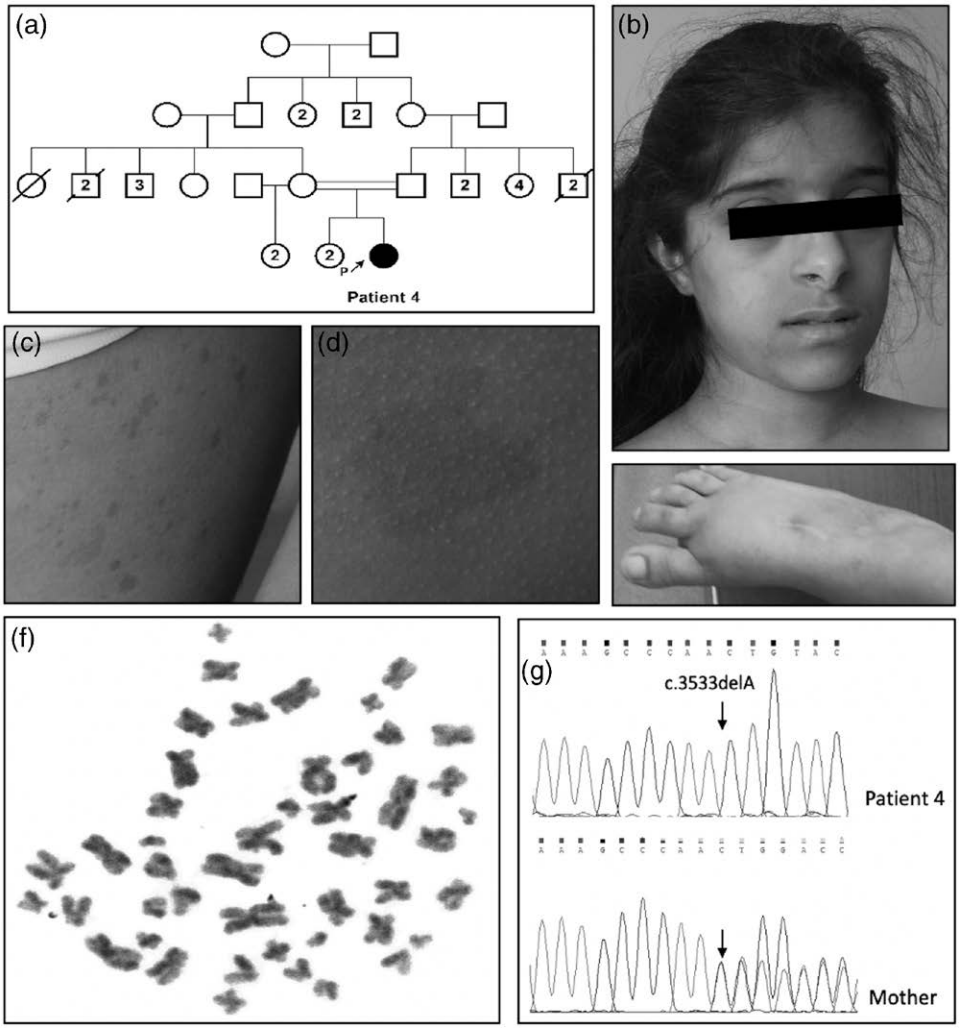
She had asthma. Her pelvic ultrasonographic examination revealed that her ovaries are smaller than normal at 17 years of age. She had her first menstrual period at the age of thirteen and since then she has had irregular periods (once in four or six months). Her intelligence is normal. Hyperinsulinism, hypothyroidism, truncal obesity and acanthosis nigricans occurring in the folds of the skin in axilla and elbow region developed during the follow-up period.

Genetic investigations

All participants provided written informed consent. The ethics committee of Cerrahpaşa medical faculty at Istanbul University-Cerrahpaşa approved the protocol. A sister chromatid exchange test (SCE test) revealed an increased frequency of sister chromatid exchange in patient 2 (40 SCE per metaphase) and patient 4 (19 SCE per metaphase) (Fig. 1h and Fig. 2f).

The *BLM* gene was screened using the Sanger sequencing method and a biallelic novel substitution in *BLM* (BLM:NM_000057.4: c.2823+1G>A) of patient 1 was identified (Table 1). This variant was not registered in the following databases: dbSNP, Clinvar and gnomAD. The variant was predicted to be pathogenic by Mutation Taster as it showed a probability value of 1 (value close to 1 indicates a high 'security' of the prediction). Varsome also classified this variant as pathogenic using ACMG criteria. This variant specifically alters the donor splice site changing from GT

Fig. 2



Family pedigree of family 2 (a). Patient 4 at the age of 11 showing her clinical features including narrow-long face, hypoplastic alae nasi, microcephaly (b) hyperpigmented area, cafe au lait patches, (c,d) sandal gap and surgically corrected pes equinovarus (e). Sister chromatid exchange test result of patient 4 revealing increased frequency (f) and genetic sequencing chromatograms demonstrating the patient 4 was homozygous and her mother was heterozygous for the c.3533delA *BLM* gene variant (g).

to AT and it is thus predicted to be disease-causing. Sanger sequencing for this variant was performed on the mother, patients 2 and 3 and their parents. The patients were homozygous for the variant whereas their parents were heterozygous for this variant (Fig. 1i,j). We identified a second biallelic novel variant in *BLM* (BLM:NM_001287247.1:c.3535delA, p.Thr1179LeufsTer3) gene in patient 4 (Table 1). This variant is predicted to be pathogenic by Mutation Taster and Varsome. The variant was validated by Sanger sequencing and her mother was proven to be heterozygous for the variant (Fig. 2g). This frameshift variant creates a premature stop codon at position 3 and it is predicted to cause a truncated or absent BLM protein due to nonsense-mediated mRNA decay.

Discussion

There are approximately 300 reported cases with Bloom syndrome (Campbell *et al*., 2018). In a comprehensive survey of 134 persons with Bloom syndrome from the Bloom syndrome Registry, 64 different disease-causing *BLM* variants were identified in 125 of them (German *et al*., 2007). In this study, we identified two further novel *BLM* variants.

All patients presented here present with most of the typical features of Bloom syndrome consisting of IUGR, characteristic facies, microcephaly and hypo/hyperpigmented lesions (Table 1, Figs. 1 and 2). They did not, however, have any sun-sensitive erythematous rash on the face nor on other parts of their body which is one of the main symptoms of Bloom syndrome. Bouman *et al*. (2018) also

described a woman with typical BS findings but without sun-sensitive facial erythema. Most Bloom syndrome patients are misdiagnosed as other rare disorders or even underdiagnosed due to the absence of typical sun-sensitive erythematous rash in the face. In addition, skeletal findings such as proximally located thumb, small hands, clinodactyly, pes equinovarus and the sandal gap that we detected in our patients (Table 1, Figs. 1,2) were not commonly reported.

The patients were followed up for 3–17 years. While current height SDS of patients 2 and 3 were –2.81 and –4.23 at 7 years and 7 months and 4 years and 10 months of age, respectively, patient 1 and 4 reached final heights of 142 and 134 cm, respectively (Table 1). Keller *et al.* (1999) reported that the mean final height is 148.5 cm for men and 141.5 cm for women in patients with BS. Growth hormone treatment is contraindicated in Bloom syndrome since there are reports of early onset of cancer in some GH-treated children (Renes *et al.*, 2013).

Immunodeficiency is one of the main features of Bloom syndrome. Schoenaker et al. (2018) reported in their study that their patients with BS had repeated ear infections, bronchitis, uveitis and low levels of immunoglobulins. In our study, patient 1 had IgA deficiency whereas patients 2 and 3 had IgG deficiency. Patients 2 and 3 had recurrent bronchitis and patient 4 had suffered from asthma.

Endocrine abnormalities such as hyperinsulinemia and hypothyroidism are common in patients with Bloom syndrome. Diaz *et al.* (2006) reported two patients with compensated hypothyroidism and six patients with hyperinsulinemia out of 11 patients with Bloom syndrome. In our study patients 1, 3 and 4 had developed compensated hypothyroidism between the age of 5–17. In addition, patient 4 had hyperinsulinemia coupled with acanthosis nigricans and truncal obesity. This patient also had small ovaries and irregular menstruation. Hypogenitalism has been reported previously in patients with BS (Cunniff *et al.*, 2017).

The great majority of the people with Bloom syndrome have intelligence within the normal range (Flanagan and Cunniff, 2019). In our study, patient 1 had speech delay and borderline intelligence with mild learning disability and patient 3 also had speech delay.

Cunniff *et al.* (2018) used the information from the Bloom syndrome registry and showed that half of the people reported in Bloom syndrome registry had developed malignancies and the most common malignancies among them are leukemia and lymphoma occurring at an earlier age than usual. At the age of 18, patient 1 was diagnosed with non-Hodgkin lymphoma.

In conclusion, we describe two novel variants in the *BLM* gene. Acanthosis nigricans and some of the skeletal findings in our patients were not previously reported. Recurrent infections, hypothyroidism, hyperinsulinism and hypogenitalism were observed during the followed-up period. Moreover, one patient was diagnosed with non-Hodgkin lymphoma at the age of 18. It is important that Bloom syndrome patients must be screened for cancer and other complications during their follow-up examination.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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