A Case of Bloom Syndrome With Uncommon Clinical Manifestations Confirmed on Genetic Testing

Wu Jian-Bing, MD; Li Cheng-Rang, MD; Ma Yi-Ping, MD; Sheng Nan, MS; Li Hui, MD; Lin Lin, MD

Bloom syndrome, a rare autosomal-recessive disorder, characteristically presents with photosensitivity, telangiectatic facial erythema, and growth deficiency. We present a case of Bloom syndrome with uncommon clinical manifestations including alopecia areata, eyebrow hair loss, flat nose, reticular pigmentation, and short sharpened distal phalanges with fingernails that were wider than they were long. We detected the Bloom syndrome gene, BLM, *which is one of the members of the RecQ family of DNA helicases, and found changes in 2 heterozygous nucleotide sites in the patient as well as her father and mother.*

Cutis. 2016;97:E10-E13.

Bloom syndrome, also called congenital telangiectatic erythema and stunted growth, was first described by David Bloom in 1954.[1] It is a rare autosomal-recessive disorder (Online Mendelian Inheritance in Man 210900) characterized by specific clinical manifestations including photosensitivity, telangiectatic facial erythema, proportionate growth deficiency, hypogonadism, immunodeficiency, and a tendency to develop various malignancies.[2] Linkage analysis revealed that the Bloom syndrome gene locus resides on chromosome arm 15q26.1,[3] and the *BLM* gene in this region has been identified as being responsible for the development of Bloom syndrome.[4,5] We report the case of a 12-year-old Chinese girl with Bloom syndrome and detected *BLM* gene. The evaluation was approved by the Institutional Ethical Review Boards of Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China).

Case Report

We evaluated a Bloom syndrome family, which consisted of the patient and her parents. The patient was a 12-year-old Chinese girl who was apparently healthy until 3 months of age when her parents noticed an erythematous eruption with blisters on the face. Exacerbation after exposure to sunlight is usual, which results in the eruption becoming prominent in summer and fainter in winter.[2] Gradually, the patient's skin lesions became more progressive, extending to the forehead, nose, and ears, with oozing, crusting, atrophy, and telangiectases developing on the face despite treatment. In the last 3 years, no blisters were present on the patient's face because of her efforts to avoid sun exposure. She had no history of recurrent infections.

On physical examination, the patient was generally healthy with normal intelligence and short stature. She weighed 26 kg and was approximately 122-cm tall. Telangiectatic erythema and slight scaling were noted on the face, which simulated lupus erythematosus (Figures 1A and 1B). She had additional abnormalities including alopecia areata (Figure 1C), eyebrow hair loss, flat nose, reticular pigmentation on the forehead and trunk, and finger swelling. The distal phalanges on all 10 fingers became short and sharpened and the fingernails

From the Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China.

The authors report no conflict of interest.

This article was supported by the China Central Public Welfare Research Foundation (grant 303-05-7059) and the National Natural Science Foundation of China (grant 81472872).

Correspondence: Lin Lin, MD, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, 12 Jiang-Wang-Miao St, Nanjing, Jiangsu, 210042 China (dr_linlin2011@aliyun.com).

became wider than they were long (Figure 1D). Laboratory investigations, including a complete blood cell count, liver and kidney function tests, stool examination, serum complement, and albumin and globulin levels, were within reference range.

After informed consent was obtained, a mutation analysis of the *BLM* gene was performed in the patient and her parents. We used a genomic DNA purification kit to extract genomic DNA from peripheral blood according to the manufacturer's protocol. Genomic DNA was used to amplify the exons of the *BLM* gene with intron flanking sequences by polymerase chain reaction with the primer described elsewhere.[6] After the amplification, the polymerase chain reaction products were purified and the *BLM* gene was sequenced. Sequence comparisons and analysis were performed using Phred/Phrap/Consed version 12.0.

The patient was found to carry changes in 2 heterozygous nucleotide sites, including c.2603C>T in exon 13 and c.3961G>A in exon 21 of the *BLM* gene. The patient's father was found to carry c.2603C>T and her mother carried c.3961G>A (Figure 2).

Comment

Patients with Bloom syndrome have a characteristic clinical appearance that typically includes photosensitivity, telangiectatic facial erythema, and growth deficiency. Telangiectatic erythema of the face develops during infancy or early childhood as red

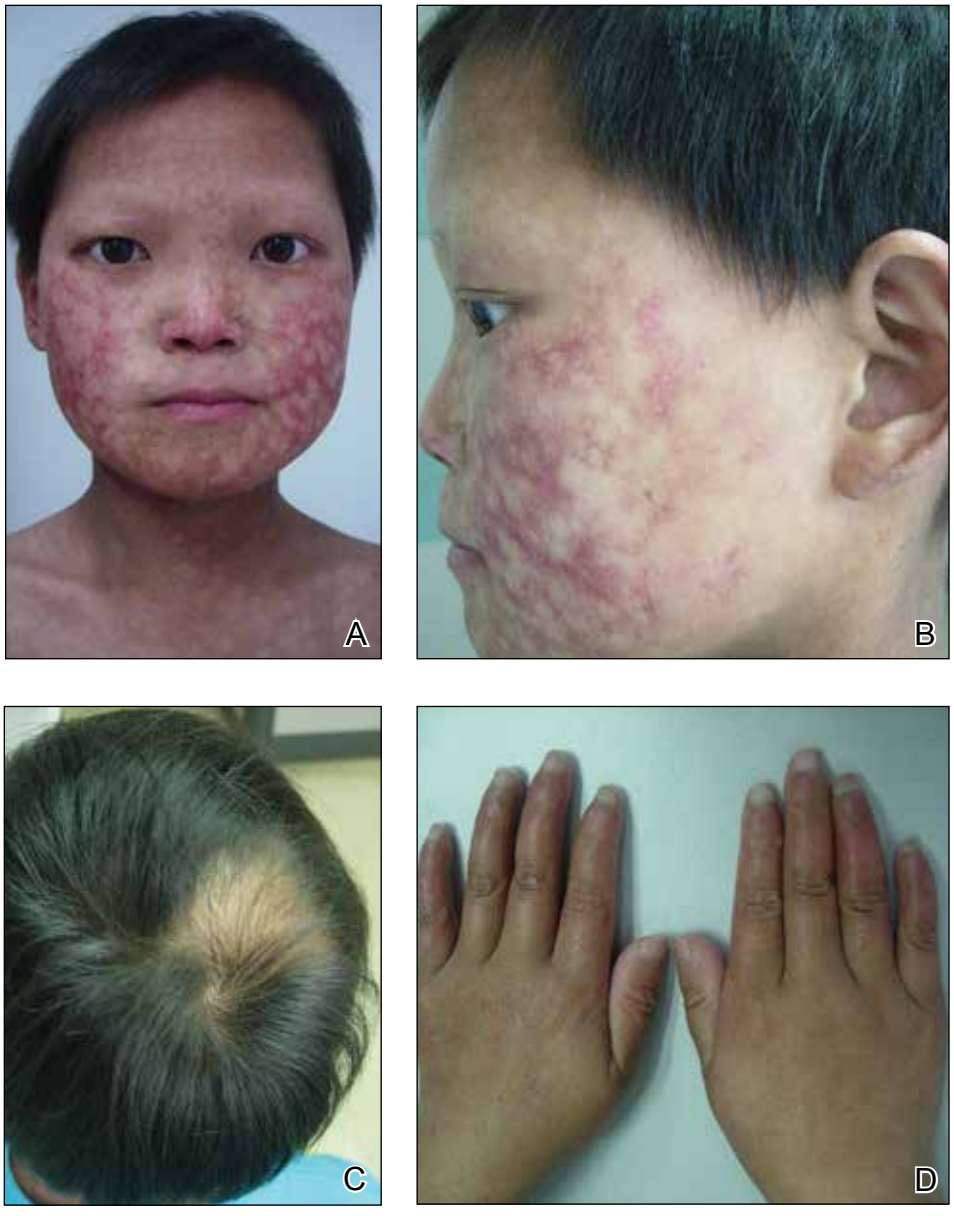

Figure 1. Uncommon clinical findings of telangiectatic facial erythema, eyebrow hair loss, and reticular pigmentation on the forehead (A), flat nose (B), alopecia areata (C), and short sharpened distal phalanges that were wider than the length of the fingernails (D) in a 12-year-old Chinese girl with Bloom syndrome that was confirmed on genetic testing.

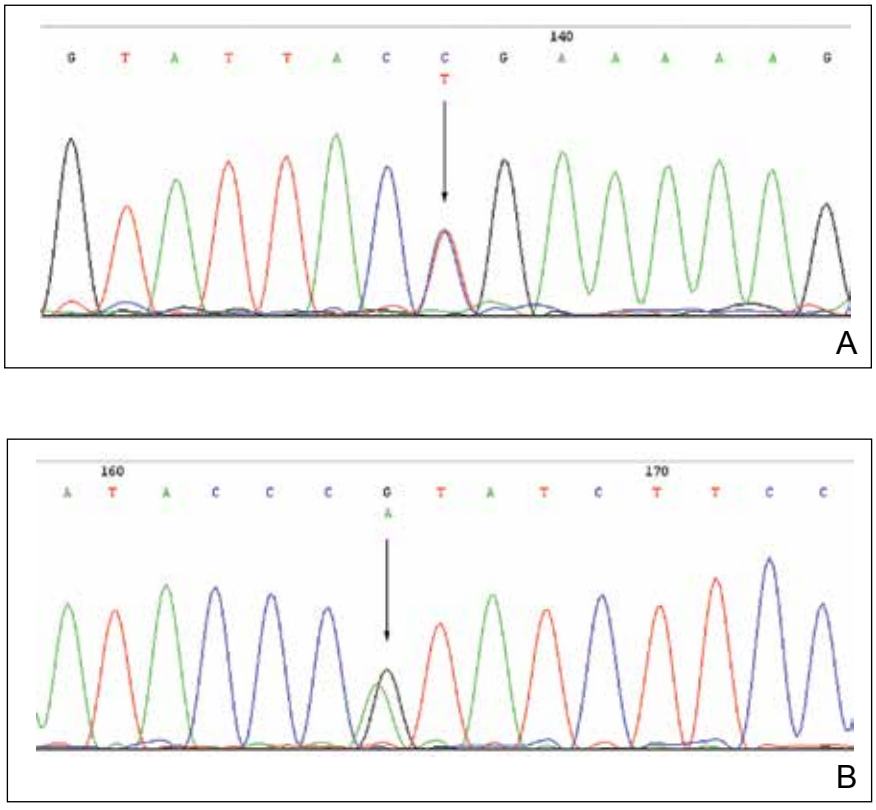

Figure 2. Changes in 2 heterozygous nucleotide sites: c.2603C>T in exon 13 (A) and c.3961G>A in exon 21 (B) of the *BLM* gene. The patient's father was found to carry c.2603C>T and her mother carried c.3961G>A.

macules or plaques and may simulate lupus erythematosus. The lesions are described as a butterfly rash affecting the bridge of the nose and cheeks but also may involve the margins of the eyelids, forehead, ears, and sometimes the dorsa of the hands and forearms. Moderate and proportionate growth deficiencies develop both in utero and postnatally. Patients with Bloom syndrome characteristically have narrow, slender, distinct facial features with micrognathism and a relatively prominent nose. They usually may have mild microcephaly, meaning the head is longer and narrower than normal.[2,7-10]

German and Takebe[11] reported 14 Japanese patients with Bloom syndrome. The phenotype differs somewhat from most cases recognized elsewhere in that dolichocephaly was a less constant feature, the facial skin was less prominent, and life-threatening infections were less common. Our patient had typical telangiectatic facial erythema without microcephaly, dolichocephaly, or any infections. She also had some uncommon manifestations such as alopecia areata, eyebrow hair loss, flat nose, reticular pigmentation, and short sharpened distal phalanges with fingernails that were wider than they were long. Although she had no recurrent infections and laboratory tests were within reference range, the alopecia areata and eyebrow hair loss may be associated with an abnormal immune response. The reasons for the short sharpened distal phalanges and the fingernail findings are unclear. The presence of reticular pigmentation also is unclear but may be associated with photosensitivity. Since the *BLM* gene was discovered to be the disease-causing gene of Bloom syndrome in 1995,[4,5] approximately 70 mutations were reported. The *BLM* gene encodes for the Bloom syndrome protein, a DNA helicase of the highly conserved RecQ subfamily of helicases, a group of nuclear proteins important in the maintenance of genomic stability.[12]

Mutation analysis of the *BLM* gene in our patient showed changes in 2 heterozygous nucleotide sites, including c.2603C>T in exon 13 and c.3961G>A in exon 21 of the *BLM* gene, which altered proline residue with leucine residue at 868 and valine residue with isoleucine residue at 1321, respectively. According to GenBank,[13,14] c.2603C>T and c.3961G>A are single nucleotide polymorphisms of the *BLM* gene. The genotypic distribution of International HapMap Project[15] showed that C=602/602 and T=0/602 on c.2603 in 301 unrelated Chinese patients and G=585/602 and A=17/602 on c.3961 in 301 unrelated Chinese patients. Because of the low prevalence of genotypes c.2603T and

c.3961A in China, the relationship between clinical features and c.2603C>T and c.3961G>A of the *BLM* gene in our patient requires further study.

In conclusion, we report a patient with Bloom syndrome with uncommon clinical manifestations. Our findings indicate that c.2603C>T and c.3961G>A of the *BLM* gene may be the pathogenic nature for Bloom syndrome in China.

Acknowledgments—The authors would like to thank the patient and her family for their participation in the study. The authors also thank Li Qi, BA, Beijing, China, for his contribution to the review of the data in the literature.

REFERENCES

1. Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. *AMA Am J Dis Child*. 1954;88:754-758.
2. German J. Bloom's syndrome, I: genetical and clinical observations in the first twenty-seven patients. *Am J Hum Genet*. 1969;21:196-227.
3. German J, Roe AM, Leppert MF, et al. Bloom syndrome: an analysis of consanguineous families assigns the locus mutated to chromosome band 15q26.1. *Proc Natl Acad Sci U S A*. 1994;91:6669-6673.
4. Passarge E. A DNA helicase in full Bloom. *Nat Genet*. 1995;11:356-357.
5. Ellis NA, Groden J, Ye TZ, et al. The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell*. 1995;83:655-666.
6. German J, Sanz MM, Ciocci S, et al. Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. *Hum Mutat*. 2007;28:743-753.
7. Landau JW, Sasaki MS, Newcomer VD, et al. Bloom's syndrome: the syndrome of telangiectatic erythema and growth retardation. *Arch Dermatol*. 1966;94:687-694.
8. Gretzula JC, Hevia O, Weber PJ. Bloom's syndrome. *J Am Acad Dermatol*. 1987;17:479-488.
9. Passarge E. Bloom's syndrome: the German experience. *Ann Genet*. 1991;34:179-197.
10. German J. Bloom's syndrome. *Dermatol Clin*. 1995;13:7-18.
11. German J, Takebe H. Bloom's syndrome, XIV: the disorder in Japan. *Clin Genet*. 1989;35:93-110.
12. Bennett RJ, Keck JL. Structure and function of RecQ DNA helicases. *Crit Rev Biochem Mol Biol*. 2004;39:79-97.
13. Reference SNP (refSNP) Cluster Report: rs2227935. National Center for Biotechnology Information website. http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2227935. Accessed February 3, 2016.
14. Reference SNP (refSNP) Cluster Report: rs7167216. National Center for Biotechnology Information website. http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=7167216. Accessed February 3, 2016.
15. Homo sapiens:GRCh37.p13 (GCF_000001405.25) Chr 1 (NC_000001.10):1 - 249.3M. National Center for Biotechnology Information website. http://www.ncbi.nlm.nih.gov/variationtools/1000genomes/?=%EF%BC%86=. Accessed February 3, 2016.