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Bloom Syndrome

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Summary

Clinical characteristics

Bloom syndrome (BSyn) is characterized by severe pre- and postnatal growth deficiency, immune abnormalities, sensitivity to sunlight, insulin resistance, and a high risk for many cancers that occur at an early age. Despite their very small head circumference, most affected individuals have normal intellectual ability. Women may be fertile but often have early menopause, and men tend to be infertile, with only one confirmed case of paternity. Serious medical complications that are more common than in the general population and that also appear at unusually early ages include cancer of a wide variety of types and anatomic sites, diabetes mellitus as a result of insulin resistance, chronic obstructive pulmonary disease, and hypothyroidism.

Diagnosis/testing

The diagnosis of BSyn is established in a proband with characteristic clinical features and biallelic pathogenic variants in *BLM* identified by molecular genetic testing.

Management

Treatment of manifestations: Increased-calorie-density formulas and foods may promote weight gain; consultation with gastroenterologist or feeding specialist and treatment for gastroesophageal reflux disease as needed; standard dietary treatment for dyslipidemia. Skin protection, including avoiding excessive sun exposure, sun-protective clothing and broad-brimmed hat, UV-blocking sunglasses, and use of broad-spectrum sunscreen with SPF of at least 30; standard treatment of skin cancers. Individuals with recurrent infections and defects in humoral immunity may be treated with immunoglobulins to decrease frequency and severity of infections. Developmental services and educational support as needed. In persons with cancer, modification of chemotherapy dosage and duration per oncologist. Fertility treatments as needed; standard treatment of diabetes mellitus and hypothyroidism. Cough assist devices, vibration vests, and daily nasal lavage for mucociliary clearance for bronchiectasis.

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Surveillance: Monitor growth, feeding, and for gastroesophageal reflux at each visit throughout childhood; annual lipid profile beginning at age ten years. Skin exam with a dermatologist upon recognition of suspicious skin lesions and annually thereafter. Assess for recurrent, severe, or opportunistic infections at each visit. Developmental, neurobehavioral, and psychological assessment as needed. Clinical assessment for hematuria and/or abdominal mass and abdominal ultrasound examination every three months until age eight years for Wilms tumor. Screening and family education regarding signs and symptoms of leukemia and lymphoma at every health visit. Whole-body MRI every one to two years beginning at age 12 to 13 years for risk of lymphoma. Annual colonoscopy beginning at age ten to 12 years. Fecal immunochemical testing every six months beginning at age ten to 12 years. Annual breast MRI in women beginning at age 18 years. Annual fasting blood glucose and hemoglobin A1c beginning at age ten years. Annual serum TSH with reflex to thyroxine beginning at age ten years. Assess for recurrent and/or chronic pulmonary disease at each visit.

Agents/circumstances to avoid: Sun exposure to the face and other exposed skin, particularly in infancy and early childhood, should be avoided. Exposure to ionizing radiation should be minimized. Dose reductions and shortened courses of chemotherapy when needed to avoid significant side effects and toxicity (including secondary malignancies). Alkylating agents and radiation therapy are considered high risk and are avoided when possible in those with BSyn.

Evaluation of relatives at risk: It is appropriate to evaluate sibs of a proband in order to identify as early as possible those who would benefit from avoidance of sun exposure and early surveillance for cancer.

Genetic counseling

BSyn is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *BLM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being a heterozygote (carrier), and a 25% chance of inheriting neither of the familial pathogenic variants. Heterozygotes (carriers) are not at risk of developing BSyn; the cancer risk of heterozygotes as a group remains unclear. Once the *BLM* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible. BSyn is included on most expanded carrier screening panels.

Diagnosis

Suggestive Findings

Bloom syndrome (BSyn) **should be suspected** in an individual with any of the following clinical or cytogenetic findings.

Clinical findings

- Prenatal-onset growth deficiency that usually affects linear growth, weight gain, and head circumference and that persists into infancy, childhood, and adulthood
- Moderate-to-severe growth deficiency and a sun-sensitive, erythematous rash that commonly involves the face and appears in a butterfly distribution
- Moderate-to-severe growth deficiency and a diagnosis of cancer, usually occurring at an earlier age than in the general population

Cytogenetic findings. Increased numbers of sister-chromatid exchanges (SCEs)

Establishing the Diagnosis

The diagnosis of BSyn **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in *BLM* identified by molecular genetic testing (see Table 1).

Note: (1) An increased frequency of SCEs on specialized cytogenetic studies may be helpful in circumstances where *BLM* variant analysis is inconclusive. SCE analysis alone is not sufficient to confirm a diagnosis of BSyn because increased SCEs are also observed in persons with biallelic pathogenic variants in *RMI1*, *RMI2*, and *TOP3A* [Hudson et al 2016, Martin et al 2018]. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *BLM* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *BLM* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Bloom Syndrome

Gene [1]	Method	% of Pathogenic Variants [2] Identified by Method
BLM	Sequence analysis [4]	96%-97% [3]
	Gene-targeted deletion/duplication analysis [5]	3%-4% [3]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. See Bloom Syndrome Registry.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Other Testing

Sister-chromatid exchanges (SCEs). Individuals with BSyn have a mean of 40-100 SCEs per metaphase (normal SCEs: <10 per metaphase). Increased frequency of SCEs is demonstrable in BSyn cultured cells (including lymphocytes, fibroblasts, and amniocytes) allowed to proliferate in a medium containing 5-bromo-2'-deoxyuridine (BrdU). Increased SCEs are not unique to BSyn. Three additional autosomal recessive disorders (*RMI1*-, *RMI2*-, and *TOP3A*-related disorders) are associated with increased SCEs and similar clinical findings to individuals with BSyn. SCE analysis may be a useful adjunct for diagnosis of BSyn, in the circumstance where only one *BLM* pathogenic variant is identified, and molecular genetic testing finds no pathogenic variants in *RMI1*, *RMI2*, or *TOP3A*. The presence of increased SCEs alone, however, is not sufficient to confirm the diagnosis of BSyn.

Clinical Characteristics

Clinical Description

The range of clinical features in persons with Bloom syndrome (BSyn) has been tracked through the Bloom Syndrome Registry. The clinical and genetic histories have been obtained from registered persons diagnosed between 1954 and 2023, and their clinical courses have been followed [German & Passarge 1989, German 1993, German & Ellis 2002]. The main clinical features of BSyn are discussed here.

Growth deficiency. The most consistent clinical feature of BSyn seen throughout all stages of life is growth deficiency affecting height, weight, and head circumference. Body proportions are normal.

The affected fetus is smaller than normal for gestational age. The mean birth weight of affected males is 1,760 g (range: 900-3,189 g) and of affected females, 1,754 g (range: 700-2,892 g). The average adult height of men is 149 cm (range: 128-164 cm) and of women, 138 cm (range: 115-160 cm).

Plasma growth hormone concentration is normal. Growth hormone therapy has not consistently increased growth rate in most persons, but some have experienced improved linear growth.

Subcutaneous adipose tissue is sparse throughout childhood and adolescence, but adults may develop central obesity. Providing increased calories in childhood and adolescence does not usually result in substantial changes in growth parameters, particularly linear growth. Studies of small cohorts have shown that supplemental feeding may result in increased fat deposition in individuals with BSyn. In addition, lipid profile abnormalities were identified in five of ten individuals tested [Diaz et al 2006].

Serial measurements of 136 individuals with BSyn (81 male, 55 female) showed that mean head circumference was below normal at all ages [Keller et al 1999]. The head shape is often described as long and narrow [Cunniff et al 2017].

Feeding problems. Most parents report that feeding is an issue for their newborns, infants, and young children. Many infants have had gastrostomy tubes placed. In a minority of infants with BSyn, nursing and eating are normal. The child with BSyn characteristically eats slowly, has a decreased appetite, and eats a limited variety of foods. Due to poor weight gain, formula and nutritional supplements with increased caloric density are prescribed in infancy and childhood. Despite these maneuvers, weight gain continues to be modest, and children rarely have a normal weight for age. Gastroesophageal reflux is common and may contribute to the feeding issues.

Facial features. The facial appearance of people with BSyn is variable and may be indistinguishable from unaffected persons of similar age and size. More commonly, the face appears narrow, with underdeveloped malar and mandibular prominences and retrognathia or micrognathia (see Figure 1). A paucity of subcutaneous fat may cause the nose and/or ears to appear prominent.

Skin lesions. The skin at birth and during early infancy appears normal; however, typically following sun exposure during the first or second year of life, a red, sun-sensitive rash appears on the nose and cheeks and sometimes also on the dorsa of the hands and forearms (see Figure 1). This rash varies in severity and extent among affected individuals; in some, it is minimal. It is usually characterized by telangiectasia but in others is described as poikiloderma. In severely affected individuals, the lesion can be bright red and can extend onto adjacent areas.

Additional dermatologic manifestations include cheilitis, blistering and fissuring of the lips, eyebrow and eyelash hair loss, alopecia areata, and vesicular and bullous lesions with excessive or intense sun exposure. Café au lait macules and areas of hypopigmented skin are more numerous and larger than in those without BSyn.

Immunodeficiency. In children and adults who have had laboratory evaluation of their immune system, the concentration of one or more of the plasma immunoglobulins is usually abnormally low. IgM and IgA levels are most commonly affected. Although the numbers of T and B cells are usually normal, variable abnormalities of the adaptive immune system suggest a possible role in the frequent infections reported in affected individuals.

Infections. Parents of children with BSyn report that their affected children have more childhood infections than their sibs and peers; none, however, has had an opportunistic infection, and few persons with BSyn have had bacterial sepsis, meningitis, or pneumonia.

Fertility. Most men with BSyn assessed for infertility have had azoospermia or severe oligospermia. There is, however, one confirmed case of paternity [Ben Salah et al 2014]. Women with BSyn, although often fertile, may enter menopause prematurely. Eleven women with BSyn followed in the Bloom Syndrome Registry have become pregnant at least once; seven of them have delivered a total of 11 healthy babies of normal size.

Intelligence. There are no systematic studies of academic achievement or cognitive performance in persons with BSyn. The great majority appear to perform within the normal range of intellectual development. Some have required academic support for attention-related issues and task orientation, but it is not clear that the prevalence of these problems is different from that seen in the general population. Many others have excelled in school, with some earning graduate degrees.

Other clinical features. Major anatomic defects are not increased in frequency. In the 294 persons in the Bloom Syndrome Registry as of 2023, only single examples of the following have occurred: tracheoesophageal fistula, cardiac malformation, absent thumbs, and absence of a toe and malformation of a thumb.

Medical complications of BSyn include cancer, diabetes mellitus, pulmonary disease, and hypothyroidism.

Cancer is the most frequent medical complication and the most common cause of death in individuals with BSyn. Although the wide distribution of cell types and anatomic sites of cancer resemble that in the general population, it occurs more frequently and at much earlier ages in individuals with BSyn. Development of multiple cancers in a single individual is also much more common. Table 2 summarizes the 251 malignant neoplasms diagnosed in 155 persons followed in the Bloom Syndrome Registry from 1954 to 2022.

Table 2. Malignant Neoplasms Diagnosed in Persons in the Bloom Syndrome Registry (1954-2022)

Malignancy Type/Tissue	Subtype	Frequency	Age at Diagnosis (Years)		
			Median	Mean	Range
Leukemia	Acute myeloid	22	18	18	2-39
	Acute lymphoblastic	13	15	18	4-40
	Other/biphenotypic/undefined	6	16	18	4-39
Lymphoma	--	42	23	23	4-49
Oropharyngeal	Tongue	10	39	40	30-48
	Pharynx	7	32	34	30-45
	Tonsil	4	39.5	37.5	25-46
	Other	7	31	30	25-34
Upper GI	Esophageal	5	39	37	25-48
	Gastric	7	27	30	21-49
	Other	1	NA	NA	NA
Colorectal	--	30	36	35	16-49
Genitourinary	Cervical	5	22	22	19-23
	Testicular	3	22	19	10-26
	Other	6	41	42	33-54
Breast	--	29	32	33	18-52
Skin	Basal cell	18	32	33	18-55
	Squamous cell (uncategorized)	8	35	34	25-42
	Other/undefined	3	35	34	25-42
Wilms tumor	--	9	3	4	1-11
Lung	--	4	36.5	36	32-40
All other	--	8	NA	NA	NA

Adapted from Sugrañes et al [2022]
GI = gastrointestinal; NA = not applicable

Myelodysplasia has been diagnosed in 24 persons in the Bloom Syndrome Registry at a median age of 23 years (range: 3-47), and it has progressed to acute myelogenous leukemia in at least seven. In all but three individuals, myelodysplasia was preceded by some form of cancer for which chemotherapy and/or radiotherapy had been administered.

Diabetes mellitus. Abnormalities in insulin release and glucose tolerance have been detected in the eight healthy children (ages nine months to 13 years) and the three healthy young adults with BSyn (ages 22, 28, and 28 years) appropriately studied [Diaz et al 2006]. Because of insulin resistance, BSyn-related diabetes mellitus resembles type 2 diabetes but has a much earlier age of onset. Paradoxically, diabetes in persons with BSyn commonly

occurs in the setting of low body mass index (BMI), rather than high BMI. Diabetes has been diagnosed in 51 of 294 persons in the Bloom Syndrome Registry (17.3%) at a mean age of 26.2 years (range: 4-48 years). Although most individuals do not have severe complications, a small number of individuals have required insulin or have developed retinopathy.

Chronic obstructive pulmonary disease. Chronic bronchitis and bronchiectasis are common, and pulmonary failure has been the cause of death in six persons.

Hypothyroidism has been recorded in 14 persons in the Bloom Syndrome Registry. Thyroid hormone replacement therapy (levothyroxine) is the commonly reported treatment for underactive thyroid in individuals with BSyn.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

Few individuals with BSyn have been reported in the medical literature since its description half a century ago [Bloom 1954], and currently 294 individuals are known to the Bloom Syndrome Registry.

Although rare in all populations, BSyn is relatively less rare among individuals of Ashkenazi Jewish descent. The predominant *BLM* pathogenic variant identified in individuals of Ashkenazi Jewish descent is c.2207_2212delinsTAGATTC, designated blm^{Ash}. The approximate carrier frequency of the blm^{Ash} allele is 1/157 Ashkenazi Jews dwelling in the United States [Fares et al 2008] and 1/111 Ashkenazi Jews dwelling in Israel [Peleg et al 2002].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *BLM*.

Differential Diagnosis

Genetic disorders of interest in the differential diagnosis of Bloom syndrome are listed in Table 3.

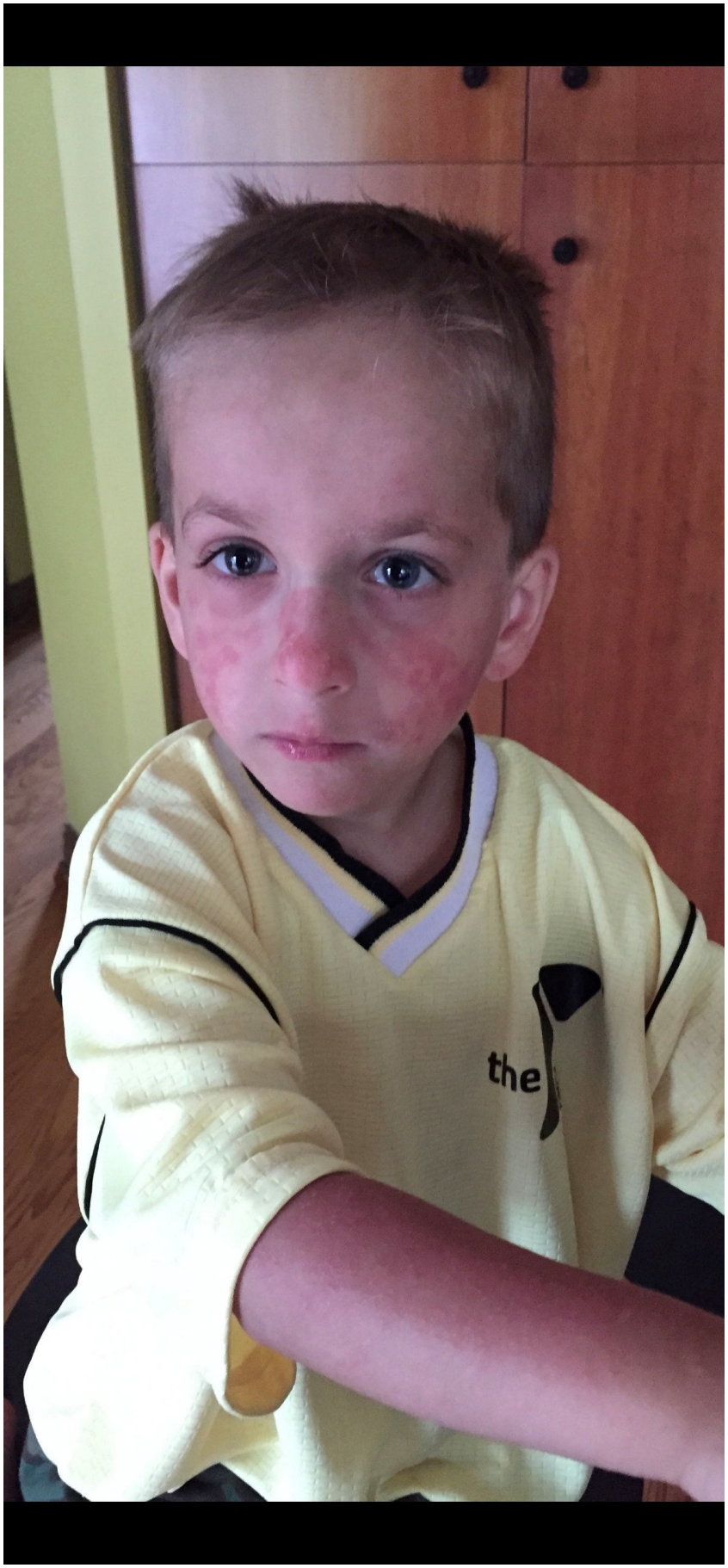

Figure 1. Individual with Bloom syndrome showing characteristic long, narrow face and erythematous rash.

Reproduced with permission from Cunniff et al [2017]

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of Bloom Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/BSyn	Distinguishing from BSyn
Disorders w/↑ SCEs & similar clinical findings to BSyn				
RMI1 [1]	RECQ-mediated genome instability 1 (OMIM 610404)	AR	Small size	• To date, cancer not observed, but reported persons are all relatively young. • No abnormal skin findings
RMI2 [1]	RECQ-mediated genome instability 2 (OMIM 612426)	AR	• Small size • Café au lait macules	To date, cancer not observed, but reported persons are all relatively young.
TOP3A [1]	Microcephaly, growth restriction, & ↑ sister-chromatid exchange 2 (OMIM 618097)	AR	• Small size • Café au lait macules • 1 person w/cervical cancer in early adulthood [2]	• No malar rash • Cardiomyopathy [2]
Disorders w/similar clinical findings to BSyn, but not assoc w/↑ SCEs				
Multiple etiologies incl: chromosome 11p15 hypomethylation & matUPD7 [3]	Silver-Russell syndrome	See footnote 3.	Growth deficiency	Ophthalmalogic abnormalities
ATM	Ataxia-telangiectasia	AR	• Small stature • Evidence of excessive genomic instability • Telangiectasias • Sinopulmonary infection • Immunodeficiency	• Progressive cerebellar ataxia from early childhood • ↑ alpha-fetoprotein levels
23 genes incl: *FANCA* *FANCC* *FANC* [4]	Fanconi anemia	AR (AD XL) [5]	• Small stature • Evidence of excessive genomic instability • ↑ cancer susceptibility • Café au lait macules, hyper- or hypopigmentation • ↓ fertility • Endocrinopathy	• Skeletal malformations • Bone marrow failure
MRE11	Ataxia-telangiectasia-like disorder (OMIM 604391)	AR	• Small stature • Evidence of excessive genomic instability	• Progressive cerebellar degeneration • No telangiectasias or immunodeficiency

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/BSyn	Distinguishing from BSyn
NBN	Nijmegen breakage syndrome	AR	• Small stature • Evidence of excessive genomic instability • Immunodeficiency • Café au lait macules • Predisposition to lymphoid malignancy	• Decline in intellectual performance • No telangiectasias
WRN	Werner syndrome	AR	• Small stature • Evidence of excessive genomic instability • ↑ incidence of diabetes	• Premature atherosclerosis • Prematurely aged appearance
RECQL4	Rothmund-Thomson syndrome	AR	• Small stature • ↑ cancer susceptibility • Alopecia	• Juvenile cataracts • True poikiloderma (not sun-sensitive rash) • Premature aging

AD = autosomal dominant; AR = autosomal recessive; BSyn = Bloom syndrome; matUPD7 = maternal uniparental disomy for chromosome 7; MOI = mode of inheritance; SCE = sister-chromatid exchange; XL = X-linked

1. *RMI1*, *RMI2*, and *TOP3A* encode proteins that make up the BTRR complex. The **B**LM protein forms the BTRR complex with topoisomerase 3-alpha (**T**OP3A) and RecQ-mediated genome instability proteins 1 and 2 (**R**MI1 and **R**MI2, respectively). Together, these proteins process double Holliday junctions that arise as a result of homologous-recombination-mediated repair of double-stranded DNA breaks during DNA synthesis.

2. Erdinc et al [2023]

3. Accurate assessment of Silver-Russell syndrome (SRS) recurrence risk requires identification of the causative genetic mechanism in the proband. In most families, a proband with SRS represents a simplex case and has SRS as the result of an apparent *de novo* epigenetic or genetic alteration (e.g., loss of paternal methylation at the H19/IGF2 imprinting center 1 or maternal uniparental disomy for chromosome 7).

4. Listed genes represent the most common genetic causes of Fanconi anemia. For other genes associated with this phenotype, see Fanconi Anemia.

5. Fanconi anemia (FA) can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

Management

Health supervision recommendations that address diagnosis, treatment, and surveillance for complications in persons with Bloom syndrome (BSyn) have been published [Cunniff et al 2018].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with BSyn, in addition to the routine medical history, family history, and physical examination, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Bloom Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Feeding/Nutrition/ Gastrointestinal	Consultation w/gastroenterologist &/or feeding specialist	Eval for gastroesophageal reflux & feeding issues
	Lipid profile	Beginning at age 10 yrs

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Dermatologic	Careful history & skin exam for sun-sensitive skin rash, abnormal nevi, & lesions suspicious for basal cell or squamous cell carcinoma	
Immune	• Immunodeficiency screening incl immunoglobulin level, antibody responses to vaccines, & quantitative B & T lymphocytes • Referral to immunologist as needed	In probands w/recurrent, severe, or opportunistic infections
Development/ Neurobehavioral/ Psychosocial	Developmental, neurobehavioral, & psychosocial assessment	As needed
Cancer	Abdominal ultrasound for Wilms tumor	In probands age ≤8 yrs
	Colonoscopy & fecal immunochemical testing to assess for colorectal cancer	In probands age ≥10 yrs
	Whole-body MRI for lymphoma	In probands age ≥12 yrs
	Breast MRI for breast cancer	In females age ≥18 yrs
Endocrine	• Men: semen analysis to assess for azoospermia, oligospermia, or asthenospermia • Women: assessment for signs of early menopause	In post-pubertal persons at time of family planning
	• Fasting blood glucose & hemoglobin A1c concentration • Assessment for polyuria, polydipsia, weight loss	In probands age ≥10 yrs to evaluate for evidence of diabetes mellitus
	Thyroid function testing: TSH w/reflex to thyroxine	In probands age ≥10 yrs
Pulmonary	Assess for recurrent/chronic pulmonary disease.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of BSyn to facilitate medical & personal decision making

BSyn = Bloom syndrome; MOI = mode of inheritance; TSH = thyroid-stimulating hormone

Treatment of Manifestations

Treatment recommendations for persons with BSyn have been published [Cunniff et al 2018]. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Bloom Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Growth deficiency	• If GH is prescribed, growth response, serum IGF-1, & IGFBP-3 should be closely monitored. • GH should be discontinued if growth velocity does not ↑ w/GH treatment.	Use of GH has been approached cautiously because of concerns regarding an ↑ risk of developing tumors.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Feeding/Nutrition/ Gastrointestinal	• Standard treatment for feeding issues incl high-calorie diet • Consider consultation w/gastroenterologist or feeding specialist. • Reflux precautions & anti-reflux medications as needed • Dietary treatment of dyslipidemia according to standard protocols	Because abnormalities have been identified in lipid profile of persons w/BSyn, caution should be exercised in use of high-fat &/or high-cholesterol diets.
Dermatologic	• ↓ excessive exposure to sunlight by seeking shade, particularly 10 am to 4 pm. • Use sun-protective clothing, incl broad-brimmed hat. • UV-blocking sunglasses • Use broad-spectrum sunscreen w/SPF 30 2x daily, or every 2-3 hrs when outdoors. • Standard treatments for precancerous lesions & skin cancers	
Immune	• Mgmt per immunologist • Recurrent infections & defects in humoral immunity: treatment w/immunoglobulins	
Development/ Neurobehavioral/ Psychosocial	• Physical, occupational, & speech therapy as needed • Educational support as needed • Family & teachers are encouraged to relate to persons w/BSyn appropriately for their chronologic age rather than the younger age suggested by their unusually small size.	
Cancer	Treatment of malignancy per oncologist & other relevant specialists: • Modification of standard cancer treatment regimens, usually incl reduction of both dosage & duration • Full weight-based dosing may be appropriate for some chemotherapeutic drugs (e.g., steroids, tyrosine kinase inhibitors).	Due to hypersensitivity to DNA-damaging chemicals & ionizing radiation; persons w/ BSyn usually tolerate doses ≤50% of standard chemotherapy dosage, w/no evidence of poorer outcomes.
	HSCT	• Nonmyeloablative transplantation is likely to be tolerated more than other regimens; required ablative therapy prior to HSCT may require modification of standard protocols because of hypersensitivity to DNA-damaging agents. • HSCT has been performed in 3 persons w/leukemia in the Bloom Syndrome Registry. 1 person had >5 yrs disease-free survival before succumbing to another cancer; the other 2 died in immediate post-transplant period.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Endocrine	• Men can consider consulting a fertility specialist. It is unclear if ART is helpful in persons w/ oligospermia or other abnormalities. • Women: consider oocyte cryopreservation in those w/early menopause; ART may be beneficial if natural conception is not possible.	The authors are not aware of any prior use of ART in this population.
	Standard treatment of diabetes mellitus per endocrinologist	
	Thyroid hormone replacement therapy is recommended according to standard protocols for treatment of hypothyroidism.	
Pulmonary disease	Cough assist devices, vibration vests, & daily nasal lavage for mucociliary clearance for bronchiectasis	

ART = assisted reproductive technology; BSyn = Bloom syndrome; GH = growth hormone; HSCT = hematopoietic stem cell transplantation; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3

Surveillance

Health supervision recommendations for surveillance in persons with BSyn have been published [Cunniff et al 2018]. It should be recognized, however, that these recommendations are based on limited data from the Bloom Syndrome Registry and on expert opinion. There are currently no clinical trials or case-control studies that address outcomes in people with BSyn. Because of the unusually high risk for early development of cancer, much of the health supervision effort is directed to early detection and treatment.

Table 6. Bloom Syndrome: Recommended Surveillance

Manifestation	Evaluation	Frequency
Growth/Feeding/ Nutrition/ Gastrointestinal	• Monitor growth. • Assess for feeding issues & gastroesophageal reflux.	At each visit throughout childhood
	Lipid profile	Annually beginning at age 10 yrs
Skin cancer	Skin exam w/dermatologist for any suspicious skin lesions	On recognition of suspicious lesions & annually thereafter
Immunology	Assess for recurrent, severe, or opportunistic infections.	At each visit
Development/ Neurobehavioral/ Psychosocial	Developmental, neurobehavioral, & psychosocial assessment	As needed
Wilms tumor	• Abdominal ultrasound • Screen for signs/symptoms incl hematuria & painless abdominal mass	Every 3 mos from time of diagnosis to age 8 yrs
Leukemia	Screening & family education on signs/symptoms incl pallor, abnormal bleeding, petechiae, fatigue, unintentional weight loss	At every health visit
Lymphoma	Screening & family education on signs/symptoms incl enlarged lymph nodes, unexplained fevers, drenching night sweats, fatigue, unintentional weight loss	
	Whole-body MRI	Every 1-2 yrs beginning at age 12-13 yrs
Colorectal cancer	Colonoscopy	Annually beginning at age 10-12 yrs
	Fecal immunochemical testing	Every 6 mos beginning at age 10-12 yrs

Table 6. continued from previous page.

Manifestation	Evaluation	Frequency
Breast cancer	Breast MRI in females	Annually beginning at age 18 yrs
Diabetes mellitus	• Fasting blood glucose & hemoglobin A1c • Screening & family education on signs/symptoms of polyuria, polydipsia, weight loss	Annually beginning at age 10 yrs
Hypothyroidism	• Serum TSH w/reflex to thyroxine • Screening & family education on signs/symptoms incl fatigue, constipation, cold sensitivity, weight gain	
Pulmonary	Assess for recurrent/chronic pulmonary disease.	At each visit

TSH = thyroid-stimulating hormone

Agents/Circumstances to Avoid

Sun exposure to the face and other exposed skin, particularly in infancy and early childhood, should be avoided.

Exposure to ionizing radiation should be minimized. People with BSyn should avoid unnecessary radiographs and CT scans; MRI and ultrasound are preferred imaging modalities when able to be used.

Chemotherapy can have significant side effects and toxicity (including secondary malignancies). Dose reductions and shortened courses of treatment are generally utilized for individuals with BSyn. Alkylating agents and radiation therapy are considered high risk and are avoided when possible in those with BSyn.

Evaluation of Relatives at Risk

It is appropriate to evaluate sibs of a proband in order to identify as early as possible those who would benefit from avoidance of sun exposure and early surveillance for cancer (see Surveillance).

- Molecular genetic testing for the *BLM* pathogenic variants identified in the proband can be used to evaluate sibs.
- An unusually low birth weight followed by short stature throughout childhood is typically present in affected sibs; sibs of normal stature are likely unaffected and may not need further testing.

See Genetic Counseling for issues related to the testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Eleven women with BSyn followed in the Bloom Syndrome Registry have become pregnant at least once; seven of them have delivered a total of 11 healthy babies of normal size.

See MotherToBaby for more information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Bloom syndrome (BSyn) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *BLM* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *BLM* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband [Woodage et al 1994].
- Heterozygotes (carriers) are not at risk of developing BSyn. The cancer risk of heterozygotes as a group remains unclear. Some studies have identified a higher rate of *BLM* heterozygotes among individuals with mesothelioma [Bononi et al 2020], endometrial cancer, and colorectal cancer [Schayek et al 2017].

Sibs of a proband

- If both parents are known to be heterozygous for a *BLM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being a heterozygote (carrier), and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are not at risk of developing BSyn. The cancer risk of heterozygotes as a group remains unclear. Some studies have identified a higher rate of *BLM* heterozygotes among individuals with mesothelioma [Bononi et al 2020], endometrial cancer, and colorectal cancer [Schayek et al 2017].

Offspring of a proband

- Children born to a female with BSyn are usually heterozygous for a *BLM* pathogenic variant. However, because approximately 1% of individuals of Ashkenazi Jewish descent carry a *BLM* pathogenic variant, the risk for BSyn in the children of a union between a female with BSyn and a reproductive partner of Ashkenazi Jewish ancestry whose BSyn carrier status has not been determined is 1/200.
- Children born to a female with BSyn and a reproductive partner who is a carrier of a pathogenic variant have a 50% chance of having BSyn and a 50% chance of being carriers.
- Males with BSyn tend to be infertile.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *BLM* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *BLM* pathogenic variants in the family.

Population Screening

Individuals of Ashkenazi Jewish ancestry. Because of the relatively increased carrier rate of the blm^{Ash} allele in the Ashkenazi Jewish population (see Prevalence), individuals of Ashkenazi Jewish ancestry should be aware of their carrier risk, and practitioners should consider screening in this population [ACOG Committee on Genetics 2017].

Expanded carrier screening. BSyn is included on most expanded carrier screening panels. The ACMG includes BSyn among those disorders for which carrier screening should be offered to all individuals who are pregnant or planning a pregnancy [Gregg et al 2021].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be offered for the reproductive partners of individuals known to be carriers of BSyn.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *BLM* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Note: Ultrasound measurements are not reliable for estimating gestation age if prenatal diagnosis confirms the diagnosis of BSyn in the fetus.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Bloom Syndrome Association**
  www.bloomssyndromeassociation.org
- **Bloom Syndrome Registry**
  Weill Cornell Medicine
  Bloom Syndrome Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Bloom Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BLM	15q26.1	RecQ-like DNA helicase BLM	BLM database BLMbase: Mutation registry for Bloom Syndrome	BLM	BLM

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Bloom Syndrome (View All in OMIM)

210900	BLOOM SYNDROME; BLM
604610	RECQ PROTEIN-LIKE 3; RECQL3

Molecular Pathogenesis

Bloom syndrome (BSyn) is the prototype of the class of human diseases sometimes referred to as the chromosome breakage syndromes [German 1969]. These include BSyn, Fanconi anemia, ataxia-telangiectasia, ataxia-telangiectasia-like disorder (OMIM 604391), Nijmegen breakage syndrome, and Werner syndrome. These clinically disparate disorders are caused by pathogenic variants in genes encoding enzymes comprising pathways of DNA replication and repair that are responsible for the maintenance of genomic stability. In all of these disorders, the diagnostic cytogenetic abnormalities are accompanied by an increased rate of spontaneous reversion (mutation) to the normal state in somatic cells. This hypermutability explains the cancer predisposition shared by these disorders.

Molecular and genetic evidence implicates RecQ-like DNA helicase BLM (BLM) in the cellular mechanisms that maintain genomic stability [Hickson et al 2001, Monnat 2010, Larsen & Hickson 2013, Suhasini & Brosh 2013, Cunniff et al 2017]. The major consequence of loss of BLM function for a somatic cell is an abnormally high rate of recombination and mutation. The pathogenic variants that arise in the cells of a person with BSyn are of several types and affect many regions of the genome. Thus, although the cancer predisposition in BSyn is attributable to the cellular hyper-recombinability and hypermutability, the proportional small size – the constant feature of BSyn – remains unexplained, as do the medical complications of BSyn other than cancer.

Mechanism of disease causation. Loss of function

Table 7. *BLM* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000057.2 NP_000048.1	c.2207_2212delinsTAGATTC [2] (2281del6/ins7)	p.Tyr736LeufsTer5 [2]	Founder variant in persons of Ashkenazi Jewish descent [Ellis et al 1998]
	c.2407dupT (insT2407)	p.Trp803LeufsTer4	Second most common variant in persons of Ashkenazi Jewish descent [Ellis et al 1998, German et al 2007]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Also known as the blm^{Ash} allele

Chapter Notes

Author Notes

The Bloom Syndrome Registry is a long-term surveillance program in which the clinical courses of persons diagnosed with Bloom syndrome (BSyn) and close members of their families are followed. The Bloom Syndrome Registry includes individuals with confirmed BSyn living in various parts of the world. The registry is the source of much of the data included in this *GeneReview*.

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References

Literature Cited

ACOG Committee on Genetics. ACOG Committee Opinion No. 691: carrier screening for genetic conditions. Obstet Gynecol. 2017;129:e41-55. PubMed PMID: 28225426.

Ben Salah G, Salem IH, Masmoudi A, Kallabi F, Turki H, Fakhfakh F, Ayadi H, Kamoun H. A novel frameshift mutation in BLM gene associated with high sister chromatid exchanges (SCE) in heterozygous family members. Mol Biol Rep. 2014;41:7373-80. PubMed PMID: 25129257.

Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. AMA Am J Dis Child. 1954;88:754-8. PubMed PMID: 13206391.

Bononi A, Goto K, Ak G, Yoshikawa Y, Emi M, Pastorino S, Carparelli L, Ferro A, Nasu M, Kim JH, Suarez JS, Xu R, Tanji M, Takinishi Y, Minaai M, Novelli F, Pagano I, Gaudino G, Pass HI, Groden J, Grzymski JJ, Metintas M, Akarsu M, Morrow B, Hassan R, Yang H, Carbone M. Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma. Proc Natl Acad Sci U S A. 2020;117:33466-73. PubMed PMID: 33318203.

Cunniff C, Bassetti JA, Ellis NA. Bloom's syndrome: clinical spectrum, molecular pathogenesis, and cancer predisposition. Mol Syndromol. 2017;8:4-23. PubMed PMID: 28232778.

Cunniff C, Djavid AR, Carrubba S, Cohen B, Ellis NA, Fein Levy C, Jeong S, Lederman HM, Vogiatzi M, Walsh MF, Zauber AG. Health supervision for people with Bloom syndrome. Am J Med Genet. 2018;176:1872-81. PubMed PMID: 30055079.

Diaz A, Vogiatzi MG, Sanz MM, German J. Evaluation of short stature, carbohydrate metabolism and other endocrinopathies in Bloom's syndrome. Horm Res. 2006;66:111-7. PubMed PMID: 16763388.

Ellis NA, Ciocci S, Proytcheva M, Lennon D, Groden J, German J. The Ashkenazic Jewish Bloom syndrome mutation blmAsh is present in non-Jewish Americans of Spanish ancestry. Am J Hum Genet. 1998;63:1685-93. PubMed PMID: 9837821.

Erdinc D, Rodríguez-Luis A, Fassad MR, Mackenzie S, Watson CM, Valenzuela S, Xie X, Menger KE, Sergeant K, Craig K, Hopton S, Falkous G; Genomics England Research Consortium; Poulton J, Garcia-Moreno H, Giunti P, de Moura Aschoff CA, Morales Saute JA, Kirby AJ, Toro C, Wolfe L, Novacic D, Greenbaum L, Eliyahu A, Barel O, Anikster Y, McFarland R, Gorman GS, Schaefer AM, Gustafsson CM, Taylor RW, Falkenberg M, Nicholls TJ. Pathological variants in TOP3A cause distinct disorders of mitochondrial and nuclear genome stability. EMBO Mol Med. 2023;15:e16775. PubMed PMID: 37013609.

Fares F, Badarneh K, Abosaleh M, Harari-Shaham A, Diukman R, David M. Carrier frequency of autosomal-recessive disorders in the Ashkenazi Jewish population: should the rationale for mutation choice for screening be reevaluated? Prenat Diagn. 2008;28:236-41. PubMed PMID: 18264947.

German J. Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. Am J Hum Genet. 1969;21:196-227. PubMed PMID: 5770175.

German J. Bloom syndrome: a mendelian prototype of somatic mutational disease. Medicine (Baltimore). 1993;72:393-406. PubMed PMID: 8231788.

German J, Ellis N. Bloom syndrome. In: Vogelstein B, Kingler RW, eds. *The Genetic Basis of Human Cancer*. 2 ed. New York, NY: McGraw-Hill; 2002:267-88.

German J, Passarge E. Bloom's syndrome. XII. Report from the Registry for 1987. Clin Genet. 1989;35:57-69. PubMed PMID: 2647324.

German J, Sanz MM, Ciocci S, Ye TZ, Ellis NA. Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. Hum Mutat. 2007;28:743-53. PubMed PMID: 17407155.

Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, Chen E, Sparks TN, Reddi HV, Rajkovic A, Dungan JS, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23:1793-806. PubMed PMID: 34285390.

Hickson ID, Davies SL, Li JL, Levitt NC, Mohaghegh P, North PS, Wu L. Role of the Bloom's syndrome helicase in maintenance of genome stability. Biochem Soc Trans. 2001;29:201-4. PubMed PMID: 11356154.

Hudson DF, Amor DJ, Boys A, Butler K, Williams L, Zhang T, Kalitsis P. Loss of RMI2 increases genome instability and causes a Bloom-like syndrome. PLOS Genetics. 2016;12:e1006483. PubMed PMID: 27977684.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Keller C, Keller KR, Shew SB, Plon SE. Growth deficiency and malnutrition in Bloom syndrome. J Pediatr. 1999;134:472-9. PubMed PMID: 10190923.

Larsen NB, Hickson ID. RecQ helicases: conserved guardians of genomic integrity. In: Spies M, ed. *DNA Helicases and DNA Motor Proteins, Advances in Experimental Medicine and Biology*. New York, NY: Springer Science; 2013:161-84.

Martin CA, Sarlós K, Logan CV, Thakur RS, Parry DA, Bizard AH, Leitch A, Cleal L, Ali NS, Al-Owain MA, Allen W, Altmüller J, Aza-Carmona M, Barakat BAY, Barraza-García J, Begtrup A, Bogliolo M, Cho MT, Cruz-Rojo J, Dhahrabi HAM, Elcioglu NH, Gorman GS, Jobling R, Kesterton I, Kishita Y, Kohda M, Le Quesne Stabej P, Malallah AJ, Nürnberg P, Ohtake A, Okazaki Y, Pujol R, Ramirez MJ, Revah-Politi A, Shimura M, Stevens P, Taylor RW, Turner L, Williams H, Wilson C, Yigit G, Zahavich L, Alkuraya FS, Surralles J, Iglesais A, Murayama K, Wollnik B, Dattani M, Heath KE, Hickson ID, Jackson AP. Mutations in TOP3A cause a Bloom syndrome-like disorder. Am J Hum Genet. 2018;103: 221–31. PubMed PMID: 30057030.

Monnat RJ. Human RECQ helicases: roles in DNA metabolism, mutagenesis and cancer biology. Semin Cancer Biol. 2010;20:329-39. PubMed PMID: 20934517.

Peleg L, Pesso R, Goldman B, Dotan K, Omer M, Friedman E, Berkenstadt M, Reznik-Wolf H, Barkai G. Bloom syndrome and Fanconi's anemia: rate and ethnic origin of mutation carriers in Israel. Isr Med Assoc J. 2002;4:95-7. PubMed PMID: 11876000.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schayek H, Laitman Y, Katz LH, Pras E, Ries-Levavi L, Barak F, Friedman E. Colorectal and endometrial cancer risk and age at diagnosis in BLMAsh mutation carriers. Isr Med Assoc J. 2017;19:365-7. PubMed PMID: 28647934.

Suhasini AN, Brosh Jr RM. DNA helicases associated with genetic instability, cancer, and aging. In: Spies M, ed. *DNA Helicases and DNA Motor Proteins, Advances in Experimental Medicine and Biology*. New York, NY: Springer Science; 2013:123-44.

Sugrañes TA, Flanagan M, Thomas C, Chang VY, Walsh M, Cunniff C. Age of first cancer diagnosis and survival in Bloom syndrome. Genet Med. 2022;24:1476-84. PubMed PMID: 35420546.

Woodage T, Prasad M, Dixon JW, Selby RE, Romain DR, Columbano-Green LM, Graham D, Rogan PK, Seip JR, Smith A, Trent RJ. Bloom syndrome and maternal uniparental disomy for chromosome 15. Am J Hum Genet. 1994;55:74-80. PubMed PMID: 7912890.

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