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Bloom's Syndrome

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Bloom's Syndrome

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Summary

Clinical characteristics. Bloom's syndrome (BSyn) is characterized by severe pre- and postnatal growth deficiency, sparseness of subcutaneous fat tissue throughout infancy and early childhood, and short stature throughout postnatal life that in most affected individuals is accompanied by an erythematous and sun-sensitive skin lesion of the face. Gastroesophageal reflux (GER) is common and very possibly responsible for infections of the upper respiratory tract, the middle ear, and the lung that occur repeatedly in most persons with BSyn. Although most affected individuals have normal intellectual ability, many exhibit a poorly defined learning disability. Women may be fertile, but menopause occurs unusually early; men are infertile. Serious medical complications that are much more common than in the general population and that also appear at unusually early ages are chronic obstructive pulmonary disease, diabetes mellitus resembling the adult-onset type, and cancer of a wide variety of types and anatomic sites. BSyn occurs rarely in all national and ethnic groups but is relatively less rare in Ashkenazi Jews.

Diagnosis/testing. The diagnosis of BSyn is established in a proband with identification of biallelic pathogenic variants in *BLM* on molecular genetic testing or, if molecular genetic testing is inconclusive, with identification of increased frequency of sister-chromatid exchanges on specialized cytogenetic studies.

Management. *Treatment of manifestations:* Supplemental feeding increases fat deposition but not linear growth. Diabetes mellitus is treated in the standard manner. In persons with BSyn who have cancer, hypersensitivity of cells to both ionizing radiation and DNA-damaging chemicals may require reduction of the dosage and/or the duration of treatment to avoid serious and even life-threatening complications.

Surveillance: Unexplained signs and symptoms that are potential indications of a malignancy should be investigated promptly and thoroughly. Screening for breast and colon cancer decades earlier, and more frequently than in general population screening programs, is advisable.

Agents/circumstances to avoid: Sun exposure to the face.

Genetic counseling. BSyn is inherited in an autosomal recessive manner. Identification of both pathogenic *BLM* alleles in a family is required for carrier (heterozygote) testing, as cytogenetic testing cannot distinguish between carriers and non-carriers. Prenatal diagnosis of pregnancies at increased risk is possible using either cytogenetic testing (specifically sister-chromatid exchange analysis) or *BLM* molecular genetic testing if the pathogenic variants have been identified in the family.

Diagnosis

Suggestive Findings

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

Clinical findings

- Unexplained, severe intrauterine growth deficiency that persists into infancy, childhood, and adulthood
- Significant growth deficiency and an erythematous skin lesion in a "butterfly shape" on the face after sun exposure
- Significant growth deficiency and a diagnosis of cancer

Cytogenetic findings

- Increased quadriradial configurations (Qrs) in cultured blood lymphocytes (a mean of 1%-2% Qrs are observed in cultured blood lymphocytes from a person with BSyn vs none in controls)
- Chromatid gaps, breaks, and rearrangements

Establishing the Diagnosis

The diagnosis of BSyn **is established** in a proband with identification of biallelic pathogenic variants in *BLM* on molecular genetic testing (Table 1) or, if molecular genetic testing is inconclusive, with identification of increased frequency of sister-chromatid exchanges (SCEs) on specialized cytogenetic studies.

Molecular testing approaches can include **single-gene testing**, use of a **multi-gene panel**, and **more comprehensive genomic testing**.

- **Single-gene testing.** Sequence analysis of *BLM* is performed first followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

In individuals of Ashkenazi Jewish ancestry, targeted analysis for the common pathogenic variant, c.2207_2212delinsTAGATTC (designated blm^{Ash}), can be performed first. Of pathogenic variants identified in individuals of Ashkenazi Jewish ancestry, 97% are the common blm^{Ash} variant.

- **A multi-gene panel** that includes *BLM* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multi-gene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multi-gene panel provides the best opportunity to identify the genetic cause of the condition at the most reasonable cost. (3) 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.

- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multi-gene panel that includes *BLM*) fails to confirm a diagnosis in an individual with features of Bloom's syndrome.

  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's Syndrome

Gene [1]	Test Method	Proportion of Pathogenic Variants [2] Detectable by This Method	
		Ashkenazi Jewish ancestry	Non-Jewish Ancestry
BLM	Targeted analysis for c.2207_2212delinsTAGTTC	97% [3]	4%
	Sequence analysis [4]	~100% [3]	87%
	Gene-targeted deletion/duplication analysis [5]	None reported [3]	Unknown [6]
Unknown [7]	NA		

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. German et al [2007]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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 that may be used include: quantitative PCR, long-range PCR,

multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. No data on detection rate of gene-targeted deletion/duplication analysis in individuals of non-Jewish ancestry are available, however, large intragenic deletions have been reported [German et al 2007].
7. In nine individuals with BSyn pathogenic variants in *BLM* were not detected, leaving open the possibility of locus heterogeneity [German et al 2007].

SCEs; a mean of 40-100 per metaphase (vs <10 in controls). Increased frequency of SCEs is demonstrable in BSyn cultured cells (including lymphocytes, fibroblasts, and exfoliated fetal cells) allowed to proliferate in a medium containing 5'bromo-2'-deoxyuridine (BrdU). BSyn is the only disorder in which such evidence of hyper-recombinability is known to occur. In an individual with BSyn the mean and range of SCEs per metaphase are higher in lymphocytes than in fibroblasts, but the differences from controls in both types of cells are so great that BSyn and normal cells are readily distinguishable.

Note: In a minority of persons with BSyn, varying numbers of lymphocytes with normal SCE rates circulate in the blood alongside cells with the characteristically increased SCE frequency and presumably are the result of mutation back to normal in a stem cell. In theory, low (normal) SCE cells could predominate, even to the exclusion of the high-SCE cells. Therefore, when the clinical phenotype of an individual strongly suggests the diagnosis of BSyn and when no lymphocytes freshly removed from the circulation display the high number of SCEs per metaphase characteristic of BSyn, cytogenetic examination of cultured dermal fibroblasts may be necessary; normal rates of SCE in fibroblasts have never been found in an individual with BSyn.

Clinical Characteristics

Clinical Description

The range of clinical features in persons with Bloom's syndrome (BSyn) has been tracked through the Bloom's Syndrome Registry. The clinical and genetic histories have been obtained from registered persons diagnosed between 1954 and 2016, and their clinical courses have been followed [German & Passarge 1989, German 1993, German & Ellis 2002].

The main clinical features of BSyn are the following:

- **Size and appearance.** The most impressive and the only constant clinical feature of BSyn seen throughout all stages of life is exceptionally small size, with roughly normal body proportions with the exception of a slightly disproportionately small cranium. Subcutaneous adipose tissue is very sparse, typically resulting in a wasted appearance. Plasma growth hormone concentration is normal.

  The affected fetus is smaller than normal for gestational age. The mean birth weight of affected males is 1760 g (range 900-3189 g) and of affected females, 1754 g (range 700-2892 g). The average adult height of men is 149 cm (range 128-164 cm) and of women, 138 cm (range 115-160 cm).

  The face in BSyn is often striking because of the small and somewhat narrow cranium, seemingly underdeveloped malar and lower mandibular areas, and a resulting relative prominence of the nose and ears (weill.cornell.edu/bsr).

  The voice is high-pitched and somewhat coarse in timbre.

- **Feeding problems.** These are prominent in the majority of newborns, infants, and young children. The child with BSyn characteristically shows a lack of interest in nursing, and then in eating. In a minority of infants with BSyn, nursing and eating are normal. Severe gastroesophageal reflux (GER) has been found in the few young infants appropriately examined and may contribute to their repeated bouts of middle ear and lung infections, via repeated micro-aspirations of gastric contents.
- **Skin lesions.** The skin at birth and during early infancy appears normal, but, typically following sun exposure during the first or second year of life, a red, sun-sensitive skin lesion appears on the nose and cheeks, sometimes faintly also on the dorsa of the hands and forearms. This lesion varies in severity and extent among affected individuals; in some the lesion is minimal. In severely affected individuals, the lesion can be bright red and can extend onto adjacent areas. Loss of the lower eyelashes and blister and fissure formation of the lower lip are common, the latter often becoming particularly bothersome and difficult to treat.

  Café-au-lait macules, typically with neighboring hypopigmented areas of skin, are more numerous and larger than in those without BSyn.
- **Immunodeficiency.** The concentration of one or more of the plasma immunoglobulins is usually abnormally low. Delayed hypersensitivity is undetected by the standard testing method.
- **Infections**. Repeated bouts of otitis media and pneumonia that respond normally to antibiotics occur throughout infancy and early childhood in at least 20% of persons with BSyn. The frequency of these infections does not appear to correlate with the severity of the immunodeficiency.
- **Fertility.** Men with BSyn appropriately examined have had azoospermia or severe oligospermia. Women with BSyn, although often fertile, enter menopause prematurely. Eleven women with BSyn followed in the Registry have become pregnant at least once; seven of them have been delivered a total of eleven healthy babies of normal size.
- **Intelligence.** Intellectual abilities of affected persons vary, being clearly limited in some and normal in others. Some persons with BSyn are reported to have a lack of interest in learning and do poorly in school in courses requiring abstract thought. However, others have excelled in school, with some earning graduate degrees.
- **Other clinical features.** Major anatomic defects are not increased in frequency. In the 272 persons in the Registry as of 2012, only single examples of the following having occurred: tracheoesophageal fistula, cardiac malformation, absent thumbs, and absence of a toe and malformation of a thumb.

Medical complications of BSyn, all serious, in order of increasing frequency are the following:

- **Lower urinary tract obstruction in men.** Several men have had a poorly characterized urethral or bladder neck obstruction, resulting in death in two individuals.
- **Chronic obstructive pulmonary disease.** Chronic bronchitis and bronchiectasis are common, and pulmonary failure has been the cause of death in five persons.

- **Diabetes mellitus.** Although the diabetes mellitus of BSyn has as yet not been well characterized, it resembles the typical adult-onset type except for an exceptionally early age of onset. Diabetes has been diagnosed in 47 of 272 persons in the Registry (17.7%) at a mean age of 26.6 years (range 4-45 years). Although most individuals do not have severe complications, 16 have required insulin, and retinopathy has developed in two.

  Abnormalities in insulin release and glucose tolerance have been detected in the eight healthy children (age 9 months to 13 years) and the three healthy young adults with BSyn (ages 22, 28, and 28 years) appropriately studied [Diaz et al 2006].

- **Myelodysplasia.** This heterogeneous group of disorders has been diagnosed in 23 persons in the Registry at a median age of 22.1 years (range 3-47), and it has progressed to leukemia in at least seven. In all but three, the myelodysplasia was preceded by some form of cancer for which chemotherapy and/or radiotherapy had been administered.

- **Cancer.** Cancer is the most frequent medical complication in BSyn and the most common cause of death. 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 BSyn. Development of multiple cancers in a single individual is also much more common. Table 2 summarizes the cancers diagnosed in individuals followed in the Registry.

Table 2.

The 207 Malignant Neoplasms Diagnosed in 131 Persons in the Bloom's Syndrome Registry, 1954-2016

Anatomic Sites/Types		Mean Age at Diagnosis (Range)	Number
Epithelial (carcinoma)	Lower enteric tract	35.0 (16-49)	31
	Integument	31.7 (18-46)	27
	Upper entero/respiratory tract	37.8 (25-48)	22
	Genitalia & urinary tract	16.6 (<1-43)	17
	Breast	35.8 (21-48)	16
	Lower respiratory tract	33.0 (26-40)	9
	Liver	15.0	1
Lymphoid	Lymphoma	21.7 (4-49)	35
	Acute lymphoblastic leukemia	19.6 (5-40)	12
Hematopoietic	Acute myelogenous leukemia	18.1 (2-47)	26
Other	Connective tissue (sarcoma)	16.3 (4-30)	4
	Germ-cell	24.0 (22-26)	2

Anatomic Sites/Types		Mean Age at Diagnosis (Range)	Number
	Central nervous system (brain)	3.0	1
	Retinoblastoma	1.0	1
	Primary site unidentified, metastatic	33.7 (28-33)	3
All		26.6 (<1-49)	207

Adapted from: Bloom's Syndrome Registry

Genotype-Phenotype Correlations

Homozygotes and compound heterozygotes. A similar phenotype is produced by either homozygosity or compound heterozygosity for any of the more than 60 pathogenic variants in *BLM* identified to date.

Prevalence

Few individuals with BSyn have been reported in the medical literature since its description half a century ago [Bloom 1954], and fewer than 300 are known to the Bloom's Syndrome Registry.

Although rare in all populations, BSyn is relatively less rare among Ashkenazi Jews. Seventy-two of the 265 persons in the Registry are of Ashkenazi Jewish ancestry. The predominant *BLM* pathogenic variant identified in Ashkenazi Jews is c.2207_2212delinsTAGATTC, a 6-bp deletion/7-bp insertion in exon 10 of *BLM*, often (for brevity) designated blm^{Ash}; the second most common pathogenic variant is c.2407dupT.

The approximate carrier frequency of the blm^{Ash} allele:

- One in 100 Ashkenazi Jews dwelling both in New York City [Li et al 1998] and in Israel [Peleg et al 2002]
- One in 37 Ashkenazi Jews dwelling in Israel, all four of whose grandparents were from Poland [Shahrabani-Gargir et al 1998]

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

A greatly increased sister-chromatid exchange (SCE) rate distinguishes Bloom's syndrome from other clinical disorders associated with growth deficiency, such as Russell-Silver syndrome, and specifically those that feature small stature and evidence of excessive genomic instability, including the following:

- Fanconi anemia

- Ataxia-telangiectasia
- Ataxia-telangiectasia-like disorder (OMIM 604391)
- Werner syndrome
- Nijmegen breakage syndrome

Management

Evaluations Following Initial Diagnosis

To evaluate an individual newly diagnosed with Bloom's syndrome (BSyn) the following are recommended in addition to the routine medical history, family history, and physical examination:

- Evaluation for gastroesophageal reflux and micro-aspirations into the lung of gastric contents
- Fasting blood glucose determination at the time of diagnosis and annually thereafter
- Determination of plasma immunoglobulin concentrations
- Observation of urination for evidence of urethral obstruction
- If diagnosis occurs in adulthood, colonoscopy and stool guaiac at the time of diagnosis
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Psychosocial. Family and teachers are encouraged to relate to persons with BSyn appropriately for their chronologic age rather than the younger age suggested by their unusually small size.

Growth. Growth hormone administration to children with BSyn has not increased growth rate or adult height in most persons, but some have experienced improved linear growth. Use of growth hormone has been approached cautiously in this population, because of the theoretic increase in their risk to develop tumors as a result of their treatment. Supplemental feeding results in increased fat deposition but not in improved linear growth.

Diabetes mellitus. Treatment of diabetes mellitus in BSyn is the same as in other persons.

Cancer. The hypersensitivity of persons with BSyn to both DNA-damaging chemicals and ionizing radiation ordinarily necessitates modification of standard cancer treatment regimens, which usually includes a reduction of both dosages and durations. Absence of information as to the ideal dosages makes such

treatment particularly challenging to the physician; nevertheless, the fact that the cancers themselves often appear unusually responsive to the treatment justifies the special effort.

Bone marrow transplantation (BMT). Too few persons with BSyn have had BMT to permit conclusions as to its value (which in theory could be great). The required ablative therapy prior to BMT often may require modification of standard protocols because of the hypersensitivity of persons with BSyn to DNA-damaging agents.

Surveillance

Families benefit from counseling regarding the risk of cancer in persons with BSyn. The wide variety of types and sites of cancer in Bsyn – plus the unusually early onset of solid tumors such as carcinomas and sarcomas – makes surveillance for cancer a life-long undertaking, requiring planning and cooperation among the affected person, the family, and the physician in charge.

- In persons younger than age 20 years, leukemia is the main type of cancer. Until evidence becomes available that treatment at the earliest stages of leukemia is more effective than treatment after full-blown symptoms appear, hematologic surveillance other than that used in general pediatrics appears unnecessary, if not contraindicated.
- Close contact between individuals age 20 years and older and their physicians is advisable, and symptoms that cannot be accounted for otherwise should be evaluated promptly as potential early indicators of cancer.
- Screening for colon cancer, the most common solid tumor in individuals with BSyn (see Table 2), should begin decades earlier than in others, and should be carried out more frequently.

  In adults, colon cancer screening may include colonoscopy every one to two years, and stool guaiac testing for blood every three to six months.

Agents/Circumstances to Avoid

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

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 to the face and early surveillance for cancer (see Surveillance).

- Molecular genetic testing can be used to evaluate sibs if the *BLM* pathogenic variants in the family are known.
- 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.

Therapies Under Investigation

Search ClinicalTrials.gov for access to 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of an individual with BSyn

- Both parents of an affected person may be assumed to be heterozygous for a pathogenic variant in *BLM*. However, a single example of uniparental disomy has been reported [Woodage et al 1994], suggesting that molecular testing of parents may be warranted to confirm their genetic status.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing BSyn.
- The cancer risk of heterozygotes as a group has been examined in association studies but is yet to be determined [Antczak et al 2013, Prokofyeva et al 2013].

Sibs of an individual with BSyn

- At conception, each sib of an individual with Bloom's syndrome has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier of a *BLM* pathogenic variant, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier of a *BLM* pathogenic variant is 2/3.
- The cancer risk of heterozygotes as a group has been examined in association studies but is yet to be determined [Antczak et al 2013, Prokofyeva et al 2013].

Offspring of a woman with BSyn

- Children born to a woman with Bloom's syndrome 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 woman with BSyn and an Ashkenazi Jewish man whose Bloom's syndrome carrier status has not been determined is 1/200.
- Children born to a woman 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.

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

Carrier (Heterozygote) Detection

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

Individuals of Ashkenazi Jewish heritage. Because of the relatively increased carrier rate of the blm^{Ash} allele in Ashkenazi Jews, population screening may be available for Ashkenazi Jewish individuals of reproductive age [ACOG Committee on Genetics 2009].

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, clarification of carrier status, and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *BLM* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis (PGD) for BSyn are possible. PGD has been successfully utilized for one couple [Bloom's Syndrome Registry, unpublished data].

Cytogenetic analysis. Prenatal diagnosis for a pregnancy at increased risk is possible by sister-chromatid exchange (SCE) analysis of fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation.

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

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's Syndrome Association (BSA)**
  P.O. Box 727
  Hanover NH 03755-0727
  Phone: 603-643-2850
  Email: info@bloomssyndromeassociation.org
  www.bloomssyndromeassociation.org
- **Bloom's Syndrome Foundation (BSF)**
  7095 Hollywood Boulevard
  #583
  Los Angeles CA 90028
  Email: info@bloomssyndrome.org
  www.bloomssyndrome.org
- **National Library of Medicine Genetics Home Reference**
  Bloom syndrome
- **Center for Jewish Genetics**
  Ben Gurion Way
  30 South Wells Street
  Chicago IL 60606
  Phone: 312-357-4718
  Email: jewishgeneticsctr@juf.org
  www.jewishgenetics.org
- **Xeroderma Pigmentosum Society, Inc (XP Society)**
  XP Society has material on their site related to UV protection/avoidance.
  437 Syndertown Road
  Craryville NY 12521

Phone: 877-XPS-CURE (877-977-2873); 518-851-2612
Email: xps@xps.org
www.xps.org

- **Bloom's Syndrome Registry**
  Weill Cornell Medicine
  505 East 70th Street
  3rd floor, Box 128
  New York NY 10021
  Phone: 646-962-2205
  Email: cmc9039@med.cornell.edu; msanz@molloy.edu
  Bloom's Syndrome Registry

- **European Society for Immunodeficiencies (ESID) Registry**
  Dr. Gerhard Kindle
  University Medical Center Freiburg Centre of Chronic Immunodeficiency
  Engesserstr. 4
  79106 Freiburg
  Germany
  Phone: 49-761-270-34450
  Email: esid-registry@uniklinik-freiburg.de
  ESID 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's Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BLM	15q26.1	Bloom syndrome protein	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's Syndrome (View All in OMIM)

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

Molecular Genetic Pathogenesis

Bloom's 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 mutation in somatic cells. This hypermutability explains the cancer predisposition shared by these disorders.

Gene structure. A 4,528-bp cDNA sequence defines *BLM*, which contains a long open reading frame encoding a 1,417-amino acid protein, BLM. *BLM* comprises 22 exons and is located at chromosome band 15q26.1. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants

- Most individuals of Ashkenazi Jewish heritage with BSyn have the pathogenic variant c.2207_2212delinsTAGATTC (Table 4) [Ellis et al 1998]. A second rarer pathogenic variant segregating in the Ashkenazi Jewish population, c.2407dupT, has been identified [Ellis et al 1998, German et al 2007].
- Pathogenic variants identified in several studies of individuals with BSyn fall into the following four broad classes [German et al 2007, Amor-Guéret et al 2008, Shastri & Schmidt 2015]:
  - **Nucleotide insertions and deletions** that result in frameshifts and elimination of the C-terminus of the protein where the nuclear localization signals of BLM are located; BLM is therefore absent from the nucleus (~1/3 of all pathogenic variants).
  - **Nonsense variants** that convert sense codons to nonsense or chain-terminating codons that predict translation of a truncated BLM protein (~1/3 of all pathogenic variants)
  - **Intron variants** that cause splicing defects (~1/6 of all pathogenic variants)
  - **Missense variants** that result in the production of non-functional BLM protein (~1/6 of all pathogenic variants)

Table 4.

BLM Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.2207_2212delinsTAGATTC [2] (2281del6/ins7) (blm^{Ash})	p.Tyr736LeufsTer5 [2]	NM_000057.2 NP_000048.1
c.2407dupT (insT2407)	p.Trp803LeufsTer4	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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

See Table 5 (pdf) for pathogenic variants identified in registered persons of various nationalities and ethnic groups.

Normal gene product. The 1417-amino-acid protein named BLM contains an amino acid domain consisting of seven motifs characteristic of DNA and RNA helicases. The helicase domain of BLM is 40%-45% identical to the helicase domain in the RecQ subfamily of DNA helicases and is known to be important in other species for the maintenance of genomic integrity. BLM is a cell cycle-regulated protein that is distributed diffusely throughout the nucleus but also is concentrated in nuclear foci, many of which have been identified as PML (promyelocytic leukemia protein) bodies [Sanz et al 2000]. DNA-dependent ATPase and DNA duplex-unwinding activities have been demonstrated for BLM; the nucleic acid substrates that it acts on in the cell remain to be identified. Molecular and genetic evidence implicates BLM in the cellular mechanisms that maintain genomic stability [Hickson et al 2001, Monnat 2010, Larsen & Hickson 2013, Suhasini & Brosh 2013].

Abnormal gene product. The major consequence for a somatic cell, in which BLM is either absent or present but non-functional, 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 of BSyn is attributable to the cellular hyper-recombinability and hypermutability, the proportional small size – the constant feature of BSyn – remains unexplained, as do the important medical complications of BSyn other than cancer.

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Chapter Notes

Author Notes

The Bloom's Syndrome Registry is a long-term surveillance program in which the clinical courses of persons diagnosed with BSyn and close members of their families are followed. The Registry comprises bona fide cases of individuals with this very rare disorder living in various parts of the world. The Registry is the source of much of the data included in this entry.

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