GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Bloom's Syndrome

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Initial Posting: March 22, 2006.

Summary

Disease characteristics. Bloom's syndrome is characterized by severe prenatal and postnatal growth retardation and a sun-sensitive erythematous skin lesion that occurs most commonly on the face. Recurrent infections (otitis media and pneumonia), chronic pulmonary disease, and diabetes mellitus are common. Many have learning disabilities. Males are infertile; females enter menopause prematurely. The most common cause of death is cancer (epithelial, hematopoietic, lymphoid, connective tissue, germ cell, nervous system, and kidney), which occurs at younger-than-usual ages.

Diagnosis/testing. Bloom's syndrome is diagnosed by clinical features and can be confirmed by chromosome analysis. A greatly increased frequency of sister chromatid exchanges (SCEs) in cells exposed to bromodeoxyuridine (BUDR) is diagnostic; Bloom's syndrome is the only disorder in which such evidence of hyper-recombination is known to occur. *BLM* is the only gene known to be mutated in Bloom's syndrome. Molecular genetic testing for the common mutation, BLM^{Ash}, is clinically available.

Management. Caloric intake and nutritional status of newborns and infants with Bloom's syndrome require monitoring; gastroesophageal reflux needs to be treated vigorously when present. Family and teachers are encouraged to relate to children with Bloom's syndrome in a manner appropriate for their age, not size. Diabetes mellitus is treated as per routine. Hypersensitivity to DNA-damaging chemicals and ionizing radiation necessitates modification of standard cancer treatment regimens, i.e., reduction of dosages and duration. Surveillance includes evaluating unexplained signs and symptoms as potential indications of malignancy; screening for colon cancer begins decades earlier and is performed more frequently than average. Sun exposure to facial skin should be avoided.

Genetic counseling. Bloom's syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, 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 is 2/3. Carrier testing for at-risk family members of individuals with the BLM^{Ash} mutation is clinically available. Prenatal diagnosis for pregnancies at increased risk is possible by the cytogenetic analysis of

fetal cells or by molecular genetic testing if both the mutated alleles of an affected family member or of carrier parents have been identified.

Diagnosis

Clinical Diagnosis

Bloom's syndrome [German & Ellis 2002] should be considered in the following:

- An individual with unexplained, severe intrauterine growth retardation that persists into infancy and childhood
- Any unusually small, well-proportioned individual with a sun-sensitive erythematous skin lesion in a "butterfly distribution" on the face
- An unusually small individual who develops cancer

Testing

Cytogenetic testing: Clinical uses

- Diagnostic testing, pre- or postnatal
- Diagnostic testing to confirm or disaffirm a clinical diagnosis or suspicion of Bloom's syndrome

Cytogenetic testing: Clinical methods

Chromosome analysis. The diagnosis of Bloom's syndrome can be confirmed or ruled out by chromosome analysis of any cell type that can be cultured [Ray & German 1983]. The most commonly used cells are blood lymphocytes, but cultures of skin fibroblasts and amniocytes also can be studied. The cytogenetic features of Bloom's syndrome cells in mitosis are increased numbers of chromatid gaps, breaks, and rearrangements and increased numbers of quadriradial configurations.

Sister chromatid exchanges (SCEs). A greatly increased frequency (e.g., greater than 50 per metaphase) of SCEs is demonstrable in Bloom's syndrome cells exposed to bromodeoxyuridine; furthermore, Bloom's syndrome is the only disorder in which such evidence of hyper-recombination is known to occur.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *BLM* is the only gene known to be mutated in Bloom's syndrome [Ellis et al 1995].

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Confirmatory diagnostic testing
- Carrier detection in families with Bloom's syndrome
- Population screening

- Prenatal diagnosis
- Preimplantation genetic diagnosis

Molecular genetic testing: Clinical method

- **Targeted mutation analysis.** The Bloom's syndrome-causing mutation identified in Ashkenazi Jewish persons is a 6-bp deletion/7-bp insertion at nucleotide 2281 of *BLM* cDNA, designated *BLM*^{Ash} [Ellis et al 1998]. Targeted mutation analysis of *BLM*^{Ash} is performed in clinical diagnostic laboratories.

  Table 1 summarizes by Jewish vs non-Jewish parental ancestry the results of molecular genetic testing for the Bloom's syndrome-causing mutations in 137 persons with Bloom's syndrome, each from a different family [German & Ellis 2002; Bloom's Syndrome Registry, unpublished data].

Molecular genetic testing: Research

- **Sequence analysis/mutation scanning.** In research laboratories, Bloom's syndrome-causing mutations in *BLM* in non-Ashkenazi Jewish families have been characterized by [German & Ellis 2002; Bloom's Syndrome Registry, unpublished data]:
  - Mutation scanning (single-stranded conformation polymorphism analysis, in vitro synthesis of protein analysis, and RNA mismatch cleavage analysis) and sequencing of DNA fragments amplified by reverse-transciptase-polymerase chain reaction on mRNAs isolated from untransformed fibroblast and lymphoblastoid cell lines
  - Mutation scanning (D-HPLC) and sequencing of exon-containing DNA fragments amplified by polymerase chain reaction of genomic DNA isolated from various sources and Southern blot analysis of selected genomic DNAs. All abnormalities identified in mutation scanning were characterized by DNA sequence analysis and confirmed by sequence analysis of DNA from the parents of the person with Bloom's syndrome when material was available.

Table 1. Molecular Genetic Testing Used in Bloom's Syndrome

Parental Ancestry [1]	Number of Probands [2]	Number of Probands/Total Number of Probands of that Parental Ancestry by Genotype [3]						Test Availability [4]
		BLM^{Ash}/ BLM^{Ash}	BLM^{Ash}/ insT2407	BLM^{Ash}/+	+/+	+/–	–/–	
A/A	28	26/28	2/28	0	0	0	0	Clinical [4] Testing and Research
A/J	2	1/2	0	1/2	0	0	0	
A/N	5	0	0	5/5	0	0	0	
J/J	1	0	0	0	0	0	1/1	
N/N	101	3/101 [5]	0	2/101 [5]	79/101	8/101	9/101	

A = Ashkenazi Jewish
J = Jewish, not Ashkenazi
N = Non-Jewish
A/A = Both parents are Ashkenazi Jewish.
A/J = One parent is Ashkenazi Jewish and one parent is Jewish but not Ashkenazi.
A/N = One parent is Ashkenazi Jewish and one parent is non-Jewish.
J/J = Both parents are Jewish, but not Ashkenazi.
N/N = Both parents are non-Jewish.
+ = Sequence alteration other than *BLM*^{Ash} and insT2407
– = No sequence alteration identified

1. The parental ancestries of persons with Bloom's syndrome and known Bloom's syndrome-causing mutations in *BLM* [Bloom's Syndrome Registry] [link]. Between 25 and 33% have Jewish ancestry; i.e. parents are A/A, A/J, A/N, or J/J.
2. The number of probands comprising the parental ancestry group
3. Technical limitation is probably the explanation for failure to detect one or neither of the Bloom's syndrome-causing mutations in *BLM* in 18 persons studied.
4. Targeted mutation analysis for BLM^{Ash} is the only test that is clinically available.
5. Those in the N/N parental ancestry group who are homozygous or compound heterozygotes for BLM^{Ash} are from one particular geographic area that once was part of Spain's *Nuevo Mundo* (Central America, Mexico, and the Southwest United States) [Ellis et al 1998].

Testing Strategy for a Proband

The diagnosis of Bloom's syndrome is established by

- Cytogenetic demonstration of an increased rate of SCE

  OR
- Molecular demonstration of homozygosity for BLM^{Ash} in Ashkenazi Jews

Genetically Related (Allelic) Disorders

Bloom's syndrome is the only phenotype known to be associated with mutations in *BLM*.

Clinical Description

Natural History

The range of clinical features of Bloom's syndrome has been elucidated in a program of clinical investigation now in effect for more than four decades referred to as the Bloom's Syndrome Registry. The clinical and genetic histories have been obtained from most persons diagnosed between 1954 and 2003 and their clinical courses have been followed [German & Passarge 1989; German 1993; German & Ellis 2002; Bloom's Syndrome Registry, unpublished data]. The main clinical features of Bloom's syndrome are the following:

- **Size.** The most constant clinical feature of Bloom's syndrome seen in all stages of life is exceptionally small size that is proportional with the exception of a slightly disproportionately small head.

  Pregnancy is normal except that the affected fetus is smaller than normal for the gestational age. The mean birth weight of affected males is 1906 g (range 930-3400 g) and of affected females is 1810 g (range 920-2667 g). The average adult height for men is 147.5 cm (range 130-162 cm) and for women is 138.6 cm (range 122-151 cm).

  Plasma growth hormone concentration is normal.

  Subcutaneous adipose tissue is sparse.

  The facies in Bloom's syndrome often are striking because of a slightly disproportionately small and somewhat narrow cranium, possibly somewhat disproportionately underdeveloped malar bone structure and lower jaw, and resulting relative prominence of the nose and ears.

  The voice is high-pitched, presumably because of the small size of the larynx.

- **Skin lesions.** The skin at birth and during early infancy appears normal. Following sun exposure during the first or second year of life, a red sun-sensitive skin lesion appears on the butterfly area of the face and sometimes on the dorsa of the hands and forearms. This lesion may become chronic with further exposure to the sun, but its severity varies and in some persons the lesion is minimal. In severe cases, the lesion can be disfiguring and can extend onto the ears, neck, shoulders, and upper chest. The loss of the lower eyelashes and the development of a fissure of the lower lip are frequent complications of the skin lesion. The latter often can be particularly bothersome and difficult to treat.

  Typical café-au-lait spots along with hypopigmented areas are increased over normal in number and often in size.

- **Immunodeficiency.** One or more of the plasma immunoglobulin concentrations are usually abnormally low. Delayed hypersensitivity is decreased. Most individuals with Bloom's syndrome have multiple episodes of otitis media and pneumonia [German 1999].

- **Fertility.** The men with Bloom's syndrome appropriately examined have been azoospermic. Women with Bloom's syndrome, although sometimes fertile, enter menopause prematurely. Five women with Bloom's syndrome followed in the Registry have given birth to nine normal, healthy babies.

- **Intelligence.** The cognitive ability of affected persons varies, some clearly limited, others normal; some have completed college and a few have earned graduate degrees. A short attention span and poor memory characterize the poorly studied learning disability that is exhibited by many persons with Bloom's syndrome, including those with average intelligence.

- **Other clinical features.** In general,d major anatomical defects are not increased in frequency; in the 238 persons in the Bloom's Syndrome Registry, one had a tracheo-esophageal fistula and one had a cardiac malformation. The thumbs were absent in one person, and in one a thumb was malformed. Several males have had a poorly characterized urethral obstruction. Minor defects such as clinodactyly of the fifth finger and a pilonidal dimple, are increased in frequency.

  The medical complications of Bloom's syndrome, all serious, are cancer, myelodysplasia, diabetes mellitus, and chronic pulmonary disease.

- **Cancer.** The most frequent complication and the most common cause of death in Bloom's syndrome is cancer. Although the wide distribution of the types and sites of cancer resembles that in the general population, it occurs much more frequently and at exceptionally early ages in Bloom's syndrome. Development of multiple primary cancers in a single individual also is common. Table 2 summarizes the malignant neoplasms diagnosed in individuals followed in the Registry during the past five decades.

Table 2. The 159 Malignant Neoplasms Diagnosed in Persons in the Bloom's Syndrome Registry, 1954-2005

Tissue Origin (Cancer Types) Site	Mean Age at Diagnosis in Years (range in years)	Number of Persons
Epithelial (carcinoma)		
Lower enteric tract	34.3 (16-47)	25
Integument	31.8 (18-42)	22
Upper entero/respiratory tract	35.4 (25-48)	12
Breast	32.5 (21-42)	9
Genitalia & urinary tract	28.4 (19-43)	8
Lower respiratory tract	33.0 (26-40)	6
Hepatocellular	15.0 (15-15)	1
Lymphoid		
Lymphoma	20.4 (4-45)	32
Acute leukemia	19.6 (5-40)	11
Hematopoietic		
Acute leukemia	16.6 (2-40)	18
Connective tissue (sarcoma)	16.3 (4-30)	3
Germ-cell	24.0 (22-26)	2
Nervous	3.0 (3-3)	1
Other		
Kidney (Wilms tumor)	3.8 (1-8)	6
Metastatic, primary site unidentified	33.7 (28-33)	3
All	25.9 (2-48)	159

- **Myelodysplasia.** This heterogenous group of disorders has been diagnosed in 14 persons in the Registry at a median age of 22.8 years (range 4-39 years), and progressed to leukemia in at least four. In all but one person, the myelodysplasia had been preceded by some form of cancer for which chemotherapy and/or radiotherapy had been given.
- **Diabetes mellitus.** Although the diabetes of Bloom's syndrome has not been well studied, it resembles the typical adult-onset type 2 diabetes, except that in Bloom's syndrome it has an earlier age of onset. Diabetes has been diagnosed in 38 of 238 persons in the Registry (16%) at a mean age of 23 years (range 4-40 years). Although most of the cases have been mild, several have required insulin; both ketoacidosis and diabetic retinopathy have occurred. Abnormalities in insulin release and glucose tolerance have been detected in eight healthy children with Bloom's syndrome (ages nine months to 13 years) and three healthy young adults with Bloom's syndrome (ages 22, 28, and 28 years) by oral glucose-tolerance testing.
- **Chronic pulmonary disease.** About 20% of individuals in the Registry have developed at least one serious bacterial infection of the respiratory tract. Left untreated, respiratory tract infections may progress to chronic bronchiectasis. Chronic pulmonary disease is the second most common cause of death in Bloom's syndrome.

Genotype-Phenotype Correlations

Homozygotes and compound heterozygotes. The same phenotype is produced either by homozygosity or compound heterozygosity for any of the 64 different Bloom's syndrome-causing mutations identified so far.

Heterozygotes. Carriers of Bloom's syndrome-causing mutations are normally developed and healthy, and, specifically, are of normal height.

The cancer risk of heterozygotes has yet to be determined. Two groups independently estimated the risk of colon cancer in *BLM*^{Ash} heterozygotes; Gruber et al (2002) found more Ashkenazi Jews with colon cancer who were heterozygous for *BLM*^{Ash} than expected, whereas Cleary et al (2003) in a less robust study found no increase. In neither study did *BLM*^{Ash} heterozygotes with colon cancer exhibit unusually early ages of onset.

Prevalence

Fewer than 300 cases of Bloom's syndrome have been reported in the medical literature since its description half a century ago [Bloom 1954]. Although very rare in all populations, Bloom's syndrome is less rare in Ashkenazi Jews. Approximately 25% of persons in the Bloom's Syndrome Registry have Ashkenazi Jewish ancestry; the Bloom's syndrome-causing mutation identified in this group of people is designated *BLM*^{Ash}.

The carrier frequency of *BLM*^{Ash} is approximately:

- One in 107 in Ashkenazi Jews in New York City [Li et al 1998]
- One percent of Ashkenazi Jews in Israel [Peleg et al 2002]
- One in 37 in Israeli Ashkenazi Jews, all of whose grandparents were from Poland [Shahrabani-Gargir et al 1998]

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

A sister chromatid exchange (SCE) analysis distinguishes Bloom's syndrome from all other disorders that feature small stature, including the following:

- **Russell-Silver syndrome (RSS).** RSS is characterized by intrauterine growth retardation accompanied by postnatal growth deficiency. Birth weight is typically two or more standard deviations (SD) below the mean, and postnatal growth two or more SD below the mean for length or height. Affected individuals typically have proportionately short stature, normal head circumference, typical facial features, and limb length asymmetry that may result from hemihypotrophy with diminished growth of the affected side. The average adult height of males is 150 cm and that of females is 139 cm. Children with RSS are at significant risk for developmental delay (both motor and cognitive) and learning disabilities. RSS is genetically heterogeneous; for most affected individuals, it represents a phenotype rather than a specific disorder. About 10% of individuals with RSS will have maternal disomy for chromosome 7.
- **Rothmund-Thomson syndrome (RTS)** RTS is characterized by poikiloderma, sparse hair, sparse eyebrows/lashes, small stature, skeletal abnormalities, cataracts, and an increased risk of cancer, especially osteosarcoma. The skin typically is normal at birth; the skin lesion of the RTS develops between age three and six months as erythema, swelling, and blistering on the face, and subsequently it spreads to the buttocks and extremities. Over months to years, the rash evolves into a chronic pattern of reticulated hypo- and hyperpigmentation, punctate atrophy, and telangiectases, collectively known as poikiloderma. *RECQL4* is the only gene known to be associated with the RTS to date. Inheritance is autosomal recessive.
- **Cockayne syndrome**. Classic Cockayne syndrome is characterized by normal prenatal growth with the onset of growth and developmental abnormalities in the first two years of life. By the time the disease has become fully manifested, height, weight, and head circumference are well below the fifth percentile. A malar facial rash

resulting from increased photosensitivity is common. Progressive impairment of vision, hearing, and central and peripheral nervous system function result in severe disability. Assay of DNA repair in skin fibroblasts or lymphoblasts may help with diagnosis in atypical cases. The two genes known to be associated with the Cockayne syndrome are *ERCC6* (75% of individuals) and *CKN1* (25% of individuals). Inheritance is autosomal recessive.

- **Ataxia-telangiectasia (A-T).** A-T is distinguished by telangiectasias of the conjunctivae, progressive cerebellar ataxia beginning between one and four years of age, oculomotor apraxia, choreoathetosis, frequent infections, immunodeficiency, and an increased risk of malignancy, particularly lymphoid leukemia and lymphoma. Individuals with A-T are unusually sensitive to ionizing radiation. *ATM* is the only gene known to be associated with A-T. Inheritance is autosomal recessive.
- **Fanconi anemia**. Fanconi anemia is distinguished by physical abnormalities in 60-75% of affected individuals (including short stature and malformations of the skeleton and multiple organ systems). Bone marrow failure typically develops in the first decade of life. The risk of hematologic malignancies (primarily acute myeloid leukemia) and solid tumors (particularly of the head and neck, skin, GI tract, and genital tract) is increased. The diagnosis of FA rests upon the detection of spontaneous chromosome aberrations, mainly chromatid breaks after culture with a DNA interstrand cross-linking agent such as mitomycin C or diepoxybutane. Eleven complementation groups [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, and L] have been identified and eight of the genes mutated have been isolated. Inheritance is autosomal recessive.

Any prominent erythematous, telangiectatic lesion that predominantly affects the non-facial areas of the body effectively rules out the diagnosis of Bloom's syndrome, even if the face is also affected.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Clinical and genetic case-history taking
- Height and weight measurements
- Inspection of the skin for the presence and severity of the photosensitive facial skin lesion and for hypo- and hyperpigmented areas on any part of the body
- Evaluation for gastro-esophageal reflux when a history of excessive vomiting or regurgitation is obtained
- Determination of fasting blood glucose concentrations

Treatment of Manifestations

Psychosocial. Family and teachers may be encouraged to relate to persons with Bloom's syndrome appropriately for their chronological age, rather than to an age suggested by their unusually small size.

Affected individuals benefit both physically and emotionally when cared for by physicians who make themselves knowledgeable about Bloom's syndrome.

Feeding. Disinterest in feeding is observed in many newborns and infants with Bloom's syndrome, and this presumably contributes to their small size and sometimes even to an emaciated appearance. Regurgitation and vomiting are unusually common in infancy.

Individuals should be evaluated for gastroesophageal reflux, whch may contribute to the poor nutritional intake and which needs to be treated vigorously when present.

Growth. The few children who have been treated with growth hormone did not increase significantly in overall height. Although far from proving a cause and effect, the report by Brock et al (1991) of cancers occurring during or following administration of growth hormone to persons with Bloom's syndrome has deterred trials.

Diabetes mellitus. Treatment of diabetes mellitus in Bloom's syndrome is as in other persons with adult-onset diabetes.

Cancer. The hypersensitivity to both DNA-damaging chemicals and ionizing radiation of persons with Bloom's syndrome necessitates modification of standard cancer treatment regimens, i.e., reduction of both dosages and durations. Information for the ideal dosages is not available [Ma et al 2001].

Surveillance

Families benefit from counseling regarding the risk of cancer, a serious risk for all persons but clearly a much greater one for those with Bloom's syndrome. The wide variety of types and sites of cancer in Bloom's syndrome, however, makes surveillance for cancer unusually challenging to both the affected person and the physician in charge.

- Close contact between individuals age 20 years and older and their physicians is advisable. In both children and adults with Bloom's syndrome, signs and symptoms that cannot be accounted for otherwise should be evaluated as potential early indications of malignancy.
- Conventional cancer detection methods are used in Bloom's syndrome, but because of the early age at which cancer arises, they are needed earlier. In persons under age 20 years, leukemia is the main type of cancer; until evidence becomes available that treatment at the very early stages is more effective than treatment after full-blown symptoms appear, hematologic surveillance other than that used in general practice appears unnecessary and even contraindicated.
- Screening for colon cancer, the most common single cancer in individuals with Bloom's syndrome of all ages (Table 2), should begin decades earlier than average, and should be carried out more frequently than usually recommended.

Agents/Circumstances to Avoid

Sun exposure to facial skin, particularly in infancy and early childhood, should be avoided.

Testing of Relatives at Risk

The striking small size of persons with Bloom's syndrome readily identifies affected sibs; sibs of normal stature need not be tested.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Bone marrow transplantation (BMT). Too few persons have been treated with BMT to draw conclusions about its value. The required ablative therapy prior to BMT requires modification

of standard protocols because of the hypersensitivity of persons with Bloom's syndrome to chemical agents and ionizing irradiation.

Growth. Feeding through indwelling feeding tubes during infancy and early childhood will increase fat deposition, but not linear growth.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Both parents of an affected person are assumed to carry a mutation in *BLM*, the Bloom's syndrome gene. However, one example of uniparental disomy has been reported [Woodage et al 1994].
- Heterozygotes (carriers) are normally developed and healthy.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, 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 is 2/3.
- Heterozygotes (carriers) are normally developed and healthy.

Offspring of a proband

- Men with Bloom's syndrome are infertile.
- Children born to a woman with Bloom's syndrome are assumed to be heterozygous for a *BLM* mutation.
- Because of the high carrier rate for Bloom's syndrome in individuals of Ashkenazi Jewish heritage, the risk for having Bloom's syndrome is approximately one in 200 for the offspring of an affected woman and her Ashkenazi Jewish reproductive partner of unknown carrier status.

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

Carrier Detection

- Carrier testing for at-risk family members of individuals with the *BLM*^{Ash} mutation is clinically available.
- **Individuals of Ashkenazi Jewish heritage.** Because of the relatively increased carrier rate in Ashkenazi Jews, population screening may be available for Ashkenazi Jewish individuals of reproductive age [ACOG 2004]. In population screening of people of Ashkenazi Jewish heritage, targeted mutation analysis for the *BLM*^{Ash} allele is performed.

Related Genetic Counseling Issues

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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Cytogenetic analysis. Prenatal diagnosis for pregnancies at increased risk is possible by the cytogenetic (SCE) analysis of fetal cells obtained by either amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements. Ultrasound measurements are not reliable if the fetus has Bloom's syndrome.

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS). Both of the Bloom's syndrome-causing mutant alleles of an affected family member or of the carrier parents must be identified before prenatal testing is possible.

Preimplantation genetic diagnosis (PGD) has been successfully utilized for one couple [unpublished data, Bloom's Syndrome Registry] and may be available for families in which the Bloom's syndrome-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Bloom's Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
BLM	15q26.1	Bloom syndrome protein

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Bloom's Syndrome

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

Table C. Genomic Databases for Bloom's Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
BLM	BLM	641 (MIM No. 210900)	BLM

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Bloom's syndrome is the prototype of the class of human diseases referred to as the 'chromosome breakage syndromes' [German 1969]. These include Bloom's syndrome, Fanconi anemia, ataxia-telangiectasia, Nijmegen breakage syndrome, Werner syndrome, and xeroderma pigmentosum. These clinically disparate disorders are caused by mutations 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 mutagen-induced mutations in somatic cells. This hypermutability explains the cancer predisposition shared by these disorders. These disorders and several others (e.g., Li-Fraumeni syndrome and HNPCC) that predispose to cancer because of some form of genomic instability at the molecular level, but lack increased chromosomal breakage, have been referred to as 'somatic mutational disorders' [German 1993].

Normal allelic variants: A 4,437-bp cDNA sequence defines the gene *BLM* that 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 [Ellis et al 1995]. Fifteen polymorphisms with no apparent clinical effect have been detected [Bloom's Syndrome Registry, unpublished data].

Pathologic allelic variants:

- Most individuals of Ashkenazi Jewish heritage with Bloom's syndrome have a 6-bp deletion/7-bp insertion at position 2281 of *BLM*, designated blm^{Ash} [Ellis et al 1998]. A second mutation segregating among the Ashkenazi Jewish population, insT2407, has been identified [Bloom's Syndrome Registry, unpublished data].
- The 64 mutations identified in 137 individuals with Bloom's syndrome fall into four broad classes [data partially reported in German and Ellis, 2002 and Bloom's Syndrome Registry, unpublished data]:
  - **Nucleotide insertions and deletions,** each of which eliminates the C-terminus of the protein where the nuclear localization signals of BLM are located; BLM is therefore absent from the nucleus (approximately one-third of all mutations).

- **Nonsense mutations** that convert sense codons to chain-terminating codons also result in truncated BLM protein (approximately one third of all mutations).
- **Intron mutations** that cause splicing defects (approximately one sixth of all mutations).
- **Missense mutations** in different functional domains of the protein that result in the production of non-functional BLM protein (approximately one sixth of all mutations).

Normal gene product: The 1417-amino-acid protein 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 present in the RecQ subfamily of DNA helicases and known to be important in other species for maintenance of genomic integrity. BLM, which is nuclear, is a cell cycle-regulated protein that is distributed diffusely throughout the nucleus but also is concentrated in foci, many of which are so-called 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 upon 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].

Abnormal gene product: The major consequence for a cell in which BLM protein is either absent or present but non-functional is an abnormally high rate of mutation and recombination. The mutations that arise in the somatic cells of a person with Bloom's syndrome are of several types and affect many, presumably all, regions of the genome. Thus, although many of the clinical characteristics and complications of Bloom's syndrome may be viewed as direct or indirect consequences of the cellular hypermutability and hyper-recombination, the proportional small size, the most constant feature of Bloom's syndrome, remains unexplained.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The Milo Gladstein Foundation for Bloom's Syndrome
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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: Email: xps@xps.org
www.xps.org

Bloom's Syndrome Registry
Cornell University Medical College
1300 York Avenue
New York NY 10021
Phone: 212-746-3956; 516 678-5000x6217
Email: jlg2003@mail.med.cornell.edu; msanz@molloy.edu

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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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 Bloom's syndrome and close members of their families are followed [German & Passarge 1989]. 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 the data included in this entry.

Bloom's Syndrome Registry Contact Information:

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Revision History

- 22 March 2006 (me) Review posted to live Web site
- 10 December 2004 (ms) Original submission