Bloom's syndrome

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Abstract
Bloom's syndrome (BS) is a rare human autosomal recessive disorder belonging to a group of "chromosomal breakage syndromes". BS is characterized by marked genetic instability, including a high level of sister chromatid exchanges, associated with a greatly increased predisposition to a wide range of cancers commonly affecting the general population. The constant clinical features of BS are proportionate pre- and postnatal growth retardation and cancer predisposition. Additional clinical features include dolichocephaly, facial sun-sensitive telangiectatic erythema, patchy areas of hyper- and hypopigmentation of the skin and moderate to severe immunodeficiency manifested by recurrent respiratory tract and gastrointestinal infections. A 10-fold increase in the rate of sister chromatid exchanges (SCEs) in BS cells compared to normal cells is the only objective criteria for BS diagnosis. Clinical diagnosis is confirmed cytogenetically by demonstrating characteristic chromosome instability. BS arises through mutations in both copies of the BLM gene which encodes a 3'-5' DNA helicase, a member of the RecQ family. The function of the BLM protein remains unclear, but several lines of evidence support a major role in maintaining genomic stability during DNA replication, recombination and repair. BS frequency in the general population is unknown, probably because this disease is very rare. In Askenazic Jewish population, the frequency of BS is approximately 1 in 48 000. This is due to a founder effect, approximately 1% of the Ashkenasi Jewish population being heterozygous carriers for the blmAsh mutation. There is no curative treatment for BS. However, a physician should carefully follow BS patients in order to ensure early diagnosis of cancer.

Key-words
Bloom's syndrome, cancer predisposition, genetic instability, sister chromatid exchanges, RecQ helicase.

Disease name/synonyms
Bloom syndrome (Bloom's syndrome) Synonyms: Bloom-Torre-Mackacek syndrome, Congenital Telangiectatic Erythema.

Definition
Bloom's syndrome (BS) is a rare human autosomal recessive disorder characterized by marked genetic instability associated with a greatly increased predisposition to a wide range of cancers commonly affecting the general population. The predominant and constant clinical feature of BS is proportionate pre- and postnatal growth retardation. Additional clinical features are dolichocephaly, narrow facies with nasal prominence and malar and mandibular hypoplasia, facial sun-sensitive telangiectatic erythema in the butterfly area, patchy areas of hyper- and hypopigmentation of the skin (café-au-lait spots), and moderate to severe immunodeficiency manifested by recurrent respiratory tract and gastrointestinal infections (German, 1993). BS was first described in 1954 as "congenital telangiectatic erythema resembling lupus erythematosus in dwarfs" (Bloom, 1954).

Differential diagnosis
Bloom's syndrome belongs to a group of "chromosomal breakage syndromes" which are genetic disorders that are typically transmitted in an autosomal recessive mode. Cells from affected individuals are characterized by an increased frequency of breaks and interchanges occurring either spontaneously or following exposure to various DNA-damaging agents. Patients with these disorders show increased predisposition to cancer. The commonly acknowledged chromosomal breakage syndromes are Fanconi anemia, ataxia telangiectasia, Xeroderma Pigmentosum and Bloom's syndrome. However, the hallmark of BS cells is an approximately 10-fold increase in the rate of sister chromatid exchanges (SCEs) compared to normal cells (Chaganti *et al.*, 1974). The increased level of SCEs is the only objective criteria for BS diagnosis. It should be noted that in about 20% of BS patients, normal levels of SCE are observed in a subpopulation of B and T lymphocytes (Ellis *et al.*, 1995a; Weksberg, 1995). These low-SCE revertant BS cells result from an intragenic crossing over between the paternal and maternal BLM alleles, generating a wild type allele in compound heterozygote patients (Ellis *et al.*, 1995a; Foucault *et al.*, 1997).

Etiology
Bloom's syndrome arises through mutations in both copies of the *BLM* gene, which is located on chromosome 15 at 15q26.1. Currently, there is no argument for a possible genetic heterogeneity in BS. Nonsense or frameshift mutations leading to a premature termination codon as well as missense mutations have been found in *BLM* gene from BS patients (Ellis *et al.*, 1995b; Foucault *et al.*, 1997; Barakat *et al.*, 2000). One particular *BLM* gene mutation corresponding to a 6-bp deletion and a 7-bp insertion at nucleotide position 2281, referred as *blmAsh* mutation, is homozygous in nearly all BS patients with Ashkenasi Jewish ancestry (Ellis *et al.*, 1995b) due to a founder effect (Ellis *et al.*, 1994).
BLM gene codes for the 1417 amino acids BLM protein with a predicted molecular mass of 159 kDa, and which belongs to the DExH box-containing RecQ helicase subfamily (Ellis *et al.*, 1995b). Recombinant (Karow *et al.*, 1997) and endogenous (Dutertre *et al.*, 2002) BLM display an ATP- and Mg2+ dependent 3'-5'-DNA helicase activity that separate the complementary strands of DNA in a 3'-5' direction. But BLM function is still unclear. BLM protein has been shown to accumulate in S and G2 phases of the cell cycle (Dutertre *et al.*, 2000; Sanz *et al.*, 2000; Bischof *et al.*, 2001a) and to localize in two distinct nuclear structures, PML nuclear bodies (also called ND10) (Ishov *et al.*, 1999) and the nucleolus (Yankiwski *et al.*, 2000). The preferred substrates for BLM are G-quadruplex DNA (Sun *et al.*, 1998; Mohaghegh *et al.*, 2001), D-loops structures (van Brabant *et al.*, 2000) and X-junctions (Karow *et al.*, 2000). BLM also promotes branch migration of RecA-generated Hollyday junctions (Karow *et al.*, 2000). BLM interacts with several proteins involved in the maintenance of genome integrity. It participates in a super complex of BRCA1-associated proteins named BASC (BRCA1-Associated genome Surveillance Complex) that includes BRCA1, mutated in some familial breast cancers, ATM, NBS1 and MRE11 proteins, defective in Ataxia Telangectasia (AT), Nijmegen syndrome and ataxia-telangiectasia-like disorder, respectively, MLH1, MSH2 and MSH6, involved in Human non-polyposis colorecal cancer (HNPCC syndrome), and several other proteins known to be involved in replicational and/or post-replicational repair process (Wang *et al.*, 2000). BLM also participates in a complex containing RPA and topoisomerase IIIa, known to interact independently with BLM (Brosh *et al.*, 2000; Wu *et al.*, 2000; Hu *et al.*, 2001), and five of the Fanconi anemia (FA) complementation group proteins (FANCA, FANCG, FANCC, FANCE and FANCF): this complex has been termed BRAFT (BLM, RPA, FA, Topoisomerase IIIa) (Meetei AR *et al.*, 2003). The other proteins

known to interact physically and/or functionally with BLM are:

- the tumor suppressor protein p53 (Garkavtsev *et al.*, 2001; Wang *et al.*, 2001; Yang *et al.*, 2002; Sengupta *et al.*, 2003)
- the WRN protein, a RecQ helicase defective in the Werner syndrome, a premature aging disease (von Kobbe *et al.*, 2002),
- MLH1, which participates in the mismatch repair pathway (Langland *et al.*, 2001; Pedrazzi *et al.*, 2001),
- RAD51, the key protein of the homologous recombination (Wu *et al.*, 2001),
- TRF2, a double-stranded telomeric DNA binding protein likely involved in the regulation of telomeric length (Opresko *et al.*, 2002; Stavropoulos *et al.*, 2002).

The BLM protein has also been shown to be:

- cleaved into 40-47 kDa N-terminal and 110-120 kDa C-terminal major fragments by caspase-3 in response to several apoptosis-inducing agents such as anti-Fas antibody, etoposide, hydroxyurea and UV-C irradiation (Bischof *et al.*, 2001b; Freire *et al.*, 2001; Ababou *et al.*, 2002a),
- phosphorylated in mitotic cells (Dutertre *et al.*, 2000; Beamish *et al.*, 2002), and in response to DNA damaging agents (Ababou *et al.*, 2000; Bishof *et al.*, 2001; Ababou *et al.*, 2002b; Franchitto and Pichierri, 2002),
- involved in DNA double-strand breaks repair (Rünger and Kraemer, 1989; Gaymes *et al.*, 2002; Langland *et al.*, 2002; Onclercq-Delic *et al.*, 2003),
- associated with telomeres and ribosomal DNA repeats (Schawalder *et al.*, 2003).

Concerning mice models of BS, among the five BS knocktout alleles that have been generated, four led to embryonic lethality when the targeted allele was homozygous (Chester *et al.*, 1998; Luo *et al.*, 2000; Goss *et al.*, 2002), and only one resulted in viable "BS" mice through a complex rearrangement of the targeted region (Luo *et al.*, 2000). Luo *et al.* (2000) proposed that an increased rate of loss of heterozygosity resulting from mitotic recombination constitutes the underlying mechanism causing tumour susceptibility in these mice.

Altogether these data support a major role for BLM in maintaining genomic stability during DNA replication, recombination and DNA repair (reviewed in Nakayama, 2002; Bachrati and Hickson, 2003).

Clinical description

A program of surveillance referred to as Bloom's Syndrome Registry has been established in 1960 in which the follow-up of 168 BS patients (93 males, 75 females) has been reported until 1991 (German *et al.*, 1977; 1979; 1984; German and Passarge, 1989). As reported in details by German (1995) on the basis of the data collected in the Bloom's Syndrome Registry, the two constant clinical features associated with BS are growth retardation starting *in utero* and persisting throughout life with normal proportioning and accompanied by dolichocephaly, and predisposition to all types of cancers. The mean adult height for men is 147,5 cm (range 130 to 162), and for women is 138,6 cm (range 122 to 151). German (1995) has also noted eleven additional clinical features that are not constant and that vary in severity among BS patients: (1) a "bird-like" facies with a narrow face and prominent nose, and malar and mandibular hypoplasia; (2) sun-sensitive erythema affecting the butterfly area of the face (similar to that caused by lupus erythematosis), and sometimes the dorsa of the hands and forearms; (3) spots of hyper- and hypopigmentation of the skin ("café au lait" spots); (4) a high-pitched voice (Mickey mouse voice); (5) a variable degree of "vomiting and diarrhea" during infancy; (6) diabetes mellitus (diagnosed at a mean age of 24,9 years in 20 of the 168 BS patients in the Registry); (7) small testes accompanied by a total failure of spermatogenesis in men and early cessation of menstruation accompanied by reduced fertility in women; (8) immunodeficiency manifested by recurrent respiratory tract infections complicated by otitis media and pneumonia (life-threatening ear and lung infections are common) and by the gastrointestinal problems mentioned in 5; (9) some minor anatomic abnormalities such as obstructing anomalies of the urethra which have been of major clinical importance in several cases; (10) average intelligence (sometimes mental deficiency); (11) clinical features which occurred in only one or few BS patients and that are not to be considered part of BS itself, such as congenital thrombocytopenia, mild anemia, asthma, psoriatic arthritis. These clinical information have also been reported in German and Ellis (1997).

The 100 cancers that had arisen in 71 of the 168 BS patients recorded in the Bloom's Syndrome Registry have been reported (German and Ellis, 1997; German, 1997), and the distribution of sites and types of these cancers is similar to that found in the general population. The main conclusions of this report are that nearly half of the registered BS (71/168) patients have had at least one cancer at a mean age of 24,7 years,

40% of whom having had more than one primary cancer (29/71). Acute leukemias, lymphomas and rare tumors (medulloblastoma, Wilm's tumor, osteogenic sarcoma) represent 21%, 23% and 5% of the cancers, respectively, and predominate in the first two decades of life, whereas carcinomas represent 51% of the cancers and occur later in the second decade (German and Ellis; German, 1997).

Diagnostic methods

The hallmark of BS cells is the elevated level of SCEs that represent the only objective criteria for the diagnosis of the disease. SCE detection is based on differential labeling of sister chromatids, which is classically done by the method developed by Wolff and Perry (1974) and modified by Morgan *et al.* (1983). In brief, blood lymphocytes stimulated by phytohemagglutinin or skin fibroblasts are cultured in a 5-bromodeoxyuridine (BrdU)-containing medium during two rounds of cell replication (BrdU is an analogue of thymidine that is incorporated specifically into DNA of replicating cells), resulting in one of the sister chromatids unifilarly substituted with BrdU and the other one bifilarly substituted. Then, colcemid is added for the last hours before fixation to arrest the cells in metaphase. Differential staining of BrdU-substituted chromatids is obtained by fluorescence-plus-Giemsa coloration of spread mitotic chromosomes. The unifilarly substituted chromatids are darkly stained (black) and the bifilarly substituted ones are stained lightly (white) (see figures 1 and 2).

SCEs frequency averages 0.24 per chromosome in normal cells and 2.12 per chromosome in BS cells (McDaniel and Schultz, 1992).

The screening for *BLM* gene mutations could also be performed by the analysis of the 21 coding exons (4437 bp in length), and it is possible to look for specific changes in the *BLM* gene, in particular for the *blmAsh* mutation.

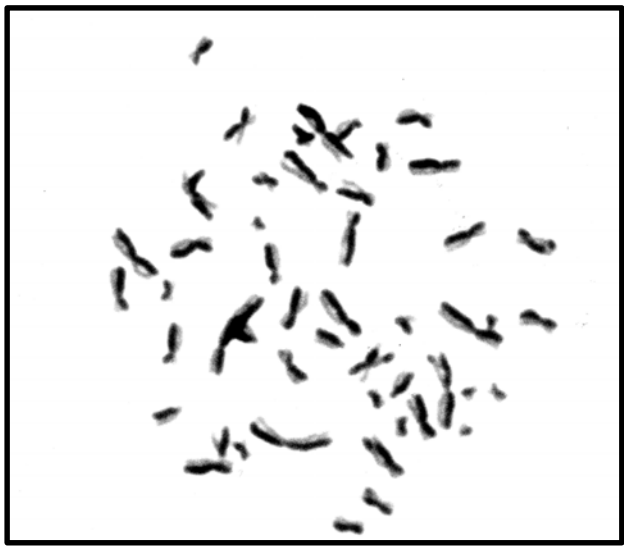

Figure 1: Normal cell metaphase

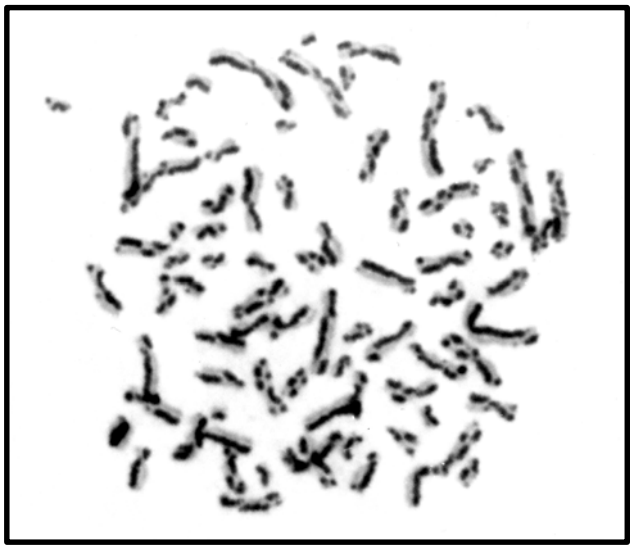

Figure 2: BS cell metaphase

Epidemiology

Bloom's syndrome is a very rare disease and its frequency in the general population is unknown. However, BS is more common in Askenazic Jewish population, reaching a frequency of approximately 1 in 48 000 (Shahrabani-Gargir *et al.*, 1998).

Genetic counseling

Due to the autosomal recessive transmission mode of BS, sibs of two heterozygous carriers are at 25% risk of having BS and 50% risk of being a carrier. It should be noted that among the Ashkenazi Jewish population, the heterozygous carrier frequency of this mutation is approximately 1% (Ellis *et al.*, 1998; Li *et al.*, 1998; Shahrabani-Gargir *et al.*, 1998). Two studies conducted to assess the cancer risk among *blmAsh* heterozygotes gave contradictory results (Gruber *et al.*, 2002; Cleary *et al.*, 2003).

Antenatal diagnosis
When the risk of BS transmission has been well evaluated, prenatal diagnosis can be proposed (SCEs analysis of fetal cells or looking for a specific *BLM* gene mutation when causative mutations are identified).

Management including treatment
There is no curative treatment for BS. However, a physician should carefully follow BS patients in order to ensure early diagnosis of cancer.

Unresolved questions
The underlying mechanisms causing BS are not well defined since BLM protein' s function(s) is still unclear.

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