Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Cancer Prone Disease Section

Mini Review

Bloom syndrome

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Published in Atlas Database: February 2005

Online updated version: http://AtlasGeneticsOncology.org/Kprones/BLO10002.html
DOI: 10.4267/2042/38199

This article is an update of: Amor-Guéret M. Bloom syndrome. Atlas Genet Cytogenet Oncol Haematol.2000;4(4):218-220.
Huret JL. Bloom syndrome. Atlas Genet Cytogenet Oncol Haematol.1998;2(2):65-66.

Identity

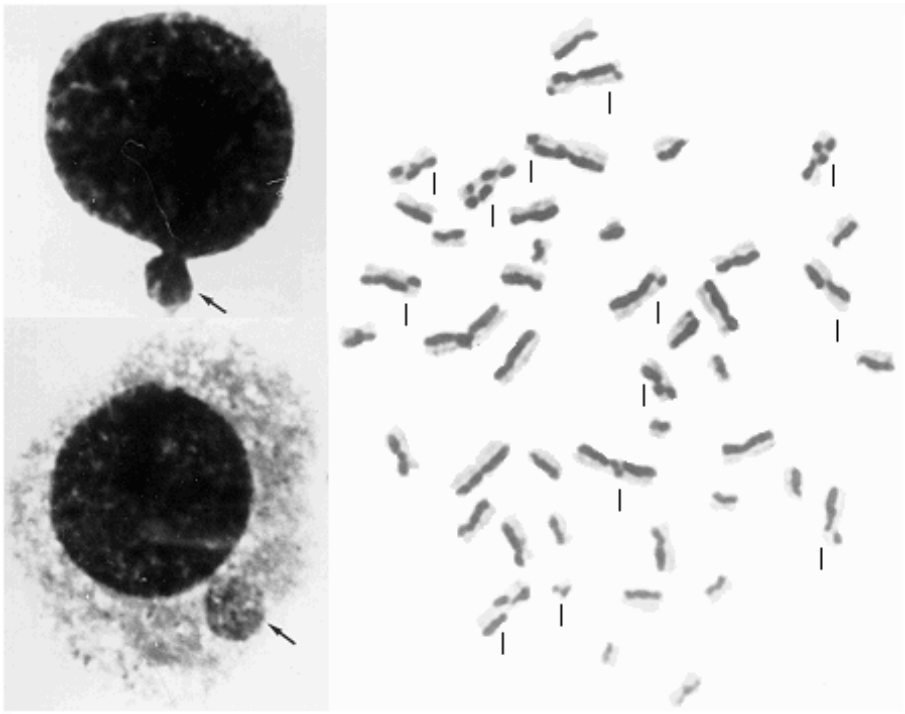
Inheritance

Autosomal recessive; frequency is about $2/10^5$ newborns in Ashkenazi Jews and in the Japanese (founder effect: affected persons descent from a common ancestor); much rarer otherwise.

Clinics

Note

168 cases have been registered in the Bloom's syndrome Registry by James German; BS patients are predisposed to all types of cancer observed in the general population; thus, BS is a model of initiation and promotion of cancer, and highligths internal causes/processes of cancers.



Micronuclei (left); sister chromatid exchange (right) in a normal subject (herein: 19 SCE, instead of the hundred found in Bloom, see below) – Editor.

Phenotype and clinics

- Phenotypic spectrum variable.
- Growth: dwarfism: intrauterine growth retardation; birth weight: below 2.3 kg; mean length: 44 cm; adult length < 145 cm.
- Skin: hyperpigmented (café au lait) spots; hypopigmented areas; sun sensitive telangiectatic erythema; in butterfly configuration across the face: resembles lupus erythematous.
- Head: microcephaly; dolichocephaly; narrow face; prominent nose and/or ears; characteristic high-pitched voice.
- Normal intelligence.
- Immune deficiency --> frequent infections (may be life-threatening).
- Other: myocardopathy; hypogonadism in male patients; hypertriglyceridemia.

Neoplastic risk

Nearly half of patients have had at least one cancer (10% of whom having had more than one primary cancer, which is quite characteristic of Bloom's); mean age at first cancer onset: 25 yrs (range: 2-49 yrs).
Acute leukaemias (ALL and ANLL) in 15 % of cases; lymphomas in 15 % as well; these occur mainly before the thirties.
Carcinomas (of a wide variety) occur in 30 % of cases, mainly after the age of 20 yrs.
Benign tumours (10%).

Evolution

Major medical complications apart from cancers are: chronic lung disease, and diabetes mellitus (in 10 %).

Prognosis

1/3 of patients are dead at mean age 24 yrs (oldest died at 49 yrs, youngest died before 1 yr) and the mean age of the 2/3 remaining alive patients is 22 yrs (range: 4-46 yrs).

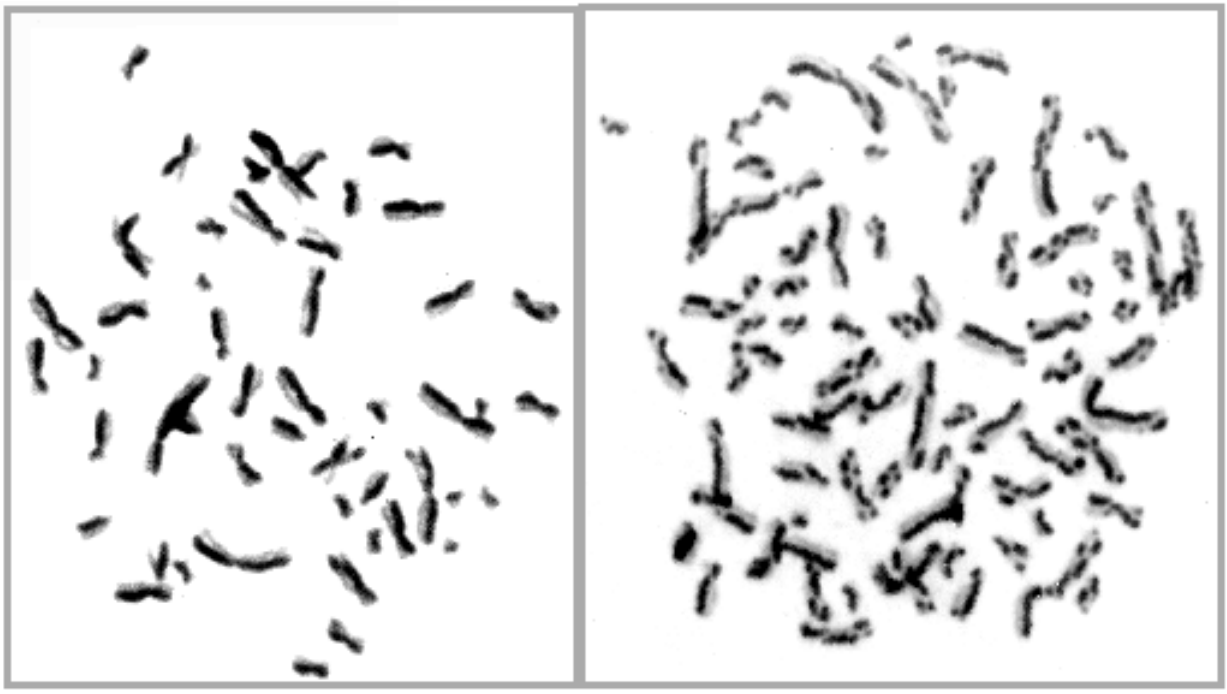
Cytogenetics

Inborn conditions

Chromatid/chromosome breaks; triradial and quadriradial figures, in particular symetrical quadriradial configuration involving homologous chromosomes (Class I qr), which are pathognomonic and which may be due to a mitotic crossing-over; micronuclei.
Diagnosis is on the (pathognomonic) highly elevated spontaneous sister chromatid exchange rate (90 SCE per cell; more than 10 times what is normally found); in some persons a minor population of low SCE cells exists, suggesting a recombination event between maternal and paternal alleles (with different mutations), giving rise to a wild type functional gene; this allowed to localize the gene in a very elegant strategy.
Heterozygotes are not detectable by cytogenetic studies.

Other findings

Note
Slowing of the cell cycle (lenthening of the G1 and S phases).
Spontaneous mutation rate 10 times higher than normal cells.



Sister chromatid exchange in a normal subject (left) and in a Bloom syndrome patient (right) (from: Mounira Amor-Guéret).

Genes involved and proteins

Complemantation groups

No complementation group.

BLM

Location

15q26.1

Protein

Description: 1417 amino acids; contains one ATP binding site, one DEAH box, and two putative nuclear localization signals.

Expression: Accumulates to high levels in S phase of the cell cycle, persists in G2/M and sharply declines in G1; hyperphoshorylated in mitosis.

Localisation: Nuclear (PML nuclear bodies and nucleolus).

Function: 3-5 DNA helicase; probable role in DNA replication and double-strand break repair.

Preferred substrates: G-quadruplex DNA, D-loops structures and X-junctions. Recombinant protein promotes ATP-dependent branch migration of Hollyday junctions.

Participates in a supercomplex of BRCA1-associated proteins named BASC (BRCA1-Associated genome Surveillance Complex) and in a complex named BRAFT (BLM, RPA, FA, Topoisomerase IIIalpha) containing five of the Fanconia Anemia (FA) complementation group proteins (FANCA, FANCG, FANCC, FANCE and FANCF).

Interacts physically and/or functionally with p53, 53BP1, WRN, MLH1, RAD51, TRF2, ligase IV, FEN1

Associated with telomeres and ribosomal DNA repeats.

Phosphorylated in mitotic cells through the cdc2 pathway, and in response to DNA damaging agents.

Homology: With the RecQ helicases.

Mutations

Germinal: Five BLM mutations introducing amino acid substitutions and four BLM mutations introducing premature nonsense codons into the coding sequence have been described to date; one BLM mutation consisting in a 6 bp deletion accompanied by a 7 bp insertion at nucleic acid position 2281 is common in patients from Ashkenazi Jewish ancestry, leading to a truncated protein of 739 amino acids in length; two BLM mutations, 631delCAA and 1610insA were detected in japanese patients.

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This article should be referenced as such:

Amor-Guéret M. Bloom syndrome. Atlas Genet Cytogenet Oncol Haematol. 2005; 9(2):177-180.