Bloom syndrome

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Identity

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

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 highlights internal causes/processes of cancers.

**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 (cafè au lait) spots; hypopigmented areas; sun sensitive telangiectatic erythema; in butterfly configuration across the face: resembles lupus erythematosus;
- 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 years (range: 2-49 years): Acute leukaemias (ALL and AML) 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 years. 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 years (oldest died at 49 years, youngest died before 1 year), and the mean age of the 2/3 remaining alive patients is 22 years (range: 4-46 years).

**Cytogenetics**

**Inborn conditions**
Chromatid/chromosome breaks; triradial and quadriradial figures, in particular symmetrical quadriradial configuration involving homologous chromosomes (Class I qr), which are pathognomonic and which may be due to a mitotic crossing-over. 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.

Genes involved and proteins

Note
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; hyperphosphorylated in mitosis.
Localisation: Nuclear.
Function: 3'-5' DNA helicase; probable role in DNA replication and repair.
Participates in a supercomplex of BRCA1-associated proteins named BASC (BRCA1-Associated genome Surveillance Complex).
Recombinant protein promotes ATP-dependent branch migration of Holliday junctions.
Homology: Homology with the RecQ helicases.

**Mutations**
Germline: 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; the mutated BLM protein is totally or partially is retained in the cytoplasm, while the normal protein is nuclear.

References


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