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Cancer Prone Disease Section

Mini Review

Bloom syndrome

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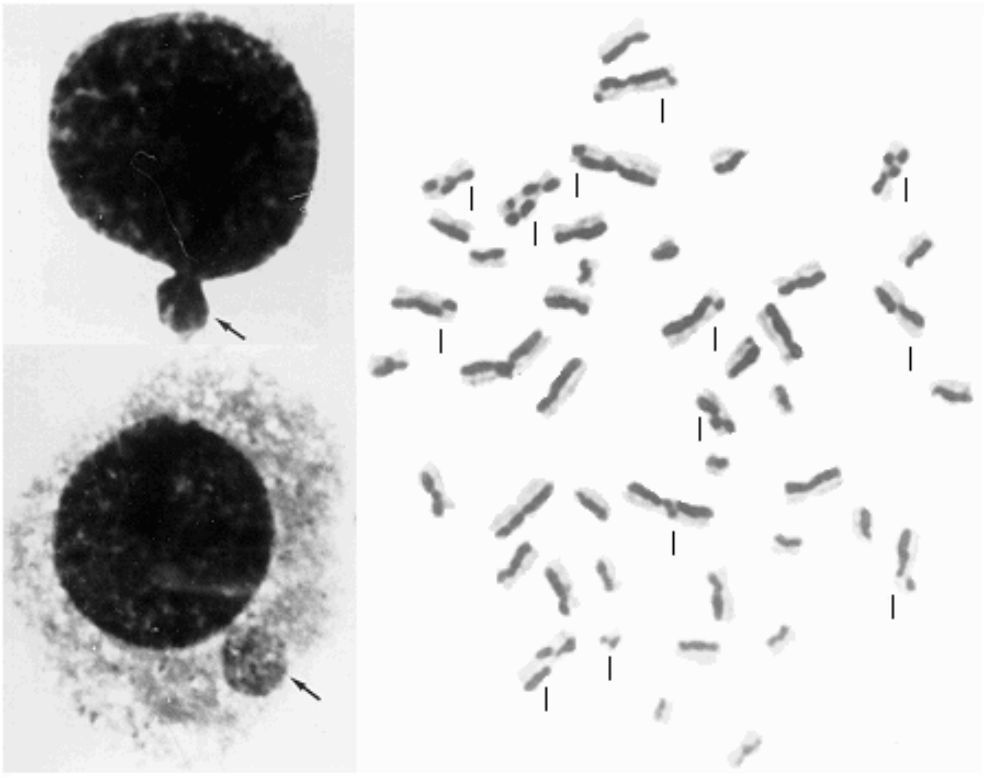
Identity



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 highligths 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 (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 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 %).

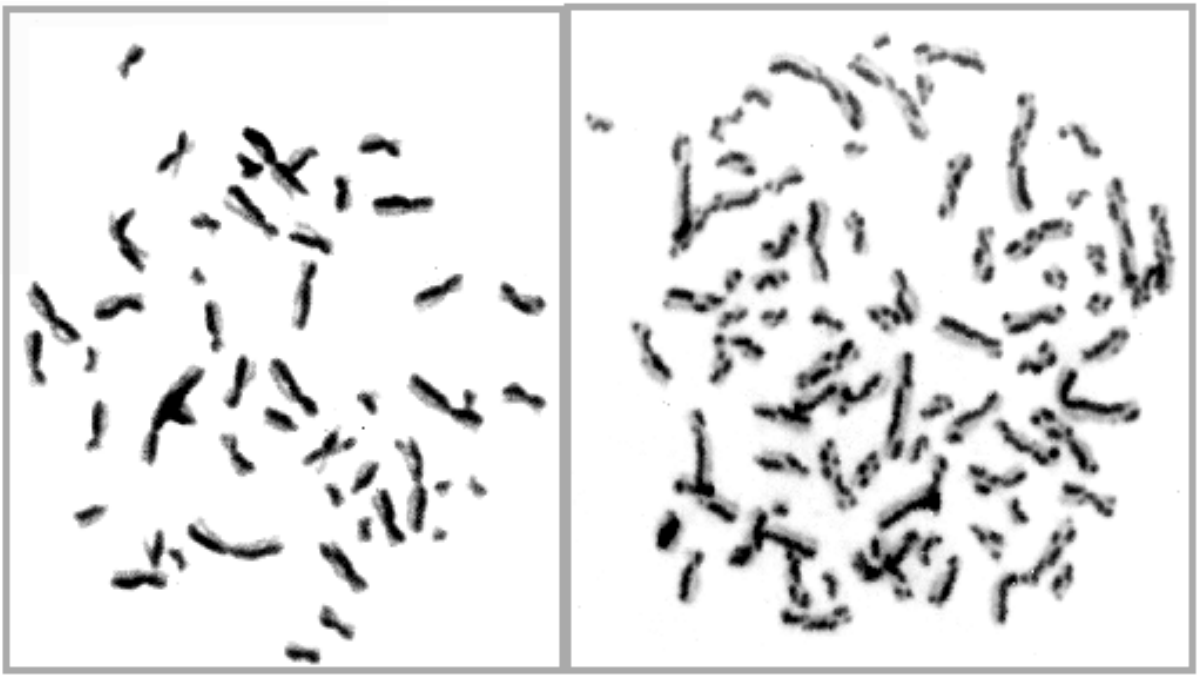
Prognosis

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 symetrical 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.



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

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; hyperphoshorylated 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
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; the mutated BLM protein is totally or partially is retained in the cytoplasm, while the normal protein is nuclear.

References

German J. Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. Am J Hum Genet. 1969 Mar;21(2):196-227

Gorlin RJ, Cohen MM, Levin LS.. Syndromes of the head and neck. Oxford Monogr Med Genet. 1990; 19: 297-300.

Ellis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S, Proytcheva M, German J. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell. 1995 Nov 17;83(4):655-66

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Ellis NA, German J. Molecular genetics of Bloom's syndrome. Hum Mol Genet. 1996;5 Spec No:1457-63

Foucault F, Vaury C, Barakat A, Thibout D, Planchon P, Jaulin C, Praz F, Amor-Guéret M. Characterization of a new BLM mutation associated with a topoisomerase II alpha defect in a patient with Bloom's syndrome. Hum Mol Genet. 1997 Sep;6(9):1427-34

German J. Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet. 1997 Jan;93(1):100-6

Kaneko H, Orii KO, Matsui E, Shimozawa N, Fukao T, Matsumoto T, Shimamoto A, Furuichi Y, Hayakawa S, Kasahara K, Kondo N. BLM (the causative gene of Bloom syndrome) protein translocation into the nucleus by a nuclear localization signal. Biochem Biophys Res Commun. 1997 Nov 17;240(2):348-53

Karow JK, Chakraverty RK, Hickson ID. The Bloom's syndrome gene product is a 3'-5' DNA helicase. J Biol Chem. 1997 Dec 5;272(49):30611-4

Barakat A, Ababou M, Onclercq R, Dutertre S, Chadli E, Hda N, Benslimane A, Amor-Guéret M. Identification of a novel BLM missense mutation (2706T>C) in a Moroccan patient with Bloom's syndrome. Hum Mutat. 2000 Jun;15(6):584-5

Dutertre S, Ababou M, Onclercq R, Delic J, Chatton B, Jaulin C, Amor-Guéret M. Cell cycle regulation of the endogenous wild type Bloom's syndrome DNA helicase. Oncogene. 2000 May 25;19(23):2731-8

Karow JK, Constantinou A, Li JL, West SC, Hickson ID. The Bloom's syndrome gene product promotes branch migration of holliday junctions. Proc Natl Acad Sci U S A. 2000 Jun 6;97(12):6504-8

Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes Dev. 2000 Apr 15;14(8):927-39

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