Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Cancer Prone Disease Section

Mini Review

Bloom syndrome

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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.

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 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 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 condition

- 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; found in 3-4% of metaphases (normal: $1/10^5$).
- Diagnosis is on the (pathognomonic) highly elevated spontaneous sister chromatid exchange rate (90 SCE per cell; more than 10 times what is normally found, which is about 8-10 SCE per cell with BrDU; spontaneous SCE rate (without DNA damaging agent) in the normal population being about 1 per cell); 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 (called somatic reversion); 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); DNA ligase I deficiency (delayed junction of Okazaki fragments).

Genes involved and Proteins

BLM

Location: 15q26.1

Protein

Description: ATP binding, DEAH box, and two putative nuclear localization signals.
Localisation: nuclear.
Function: DNA helicase; probable role in DNA replication and repair.
Homology with the RecQ helicases.

Mutations

Germinal: the mutated BLM protein is retained in the cytoplasm or both in the cytoplasm and the nucleus, while the normal protein is nuclear.

Somatic: random somatic mutations in random DNA segments appear to randomly cause tumour initiation and/or progression: every cancer type is over-represented in this syndrome, and at a much earlier age than normal.

References

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