Cancer Prone Disease Section
Mini Review

Fanconi anaemia
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Identity

Other names: Fanconi pancytopenia
Inheritance: autosomal recessive; frequency is about 2.5/10^5 newborns.

Clinics

Note: Fanconi anaemia is a chromosome instability syndrome with progressive bone marrow failure and an increased risk of cancers.

Phenotype and clinics
- Growth retardation (70% of cases).
- Skin abnormalities: hyperpigmentation and/or café au lait spots in 80%.
- Skeletal malformations (60%), particularly radius axis defects (absent or hypoplastic thumb or radius...).
- No immune deficiency (in contrast with most other chromosome instability syndromes).
- Progressive bone marrow failure; mean age of onset of anaemia: 8 yrs; diagnosis made before onset of haematologic manifestations in only 30%.
- Other: renal anomalies, hypogonadism, mental impairment, heart defects, and perhaps diabetes mellitus, also occur in 10 to 30% of cases.

Neoplastic risk
- Myelodysplasia (MDS) and acute non lymphocytic leukaemia (ANLL): 10% of cases; i.e. a 15000 fold increased risk of MDS and ANLL has been evaluated in FA, and it has been assumed that ‘it is reasonable to regard the Fanconi anaemia genotype as ‘preleukaemia’; mean age at diagnosis: 15 yrs.
- Hepatocarcinoma (androgen-therapy induced) in 10%; mean age at diagnosis: 16 yrs.
- Other cancers in 2-5%; in particular squamous cell carcinoma.

Treatment
Androgens and steroids to improve haematopoietic functions; bone marrow transplantation prevents from terminal pancytopenia, and from ANLL as well.

Prognosis
Mean age at death: 16 years; most patients die from marrow aplasia (haemorrhage, sepsis), and others from malignancies; MDS and ANLL in FA bear a very poor prognosis (median survival of about 6 mths); survival is also poor in the case of a squamous cell carcinoma.

Cytogenetics

Inborn condition
- Spontaneous chromatid/chromosome breaks, triradials, quadriradials.
- Hypersensitivity to the clastogenic effect of DNA cross-linking agents (increased rate of breaks and radial figures); diepoxybutane, mitomycin C, or mechlorethamine hydrochlorid are used for diagnosis.

Cancer cytogenetics
- Various clonal anomalies are found in MDS or ANLL in Fanconi anaemia patients, such as the classical -5/del(5q), and -7/del(7q), found in 10 % of cases; telomeres appear to be non randomly involved in FA’s clonal anomalies.

Other findings

Note:
- Slowing of the cell cycle (G2/M transition, with accumulating of cells in G2).
- Impaired oxygen metabolism.
- Defective P53 induction.
**Genes involved and Proteins**

**Complementation groups:**
4 well known complementation groups: group A (gene FA1 in 16q24, perhaps another gene 20q13), group B, group C (gene FACC in 9q22), group D (gene FAD in 3p24 has sometimes been located in 11q23); a fifth group, group E, may, per se, be heterogenous; however, the different complementation groups display similar phenotypes, and genes may therefore be functionally related (recently was found that FA1 and FACC form heterodimers).

**FA1**
**Location:** 16q24
**Protein**
Expression: wide.
Localisation: mostly cytoplasmic.
Function: binds to the protein encoded by FACC (see below), the dimer being found in the cytoplasm and the nucleus.
Homology: no known homology.

**Mutations**
Germinal: various nucleotide substitutions, deletions, or insertions.

**FACC**
**Location:** in 9q22
**Protein**
Expression: wide.
Localisation: cytoplasmic when unbound.
Function: peak expression during the G2/M transition; binds to cdc2 (mitotic cyclin-dependent kinase); probably involved in basic aspect(s) of the cell protection against DNA damages: role in the cell cycle regulation and/or in DNA repair and/or in the prevention of cellular apoptosis; binds to FAA, the protein encoded by FA1 (see above), the dimer being found in the cytoplasm and the nucleus.
Homology: no known homology.

**Mutations**
Germinal: nucleotide substitutions.

**FAD**
**Location:** 3p24

**To be noted**
Clinical diagnosis may, in certain cases, be very difficult; cytogenetic ascertainment is then particularly useful; however, cytogenetic diagnosis may also, at times, be very uncertain; this is a great problem when bone marrow engraftment has been decided in a pancytopenic patient: if this patient has FA, bone marrow conditioning must be very mild, as FA cells are very clastogen sensitive.
FA patients (i.e. patients with defective alleles) may have, in a percentage of cells, a somatic reversion (by revert mutation towards wild-type gene); such a phenomenon is also known in Bloom syndrome, another chromosome instability syndrome.

**References**

Alter BP, Potter NU. Chromosome Mutation and neoplasia. J German Ed. AR Liss 1983; pp 43.

This article should be referenced as such: