Ataxia telangiectasia
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Identity
Other names: Louis-Bar syndrome
Inheritance: Autosomal recessive; frequency is about 1 to 2.5/10^5 newborns; as there are complementation groups, heterozygotes may be as frequent as 2% of the general population; a founder effect is found in some areas.

Clinics
Ataxia telangiectasia is a chromosome instability syndrome with cerebellar degeneration, immunodeficiency, and an increased risk of cancers.

Phenotype and clinics
- Onset of the disease is often during the second year of life: there is progressive cerebellar ataxia (initially truncal, with further peripheral extend); ataxia is a constant feature in this disease; oculomotor apraxia, dysarthria, and dystonia; leading to muscular atrophy.
- Telangiectasia: facial region exposed to sunlight, and eyes (conjunctiva).
- Combined immunodeficiency (in 70 %): thymus hypoplasia, and IgG2 and 4, IgA, IgE deficiency.
- Other features: growth retardation; hypogonadism; diabetes mellitus.
- Mental retardation may occur.

Neoplastic risk
Risk of cancers is X 100:
- Mainly T-cell malignancies (a 70 fold and 250 fold increased risks of leukaemia and lymphoma respectively),
- But also: carcinomas of the skin, the ovary, the breast, the stomach...; B-cell malignancies; but no myeloid leukaemia.

Evolution
Progressive cerebellar degeneration: patients are in a wheelchair by the age of ten.

Prognosis
Respiratory infections are the common cause of death (80%); and cancers are responsible for the remaining 20%; survival rarely exceeds 30 yrs; median survival: 17 yrs.

Cytogenetics

Inborn condition
- Spontaneous chromatid/chromosome breaks, triradials, quadriradials (less prominent phenomenon than in Fanconi anaemia); telomeric associations.
- The best diagnosis test is on the (pathognomonic) highly elevated level (10% of mitoses) of inv(7)(p14q35), t(14;14)(q11;q32), and other non clonal stable chromosome rearrangements involving 2p12, 7p14, 7q35, 14q11, 14q32, and 22q11 (illegitimate recombinations between immunoglobulin superfamilly genes Ig and TCR); normal level of those rearrangements are: 1/500 (inv(14)), 1/200 (t(7;14)), 1/10 000 (inv(7)).
- Clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14).

Cancer cytogenetics
Clonal rearrangements in T-cell ALL and T-PLL (prolymphocytic leukaemia) in AT patients are complex, with the frequent involvement of t(14;14), or t(X;14), implicating the genes TCL1 or MTCPI respectively, as is found in T-PLL in non-AT patients.
Other findings

Note:
- High sensitivity to radiations and to radioimetic drugs (diagnostic may in part be based on the hypersensitivity of AT lymphocytes to killing by gamma irradiation); cell irradiation does not inhibit S phase (DNA synthesis); this is quite pathognomonic of AT, and shows that G1 checkpoint is deficient; there is a lack of P53, GADD45 and P21 induction, and a fall in radiation-induced apoptosis.
- Lengthening of the cell cycle.
- Difficulty to grow cells with phytohemaglutinin: karyotypes should be performed with interleukine 2 in 4 days cultures.
- Other: increased level of serum alpha-fetoprotein.

Genes involved and Proteins

Complementation groups :
4 complementation groups: A, C, D, and E; although there is only 1 gene involved in this disease.

**ATM**

**Location:** 11q22

**DNA / RNA**
Description: 66 exons.

**Protein**
Description: contains a PI 3-kinase-like domain.

Localisation: mostly in the nucleus.

Function: in the cell cycle regulation (G1/S and S phase): mediating cell cycle arrest in response to radiations.

**Mutations**
Germinal: various types of mutations, dispersed throughout the gene, and therefore most patients are compound heterozygotes; however, most mutations appear to inactivate the ATM protein by truncation, large deletions, or annulation of initiation or termination.

To be noted
- As ataxia telangiectasia patients have a high sensitivity to radiation, they cannot tolerate the therapeutic radiation usually given to cancer patients.
- Heterozygous for AT may be at increased (up to X 7) risk of breast cancer; i.e. 10 to 20% of patients with breast cancer could be heterozygous for AT (Swift et al. 1991), and may also have a X 3 risk for other cancers.
- Nijmegen variant of AT does not implicate the same gene.

References


