Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Cancer Prone Disease Section

Mini Review

Ataxia telangiectasia

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Identity

Alias
Louis-Bar syndrome

Note
See also, in Deep Insight section: Ataxia-Telangiectasia and variants.

Inheritance
Autosomal recessive; frequency is about 1 to 2.5/105 newborns; heterozygotes are estimated to be 1% of the general population; founder effect are found in some isolated population.

Clinics

Note
Ataxia telangiectasia is a chromosome instability syndrome with cerebellar degeneration, immunodeficiency, and an increased risk of cancers; A-T cells are defective in recognizing double-strand DNA damage to signal for repair.

Phenotype and clinics

- Onset of the disease is often noted during the second year of life: there is progressive cerebellar ataxia (initially truncal, with further peripheral extension); ataxia is a constant feature in this disease; oculomotor apraxia, dysarthria, and dystonia; leading to muscular atrophia.
- 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; occasionally diabetes mellitus.

Neoplastic risk

- Risk of cancers is X 100, consisting mainly of T-cell malignancies (a 70-fold and 250-fold increased risk and B-cell malignancies, but not myeloid leukemia; carcinomas of the skin, ovary, breast, and stomach have also been described.
- Cancer treatment is complicated by radiation- and chemo-sensitivity.

Evolution

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

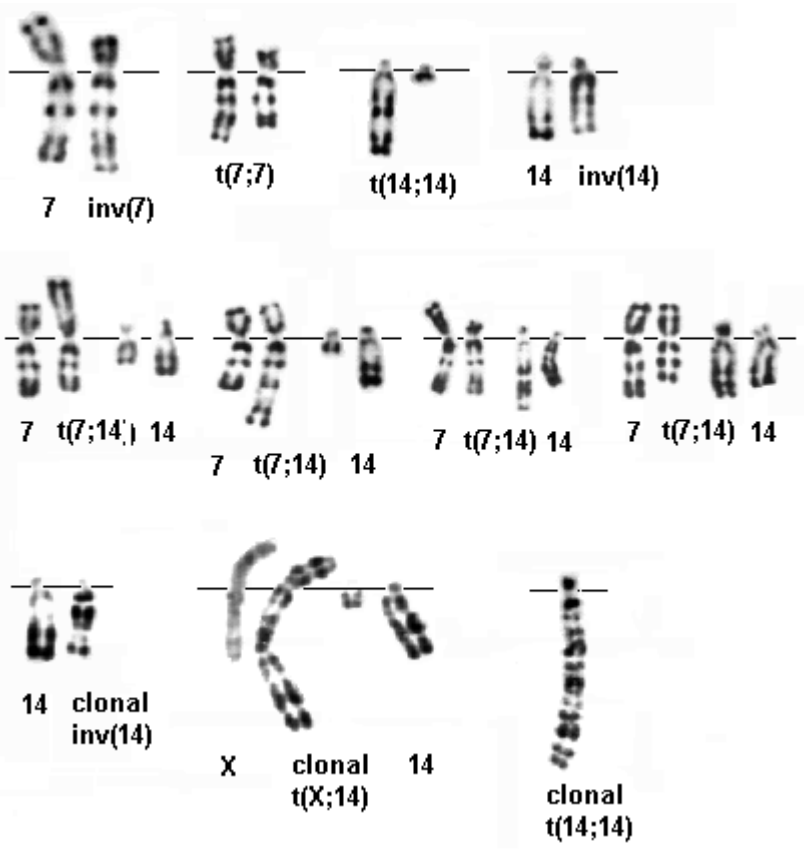
Prognosis

- Respiratory infection is the common cause of death, with cancer being the second most common.
- Survival is often into fourth decade today where optimal medical care is available.

Cytogenetics

Inborn conditions

- 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)).



Sporadic (rows 1 and 2) and clonal (row 3) rearrangements in ataxia telangiectasia (R- banding). Row 1, from left to right: inv(7)(p14q35), t(7;7)(p14;q35), t(14;14)(q11;q32), inv(14)(q11q32); Row 2:, from left to right: t(7;14)(p14;q11), t(7;14)(q35;q11), t(7;14)(p14;q32), t(7;14)(q35;q32); Row 3, from left to right: inv(14)(q11;q32), t(X;14)(q28;q11) (note the late replicating X on the left), t(14;14)(q11;q32) - Courtesy Alain Aurias (modified figure reprinted from Médecine/Sciences 1986; 2: 298-303., by permission of the publisher Masson).

- Clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14).

Cytogenetics of cancer

Clonal rearrangements in T-cell ALL and T-PLL (prolymphocytic leukaemia) in AT patients are complex, with the frequent involvement of t(14;14)(q11;q32)(q11;q32), or t(X;14)(q28;q11), implicating the genes TCL1 or MTCP1 respectively, as is found in T-PLL in non-AT patients.

Other findings

Note

- High sensitivity to ionizing radiations and to radiomimetic 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; P53 phosphorylation at ser15 is deficient.
- Lenthening of the cell cycle.
- Difficult 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

ATM (Ataxia telangiectasia mutated)

is responsible for the vast majority of A -T cases.

Location

11q22-q23.1

DNA/RNA

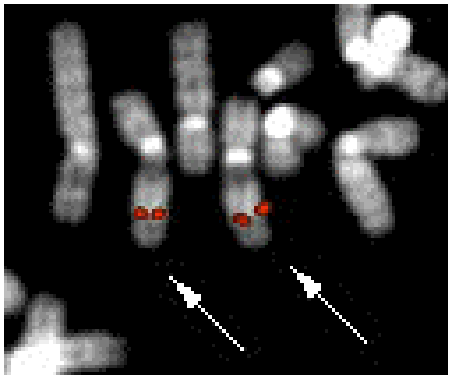
Description: 66 exons spanning 184 kb of genomic DNA.

Protein

Description: 3056 amino acids; 350 kDa; contains a Pl 3-kinase-like domain.

Localisation: Mostly in the nucleus in replicating cells, cytoplasm in differentiating cells.

Function: Mediates cell cycle arrest in response to ionizing radiation through the phophorylation of targets including p53, cAbl, BRCA1, H2AX, IkB-alpha and chk1.



ATM (11q22.3) in normal cells: PAC 891P24 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

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. Missense mutations have been described in breast cancer patients, but do not seem to contribute to ataxia-telangiectasia.

To be noted

Note

- Heterozygote cancer risk: the relative risk of breast cancer in A-T heterozygote women has been estimated through epidemiological studies to be 3.9 (CI 2.1-7.1), and through haplotype analysis to be 3.32 (CI 1.75-6.38); since the A-T heterozygote frequency is about 1%, 2-4% of breast cancer cases may be due to ATM heterozygosity; the risk of other types of cancer in A-T heterozygotes is low.
- The A-T variant Nijmegen breakage syndrome does not involve the same gene.

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