Cancer Prone Disease Section
Mini Review

Nijmegen breakage syndrome

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Identity

Alias
Ataxia-telangiectasia, variant VI; Seemanova syndrome II ; Microcephaly with normal intelligence, immunodeficiency, lymphoreticular malignancies ; Immunodeficiency, microcephaly, chromosomal instability

Note
Belongs to the group of inherited chromosomal instability syndromes including:
- Bloom's syndrome,
- Fanconi's disease, and
- Ataxia telangiectasia (AT); see also, in Deep Insight section: Ataxia-Telangiectasia and variants.

Inheritance
Autosomal recessive disease; since the recognition of the Nijmegen breakage syndrome (NBS) in 1981, about 70 patients are included in the NBS Registry in Nijmegen; the disease appears to have originated in central Europe, in the Slavic population, and to have spread through a founder effect.

Clinics

Note
The condition is characterised by growth and mental retardation, craniofacial dysmorphy, ovarian failure, immunodeficiency, chromosome instability, predisposition to lymphoid malignancies, and radiosensitivity.

Phenotype and clinics
growth and mental development: 30% of children have low birth weight and short stature, and 75% a head circumference at birth below the 3rd percentile; all patients develop a severe microcephaly during the first months of life; mental development is normal in 35% of the patients, moderately retarded in the others, though the mental retardation appears to be progressive; cerebellar ataxia is absent; alphafoetoprotein levels are normal, in contrast to AT patients.
- Craniofacial dysmorphy: progressive and severe microcephaly, "bird-like" face with prominent midface, long nose and receding mandible.
- Immunodeficiency: severe combined deficiency with agammaglobulinemia, IgA, IgG2 and IgG4 deficiencies, decreased CD3+ and CD4+ lymphocytes, and decreased CD4+ / CD8+ ratio; these disturbances are responsible of frequent respiratory, garstrointestinal and urinary infections.

Neoplastic risk
High frequency and early development of lymphomas, more often involving B-cells, in contrast with those found in AT.
Other forms of cancer may also be at higher risk.

Cytogenetics

Inborn conditions
- Lymphocyte cultures often show low mitotic index.
- Structural chromosome aberrations are observed in 10-30% of metaphases; most of the rearrangements occur in or between chromosomes 7 and 14, at bands 7p13, 7q35, 14q11, and 14q32, as in AT; these bands contain immunoglobulin and T-cell receptor genes; the most frequent rearrangement is the inv(7)(p13q35).

Other findings

Note

Radiosensitivity: increased sensitivity of both lymphocytes and fibroblasts to ionising radiations and radiomimetics, radio-resistant DNA synthesis.

Genes involved and proteins

NBS1

Location

8q21

DNA/RNA

Description: 16 exons

Protein

Function: The product of NBS1, nibrin (p95), associates with Mre and Rad50 to control the repair of double-strand DNA breaks involved, for example, in VDJ joining in immunoglobulin and T-cell receptor genes recombination process, in meiotic recombination, and in radio-induced DNA lesions; this suggests that nibrin and the product of ATM could act in a common pathway of detection or repair of double-strand breaks, and indeed, ATM phosphorylates nibrin in response to DNA damage. Nibrin/p95 is found associated with Rad50 and Mre11 at sites of DNA double-strand breaks and is essential for the nuclear localization of the complex.

Mutations

Germinal: All NBS patients show truncating mutations. The common 657del5 allele has been shown to produce a short N-terminal protein of no detectable function, and also a C-terminal protein produced through an alternative translation initiation signal in the deleted mRNA. Data from knockout mice indicates that this C-terminal protein is partially functional, as Nbs1 null alleles are lethal.

Somatic: Missence mutations in NBS1 have been associated with childhood acute lymphoblastic leukemia.

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