

# 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:

- Bloom's syndrome,
- Fanconi's disease,
- 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 50 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 dysmorphism, 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 dysmorphism: 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, gastrointestinal 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), should have a role in the control 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; nibrin/p95 is found associated with Rad50 and Mre11 at sites of DNA double-strand breaks.

#### Mutations

Germinal: All Nijmegen patients show truncating mutations.

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