Neurofibromatosis type 2 (NF2)

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Published in Atlas Database: February 2001
Online updated version: http://AtlasGeneticsOncology.org/Kprones/NF2Kpr10007.html
DOI: 10.4267/2042/37742

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Identity

Alias
Central neurofibromatosis
Bilateral acoustic neurofibromatosis
Bilateral acoustic neurinoma
Bilateral acoustic schwannomas

Inheritance
Autosomal dominant with almost complete penetrance; frequency is 3/10^5 newborns; neomutation represent 50% of cases; variable expressivity from mild disease through life (Gardner type) to severe condition at young age (Wishart type: with more than 3 tumours).

Clinics

Note
NF2 is an hamartoneoplastic syndrome; hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; they are heritable malformations that have a potential towards neoplasia.

Phenotype and clinics
Bilateral vestibular (8th cranial pair) schwannomas; other central or peripheral nerve schwannomas; meningiomas; ependymomas.
Hearing loss (average age 20 yrs), tinnitus, imbalance, headache, cataract in 50%, facial paralysis.
Café-au-lait spots and cutaneous and peripheral neurofibromas may be present, but far less extensively than in neurofibromatosis type 1.

Neoplastic risk
NF2 cases represent about 5% of schwannomas and meningiomas (i.e. risk increased by 2000), appearing at the age of 20, while they are found in the general population at the age of 50 and over.

Prognosis
These tumours are usually benign, but their location within the central nervous system gives them a grave prognosis; patients with the Wishart severe form usually do not survive past 50 yrs.

Cytogenetics

Inborn conditions
Normal.

Cytogenetics of cancer
Chromosome 22 loss is very frequent both in sporadic and in NF2 schwannomas and meningiomas.

Genes involved and proteins

NF2 (neurofibromatosis 2)
Location: 22q12
DNA/RNA
Description: 17 exons (1-15, 17 constitutive, 16 alternatively spliced).
Protein
Description: Isoform 1 595 amino acids, isoform 2 590 amino acids (due to inclusion of exon 16 in transcript);
contains a FERM domain and a large a helix domain. 
Expression: Wide.
Function: Membrane-cytoskeleton anchor; tumour suppressor.
Homology: Band 4.1 family, ezrin, radixin, moesin.

Mutations
Germline: Germ-line mutations in NF2 patients lead to protein truncation; splice-site or missense mutations are also found; phenotype-genotype correlations are observed (i.e. that severe phenotype are found in cases with protein truncations rather than those with amino acid substitution).
Somatic: Mutation and allele loss events in tumours in neurofibromatosis type 2 and in sporadic schwannomas and meningiomas are in accordance with the two-hit model for neoplasia.

References
McClatchey AI, Saotome I, Ramesh V, Gusella JF, Jacks T. The NF2 tumor suppressor gene product is essential for extraembryonic development immediately prior to gastrulation. Genes Dev. 1997 May 15;11(10):1253-65

This article should be referenced as such: