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Cancer Prone Disease Section
Mini Review

Neurofibromatosis type 1 (NF1)

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Identity

Other names: Von Recklinghausen neurofibromatosis; Peripheral neurofibromatosis
Inheritance: autosomal dominant with almost complete penetrance; frequency is $30/10^5$ newborns (and 1 of 200 mentally handicapped persons): one of the most frequent genetically inheritable disease; neomutation in 50%, mostly from the paternal allele; highly variable expressivity, from very mild to very severe; expressivity is also age-related.

Clinics

NF1 is an hamartoneoplastic syndrome; hamartomas are localized tissue proliferations with faulty differenciation and mixture of component tissues; they are heritable malformations that have a potential towards neoplasia; the embryonic origin of dysgenetic tissues involved in NF1 is ectoblastic.

Phenotype and clinics

Diagnosis is made on the ground of at least 2 of the following:
- café-au-lait spots (no 6 or more with 0.5 cm of diameter (in pre-puberty));
- 2 neurofibromas or 1 plexiform neurofibromas (mainly cutaneous);
- 2 Lisch nodules (melanocytic hamartomas of the iris);
- freckling in the axillary/inguinal region (Crowe's sign);
- glioma of the optic nerve;
- distintive bone anomalies (scoliosis, pseudoarthroses, bony defects (orbital wall)...);
- positive family history.

Other features:
- macrocephaly;
- epilepsy;
- mental retardation in 10 %; learning diabilities in half patients;
- sexual precocity and other endocrine anomalies;
- hypertension (renal artery stenosis).

Neoplastic risk

- 5% of NF1 patients experience a malignant neoplasm;
- neurofibromas, especially the plexiform variety; polyclonal (benign) proliferation; may be present at birth or appear later, may be a few or thousands, small or enormous, occur in the skin and in various tissus and organs; neurofibromas localized to the spine are extremely difficult to manage.
- neurofibrosarcomatous transformation (malignant) of these in 5-10 %;
- optic nerve gliomas;
- childhood MDS (myelodysplasia) and ANLL, often with monosomy 7 (monosomy 7 syndrome, 'juvenile myelomonocytic leukaemia'): risk, increased by X 200 to 500, is still low, as JMML is rare; M>F; most often before the age of 5 years; no increased risk of leukaemia in the adult.
- pheochromocytomas;
- various other neoplasias, of which are rhabdomyosarcomas

Treatment

Early diagnosis, lifetime monitoring and surgery are essential

Cytogenetics

Inborn condition

No special feature.

Cancer cytogenetics

According to the cancer type in most cases
JMML: monosomy 7.

Genes involved and Proteins

NF1

Location: 17q11.2

Protein

Description: the protein has been called neurofibromin; GTPase activating protein (GAP); tumour suppressor.

Mutations

Germinal: mainly nucleotide substitutions (splicing defects, nonsense mutations, missense mutations) and frameshift alterations, microdeletions (5-10%), some intragenic copy number changes on one allele.
Somatic: the second allele is often lost in the neoplatic cell owing to copy number loss and mitotic recombination events, but also minor lesion mutations are found.

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