

Oncogenetic testing for persons with Neurofibromatosis type 1

Neurofibromatosis type 1 is a relatively common inherited disorder that affects about one in 2 500 to one in 3 000 people worldwide, irrespective of sex or ethnic origin. Individuals with neurofibromatosis type 1 are prone to develop benign and malignant tumours of the central nervous system and peripheral nervous system, in addition to malignant diseases affecting other parts of the body.

Tumours that are associated with the disorder include glomus tumour of the digits, glioma of the optic pathway, glioblastoma, malignant peripheral nerve sheath tumour, gastrointestinal stromal tumour, breast cancer, juvenile myelomonocytic leukemia (JMML), pheochromocytoma, duodenal carcinoid tumour, and rhabdomyosarcoma.¹

Clinical recommendations

- Diagnostic criteria (National Institute of Health, NIH criteria): two or more of the following criteria are required for diagnosis:
 - 6 or more *café au lait* macules (>0.5 cm in children or >1.5 cm in adults)
 - 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
 - Axillary or inguinal freckling
 - Optic pathway glioma
 - 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
 - Bony dysplasia (sphenoid wing dysplasia, bowing of long bone \pm pseudarthrosis)
 - First degree relative with NF1
- Patients suspected with NF1 should be referred to a centre for genetic counselling and testing.
- Testing after counselling should be considered especially in case of:
 - Unclear presentation that is suggestive but not sufficient to make the diagnosis of the syndrome
 - Incomplete presentation at an early age
 - Reproductive decisions
- Patients presenting with multiple (6 or more) *café-au-lait* spots with or without axillary or inguinal freckling but no other NF1 related criteria should first be tested for mutations in the NF1 gene and if negative for SPRED1.
- Genetic counselling prior to conception is advised in all NF1 individuals of reproductive age.
- Preimplantation and prenatal diagnosis for neurofibromatosis can be offered.



- Children should be followed up every 6 to 12 months up to the age of 7 and annually until the age of 18. The following should be recorded :
 - Development and progress at school
 - Visual symptoms, visual acuity and fundoscopy until age 7 years (optic pathway glioma, glaucoma)
 - Head circumference (rapid increase might indicate tumour or hydrocephalus)
 - Height (abnormal pubertal development)
 - Weight (abnormal pubertal development)
 - Pubertal development (delayed/precocious puberty due to pituitary/hypothalamic lesion)
 - Blood pressure (consider renal artery stenosis, phaeochromocytoma)
 - Cardiovascular examination (congenital heart disease, especially pulmonary stenosis)
 - Evaluation of spine (scoliosis with or without underlying plexiform neurofibromas)
 - Evaluation of the skin (cutaneous, subcutaneous and plexiform neurofibromas)
 - Examination of other systems if specific symptoms are present
- After the age of 18 they should be seen every 2 to 3 years at a specialised multidisciplinary NF1 clinic.
- Blood pressure should be monitored regularly (at least annually).
- Annual breast cancer screening should be done from 40 years on.
- Patients should be instructed to consult if there is any rapid growth, pain, change in texture of a neurofibroma.
- Patients with a NF1 microdeletion or a high volume of neurofibromas should be seen annually in specialised care to monitor for malignancies.

Reference

1. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol.* 2014;13(8):834-43.

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