PRIMEVIEW

NEUROFIBROMATOSIS TYPE 1

nature REVIEWS DISEASE PRIMERS

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Neurofibromatosis type 1 is caused by mutations in the *NF1* tumour suppressor gene, which encodes neurofibromin, a protein expressed by several cell types, including neurons, glial cells and immune cells. Clinical manifestations include the formation of brain and nerve sheath tumours (neurofibromas), pigmentary lesions (such as café-au-lait macules), skeletal abnormalities and cognitive disabilities.

DIAGNOSIS

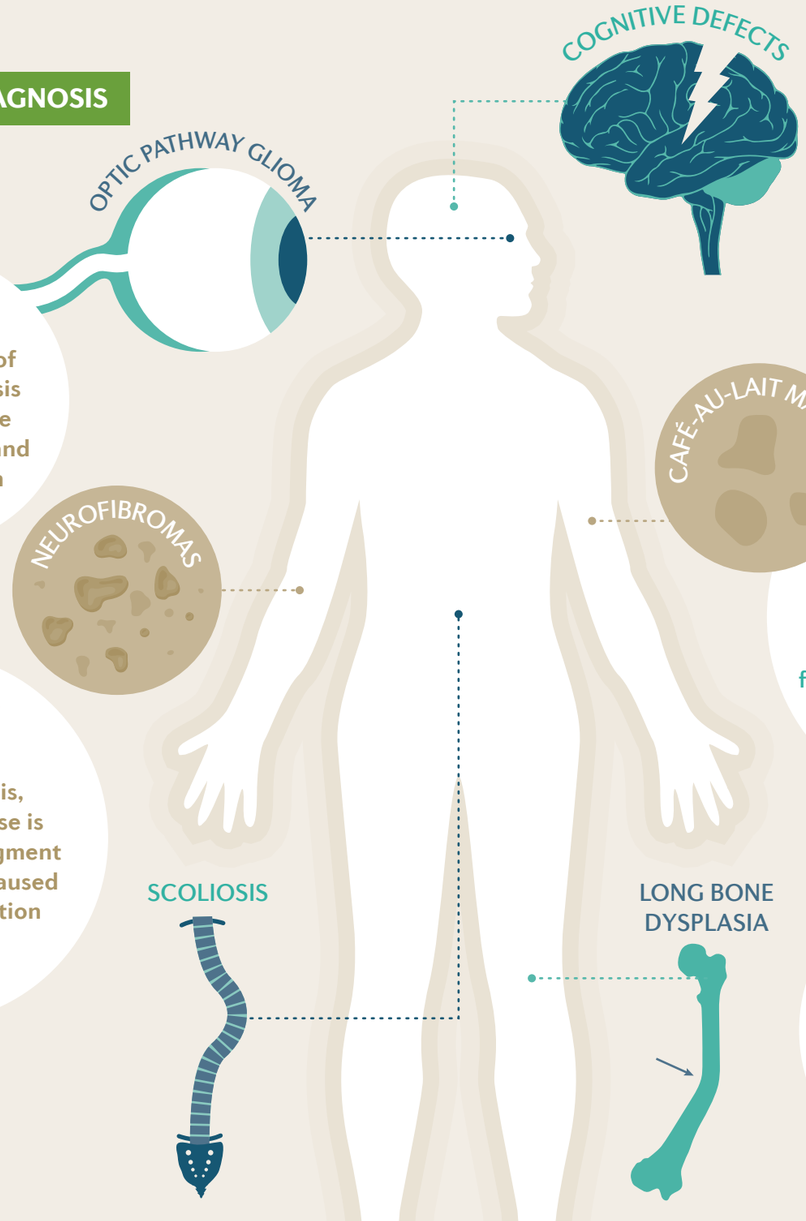
The main clinical manifestations of neurofibromatosis type 1 affect the skin, bone, eyes and nervous system

Some patients can have segmental neurofibromatosis, whereby the disease is restricted to one segment of the body and is caused by a somatic mutation during fetal development

Generally, diagnosis includes the assessment of patient history and physical examination

Patients with an unusual phenotype (such as those with spinal nerve root neurofibromas), or young children with multiple café-au-lait macules and no family history of these features, might require genetic testing to confirm the diagnosis

Prenatal genetic testing is available when the causative *NF1* mutation has been identified in the parent, but does not predict disease severity in the offspring



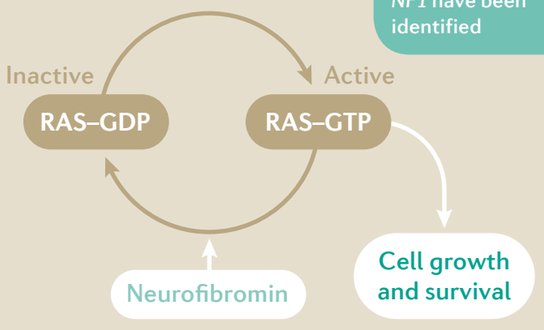
MANAGEMENT

Management of patients with neurofibromatosis type 1 is largely focused on the early detection and treatment of individual manifestations. Children and adults should undergo yearly clinical assessment to monitor disease progression and complications. Treatments can vary depending on the severity and manifestations of disease. For example, dermal neurofibromas can be treated using surgical removal, moisturizers and psychological support; scoliosis can be treated with corrective surgery or bracing.

MECHANISMS

Neurofibromatosis type 1 is usually inherited in an autosomal dominant manner; although sporadic, somatic mutations in *NF1* can also lead to disease. Neurofibromin acts as a negative regulator of the RAS GTPase. *NF1* mutations are thought to result in loss of neurofibromin function, which is predicted to increase RAS signalling, leading to enhanced cell growth and survival. This increased cell growth and survival is speculated to underlie many of the manifestations of neurofibromatosis type 1, including the development of nerve sheath tumours and the formation of gliomas. The cognitive and behavioural defects associated with neurofibromatosis type 1 are probably caused by defective inhibitory and/or dopaminergic neurotransmission.

To date, >3,000 germline mutations in *NF1* have been identified



EPIDEMIOLOGY

Patients with neurofibromatosis type 1 have an increased risk of several malignancies, including malignancies of the brain, breast, endocrine tissues, connective tissues and blood. In addition, patients have an increased risk of non-neoplastic conditions, including learning difficulties, autism spectrum disorder, epilepsy and sleep disorders.

The average prevalence of neurofibromatosis type 1 is ~1 case per 3,000 individuals

QUALITY OF LIFE

The wide range of manifestations of neurofibromatosis type 1 can adversely affect quality-of-life outcomes in children, adolescents and adults. In adolescents, a poorer quality of life is associated with worse disease severity, pain, visible signs of disease (such as dermal neurofibromas) and cognitive impairments. In adults with neurofibromatosis type 1, the physical, social and emotional domains of quality of life are reduced relative to the general population.

Measures of quality of life are being incorporated into clinical trials and provide unique information beyond the efficacy of the treatment

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