Neurofibromatosis type I

Genetics

-NF1 (Neurofibromin, 17q11)

-AD, 50% de novo

Clinical findings/Dysmorphic features

-Multiple café au lait spots; axillary and inguinal freckling; multiple cutaneous neurofibromas; Lisch nodules; choroidal freckling; plexiform neurofibromas (50%); learning disabilities (50%)

-Less common but serious: optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, scoliosis, tibial dysplasia, vasculopathy

Etiology

-Most common dominantly inherited genetic disorder: incidence 1:3000

Pathogenesis

-Neurofibromin GTPase-activating protein (GAP) that negatively regulates Ras pathway

-Increases the hydrolysis of Ras-bound guanosine triphosphate (GTP) --> controls proliferation/acts as a tumor suppressor

Genetic testing/diagnosis

-NIH diagnostic criteria are met in an individual who has ≥ 2 of:

1) ≥ 6 café au lait macules (>5 mm in prepubertal ind./>15 mm in postpubertal ind.

2) ≥ 2 neurofibromas of any type or one plexiform neurofibroma

3) Freckling in the axillary or inguinal regions

4) Optic glioma

5) Two or more Lisch nodules (iris hamartomas)

6) A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis

7) A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

-Diagnosis usually based on clinical findings, molecular genetic testing is rarely needed, except: --> NF1 is suspected but NIH diagnostic criteria not fulfilled

--> In child with serious tumor (e.g., optic glioma) in whom diagnosis would affect management --> Prenatal or preimplantation genetic diagnosis in a current or future pregnancy

--> Spinal NF1 or NF1 c.2970-2972 delAAT pathogenic variant often do not meet criteria

->500 mutations reported, usually unique to a particular family

Others

-Majority normal lifespan; surgery for bone malformations or painful or disfiguring tumors; MEK inhibitors for plexiform neurofibromas; risk of malignant peripheral nerve sheath tumors in adolescence and young adulthood

-Vitamin D supplementation