

## NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES)

A number of genetic disorders are characterized by cutaneous lesions and an increased risk of brain tumors. Most of these disorders have an autosomal dominant inheritance with variable penetrance.

### ■ NEUROFIBROMATOSIS TYPE 1 (von RECKLINGHAUSEN'S DISEASE)

NF1 is an autosomal dominant disorder with variable penetrance and an incidence of ~1 in 2600–3000. Approximately one-half of cases are familial; the remainder are caused by new mutations arising in patients with unaffected parents. The *NF1* gene is located on chromosome 17q11.2 and encodes neurofibromin, a guanosine triphosphatase (GTPase) activating protein (GAP) that is a negative regulator of the RAS–mitogen-activated protein (MAP) kinase signaling pathway, which includes the downstream kinase MEK. It is a classic tumor suppressor, and biallelic loss can result in a variety of nervous system tumors including neurofibromas, plexiform neurofibromas, optic nerve gliomas, astrocytomas, and meningiomas. In addition to neurofibromas, which appear as multiple, soft, rubbery cutaneous tumors, other cutaneous manifestations of NF1 include café-au-lait spots and axillary freckling. NF1 is also associated with hamartomas of the iris termed Lisch nodules, pheochromocytomas, pseudoarthrosis of the tibia, scoliosis, epilepsy, and mental retardation. The MEK inhibitor selumetinib has activity against inoperable plexiform neurofibromas and is the only treatment that targets the dysregulated signaling pathway.

### ■ NEUROFIBROMATOSIS TYPE 2

NF2 is less common than NF1, with an incidence of 1 in 25,000–40,000. It is an autosomal dominant disorder with full penetrance. As with NF1, approximately one-half of cases arise from new mutations. The *NF2* gene on 22q encodes a cytoskeletal protein, merlin (moesin, ezrin, radixin-like protein), that functions as a tumor