- *Neuropathies associated with monoclonal gammopathies*. Neoplastic B cells may secrete monoclonal immunoglobulins or immunoglobulin fragments (so-called paraproteins) that damage nerves. For example, tumors that secrete IgM immunoglobulin may be associated with a demyelinating peripheral neuropathy. In most cases, the pathogenic IgM paraprotein is thought to bind directly to myelin-associated antigens such as myelin associated glycoprotein (MAG). Deposition of IgM can be seen ultrastructurally between the membrane layers of the myelin sheath. IgG or IgA paraproteins may also be associated with peripheral neuropathy. One distinctive presentation is *POEMS syndrome* (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), in which patients often develop a demyelinating neuropathy associated with deposition of paraprotein between noncompacted myelin lamellae. Finally, excess immunoglobulin light chain may deposit as amyloid (Chapter 6), which can lead to peripheral neuropathy due to vascular insufficiency or a direct toxic effects.

Neuropathies Caused by Physical Forces

Peripheral nerves are commonly injured by trauma or entrapment. *Lacerations* result from cutting injuries and from sharp fragments of fractured bone, both of which may sever a nerve. *Avulsion* of a nerve may occur when tension is applied, often to one of the limbs. *Compression neuropathy (entrapment neuropathy)* occurs when a peripheral nerve is chronically subjected to increased pressure, often within an anatomic compartment. *Carpal tunnel syndrome*, the most common entrapment neuropathy, results from compression of the median nerve at the level of the wrist within the compartment delimited by the transverse carpal ligament. Women are more commonly affected than men, and the problem is frequently bilateral. The disorder may be observed in association with many conditions including tissue edema, pregnancy, inflammatory arthritis, hypothyroidism, amyloidosis (especially that related to β_2-microglobulin deposition in individuals on renal dialysis), acromegaly, diabetes mellitus, and excessive repetitive motions of the wrist. Symptoms are limited to dysfunction of the median nerve and typically include numbness and paresthesias of the tips of the thumb and first two digits. Other nerves prone to compression neuropathies include the ulnar nerve at the level of the elbow, the peroneal nerve at the level of the knee, and the radial nerve in the upper arm; the latter occurs from sleeping with the arm in an awkward position ("Saturday night palsy"). Another form of compression neuropathy is found in the foot, affecting the interdigital nerve at intermetatarsal sites. This problem, which occurs more often in women than in men, leads to foot pain (metatarsalgia) and is associated with a histologic lesion called a *Morton neuroma*, which is marked by perineural fibrosis.

Inherited Peripheral Neuropathies

Inherited peripheral neuropathies are a group of genetically diverse disorders with overlapping clinical phenotypes that often present in adults. Even with delayed onset, the possibility of an inherited neuropathy has to be considered in the differential diagnosis for any patient that presents with a peripheral neuropathy. The major types of inherited peripheral neuropathies include (1) hereditary motor and sensory neuropathies, also known as *Charcot-Marie-Tooth* (CMT) disease, (2) hereditary motor neuropathies, (3) hereditary sensory neuropathies, with or without autonomic neuropathy, and (4) other inherited conditions causing neuropathy, including familial amyloidosis and inherited metabolic diseases.

Historically, these diseases were classified based on their inheritance pattern and clinical features. Now there is a continuously growing list of genetic defects that are linked to these. The complexity of the genetics of inherited neuropathies is no doubt a reflection of the complicated homeostatic mechanisms that sustain normal peripheral nerve function. There is no simple unifying concept tying all the implicated genes together, but subsets of involved genes can be clustered into the following functionally related groups:

- Genes encoding myelin-associated proteins (Fig. 27-1)
- Genes encoding growth factors and growth factor receptors
- Genes encoding proteins that regulate mitochondrial function
- Genes encoding proteins that are involved in vesicle and axonal transport
- Genes encoding heat shock proteins, which may prevent protein aggregation
- Genes encoding proteins that are involved in cell membrane structure or function

Many areas of the classification are muddy, and genotype/phenotype relationships are not always clear-cut. For example, mutations in the *HSPB1* gene, which encodes the heat shock protein HSP27, may be associated with a clinical picture resembling CMT disease or a hereditary motor neuron disorder. Below, some of the more common and distinctive types of inherited peripheral neuropathies are described in brief.

Hereditary motor and sensory neuropathies/ Charcot-Marie-Tooth (CMT) disease

These are by far the most common inherited peripheral neuropathies, affecting up to 1 in 2500 people. The initial description of these disorders, based on clinical features, was deceptively simple—an inherited disease associated with distal muscle atrophy, sensory loss, and foot deformities. It is now appreciated that this clinical phenotype encompasses mutations in more than 50 different genes, some with relatively distinctive clinical features. Current systems classify hereditary motor and sensory neuropathies based on the mode of inheritance and the pattern of injury (e.g., axonal, demyelinating, or mixed). Demyelinating forms of CMT are associated with morphologic features of demyelination and remyelination including Schwann cell hyperplasia and onion bulb formation, which may be so severe that the involved nerve is palpably enlarged. Listed are a few more common variants:

- CMT1 encompasses a group of autosomal dominant disorders that collectively are the most common subtype of hereditary motor and sensory neuropathy. CMT1A accounts for some 55% of genetically defined CMT cases and 37% of all CMT disease. It is caused by a duplication