Pathologically, they are characterized by neuronal loss from the affected areas and secondary degeneration of white-matter tracts.

Molecular Genetics. The list of SCAs has expanded to more than 30 distinct entities, with genetic loci determined for more than half of them. Three distinct types of mutations have been recognized:

- *Polyglutamine diseases* linked to expansion of a CAG repeat, similar to HD. Each of the seven forms of SCA associated with this mechanism has a distinct protein in which the expanded polyglutamine tract occurs, with intranuclear inclusions occurring in neurons, suggesting the involvement of pathogenic mechanisms previously discussed for Huntington disease. The group of polyglutamine diseases includes SCA1, SCA2, SCA3 (also known as *Machado-Joseph disease*), SCA6, SCA7 (relatively unique in that it includes visual impairment), SCA17, and dentatorubropallidoluysian atrophy (DRPLA).
- *Expansion of non-coding region repeats*, similar to myotonic dystrophy. There are currently five forms of SCA in which this mechanism appears to underlie the disease, each linked to a difference genetic locus. This group includes SCA8, SCA10, SCA12, SCA31, and SCA36. The connection between the expansion of these repeats and disease manifestations remains obscure.
- *Point mutations*. Another 10 of the SCAs are associated with mutations in a variety of genes whose expression is not restricted to neurons and which code for proteins of mostly unknown functions.

There remains a significant need for investigation to bridge this gap between genetic insight and disease pathogenesis.

Friedreich Ataxia

Friedreich ataxia is an autosomal recessive disease with progressive ataxia, spasticity, weakness, sensory neuropathy, and a cardiomyopathy. It generally begins in the first decade of life with gait ataxia, followed by hand clumsiness and dysarthria. Deep tendon reflexes are depressed or absent, but an extensor plantar reflex is typically present. Joint position and vibratory sense are impaired, and there is sometimes loss of pain, temperature sensation, and light touch. Most affected individuals develop pes cavus and kyphoscoliosis. Most patients become wheelchair-bound within about 5 years of onset, and life expectancy is typically limited to 40 or 50 years of age. The accompanying cardiomyopathy is associated with a high incidence of arrhythmias and congestive heart failure, which contribute to the deaths of most affected individuals. Concomitant diabetes is found in up to 25% of patients.

Friedreich ataxia is caused by expansion of a GAA trinucleotide repeat in the first intron of a gene on chromosome 9q13 that encodes *frataxin*, a protein found in the mitochondrial inner membrane where it is involved in assembly of iron-sulfur cluster enzymes of complex I and II. Affected individuals have extremely low levels of the protein, and the severity of the disease course may correlate better with the level of frataxin than with the degree of GAA-repeat expansion. With reduced mitochondrial frataxin, there is decreased mitochondrial oxidative phosphorylation (similar to the defect in mitochondrial encephalomyopathies) as well as increased free iron; the presence of free iron within the mitochondria may contribute to oxidative stress. Nearly all cases of Friedreich ataxia are associated with GAA repeat expansion in both alleles, but the same disease phenotype is observed when one allele has a repeat expansion and the other harbors a point mutation.

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The spinal cord shows loss of axons and gliosis in the posterior columns, the distal portions of corticospinal tracts, and the spinocerebellar tracts. There is degeneration of neurons in the spinal cord (Clarke column), the brainstem (cranial nerve nuclei VIII, X, and XII), the cerebellum (dentate nucleus and the Purkinje cells of the superior vermis), and the Betz cells of the motor cortex. Large dorsal root ganglion neurons are also decreased in number; their large myelinated axons, traveling both in the dorsal roots and in dorsal columns, undergo secondary degeneration. The heart is enlarged and may have pericardial adhesions. Multifocal destruction of myocardial fibers with inflammation and fibrosis is detectable in about half the affected individuals who come to autopsy.

Ataxia-Telangiectasia

Ataxia-telangiectasia (Chapter 7) is an autosomal recessive disorder characterized by an ataxic-dyskinetic syndrome beginning in early childhood, with the subsequent development of telangiectasias in the conjunctiva and skin, along with immunodeficiency. The ataxia-telangiectasia mutated (*ATM*) gene on chromosome 11q22-q23 encodes a kinase with a critical role in orchestrating the cellular response to double-stranded DNA breaks. In addition to this critical cellular role, the ATM protein also contributes to various other pathways including facilitation of apoptosis, maintenance of telomeres, mitochondrial homeostasis, response to oxidative stress, and maintenance of the ubiquitin-proteosomal degradation system. It remains unclear which of these pathways contribute to the degenerative phenotype observed in the setting of loss of ATM protein in neurons. Intriguingly, there are comparable patterns of neurodegeneration associated with other diseases linked to disruption in single-stranded DNA break repair processes.

MORPHOLOGY

The abnormalities are predominantly in the cerebellum, with loss of Purkinje and granule cells; there is also degeneration of the dorsal columns, spinocerebellar tracts, and anterior horn cells, and a peripheral neuropathy. Telangiectatic lesions are found in the CNS as well as in the conjunctiva and skin of the face, neck, and arms. Cells in many organs (e.g., Schwann cells in dorsal root ganglia and peripheral nerves, endothelial cells, pituicytes) show a bizarre enlargement of the nucleus to two to five times normal size and are referred to as *amphicytes*. The lymph nodes, thymus, and gonads are hypoplastic.

Clinical Features. The disease is relentlessly progressive, with death early in the second decade. The initial symptoms are commonly recurrent sinopulmonary infections