Neurology Review

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INTRODUCTION

In the past half century, an explosion of knowledge in the field of molecular genetics has revolutionized our understanding of human diseases. One third of known single gene defects cause diseases that affect the nervous system, so knowledge of the clinical approach to genetic disorders is essential for the practicing neurologist. This manual provides a survey of single gene defects that affect the nervous system, based on the most prominently affected neuroanatomic region.

BASIC CONCEPTS

Genetic Basis of Inheritance

Humans have 22 pairs of autosomes and 1 pair of sex chromosomes. Each chromosome is made up of 2 complementary strands of DNA consisting of a double helical structure surrounding matched nucleotide base pairs (guanine with cytosine, adenine with thymine). Each set of 3 DNA base pairs, or codon, codes for 1 amino acid. DNA is transcribed into messenger RNA (mRNA) by RNA polymerase and then translated into protein. Introns and untranslated regions are portions of the DNA sequence that are transcribed but not translated.

A gene is a portion of the DNA sequence that is the basic unit of inheritance. Genotype is an individual’s genetic makeup; phenotype is an individual’s physical traits or morphology. Expressivity of a gene is the degree to which a trait attributable to the gene is evident in the phenotype. Gene expression is more frequently used to describe the quantity and location of mRNA and protein transcribed and translated from the gene. Transcription factors are proteins that bind to DNA to regulate gene expression.

Alleles are variations in the sequence of nucleotides that make up a gene. An individual inherits 2 alleles of each gene, 1 from each parent. If the alleles are identical, the genotype is homozygous; if they are different, the genotype is heterozygous. The penetrance of an allele is the proportion of individuals that express its phenotypic manifestations (ie, disease). Penetrance is frequently variable, particularly in autosomal dominant disorders. A proband is the first person within a family or kinship to be identified with a genetic disorder. Founder effect is when a particular (especially recessive) mutation is overrepresented in a population due to a small genetic pool. An example would be the propagation of X-linked hemophilia in European royalty in the nineteenth and twentieth centuries. A polymorphism is an allele (DNA sequence variation) that occurs in at least 1% of the normal population.

Genomic imprinting is the preferential inactivation (by methylation) of some regions of a chromosome based on its parental origin. The most striking examples of imprinting are Prader-Willi syndrome and Angelman’s syndrome, both caused by deletion of genes on the proximal long arm of chromosome 15. Prader-Willi syndrome (obesity, hypotonia, mild mental retardation, small hands and feet) is caused by a deficiency of paternal gene expression within this region, whereas Angelman’s syndrome (severe mental retardation, epilepsy, facial abnormalities, jerky movements, hypopigmentation, frequent laughter) is caused by a deficiency of maternal gene expression.

Patterns of Inheritance

Single gene disorders are traits produced by the effects of a single gene or gene pair. Such traits are inherited in patterns originally described by Mendel as either dominant (transmitted virtually unchanged by hybridization) or recessive (masked in the process). Four inheritance patterns are seen in genetic disorders of the nervous system: autosomal dominant, autosomal recessive, X-linked, and mitochondrial. A patient presenting with a genetic disease without a family history is said to be a sporadic or isolated case; explanations that should be considered in such cases include new mutations (common in certain conditions), false paternity, variable penetrance, and recessive inheritance.

Autosomal dominant. A dominant trait will manifest in both the heterozygote and homozygote, meaning that a single copy of the mutant allele is sufficient to produce the trait. Characteristics of an autosomal dominant disorder include: multiple successive generations are affected, males and females are affected in similar proportions, both males and females transmit disease, and at least 1 instance of male-to-male transmission is seen.
Autosomal recessive. A recessive trait will manifest only in the homozygote, meaning that both copies of the allele must be mutant to produce the trait. Characteristics of an autosomal recessive disorder include: both males and females are affected, the disorder frequently occurs in only 1 generation (usually among siblings), and the parents may be consanguineous. An individual with 1 recessive allele is referred to as a carrier.

X-linked. Because men have only 1 X chromosome, loss of function mutations in genes carried on this chromosome will result in disease. Characteristics of X-linked recessive inheritance include: males are affected almost exclusively, transmission occurs through unaffected carrier females to their sons, daughters of affected males become carriers, and male-to-male transmission does not occur. Some X-linked disorders, such as Duchenne muscular dystrophy, do produce a mild phenotype in carrier females. X-linked dominant disorders are rare and imply that females who harbor the mutation are affected.2

Mitochondrial. Mitochondria are cytoplasmic organelles that are a critical source of ATP for cell function. Each mitochondrion contains 2 to 15 copies of mitochondrial DNA (mtDNA), which contains 37 genes that code for some of the polypeptides involved in oxidative phosphorylation (OXPHOS), 22 mitochondrial transfer RNAs (tRNAs), and 2 ribosomal RNAs. Aspects of mitochondrial OXPHOS important for disease pathogenesis include energy production, generation of reactive oxygen species, and regulation of programmed cell death (apoptosis).3 Because mitochondria are inherited from the oocyte cytoplasm, diseases caused by defects in mtDNA follow a maternal inheritance pattern. Thus, only mothers can transmit disease to male or female offspring. Mutations in nuclear genes that code for mitochondrial proteins may be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion.

Types of Mutations

The normal DNA sequence is referred to as wild-type. A mutation is an alteration in the DNA sequence that has the potential to cause disease. Mutations range from changes in a single base pair to large alterations in a part of or an entire chromosome (eg, trisomy 21). The main types of single gene mutations are:

- Deletions (removal of DNA material) or expansions (insertion or duplication of DNA material)
- Single base pair substitutions (also called point mutations), which include missense mutations (alteration in an amino acid in the protein product) and nonsense mutations (truncation of the protein product due to introduction of a stop codon)
- Frame shifts, which disrupt the reading frame of RNA polymerase due to the excision or addition of base pairs, resulting in the production of an incorrect amino acid sequence
- Dynamic mutations (repeat sequences that can change size on transmission [eg, trinucleotide repeat disorders])

Although the consequences of mutations vary widely depending on how cellular proteins are altered, in general, mutations produce their effect through a loss or gain of protein function. The majority of mutations are loss of function mutations. In most cases, protein synthesized from the normal (wild-type) allele is sufficient to maintain cellular processes, so only individuals with 2 mutant alleles will express disease (ie, recessive inheritance pattern). In some cases, a reduction in protein quantity or activity due to heterozygous mutation will result in less severe disease than does the homozygous state; this condition is termed haploinsufficiency. One generalization is that autosomal recessive disorders often have a more severely affected phenotype than do autosomal dominant disorders because recessive disorders involve a complete rather than partial alteration in protein function.

Gain of function mutations result in critical changes in protein dosage; a simple example of this would be trisomy 21 (Down syndrome). Gain of function mutations usually produce dominant phenotypes.

Molecular Genetics Testing

Discoveries in molecular genetics are making possible the development of tools for precise DNA-based diagnosis, which have the potential to provide valuable prognostic and genetic counseling information. Although a discussion of genetic testing for heritable neurologic disorders is beyond the scope of this review, a few essential points are noted.

Techniques. Beginning with a family in which some individuals are affected by a genetic trait or disease, molecular biologic techniques can be used to find the chromosomal location of the gene that causes the trait. Positional cloning uses linkage analysis (degree of association during meiotic segregation) between the disease trait and other traits of known location with the genome to determine the chromosomal location of the trait of interest. During this process, restriction endonucleases can be used to cut DNA where specific sequences occur; gel electrophoresis is used to separate fragments of DNA, RNA, or protein by their size (molecular weight); and polymerase chain reaction is invariably used to selectively increase the copy number of segments of DNA for
further analysis. **DNA sequencing** is used to determine the specific sequence of nucleotides that make up a segment of DNA. Recognition of elements with typical functions within a DNA sequence and comparison to known genes in other organisms also helps determine which portion of the sequence constitutes the gene. Commercially available genetic tests may use various techniques for mutation analysis (not always DNA sequencing). Therefore, these tests may not detect all possible mutations that give rise to a particular disease.

**Ethical issues.** Genetic tests are one of the few predictive tests available in medicine, and several ethical issues accompany this fact. The disease that the test predicts may be untreatable and a positive result, therefore, seen as a "death sentence." Patients with a positive test result may be at risk for suicide, whereas those with a negative result may be at risk for "survivor guilt." When ordering a genetic test for a patient, the neurologist must also consider implications of a positive result for family members who are at risk for the disease. For example, a positive test for an autosomal dominant mutation in the patient and the patient’s maternal grandmother may unmask the patient’s mother as an "obligate carrier" of the mutation.

Patients at risk for genetic conditions may be symptomatic or asymptomatic, adults or children, or cognitively competent or cognitively impaired. Special considerations must be taken when testing vulnerable groups, particularly children, for presymptomatic disease. Test of presymptomatic children prior to age 18 years is discouraged unless treatment can be offered. Particularly in asymptomatic individuals, genetic counseling is recommended for the patient and family prior to DNA testing.

**Online resources.** Extensive neurogenetic information to support the clinical neurologist is available in public databases. One of the most useful online databases of information for genetic diagnosis and testing is Online Mendelian Inheritance in Man (OMIM), which can be searched by disease name, symptom/sign, gene symbol, or protein name. OMIM searches can be entered using the Entrez system on PubMed (www.pubmed.gov).

**NEUROLOGIC DISORDERS WITH GENETIC ASSOCIATIONS**

**MITOCHONDRIAL, TRINUCLEOTIDE REPEAT, AND ION CHANNEL DISORDERS**

Genetic disorders that are frequently discussed together due to thematic similarities include the mitochondrial disorders, trinucleotide repeat disorders, and channelopathies.

**Mitochondrial Disorders**

Manifestations of mitochondrial disorders can vary significantly between individuals; different mtDNA mutations can cause similar phenotypes, and different phenotypes can be seen in patients with identical mtDNA defects. This variation has been explained partially by **heteroplasmy** (presence of wild-type and mutant mitochondrial genomes in the same cell), tissue **mosaicism** (disproportionate distribution of mutant mtDNA to progenitor cells during cell division), and **threshold effects** (a certain proportion of mtDNA must carry the mutation to produce disease). Implications of mosaicism for the clinician are that it is best to select affected tissues for genetic testing because the mutation can sometimes be missed in serologic tests. Long-lived tissues with high metabolic demand have a lower threshold for the expression of mitochondrial disease. In particular, brain, heart, skeletal muscle, retina, renal tubules, and endocrine glands tend to be affected. The classic manifestation in skeletal muscle is the ragged red fiber, a contracted irregular muscle fiber with a rim that is red on Gomori trichrome stain due to proliferation and accumulation of mitochondria inside the cell membrane.

General neurologists should be familiar with the classic mtDNA disorders that have primarily neurologic manifestations (Table 1). **Leigh syndrome** (familial bilateral striatal necrosis) presents in infancy or early childhood with encephalopathy, cranial nerve abnormalities,
and ataxia associated with hyperintensity or necrosis in the basal nuclei, cerebellum, and brainstem on T2-weighted magnetic resonance imaging (MRI). Mutations in both nuclear and mitochondrial genes, most notably nuclear-encoded OXPHOS subunits and the gene encoding subunit 6 of mitochondrial ATPase (ATPase 6), have been associated with this phenotype. Kearns-Sayre syndrome (KSS) and chronic progressive external ophthalmoplegia (CPEO) are characterized by ptosis, ophthalmoplegia, and ragged red fiber myopathy and are variably associated with other organ system involvement and ataxia. KSS is a more severe syndrome, whereas CPEO is less severe, with potentially an adult or adolescent onset. Myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial myopathy, encephalopathy, and lactic acidosis with stroke-like episodes (MELAS) are caused by mutations in mitochondrial tRNA genes; both conditions have been associated with this phenotype. Trinucleotide Repeat Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Repeat Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome</td>
<td>XLD</td>
<td>FMR1</td>
<td>X</td>
<td>CGG</td>
</tr>
<tr>
<td>Kennedy’s disease</td>
<td>XLD</td>
<td>Androgen receptor</td>
<td>X</td>
<td>CAG</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>AD</td>
<td>Huntingtin</td>
<td>4</td>
<td>CAG</td>
</tr>
<tr>
<td>Myotonic dystrophy 1</td>
<td>AD</td>
<td>DMPK</td>
<td>19</td>
<td>CTG</td>
</tr>
<tr>
<td>Myotonic dystrophy 2/PROMM</td>
<td>AD</td>
<td>ZNF9</td>
<td>3</td>
<td>CCTG</td>
</tr>
<tr>
<td>Friedreich’s ataxia</td>
<td>AR</td>
<td>Frataxin</td>
<td>9</td>
<td>GAA</td>
</tr>
<tr>
<td>DRPLA</td>
<td>AD</td>
<td>DRPLA/Atrophin 1</td>
<td>12</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA1</td>
<td>AD</td>
<td>Ataxin 1</td>
<td>6</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA2</td>
<td>AD</td>
<td>Ataxin 2</td>
<td>12</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA3 (MJD)</td>
<td>AD</td>
<td>Ataxin 3 (josephin)</td>
<td>14</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA6</td>
<td>AD</td>
<td>CACNA1A</td>
<td>19</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA7</td>
<td>AD</td>
<td>Ataxin 7</td>
<td>3</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA8</td>
<td>AD</td>
<td>Unknown</td>
<td>13</td>
<td>CTG</td>
</tr>
<tr>
<td>SCA10</td>
<td>AD</td>
<td>Ataxin 10</td>
<td>22</td>
<td>ATTCT</td>
</tr>
<tr>
<td>SCA12</td>
<td>AD</td>
<td>PP2A</td>
<td>5</td>
<td>CAG</td>
</tr>
<tr>
<td>SCA17</td>
<td>AD</td>
<td>TATA box-binding protein</td>
<td>6</td>
<td>CAG</td>
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<tr>
<td>OPMD</td>
<td>AD</td>
<td>PABP2</td>
<td>14</td>
<td>GCG</td>
</tr>
</tbody>
</table>

Table 2. Trinucleotide Repeat Disorders

AD = autosomal dominant; AR = autosomal recessive; CACNA1A = voltage-dependent calcium channel alpha-1A subunit; DMPK = dystrophia myotonica protein kinase; DRPLA = dentatorubropallidolysian atrophy; FMR1 = fragile X mental retardation 1; MJD = Machado-Joseph disease; OPMD = oculopharyngeal muscular dystrophy; PABP2 = polyadenylate-binding protein 2; PME = progressive myoclonic epilepsy; PP2A = protein phosphatase 2A; PROMM = proximal myotonic myopathy; SCA = spinocerebellar ataxia; XLD = X-linked dominant; ZNF9 = zinc finger protein 9.

and ataxia associated with hyperintensity or necrosis in the basal nuclei, cerebellum, and brainstem on T2-weighted magnetic resonance imaging (MRI). Mutations in both nuclear and mitochondrial genes, most notably nuclear-encoded OXPHOS subunits and the gene encoding subunit 6 of mitochondrial ATPase (ATPase 6), have been associated with this phenotype. Kearns-Sayre syndrome (KSS) and chronic progressive external ophthalmoplegia (CPEO) are characterized by ptosis, ophthalmoplegia, and ragged red fiber myopathy and are variably associated with other organ system involvement and ataxia. KSS is a more severe syndrome, whereas CPEO is less severe, with potentially an adult or adolescent onset. Myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial myopathy, encephalopathy, and lactic acidosis with stroke-like episodes (MELAS) are caused by mutations in mitochondrial tRNA genes; both conditions have been associated with this phenotype.

**Trinucleotide Repeat Disorders**

Human genomic DNA contains numerous spans of repeated trinucleotide elements. When these sequences expand beyond the normal length, they can alter gene expression such that disease results (Table 2). In most cases, the disorders are autosomal dominant (toxic gain of function). CAG expansions code for polyglutamine tracts that accumulate in neuronal nuclear inclusions thought to be the result of altered protein compartmentalization and degradation. In some conditions (eg, fragile X syndrome, myotonic dystrophy, Friedreich’s ataxia, spinocerebellar ataxia type 8 [SCA8], SCA12), the trinucleotide element involves untranslated regions of DNA. Generally, the phenotypes of trinucleotide repeat disorders correlate with the repeat length; larger expansions cause more severe disease. The repeat length can change (frequently expanding) during gametogenesis, leading to earlier disease onset and more severe disease in successive generations (anticipation). In some cases, parents...
of patients affected by these disorders carry a *premutation*, a trinucleotide repeat expansion of insufficient length to cause disease in the parent. In fragile X syndrome, premutations are more likely to expand with maternal transmission. In Huntington’s disease, allele expansion is more likely to occur with paternal transmission. In Huntington’s disease, allele expansion is more likely to occur with paternal transmission. In Huntington’s disease, allele expansion is more likely to occur with paternal transmission.

**Gene families that probably evolved from a common ancestral gene** by gene duplication and divergence. Disorders caused by mutations in ion channel genes are typically autosomal dominant (cystic fibrosis is an exception) and are characterized by episodic attacks that can be precipitated by particular stressors such as exercise, dietary factors, or neuromuscular blocking agents. Classic examples of channelopathies are long QT syndrome, periodic paralyses, paramyotonia congenita, and malignant hyperthermia. Several disorders are caused by allelic defects in the P/Q type voltage-dependent calcium channel, including SCA6, episodic ataxia type 2, and familial hemiplegic migraine. 6–8

**CEREBRAL CORTEXAL DISORDERS**

**Developmental Delay**

Encephalopathy and developmental delay can be associated with one of many inborn errors of metabolism. These disorders will not be discussed in detail. Most single gene defects that affect development are associated with dysmorphic features. Two common disorders are *trisomy 21* (Down syndrome) and *fragile X syndrome*. About half of live births with trisomy 21 survive until age 50 years. Some morphologic features of trisomy 21 include a third fontanelle, large tongue, single palmar crease, clinodactyly, epicanthic folds, and Brushfield’s spots of the iris. Obesity, short stature, and congenital heart defects are common.

Fragile X syndrome is caused by an expansion of more than 200 CGG repeats in an untranslated region of the FMR1 gene on the distal long arm of the X chromosome. The expansion leads to transcriptional silencing of the FMR1 gene due to abnormal methylation. The expansion is visualized as a constriction in the chromosome in folate-deficient media. Boys with fragile X syndrome have hyperextensible joints, a high-arched palate and high-pitched voice, pectus excavatum, macroorchidism, developmental delay, and frequently autistic features. Men who carry a premutation of about 80 to 100 repeats may develop action tremor with parkinsonism in the sixth decade.9

**Neurocutaneous Syndromes**

Congenital syndromes with skin and nervous system manifestations are listed in *Table 4*; tuberous sclerosis and neurofibromatosis are most common. Although genetically unrelated, many neurocutaneous syndromes are caused by defects in tumor suppressor genes.

**Tuberous sclerosis** is caused by a mutation in the TSC1 gene on chromosome 9, which codes for hamartin, or a mutation in the TSC2 gene on chromosome 16, which codes for tuberin; half to three quarters...
of cases are sporadic. Both tuberin and hamartin have tumor suppressor activity. Cutaneous manifestations of tuberous sclerosis include hypomelanotic leaf-shaped macules (ash-leaf spots), facial angiofibromas, periungual fibromas, and shagreen patches. Ash-leaf spots are the most frequent lesion present at the earliest age; patients typically have 3 or more.10 Systemic manifestations include retinal lesions, cardiac rhabdomyomas, renal angiomyolipomas, and pulmonary lymphangiomatosis. Seizures, especially infantile spasms, occur in at least 80% of diagnosed cases. Central nervous system (CNS) lesions include calcified subependymal nodules, cortical hamartomas, heterotopic grey matter, and subependymal giant cell astrocytomas (which may cause acute hydrocephalus). Although cognitive and behavioral problems are common, only about 50% of patients have mental retardation.11

**Neurofibromatosis.** Neurofibromatosis type 1 (NF1; von Recklinghausen’s disease) is caused by a mutation in a gene on chromosome 17 that codes for neurofibromin; NF2 is caused by a mutation in a gene on chromosome 22 that codes for neurofibromin-2 (also called merlin or schwannomin). Both genes have tumor suppressor activity. NF1 is a predominantly a peripheral nervous system

### Table 4. Neurocutaneous Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Cutaneous Features</th>
<th>Neurologic Features</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR</td>
<td>Conjunctival telangiectasia, skin telangiectasis (late)</td>
<td>Ataxia, intention tremor, decreased tendon reflexes, abnormal saccades</td>
<td>ATM</td>
<td>DNA repair</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>XLR</td>
<td>Angiokeratomas</td>
<td>Painful neuropathy, stroke</td>
<td>GLA</td>
<td>α-Galactosidase A deficiency</td>
</tr>
<tr>
<td>Hypomelanosis of Ito</td>
<td>AD</td>
<td>Linear or swirling hypopigmented areas</td>
<td>Mental retardation, epilepsy</td>
<td>Mosaic of incontinentia pigmenti</td>
<td>—</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>XLD (90% of females)</td>
<td>Neonatal: erythematous, macular, papular, vesicular lesions; later: pigmented macules, whorls</td>
<td>Mental retardation, epilepsy, microphally, spasticity</td>
<td>X/autosomal translocation</td>
<td>Transcription factor activator</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>XLR</td>
<td>Self-mutilation, especially of digits and lips</td>
<td>Mental retardation, dystonia</td>
<td>HPRT1</td>
<td>Defective purine metabolism</td>
</tr>
<tr>
<td>Linear sebaceous nevus syndrome</td>
<td>Sporadic</td>
<td>Linear verrucous lesion near midline of face or scalp</td>
<td>Epilepsy, mental retardation, focal deficits</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Menkes (kinky hair) disease</td>
<td>XL</td>
<td>Colorless, friable hair, pili torti (kinky hair), trichorrhexis nodosa (hair fractures)</td>
<td>Seizures, hypotonia, developmental delay and regression</td>
<td>MNK</td>
<td>Gut copper-binding protein</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>AD</td>
<td>Café-au-lait spots, axillary freckling, Lisch nodules of iris, cutaneous neurofibromas, plexiform neurofibromas</td>
<td>Learning disability, cognitive impairment, neuro-axis tumors</td>
<td>NF1</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>AD</td>
<td>Skin tumors</td>
<td>Neuro-axis tumors</td>
<td>NF2</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Olsler-Weber-Rendu disease</td>
<td>AD</td>
<td>Cutaneous and membrane telangiectasias</td>
<td>Abscess, meningitis, embolism, cerebral vascular abnormalities</td>
<td>Endoglin (ENG)</td>
<td>TGF binding protein</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>Sporadic</td>
<td>Facial port-wine stain, glaucoma</td>
<td>Epilepsy, mental retardation, focal deficits</td>
<td>TSC1, TSC2</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>AD</td>
<td>Hypomelanotic macules, ungual fibromas, shagreen patches, facial angiofibromas</td>
<td>Epilepsy, mental retardation, autism, giant cell astrocytoma</td>
<td>?Somatic 4q inversion</td>
<td>Altered fibronectin expression</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>AD</td>
<td>Retinal hemangioblastoma</td>
<td>Cerebellar hemangioblastoma</td>
<td>VHL</td>
<td>Tumor suppressor</td>
</tr>
</tbody>
</table>

**AD** = autosomal dominant; **AR** = autosomal recessive; **HPRT1** = hypoxanthine guanine phosphoribosyltransferase 1; **TGF** = transforming growth factor; **XL** = X-linked; **XLD** = X-linked dominant; **XLR** = X-linked recessive. (Modified from Conneally M, Bird T, Engel AG, et al. Neurogenetics. Continuum 2000;6[6]:36.)

**AD = autosomal dominant; AR = autosomal recessive; HPRT1 = hypoxanthine guanine phosphoribosyltransferase 1; TGF = transforming growth factor; XL = X-linked; XLD = X-linked dominant; XLR = X-linked recessive. (Modified from Conneally M, Bird T, Engel AG, et al. Neurogenetics. Continuum 2000;6[6]:36.)**
disease, although it does have some CNS manifestations including high signal lesions in the basal nuclei on T2-weighted MRI. Mild cognitive abnormalities and psychiatric symptoms may occur. NF1 is a cause of moyamoya disease. Diagnosis of NF1 requires the presence of 2 or more of the following criteria: 6 or more café-au-lait spots (> 5 mm in diameter before puberty or 15 mm in diameter after), axillary or inguinal freckling, optic glioma, 2 or more neurofibromas or 1 plexiform neurofibroma, a first-degree relative with NF1, and a characteristic bone lesion (ie, sphenoid dysplasia). NF2 has primarily CNS and cranial nerve manifestations, especially bilateral vestibular schwannomas. Both NF1 and NF2 are associated with CNS neoplasms (eg, ependymomas, meningiomas, astrocytomas).

Sturge-Weber syndrome typically presents as a facial port-wine stain, most commonly involving the ophthalmic distribution of the trigeminal nerve. The facial angiomata is frequently associated with an ipsilateral leptomeningeal angiomata that is calcified on computed tomography and enhances on MRI. Affected individuals often develop progressive neurologic problems, including difficult to control seizures, migraines, stroke-like episodes, mental retardation, and hemiparesis. The syndrome is postulated to result from a somatic mutation resulting in mosaic alteration in fibroblastin gene expression.

von Hippel-Lindau disease consists of angiogenic tumors in a variety of organs, especially hemangioblastoma of the CNS and retina, renal cell carcinoma, pheochromocytoma, and pancreatic neuroendocrine tumors. A variety of defects in the VHL gene (chromosome 11) impair its tumor suppressor activity.

Neuronal Migration Disorders

During brain development, neurons migrate along radial glial fibers from the ependymal zone (along the cerebral ventricles) to the cerebral cortex. Disruption of this process results in cerebral cortical malformations and heterotopias. One such disorder is classic lissencephaly (4-layered cortex lacking gyri or sulci), which is caused by a mutation in the LIS1 gene on chromosome 17. LIS1 codes for a subunit of platelet-activating factor that, when inhibited, suppresses neuronal migration. Classic lissencephaly is characterized by profound mental retardation and epilepsy; it may occur alone or in association with facial dysmorphism as part of the Miller-Dieker syndrome.

Another gene responsible for lissencephaly, the double cortex (DC) gene, was identified on the X chromosome. DC mutations cause an X-linked dominant disorder characterized by classic lissencephaly in hemizygous males and milder mental retardation and seizures (subcortical band heterotopia) in heterozygous females. It is hypothesized that in females, X chromosome inactivation leads to 2 distinct populations of migrating neurons—normal neurons that form the cortex and neurons in which the normal DC allele has been inactivated, which fail to migrate normally, forming the subcortical band heterotopia.

Epilepsy

Several genes responsible for familial epilepsy syndromes have been mapped. Many of these are mutations in genes that code for ion channels (see Table 3). Autosomal dominant nocturnal frontal lobe epilepsy is caused by mutations that cause defects in the neuronal nicotinic acetylcholine receptor. Patients experience clusters of brief motor seizures (usually with consciousness preserved) during non-rapid eye movement sleep. Ictal findings on electroencephalogram (EEG) are characteristically inconclusive, potentially leading to a diagnosis of psychogenic seizures. Benign familial neonatal convulsions is a rare autosomal dominant disorder caused by a mutation in a voltage-gated potassium channel that is one of the major regulators of neuronal excitability in the brain. Brief, multifocal or generalized tonic clonic seizures typically begin at about 3 days of life. The seizures are associated with suppression of EEG background. Seizures resolve within the first few months of life but may recur later in life. Generalized epilepsy with febrile seizures is probably autosomal dominant with variable penetrance and is the cause of a prolonged course of febrile seizures (lasting beyond age 6 years) and some more grave phenotypes. It is caused by mutations in voltage-gated sodium channel subunits. Alexander disease—a rare cause of childhood epilepsy, macrocephaly, and progressive neurodegeneration with Rosenthal fibers—has recently been linked to mutations in a gene encoding glial fibrillary acidic protein (GFAP).

Dementia

Alzheimer’s disease (AD), the most common late-onset dementia, is characterized by early deficits in formation of new memories. Having a first-degree relative with AD doubles the risk of developing late-onset AD. The apolipoprotein E4 polymorphism is a risk factor for late-onset disease and a dose-dependent modifier of age of onset. Autosomal dominant mutations in amyloid beta protein precursor (APP; chromosome 21), presenilin 1 (PS1; chromosome 14), and presenilin 2 (PS2; chromosome 1) account for a significant proportion of early-onset AD (onset before age 60 years).
Pathologically, brains of patients with AD bear neurofibrillary tangles consisting of paired helical filaments of hyperphosphorylated tau protein (microtubule-associated protein tau [MAPT]; chromosome 17) and senile plaques containing insoluble aggregates of amyloid-beta (A-beta) protein. The protein product of APP is cleaved by proteases (β secretase, γ secretase) to form A-beta proteins of various lengths. Longer fragments 42 to 42 amino acids in length (A-beta-42) are prone to forming amyloid plaques. Mutations in PS1 and PS2 are thought to alter γ secretase activity such that a higher proportion of amyloidogenic A-beta-42 is produced.17

**Frontotemporal dementia.** Several neurodegenerative disorders including frontotemporal dementia (FTD) have been categorized as tauopathies on the basis of neurofibrillary tangles pathology. Tau isoforms present in the tangles differ somewhat among disorders. FTD typically causes a presenile dementia characterized by early executive and language dysfunction. Autosomal dominant FTD with parkinsonism is associated with missense and splice site mutations in the tau gene on chromosome 17.18

**Prion disease.** A small proportion of diseases linked to proteinaceous infectious particles (prions) are inherited as autosomal dominant traits. All of these conditions are caused by mutations in the human prion protein (PRNP) gene on chromosome 20. PRNP mutations are associated with Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler disease (GSD), and familial fatal insomnia (FFI). CJD is characterized by dementia, ataxia, and stimulus-sensitive myoclonus with spongiform insomnia followed by progressive dementia, ataxia, dysarthria, myoclonus, and pyramidal signs associated with degeneration of the thalamus.

Although several PRNP mutations have been associated with human disease, a glutamic acid to lysine change at codon 200 (E200K mutation) is the most frequent cause of inherited CJD, a proline to leucine substitution at codon 102 (P102L mutation) is most commonly associated with GSD, and a mutation at codon 127 (D127N mutation) accounts for FFI. In the presence of the D127N mutation, disease phenotype is determined by the type of polymorphism present at codon 129; valine at codon 129 plus the D127N mutation causes familial CJD, while methionine at codon 129 plus D127N produces FFI.19 The valine-methionine polymorphism at codon 129 also influences susceptibility to CJD; 100% of cases of new variant CJD were homozygous for methionine at codon 129, and a high percentage of patients with sporadic and iatrogenic CJD are homozygous for either methionine or valine at codon 129.20

**CEREBROVASCULAR DISEASE**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a nonamyloid form of small-vessel disease caused by mutations in the NOTCH3 gene on chromosome 19. NOTCH3 is one of a family of transmembrane receptors that have many roles in organizational development. Clinical manifestations include migraine with aura and recurrent deep white matter infarcts, leading to cognitive decline and pseudobulbar symptoms (worse in men); average age of onset is 45 years.21,22

**Cerebral cavernous malformations (CCMs)** are dominantly inherited vascular malformations that cause seizures and cerebral hemorrhages, with associated focal neurologic deficits. Three CCM loci have been mapped, two to chromosome 7 (CCM1, CCM2) and one to chromosome 3 (CCM3). Loss of function mutations have been identified in the KRIT1 (CCM1) and malcavernin (CCM2) genes. CCM3 is caused by a mutation in a programmed cell death gene (PDGCD10).23

The vascular type of Ehlers-Danlos syndrome (EDS IV), an autosomal dominant cause of structural defects in type III collagen, is associated with dissection of intracranial arteries, aneurysm, carotid-cavernous fistula, and spontaneous rupture of bowel. Skin is thin, translucent, and mildly extensible. The collagen defect can be identified in cultured skin fibroblasts.

**Marfan syndrome,** caused by a defect in the connective tissue protein fibrillin 1, causes asthenic body and facial type, mild to moderate joint laxity, vertebral column abnormalities, subluxation of the lenses (ectopia lentis), dural ectasia, and spontaneous dissection of the aortic and cerebral vessels.

**BASAL GANGLIA DISORDERS**

**Huntington’s Disease**

Huntington’s disease (HD) is an autosomal dominant disorder characterized by chorea, cognitive decline, and early degeneration of the caudate nucleus; it is caused by expansion of a polymorphic trinucleotide repeat (CAG) in the 5’ coding region of the huntingtin gene on chromosome 4. Repeats range in number from 9 to 37 in normal individuals and from 37 to 86 in HD patients; genes with 42 or more CAG repeats are 100% penetrant. In the disease state, intranuclear inclusions consisting of polyglutamine fragments and truncated huntingtin protein are found. The mean age of onset is
between 35 and 44 years, leading to death after about 15 years. Onset earlier than age 20 years (Westphal variant) is frequently associated with akinetic/rigid clinical signs and 60 or more CAG repeats.24 Dentatorubropalidoluysian atrophy (DRPLA) is in the differential diagnosis of these cases.

Parkinson’s Disease

Although Parkinson’s disease (PD) usually is sporadic, 10 genetic loci (PARK1–10) have been linked to PD (Table 5). Several of these mutations affect proteins involved in or degraded by the ubiquitin-proteasomal pathway. The most extensively studied and most common mutation in cases of early-onset PD (autosomal recessive juvenile parkinsonism [AR-JP]) are mutations in the parkin gene (PARK2) on chromosome 6, which codes for a ubiquitin-protein ligase. Features of this disease include early psychiatric symptoms, dystonia, excellent response to levodopa, susceptibility to medication-induced dyskinesias, and relatively slow progression. PARK2 mutations are found in as many as 77% of sporadic cases when onset occurs earlier than age 20 but in only 3% when onset occurs later than age 30 years.25 Most cases of genetic parkinsonism do not have Lewy bodies.

Dystonia

At least 14 genetic loci (DYT1–14) have been linked to dystonia (Table 6). With the exception of DYT2 dystonia, and the autosomal recessive form of dopa-responsive dystonia, the disorders are autosomal dominant with variable penetrance.26 The following dystonias are the most clinically relevant to the neurologist.

DYT1 dystonia is strongly represented in Ashkenazi Jewish populations and typically causes early-onset generalized dystonia that initially involves 1 foot (also known as primary or idiopathic torsion dystonia). The genetic defect is deletion of 1 of a pair of CAG repeats in the gene encoding torsinA, leading to aggregation of the protein in perinuclear inclusions.27

Dopa-responsive dystonia (DRD; Segawa syndrome) can result from any of several genetic defects that impair dopamine synthesis. DRD is an early-onset generalized dystonia associated with diurnal fluctuations, parkinsonism, dramatic response to levodopa, and low levels of the dopamine metabolite homovanillic acid in cerebrospinal fluid. The condition may be confused with AR-JP and cerebral palsy. A dominant form of DRD is caused by a mutation in the gene encoding GTP cyclohydrolase 1 (GCH1; chromosome 14), which impairs biosynthesis of tetrahydrobiopterin, a cofactor for tyrosine hydroxylase. A defect in the tyrosine hydroxylase gene (chromosome 11), which codes for the rate-limiting enzyme in dopamine synthesis, causes a recessive form of DRD.28

Wilson’s Disease

Wilson’s disease is a recessively inherited form of hepatolenticular degeneration that can present with an ataxic, extrapyramidal, psychiatric, or mixed phenotype. In Wilson’s disease, inadequate function of a copper transporting ATPase (ATP7B) on chromosome 13 results in excessive free serum copper that accumulates in tissues, especially the liver, brain, and cornea (Kayser-Fleischer ring seen on slit-lamp examination).

Pantothenate Kinase-associated Neurodegeneration

Since it was described by Hallervorden and Spatz in 1922, this diagnosis has been applied to children and young adults who develop progressive and inevitably fatal dystonia, dysarthria, and rigidity associated with iron deposition in the basal nuclei (“eye of the tiger” sign on T2-weighted MRI). Classic cases and one third of atypical cases are correlated with mutations in the PANK2 gene, which encodes a pantothenate kinase that regulates coenzyme A synthesis.29
Autosomal recessive forms are typically of earlier onset (< 20 years of age), whereas autosomal dominant SCAs generally are of later onset (> 25 years of age), although some have onset in childhood. X-linked SCAs are rare.

**Autosomal Recessive Forms**

Friedreich’s ataxia is the most common hereditary form of spinocerebellar degeneration, characterized by progressive limb and gait ataxia, neuropathy, areflexia, dystarthis, and pyramidal signs. A trinucleotide repeat expansion on chromosome 9 causes diminished expression of frataxin, a mitochondrial protein encoded in the nucleus, which plays a role in iron homeostasis.30 Although rare, ataxia caused by vitamin E deficiency (due to a defect in the α-tocopherol transfer protein) has a similar phenotype to Friedreich’s ataxia and responds to vitamin E. Ataxia-telangiectasia presents in childhood with progressive ataxia, ocular and cutaneous telangiectasia, extrapyramidal signs, and cognitive decline; it is caused by a defect in DNA repair (ATM gene). The disease is associated with a high risk of hematologic malignancies and low serum IgA levels.

**Autosomal Dominant Forms**

As medical genetics advances, the autosomal dominant cerebellar ataxias (ADCAs) continue to grow into a bewildering number of genetically defined conditions. Although it may be of limited utility to memorize these conditions, it is important to recognize particular phenotypes. These disorders were initially classified by Harding31 according to 3 clinical phenotypes: ADCA type I (associated with varying degrees of dementia and pyramidal, extrapyramidal, peripheral neuropathic, and ophthalmologic signs), ADCA type II (cerebellar and retinal degeneration), and ADCA type III (pure cerebellar syndrome). The prototype of ADCA type I is Machado-Joseph disease (SCA3), the most common form of SCA. This condition was initially described in Azorean Greek families but is now known to affect patients in many ethnic groups; expanded alleles may be quite large (up to 200 CAG repeats). SCA1 and SCA2 are phenotypically similar to SCA3, although SCA2 is characterized by early slow saccades. The prototype for ADCA type II is SCA7, which causes optic atrophy and pigmentary retinopathy. The ADCA type III phenotype is characteristic of SCAs 5, 6, 10, 11, 14, 15, 16, and 22. Many ADCAs have onset in the third or fourth decade. The earliest is SCA13, which presents in early childhood with ataxia associated with motor and cognitive delay. The latest is typically SCA6, a pure cerebellar late-onset syndrome associated with ophthalmoplegia. Episodic ataxia type 1 (EA1) and episodic ataxia type 2 (EA2) typically have onset in childhood to adolescence. EA1 causes facial myokymia and very brief episodes of ataxia that are responsive to acetazolamide. EA2 causes attacks of ataxia.

### Table 6. Dystonia Genetic Loci

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Gene Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>9q34</td>
<td>AD</td>
<td>Early limb onset</td>
<td>TorsinA</td>
</tr>
<tr>
<td>DYT2</td>
<td>Not mapped</td>
<td>AR</td>
<td>Early onset</td>
<td>—</td>
</tr>
<tr>
<td>DYT3</td>
<td>Xq13.1</td>
<td>XR</td>
<td>Filipino dystonia/parkinsonism</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT4</td>
<td>Not mapped</td>
<td>AD</td>
<td>Whispering dysphonia</td>
<td>—</td>
</tr>
<tr>
<td>DYT5</td>
<td>1q22.1</td>
<td>AD</td>
<td>DRD/parkinsonism</td>
<td>GCH1</td>
</tr>
<tr>
<td>TH</td>
<td>11p15.5</td>
<td>AR</td>
<td>DRD</td>
<td>TH</td>
</tr>
<tr>
<td>DYT6</td>
<td>8p</td>
<td>AD</td>
<td>Mixed</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT7</td>
<td>18p</td>
<td>AD</td>
<td>Adult cervical</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT8</td>
<td>2q33-35</td>
<td>AD</td>
<td>PDC/PNKD</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT9</td>
<td>1p21</td>
<td>AD</td>
<td>Episodic choreoathetosis/ataxia/spasticity</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT10</td>
<td>16</td>
<td>AD</td>
<td>PKC/PKD</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT11</td>
<td>7q21</td>
<td>AD</td>
<td>Myoclonus dystonia</td>
<td>Epsilon-sarcoglycan</td>
</tr>
<tr>
<td>DYT12</td>
<td>19q</td>
<td>AD</td>
<td>Rapid-onset dystonia/parkinsonism</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT13</td>
<td>1p26.13-p36.32</td>
<td>AD</td>
<td>Cervical/cranial/brachial</td>
<td>Not identified</td>
</tr>
<tr>
<td>DYT14</td>
<td>1q13</td>
<td>AD</td>
<td>DRD</td>
<td>Not identified</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; DRD = dopa-responsive dystonia; GCH1 = GTP cyclohydrolase 1; PDC = paroxysmal dystonic choreoathetosis; PKC = paroxysmal kinesigenic choreoathetosis or dyskinesia; PKD = paroxysmal kinesigenic dystonia; PNKD = paroxysmal non-kinesigenic dystnesia; TH = tyrosine hydroxylase; XR = X-linked recessive. (Adapted with permission from Bressman SB. Dystonia genotypes, phenotypes, and classification. In: Fahn S, Hallett M, DeLong MR, editors. Dystonia 4: advances in neurology. Vol. 94. Philadelphia: Lippincott Williams & Wilkins; 2004:103.)
and signs of vestibulocerebellar dysfunction lasting minutes to days, which are acetazolamide-unresponsive. SCA12 presents with upper extremity and head tremor.

DRPLA, which is most common in Japanese populations, is associated with myoclonus, chorea, dementia, parkinsonism, and epilepsy; the genetic defect is a CAG repeat expansion in atrophin 1 on chromosome 12. DRPLA, SCA10, and SCA7 may be associated with epilepsy.5,32,33

**SPINAL CORD DISORDERS**

The hereditary spastic paraplegias (HSPs) are disorders characterized by insidiously progressive lower limb weakness and spasticity that produce progressive difficulty walking.34 At least 21 loci have been linked to HSP. Some HSPs are uncomplicated syndromes characterized only by progressive paraparesis; others are associated with additional neurologic abnormalities. The most notable forms for which genes have been mapped are listed in Table 7. Some of the mutations that cause HSP code for proteins that may be involved in axonal transport (spastin, kinesin heavy chain, proteolipid protein). Some are mitochondrial proteins (paraplegin, chaperonin [heat shock protein] 60). Some are X-linked (proteolipid protein, L1 cell adhesion molecule). Pelizaeus-Merzbacher disease, a progressive leukodystrophy associated with “tigroid” dysmyelination, is allelic with an X-linked form of HSP.

**ANTERIOR HORN CELL DISORDERS**

The spinal muscular atrophies (SMAs) cause genetically predetermined degeneration of spinal and bulbar motor neurons. SMAs have been classified on the basis of age of onset and severity into 5 types (Table 8). Most are the result of recessive (loss of function) mutations. The most important mutation associated with SMA is in the gene encoding the survival motor neuron (SMN) protein. Several other genetic factors are phenotypic modifiers of SMN deletions, thought to produce disease phenotypes of varying severity. Kennedy’s disease (X-linked spinal-bulbar muscular atrophy) is an X-linked recessively inherited disease caused by a CAG repeat expansion in the androgen receptor gene. The androgen receptor is a ligand-dependent transcription factor that may play a role in apoptosis. This disease, like many polyglutamine repeat disorders, is associated with intracellular aggregates.

**Amyotrophic lateral sclerosis** (ALS) is the most common sporadic cause of motor neuron degeneration. In a minority of patients with familial ALS, a mutation in the gene that codes for superoxide dismutase 1 (SOD1; copper-zinc superoxide dismutase) causes an autosomal dominant form of the disease. SOD1 is a cytoplasmic protein that catalyzes detoxification of oxygen free radicals generated by mitochondrial electron transport and the cytochrome P-450 system.35

**PERIPHERAL NERVE DISORDERS**

A clinical classification was created in 1975 for the hereditary motor and sensory neuropathies (HMSN), designating these disorders as HMSN I-VII. Once the genetic defects responsible for some of these disorders were mapped, this classification made less sense from a genetic point of view. HMSN I (demyelinating type) is the same as Charcot-Marie-Tooth disease type 1 (CMT1), and HSM II (axonal type) is the same as CMT2, but HMSN III (Dejerine-Sottas disease) can be caused by point mutations in the same genes that contain deletions in CMT1. A more current classification of CMT neuropathies is shown in Table 9.36

**CMT Type 1 (CMT1)**

CMT1A–D are autosomal dominant disorders (sporadic in 20%) with onset in childhood or early adulthood. These disorders are characterized by demyelinating and re-myelinating neuropathy leading to nerve hypertrophy (onion bulbs on pathologic nerve section), distal weakness, pes cavus, loss of stretch reflexes, and postural (Roussy-Levy) tremor in one third of patients. Median nerve conduction velocities are less than 38 m/sec. CMT1A is caused by a duplication or point
mutation in the peripheral myelin protein-22 (PMP22) gene on chromosome 17. The protein product is localized to the compact portion of peripheral myelin, contains 4 transmembrane domains, and is highly conserved in evolution. The interesting aspect of PMP22 mutations is that a duplication of this genetic material causes early-onset demyelinating neuropathy, but a deletion in this gene causes the less severe phenotype, hereditary neuropathy with liability to pressure palsies (HNPP). CMT1B is caused by point mutations or small deletions in the myelin protein zero (P0) gene, linked to the Duffy blood group on chromosome 1q. CMT1D has been linked to mutations in early growth response gene 2 (EGR2), a zinc finger protein that has homology to a mouse transcription factor.

CMT Type 2 (CMT2)

CMT2 is an axonal neuropathy (median nerve conduction velocities > 38 m/sec) that is inherited as an autosomal dominant, autosomal recessive, or X-linked trait. The recessive and X-linked forms are rare. The disorder typically presents later than CMT1 with distal sensory loss and muscle weakness and atrophy. CMT2B is associated with poorly healing ulcers. CMT2C is associated with distal spinal muscular atrophy and vocal cord paralysis. CMT2A and CMT2B have now been linked to more than 1 gene each, and CMT2D–K have been described based on genetic linkage.37

Dejerine-Sottas Disease

Dejerine-Sottas disease (DSD) is a severe (usually

### Table 8. Clinical Classification of Spinal Muscular Atrophies (SMAs)

<table>
<thead>
<tr>
<th>Type</th>
<th>Main Mode of Inheritance</th>
<th>Age of Onset</th>
<th>Pathologic Features</th>
<th>Hallmark</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA type I (Werdnig-Hoffmann disease)</td>
<td>AR or XL (rare)</td>
<td>In utero to 6 mo</td>
<td>Hypotonia and weakness; problems with sucking, swallowing, and breathing</td>
<td>Never able to sit without support</td>
<td>Avg life expectancy is 8 mo; 95% dead before age 1 y</td>
</tr>
<tr>
<td>SMA type II (Dubowitz disease, intermediate form)</td>
<td>AR</td>
<td>3–15 mo</td>
<td>Proximal leg weakness, fasciculations, fine hand tremor</td>
<td>Can sit but never able to stand; facial muscles spared</td>
<td>Death usually occurs after age 2 y</td>
</tr>
<tr>
<td>SMA type III (Wohlfart-Kugelberg-Welander disease, chronic SMA)</td>
<td>AD, AR</td>
<td>15 mo to teen years</td>
<td>Proximal leg weakness, delayed motor milestones</td>
<td>Varies depending on extent and timing of respiratory complications</td>
<td>Life expectancy not markedly reduced</td>
</tr>
<tr>
<td>SMA type IV (adult-onset SMA)</td>
<td>AD, AR</td>
<td>37 y (avg)</td>
<td>Proximal weakness variable and more severe in AD form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal SMA type V (progressive SMA, Charcot-Marie-Tooth type-SMA)</td>
<td>AD, AR</td>
<td>AR: birth or infancy, AD: adulthood</td>
<td>Distal weakness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; XL = X-linked. (Adapted with permission from Cole N. Genetic disorders of motor neurons. Semin Neurol 1999;19:408.)

### Table 9. Charcot-Marie-Tooth (CMT) Neuropathies and Related Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Chromosome Locus</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT type 1 (CMT1)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT1A</td>
<td>17p11.2-12</td>
<td>PMP22</td>
</tr>
<tr>
<td>CMT1B</td>
<td>1q22-23</td>
<td>Po</td>
</tr>
<tr>
<td>CMT1C</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>CMT type 2 (CMT2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT2A</td>
<td>1p36</td>
<td>Unknown</td>
</tr>
<tr>
<td>CMT2B</td>
<td>3q13-22</td>
<td>Unknown</td>
</tr>
<tr>
<td>CMT2C</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>CMT2D</td>
<td>7p14</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dejerine-Sottas disease (DSD)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSDA</td>
<td>17p11.2-12</td>
<td>PMP22</td>
</tr>
<tr>
<td>DSDB</td>
<td>1q22-23</td>
<td>Po</td>
</tr>
<tr>
<td>CMT type 4 (CMT4)</td>
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<td></td>
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<tr>
<td>CMT4A</td>
<td>8q13-21.1</td>
<td>Unknown</td>
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<tr>
<td>CMT4B</td>
<td>11q23</td>
<td>MTMR2</td>
</tr>
<tr>
<td>CMT4C</td>
<td>5q23-33</td>
<td>Unknown</td>
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<tr>
<td>CMTX</td>
<td>Xq13.1</td>
<td>Connexin 32</td>
</tr>
<tr>
<td>HNPPA</td>
<td>17p11.2-12</td>
<td>PMP22</td>
</tr>
<tr>
<td>HNPPB</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

CMTX = X-linked dominant Charcot-Marie-Tooth disease; HNPP = hereditary neuropathy with liability to pressure palsies; MTMR2 = myotubularin-related protein-2. (Adapted with permission from Mendell JR, Kissel JT, Cornblath DR. Diagnosis and management of peripheral nerve disorders. New York: Oxford University Press; 2001:430. Copyright © 2001.)

*Early growth response gene mutations on chromosome 10q21.1-22.2 cause CMT1 and DSD.
sporadic but also autosomal dominant) hypertrophic, demyelinating neuropathy with severe slowing of conduction velocities and onset in infancy or early childhood. DSD is frequently caused by point mutations in PMP22, P0, and others.

**CMT Type 4**

CMT4 neuropathies are autosomal recessive demyelinating disorders. CMT4A and CMT4B have very early onset (before age 3 years) and delayed motor milestones. CMT4C is characterized by severe scoliosis and mild distal neuropathy, presenting prior to age 10 years.

**X-Linked Dominant CMT**

X-linked dominant CMT (CMTX) has a more severe phenotype and earlier onset in males. The phenotype is similar to CMT1, although in contrast to CMT1, affected males may have delayed central conduction on brain stem auditory evoked responses. CMTX is the result of a point mutation in a gap junction protein (connexin 32) and, thus, is also a channelopathy, but it does not have episodic features.

**NEUROMUSCULAR JUNCTION DISORDERS**

The congenital myasthenic syndromes (CMS) are disorders of the neuromuscular junction classified by the site of the transmission defect (ie, presynaptic, synaptic, postsynaptic). The majority of these syndromes are caused by recessive mutations in genes encoding subunits of the muscle nicotinic acetylcholine receptor. Slow channel postsynaptic syndromes are caused by autosomal dominant gain-of-function mutations. CMS is characterized by significant fatigable weakness with onset in childhood, decremental response to 2-Hz stimulation on electromyelography, and negative acetylcholine receptor antibodies.

**MUSCLE DISORDERS**

**Periodic Paralyses**

Hypokalemic periodic paralysis is in most cases caused by point mutations in the alpha 1 subunit of the L-type (dihydropyridine-sensitive) calcium channel. Onset is most common in the second decade and consists of attacks of generalized weakness lasting hours to 1 day. Respiration is not compromised. Attacks are precipitated by exercise, heavy carbohydrate load, or other conditions that increase insulin (thus lowering serum potassium).

Hyperkalemic periodic paralysis is characterized by attacks of muscle stiffness and ache followed by diffuse muscle weakness lasting 15 minutes to 1 hour, beginning in the first decade of life. The attacks tend to occur in the morning, can be precipitated by potassium intake or exercise, and are improved by oral glucose intake. In this condition, single amino acid substitutions in the alpha subunit of the skeletal muscle voltage-gated sodium channel cause defective inactivation of the open channel. Different point mutations in the same channel cause paramyotonia congenita or overlap syndromes. Paramyotonia congenita causes muscle stiffness, particularly involving the neck, face, and hands and provoked by cold exposure of exercise. Some forms are responsive to acetazolamide.

**Malignant Hyperthermia**

In skeletal muscle, excitation-contraction coupling is accomplished by an interaction between voltage-dependent L-type calcium channels in the T tubule membrane and calcium release channels along the sarcoplasmic reticulum. Both L-type channel and sarcoplasmic reticulum calcium release channel complexes are named for their ligands, dihydropyridine (a calcium channel blocker) and ryanodine (a plant alkaloid), respectively. Malignant hyperthermia is an autosomal dominant condition caused by mutations in the ryanodine receptor, which result in excessive calcium release from the sarcoplasmic reticulum in response to halothane and succinylcholine. Affected individuals who have been given these agents develop masseter spasm, rigidity, hyperpyrexia, hemodynamic instability, and rhabdomyolysis.

**Muscular Dystrophies**

**Dystrophin deficiency disorders.** Duchenne muscular dystrophy is an X-linked disorder characterized by early onset progressive proximal muscle weakness, calf pseudohypertrophy, cardiomyopathy, massively elevated creatine kinase, and limited life span. In Duchenne muscular dystrophy, muscle immunocytochemistry reveals almost complete loss of dystrophin protein. Dystrophin, syntrophins, sarcoglycans, and dystroglycans are structural elements of the dystrophin-glycoprotein complex that links the muscle cell cytoskeleton with the extracellular matrix. A milder variant, Becker muscular dystrophy, is associated with a milder reduction in dystrophin staining. About one third of cases of Duchenne and Becker muscular dystrophy result from new mutations, probably in part due to the dystrophin gene (locus, Xp21) being one of the largest known genes. Most of the mutations that produce complete loss of functional dystrophin cause a frame shift. About 8% of female carriers are affected. In about 60% of cases the diagnosis can be made by DNA analysis. In the remainder (point mutations), diagnosis must be made by muscle immunocytochemistry.
Limb-girdle muscular dystrophy (LGMD) refers to genetic conditions that cause gradually progressive proximal weakness, often beginning in the hip girdle, then shoulder girdle, and then distal muscles. Trapezius atrophy may be striking. Age of onset varies from childhood to adulthood, depending on the genetic defect. LGMD occurs in both autosomal dominant and autosomal recessive forms, with the latter more common. Many of the recessive LGMDs are caused by mutations in genes that code for sarcoglycans of the dystrophin-glycoprotein complex.

Myotonic dystrophy is an autosomal dominant disorder caused by a CTG repeat in an untranslated region of chromosome 19. Clinical findings include myotonia, progressive proximal muscle weakness, cataracts, hypogonadism, frontal balding, cardiac conduction abnormalities, respiratory insufficiency, insulin resistance, mild cognitive disorder, and other systemic symptoms. In classic myotonic dystrophy (type 1), the number of CTG repeats in leukocytes may be 100 to 750, but the number of CTG repeats in skeletal muscle may be as many as 5000, suggesting that the repeat expands dur-}

REFERENCES

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