Single-Gene Disorders with Nonclassic Inheritance

It has become increasingly evident that transmission of certain single-gene disorders does not follow classic Mendelian principles. This group of disorders can be classified into four categories:

- Diseases caused by trinucleotide-repeat mutations
- Disorders caused by mutations in mitochondrial genes
- Disorders associated with genomic imprinting
- Disorders associated with gonadal mosaicism

Clinical and molecular features of some single-gene diseases that exemplify nonclassic patterns of inheritance are described next.

Diseases Caused by Trinucleotide-Repeat Mutations

Expansion of trineuclotide repeats is an important genetic cause of human disease, particularly neurodegenerative disorders. The discovery in 1991 of expanding trinucleotide repeats as a cause of fragile X syndrome was a landmark in human genetics. Since then the origins of about 40 human diseases (Table 5-8) have been traced to unstable nucleotide repeats, and the number continues to grow. Some general principles that apply to these diseases are as follows:

- The causative mutations are associated with the expansion of a stretch of trinucleotides that usually share the nucleotides G and C. In all cases the DNA is unstable, and an expansion of the repeats above a certain threshold impairs gene function in various ways, discussed later. In recent years diseases associated with unstable tetra-, penta-, and hexa- nucleotides have also been found establishing this as a fundamental mechanism of neuromuscular diseases.
- The proclivity to expand depends strongly on the sex of the transmitting parent. In the fragile X syndrome, expansions occur during oogenesis, whereas in Huntington disease they occur during spermatogenesis.
- There are three key mechanisms by which unstable repeats cause diseases: (1) *Loss of function* of the affected gene, typically by transcription silencing, as in fragile X syndrome. In such cases the repeats are generally in non-coding part of the gene (2) *A toxic gain of function* by alterations of protein structure as in Huntington disease and spinocerebellar ataxias. In such cases the expansions occur in the coding regions of the genes. (3) *A toxic gain of function mediated by mRNA* as is seen in fragile X tremor-ataxia syndrome. As in fragile X syndrome, the noncoding parts of the gene are affected (Fig. 5-23**).**

The pathogenetic mechanisms underlying disorders caused by mutations that affect coding regions seem to be distinct from those in which the expansions affect noncoding regions. The former usually involve CAG repeats coding for polyglutamine tracts in the corresponding proteins. Such "polyglutamine diseases" are characterized by progressive neurodegeneration, typically striking in midlife. Polyglutamine expansions lead to toxic gain of function, whereby the abnormal protein may interfere with the function of the normal protein (a dominant negative activity) or acquire a novel pathophysiologic toxic activity. The precise mechanisms by which expanded polyglutamine proteins cause disease is not fully understood. In most cases the proteins are misfolded and tend to aggregate; the aggregates may suppress transcription of other genes, cause mitochondrial dysfunction, or trigger the unfolded-protein stress response and apoptosis (Chapter 1). *A*

Table 5-8 Examples of Trinucleotide-Repeat Disorders

Disease	Gene	Locus	Protein	Repeat	No. of Repeats	
					Normal	Disease
Expansions Affecting Noncoding Regions						
Fragile X syndrome	*FMRI (FRAXA)*	Xq27.3	FMR-1 protein (FMRP)	CGG	6-55	55-200 (pre); >230 (full)
Friedreich ataxia	*FXN*	9q21.1	Frataxin	GAA	7-34	34-80 (pre); >100 (full)
Myotonic dystrophy	*DMPK*	19q13.3	Myotonic dystrophy protein kinase (DMPK)	CTG	5-37	34-80 (pre); >100 (full)
Expansions Affecting Coding Regions						
Spinobulbar muscular atrophy (Kennedy disease)	*AR*	Xq12	Androgen receptor (AR)	CAG	9-36	38-62
Huntington disease	*HTT*	4p16.3	Huntingtin	CAG	6-35	36-121
Dentatorubral-pallidoluysian atrophy (Haw River syndrome)	*ATNL*	12p13.31	Atrophin-1	CAG	6-35	49-88
Spinocerebellar ataxia type 1	*ATXN1*	6p23	Ataxin-1	CAG	6-44	39-82
Spinocerebellar ataxia type 2	*ATXN2*	12q24.1	Ataxin-2	CAG	15-31	36-63
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	*ATXN3*	14q21	Ataxin-3	CAG	12-40	55-84
Spinocerebellar ataxia type 6	*CACNA2A*	19p13.3	α_{1A}-Voltage-dependent calcium channel subunit	CAG	4-18	21-33
Spinocerebellar ataxia type 7	*ATXN7*	3p14.1	Ataxin-7	CAG	4-35	37-306