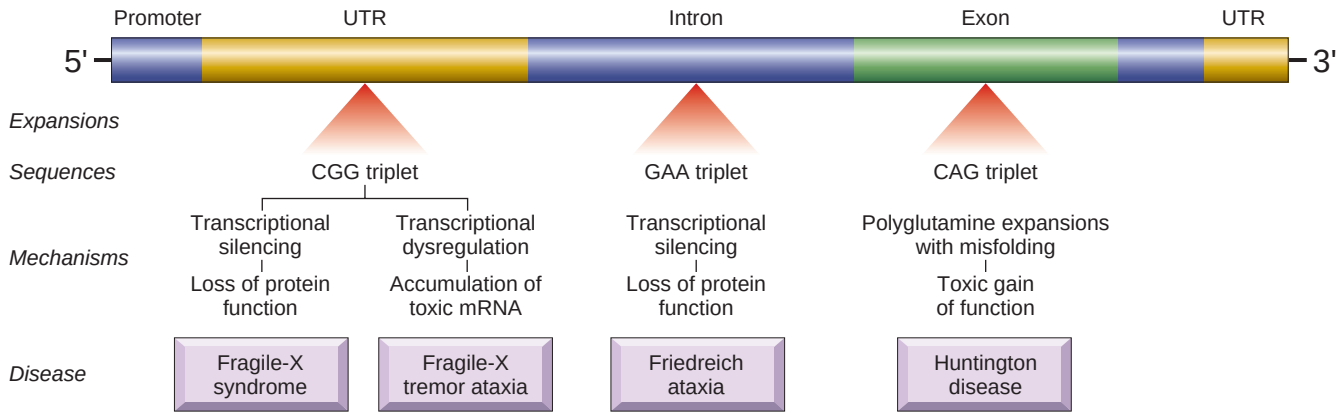

Figure 5-23 Sites of expansion and the affected sequence in selected diseases caused by nucleotide-repeat mutations. UTR, Untranslated region.

morphologic hallmark of these diseases is the accumulation of aggregated mutant proteins in large intranuclear inclusions. While formation of aggregates is common to many "polyglutamine disease," evidence of a direct toxic role of aggregates is not universal. In fact some observers believe that aggregation may be protective by sequestration of the misfolded protein. Other models of pathogenicity implicate downstream effects mediated by proteolytic fragments of the polyglutamine fragment. Much more needs to be learned before therapeutic strategies can be developed.

Fragile X Syndrome and Fragile X Tremor/Ataxia

Fragile X syndrome is the prototype of diseases in which the mutation is characterized by a long repeating sequence of three nucleotides. Although the specific nucleotide sequence that undergoes amplification differs in the 20 or so disorders included in this group, in most cases the affected sequences share the nucleotides guanine (G) and cytosine (C). The ensuing discussion considers the clinical features and inheritance pattern of the fragile-X syndrome, followed by the causative molecular lesion. The remaining disorders in this group are discussed elsewhere in this text. Although distinct diseases, fragile X syndrome and fragile X tremor/ataxia share common features and so are discussed together.

Fragile X syndrome is the second most common genetic cause of mental retardation after Down syndrome. It is caused by a trinucleotide mutation in the familial mental retardation-1 (FMR1) *gene.* Fragile-X-syndrome has a frequency of 1 in 1550 for affected males and 1 in 8000 for affected females and is characterized by an inducible cytogenetic abnormality in the X chromosome within which the *FMR1* gene maps. The cytogenetic alteration was discovered as a discontinuity of staining or as a constriction in the long arm of the X chromosome when cells are cultured in a folate-deficient medium. Because it appears that the chromosome is "broken" at this locale, it was named as a *fragile site* (Fig. 5-24). There are more than 100 "fragile sites" in the human genome of unknown significance; many are present in normal individuals.

In fragile X syndrome, the affected males are *mentally retarded,* with an IQ in the range of 20 to 60. They express a characteristic physical phenotype that includes a *long face with a large mandible, large everted ears,* and *large testicles (macro-orchidism).* Hyperextensible joints, a high arched palate, and mitral valve prolapse noted in some patients mimic a connective tissue disorder. These and other physical abnormalities described in this condition, however, are not always present and, in some cases, are quite subtle. *The most distinctive feature is macro-orchidism, which is observed in at least 90% of affected postpubertal males.*

As with all X-linked diseases, fragile X syndrome affects males. Analysis of several pedigrees, however, reveals some patterns of transmission not typically associated with other X-linked recessive disorders (Fig. 5-25). These include the following:

- *Carrier males:* Approximately 20% of males who, by pedigree analysis and by molecular tests, are known to carry a fragile X mutation are clinically and cytogenetically normal. Because carrier males transmit the trait through all their phenotypically normal daughters to affected grandchildren, they are called *normal transmitting males.*
- *Affected females:* 30% to 50% of carrier females are affected (i.e., mentally retarded), a number much higher than that in other X-linked recessive disorders.
- *Risk of phenotypic effects:* Risk depends on the position of the individual in the pedigree. For example, brothers of transmitting males are at a 9% risk of having mental retardation, whereas grandsons of transmitting males incur a 40% risk.
- *Anticipation:* This refers to the observation that clinical features of fragile X syndrome worsen with each successive generation, as if the mutation becomes increasingly deleterious as it is transmitted from a man to his grandsons and great-grandsons.

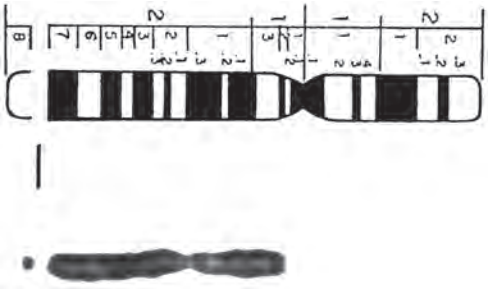

Figure 5-24 Fragile X seen as discontinuity of staining. (Courtesy of Dr. Patricia Howard-Peebles, University of Texas Southwestern Medical Center, Dallas, TX.)