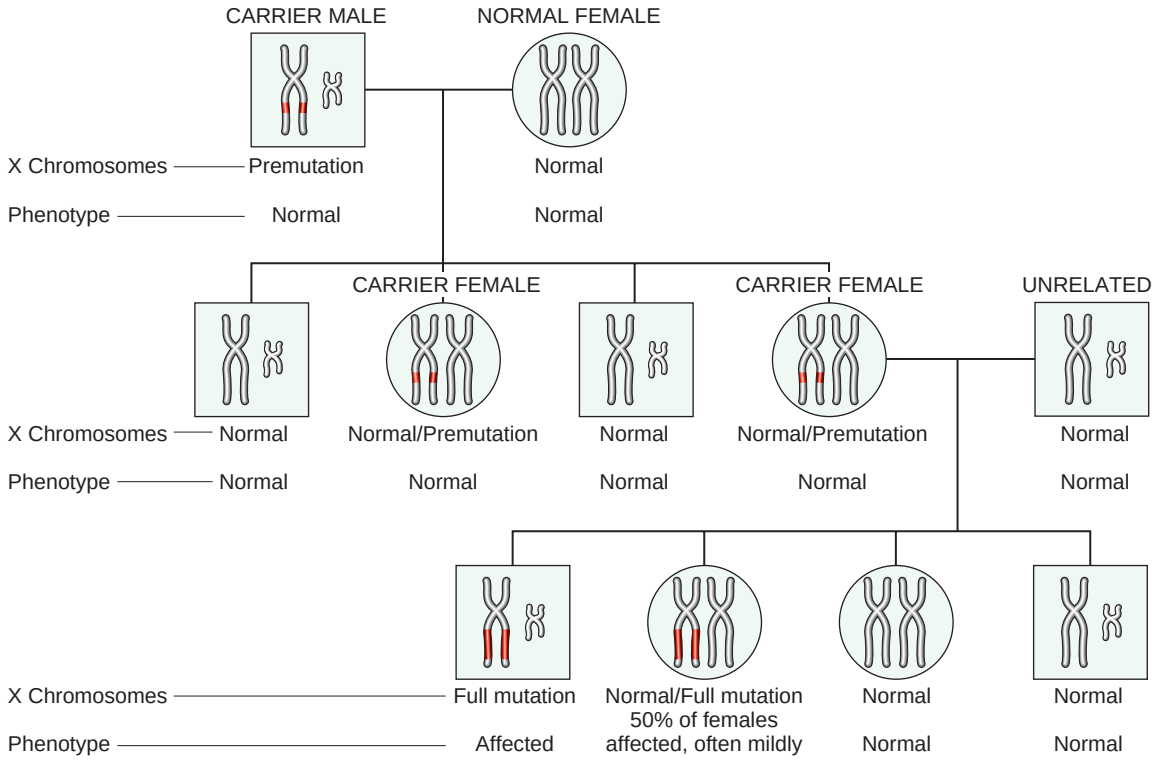

Figure 5-25 Fragile X pedigree. Note that in the first generation all sons are normal and all females are carriers. During oogenesis in the carrier female, premutation expands to full mutation; hence, in the next generation all males who inherit the X with full mutation are affected. However, only 50% of females who inherit the full mutation are affected, and only mildly. (Courtesy of Dr. Nancy Schneider, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)

The first breakthrough in resolving these perplexing observations came when linkage studies localized the mutation responsible for this disease to Xq27.3, within the cytogenetically abnormal region. Within this region lies the *FMR1* gene, characterized by multiple tandem repeats of the nucleotide sequence CGG in its 5′ untranslated region. In the normal population, the number of CGG repeats is small, ranging from 6 to 55 (average, 29). The presence of clinical symptoms and a cytogenetically detectable fragile site is related to the amplification of the CGG repeats. Thus, normal transmitting males and carrier females carry 55 to 200 CGG repeats. Expansions of this size are called *premutations.* In contrast, affected individuals have an extremely large expansion of the repeat region (200 to 4000 repeats, or *full mutations*). Full mutations are believed to arise by further amplification of the CGG repeats seen in premutations. How this process takes place is quite peculiar. Carrier males transmit the repeats to their progeny with small changes in repeat number. When the premutation is passed on by a carrier female, however, there is a high probability of a dramatic amplification of the CGG repeats, leading to mental retardation in most male offspring and 50% of female offspring. Thus, *it seems that during the process of oogenesis, but not spermatogenesis, premutations can be converted to mutations by triplet-repeat amplification*. This explains the unusual inheritance pattern; that is, the likelihood of mental retardation is much higher in grandsons than in brothers of transmitting males because grandsons incur the risk of inheriting a premutation from their grandfather that is amplified to a "full mutation" in their mothers' ova. By comparison, brothers of transmitting males, being "higher up" in the pedigree, are less likely to have a full mutation. These molecular details also provide a satisfactory explanation of anticipation—a phenomenon observed by clinical geneticists but not believed by molecular geneticists until triplet-repeat mutations were identified. Why only 50% of the females with the full mutation are clinically affected is not clear. Presumably in those that are clinically affected there is unfavorable lyonization (i.e., there is a higher frequency of cells in which the X chromosome carrying the mutation is active).

The molecular basis of mental retardation and other somatic changes is related to a loss of function of the familial mental retardation protein (FMRP). As mentioned earlier, the normal *FMR1* gene contains up to 55 CGG repeats in its 5′ untranslated region. When the trinucleotide repeats in the *FMR1* gene exceed approximately 230, the DNA of the entire 5′ region of the gene becomes abnormally methylated. Methylation also extends upstream into the promoter region of the gene, resulting in transcriptional suppression of *FMR1.* The resulting absence of FMRP is believed to cause the phenotypic changes.

FMRP is a widely expressed cytoplasmic protein, most abundant in the brain and testis, the two organs most affected in this disease. Its proposed functions are the following:

- *FMRP selectively binds mRNAs associated with polysomes and regulates their intracellular transport to dendrites.* FMRP binds to approximately 4% of mammalian brain mRNAs. Unlike other cells, in neurons protein synthesis