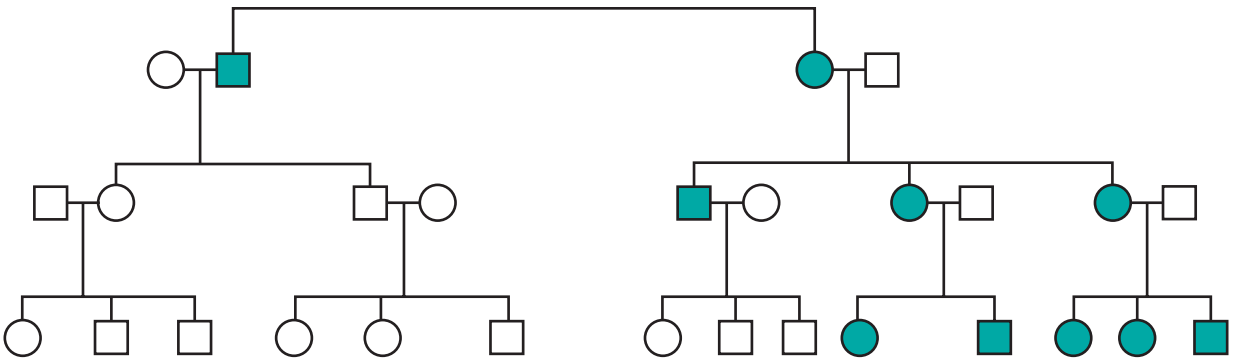

Figure 5-27 Pedigree of Leber hereditary optic neuropathy, a disorder caused by mutation in mitochondrial DNA. Note that all progeny of an affected male (shaded squares) are normal, but all children, male and female, of the affected female (shaded circles) manifest disease to a variable degree as discussed in the text.

- Each mitochondrion contains thousands of copies of mtDNA, and, typically, deleterious mutations of mtDNA affect some but not all of these copies. Thus, tissues and, indeed, individuals may harbor both wild-type and mutant mtDNA, a situation called *heteroplasmy*. A minimum number of mutant mtDNA must be present in a cell or tissue before oxidative dysfunction gives rise to disease. This is called the "threshold effect." Not surprisingly, the threshold is reached most easily in the metabolically active tissues listed earlier.
- During cell division, mitochondria and their contained DNA are randomly distributed to the daughter cells. Thus, when a cell containing normal and mutant mtDNA divides, the proportion of the normal and mutant mtDNA in daughter cells is extremely variable. Therefore, the expression of disorders resulting from mutations in mtDNA is quite variable.

Diseases associated with mitochondrial inheritance are rare and, as mentioned earlier, many of them affect the neuromuscular system. *Leber hereditary optic neuropathy* is a prototype of this type of disorder. It is a neurodegenerative disease that manifests as a progressive bilateral loss of central vision. Visual impairment is first noted between ages 15 and 35, leading eventually to blindness. Cardiac conduction defects and minor neurologic manifestations have also been observed in some families.

Genomic Imprinting

We all inherit two copies of each autosomal gene, carried on homologous maternal and paternal chromosomes. In the past, it had been assumed that there is no functional difference between the alleles derived from the mother or the father. Studies over the past two decades have provided definite evidence that, at least with respect to some genes, important functional differences exist between the paternal allele and the maternal allele. These differences result from an epigenetic process called *imprinting*. In most cases, imprinting selectively inactivates either the maternal or paternal allele. Thus, *maternal imprinting* refers to transcriptional silencing of the maternal allele, whereas *paternal imprinting* implies that the paternal allele is inactivated.

Imprinting occurs in the ovum or the sperm, before fertilization, and then is stably transmitted to all somatic cells through mitosis. As with other instances of epigenetic regulation, imprinting is associated with differential patterns of DNA methylation at CG nucleotides. Other mechanisms include histone H4 deacetylation and methylation (Chapter 1). Regardless of the mechanism, it is believed that such marking of paternal and maternal chromosomes occurs during gametogenesis, and thus it seems that from the moment of conception some chromosomes remember where they came from. The exact number of imprinted genes is not known; estimates range from 200 to 600. Although imprinted genes may occur in isolation, more commonly they are found in groups that are regulated by common *cis*-acting elements called imprinting control regions. Genomic imprinting is best illustrated by considering two uncommon genetic disorders: Prader-Willi syndrome and Angelman syndrome which were originally believed to be unrelated until the genetic lesions responsible for them were mapped to the very same location. They are described next.

Prader-Willi Syndrome and Angelman Syndrome

Prader-Willi syndrome is characterized by mental retardation, short stature, hypotonia, profound hyperphagia, obesity, small hands and feet, and hypogonadism. In 65% to 70% of cases, an interstitial deletion of band q12 in the long arm of chromosome 15, del(15)(q11.2q13), can be detected. In most cases the breakpoints are the same, causing a 5-Mb deletion. *It is striking that in all cases the deletion affects the paternally derived chromosome 15.* In contrast with the Prader-Willi syndrome, patients with the phenotypically distinct Angelman syndrome are *born with a deletion of the same chromosomal region derived from their mothers.* **Patients with Angelman syndrome are also mentally retarded, but in addition they present with ataxic gait, seizures, and inappropriate laughter.** Because of their laughter and ataxia, they have been referred to as "happy puppets." A comparison of these two syndromes clearly demonstrates the *parent-of-origin* effects on gene function.

The molecular basis of these two syndromes lies in the genomic imprinting (Fig. 5-28). Three mechanisms are involved:

- *Deletions*. It is known that a gene or set of genes on maternal chromosome 15q12 is imprinted (and hence silenced), and thus the only functional allele(s) are provided by the paternal chromosome. When these are lost as a result of a deletion, the person develops