

FIGURE 466-8 A few genomic regions are imprinted in a parent-specific fashion. The unmethylated chromosomal regions are actively expressed, whereas the methylated regions are silenced. In the germline, the imprint is reset in a parent-specific fashion: both chromosomes are unmethylated in the maternal (mat) germline and methylated in the paternal (pat) germline. In the zygote, the resulting imprinting pattern is identical with the pattern in the somatic cells of the parents.

Remarkably, epigenetic differences also occur among monozygotic twins. Although twins are epigenetically indistinguishable during the early years of life, older monozygotic twins exhibit differences in the overall content and genomic distribution of DNA methylation and histone acetylation, which would be expected to alter gene expression in various tissues.

In cancer, the epigenome is characterized by simultaneous losses and gains of DNA methylation in different genomic regions, as well as repressive histone modifications. Hyper- and hypomethylation are associated with mutations in genes that control DNA methylation. Hypomethylation is thought to remove normal control mechanisms that prevent expression of repressed DNA regions. It is also associated with genomic instability. Hypermethylation, in contrast, results in the silencing of CpG islands in promoter regions of genes, including tumor-suppressor genes. Epigenetic alterations are considered to be more easily reversible compared to genetic changes; modification of the epigenome with demethylating agents and histone deacetylases is being used in the treatment of various malignancies.

■ TRANSMISSION OF GENETIC DISEASE

Origins and Types of Mutations The term *mutation* or *variant* is used to designate the process of generating genetic variations as well as the outcome of these alterations. A *mutation* can be defined as any change in the primary nucleotide sequence of DNA regardless of its functional consequences, although it often has a negative connotation. The more neutral term *variation* is now increasingly used to describe sequence changes and is recommended by several professional organizations and guidelines instead of *mutation*. Some variations may be lethal, others are less deleterious, and some may confer an evolutionary advantage.