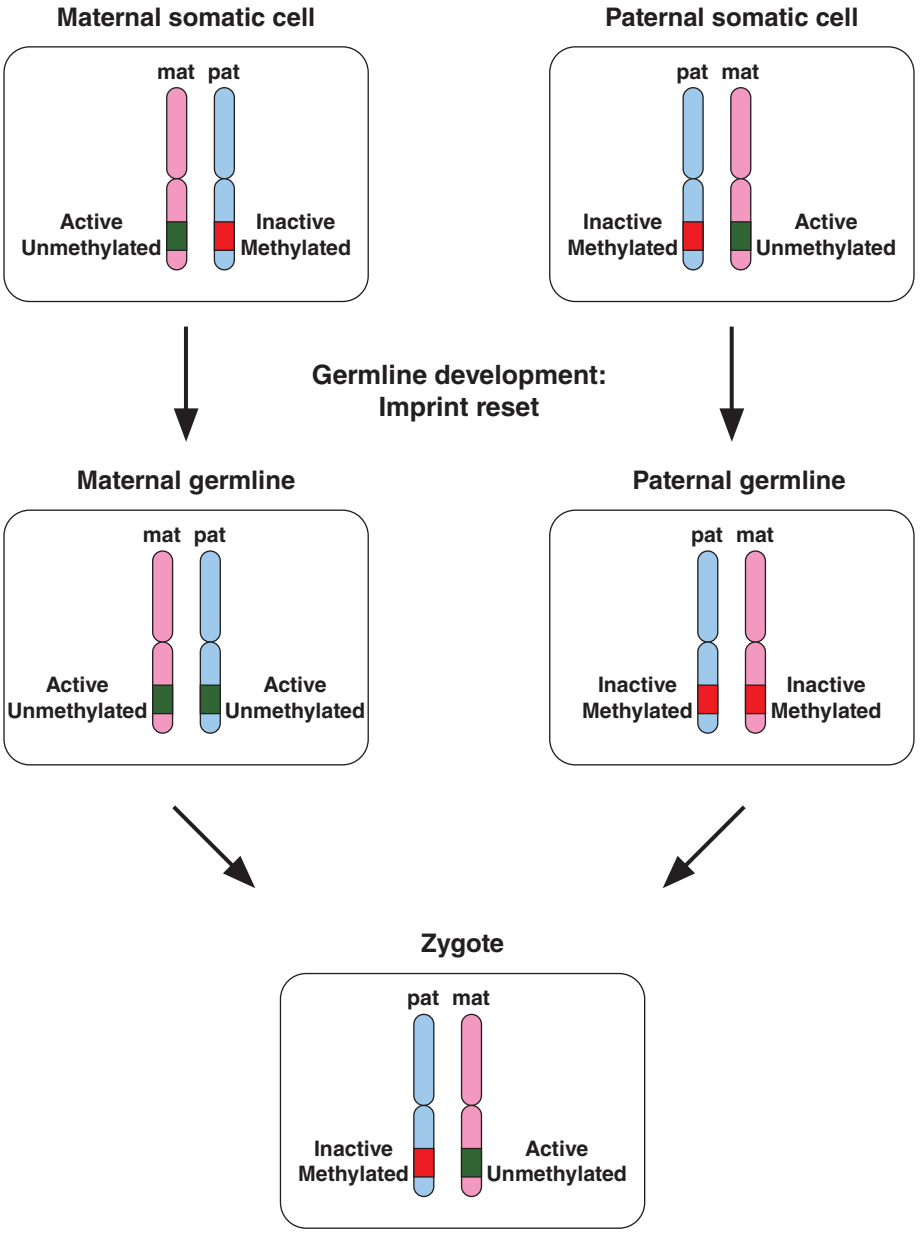

FIGURE 82-8 A few genomic regions are imprinted in a parent-specific fashion. The unmethylated chromosomal regions are actively expressed, whereas the methylated regions are silenced. In the germline, the imprint is reset in a parent-specific fashion: both chromosomes are unmethylated in the maternal (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.

to human physiology reflects a surprising conservation of genetic pathways and gene function. Transgenic mouse models have been particularly valuable, because many human and mouse genes exhibit similar structure and function and because manipulation of the mouse genome is relatively straightforward compared to that of other mammalian species. Transgenic strategies in mice can be divided into two main approaches: (1) expression of a gene by random insertion into the genome, and (2) deletion or targeted mutagenesis of a gene by homologous recombination with the native endogenous gene (knock-out, knock-in). Previous versions of this chapter provide more detail about the technical principles underlying the development of genetically modified animals. Several databases provide comprehensive information about natural and transgenic animal models, the associated phenotypes, and integrated genetic, genomic, and biologic data (Table 82-1).

TRANSMISSION OF GENETIC DISEASE

Origins and Types of Mutations A *mutation* can be defined as any change in the primary nucleotide sequence of DNA regardless of its functional consequences. Some mutations may be lethal, others are less deleterious, and some may confer an evolutionary advantage. Mutations can occur in the germline (sperm or oocytes); these can be transmitted to progeny. Alternatively, mutations can occur during embryogenesis or in somatic tissues. Mutations that occur during development lead to *mosaicism*, a situation in which tissues are composed of cells with different genetic constitutions. If the germline is mosaic, a mutation can be transmitted to some progeny but not others, which sometimes leads to confusion in assessing the pattern of inheritance. Somatic mutations that do not affect cell survival can sometimes be detected because of variable phenotypic effects in tissues (e.g., pigmented lesions in McCune-Albright syndrome). Other somatic mutations are associated with neoplasia because they confer a growth advantage to cells. Epigenetic events may also influence gene expression or facilitate genetic damage. With the exception of triplet nucleotide repeats, which can expand (see below), mutations are usually stable.

Mutations are structurally diverse—they can involve the entire genome, as in triploidy (one extra set of chromosomes), or gross numerical or structural alterations in chromosomes or individual genes (Chap. 83e). Large deletions may affect a portion of a gene or an entire gene, or, if several genes are involved, they may lead to a *contiguous gene syndrome*. Unequal crossing-over between homologous genes can result in fusion gene mutations, as illustrated by color blindness. Mutations involving single nucleotides are referred to as *point mutations*. Substitutions are called *transitions* if a purine is replaced by another purine base (A ↔ G) or if a pyrimidine is replaced by another pyrimidine (C ↔ T). Changes from a purine to a pyrimidine, or vice versa, are referred to as *transversions*. If the DNA sequence change occurs in a coding region and alters an amino acid, it is called a *missense mutation*. Depending on the functional consequences of such a missense mutation, amino acid substitutions in different regions of the protein can lead to distinct phenotypes.

Mutations can occur in all domains of a gene (Fig. 82-9). A point mutation occurring within the coding region leads to an amino acid substitution if the codon is altered (Fig. 82-10). Point mutations that introduce a premature stop codon result in a truncated protein. Large deletions may affect a portion of a gene or an entire gene, whereas small deletions and insertions alter the reading frame if they do not represent a multiple of three bases. These "frameshift" mutations lead to an entirely altered carboxy terminus. Mutations in intronic sequences or in exon junctions may destroy or create splice donor or splice acceptor sites. Mutations may also be found in the regulatory sequences of genes, resulting in reduced or enhanced gene transcription.

Certain DNA sequences are particularly susceptible to mutagenesis. Successive pyrimidine residues (e.g., T-T or C-C) are subject to the formation of ultraviolet light–induced photoadducts. If these pyrimidine dimers are not repaired by the nucleotide excision repair pathway, mutations will be introduced after DNA synthesis. The dinucleotide C-G, or CpG, is also a hot spot for a specific type of mutation. In this case, methylation of the cytosine is associated with