to develop the mutant phenotype, regardless of whether the mutation is dominant or recessive. A female may be either heterozygous or homozygous for the mutant allele, which may be dominant or recessive. The terms *X-linked dominant* or *X-linked recessive* are therefore only applicable to expression of the mutant phenotype in women. In addition, the expression of X-chromosomal genes is influenced by X chromosome inactivation.

Y-LINKED DISORDERS The Y chromosome has a relatively small number of genes. One such gene, the sex-region determining Y factor (*SRY*), which encodes the testis-determining factor (*TDF*), is crucial for normal male development. Normally there is infrequent exchange of sequences on the Y chromosome with the X chromosome. The *SRY* region is adjacent to the pseudoautosomal region, a chromosomal segment on the X and Y chromosomes with a high degree of homology. A crossing-over event occasionally involves the *SRY* region with the distal tip of the X chromosome during meiosis in the male. Translocations can result in XY females with the Y chromosome lacking the *SRY* gene or XX males harboring the *SRY* gene on one of the X chromosomes **(Chap. 410)**. Point mutations in the *SRY* gene may also result in individuals with an XY genotype and an incomplete female phenotype. Most of these mutations occur de novo. Men with oligospermia/azoospermia frequently have microdeletions on the long arm of the Y chromosome that involve one or more of the azoospermia factor (*AZF*) genes.

Exceptions to Simple Mendelian Inheritance Patterns • ***MITOCHONDRIAL DISORDERS*** Mendelian inheritance refers to the transmission of genes encoded by DNA contained in the nuclear chromosomes. In addition, each mitochondrion contains several copies of a small circular chromosome **(Chap. 85e)**. The mitochondrial DNA (mtDNA) is ~16.5 kb and encodes transfer and ribosomal RNAs and 13 core proteins that are components of the respiratory chain involved in oxidative phosphorylation and ATP generation. The mitochondrial genome does not recombine and is inherited through the maternal line because sperm does not contribute significant cytoplasmic components to the zygote. A noncoding region of the mitochondrial chromosome, referred to as D-loop, is highly polymorphic. This property, together with the absence of mtDNA recombination, makes it a valuable tool for studies tracing human migration and evolution, and it is also used for specific forensic applications.

Inherited mitochondrial disorders are transmitted in a matrilineal fashion; all children from an affected mother will inherit the disease, but it will not be transmitted from an affected father to his children **(Fig. 82-13*D*)**. Alterations in the mtDNA that involves enzymes required for oxidative phosphorylation lead to reduction of ATP supply, generation of free radicals, and induction of apoptosis. Several syndromic disorders arising from mutations in the mitochondrial genome are known in humans and they affect both protein-coding and tRNA genes **(Chap. 85e)**. The broad clinical spectrum often involves (cardio) myopathies and encephalopathies because of the high dependence of these tissues on oxidative phosphorylation. The age of onset and the clinical course are highly variable because of the unusual mechanisms of mtDNA transmission, which replicates independently from nuclear DNA. During cell replication, the proportion of wild-type and mutant mitochondria can drift among different cells and tissues. The resulting heterogeneity in the proportion of mitochondria with and without a mutation is referred to as *heteroplasmia* and underlies the phenotypic variability that is characteristic of mitochondrial diseases.

Acquired somatic mutations in mitochondria are thought to be involved in several age-dependent degenerative disorders affecting predominantly muscle and the peripheral and central nervous system (e.g., Alzheimer's and Parkinson's diseases). Establishing that an mtDNA alteration is causal for a clinical phenotype is challenging because of the high degree of polymorphism in mtDNA and the phenotypic variability characteristic of these disorders. Certain pharmacologic treatments may have an impact on mitochondria and/or their function. For example, treatment with the antiretroviral compound azidothymidine (AZT) causes an acquired mitochondrial myopathy through depletion of muscular mtDNA.

MOSAICISM Mosaicism refers to the presence of two or more genetically distinct cell lines in the tissues of an individual. It results from a mutation that occurs during embryonic, fetal, or extrauterine development. The developmental stage at which the mutation arises will determine whether germ cells and/or somatic cells are involved. Chromosomal mosaicism results from nondisjunction at an early embryonic mitotic division, leading to the persistence of more than one cell line, as exemplified by some patients with Turner's syndrome **(Chap. 410)**. Somatic mosaicism is characterized by a patchy distribution of genetically altered somatic cells. The McCune-Albright syndrome, for example, is caused by activating mutations in the stimulatory G protein α (Gsα) that occur early in development **(Chap. 424)**. The clinical phenotype varies depending on the tissue distribution of the mutation; manifestations include ovarian cysts that secrete sex steroids and cause precocious puberty, polyostotic fibrous dysplasia, café-au-lait skin pigmentation, growth hormone–secreting pituitary adenomas, and hypersecreting autonomous thyroid nodules **(Chap. 412)**.

X-INACTIVATION, IMPRINTING, AND UNIPARENTAL DISOMY According to traditional Mendelian principles, the parental origin of a mutant gene is irrelevant for the expression of the phenotype. There are, however, important exceptions to this rule. *X-inactivation* prevents the expression of most genes on one of the two X chromosomes in every cell of a female. Gene inactivation through genomic imprinting occurs on selected chromosomal regions of autosomes and leads to inheritable preferential expression of one of the parental alleles. It is of pathophysiologic importance in disorders where the transmission of disease is dependent on the sex of the transmitting parent and, thus, plays an important role in the expression of certain genetic disorders. Two classic examples are the Prader-Willi syndrome and Angelman's syndrome **(Chap. 83e)**. Prader-Willi syndrome is characterized by diminished fetal activity, obesity, hypotonia, mental retardation, short stature, and hypogonadotropic hypogonadism. Deletions of the paternal copy of the Prader-Willi locus located on the short arm of chromosome 15 result in a contiguous gene syndrome involving missing paternal copies of the *necdin* and *SNRPN* genes, among others. In contrast, patients with Angelman's syndrome, characterized by mental retardation, seizures, ataxia, and hypotonia, have deletions involving the maternal copy of this region on chromosome 15. These two syndromes may also result from *uniparental disomy*. In this case, the syndromes are not caused by deletions on chromosome 15 but by the inheritance of either two maternal chromosomes (Prader-Willi syndrome) or two paternal chromosomes (Angelman's syndrome). Lastly, the two distinct phenotypes can also be caused by an imprinting defect that impairs the resetting of the imprint during zygote development (defect in the father leads to Prader-Willi syndrome; defect in the mother leads to Angelman's syndrome).

Imprinting and the related phenomenon of allelic exclusion may be more common than currently documented, because it is difficult to examine levels of mRNA expression from the maternal and paternal alleles in specific tissues or in individual cells. Genomic imprinting, or uniparental disomy, is involved in the pathogenesis of several other disorders and malignancies **(Chap. 83e)**. For example, hydatidiform moles contain a normal number of diploid chromosomes, but they are all of paternal origin. The opposite situation occurs in ovarian teratomata, with 46 chromosomes of maternal origin. Expression of the imprinted gene for insulin-like growth factor II (IGF-II) is involved in the pathogenesis of the cancer-predisposing Beckwith-Wiedemann syndrome (BWS) **(Chap. 101e)**. These children show somatic overgrowth with organomegalies and hemihypertrophy, and they have an increased risk of embryonal malignancies such as Wilms' tumor. Normally, only the paternally derived copy of the *IGF-II* gene is active and the maternal copy is inactive. Imprinting of the *IGF-II* gene is regulated by *H19*, which encodes an RNA transcript that is not translated into protein. Disruption or lack of *H19* methylation leads to a relaxation of *IGF-II* imprinting and expression of both alleles. Alterations of the epigenome through gain and loss of DNA methylation, as well as altered histone modifications, play an important role in the pathogenesis of malignancies.