SOMATIC MUTATIONS Cancer can be considered a genetic disease at the cellular level (Chap. 101e). Cancers are monoclonal in origin, indicating that they have arisen from a single precursor cell with one or several mutations in genes controlling growth (proliferation or apoptosis) and/or differentiation. These acquired somatic mutations are restricted to the tumor and its metastases and are not found in the surrounding normal tissue. The molecular alterations include dominant gain-of-function mutations in oncogenes, recessive loss-of-function mutations in tumor-suppressor genes and DNA repair genes, gene amplification, and chromosome rearrangements. Rarely, a single mutation in certain genes may be sufficient to transform a normal cell into a malignant cell. In most cancers, however, the development of a malignant phenotype requires several genetic alterations for the gradual progression from a normal cell to a cancerous cell, a phenomenon termed *multistep carcinogenesis* (Chaps. 101e and 102e). Genome-wide analyses of cancers using deep sequencing often reveal somatic rearrangements resulting in fusion genes and mutations in multiple genes. Comprehensive sequence analyses provide further insight into genetic heterogeneity within malignancies; these include intratumoral heterogeneity among the cells of the primary tumor, intermetastatic and intrametastatic heterogeneity, and interpatient differences. These analyses further support the notion of cancer as an ongoing process of clonal evolution, in which successive rounds of clonal selection within the primary tumor and metastatic lesions result in diverse genetic and epigenetic alterations that require targeted (personalized) therapies. The heterogeneity of mutations within a tumor can also lead to resistance to target therapies because cells with mutations that are resistant to the therapy, even if they are a minor part of the tumor population, will be selected as the more sensitive cells are killed. Most human tumors express telomerase, an enzyme formed of a protein and an RNA component, which adds telomere repeats at the ends of chromosomes during replication. This mechanism impedes shortening of the telomeres, which is associated with senescence in normal cells and is associated with enhanced replicative capacity in cancer cells. Telomerase inhibitors provide a novel strategy for treating advanced human cancers.

In many cancer syndromes, there is an inherited *predisposition* to tumor formation. In these instances, a germline mutation is inherited in an autosomal dominant fashion inactivating one allele of an autosomal tumor-suppressor gene. If the second allele is inactivated by a somatic mutation or by epigenetic silencing in a given cell, this will lead to neoplastic growth (Knudson two-hit model). Thus, the defective allele in the germline is transmitted in a dominant mode, although tumorigenesis results from a biallelic loss of the tumor-suppressor gene in an affected tissue. The classic example to illustrate this phenomenon is retinoblastoma, which can occur as a sporadic or hereditary tumor. In sporadic retinoblastoma, both copies of the retinoblastoma (*RB*) gene are inactivated through two somatic events. In hereditary retinoblastoma, one mutated or deleted *RB* allele is inherited in an autosomal dominant manner and the second allele is inactivated by a subsequent somatic mutation. This two-hit model applies to other inherited cancer syndromes such as MEN 1 (Chap. 408) and neurofibromatosis type 2 (Chap. 118).

NUCLEOTIDE REPEAT EXPANSION DISORDERS Several diseases are associated with an increase in the number of nucleotide repeats above a certain threshold (Table 82-4). The repeats are sometimes located within the coding region of the genes, as in Huntington's disease or the X-linked form of spinal and bulbar muscular atrophy (SBMA; Kennedy's syndrome). In other instances, the repeats probably alter gene regulatory sequences. If an expansion is present, the DNA fragment is unstable and tends to expand further during cell division. The length of the nucleotide repeat often correlates with the severity of the disease. When repeat length increases from one generation to the next, disease manifestations may worsen or be observed at an earlier age; this phenomenon is referred to as *anticipation*. In Huntington's disease, for example, there is a correlation between age of onset and length of the triplet codon expansion (Chap. 444e). Anticipation has also been documented in other diseases caused by dynamic mutations in trinucleotide repeats (Table 82-4). The repeat number may also vary in a tissue-specific manner. In myotonic dystrophy, the CTG repeat may be tenfold greater in muscle tissue than in lymphocytes (Chap. 462e).

Complex Genetic Disorders The expression of many common diseases such as cardiovascular disease, hypertension, diabetes, asthma, psychiatric disorders, and certain cancers is determined by a combination of genetic background, environmental factors, and lifestyle. A trait is called *polygenic* if multiple genes contribute to the phenotype or *multifactorial* if multiple genes are assumed to interact with environmental factors. Genetic models for these complex traits need to account for genetic heterogeneity and interactions with other genes and the environment. Complex genetic traits may be influenced by modifier genes that are not linked to the main gene involved in the pathogenesis of the trait. This type of gene-gene interaction, or *epistasis*, plays an important role in polygenic traits that require the simultaneous presence of variations in multiple genes to result in a pathologic phenotype.

Type 2 diabetes mellitus provides a paradigm for considering a multifactorial disorder, because genetic, nutritional, and lifestyle factors are intimately interrelated in disease pathogenesis (Table 82-5) (Chap. 417).

TABLE 82-4 SELECTED TRINUCLEOTIDE REPEAT DISORDERS

Disease	Locus	Repeat	Triplet Length (Normal/Disease)	Inheritance	Gene Product
X-chromosomal spinobulbar muscular atrophy (SBMA)	Xq11-q12	CAG	11–34/40–62	XR	Androgen receptor
Fragile X syndrome (FRAXA)	Xq27.3	CGG	6–50/200–300	XR	FMR-1 protein
Fragile X syndrome (FRAXE)	Xq28	GCC	6–25/>200	XR	FMR-2 protein
Dystrophia myotonica (DM)	19q13.2-q13.3	CTG	5–30/200–1000	AD, variable penetrance	Myotonin protein kinase
Huntington's disease (HD)	4p16.3	CAG	6–34/37–180	AD	Huntingtin
Spinocerebellar ataxia type 1 (SCA1)	6p21.3-21.2	CAG	6–39/40–88	AD	Ataxin 1
Spinocerebellar ataxia type 2 (SCA2)	12q24.1	CAG	15–31/34–400	AD	Ataxin 2
Spinocerebellar ataxia type 3 (SCA3); Machado-Joseph disease (MD)	14q21	CAG	13–36/55–86	AD	Ataxin 3
Spinocerebellar ataxia type 6 (SCA6, CACNAIA)	19p13.1-13.2	CAG	4–16/20–33	AD	Alpha 1A voltage-dependent L-type calcium channel
Spinocerebellar ataxia type 7 (SCA7)	3p21.1-p12	CAG	4–19/37 to >300	AD	Ataxin 7
Spinocerebellar ataxia type 12 (SCA12)	5q31	CAG	6–26/66–78	AD	Protein phosphatase 2A
Dentatorubral pallidoluysian atrophy (DRPLA)	12p	CAG	7–23/49–75	AD	Atrophin 1
Friedreich's ataxia (FRDA1)	9q13-21	GAA	7–22/200–900	AR	Frataxin

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.