Clinical Conditions

Genetic Variation

CLINICAL COMMENTARY 3-2
Xeroderma Pigmentosum: A Disease of Faulty DNA Repair

An inevitable consequence of exposure to UV radiation is the formation of potentially dangerous pyrimidine dimers in the DNA of skin cells. Fortunately, the highly efficient nucleotide excision repair (NER) system removes these dimers in normal persons. Among those affected with the rare autosomal recessive disease xeroderma pigmentosum (XP), this system does not work properly, and the resulting DNA replication errors lead to base-pair substitutions in skin cells. XP varies substantially in severity, but early symptoms are usually seen in the first 1 to 2 years of life. Patients develop dry, scaly skin (xeroderma) along with extensive freckling and abnormal skin pigmentation (pigmentosum). Skin tumors, which can be numerous, typically appear by 10 years of age. It is estimated that the risk of skin tumors in persons with XP is elevated approximately 1000-fold. These cancers are concentrated primarily in sun-exposed parts of the body. Patients are advised to avoid sources of UV light (e.g., sunlight), and cancerous growths are removed surgically. Neurological abnormalities are seen in about 30% of persons with XP. Severe, potentially lethal malignancies can occur before 20 years of age.

The NER system is encoded by at least 28 different genes, and inherited mutations in any of seven of these genes can give rise to XP. These genes encode helicases that unwind the double-stranded DNA helix; an endonuclease that cuts the DNA at the site of the dimer; an exonuclease that removes the dimer and nearby nucleotides; a polymerase that fills the gap with DNA bases (using the complementary DNA strand as a template); and a ligase that rejoins the corrected portion of DNA to the original strand.

It should be emphasized that the expression of XP requires inherited germline mutations of an NER gene as well as subsequent uncorrected somatic mutations of genes in skin cells. Some of these somatic mutations can affect genes that promote cancer (see Chapter 11), resulting in tumor formation. The skin-cell mutations themselves are somatic and thus are not transmitted to future generations.

NER is but one type of DNA repair. The table below provides examples of a number of other diseases that result from defects in various types of DNA repair mechanisms (Fig. 3-12) (Table 3-2).

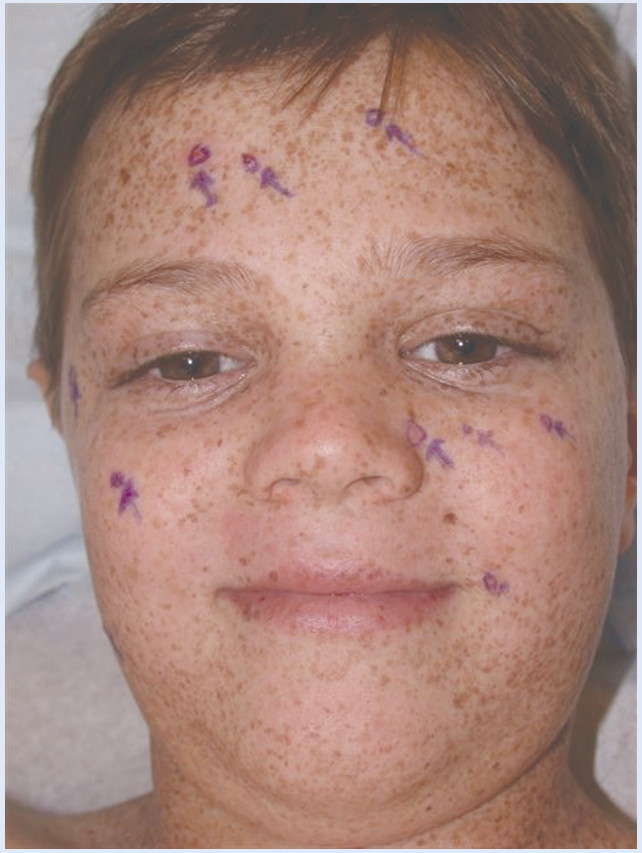

FIG 3-12 Xeroderma pigmentosum. This patient's skin has multiple hyperpigmented lesions, and skin tumors on the forehead have been marked for excision.

TABLE 3-2 Examples of Diseases That Are Caused by a Defect in DNA Repair

DISEASE	FEATURES	TYPE OF REPAIR DEFECT
Xeroderma pigmentosum	Skin tumors, photosensitivity, cataracts, neurological abnormalities	Nucleotide excision repair defects, including mutations in helicase and endonuclease genes
Cockayne syndrome	Reduced stature, skeletal abnormalities, optic atrophy, deafness, photosensitivity, mental retardation	Defective repair of UV-induced damage in transcriptionally active DNA; considerable etiological and symptomatic overlap with xeroderma pigmentosum and trichothiodystrophy
Fanconi anemia	Anemia; leukemia susceptibility; limb, kidney, and heart malformations; chromosome instability	As many as eight different genes may be involved, but their exact role in DNA repair is not yet known
Bloom syndrome	Growth deficiency, immunodeficiency, chromosome instability, increased cancer incidence	Mutations in the reqQ helicase family
Werner syndrome	Cataracts, osteoporosis, atherosclerosis, loss of skin elasticity, short stature, diabetes, increased cancer incidence; sometimes described as "premature aging"	Mutations in the reqQ helicase family
Ataxia-telangiectasia	Cerebellar ataxia, telangiectases,* immune deficiency, increased cancer incidence, chromosome instability	Normal gene product is likely to be involved in halting the cell cycle after DNA damage occurs
Hereditary nonpolyposis colorectal cancer	Proximal bowel tumors, increased susceptibility to several other types of cancer	Mutations in any of six DNA mismatch-repair genes

*Telangiectases are vascular lesions caused by the dilatation of small blood vessels. This typically produces discoloration of the skin.