Understanding photodermatoses associated with defective DNA repair

Syndromes with cancer predisposition

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Learning objectives
After completing this learning activity, the participant should be able to describe the malignancies (both cutaneous and noncutaneous) associated with each genodermatosis; discuss the screening/management practices for photosensitive genodermatoses and describe appropriate methods of photoprotection and chemoprevention for cutaneous malignancies.

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Hereditary photodermatoses are a spectrum of rare photosensitive disorders that are often caused by genetic deficiency or malfunction of various components of the DNA repair pathway. This results clinically in extreme photosensitivity, with many syndromes exhibiting an increased risk of cutaneous malignancies. This review will focus specifically on the syndromes with malignant potential, including xeroderma pigmentosum, Bloom syndrome, and Rothmund–Thomson syndrome. The typical phenotypic findings of each disorder will be examined and contrasted, including noncutaneous identifiers to aid in diagnosis. The management of these patients will also be discussed. At this time, the mainstay of therapy remains strict photoprotection; however, genetic therapies are under investigation. (J Am Acad Dermatol 2016;75:855-70.)

Key words: Bloom syndrome; carcinogenic syndrome; nucleotide excision repair; photodermatoses; photosensitivity; Rothmund–Thomson; xeroderma pigmentosum.

Hereditary photodermatoses are characterized by an increased sensitivity to sunlight caused by a genetic defect. Most are autosomal recessive and manifest during infancy. While relatively rare, this spectrum of DNA repair–deficiency disorders is linked in some cases with early development of cutaneous and internal malignancies. Early recognition and diagnosis is crucial to prevent actinic injuries that can lead to cutaneous malignancies. The first article in this continuing medical education series highlights genetic syndromes with associated carcinogenic potential (summarized in Tables I and II). The second article in this series focuses on genetic syndromes with photosensitivity but without associated malignancies.

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Abbreviations used:

6-4PP:	(6-4) pyrimidine-pyrimidone photoproduct
BCC:	basal cell carcinoma
BER:	base excision repair
CPD:	cyclobutane pyrimidine dimer
DSC:	De Sanctis–Cacchione
ERCC:	excision repair cross-complementing
NER:	nucleotide excision repair
PCNA:	proliferating cell nuclear antigen
ROS:	reactive oxygen species
RECQL:	RecQ-like
RTS:	Rothmund–Thomson syndrome
SCC:	squamous cell carcinoma
TCR:	transcription-coupled repair
UV:	ultraviolet
XP:	xeroderma pigmentosum

NUCLEOTIDE EXCISION REPAIR

Key points

- **Defects in the nucleotide excision repair pathway can result in photosensitivity and, in some cases, an increased incidence of skin cancer**
- **Cyclobutane pyrimidine dimers, 6-4 pyrimidine-pyrimidone photoproducts, and Dewar isomers are examples of DNA damage caused by ultraviolet radiation**
- **Lesions that significantly alter the double stranded helix of DNA are detected and repaired by a variety of proteins that, when mutated, result in deficient DNA repair and subsequently clinical disease**

Ultraviolet light–induced damage to the genome

Living organisms on Earth are exposed to radiation emitted by the sun and have evolved to take advantage of sunlight, both for photosynthesis in plants and for photochemical synthesis of vitamin D in mammals. However, molecular damage in cells can occur after exposure to solar radiation, particularly that in the ultraviolet (UV) light range. UV radiation is divided into 3 spectral regions: UVC, UVB, and UVA.

UVC (100-290 nm). UVC light is the most harmful UV light, but it is filtered by atmospheric dioxygen and the ozone layer and therefore, does not reach the Earth's surface.

UVB (290-320 nm). UVB light is attenuated by the ozone layer, but the fraction that reaches the Earth's surface is sufficient to affect all life forms. UVB light comprises 5% of UV light that reaches the Earth's surface. The primary targets of UVB light are DNA and RNA, and the primary products are cyclobutane pyrimidine dimers (CPDs), 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs), and Dewar isomers (Fig 1), which can form between adjacent pyrimidines in nucleic acids.

UVA (320-400 nm). Ninety-five percent of UV light that reaches the Earth's surface is UVA light. UVA light interacts with proteins and other biomolecules, resulting in the generation of reactive oxygen species (ROS) and oxidation of DNA bases.[3,4] It has also been shown to induce CPD (but not 6-4PP) formation.[5] CPDs generated hours after exposure to UVA light have recently been ascribed to excitation of melanin by a combination of UVA-induced ROS and nitrogen species.[6]

CPDs and 6-4PPs are repaired in DNA via the nucleotide excision repair (NER) pathway, which appeared early in evolution and exists across the entire range of life forms, from unicellular bacteria to plants and humans. Oxidized bases in DNA are repaired by the base excision repair pathway. There are currently no human syndromes for which photosensitivity is caused by deficient repair of oxidized DNA bases. Although NER-deficient human cell lines have been reported to be hypersensitive to ROS,[7,8] mutation spectra analyses in skin tumors from patients defective in NER reveal that essentially all mutations had been caused by CPD or 6-4PP.[9]

Nucleotide excision repair in humans

NER in eukaryotes (Fig 2) has been the subject of extensive reviews.[10-12] This versatile mechanism removes a large variety of helix-distorting lesions and structures from the genome.

The spectrum of human disorders resulting from mutations in NER proteins has been presented in several recent reviews.[13-18] These inherited diseases are recessive, and therefore their incidence is highest among isolated populations with high rates of intermarriage.

DEFECTIVE NUCLEOTIDE EXCISION REPAIR PATHWAY AND CANCER: XERODERMA PIGMENTOSUM

Key points

- **Xeroderma pigmentosum is comprised of 8 nucleotide excision repair–deficient complementation groups, with groups A, C, and D being the most common**
- **Xeroderma pigmentosum variant is the result of a defective DNA polymerase η**
- **Photosensitivity is the most common presenting sign of xeroderma pigmentosum and is often evident during infancy**
- **Patients with xeroderma pigmentosum can have cutaneous, ocular, neurologic, and cognitive abnormalities, with an increased incidence of cutaneous and internal malignancies**