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Dr. Jennifer Black declares she has no conflict(s) of interest to disclose.
Introduction: Xeroderma Pigmentosum

Xeroderma Pigmentosum (XP):
- Rare autosomal recessive disorder
- Prevalence: 1-45/million, variable ethnic frequency
- UV radiation sensitivity disorder characterized by:
  - Severe skin burning following minimal sun exposure
  - Early freckling (before 2 years of age)
  - Skin cancer at an early age
  - Ocular disease
  - Neurologic disease

Introduction: Xeroderma Pigmentosum

XP Clinical Spectrum:
- Skin Changes:
  - Early freckling and subsequent checkered pigmentation
  - Thin, dry, contracted skin
  - Telangiectasias
  - Skin cancers:
    - Squamous cell carcinoma
    - Basal cell carcinoma
    - Melanoma

Introduction: Xeroderma Pigmentosum

Squamous Cell Carcinoma

Introduction: Xeroderma Pigmentosum

Basal Cell Carcinoma
Melanocytic Lesions
- 50% PTEN mutations

Introduction: Xeroderma Pigmentosum
Ocular Manifestations of Disease

<table>
<thead>
<tr>
<th>OCULAR ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Eyelid Abnormalities:</td>
</tr>
<tr>
<td>Entropion</td>
</tr>
<tr>
<td>Ectropion</td>
</tr>
<tr>
<td>Lagophthalmos</td>
</tr>
<tr>
<td>Blepharitis</td>
</tr>
<tr>
<td>Keratinization</td>
</tr>
<tr>
<td>Loss of Eyelashes</td>
</tr>
<tr>
<td>Neoplasms of the Ocular Surface and Eyelids:</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>Basal Cell Carcinoma</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Melanosis*</td>
</tr>
<tr>
<td>Xerosis</td>
</tr>
<tr>
<td>Corneal Abnormalities:</td>
</tr>
<tr>
<td>Neovascularization</td>
</tr>
<tr>
<td>Pterygium</td>
</tr>
<tr>
<td>Scarring</td>
</tr>
<tr>
<td>Opacification</td>
</tr>
<tr>
<td>Other: Photophobia</td>
</tr>
</tbody>
</table>

Introduction: Xeroderma Pigmentosum
Neurologic Manifestations of Disease
- 24% XP Patients
- Progressive Neurologic Degeneration:
  - Cognitive deterioration
  - Impaired hearing
  - Abnormal speech
  - Areflexia
  - Progressive ataxia
  - Spasticity
  - Peripheral neuropathy
- Brain tumors: Glial tumors
  - Pontine glioma, glioblastoma, spinal cord astrocytoma

Xeroderma Pigmentosum:
{ Disease Pathophysiology

Xeroderma Pigmentosum: Pathophysiology

**Historical Studies:**
- XP cells demonstrate UV radiation hypersensitivity (Gartler 1964)
- Deficient repair observed in cultured XP skin fibroblasts (Cleaver 1968)
- Stable DNA photoproducts identified following UV radiation (Setlow 1962), not removed by XP cells (Setlow 1969, Cleaver and Trosko 1970)
- Defective repair in XP cells demonstrated in vitro (Reed 1969) and in vivo (Epstein 1970)
- Cell fusion studies demonstrated heterogeneity of XP molecular defects (De Weerd-Kastelein 1972)
  - Fusion of fibroblasts from different XP patients form heterokaryons that demonstrate corrected DNA repair mechanisms.
  - Characterization of different complementation groups, A-G (Kramer 1975, Arase 1979, Keijer 1979)

**Xeroderma Pigmentosum: Complementation Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gene</th>
<th>Normal Protein Function</th>
<th>Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>XP-A</td>
<td>XPA</td>
<td>Protein that assists with DNA unwinding</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XP-B</td>
<td>XPB/ERCC3</td>
<td>Helicase involved with DNA unwinding</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XP-C</td>
<td>XPC</td>
<td>Protein recognizing global genome defects</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer</td>
</tr>
<tr>
<td>XP-D</td>
<td>XPD/ERCC2</td>
<td>Helicase involved with DNA unwinding</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration, brain tumors</td>
</tr>
<tr>
<td>XP-E</td>
<td>XPE/ERCC6</td>
<td>Protein recognizing global genome defects</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XP-F</td>
<td>XPF/ERCC4</td>
<td>Forms an endonuclease together with ERCC1 that incises damaged DNA for repair</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XP-G</td>
<td>XPG/ERCC8</td>
<td>Endonuclease that incise damaged DNA</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XP-Variant</td>
<td>XPV/POLH</td>
<td>DNA-polymerase eta (pol-eta), performs translesion DNA synthesis past ultraviolet (UV) damage</td>
<td>Milder photosensitivity and poikiloderma</td>
</tr>
</tbody>
</table>
### Xeroderma Pigmentosum: Pathophysiology

<table>
<thead>
<tr>
<th>Gene</th>
<th>Normal Protein Function</th>
<th>Syndrome</th>
<th>Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>XPB/ERCC3</td>
<td>Helicase involved with DNA unwinding</td>
<td>XPF, CS, TTD</td>
<td>Photosensitivity, pigmentation, lentigines, skin cancer, neurodegeneration</td>
</tr>
<tr>
<td>XPD/ERCC2</td>
<td>Helicase involved with DNA unwinding</td>
<td>XP-P, TTD, CS, COFS</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration, brain tumors</td>
</tr>
<tr>
<td>XPF/ERCC4</td>
<td>Forms an endonuclease together with ERCC1 that incises damaged DNA for repair</td>
<td>XP-F, XFE, progeroid syndrome, Fanconi anemia</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration, brain tumors</td>
</tr>
<tr>
<td>ERCC1</td>
<td>Forms an endonuclease together with XPB/ERCC3 that incises damaged DNA for repair</td>
<td>CS, COFS</td>
<td>Photosensitivity, poikiloderma, lentigines, skin cancer, neurodegeneration, brain tumors</td>
</tr>
<tr>
<td>CSA/ERCC8</td>
<td>DNA excision repair protein involved in the NER pathway</td>
<td>CS</td>
<td>Growth failure, impaired neurodevelopment, photosensitivity, eye disorders, premature aging</td>
</tr>
<tr>
<td>CSB/ERCC6</td>
<td>DNA excision repair protein involved in the NER pathway</td>
<td>CS, COFS</td>
<td>Growth failure, severely impaired neurodevelopment, photosensitivity, eye disorders, premature aging</td>
</tr>
<tr>
<td>GTF2H5</td>
<td>Regulates release and cytokinesis of the DNA strand for repair</td>
<td>TTD</td>
<td>Brittle hair, intellectual impairment, photosensitivity</td>
</tr>
</tbody>
</table>

### Xeroderma Pigmentosum: Overlap Syndromes

#### Cockayne Syndrome (CS)
- Mutations in the CSA and CSB genes of the NER pathway
- Features:
  - Short stature, kyphoscoliosis, gait defects
  - Microcephaly
  - Pigmentary retinal degeneration, sensorineural deafness
  - Distinct facial features (deep-set eyes, prominent ears, "wizened appearance")
- Neurodegenerative Features; Demyelination (increased DTRs)
- Neuroimaging: cerebral atrophy, ventricular dilatation, calcification of basal ganglia and cortex, neuronal loss
- Multiple Types:
  - Type I: moderate phenotype, normal prenatal development, abnormalities evident in first 2 years of life
  - Type II: Severe phenotype, growth failure at birth, death within decade
  - Type III: Mild symptoms, late onset; photosensitivity with normal pigmentation, no increased risk of cutaneous malignancy

#### Trichothiodystrophy (TTD)
- Features:
  - Photosensitivity (with XPD, XPB, TTDA but not TTD1 mutations)
  - Abnormal hair
  - Decreased fertility
  - Short stature
  - Ichthyosis
- Normal skin pigmentation
- Intellectual impairment without neurodegeneration
  - Neuroimaging: demyelination, cortical heterotopia, partial agenesis of the corpus callosum, periventricular fibrosis of the spinal cord, intracranial calcifications


Xeroderma Pigmentosum: Overlap Syndromes

Cerebro-Oculo-Facio-Skeletal Syndrome (COFS):
- Autosomal recessive disorder
- Mutations involve CSB, XPD, XPG, and ERCC1 genes
- Features:
  - Microcephaly
  - Congenital cataracts
  - Arthrogryposis
  - Severe developmental delay
  - Severe postnatal growth failure
  - Photosensitivity
  - Facial dysmorphism (prominent nasal root and overhanging upper lip)

Xeroderma Pigmentosum: Long Term Survival

Leading Cause of Death: Skin Cancer and Metastasis

Increased Lifetime Cancer Risk:
- 33% XP patients do not develop cancer
- Squamous Cell and Basal Cell Carcinoma (NMSC): 10,000 fold lifetime risk
  - Median age at first cancer = 9 years (range 1-32 years)
  - 58-year reduction in age at first NMSC
- Melanoma: 2,000 fold lifetime risk
  - Median age at first cancer = 22 years (range 2-47 years)
  - 33-year reduction in age at first melanoma
- Other Cancer:
  - Increased risk of brain tumors
  - Increased risk lung cancer in XP smokers

Xeroderma Pigmentosum: Long Term Survival

Neurodegeneration: Second Leading Cause of Death

- More common in XPA, XPB, XPD, XPF, XPG (Rare in XPC, XPE)
- Associated with decreased median age of death compared to XP patients without neurodegeneration (29 vs 37 years)
Xeroderma Pigmentosum: Disease Treatment and Prevention

- Prevention:
  - Aggressive photoprotection recommended
  - Surgical resection of skin cancers
  - Early resection important for long-term survival

- Systemic Therapy:
  - Retinoids
  - Antioxidant therapy
  - Vitamin D supplementation
  - Gene therapy

Xeroderma Pigmentosum: Conclusions

- Patients with XP have mutations in genes that are necessary for nucleotide excision repair of damaged DNA:
  - Exploration of the disease pathogenesis has elucidated DNA repair processes.
  - XP patients exhibit:
    - Photosensitivity with a tendency for skin burning
    - Markedly increased risk of developing cutaneous malignancy among other cancers
    - Susceptibility for neurodegenerative and ocular disease
- Long term survival is improved by avoidance of UV radiation and use of photoprotection

Selected References


Thank you
THANK YOU