Photosensitivity Disorders

By Diana C. Valentín Colón, MD, Nicole M. Rochet, MD, MSc, and Sheila M. Valentín Nogueras, MD

### Inherited photosensitivity disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance/Mutation</th>
<th>Clinical features</th>
<th>Buzzwords/Comments</th>
</tr>
</thead>
</table>
| Bloom Syndrome                              | AR BLM gene RecQL3 (DNA helicase) (RecQL2 by some sources) | - Skin: early-onset photo-induced erythema and telangiectasias in face, hands and forearms (photo-distributed poikiloderma), CALM s, dyspigmentation, hypertrichosis, cheilitis  
- Failure to thrive ("proportionate dwarfism"), distinct facies [small and narrow] with oversized ears, long limbs; immunodeficiency, increased risk of malignancy and type 2 DM | - Ashkenazi Jews  
- Associated malignancies: leukemia (most common before 20 y/o), lymphoma, GI adenocarcinoma, sarcomas (avoid treatment with alkylating agents and radiation)  
- Reduced serum IgM and IgA; early death from pneumonia  
- Quadriradial configuration in chromosomes is pathognomonic |
| Rothmund Thompson Syndrome (Poikiloderma congenitale) | AR RecQL4 gene defect (DNA helicase) | - Skin: early, acute PS results in poikiloderma of the face and extensor extremities; alopecia, nail dystrophy, premalignant acral keratosis, increased cutaneous malignancies: BCC, SCC, melanoma  
- Juvenile subcapsular bilateral cataracts; radiologic bony abnormalities; osteoporosis, hypogonadism, cryptorchidism | - Hypoplastic thumbs; radii and ulna  
- Ostessarcoma (most common malignancy) may be multicentric and resistant to radiation. Recommended screening: baseline radiologic survey and by age 3 (and yearly if abnormal). |
| Xeroderma Pigmentosum (XP)                   | -All AR, [except XPF: AD] Multiple gene disorder- 7 nucleotide excision repair (NER) deficient complementation groups:  
-XPA  
-XPF/ERCC1  
-XPC  
-XPF/ERCC2  
-XPF/DBD2  
-XPF/ERCC4  
-XPF/ERCC5 | -XPA: Most severe variant. PS, severe neurologic impairment, deafness, growth delay  
-XPF: PS, pigmentary retinopathy, basal ganglia calcification  
-XPC: At greatest risk for skin cancer (melanoma); rare neurologic involvement  
-XPF: Poikiloderma, early onset skin cancer, decreased intelligence, ocular damage, neurologic impairment  
-XPE: Mildest skin/cataral PS; rare neurologic involvement  
-XPG: Mild PS, freckling, rare neurologic/ocular involvement  
-XPF: Mild skin changes, rare skin cancer, rare neurologic/ocular, except when XP/CS overlap  
- General skin findings: dry, atrophic, parchment-like texture with freckling, dyspigmentation/poikiloderma | - Groups A, B and C are most common: XPC in US/Europe vs. XPA in Japan  
- Group A: AKA DeSanctis-Cacchione syndrome – severe neurologic abnormalities  
- XPF variant: defective DNA polymerase (pol y) leads to increased risk of skin cancer; no neurologic abnormalities  
- PS is the most common presenting sign in all groups; excessive in groups: A, B, D, F, G, except C and E.  
- Up to 10,000x increase in risk of malignancies in anterior 2/3 of the tongue (SCC, angiosarcoma)  
- XPC, XPD, XPA: associated with increased risk of cutaneous melanoma |
| Cockayne Syndrome (CS)                       | AR CSA/ERCC8 and CSB/ERCC6 Defective transcription-coupled repair subpathway of NER Unable to repair cyclobutene pyrimidine dimers | - Skin: PS, dry hair and skin, anhidrosis, acral cyanotic livedes, edema  
- Microcephaly, stunted growth, progressive neurological dysfunction due to leukodystrophy, mental retardation, basal ganglia calcifications, cataracts, dental caries | - Cachectic dwarfism: lipatrophy of the face, sunken eye appearance, "bird headed facies, Mickey mouse appearance"  
-Salt and pepper retinal pigmentation  
- No increased incidence of skin cancer or sun induced pigmentation  
- Mutations in XPF may also cause CS and CS/XP/Fanoconei anemia phenotype.  
- XP/CS overlap syndrome with mutations in XPF, XPD and XPG have more neurologic, than cutaneous involvement typical for XP. |
| Cerebro-oculoskeletal (COS) syndrome          | AR Mutations in CBS, ERCC1, XPD, XPG | Typical features of CS with hypotonia, impaired reflexes, poor vision and distinctive facial characteristics (small eyes +/- congenital cataracts, low set, small jaw) | - Arthrogryposis (congenital joint contractures) and microphthalmia differentiate from severe CS |
| Ultraviolet-sensitive syndrome (UVS)          | AR Defective transcription-coupled repair with mutations in 3 complementation groups (CSA, CSB and UVSSA) | - Skin: acute PS/ sunburn, dryness, freckling, photodistributed dyspigmentation, telangiectasia | - No increased incidence of skin cancer (normal global genomic repair) |
| Trichothiodystrophy aka “Tay syndrome,” (PIBIDS) | AR Defective complementation groups in global and transcription-coupled NER subpathways (PS in XPD/ERCC2, XPF/ERCC3 and TTDA gene mutations) | - BIDS, IBIDS, PIBIDS, PIBIDS: photosensitivity, ichthyosis, brittle hair (sulfur deficient trichoschisis), intellectual impairment, decreased fertility (if/ hypogonadism), short stature  
- Microcephaly, cataracts, hearing loss, recurrent infections/hypergammaglobulinemia, osteoporosis, dental caries; nail abnormalities  
- May present as collobiion baby  
- Tiger-tail-like pattern of hair under polarized light. Also trichorrhexis nodosa, râbinning  
- Overlap with XPF, XPD | - Subtype of epidermolysis bullosa |
| Kindler syndrome                             | AR KIND1 (aka FERM1T) gene (encodes the focal adhesion protein fermin family homolog-1) | - Skin: Congenital and neonatal blistering/ transient early-onset PS, progressive poikiloderma with marked cutaneous atrophy [cigarette paper-like atrophy], dental caries, nail dystrophy, palmoplantar hyperkeratosis  
- Ectropion, colitis, phimoses, pseudoainhum, digital webbing | - Subtype of epidermolysis bullosa |
### Photosensitivity Disorders (continued)

By Diana C. Valentin Colón, MD, Nicole M. Rochet, MD, MSc, and Sheila M. Valentin Noguera, MD

#### Acquired Disease/Immunologically mediated

<table>
<thead>
<tr>
<th>Disease</th>
<th>Epidemiology</th>
<th>Clinical features</th>
<th>Pathophysiology</th>
<th>Action Spectrum</th>
<th>Pathology</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMLE</td>
<td>Women &gt; Men 2nd and 3rd decades</td>
<td>Repeated outbreaks of lesions on sun-exposed skin during spring and summer</td>
<td>Delayed cellular hypersensitivity reaction to an unidentified photo-induced antigen</td>
<td>UVB, UVA</td>
<td>Epidermal spongiosis, superficial and deep, peri-vascular and periadnexal, lymphohistiocytic dermal infiltrate; may have eosinophils and neutrophils Significant papillary dermal edema</td>
<td>Mild disease: photoprotection</td>
<td>Juvenile spring eruption is considered a clinical variant of PMLE in boys. Helices of the ear are the most common affected area. PMLE may be lifelong</td>
</tr>
</tbody>
</table>

#### Actinic prurigo (Hutchinson’s summer prurigo)

| Common in Native Americans (familial form), but can occur in all races Childhood onset (earlier than PMLE), most common in girls, often resolution by adolescence (may persist) | Erythematous papules or nodules, sometimes with hemorrhagic crust; marked pruritus May heal with fine linear or pitted scars Most common locations: face (including the nose) and distal limbs May have exudative chelitis favoring lower lip or conjunctivitis | UVR exposure is the provocative factor | UVR, UVA | Epidermal spongiosis, acanthosis, and dermal mononuclear cell infiltrate (occasional eosinophil) | Papillary edema in early lesions | Photo-protection Mild disease: topical corticosteroids and topical tacrolimus Phototherapy with NB-UVB and PUVA (hardening) Resistant disease: oral thalidomide Other oral treatments: corticosteroids, azathioprine and cyclosporine | Association with HLA DR4 (DRB1*0401) and subtype DRB1*0407 |

#### Hydroa vacciniforme (Hydroa = vesicles Vaccinum = scarring)

| Predilection for lightly pigmented individuals Childhood onset (boys-girls), resolves by adolescence | Symmetrical, clustered, pruritic or stinging erythematous macules Lesions can increase in size, become vesicular, umbilicate and progress with extensive crustng Healing over weeks: leaves varioliform scars Photo-distribution: face and dorsal aspect of hands Can be associated with general malaise (fever and headaches) May have ocular symptoms: photophobia, lacrimation, conjunctivitis or corneal lesions | Nature of the reaction is unknown. Summer sun-light generally provokes the eruption Epstein-Barr viral infection has been detected in a number of patients | UVA | Early epidermal spongiosis with perivascular lymphohistiocytic infiltrate Prominent reticular keratinocyte degeneration, intra-epidermal vesicles with fibrin and acute inflammatory cells; confluent epidermal and focal upper dermal necrosis | Photo-protection Almost always refractory to treatment. Anecdotal treatments: BB-UVB, NB-UVB, PUVA, β-carotenes, antimicrobials, azathioprine, and thalidomide | Rare: finger, nose or ear disfiguration In Hydroa vacciniforme-like eruptions associated with systemic EBV-related disease (including lymphoma), the skin lesions are more severe and more widespread. Can also have facial swelling, ulcerated nodular lesions, high-grade fever, and hepatosplenomegaly |

#### Solar urticaria

| Women > men 4th and 5th decade | Wheals limited to sun-exposed areas that appear a few minutes after exposure. Lesions resolve after 1 – 2 hours Anaphylactic shock may occur May last several years | IgE-mediated response against photo-induced, endogenous, cutaneous antigens | UVA, UVB, UVC, visible light | Mild dermal edema with perivascular mixed neutrophilic and eosinophilic infiltrate | Phototherapy Oral antihistamines Hardening with UVA or PUVA Refractory disease: plaques, plaques, emolulzumab or IV Ig | Fixed solar urticaria is limited to one area (most cell alteration at that site) |

#### Chronic actinic dermatitis

| Most common in men over 50 years of age | Persistent, pruritic eczematous dermatitis with infiltrated papules and plaques located in sun-exposed areas (may extend to covered areas) Often spares: forearms, upper eyelids, finger webs, Nasolabial folds or post-auricular areas Patients can develop erythromela Chronic lesions become lichenified Other findings: palmoplantar eczematous changes, loss of eyebrows or scalp hair from scratching | Delayed type hypersensitivity response (unlinked endogenous, photo-induced, cutaneous antigen) Often patients have an existing allergic or photo-allergic dermatitis to exogenous sensitizer (plants or fragrances) | UVA, UVB, visible light | Epidermal spongiosis and acanthosis, lymphohistiocytic exocytosis, superficial and deep dermal lymphohistiocytic infiltrate (may have eosinophils and plasma cells) | Strict photo-protection (including car window filters) Avoidance of relevant contact allergens Topical or oral corticosteroids, topical tacrolimus Refractory disease: low dose PUVA with initial high-dose steroids, azathioprine, cyclosporine, and mycophenolate mofetil | Lympohocytic infiltrate can mimic cutaneous T-cell lymphoma Chronic actinic dermatitis infiltrates are predominantly CD8+ |

### Abbreviations:
- PS: Photosensitivity
- CALMs: cafe au lait macules

### References: