

## XERODERMA PIGMENTOSUM

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### ABSTRACT

Rare disease causes an extreme sensitivity to sunlight. Everyone has sun-sensitive skin. It's the reason we tan and sunburn. It's why freckles, age spots, and skin cancers appear. Some people are born more sun sensitive than others. People who have an extreme sensitivity to sunlight are born with a rare disease known as xeroderma pigmentosum (XP). They must take extreme measures to protect their skin from ultraviolet (UV) light. Anything that emits UV light, including the sun and some lightbulbs, can damage their skin. When people with XP go outdoors during daylight, they need to cover up. Dermatologists recommend that they wear clothing that offers maximum protection from UV light. To protect their face and eyes, they should put on UV-protective sunglasses, goggles, or a face shield. Beneath this outer protective layer, they have sunscreen, which is necessary should any skin become uncovered.

When you have a rare disease called XP, you must take extreme precautions to protect your skin from the sun.

**Keywords-** xeroderma pigmentosum, nucleotide excision repair, personalized medicine, liposomes, Dimericine

### 1. INTRODUCTION

Xeroderma pigmentosa (XP) was described in Vienna by a Hungarian professor of dermatology Moriz Kaposi in 1870 (Hebra and Kaposi, 1874). The disorder was first called "xeroderma or parchment skin" and in 1882, the term "pigmentosum" was added to emphasize the striking pigmentary abnormality (Kaposi, 1883). Neisse (1883) described two siblings who had XP with progressive neurological degeneration beginning in the second decade. In 1932 two Italian physicians, Carlos Desanctis and Aldo Cacchione described three brothers with cutaneous features of XP with progressive neurological degeneration beginning at 2 years of age associated with dwarfism and immature sexual development, the so called DeSanctis Cacchione syndrome (Reed et al., 1977). The first description of XP in a black African was published in Loewenthal and Trowell (1938). In an American black the first description was by King and Hamilton (1940). Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by a deficiency in nucleotide excision repair (NER) caused by single-nucleotide mutations. Sunlight exposure is usually the trigger for UV-induced damage to DNA, which normally is repaired through the NER pathway, consisting in more than 30 proteins responsible for DNA damage recognition, incision, ligation, and resynthesis. The location of the affected gene in the NER pathway Does not confer the severity of DNA repair deficiency and Subsequent clinical manifestation of the disease. Therefore, Accurate diagnosis of XP, CS, and TTD currently relies on Clinical assessment and identification of mutations in the NER genes.

#### Nucleotide Excision Repair:

The nucleotide excision repair (NER) pathway can start with DNA damage recognition in two different ways:

1. global Genome (GG)

2. transcription-coupled (TC)

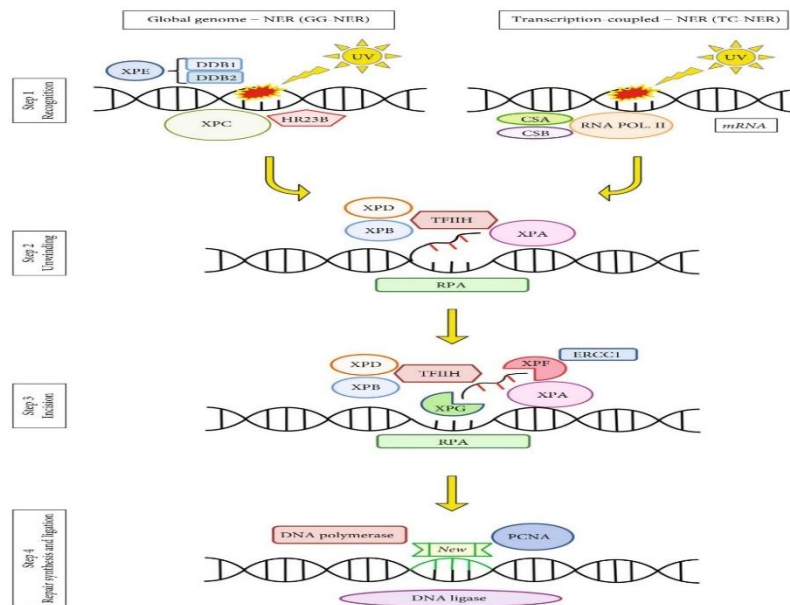
Via global genome, the damage detection occurs across

STEP 1:-The remainder of the genome and involves XPC and the Damage DNA-binding protein 1 and 2 (DDB1/DDB2) complex.

STEP 2:-Otherwise, the transcription-coupled system detects DNA damage during transcription when RNA polymerase, II stalls at a site of damage recruiting Cockayne syndrome, Group A and B proteins (CSA, CSB). After the DNA damage is detected via GG or TC, the Remainers of the XP proteins are involved in DNA unwinding (XPA, XPB, and XPD)

STEP 3:-and excision of the damage (XPF, ERCC1, and XPG)

STEP 4:-Next, the DNA polymerase delta (Pol  $\delta$ ) initiates missing, Strand synthesis recruiting the proliferating cell nuclear antigen (PCNA), the cofactor for DNA clamping, while the DNA ligase connects the two strands by forming a bond Between the phosphate group of one strand and the deoxyribose group on another, so maintaining DNA integrity during the repair process.



**Figure 1.** The nucleotide excision repair (NER) pathway.

Step 1: DNA damage recognition through two different ways: global genome (GGNER) or transcription-coupled (TC-NER).

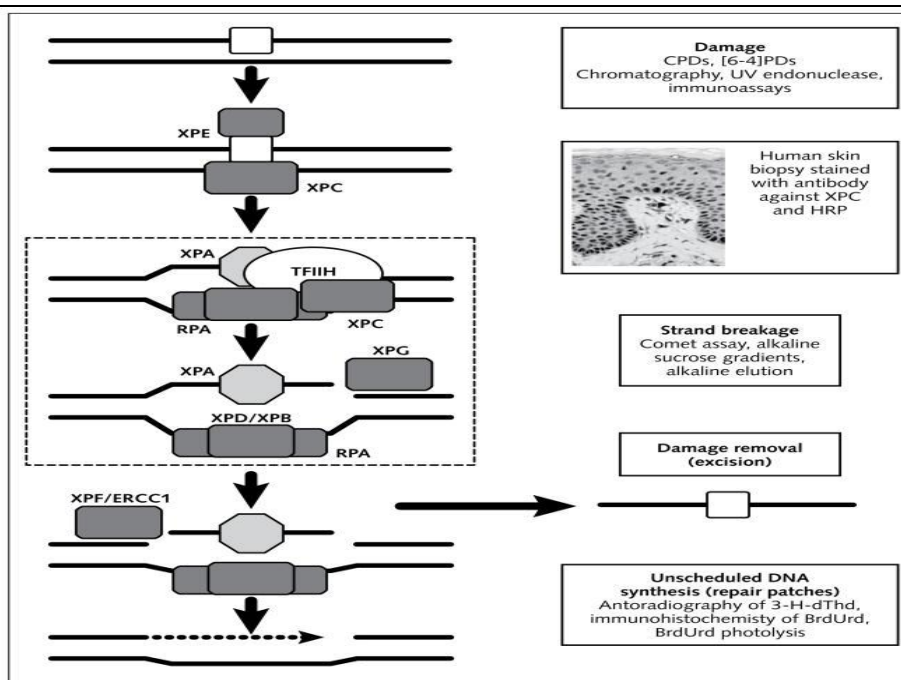
Step 2: DNA unwinding.

Step 3: DNA damage excision.

Step 4: missing strand synthesis and ligation.

## 2. BIOCHEMISTRY OF DIAGNOSTIC

ognized in nuclear DNA within different functional domains (Figure) . Damage in transcriptionally inactive regions is detected by the damage DNA-binding protein complex DDB1/DDB2 (DDB2 is also known as XPE) and by XPC/homologous recombination protein 23B (HR23B)/centrin2. Damage in transcriptionally active regions is detected through arrest of the transcriptional machinery involving RNA polymerases I and II, and requires the CSA and CSB proteins that are mutated in the CS disorder. The damaged site is then remodeled through a series of preincision complexes . XPA, replication protein A (RPA), XPC, and the transcription DNA repair factor IIIH (TFIIH) assemble in a random but cooperative order on the damaged site. They form an unstable preincision complex that is stabilized once the DNA is unwound by the ATPase activity of XPB and the ATPase/helicase activity of XPD in TFIIH . TFIIH is a 10-component transcription factor containing XPB and XPD. XPC recruits XPG and is displaced from the complex. Cleavage then occurs on both sides of the damaged site, firstly by the XPG 3' nuclease and then by the XPF/excision repair cross-complementing protein 1 (ERCC1) 5' nuclease. The nucleases are anchored by the XPA/RPA complex, which serves to define the cleavage sites and strand specificity. Once the damaged oligonucleotide is removed, a patch is resynthesized by the proliferating cell nuclear antigen, the polymerases delta, epsilon, or kappa ( $\delta$ ,  $\epsilon$  or  $\kappa$ ), and a ligase enzyme . In quiescent cells, ligation involves X-ray repair cross-complementing protein 1 (XRCC1) and ligase III; in proliferating cells, ligation involves ligase I. NER can remove DNA damage before DNA replication begins and, consequently, plays a major role in reducing the amount of damage that becomes fixed as mutations during replication Specialized polymerases are required to replicate DNA photoproducts because the normal DNA polymerases – alpha, delta, and epsilon ( $\alpha$ ,  $\delta$ , and  $\epsilon$ ) – cannot accommodate large distortions such as DNA photoproducts or adducts in their active sites . These damage-specific polymerases have relaxed substrate specificity, and the most important is the low-fidelity polymerase Pol eta ( $\eta$ ) . This is mutated in the XPV condition, which is often clinically indistinguishable from NER-deficient XPPathways of nucleotide excision repair and diagnostic methods. The proteins indicated are the main ones involved in XP; binding partners and other components are omitted for clarity. Left column: schematic of NER. The initial damage (top) is recognized by the XPE and XPC DNA-binding proteins. The damaged site is then remodeled through a series of preincision complexes, indicated within the hatched box . XPA, RPA, and XPC/TFIIH form an initial preincision complex that is stabilized once the DNA is unwound by the ATPase activity of XPB and ATPase/helicase activity of XPD in TFIIH . XPC recruits XPG and is displaced from the complex. Cleavage then occurs on both sides of the damaged site, firstly by the XPG 3' nuclease and then by the XPF/ERCC1 5' nuclease. Once the damaged oligonucleotide



is removed, a patch is resynthesized and is completed by polymerases and ligases. Right column: steps in NER that have been addressed for diagnosing repair by (top to bottom) damage detection, protein expression by immunohistochemistry, strand breakage, damage removal, and unscheduled DNA synthesis. BrdUrd: bromodeoxyuridine; dThd: tritiated thymidine; ERCC1: excision repair cross-complementing protein 1; HRP: horseradish peroxidase counter stain for XPC antibody; NER: nucleotide excision repair; RPA: replication protein A; TFIID: transcription/DNA repair factor IID; UV: ultraviolet; XP: xeroderma pigmentosum

### 3. MANAGMENT

At present, there is no cure for XP. Therefore, prevention of complications is crucial for this disfiguring and potentially lethal disease. Strict and consistent sun avoidance and protection and early detection and treatment of premalignant and malignant skin lesions are the mainstays of management. These and other treatment options are summarized as follows. Regular paediatric, dermatological, ophthalmological and neurological follow-up is essential.

#### Treatment options for xeroderma pigmentosum:-

- A. Sun avoidance and sun protection
  1. Sun avoidance
  2. Sun protection (regular use of broad-spectrum sunscreens)
- B. Chemoprevention of skin cancers
  1. Oral isotretinoin
  2. Topical imiquimod
  3. Topical fluorouracil
- C. Treatment of poikiloderma
  1. Chemical peeling
  2. Dermabrasion
  3. Carbon dioxide (CO<sub>2</sub>) or erbium-YAG laser resurfacing
- D. Treatment of actinic keratosis
  1. Cryotherapy
  2. Topical imiquimod
  3. Topical 5-fluorouracil
  4. Chemical peeling
  5. Excision
  6. CO<sub>2</sub> or erbium-YAG laser resurfacing

7. Fractional/pulsed laser therapy
8. Photodynamic therapy
- E. Treatment of skin cancers
  1. Photodynamic therapy
  2. Curettage with electrodesiccation
  3. Aggressive cryosurgery
  4. Surgical excision
  5. Oral vismodegib, pembrolizumab, nivolumab and cemiplimab
  6. Ocular management
  7. Methylcellulose eyedrops
  8. Soft UV-protective contact lens
  9. For ocular surface squamous neoplasia
    - a. Surgical resection and intraoperative cryotherapy
    - b. Subconjunctival injection of IFN $\alpha$ 2b with topical cycles of mitomycin C eyedrops
- F. Neurological management
  1. May need hearing aids, speech therapy, physical therapy and occupational therapy
  2. No effective treatment for neurodegeneration
- G. Investigational therapies
  1. Topical T4 endonuclease-V
  2. Oral vismodegib
  3. Oral nicotinamide
  4. Oral *Polypodium leucotomos* extract
  5. Oral coenzyme Q<sub>10</sub>
  6. Gene therapy
- H. Genetic counselling
- I. Psychological counselling

#### 4. CONCLUSION

Skin tumors may be not “appealing” for genetic researchers with respect to gastrointestinal or lung or breast cancer, but their impact on the patient’s quality of life can be tremendous, especially when skin cancer starts occurring during childhood without ever ending. Patients and their families experience the tragedy of a sunless life, since the major triggers for skin cancer development are UV rays. Despite efforts made to avoid sun exposure with clothes and sunscreens, from adolescence on melanoma and NMSC have great chance to occur on all the body surfaces, even if the head and neck area and dorsum of the hands remain the more subjected to disease. Studies with better scientific evidence are needed. Randomized trials or prospective cohort studies should be encouraged in care centers of patients with xeroderma pigmentosum. Far from obtaining conclusive results, this analysis has some strengths. First, this is a systematic review specifically focused on correlation between XP and skin cancers that was never been conducted before. Second, the quality of eligible studies included in the current review was satisfactory and met our inclusion criteria. Third, we succeeded in pointing out the lack of studies and research in the literature on this field, taking into account that many meta-analyses report the same studies, now dated, and characterized by similar publication bias.

Undoubtedly, the absence of a statistical analysis of the stratified sources to obtain adjusted estimates and the small sample of investigations analysed represent the limits of this study.

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