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*Review Article*

# Impact of UV Radiation on DNA Repair Mechanism in Xeroderma Pigmentosum

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## Abstract

Xeroderma Pigmentosum, an autosomal recessive disorder first described by Kaposi in 1874, is caused by mutations in one or more of the 7-8 XP genes that are involved in the nucleotide excision repair system (NER). This disorder results in the accumulation of cyclobutane pyrimidine dimers or 6-4 photoproducts in the DNA of affected individuals due to high UV exposure. These individuals exhibit low tolerance to sunlight and may experience inflammation even with short periods of sun exposure. In affected organisms, the photolyase enzyme responsible for reversing thymine dimers becomes inactive, leading to excessive sunburns, lentigines, and dermal pigmentation on the skin.

The normal functioning of all 7-8 XP genes is crucial for proper DNA repair, and any alterations can result in various abnormalities. The first set of XP genes (XP-A, XP-C, and XP-E) recognize the affected DNA region, followed by XP-B and XP-D, which unwind the distorted area. XP-F and XP-G then act as endonucleases and remove the lesioned part of approximately 30 nucleotides.

The present paper provides detailed information on each XP gene in both its unmutated and mutated forms, as well as the various signs and symptoms associated with Xeroderma Pigmentosum.

*Key words: Xeroderma Pigmentosum, XP gene, Mutation, Thymine dimers, UV rays, Lesion, NER system, Cyclobutane pyrimidine dimer, 6-4 Photoproducts, skin cancer*.

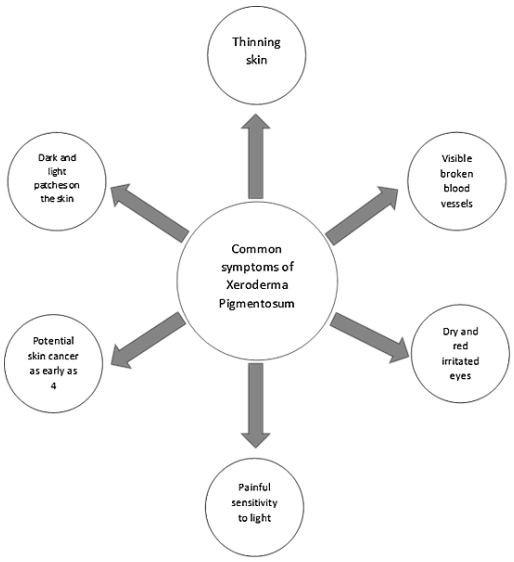
## Introduction

Xeroderma pigmentosum (XP) is a genetic disorder resulting from a defect in the nucleotide excision repair system, a crucial DNA repair mechanism (Black, 2016; Kraemer and Slor, 1985). Individuals with XP exhibit high sensitivity to environmental factors such as UV rays, which exacerbate their condition (Cleaver and Bootsma, 1975; Kraemer and Slor, 1985; and Norgauer et al., 2003).

XP is an autosomal recessive disorder, and its discovery dates back to 1874 when Moritz Kaposi first described it. It was not until 100 years later that James Cleaver reported that XP was caused by defective DNA repair in XP cells (Cleaver and Bootsma, 1975; Lehmann et al., 2011). Normal cells have seven complementation groups from XP-A to XP-G, which work in a coordinated manner, but XP cells have mutations in one or more of these genes, leading to the persistence of thymine dimers (Cleaver, 1968; Norgauer et al., 2003). Exposure to UV rays from sunlight induces cyclobutene pyrimidine dimers (CPDs) or 6-4 photoproducts (6-4 PPs) that alter DNA structure,

resulting in reduced minimal erythema dose during early life. Other symptoms of XP include excessive freckling, lentiginous pigmentation, poikiloderma, and degenerative changes in the skin and eyes, which can cause neoplasia. Liposomal encapsulated T4 endonuclease V or photolyase, which are supposed to repair CPDs through photoreactivation, are also ineffective in XP cells (Cleaver, 1968).

Data indicates that XP occurs more frequently in the Japanese population, affecting one in every 20,000 people, while in the US, it affects one in every 300,000 people, and in Western Europe, it affects about 2.3 per million people (Norgauer et al., 2003).




**XP genes in healthy individuals**

The eight risk genes including the variant type gene is responsible for causing different types of xeroderma pigmentosum in eukaryotic organisms. A cell with normal repair mechanism has all the XP genes playing their role accurately that repairs mutation in DNA. (Cleaver, 1968; Lehmann et al., 2011) Series of these risk genes, XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G and a variant type as XP-V, removes the bulky chemical lesions from DNA. Accessory factors like DNA polymerase, PCNA, RPA and DNA ligase are required to reseal the DNA fragment through de-novo DNA synthesis. (DiGiovanna and Kraemer, 2012; Gratchev et al., 2003 and Sugasawa, 2008)

This genome repair system functioning in all eukaryotes, called nucleotide excision repair system functions when the UV induced CPDs or 6-4 PPs blocks the progress of RNA polymerase during pathway of molecular expression. (DiGiovanna and Kraemer, 2012) The mechanism is initiated when three of total XP genes recognizes the lesion. These genes are XP-A, XP-C and XP-E, with XP-C as central molecule. Once the area of lesion is determined, another pair of XP genes called XP-B that works along with ERCC-3 and XP-D that works with ERCC-2, functioning along with transcription factor II, starts unwinding the DNA surrounding the area of lesion via its helicase activity. (DiGiovanna and Kraemer, 2012; Sugasawa, 2008). The single stranded DNA is now worked upon by another set of XP gens called XP-F and XP-G having endonuclease activity. XP-F works with ERCC-1 on the 5’ side of distorted DNA and makes a cut about 8 nucleotides away, meanwhile XP-G makes a cut on 3’ side of target DNA resulting in the excision patch removal of around 30 nucleotides containing the lesioned part.

After the removal of DNA patch, XP-B and XP-D are no longer associated with the complex and the resultant gap is filled by polymerization activity of DNA polymerase delta accompanied by gap sealing activity of DNA ligase-ATPase complex. (DiGiovanna and Kraemer, 2012)

The entire system is so co-ordinated that mutation in even one of the XP gene can result in complete misfunctioning and hence persistence of CPDs or 6-4 PPs occurs in DNA causing Xeroderma Pigmentosum.

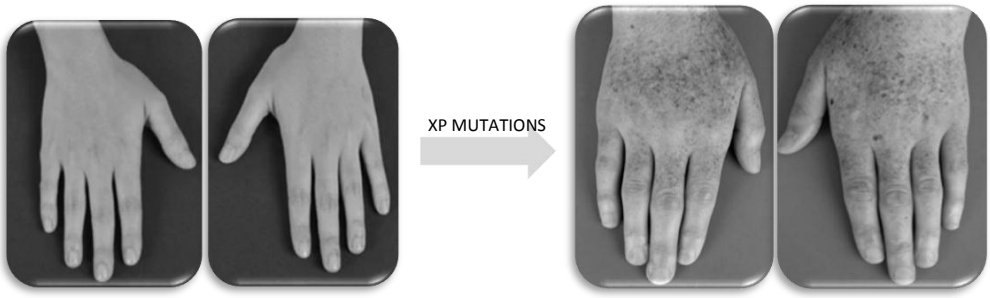



Fig-1: - A-Normal skin, B- Pigmented skin

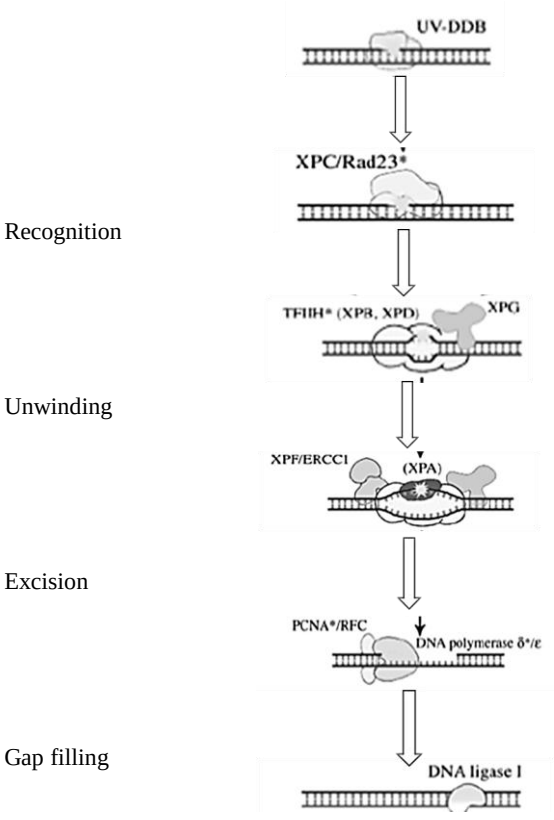



Fig-2: - Global genome repair (GGR) showing NER system

**Mutation in XP genes**

Out of all seven to eight XP genes, each one of them affect different steps of mechanism making it worse against the protection of UV.

**XP-A**

The gene product of XP-A, earlier thought to be responsible for identification of damaged DNA, is now considered to be recruited after TF II-H factor. (Sugasawa, 2008) Another protein called RPA works along with XP-A, this RPA-XP-A complex is known to bind and stabilize the unwinded part of DNA. (DiGiovanna and Kraemer, 2012; Sugasawa, 2008) Its location is precisely on the q arm of 9th chromosome at designated region of 22.3. (Xeroderma Pigmentosum 2019, Sugasawa, 2008) Mutation in XP-A gene product causes severe form of xeroderma pigmentosum as the ability to repair DNA vanishes, resulting in increased sensitivity towards UV light. People with XP-A mutation shows initiation of skin cancer at early age and severe neurological abnormalities. With mutation rate of only 25%, XP-A is majorly involved in formation of pre-incision complex also. (Sugasawa, 2008).

**XP-B/ERCC-3**

XP acts as co-worker of ERCC-3, it is one of the ten factors of TF II-H. XP-B protein has 3' - 5' helicase activity that is essential for unwinding the distorted part of DNA. Along with XP-D, XP-B moves on the DNA strand making it single stranded in the lesioned area. (Sugasawa, 2008) With the least frequency out of all XP types, affected individuals with mutated XP-B shows increased sensitivity to UV light. The appearance of symptoms of Cockayne syndrome might be the indicator of XP-B mutation. Located on q arm of 2nd chromosome's 21st region, its mutation can also result in mild neurological abnormalities.

**XP-C**

Specific for global genome repair, XP-C acts as central molecule that recognizes the distortion and recruits another XP gene products i.e., XP-A and XP-E. The heterotrimer structure of XP-C with two human orthologs of Saccharomyces cerevisiae as Rad23p and Centrin-2 is involved in stabilization of XP gene product. Out of these two, Centrin-2 has the ability to potentially identify the lesion. (Sugasawa, 2008) Located at p arm of 3rd chromosome's 25th position, XP-C prefers to bind at a junction of double and single stranded regions, hence XP-C recognition is best identified when DNA helical distortion is associated with local unwinding. (Xeroderma Pigmentosum 2019, Sugasawa, 2008) Mutation in XP-C is considered the most frequent type of XP in Caucasian population. Although its mutation shows increased sensitivity towards UV light, this variant has highest ability to repair DNA. Individuals with affected XP-C gene products show no neurological disability but may express a typical and severe lentigines at sun exposed area including ocular abnormalities.

**XP-D/ERCC-2**

Another component of TF II-H, XP-D is the helicase containing XP gene product that opens DNA in the direction of 5' to 3'. The helicase activity of XP-D is in the opposite direction to XP-B and both these XP gene products are considered to migrate together on double stranded DNA. (DiGiovanna and Kraemer, 2012; Sugasawa, 2008) With mutation rate of only 15%, affected individuals shows sensorineural deafness, ataxia and mental retardation. Located on q arm of 19th chromosome's 13.2-13.3 region, mutation at this position results in increased UV sensitivity. (Xeroderma Pigmentosum 2019) Additional functions of XP-D might involve formation of pre-incision complex and opening of promoter assembly. (Sugasawa, 2008).

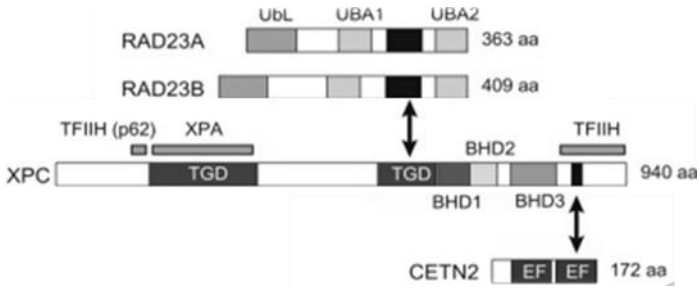



Fig-3: - XP-C gene on chromosome number 3

**XP-E/DDB-1; DDB-2**

Located on p arm of 11th chromosome's 11-12 position and q arm of 11th chromosome's 12-13 position, XP-E gene product plays a side role in identification of distorted part of DNA. With very low frequency of XP type, it is very aggressive and restricted to some dermal infections only. Skin cancer may develop at later stage. (DiGiovanna and Kraemer, 2012).

**XP-F/ERCC-4**

Once the pre-incision complex is assembled by XP-A, two gene products namely XP-F and XP-G are introduced to single stranded portion containing CPDs or 6-4PPs, making a cut at both the ends of lesion. XP-F specifically cleaves at the 5' end of single stranded DNA few nucleotides away from distortion. (Sugasawa, 2008) Located on p arm of 16th chromosome's 13.3 region, its mutation can cause cutaneious cancer in Japanese population.

**XP-G/ERCC-5**

Located on q arm of 13th chromosomes' 32-33 region, mutation in this occurs with very less frequency but is aggressive. (Xeroderma Pigmentosum 2019) Normally, XP-G making a cut at 3' end of single strand DNA belongs to flap endonuclease-I family. Depending on the type of lesions or dimers, the exact position of XP-F and XP-G cut can vary significantly, but the excised patch is usually ranged between 24-32 nucleotides. (DiGiovanna and Kraemer, 2012; Sugasawa, 2008).

| S. No. | XP gene | Related gene | Location | Normal function | Symptoms of mutation |
|---|---|---|---|---|---|
| 1. | A | - | 9q22.3 | Thymine dimer recognition | Early age skin cancer, neurological abnormalities |
| 2. | B | ERCC-3 | 2q21 | 3'-5' helicase | Characteristics of Cockayne syndrome |
| 3. | C | - | 3p25 | Initial damage recognition | Typical and dense lentigines, eye problems |
| 4. | D | ERCC-2 | 19q13.2-q13.3 | 5'-3' helicase | Sensorineural deafness, ataxia, mental retardation |
| 5. | E | DDB-1; DDB-2 | 11p11-p12; 11q12-q13 | Damage recognition | Cutaneous cancer |
| 6. | F | ERCC-4 | 16p13.3 | 5' endonuclease | Cutaneous cancer |
| 7. | G | ERCC-5 | 13q32-q33 | 3' endonuclease | Skin cancer, neurological abnormalities |

Table-1: Comparison of XP genes

Once the distorted part is removed off from the DNA, the gap filling activity is to be performed by DNA polymerase. Additional factors like PCNA and RFC enhances the polymerization activity. (Sugasawa, 2008).

Following this, the final gap between last two nucleotides is sealed by DNA ligase. Once the gap is filled and sealed, the CPDs or 6-4PPs is now being vanished and in place of that normal nucleotide inserted making it unaffected for later DNA replication.

**Conclusion**

Xeroderma Pigmentosum is a genetic disorder caused by mutations in the XP gene products, leading to significant impacts on affected individuals. Although not fatal, this condition manifests with various phenotypic defects, including neurological irregularities, CNS tumors, and malignant melanomas. One crucial indicator of Xeroderma Pigmentosum is the hyperplasia of melanocytes, resulting in severe lentigines on the skin.

Researchers have made substantial efforts to identify the precise locus of each XP gene and its functions in both healthy and affected states. Currently, the focus is on investigating the underlying causes of each mutation, and finding the most effective approach towards a cure. While significant progress has been made in developing medication strategies, further research is needed to understand the precise mechanism of each XP gene responsible for causing Xeroderma Pigmentosum. Therefore, it is imperative to prioritize ongoing research efforts to enhance our understanding of this debilitating condition and develop effective treatment options.

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