

XERODERMA PIGMENTOSUM



- ◆ Xeroderma Pigmentosum (XP) is a rare genetic disorder that occurs worldwide in all races and ethnic groups.
- ◆ First described by Hebra and Kaposi in 1874 the disorder is characterised by marked photosensitivity and premature onset of all major types of skin cancer ^[1].



Definition:

- It is characterised by inability of a cell to repair damage caused by UV leading to genetic instability and skin cancer.

Xeroderma Pigmentosa

- **Xeroderma pigmentosa**, or XP, is an autosomal recessive genetic disorder .
- In XP, thymine dimers in DNA caused by ultraviolet (UV) light cannot be repaired due to mutations in the genes that code for the repair enzymes. Therefore, the repair enzymes(proteins) are not made.
- This disorder leads to multiple basalomas and other skin malignancies at a young age.
- In severe cases, it is necessary to avoid sunlight completely.
- The two most common causes of death for XP victims are metastatic malignant melanoma and squamous cell carcinoma.
- For some reason, XP is about six times more common in Japanese people than in other groups.

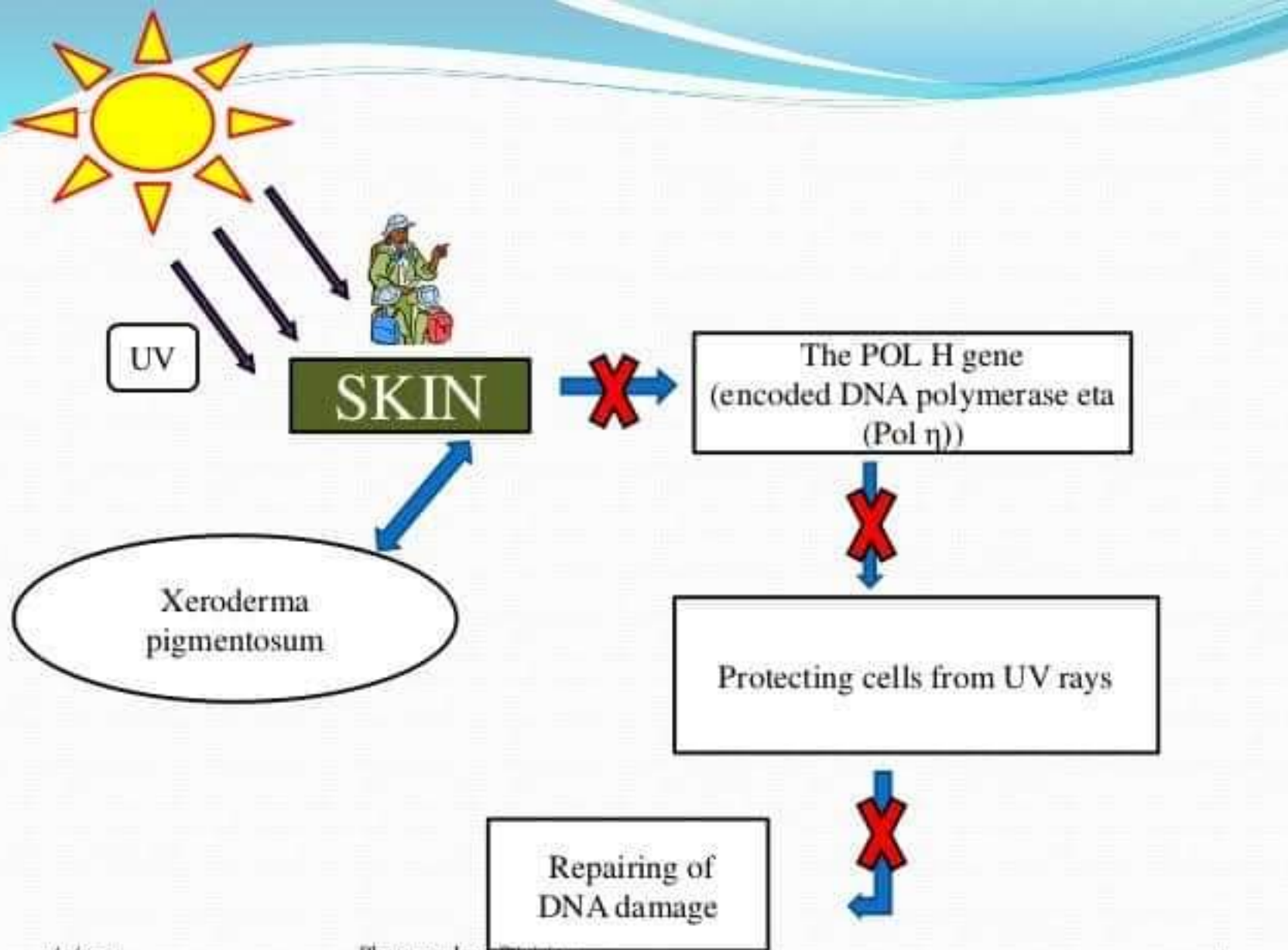
Cause of XP

- Metastatic malignant melanoma
- Squamos cell carcinoma
- Autosomal recessive genetic disorder
- Nucleotide excision repair enzymes are mutated
- Reduced and/or eliminated number of NER enzymes
- Disorder leads to cancer and tumors

Causes of XP

- Autosomal recessive genetic disorder
- Defect in nucleotide excision repair (NER)
 - 2 types of NER:
 - ~Global Genome (GG-NER)
 - ~Transcription coupled (TC-NER)
- Defected, unable to repair DNA damaged by UV radiation

- Patients defective in the *XPC* or *XPE* genes do not, in general, have the extreme sunburn reactions or neurological abnormalities.
- Defects in the eighth XP gene do not affect NER ⁷.
- The DNA polymerases that normally replicate DNA cannot deal with damage in the DNA template and specialised polymerases have to be employed to get past the damage (translesion synthesis).
- For UV damage, the cell uses DNA polymerase η , encoded by the gene *POLH* and this gene is mutated in XP-V patients ⁸.
- Like XP-C and XP-E patients, XP-V patients rarely have extreme sunburn reactions or neurological problems.



DNA DAMAGES

Exposure to UV light



Thymine dimer



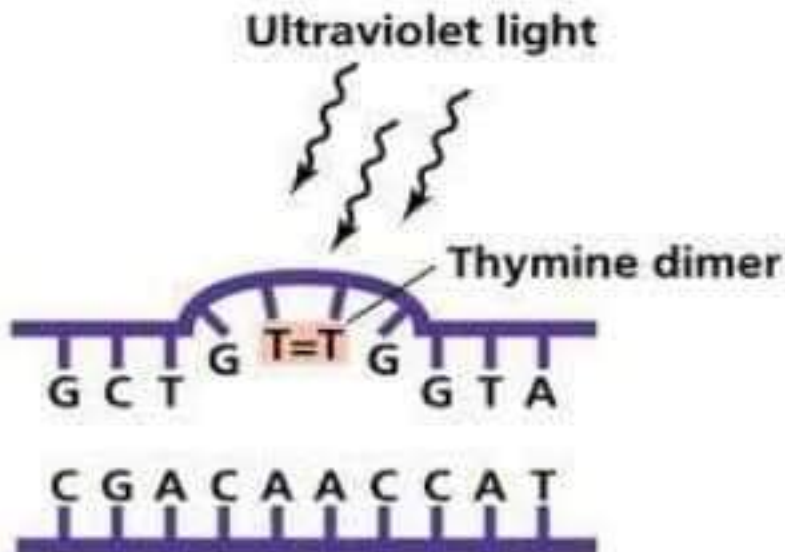
DNA damage



NER

No replication of

DNA strand



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DNA Repair Failure

- Xeroderma pigmentosum is a genetic failure of DNA repair molecules
 - Normally repair thymine dimers and other UV damage
- Extremely sensitive to sunlight and blacklights
- Individuals are at great risk of skin cancer



Signs and Symptoms of Xeroderma Pigmentosum

- Severe sunburn.
- Development of many freckles at an early age.
- Rough-surfaced growths (solar keratoses), and skin cancers.
- Eyes that are painfully sensitive to the sun and may easily become irritated, bloodshot and clouded.
- Blistering or freckling on minimum sun exposure.

Symptoms & Signs of Xeroderma Pigmentosum



Freckles



Photophobia



Skin cancer



**Tumor
of the eye**



**Premature
skin ageing**



**Neurological
problems**

Diagnosis

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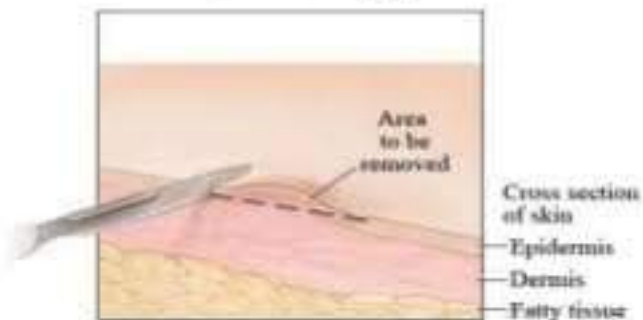
After birth:

Measuring the DNA repair factor from skin or blood sample

Some test are performed

- Skin biopsy

Skin biopsy



Diagnosis

1/ functional assays of DNA repair.

- cellular ultraviolet (UV) hypersensitivity
- unscheduled DNA synthesis (UDS)
- host-cell reactivation

2/ molecular genetic testing

- Sequence analysis of XPA, XPC, ERCC2, ERCC5, ERCC1, and ERCC3

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



Tips to Prevent & Manage Xeroderma Pigmentosum



**Use Sunscreen
to Protect
your Skin**



**Wear Hat
along with
sunglasses**



**Periodic
Skin Check**



**Routine
Eye
Examination**



**Regular
blood tests**



**Avoid
exposure
to smoking**

Treatment

- Cryotherapy

Removal of heat from the body.

- Fluorouracil

Pyrimidine analogue used to treat cancer

- Reduced exposure to sun's UV rays

Cryotherapy



(Yasuda et al., 2007)

Xeroderma Pigmentosum

Management



Physically

Reducing exposure to the sun

- Sun glasses
- Clothing (long sleeves, long pants, gloves)
- Optical filtration
- Lots and lots of sunscreens

Chemically

- Reducing the number of keratoses with Isotretinoin

Housing

- Halogen lamps

* Keratoses – keratin (on the skin)

Thank you

