Xeroderma Pigmentosum (XP):

A Defect in Nucleotide Excision Repair (NER)

By: Gabrielle Chen

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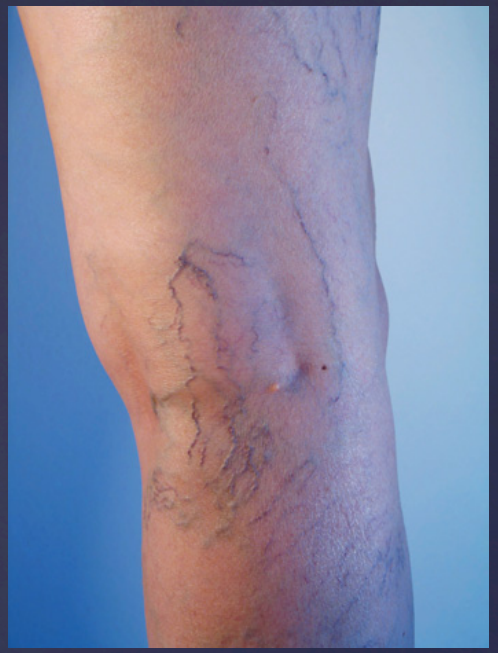


Physiology:

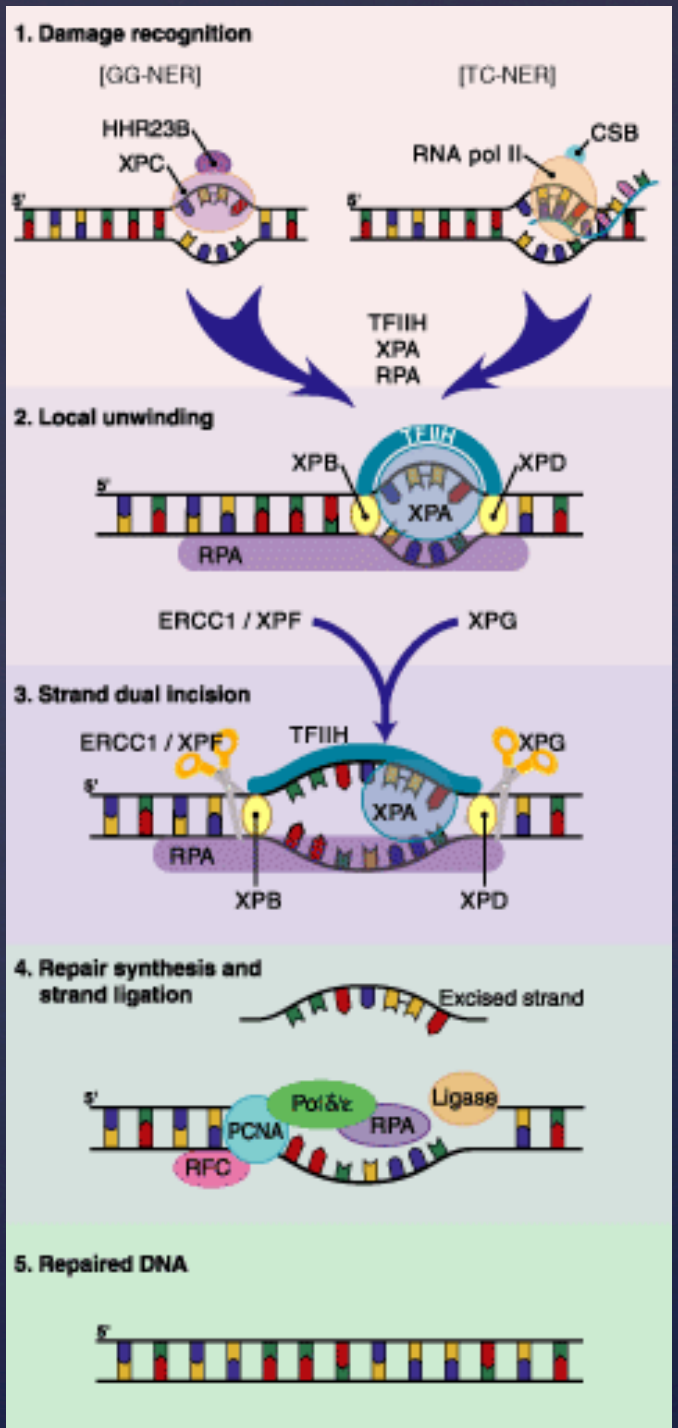
- Autosomal recessive
- Overly sensitive condition to ultraviolet radiation, usually in the form of sunlight
- Rare disorder (1 in 1 million people have XP in the US & Europe)
- Name comes from symptoms: xeroderma-dry skin, pigmentation- skin coloring
- Symptoms (in general):
  - Sunburns (redness & blistering) that don't heal after a few minutes
  - Freckles on skin
  - Bloodshot or irritated eyes due to photophobia (sensitivity to sunlight)
  - Discolored skin
  - Scaly and crusty skin
  - Premature skin aging
  - Skin thinning
  - Blindness caused by (non)cancerous tumors on the eye
  - Spider-like blood vessels
  - Other symptoms:
    - Cloudy cornea
    - Eyelashes falling out
    - Thin eyelids that abnormally turn in-/outwards

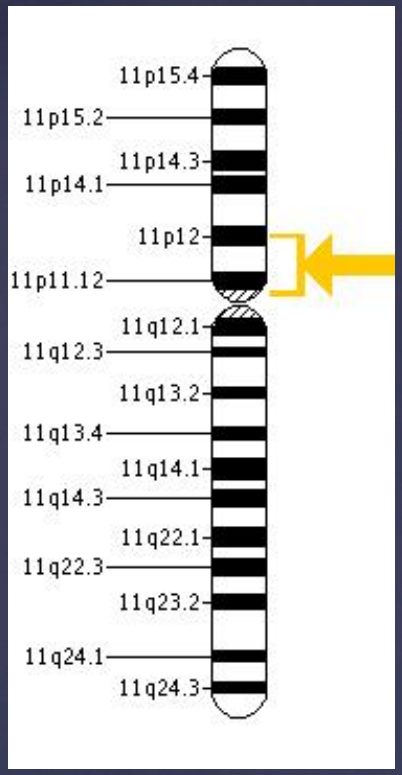
- XP is caused by a defect in gene(s) that does not allow for proper protein formation
- Therefore, the ultraviolet-damaged DNA cannot be repaired or checked.
- There are mutations in eight genes that cause XP:
  - DDB2 (damage-specific DNA binding protein 2)
    - Normal function: encodes necessary protein for UV-damaged DNA repair
    - Located on Chromosome 11 arm p, the short arm (11p12-p11)
  - ERCC2 (excision repair cross-complementing rodent repair deficiency, complementation group 2)
    - Normal function: contains information needed to make XPD (xeroderma pigmentosum group D) protein, which helps repair damaged DNA
    - Located on Chromosome 19 arm q, the long arm (19q13.2)
  - ERCC3 (excision repair cross-complementing rodent repair deficiency, complementation group 3)
    - Normal function: contains information needed to make XPB (xeroderma pigmentosum group B) protein, ATP dependent DNA helicase, which may be involved in the unwinding of DNA (5') of a damaged base
    - Located on Chromosome 2 arm q (2q21)
  - ERCC4 (excision repair cross-complementing rodent repair deficiency, complementation group 4)
    - Normal function: encodes a protein (endonuclease) involved in the 5' incision made during nucleotide excision repair
    - Located on Chromosome 16 arm p (16p13.3)
  - ERCC5 (excision repair cross-complementing rodent repair deficiency, complementation group 5)
    - Normal function: encodes endonuclease, which makes 3' incision during DNA excision repair after ultraviolet radiation damage
    - Located on Chromosome 13 arm q (13q32-33)
  - POLH (polymerase (DNA directed), eta)
    - Normal function: contains information to make DNA polymerase eta, which skips over the abnormal segment of ultraviolet radiation damaged DNA during replication
    - Located on Chromosome 6 arm p (6p21.1)
  - XPA (xeroderma pigmentosum, complementation group A)
    - Normal function: contains information to make protein that repairs damaged DNA
    - Located on Chromosome 9 arm q (9q22.3)
  - XPC (xeroderma pigmentosum, complementation group C)
    - Normal function: same as XPA
    - Located on Chromosome 3 arm p (3p25.1)

Molecular Cause

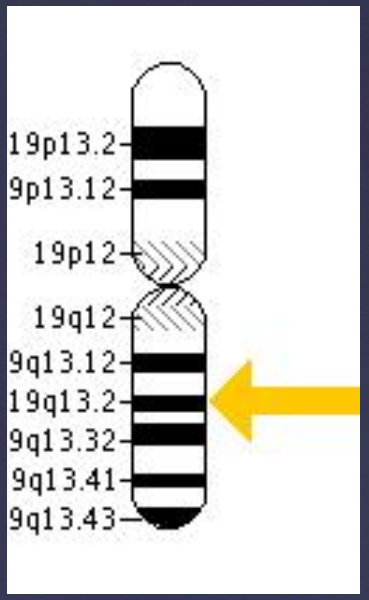
RNA polymerase II codes
for mRNAs, which carries
instructions for making protein
from DNA.

Transcription factor II H (TFIIH)
is a protein complex which activates
the RNA polymerase II preinitiation complex.
In NER, TFIIH contains helicases needed for
unwinding the DNA.

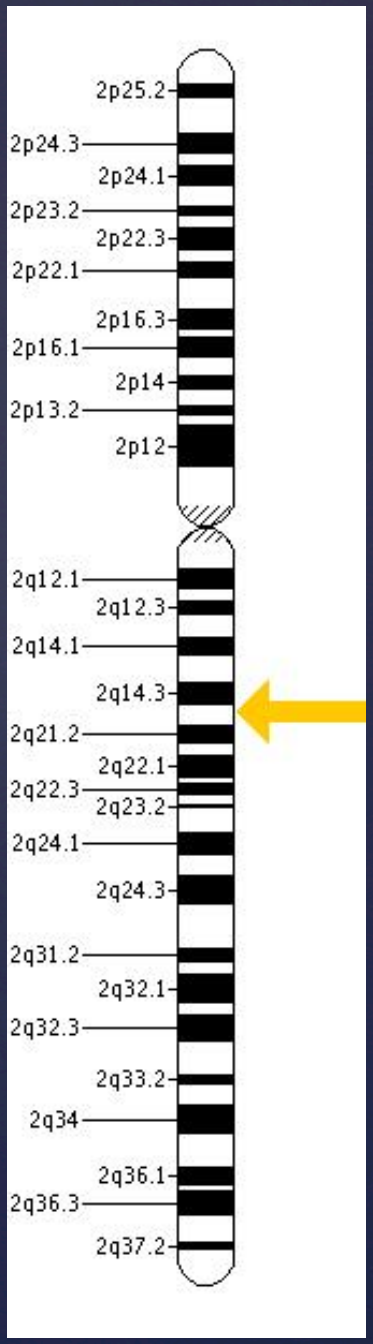




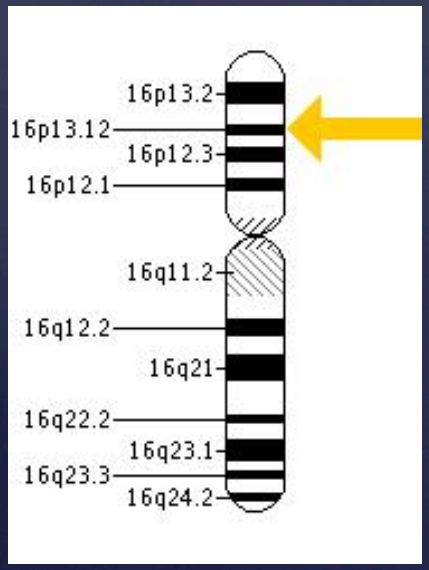
DDB2



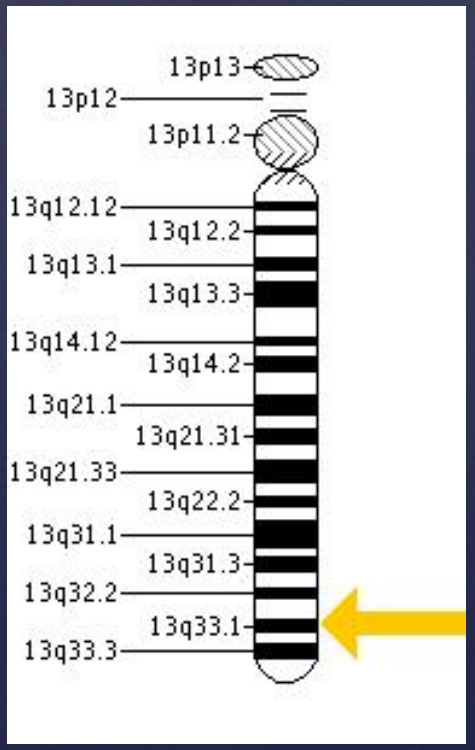
ERCC2



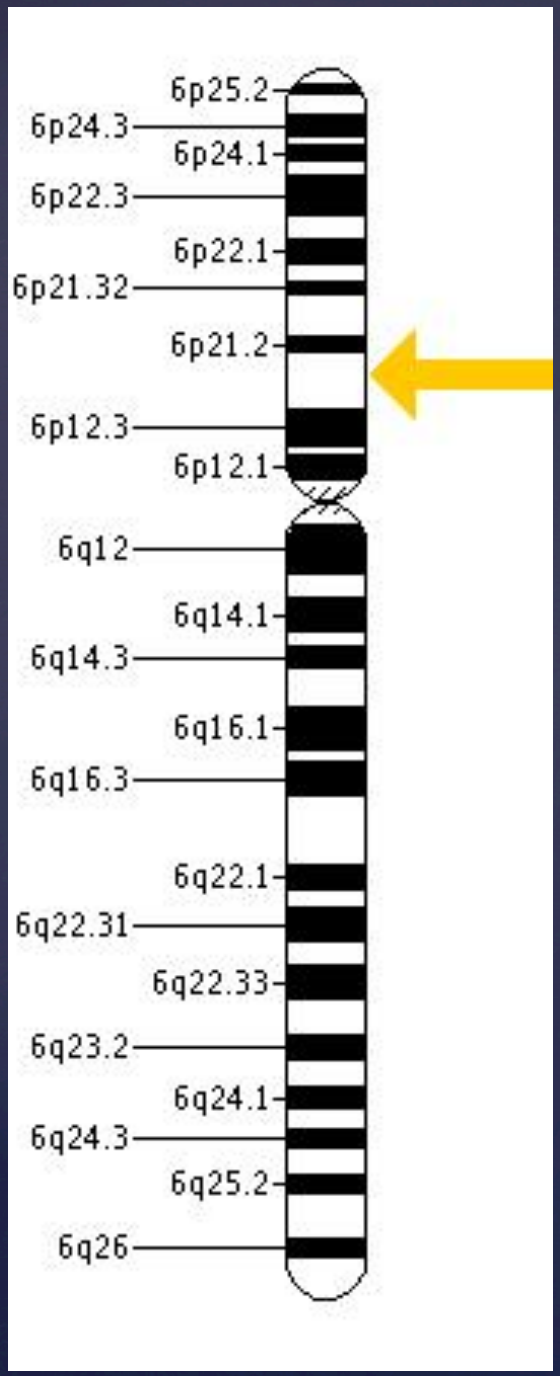
ERCC3



ERCC4



ERCC5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6p24.3
6p24.1
6p22.3
6p22.1
6p21.32
6p21.2
6p12.3
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6q12
6q14.1
6q14.3
6q16.1
6q16.3
6q22.1
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6q22.33
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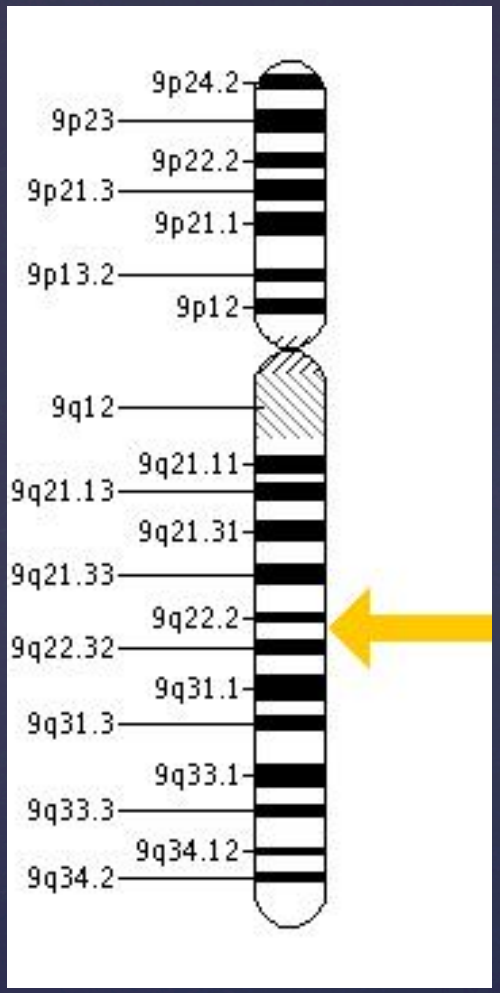
6q24.1
6q24.3
6q25.2
6q26

POLH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9p23
9p22.2
9p21.3
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9p13.2
9p12
9q12
9q21.11
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9q21.31
9q21.33
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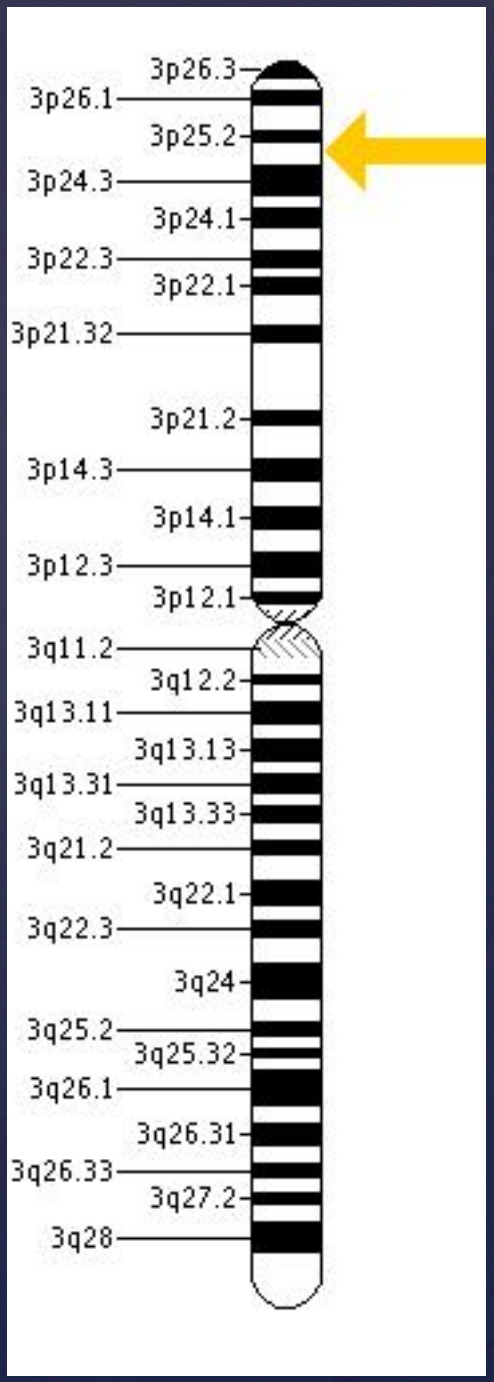
9q33.1
9q33.3
9q34.12
9q34.2

XPA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3p24.3
3p24.1
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3p14.3
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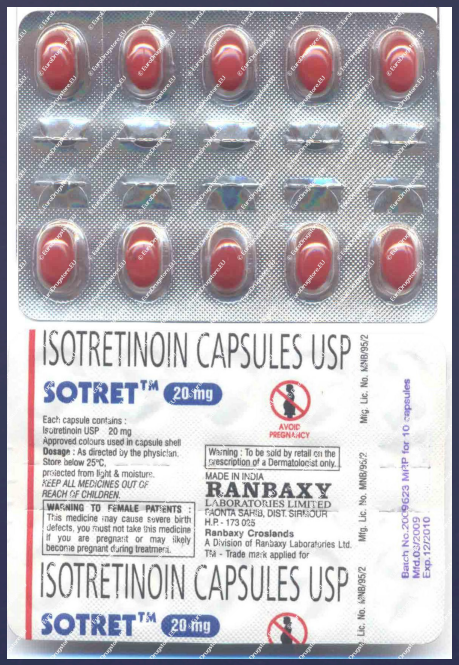
3q12.2
3q13.11
3q13.13
3q13.31
3q13.33
3q21.2
3q22.1
3q22.3
3q24
3q25.2
3q25.32
3q26.1
3q26.31
3q26.33
3q27.2
3q28

XPC

- Prenatal Diagnosis:
  - Amniocentesis- fetal cells are extracted from amniotic fluid (~20 mL), grown in a culture medium, and stained-->chromosomes are examined for abnormalities
  - Chorionic villus sampling (CVS)- chorionic villi cells are removed from the placenta and are sent to a genetics lab for analysis
- Cellular hypersensitivity to ultraviolet radiation and chromosomal breakage:
  - Xeroderma pigmentosum fibroblasts (cells that synthesizes the structural framework for tissues; in connective tissue) are stressed with different doses of UV radiation.
  - Chromosomal breakage is evaluated in at least 100-200 cells, with at least 2 replicates for each dose.
  - Cells from the patient are compared with those from the patient's parents.
  - Cells from unrelated healthy individuals are used as control.

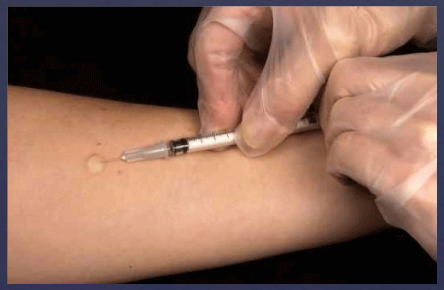
XP Detection Methods



- No cure for xeroderma pigmentosum
- Use sunscreen, protective clothing, hats and sunglasses to minimize amount of skin exposed to ultraviolet radiation
- Avoid ultraviolet radiation and sunlight by staying indoors and blocking the sun
- Use oral retinoids: "Oral retinoids have been shown to decrease the incidence of skin cancer in patients with xeroderma pigmentosum."
  - In an article in *The New England Journal of Medicine* published June 23, 1988, it is stated that a three-year controlled study was done on five xeroderma pigmentosum patients. "Patients were treated with isotretinoin (a retinoid) at a dosage of 2 mg per kilogram of body weight per day for two years… The patients had a total of 121 tumors (mean-24) in the two-year interval before treatment. During two years of treatment with isotretinoin, there were 25 tumors (mean-5) with an average reduction in skin cancers of 63%".

Treatments/Risks & Limits

- Laser surgery to remove moles and tumors, both benign and malignant
  - Mole removal does not use ultraviolet rays
  - Instead, carbon dioxide lasers are used
  - Lasers used for tumors can either kill the tumor (remove it completely) or shrink it
- Inject monthly or weekly doses for the defected protein(s) depending on the chromosome(s) and gene(s) affected.
  - The injection would be possible using a needle into the skin
  - This technique is similar to the protein injection done in the brains of mice.
  - Doing this will hopefully make symptoms less severe and will allow for DNA (even partial DNA) to be repaired.
- Use lotion such as shea butter and aloe gel to sooth the blistering because blisters hurt a lot.
  - Shea butter is made from fat from the nut of the African shea tree.
  - Aloe gel is also known as aloe vera.



Proposed Cure & Limits

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