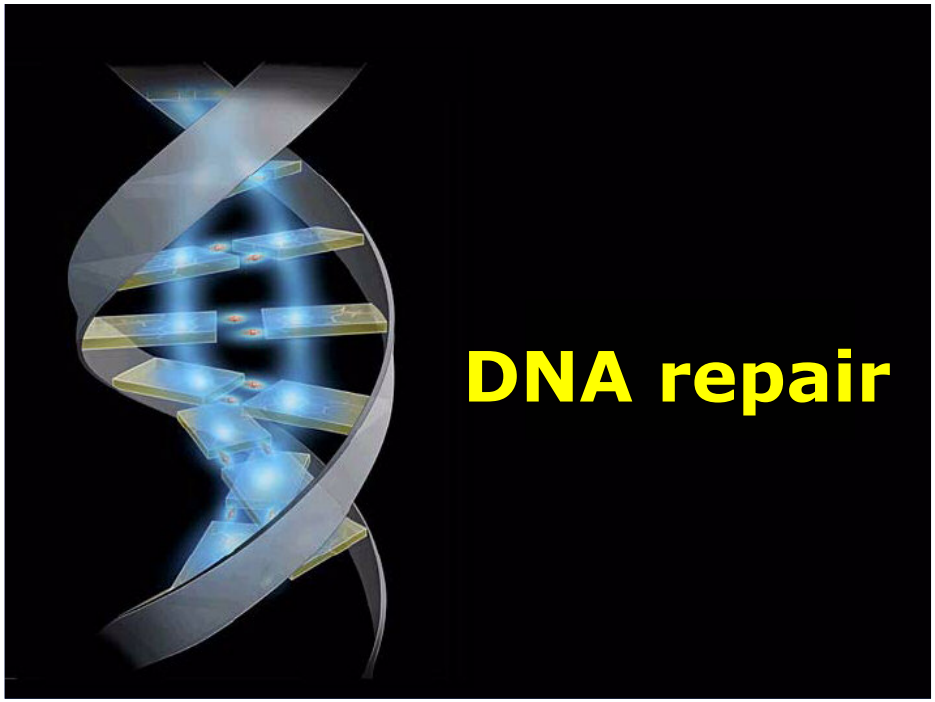


DNA repair

Classification of the mutation

- spontaneous vs. induced mutation
- gametic vs. somatic mutation
- lethal or conditional mutation

Spontaneous mutations

- are those that happen naturally
- no specific agents are associated with their occurence
- and they are generally assumed to be random changes in the nucleotide sequences of genes

Induced mutations

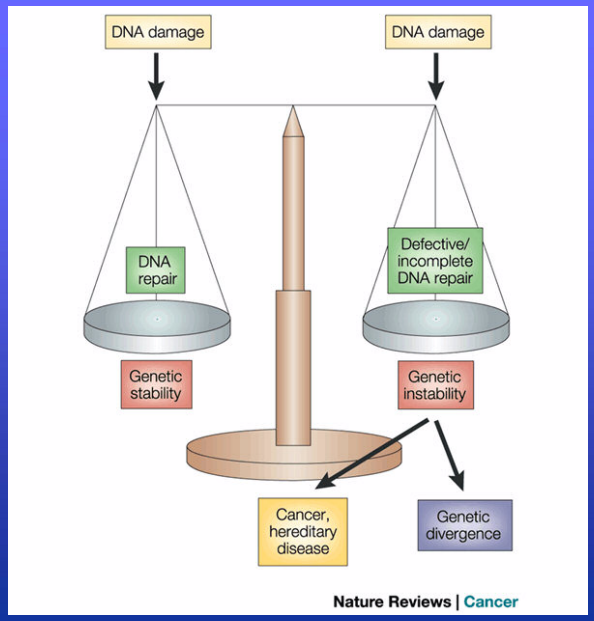
- those that result from the influence of any artificial factor
- various forms of radiation
- a wide spectrum of chemical agents
- biological agents (e.g. viruses)

Gametic vs. somatic mutations

- Mutation arising in somatic cells are not transmitted to future generations
- Mutations in gametes or gamete-forming tissue are of greater significance because they are transmitted to offspring as part of the germ line
- dominant
- recessive
- X-linked

Lethal vs. conditional mutations

- Mutation may interrupt a process that is essential to the survival of the organism
  - in this case, it is reffered to as a lethal mutation
- Conditional mutation is present in the genome of an organism, but it is expressed and can be detected only under certain conditions



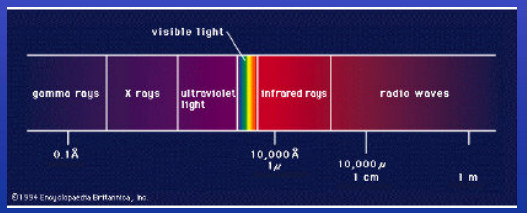
Induced mutagenesis

Can be caused by environmental agents that damage DNA:

- **UVlight**
- **X rays and -rays**
- **Chemical carcinogens e.g. cigarette smoke**

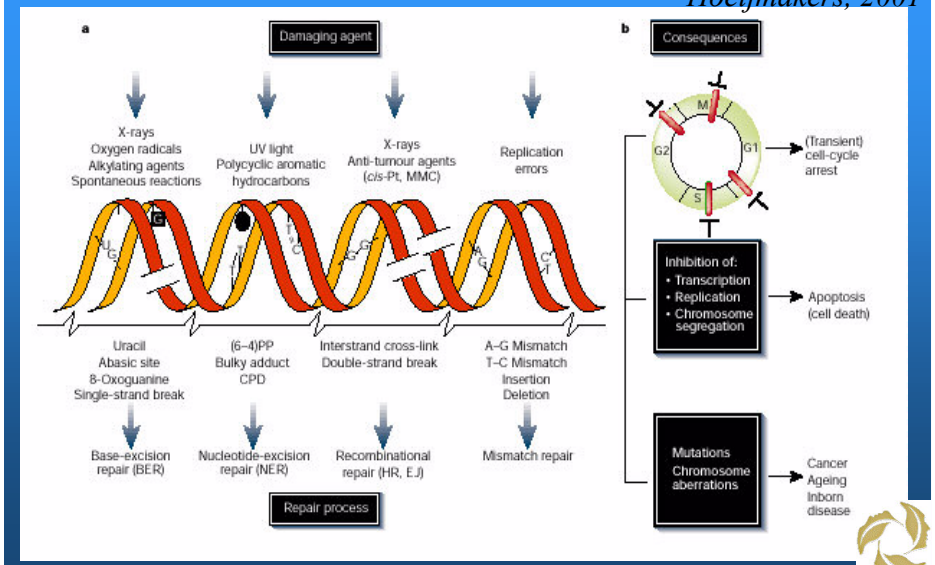
DNA damage can lead to mutations unless it is removed by DNA repair enzymes

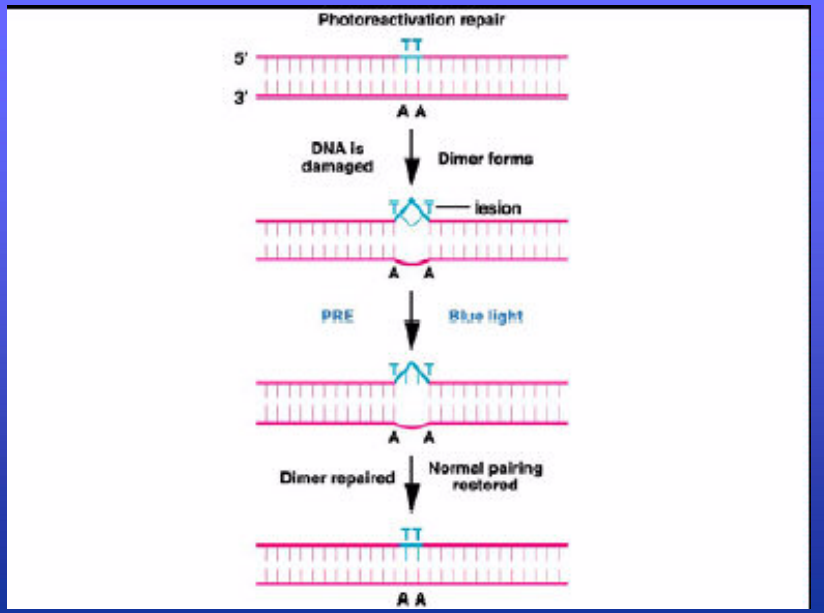
Unrepaired damage can have serious consequences



IMPORTANCE OF DNA REPAIR

Hoeijmakers, 2001





Photoactivation Repair in E. coli

- Exposing UV treated cells to blue light results in a reversal of the thymine dimer formation
- Enzyme, photoactivation repair enzyme (PRE)absorbs a photon of light (from blue light) and is able to cleave the bond forming the thymine dimer.
- Once bond is cleaved, DNAis back to normal

Excision Repair

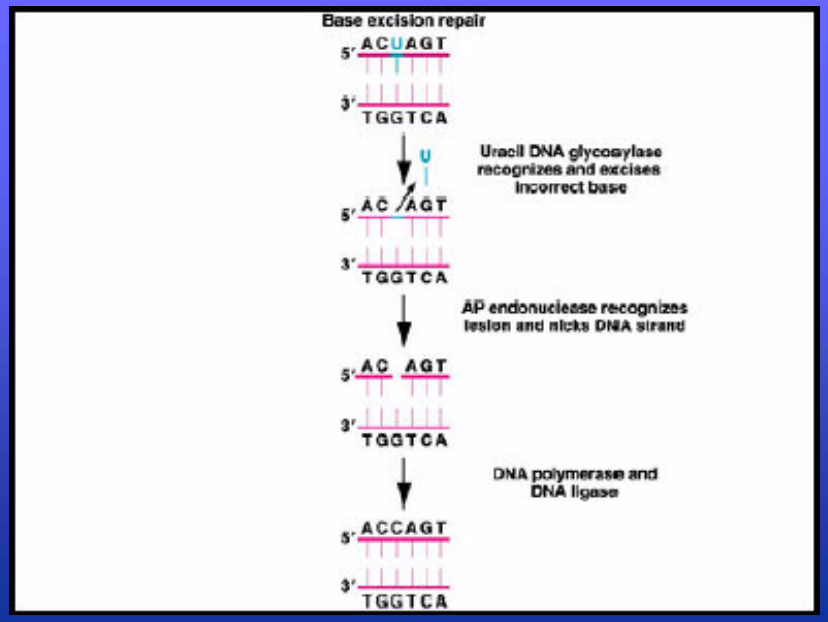
- Conserved throughout evolution, found in all prokaryotic and eukaryotic organisms
- Three step process:
  - 1. Error is recognized and enzymatically clipped out by a nuclease that cleaves the phosphodiester bonds (uvr gene products operate at this step)
  - 2. DNA Polymerase I fills in the gap by inserting the appropriate nucleotides
  - 3. DNA Ligase seals the gap

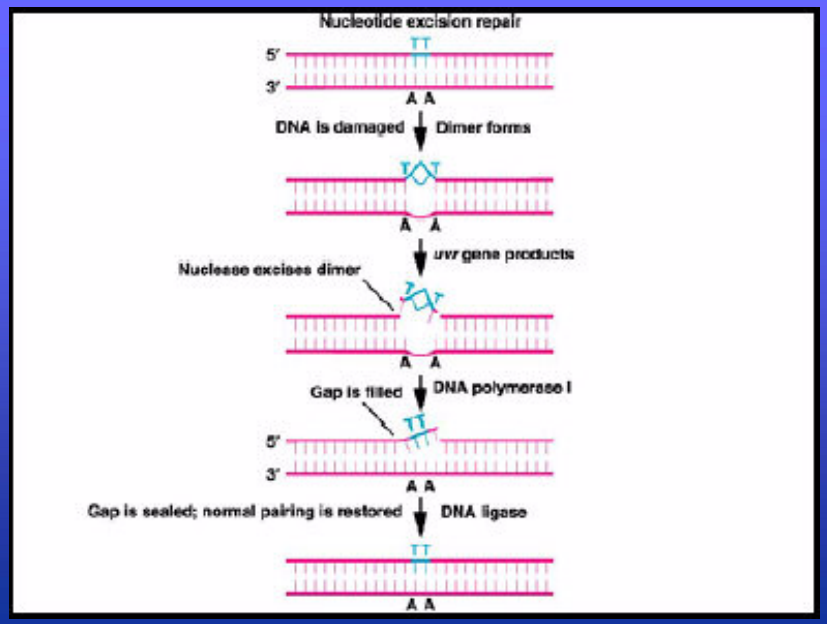
Excision Repair

• Two know types of excision repair

– Base excision repair (BER)
• corrects damage to nitrogenous bases created by the spontaneous hydrolysis of DNA bases as well asthe hydrolysis of DNA bases caused by agents that chemically alterthem

– Nucleotide excision repair (NER)
• Repairs "bulky" lesions in DNA that alteror distort the regular DNA doublehelix
• Group of genes (uvr) involved in recognizing and clipping out the lesions in the DNA
• Repair is completed by DNA pol I and DNA ligase





Proofreading and Mismatch Repair

• In bacterial systems, proofreading decreases the error rate in DNA replication by two orders of magnitude
– from 1 mismatch in every 105 nucleotide pairs to 1 in every 107 base pairs

• Mismatch repair is another mechanism by which mismatches can be fixed in the DNA strand

• In bacteria, mismatch repair is based onthe process of DNA Methylation, which labels one strand, providing a basis for the mismatch repair.

Post-Replication Repair

- Post-replication repair– Discovered in *E. coli* by Miroslav Radman
  - – Responds when damaged DNA escapes repair and the damage disrupts replication
  - – Rec A protein stimulates recombination between donor strand and new strand
  - – Creates gap in donor strand which can be repaired
  - – DNA Polymerase and DNA Ligase involved

Diseases in which DNA repair is damage

- **Xeroderma pigmentosum** (XP): Patients are hypersensitive to UV light; patients often develop malignancies of the skin.
- **Ataxia telangiectasia** (AT): Patients are sensitive to gamma irradiation; patients develop neurological and skin lesions.
- **Fanconi's anemia:** Patients demonstrate aplastic anemia, growth retardation, and congenital anomalies; related to a deficiency in repair of DNA cross-links.

Xeroderma Pigmentosum (XP) and DNA Repair Defects

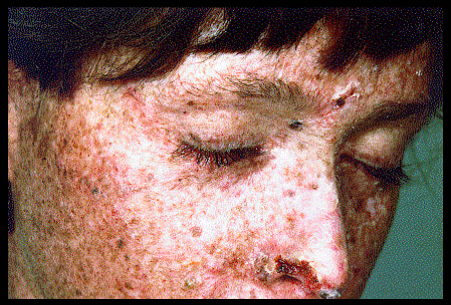
- **XP is an autosomal recessive disease associated with dry skin, freckling, corneal ulceration, and skin tumors**
- **Many patients die before age 30from metastases of malignant skin tumors**
- **One form of XP is produced by a defect in the human endonuclease that removes pyrimidine dimers**
- **Mutations in at least seven other genes involved in repairing UV-damaged DNA can cause XP**

DNA Repair and Clinical Syndromes: Increased Sensitivity; Chromosomal Instability and Increased Cancer Risk

Table 1 Human syndromes with defective genome maintenance

Syndrome	Affected maintenance mechanism	Main type of genome instability	Major cancer predisposition
Xeroderma pigmentosum	NER (± TCR)	Point mutations	UV-induced skin cancer
Cockayne syndrome	TCR	Point mutations	None*
Trichothiodystrophy	NER / TCR	Point mutations	None*
Ataxia telangiectasia (AT)	DSB response/repair	Chromosome aberrations	Lymphomas
AT-like disorder	DSB response/repair	Chromosome aberrations	Lymphomas
Nijmegen breakage syndrome	DSB response/repair	Chromosome aberrations	Lymphomas
BRCA 1/BRCA2	HR	Chromosome aberrations	Breast (ovarian) cancer
Werner syndrome	HR?/TLS?	Chromosome aberrations	Various cancers
Bloom syndrome	HR?	Chromosome aberrations (SCE↑)	Leukaemia, lymphoma, others

Xeroderma Pigmentosum (XP)

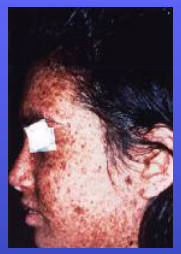


Symptoms include:

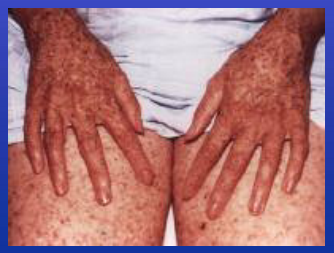
--- Extreme sensitivity to sunlight

--- Early onset of skin cancer

XP cases

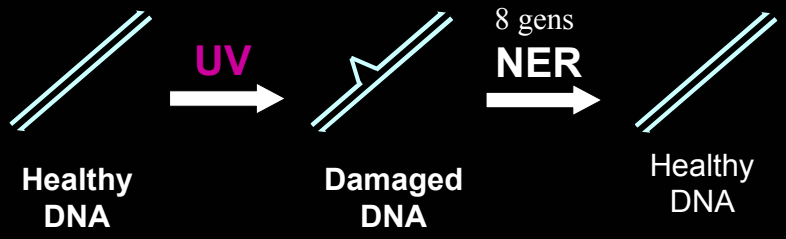


Sunlight-induced dermatologic abnormalities in a patient with xeroderma pigmentosum.



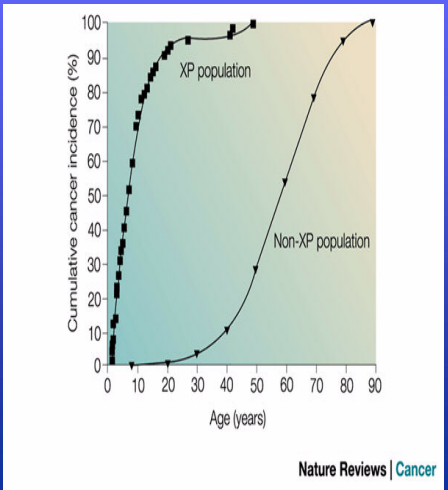
Typical skin manifestation of xeroderma pigmentosum with numerous areas of hypopigmentation and freckles (ie, solar lentigines) with different intensities of pigmentation.

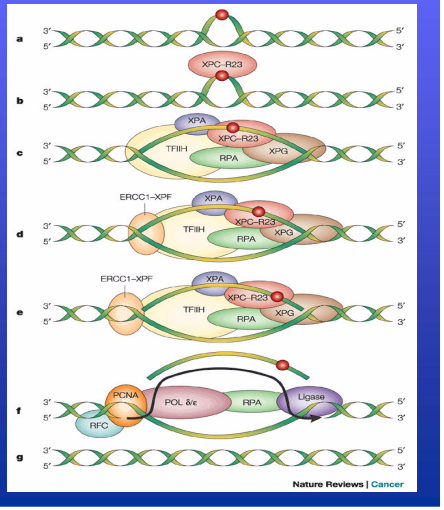
Why are XP patients sensitive to sunlight?



Why are XP patients sensitive to sunlight?

XP: Skin Cancer Incidence Rapid Secondary to NER Faulty Repair of UV-induced DNA Damage and Genetic NER Mutations





Molecular Genetics of Xeroderma Pigmentosum

Complementation Group	Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
A	XPA	*XPA*	9q22.3	DNA-repair protein complementing XP-A cells
B	XPB	*ERCC3*	2q21	TFIIH basal transcription factor complex helicase XPB subunit
C	XPC	*XPC*	3p25	DNA-repair protein complementing XP-C cells
D	XPD	*ERCC2*	19q13.2-q13.3	TFIIH basal transcription factor complex helicase subunit
E	XPE	*DDB2*	11p12-p11	DNA damage binding protein 2
F	XPF	*ERCC4*	16p13.3-p13.13	DNA-repair protein complementing XP-F cells
G	XPG	*ERCC5*	13q33	DNA-repair protein complementing XP-G cells
XP variant		*POLH*	6p21.1-p12	Error prone DNA photoproduct bypass polymerase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

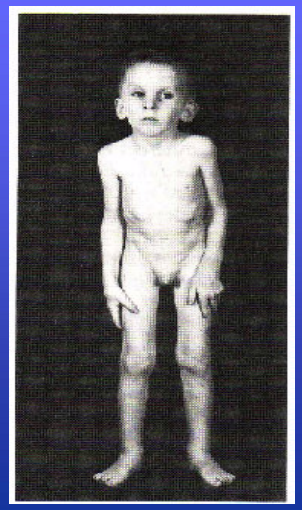
Fanconi anemia (FA)

- Fanconi anemia (FA) is an autosomal recessive disease characterized by progressive bone marrow failure due to defective stem cell function.
- FA cells are hypersensitive to DNA cross-linking agents such as mitomycin C (MMC) resulting in cytogenetic aberrations, G2-M cell cycle arrest, apoptosis, and cell death.
- Seven complementation groups (termed FANCA-G) are identified. Group A (FANCA) mutations are the most prevalent (70%).
- There are at least seven FA genes: A, C, D2, E, F, G and BRCA2
- The function of the FANC genes are still unclear. Involvement in DNA repair system is suggested.

Cockayne's Syndrome

- Occurrence: 1 per million population
- Sensitivity: ultraviolet radiation (sunlight)
- Disorder: arrested development, mental retardation, dwarfism, deafness, optic atrophy, intracranial calcifications; (no increased risk of cancer)
- Biochemical: defect in NER
- Genetic: autosomal recessive, five genes (A, B and XPB, D & G)

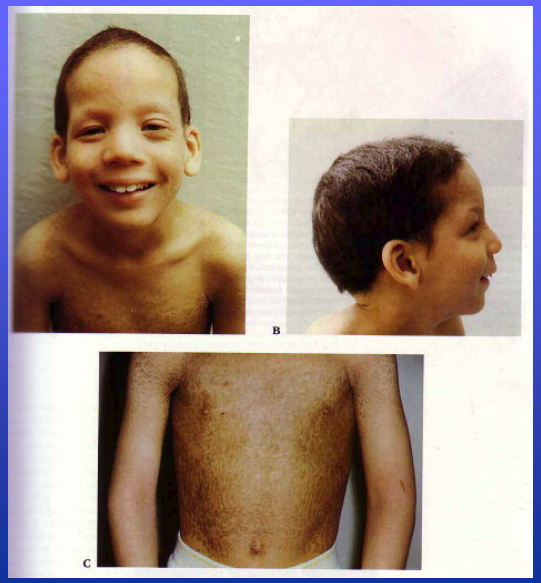
Cockayne's Syndrome



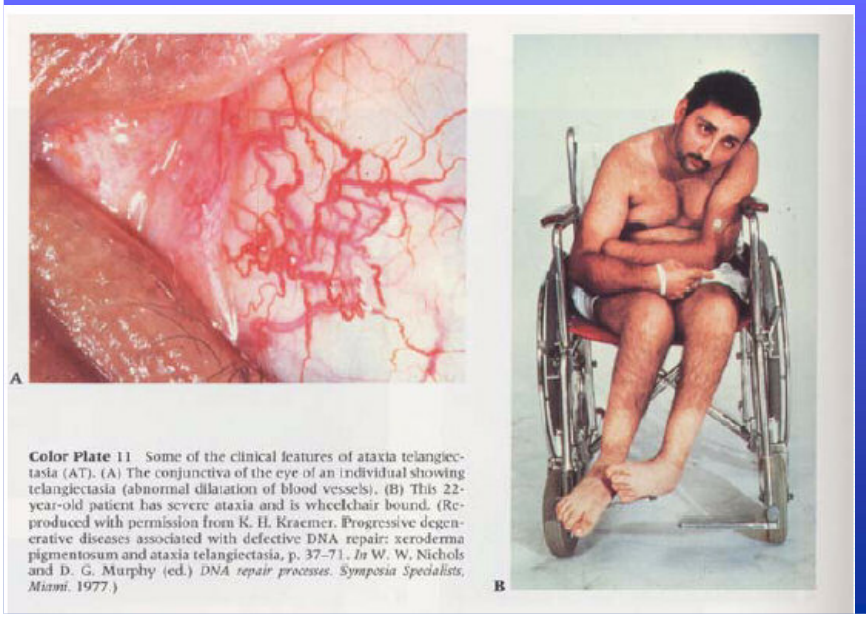
Trichothiodystrophy

- Occurrence: 1-2 per million population
- Sensitivity: ultraviolet radiation (sunlight) in subset of patients
- Disorder: sulfur deficient brittle hair, mental and growth retardation, peculiar face with receding chin, ichthyosis; (no increased cancer risk)
- Biochemical: defect in NER
- Genetic: autosomal recessive, three genes (TTDA, XPB, XPD)

Trichothiodystrophy



Ataxia telangiectasia (AT):



Color Plate 11 Some of the clinical features of ataxia telangiectasia (AT). (A) The conjunctiva of the eye of an individual showing telangiectasia (abnormal dilatation of blood vessels). (B) This 22-year-old patient has severe ataxia and is wheelchair bound. (Reproduced with permission from K. H. Kraemer. Progressive degenerative diseases associated with defective DNA repair: xeroderma pigmentosum and ataxia telangiectasia, p. 37–71. *In* W. W. Nichols and D. G. Murphy (ed.) *DNA repair processes. Symposia Specialists, Miami.* 1977.)