Severity of a Mutation Depends on Several Factors

1) Cell Lineage

2) Timing during development

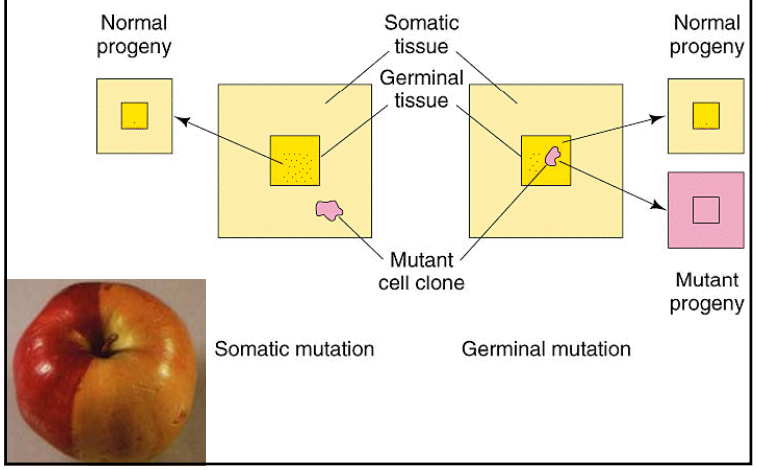
3) Dominance relationship of the mutation

4) Chromosome location (autosome vs X chromosome)

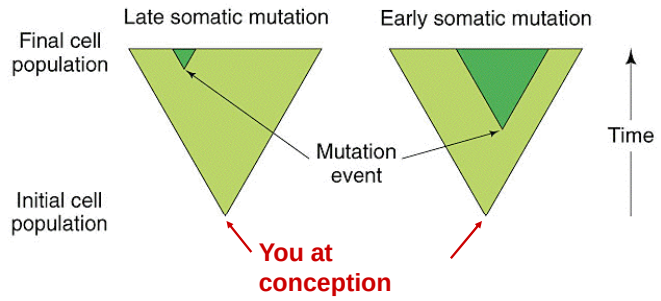
5) Position of mutation (third vs second base of a codon, intron vs exon, catalytic site in an enzyme).

6) Kind of gene mutated (structural, enzyme, regulatory)
Imagine the severity of a mutation in a Transcription Factor, splicing protein, polymerase, genes involved in regulating cell division....

1) Severity depends on cell lineage.



2) Severity depends on timing during development



3) Dominant (gain of function mutation) vs. recessive (loss of function mutation).

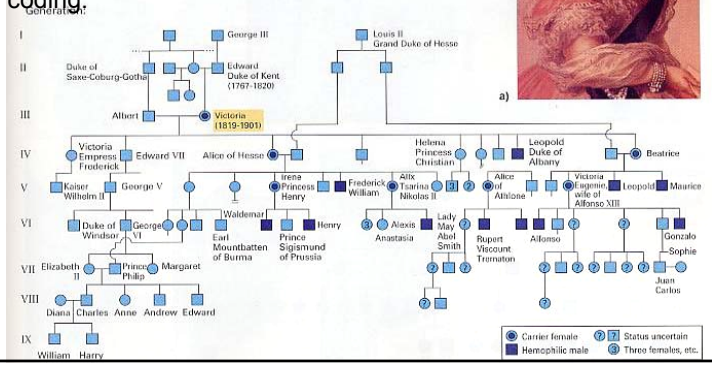
Dominant mutations will be expressed immediately and if severe, may be lost quickly.

Recessive mutations will not be expressed, but will be retained in the populations.

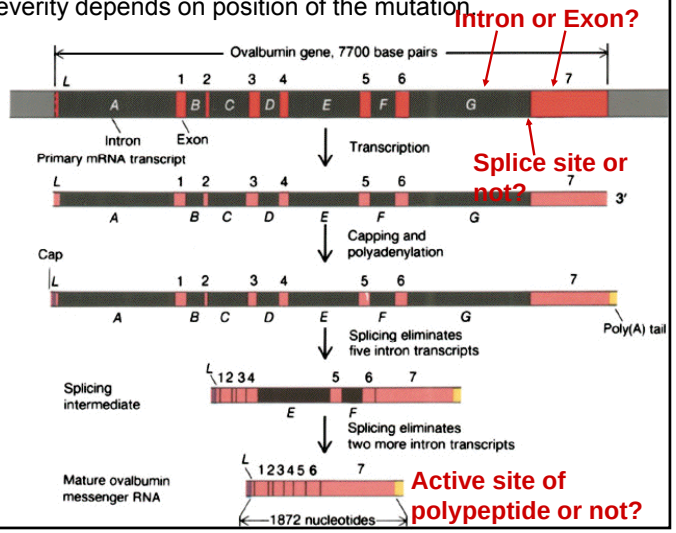
Each of you carries approximately 4 lethal equivalents!!!

(a) Painting of Queen Victoria as a young woman. (b) Pedigree of Queen Victoria (III.2) and her descendants, showing the inheritance of hemophilia. [Refer to Figure 2.19, p. 38, for an explanation of symbols used in pedigrees. In the pedigree shown here, in many cases the marriage partner has been omitted as a shorthand way to save space. Those marriage partners were normal with respect to the trait.] Since Queen Victoria was heterozygous for the sex-linked recessive hemophilia allele with no cases in her ancestors, the trait may have arisen as a mutation in one of her parents' germ cells (the cells that give rise to the gametes).

4) Chromosomal location, autosome vs sex chromosome. Coding vs non-coding.



5) Severity depends on position of the mutation

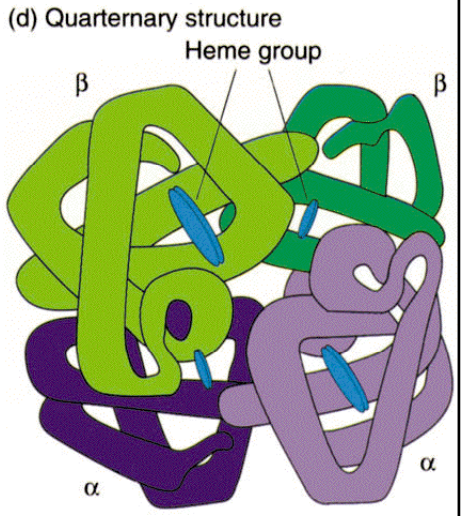


Which is more likely to cause a problem, a mutation in the third or second position ?

Second letter

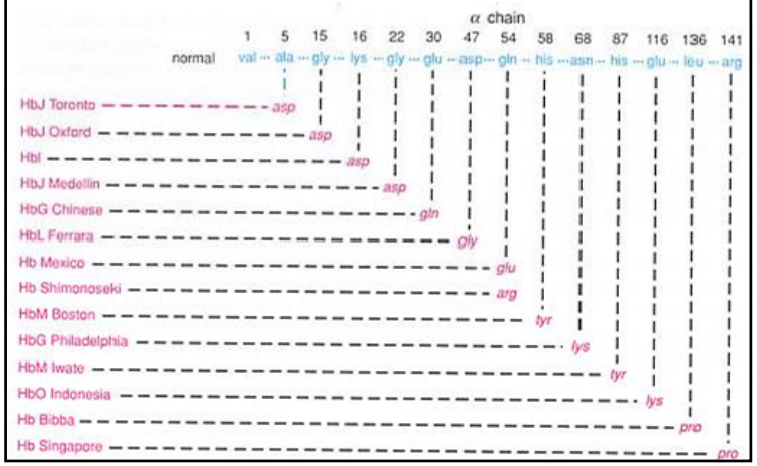
First letter	U	C	A	G	Third letter
U	UUU Phe, UUC Phe, UUA Leu, UUG Leu	UCU Ser, UCC Ser, UCA Ser, UCG Ser	UAU Tyr, UAC Tyr, UAA Stop, UAG Stop	UGU Cys, UGC Cys, UGA Stop, UGG Trp	U C A G
C	CUU Leu, CUC Leu, CUA Leu, CUG Leu	CCU Pro, CCC Pro, CCA Pro, CCG Pro	CAU His, CAC His, CAA Gln, CAG Gln	CGU Arg, CGC Arg, CGA Arg, CGG Arg	U C A G
A	AUU Ile, AUC Ile, AUA Ile, AUG Met	ACU Thr, ACC Thr, ACA Thr, ACG Thr	AAU Asn, AAC Asn, AAA Lys, AAG Lys	AGU Ser, AGC Ser, AGA Arg, AGG Arg	U C A G
G	GUU Val, GUC Val, GUA Val, GUG Val	GCU Ala, GCC Ala, GCA Ala, GCG Ala	GAU Asp, GAC Asp, GAA Glu, GAG Glu	GGU Gly, GGC Gly, GGA Gly, GGG Gly	U C A G

Critical site or not?



Mutations known to affect α Hemoglobin

Why are there no mutants known for aa 2, 3, 4, 6, 7, 8...?



Mutations Rates Vary

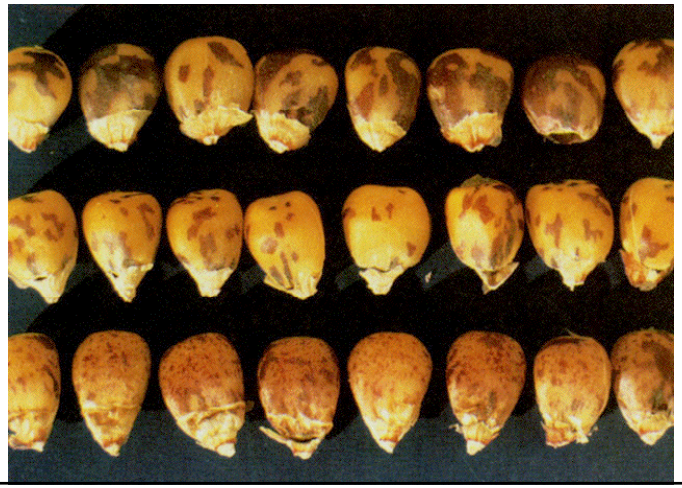
Why is R gene (red pigment) mutation rate so high?

Table 7-1 Foreward Mutation Frequencies at Some Specific Corn Loci

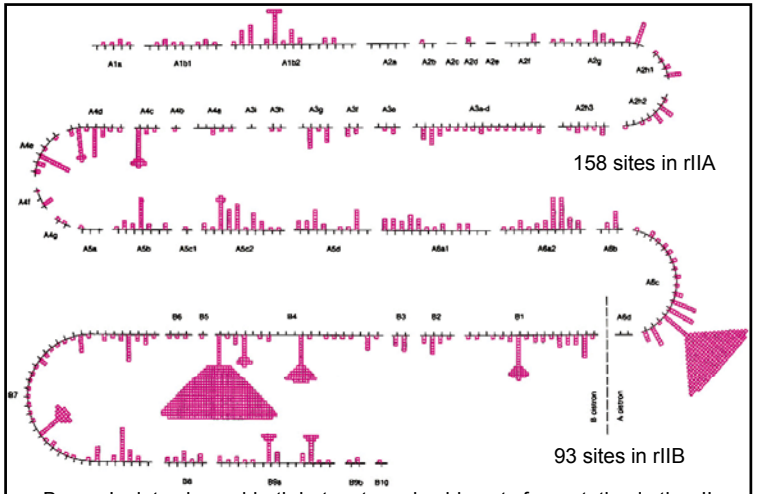
Gene	Number of gametes tested	Number of mutations	Average number of mutations per million gametes
$R \rightarrow r$	554,786	273	492.0
$I \rightarrow i$	265,391	28	106.0
$Pr \rightarrow pr$	647,102	7	11.0
$Su \rightarrow su$	1,678,736	4	2.4
$Y \rightarrow y$	1,745,280	4	2.2
$Sh \rightarrow sh$	2,469,285	3	1.2
$Wx \rightarrow wx$	1,503,744	0	0.0

Ac Activator in Maize

Barbara McClintock Noble Prize 1983



Mutation for Mendel's Round vs Wrinkled seeds appears to be caused by a transposon!!

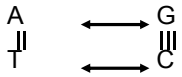


Benzer's data showed both hotspots and cold spots for mutation in the rII genes of T4 phage. There are specific sequences that are highly mutable!

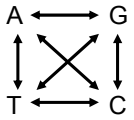
Categories of Mutations

At the DNA level

1) Transitions – Purine to Purine or Pyrimidine to Pyrimidine



2) Transversions – Purines ⟷ Pyrimidines



3) Deletions and Additions

Categories of Mutations

At the Protein Level

Silent	AGG to CGG – both are Arginine
Neutral	AAA to AGA – Lys and Arg are both basic amino acids
Missense	CUU to CGU – Leu (non-polar) to Arg (basic)
Nonsense	CAG to UAG – Glutamine to Stop
Frameshifts	

What is the genetic basis of some heritable human diseases that have been mentioned in class?

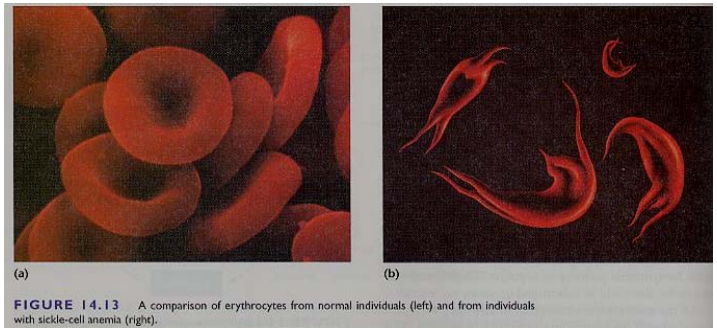


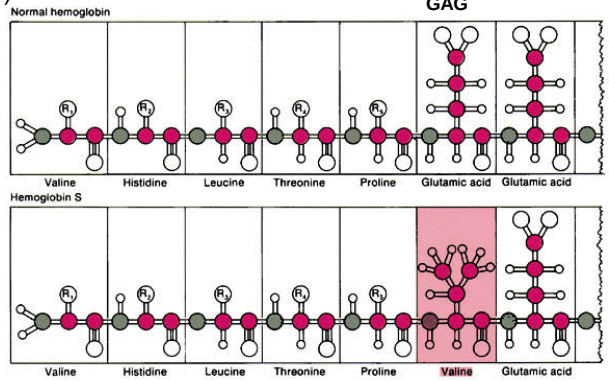
FIGURE 14.13 A comparison of erythrocytes from normal individuals (left) and from individuals with sickle-cell anemia (right).

Sickle Cell Anemia

β hemoglobin gene (Chromosome 11)

GAA

GAG



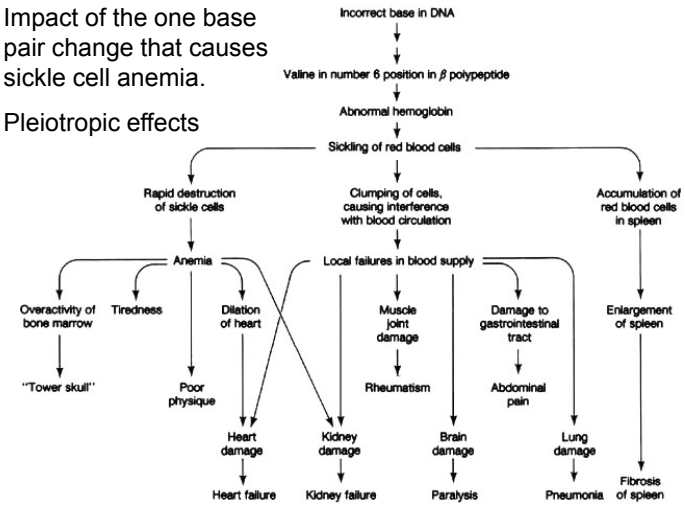
GUA

GUG

Transversion, Missenese Mutation

Impact of the one base pair change that causes sickle cell anemia.

Pleiotropic effects



I^A A type

Add acetylgalactosamine

I^O O type

Add zippo

Differs from I^A by frameshift

I^B B type

Add Galactose

Differs from I^A by 4 bp

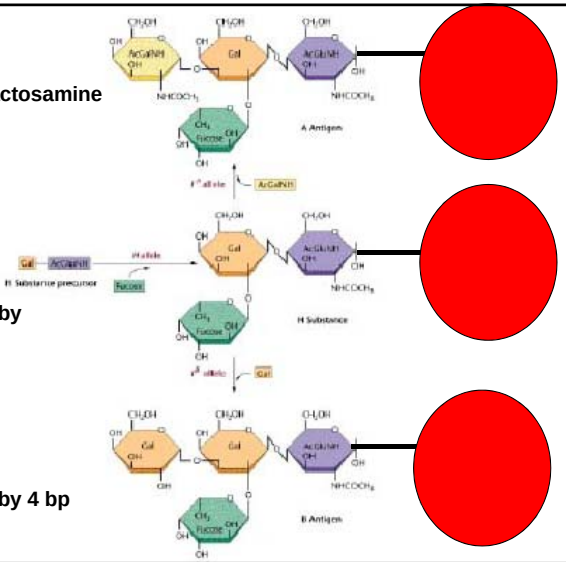


Fig. 4.2

A very early checkup

Genetic screening of embryos helps ease parents' fears, but is it a step toward 'designer babies?'

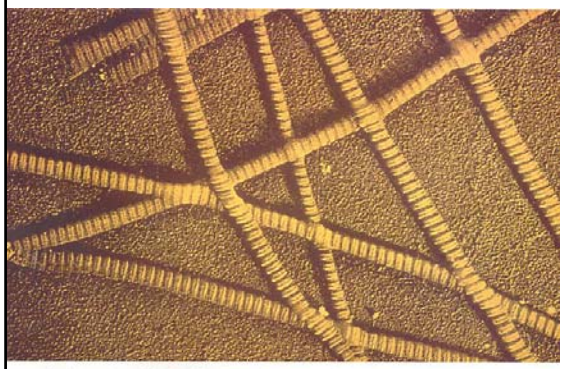
Designer Babies????

Family with a history of Duchenne Muscular Dystrophy (progressive muscle degeneration results in death as adults).

Milder form Becker MD Cause?

DMD: frameshift or nonsense mutation in gene for dystrophin; non-functional

BMD: base substitutions



An electron micrograph of collagen fibers, the most abundant protein found in vertebrates.

Osteoporosis: base substitution in collegen gene yields missense mutation serine replaces glycine creates weaker bonds

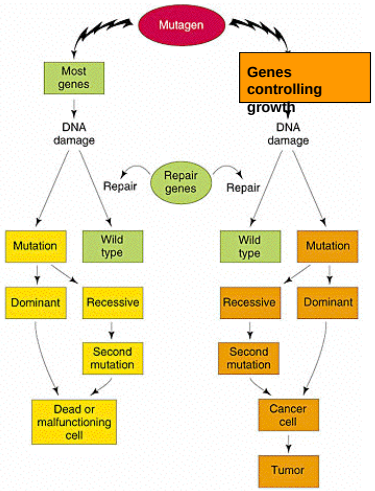
Impact of mutation depends on the type of gene mutated.

Essential genes vs. non-essential genes.

e.g. DNA polymerase (lethal) vs. eye color pigment.

Many “less” extreme cases!

Special case of genes regulating cell growth.

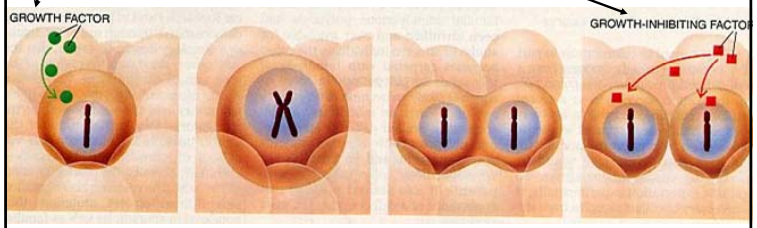


Two Categories of Cancer Genes

Oncogenes and Tumor Suppressor Genes

Oncogenes are dominant and part of growth stimulatory pathways

Tumor suppressors are recessive and part of growth inhibitory pathways.



History of Oncogenes

Peyton Rous 1910 discovered a virus that induced a tumor of the connective tissue (sarcoma) in chickens.

Virus carried v-src gene (protein kinase that phosphorylases tyrosine on certain targets). Signaling system.

Where did the v-src come from?

Stolen from the host (c-src).

Why?

If you were a virus and “wanted” to spread rapidly, residing in rapidly growing cells (cancer cells) would be ideal!!

Viruses with v-src have a selective advantage (Natural Selection from the viral perspective).

What is the function of proto-oncogenes?

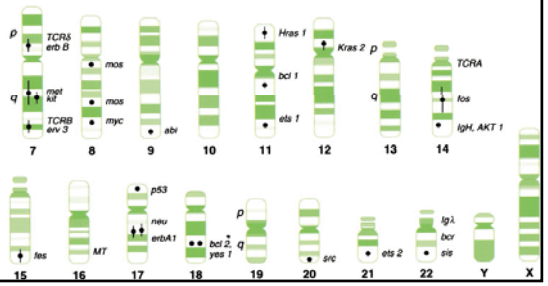
Transcription factors, parts of signaling pathways, growth factors.

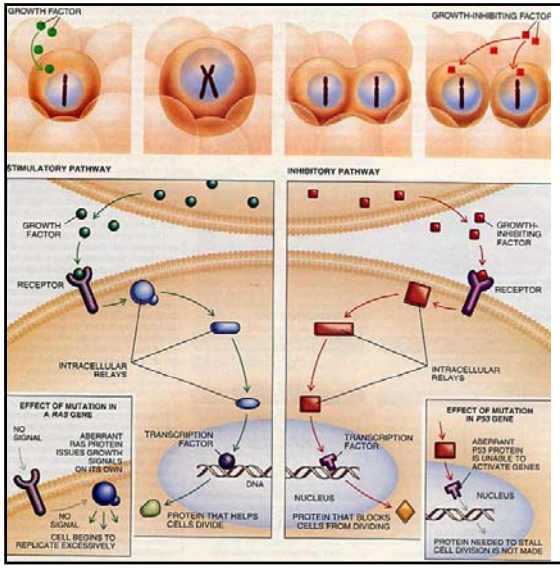
How many proto-oncogenes do we have?

Lots!!

What happen to Peyton Rous?

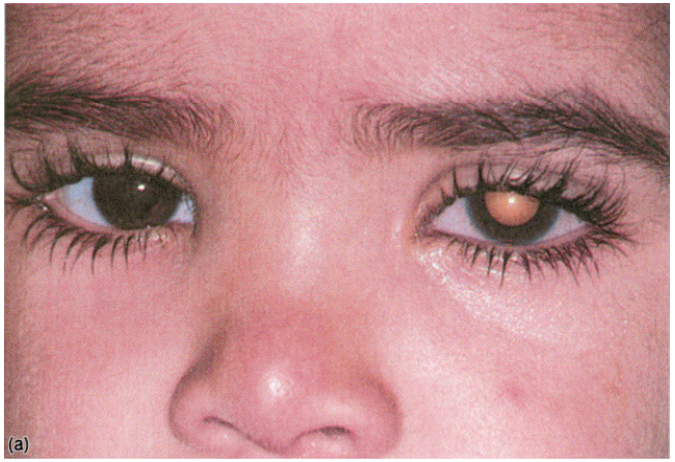
Nobel Prize 56 years later in 1966.

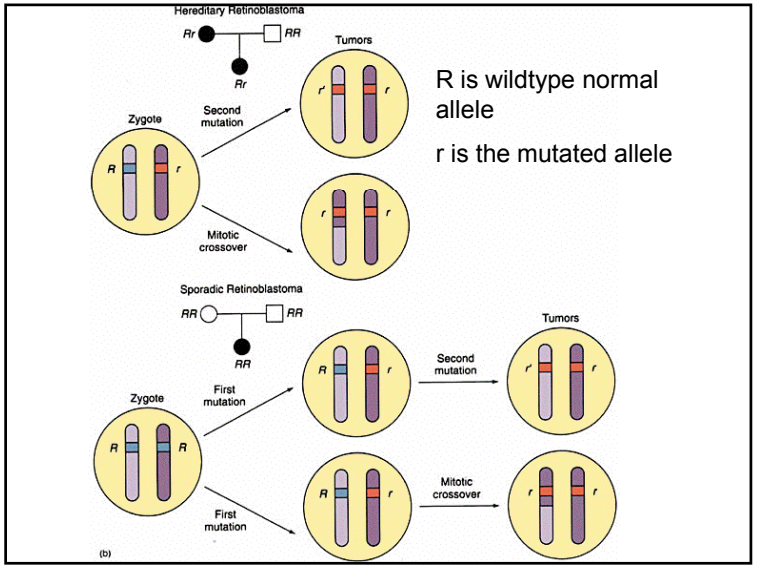




Can you see why Oncogenes would be dominant and Tumor suppressor genes recessive?

Tumor Suppressors: Potentially “heritable” (predisposition) cancers; Example of Retinoblastima



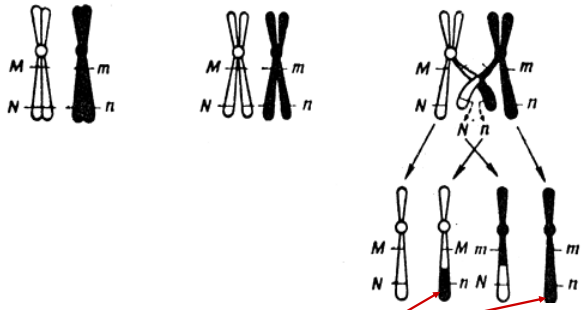


R is wildtype normal allele

r is the mutated allele

Mitotic Recombination

G2 stage of the cell cycle



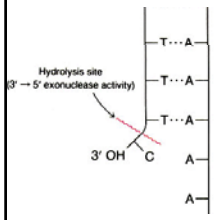
If ***n*** was a Tumor Suppressor mutant allele in the heterozygous individual, and the daughter cell received these 2 chromatids during mitosis, it would be cancerous!

With mutagenic agents floating around, how do we survive?

1) Avoid mistakes in the first place.

A. Good proofreading: during

DNApol III mismatches	without proofreading	$1/10^5$
	with proofreading	$1/10^7$
mismatches		

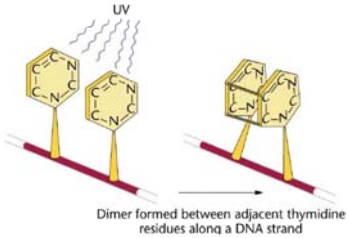


B. Various enzymes that inactivate potential mutagens. Superoxide dismutase

2) Several repair mechanisms that recognize errors caused by mutagenic agents (UV or chemical) and fix them.

2) Detect and Reverse Mutation: **Photo Reactivation Repair**

using Photo Reactivation



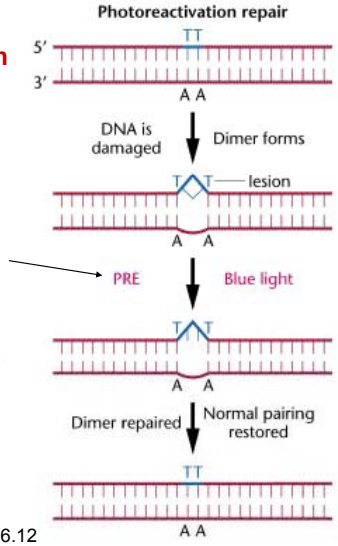


Fig. 16.12

3) Detect and remove base: **Base Excision Repair**

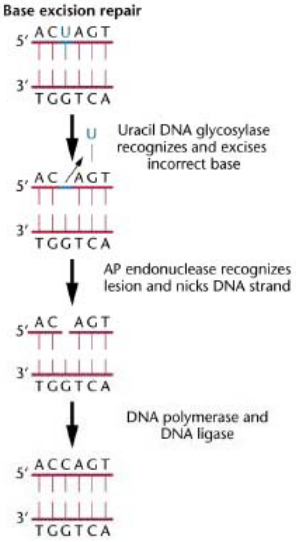


Fig. 16.13

4) Detect and remove nucleotides:

Nucleotide Excision Repair

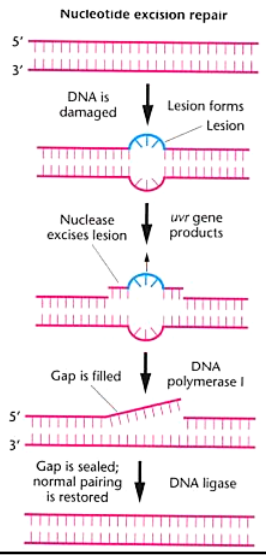


Fig. 16.14

Genes for Recognizing and cutting 12 base segment

uvrA (ultraviolet repair),

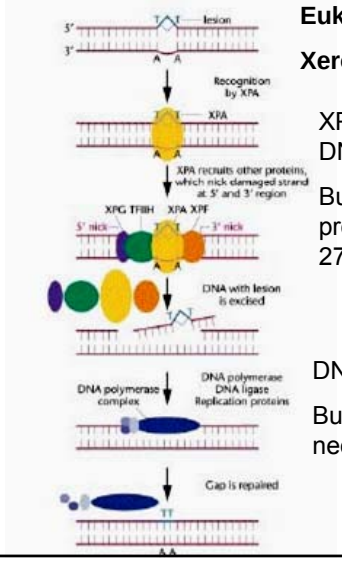
uvrB, uvrC

Genes for Repair

Helicase

DNA pol I

DNA ligase



Eukaryotes

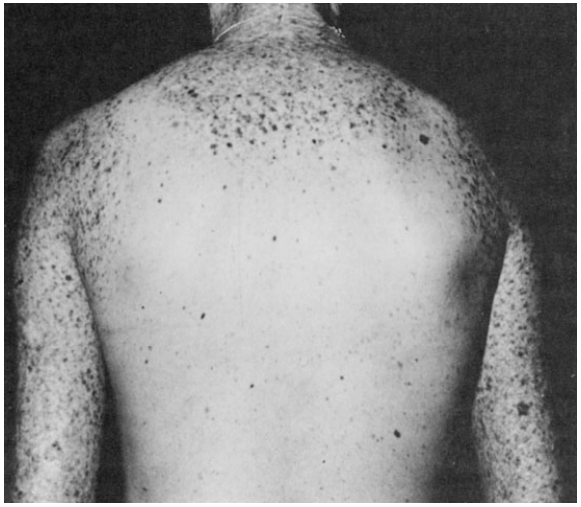
Xeroderma pimentosum

XPA binds to damaged DNA

Bunches (16) of other proteins needed to excise 27-29 base segment

DNA repair

Bunches (9) of proteins needed for repair



THE END!!!

Study hard and have a nice holiday break!