Genetics of Cancer

Lecture 35

Tumor Suppressors, DNA Damage & Mutations

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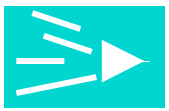
Based on a lecture by Prof. Leona Samson

Normal Cell → Metastatic Cancer: Many Changes Necessary

"Go!"
Growth Signal Independent

"Don't Stop"
Resist anti-growth signals



"Hurry Up!"
Resist signals to wait for repairs

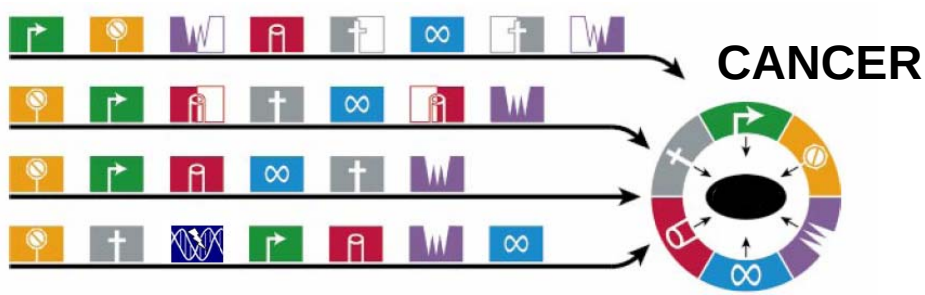
"Don't Die"
Resist Apoptosis

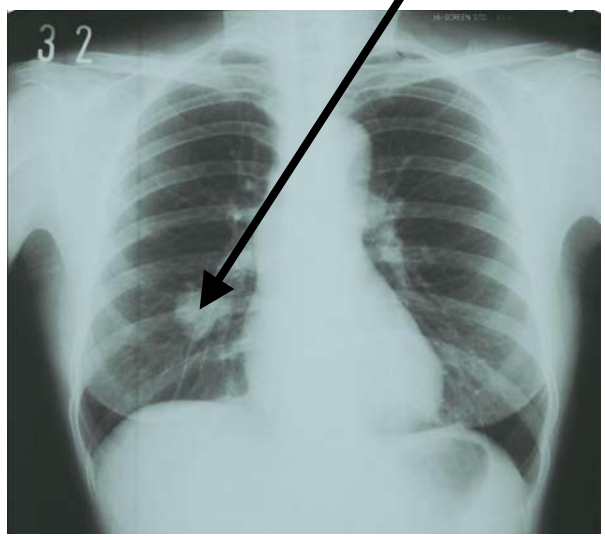
"Keep Going"
Be Immortal

"Feed Me"
Recruit & Sustain Blood Flow

"Take Over"
Escape/Invade = Metastasize

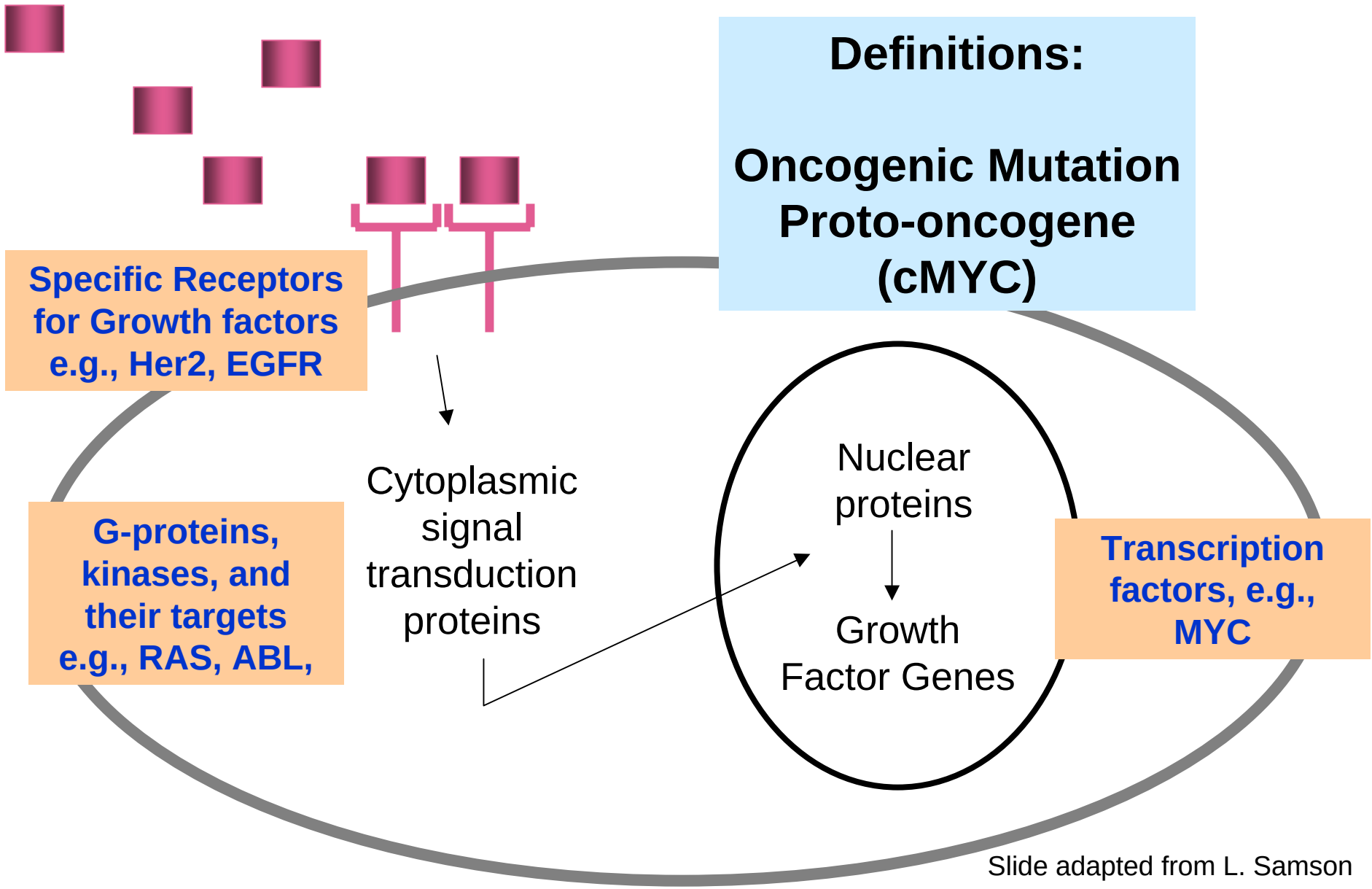
"Mutate!"





Concept & parts of figure from Hanahan and Weinberg

Signal Transduction and Growth Regulation



Slide adapted from L. Samson

Take-Home Messages

- RTK→RAS→RAF→MEK→MAPK→TF→“Go!”
- Cancer is a disease of over-prolif; it’s advantageous to cancer cells to trick cells into “Go!”
- Cancer cells need many new traits, therefore multiple mutations (proliferation is one such trait)
- Many cancers experience a high mutation rate, so its hard to know which mutations matter to cancer
- Most carcinogenic mutations occur in somatic cells, but they can also arise in germline or during development

Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes

gene that makes a cell cancerous

dominant gain-of-function mutations

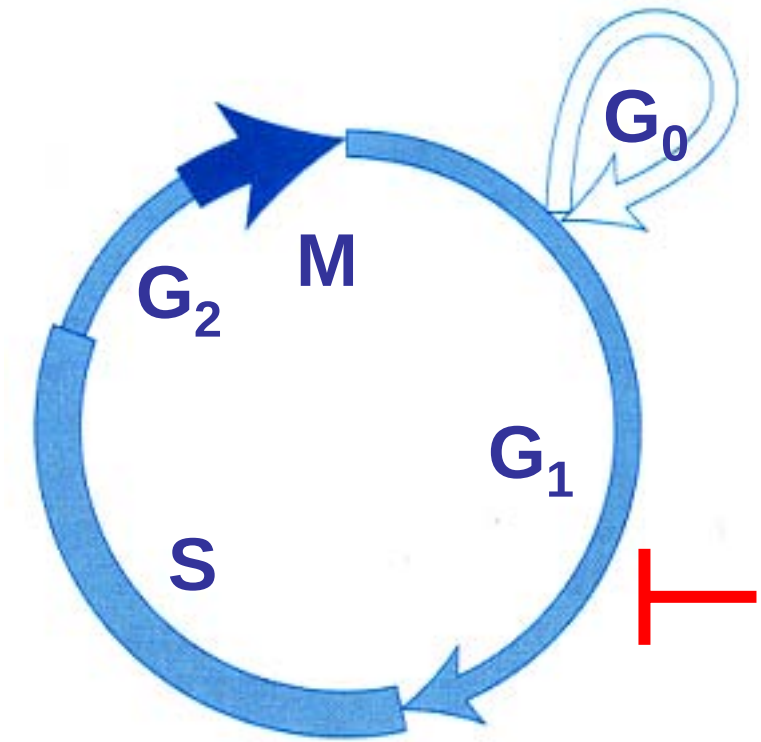
Tumor suppressor genes

genes that normally restrain growth

recessive, loss-of-function mutations

Example of a Tumor Suppressor Gene:

RB - Normally this protein inhibits proliferation
Loss of RB promotes cell division



Definitions:

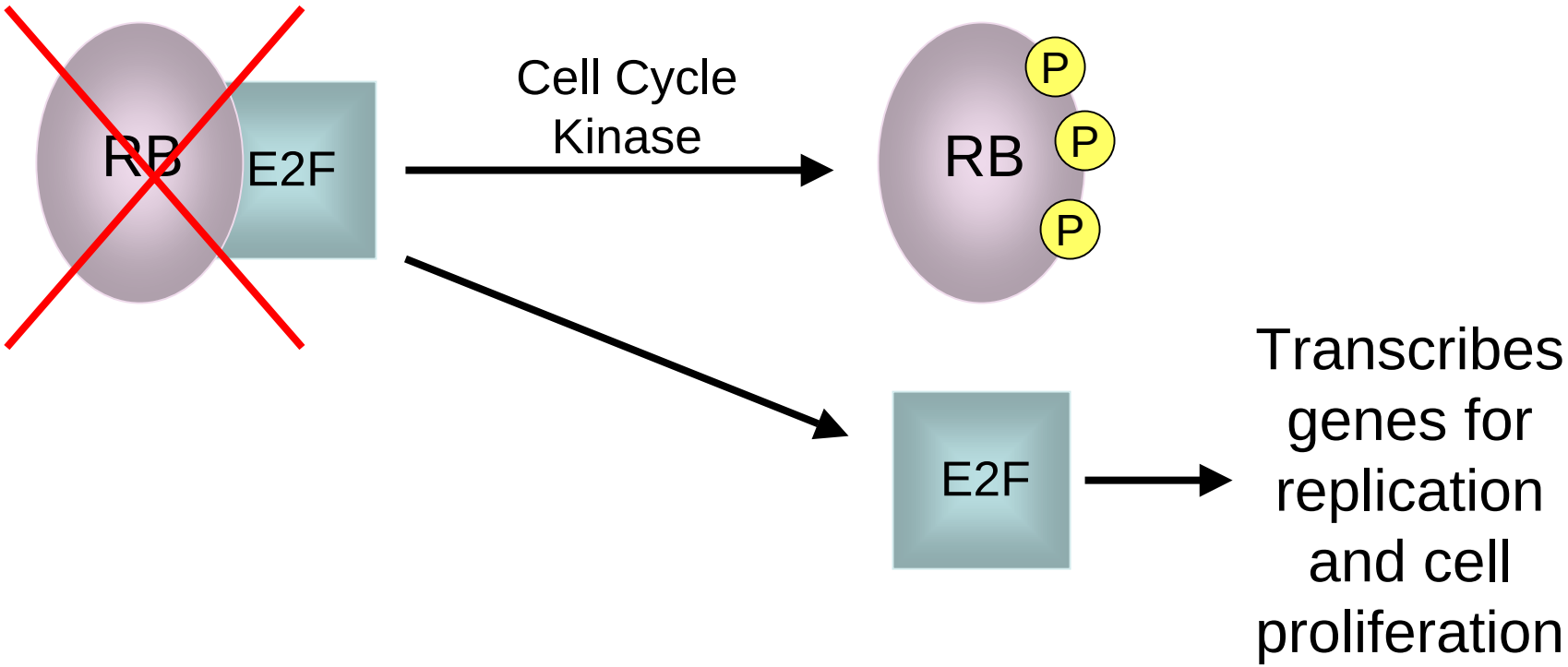
Retinoblastoma (RB)
Restriction Point

RB controls the Restriction Point

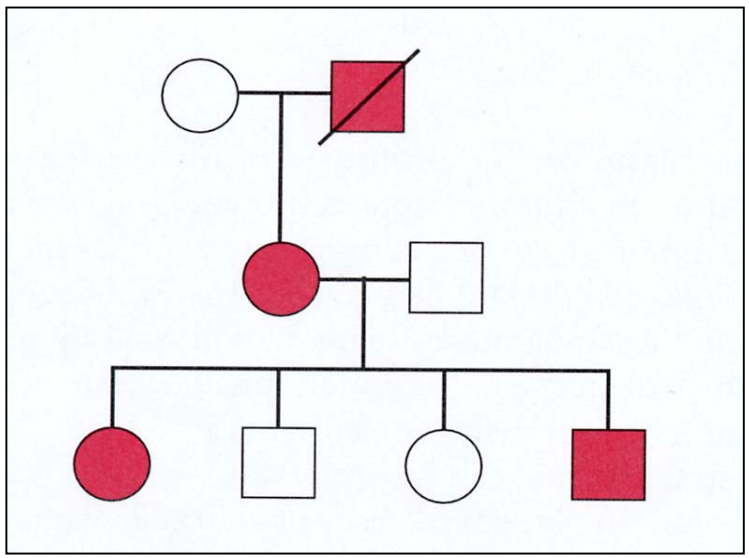
Slide from L. Samson

Phosphorylation of RB at the appropriate time in G1 allows release of the E2F Transcription Factor

"Go!"



The Retinoblastoma disease behaves as an autosomal **dominant** trait



- In order to lose cell cycle control MUST lose function of both alleles

- But, for Mendelian inheritance of RB, children need only inherit only one non-functional allele

- To explain this, the “TWO HIT” hypothesis was proposed

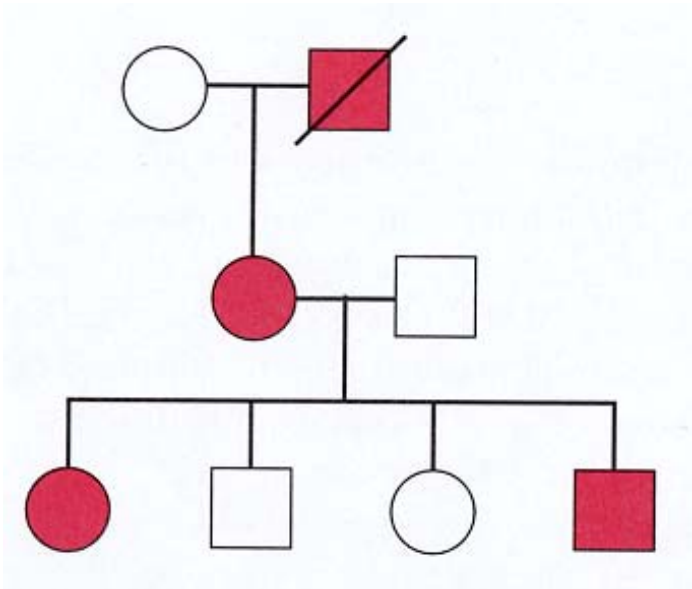
- During development of the retina a second mutation is almost certain to occur

- RB is one of the very few cancers that seems to require defects in only one gene (but in both alleles)

Slide from L. Samson

Two ways to get retinal tumors due to loss of RB function

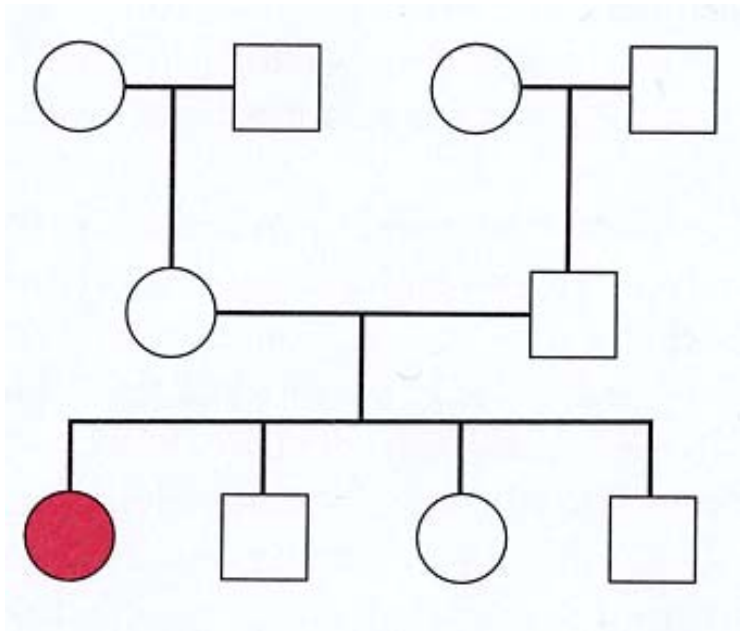
Mendelian



Germline Mutation + Somatic Mutation

Bilateral
Early Onset

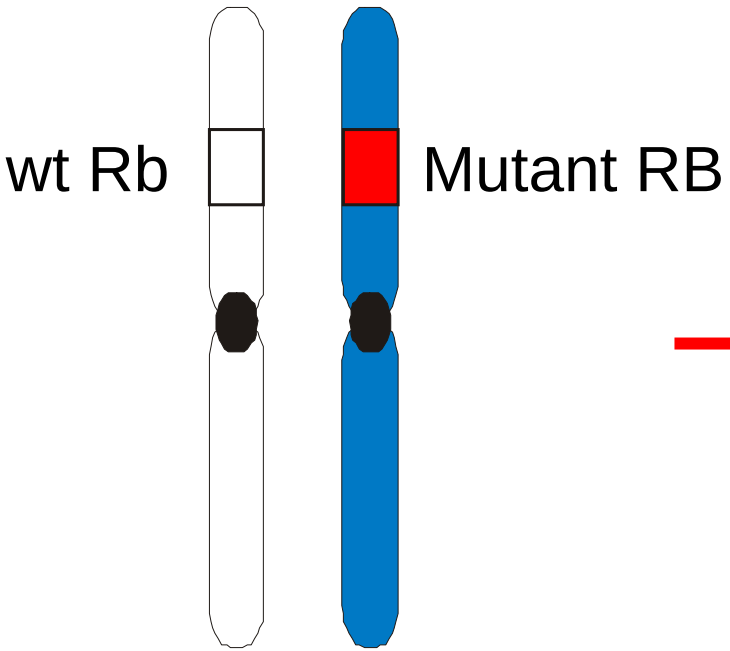
Sporadic



Somatic Mutation + Somatic Mutation

Single Tumor
Unilateral
Later Onset

How is the second RB allele rendered non-functional?



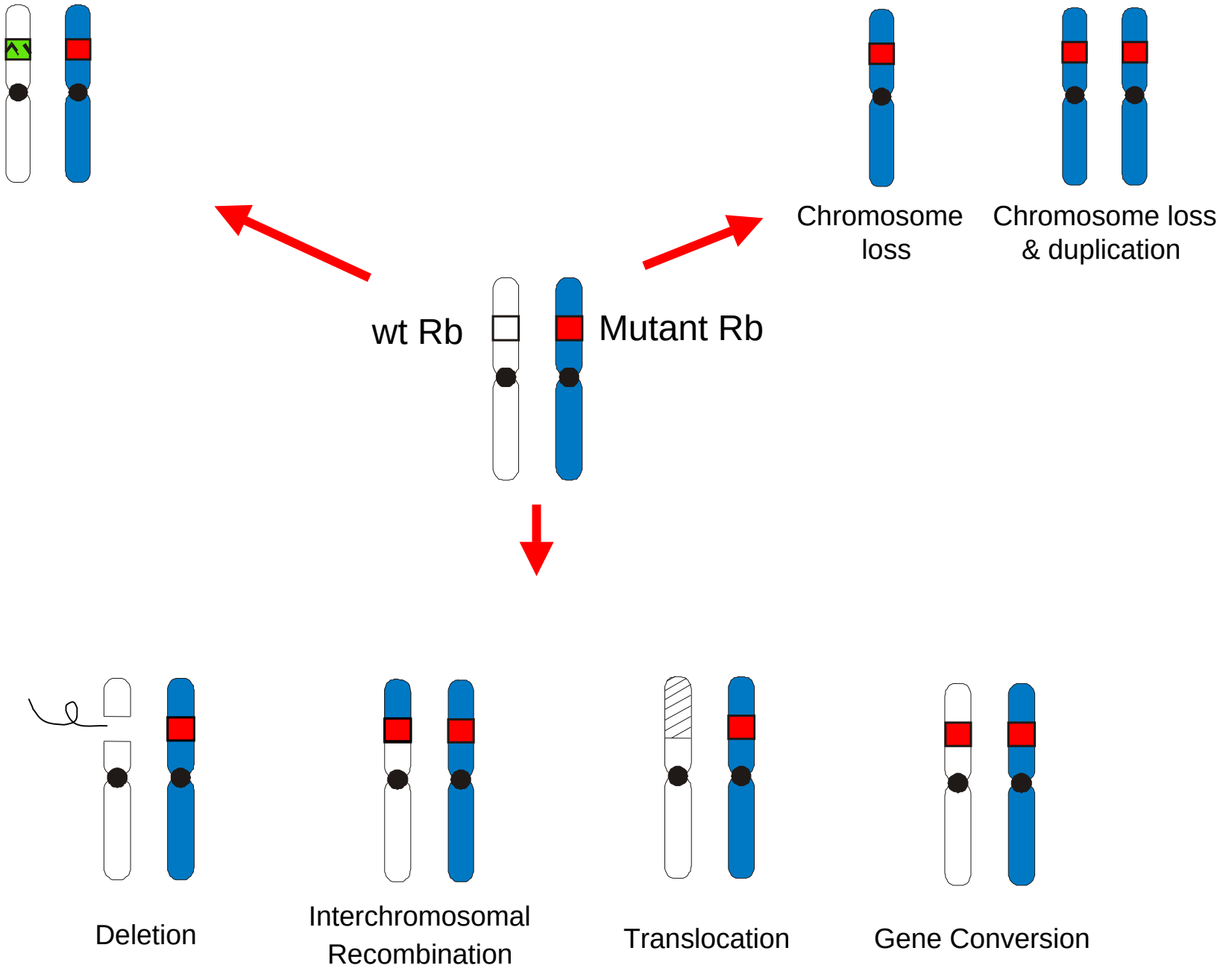
Heterozygous for RB mutation

Loss of Heterozygosity

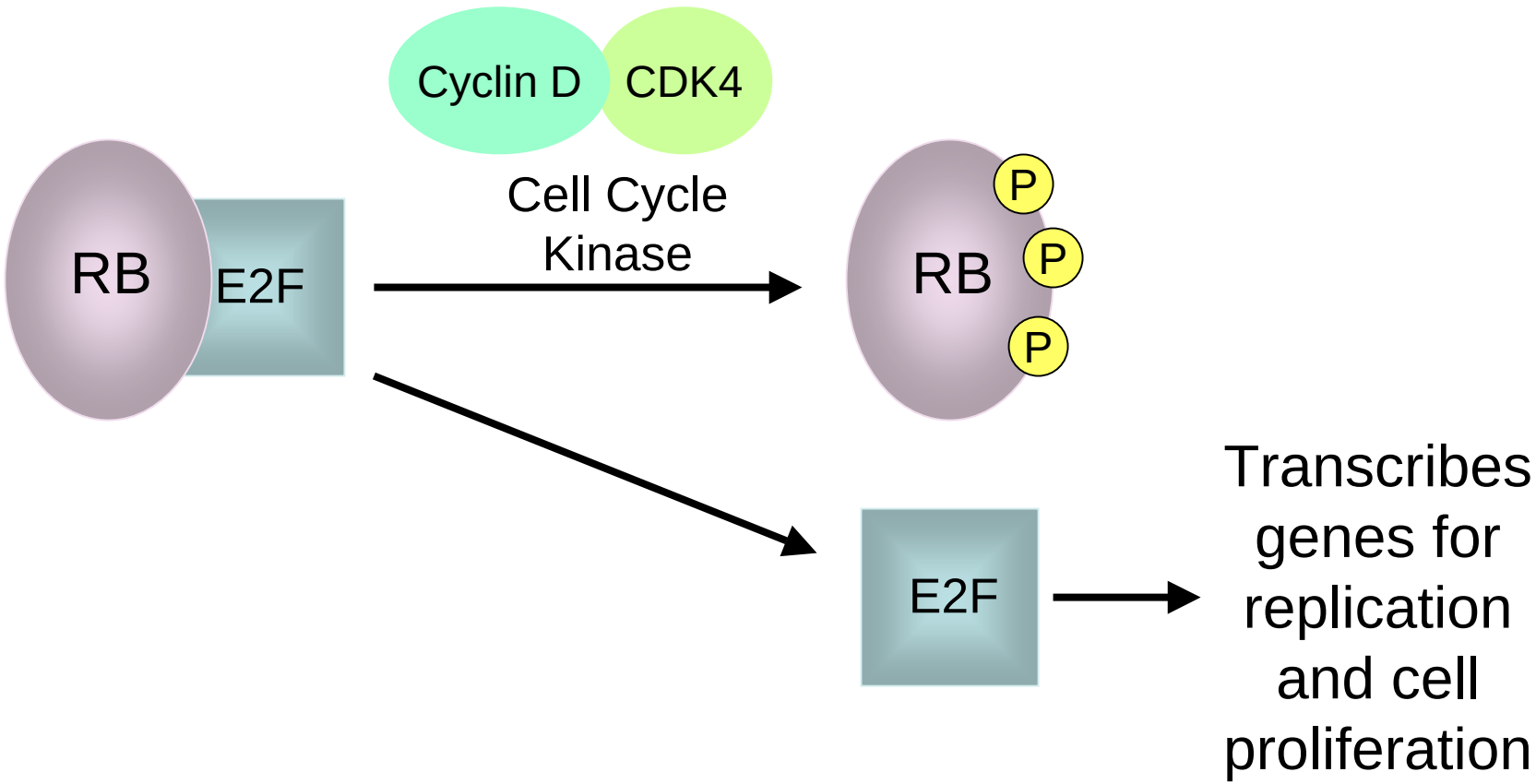
LOH

This can happen is several ways

Slide from L. Samson


Chromosome loss
Chromosome loss & duplication
wt Rb
Mutant Rb
Deletion
Interchromosomal Recombination
Translocation
Gene Conversion

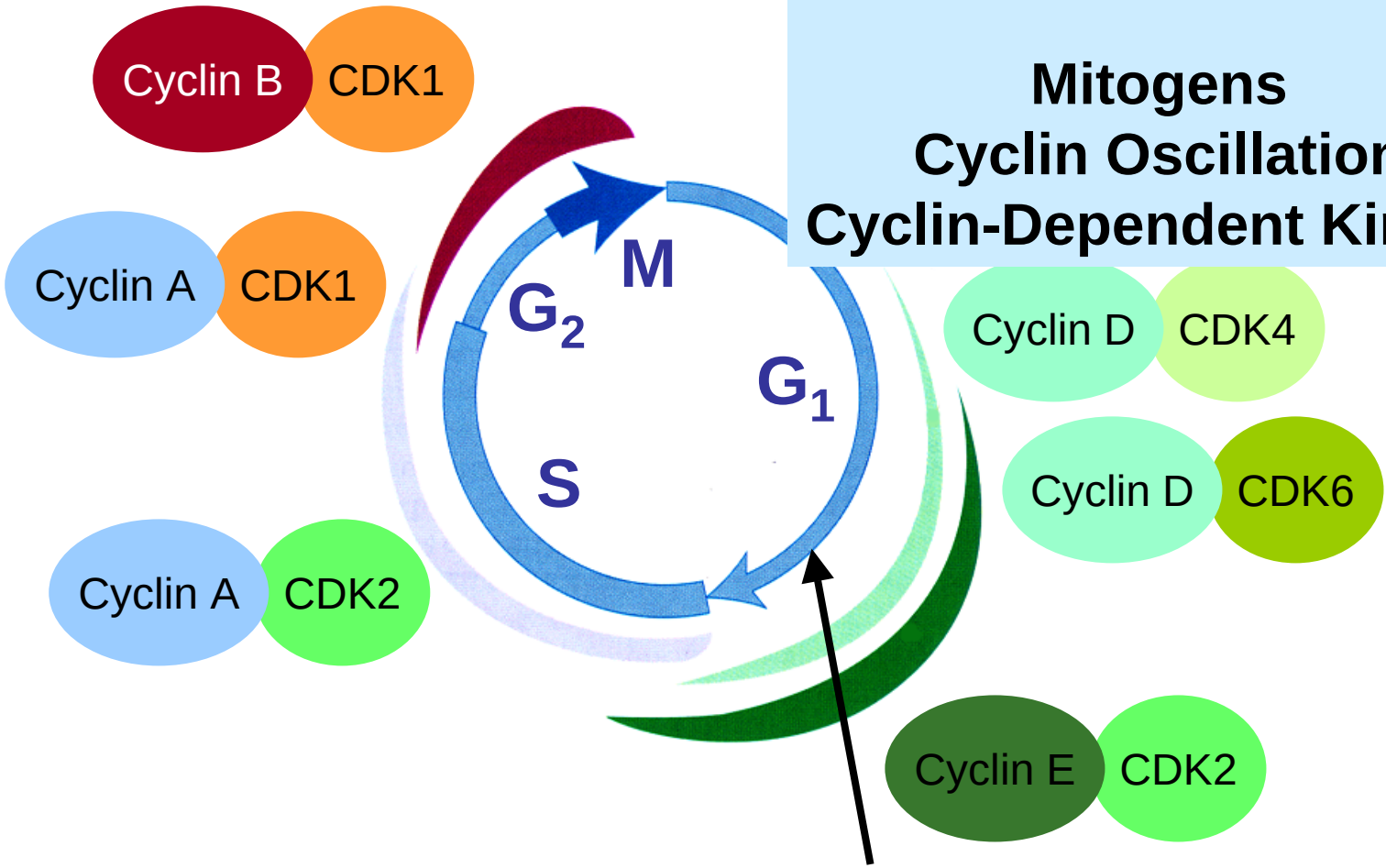
Cyclin-CDKs Regulate RB



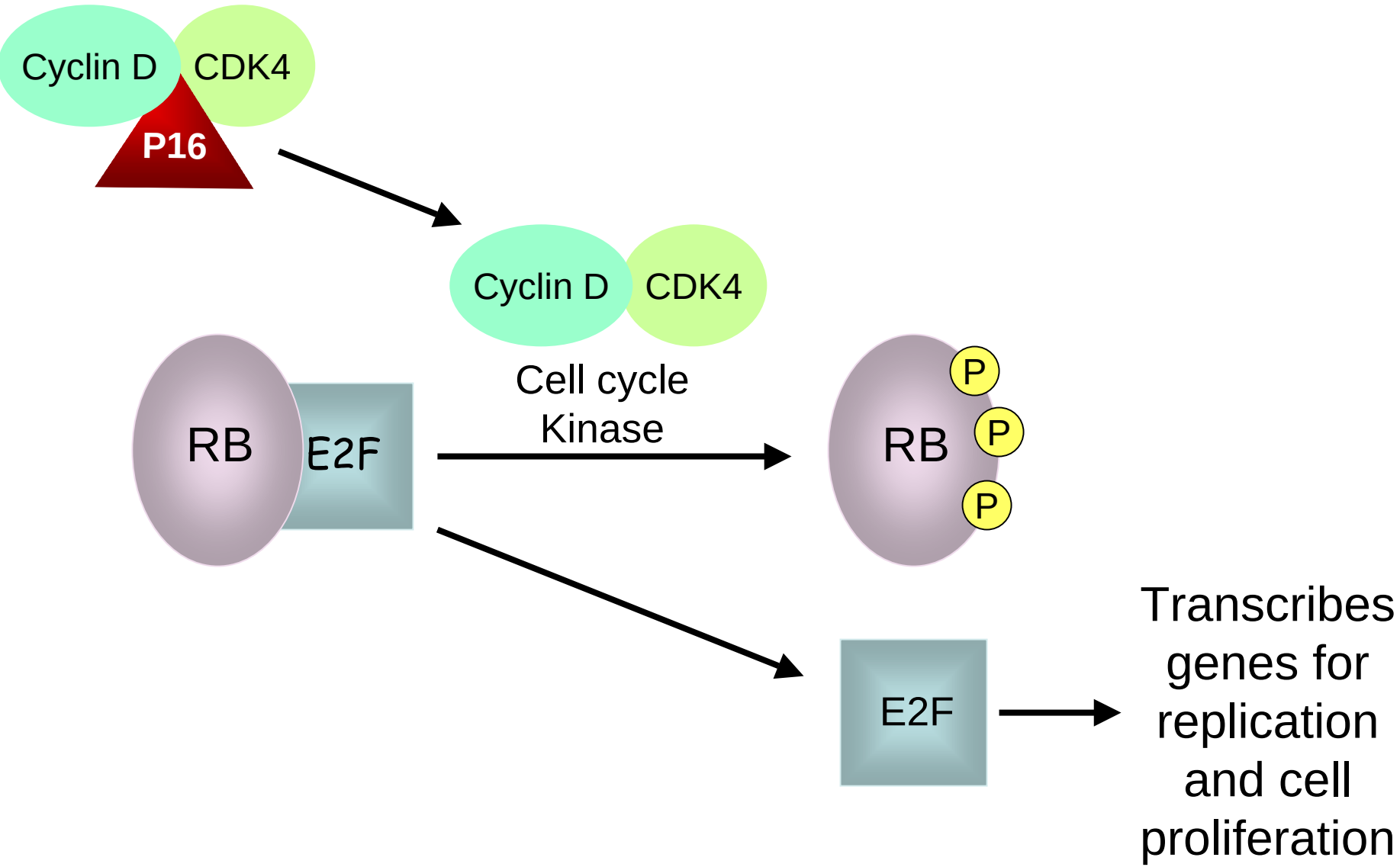
Autonomous “Cell Cycle Clock”: Cyclins & CDKs

Definitions:

Mitogens
Cyclin Oscillation
Cyclin-Dependent Kinase



RB is part of a Pathway: Several Vulnerable Steps



Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes

gene that makes a cell cancerous
dominant gain-of-function mutations

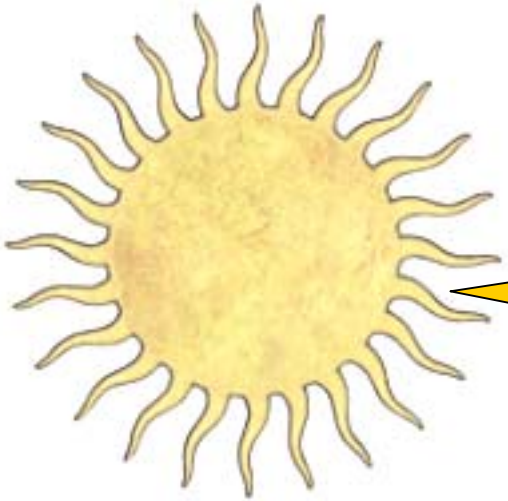
Example of a Mutator Gene:

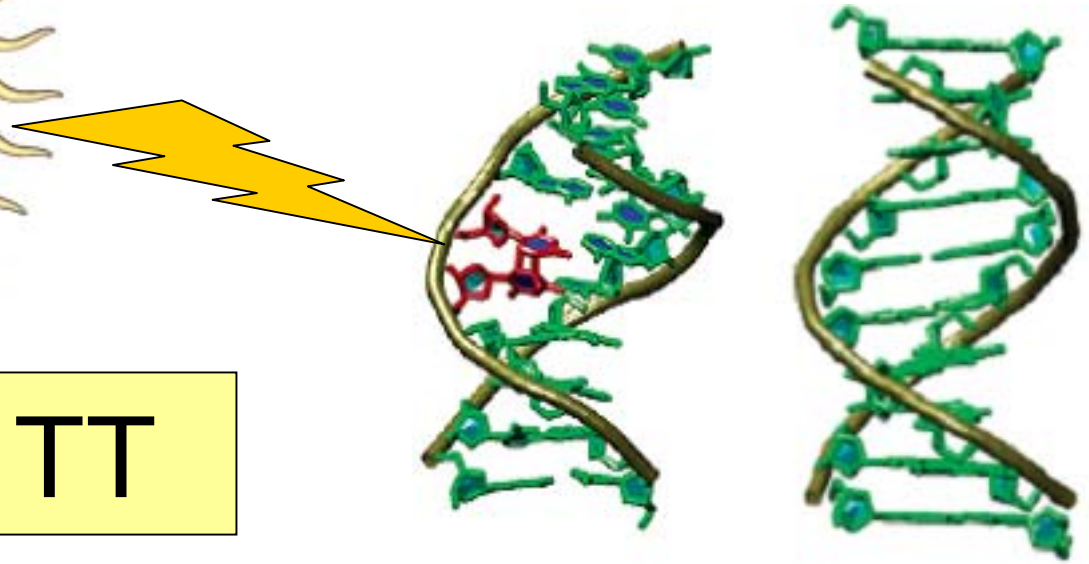
UvrA - Normally helps repair DNA damage
LOSS of UvrA ↑ Odds of Sunlight-Induced Mutation

Mutator genes

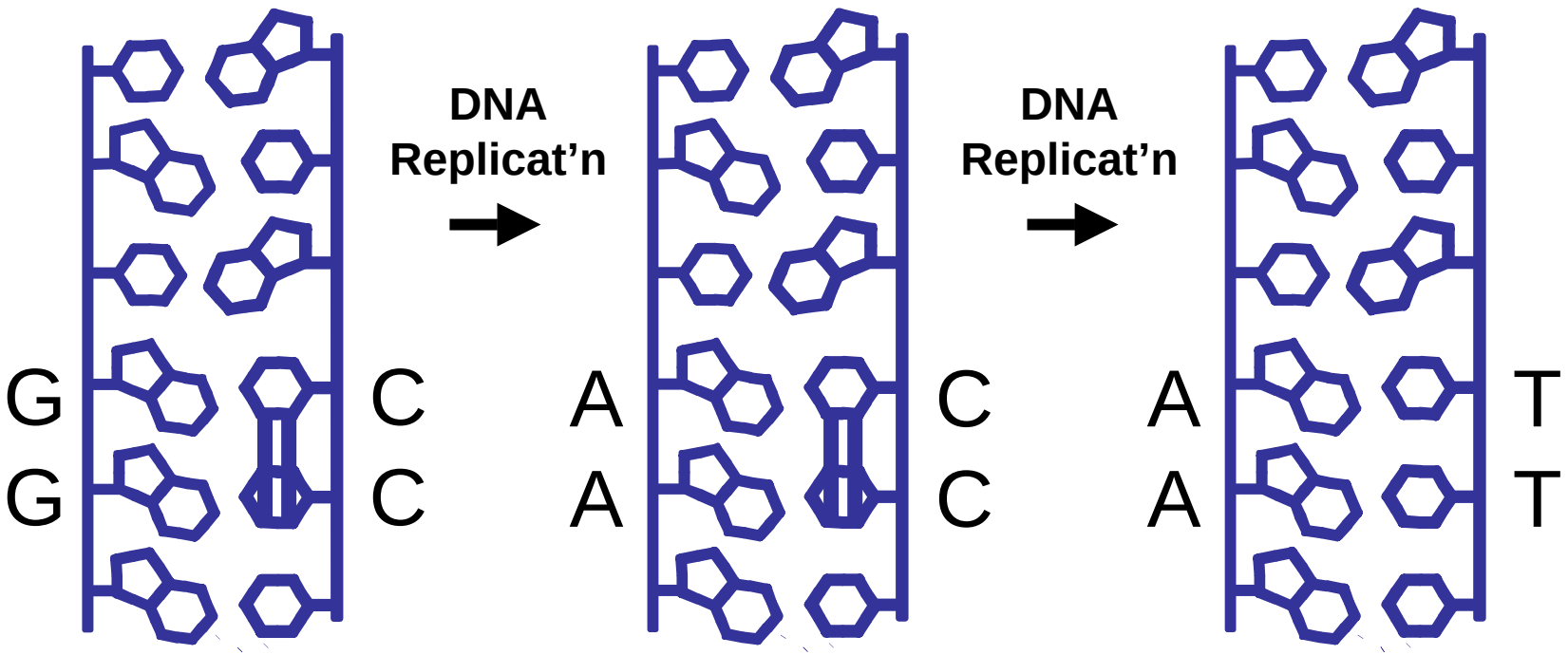
↑ spont. & environmentally induced mutation rates
usually recessive, loss-of-function mutations

Sunlight Damages DNA

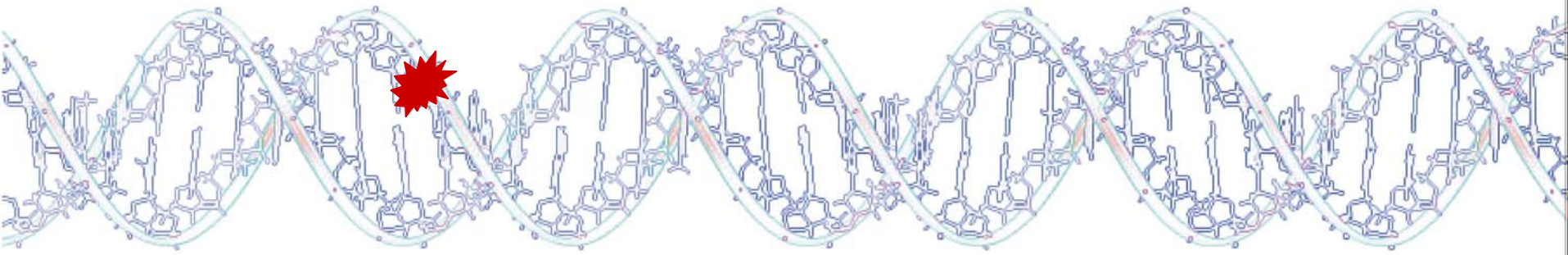


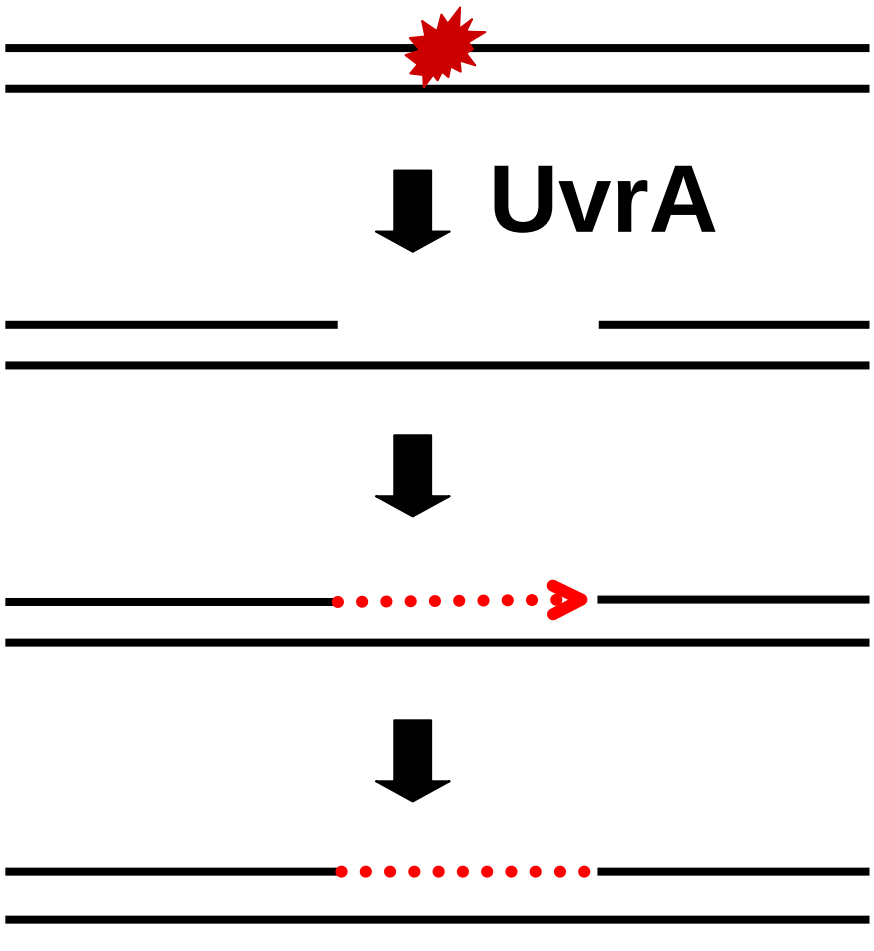


CC to TT



Nucleotide Excision Repair (NER)





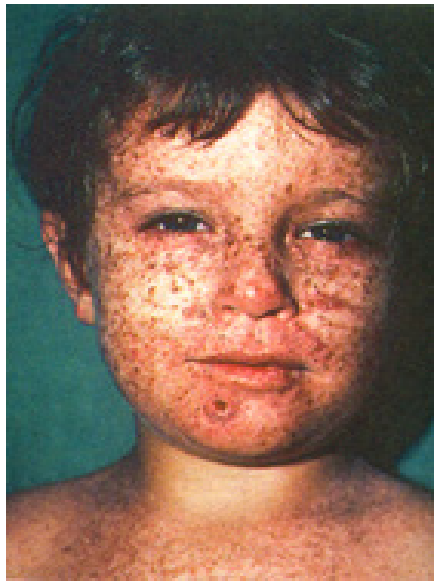
Proteins Detect Damage

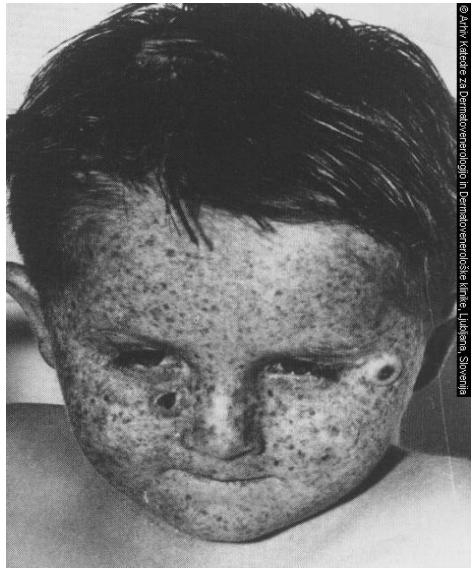
Enzymes Excise DNA Segment with Damage

DNA Polymerase Copies the Undamaged Strand

DNA Ligase Seals the ends together

Xeroderma Pigmentosum (NER deficiency)



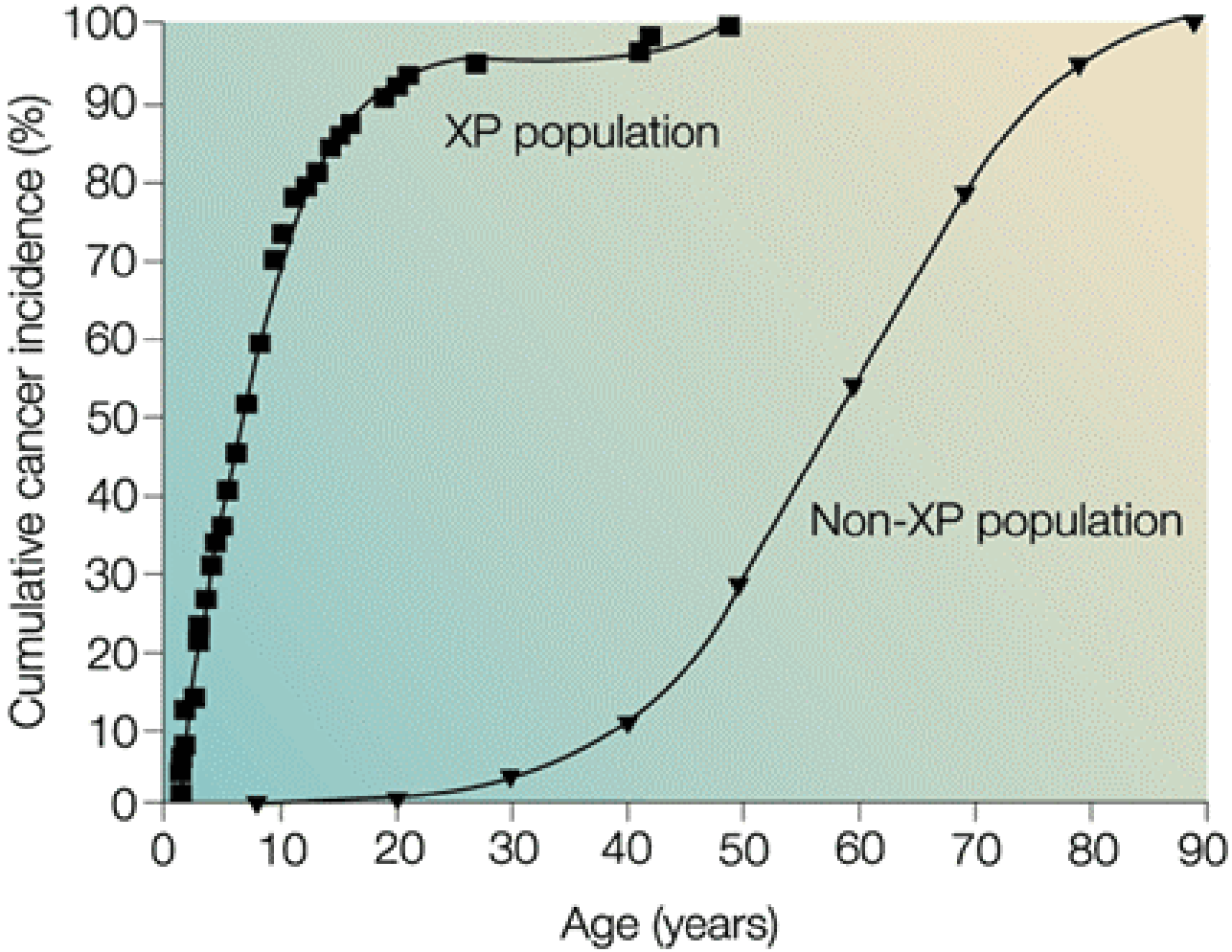


Inheritance of two mutant copies of UvrA can cause XP

Autosomal Recessive Disease

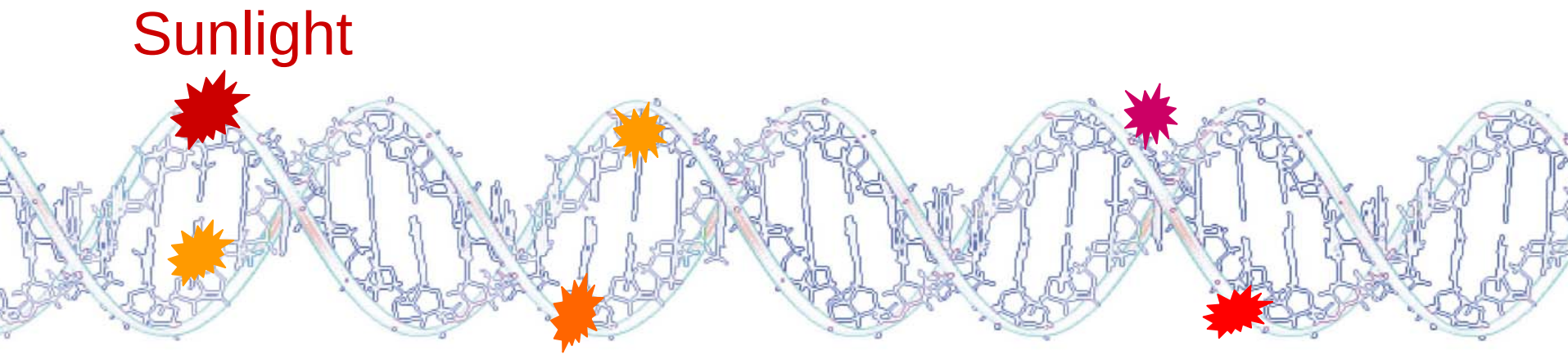
2000-fold increased risk of skin cancer

Age at First Skin Cancer

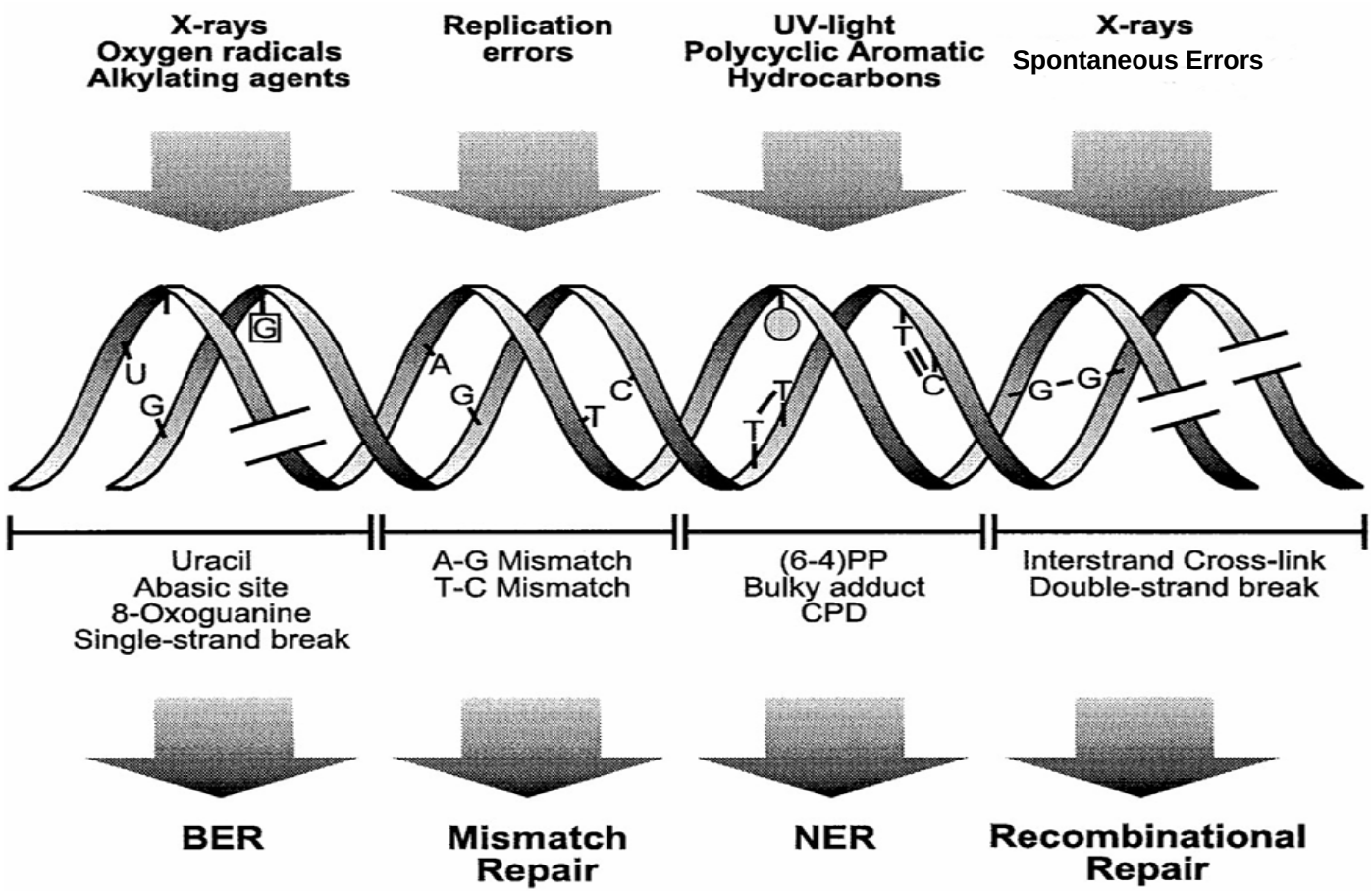


NER Pathway - Normally helps repair DNA damage
Mutator phenotype accelerates cancer onset

UV is one of Many Types of DNA Damage



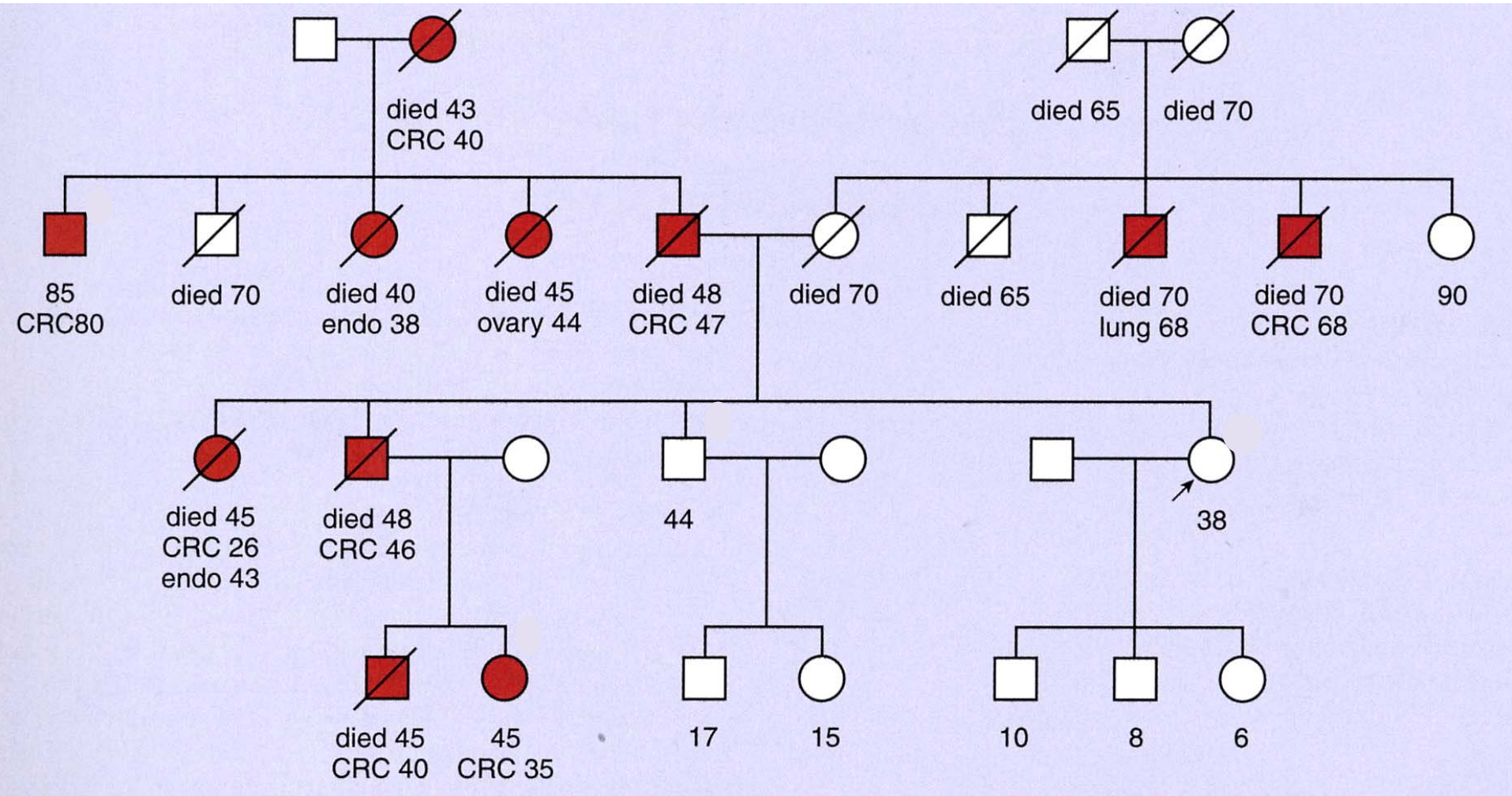
Many Other Cancer Prone Syndromes are caused by Deficiencies in DNA Repair



If DNA Repair pathway is defective →

BER	Mismatch Repair	NER	Recombinational Repair
Colon	Colon Ovary Endometrial	Skin	Breast Ovary Leukemias

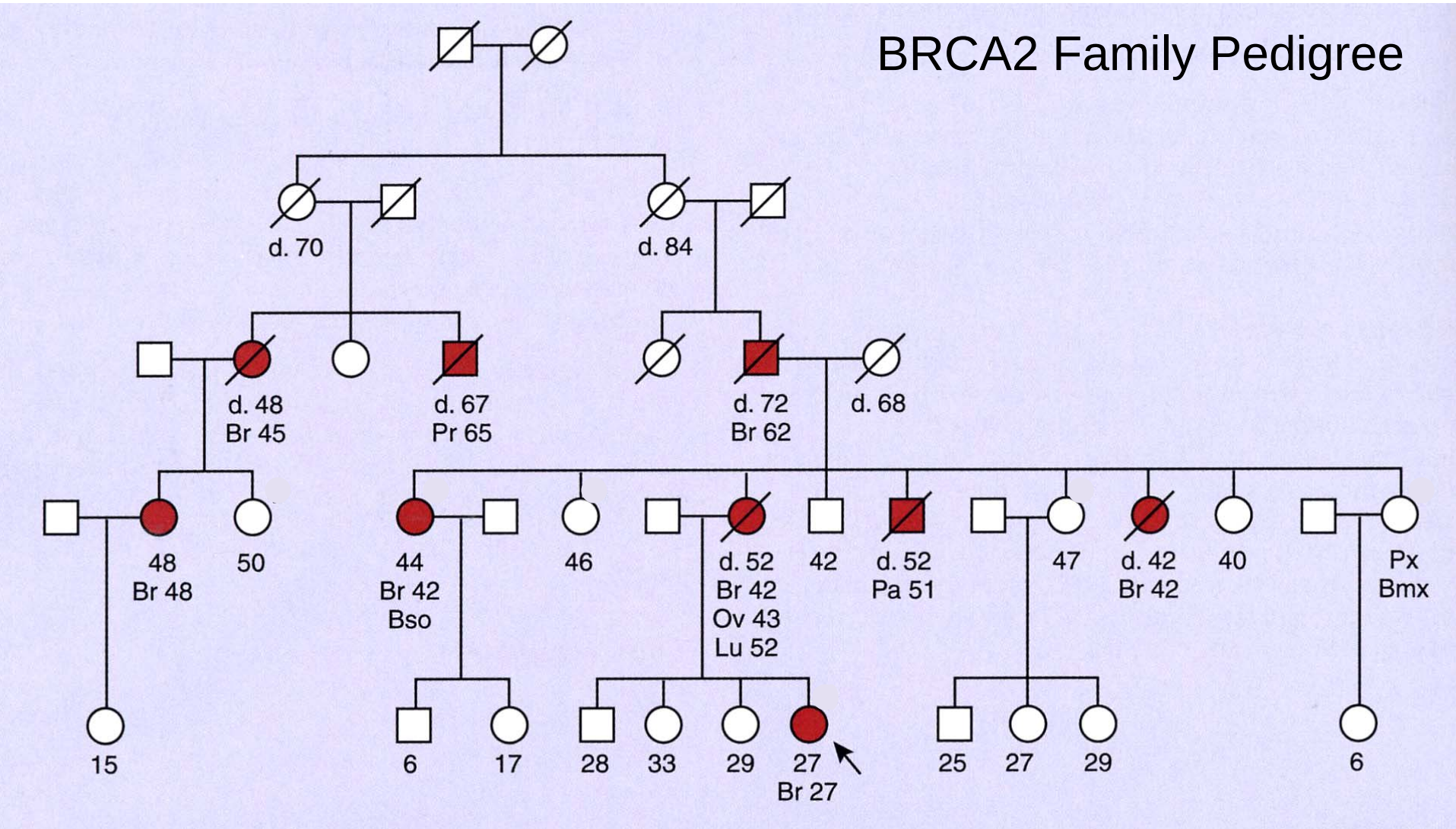
Hereditary Nonpolyposis Colon Cancer
DNA Mismatch Repair Defect
Syndrome inherited as Autosomal Dominant



Hereditary Breast Cancer Susceptibility

DNA Recombination Repair Defect

Syndrome inherited as Autosomal Dominant



Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

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dominant gain-of-function mutations

Tumor suppressor genes

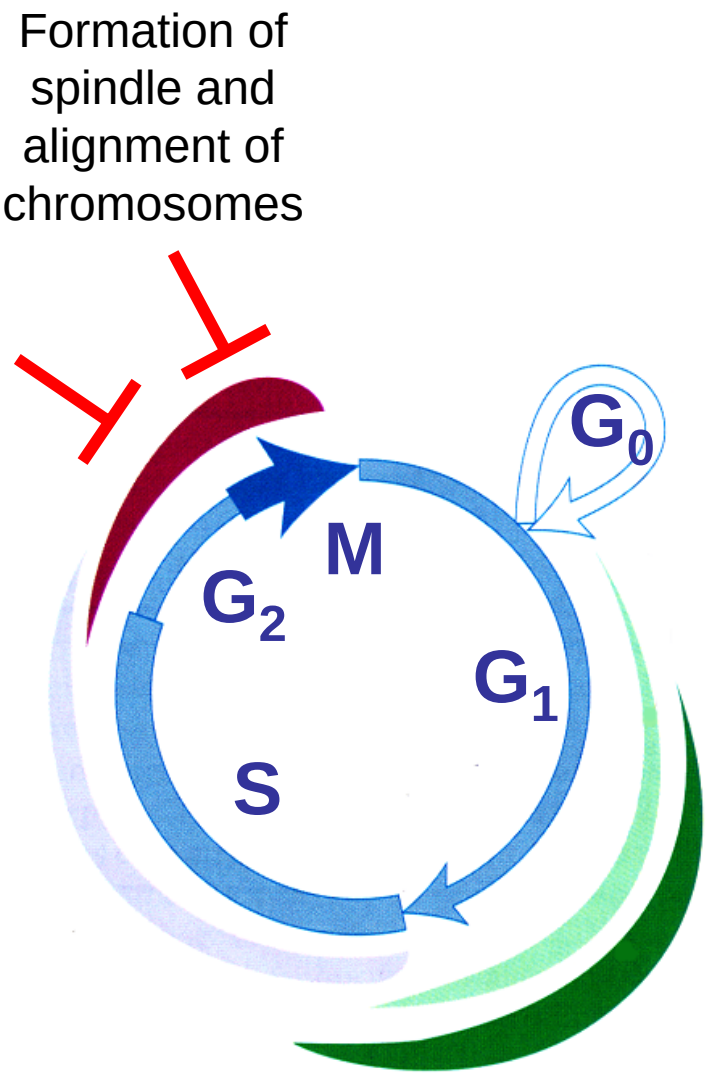
genes that normally restrain growth

recessive, loss-of-function mutations

Checkpoint Genes are Tumor Suppressors:

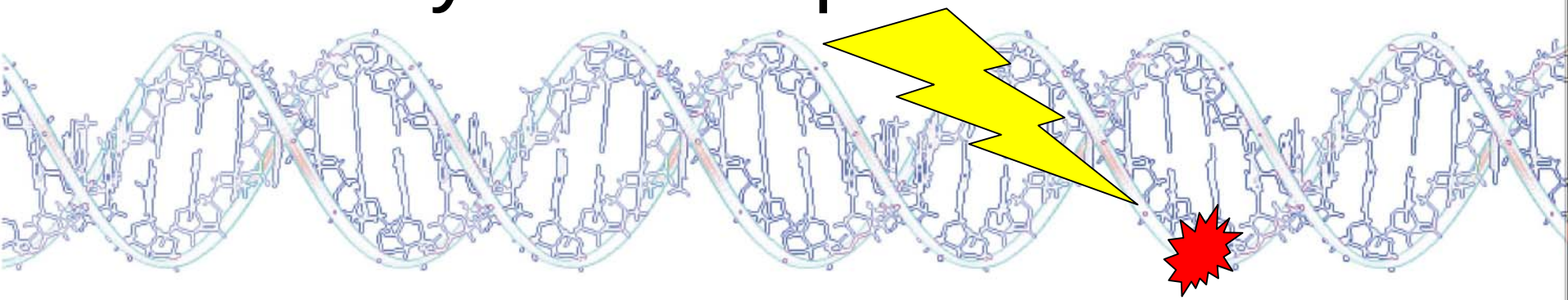
p53 - Signals cells to "WAIT!" if there is DNA Damage
Loss of normal p53 function increases mutation rate

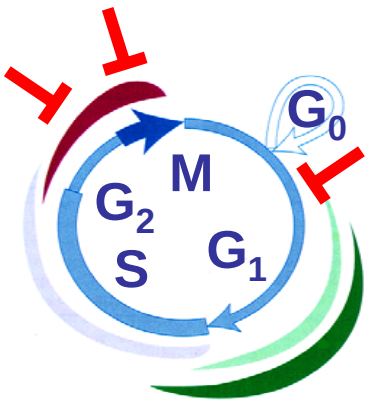
Checkpoint Control Pathways provide Negative Feedback on the Cell Cycle



Loss of Checkpoint Control is a common feature of many cancer cells. If cells "Hurry Up!" and don't wait for repairs, they are driving recklessly – this can force cells to replicate damaged DNA = ↑ mutation rate.

P53 Helps Cells to Stop for Repairs & has many other important functions





G1, G2, & M arrest

DNA damage is sensed

Signal Transduction KINASES are activated

Apoptosis

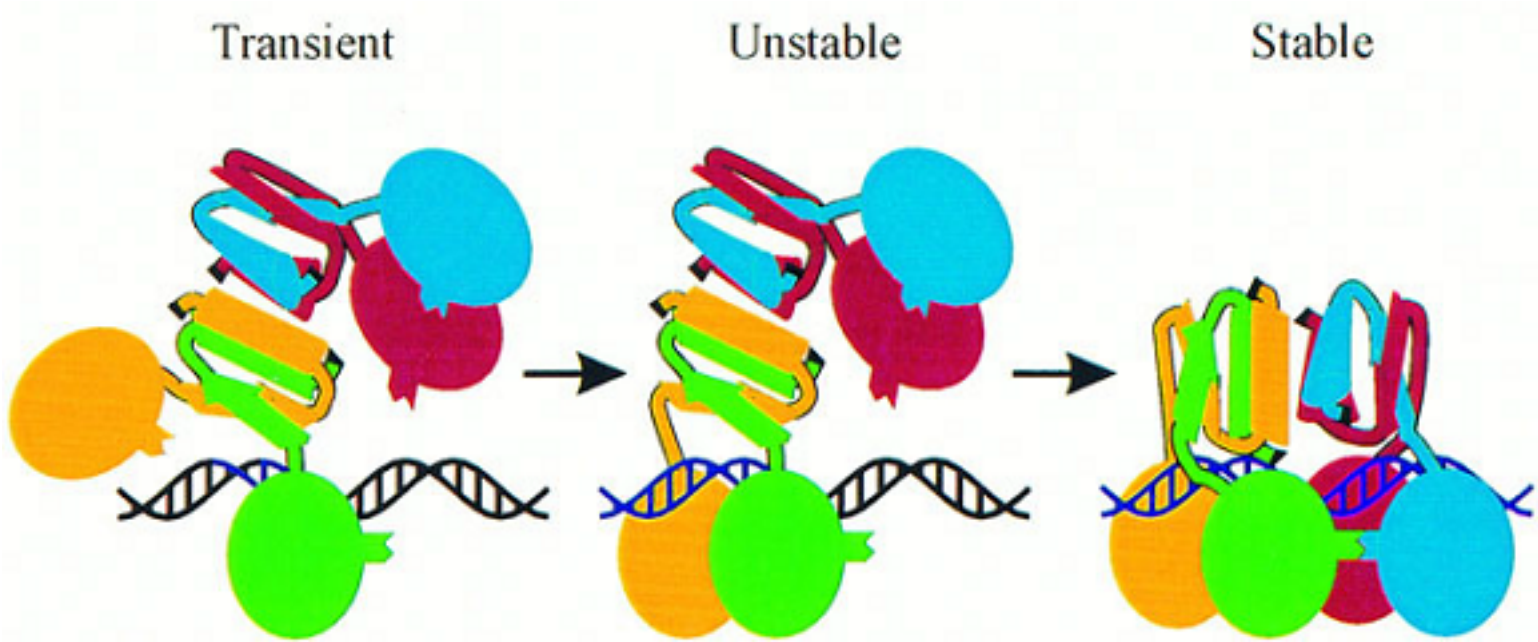
Increased DNA repair

P P P p53

p53

Slide from L. Samson

P53 is a Tetrameric Transcription Factor

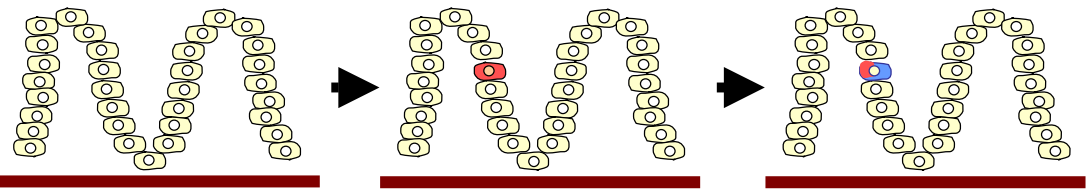


McLure & Lee

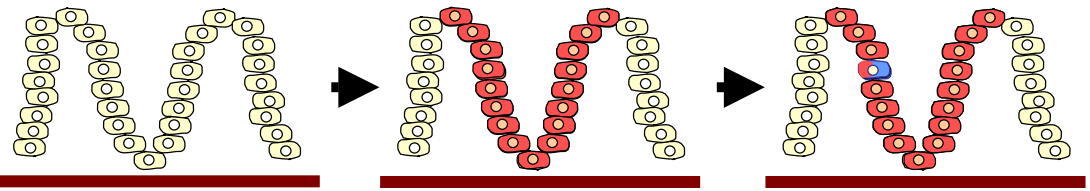
DOMINANT NEGATIVE mutations are common in most cancers

Most fully blown cancers require many mutations

How do you get two mutations into the same cell?

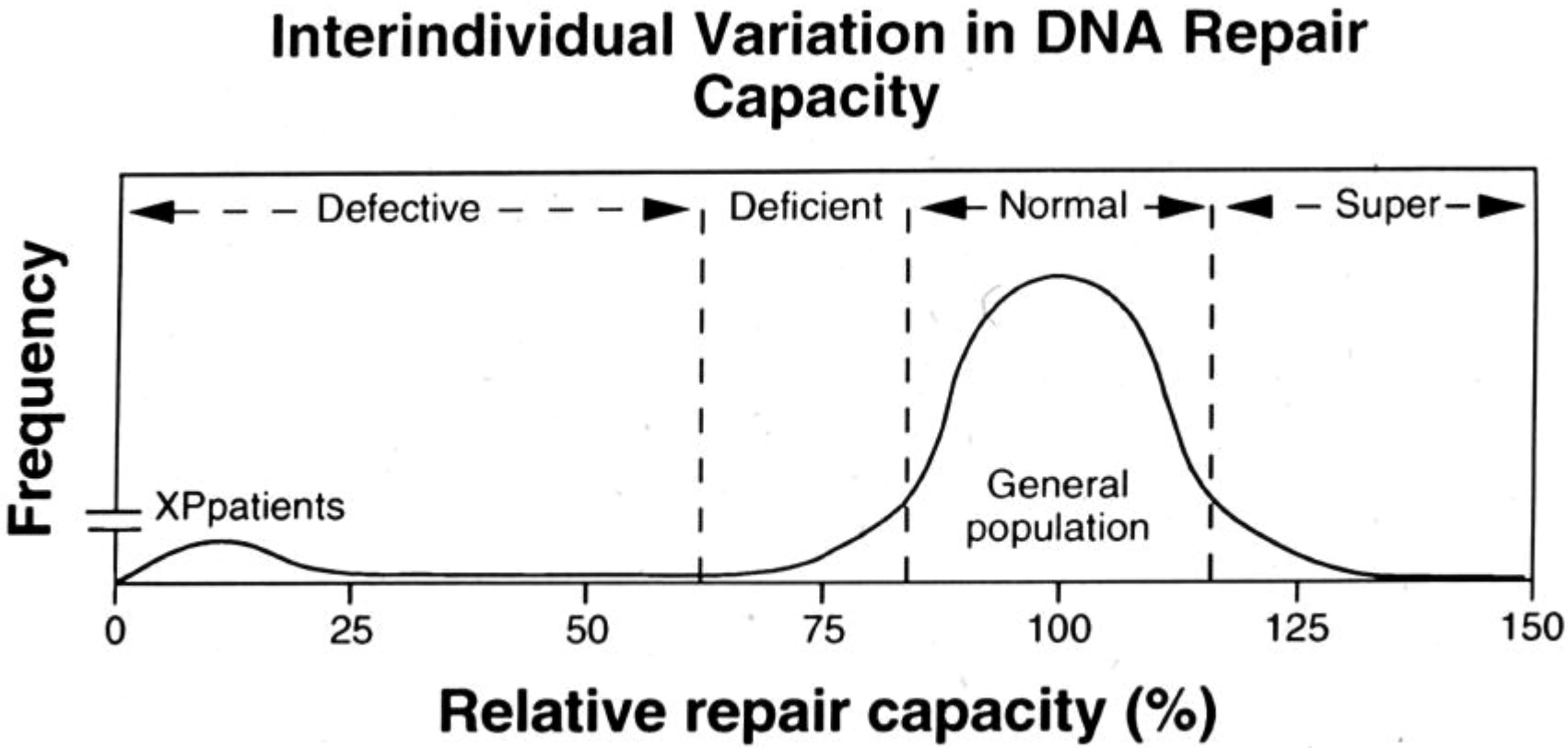


Mutation 1 Mutation 2



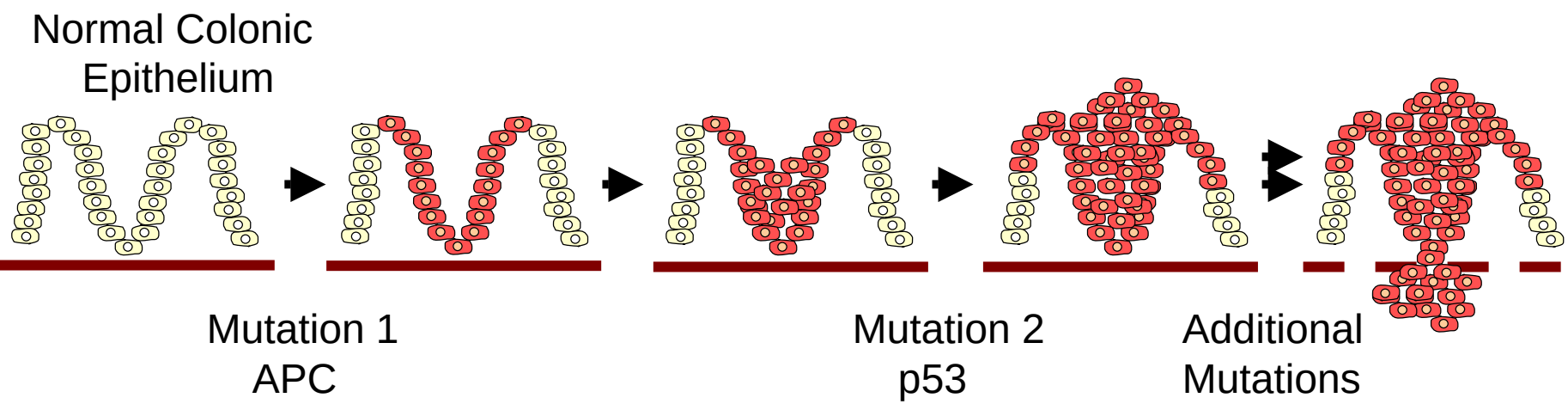
Mutation 1 Mutation 2

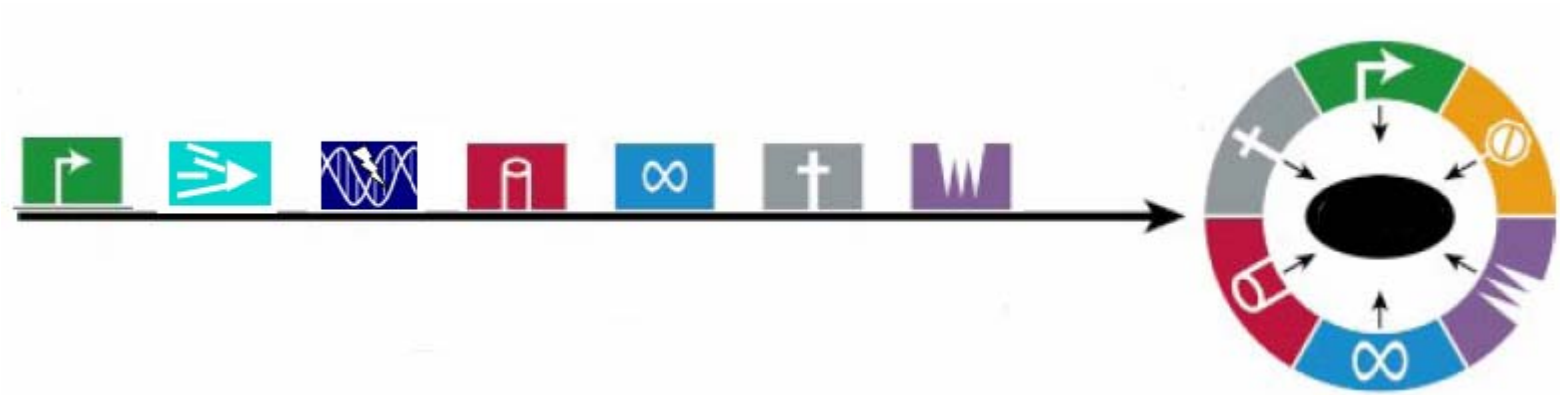
Xeroderma Pigmentosum ~ 1/250,000



Wei *et al.*, Clinical Chemistry, Vol. 41, No. 12, 1995

One thing leads to another…





http://music.msn.com/album/?album=29452880#

Take-Home Messages

- Tumor suppressors are recessive genes; inheritance of one broken copy can lead to a dominant trait

- Mutator Genes are a class of tumor suppressors that, if lost, lead to a mutator phenotype

- There are many more ways to inactivate a gene than to create an oncogenic mutation; thus it is difficult to screen the population for carriers

- Four ways to increase the odds of a cancer-promoting mutation: decrease DNA repair, increase DNA damage, disrupt checkpoints, clonally expand – these are all cancer traits