Mutation

Change in the base sequence of DNA

Types of Mutation (pg 220, pg 500)

Substitution

ATG CAG TCA
ATG CAG TCC

One base substituted for the other

Number of codons affected: one

Effect on phenotype:

Silent: Codon changed, amino acid stays the same

Missense: Codon changed, amino acid changed
E.g sickle cell anaemia

Nonsense: Codon changed to a stop codon

Addition mutation (pg 501)

ATG CAG TCA
ATG GCA GTC

Number of codons affected: all downstream of the mutation

Effect on phenotype:

Causes a shift in the reading frame of all codons downstream of the mutation - "frameshift" mutation

Large effect on phenotype, as protein is often defective or truncated

Addition mutation can be non-frameshift if 3 bases are added

Huntington's : Duplication of CAG bases in the *HTT gene*, abnormal length huntingtin protein

Deletion mutation (pg 220, pg 500)

ATG CAG TCA
ATC AGT CAX

Number of codons affected: all downstream of the mutation

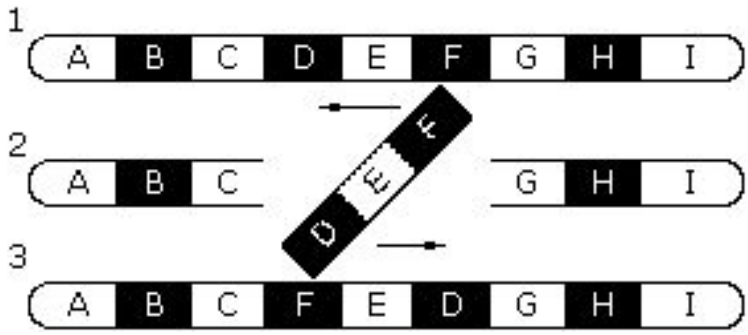
Effect on phenotype: same as addition

Example: Cystic Fibrosis, CFTR gene

- Three bases deleted
- One amino acid deleted
- CFTR protein channel defective

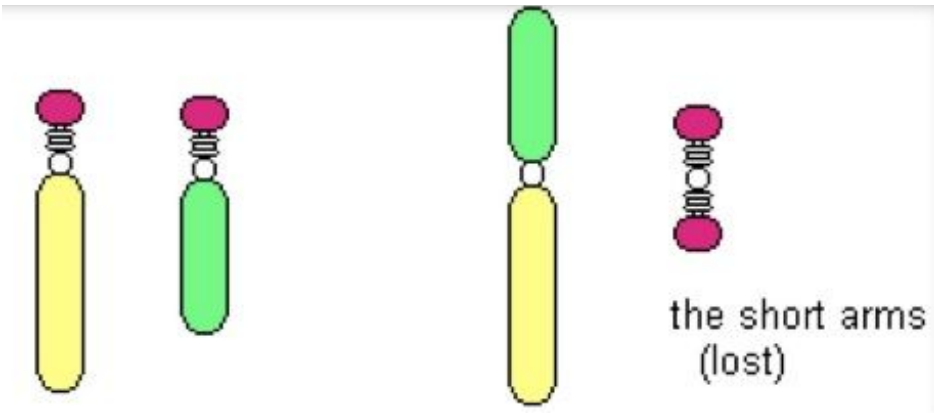
Inversion mutation (pg 501)

Group of bases inverted



Translocation (pg 501)

Portions of non-homologous chromosomes joined together e.g. in one form of Downs, the long arms of chromosome 14 and 21 are joined together



Chromosome mutations

Whole chromosomes affected

1. Polyploidy in wheat

- Gametes are diploid, chromosomes do not separate during meiosis
- Offspring are tetraploid

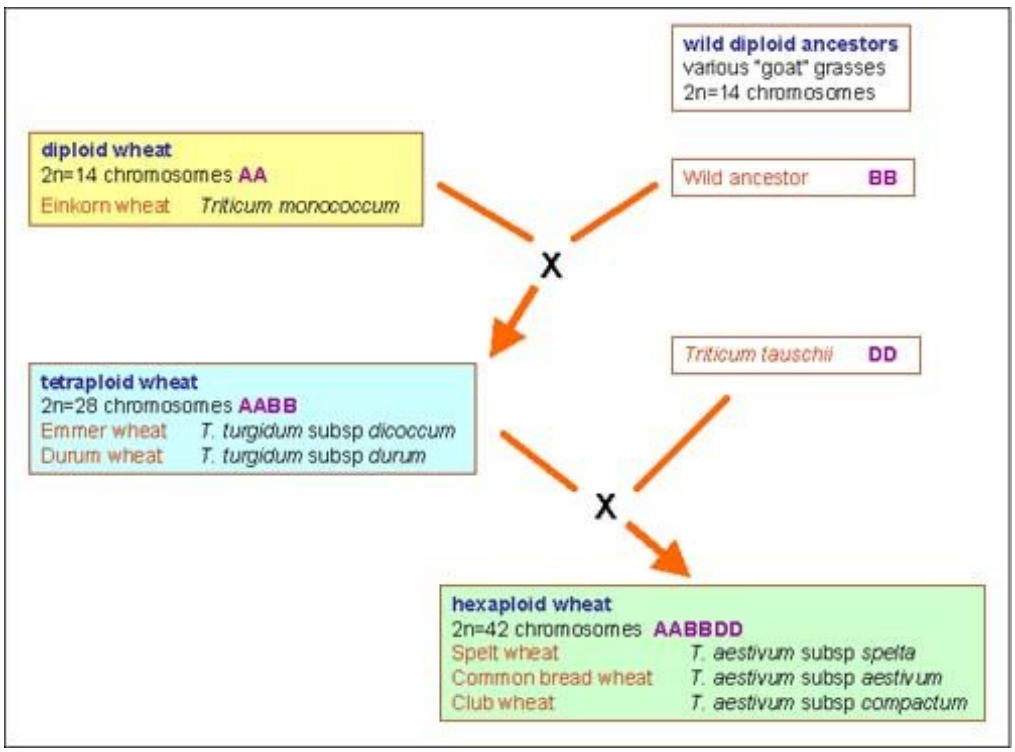
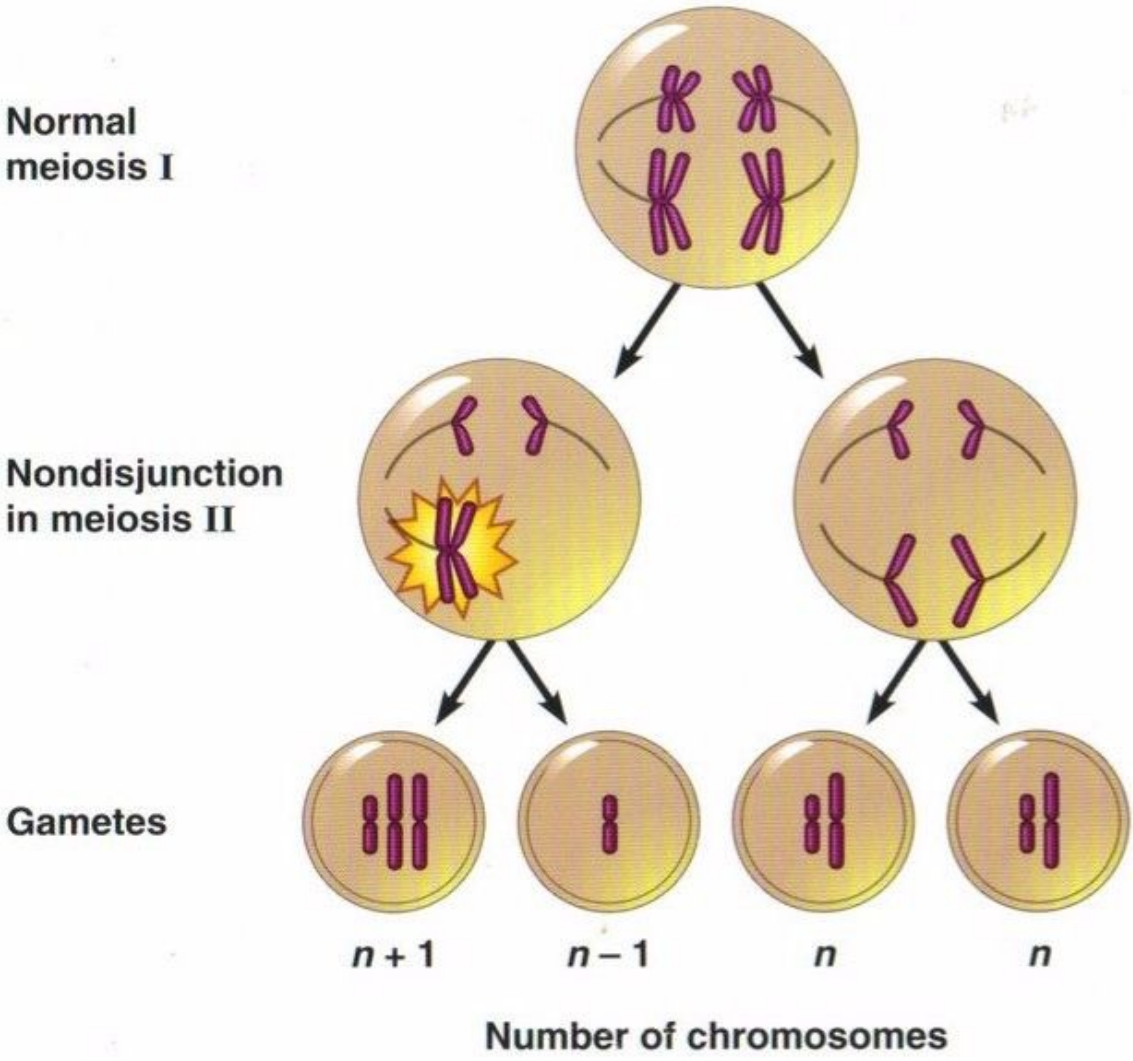


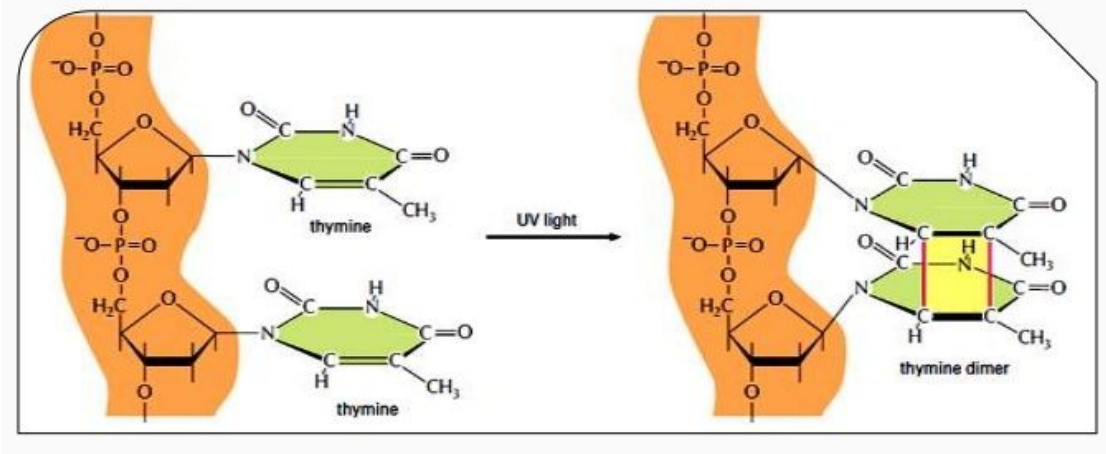
Fig 6, Page 223

2. Non-disjunction: one pair of chromosomes does not separate during meiosis e.g. Downs Syndrome, chromosome 21 (pg 221) ~ trisomy



Causes of mutation

1. Ionizing radiation like U.V. light (pg 501, pg 503)



★ Thymine bases cross-linked

★DNA Polymerase cannot recognise bases

★Inserts random base opposite

2. Chemical carcinogens like

- benzopyrene from cigarette smoke, which alters G into a T
    - GC pair replaced by TA pair

- Nitrous acid in smoked food, which alters C into U
    - CG pair replaced by UT pair

Effects of gene mutation on cells

Gene mutations in cells can lead to tumours, which can be malignant or benign (pg 519)

Benign	Malignant
Grow slowly	Grow rapidly
Well-defined capsule	Not encapsulated
Not invasive	Invasive
Well differentiated	Poorly differentiated
Low mitotic index	High mitotic index
Do not metastasize	Can spread distantly (metastasis)

Effects of mutation on genes

(a) **Proto-oncogenes** (pg 520)

- Genes involved in regulating the cell cycle

- Under normal conditions, proto-oncogenes are only turned **ON** at checkpoints (OFF state at other times)

- Turning ON a proto-oncogenes can lead the activation of a gene that produces a cell surface receptor

- Receptor binds to growth hormone, allowing cell to proceed to next stage of the cell cycle

Protooncogenes are stimulators of cell division

Effect of mutation on proto-oncogenes

(diagram on next page)

- A mutation in DNA can change a proto-oncogene to an oncogene (cancer-causing gene)

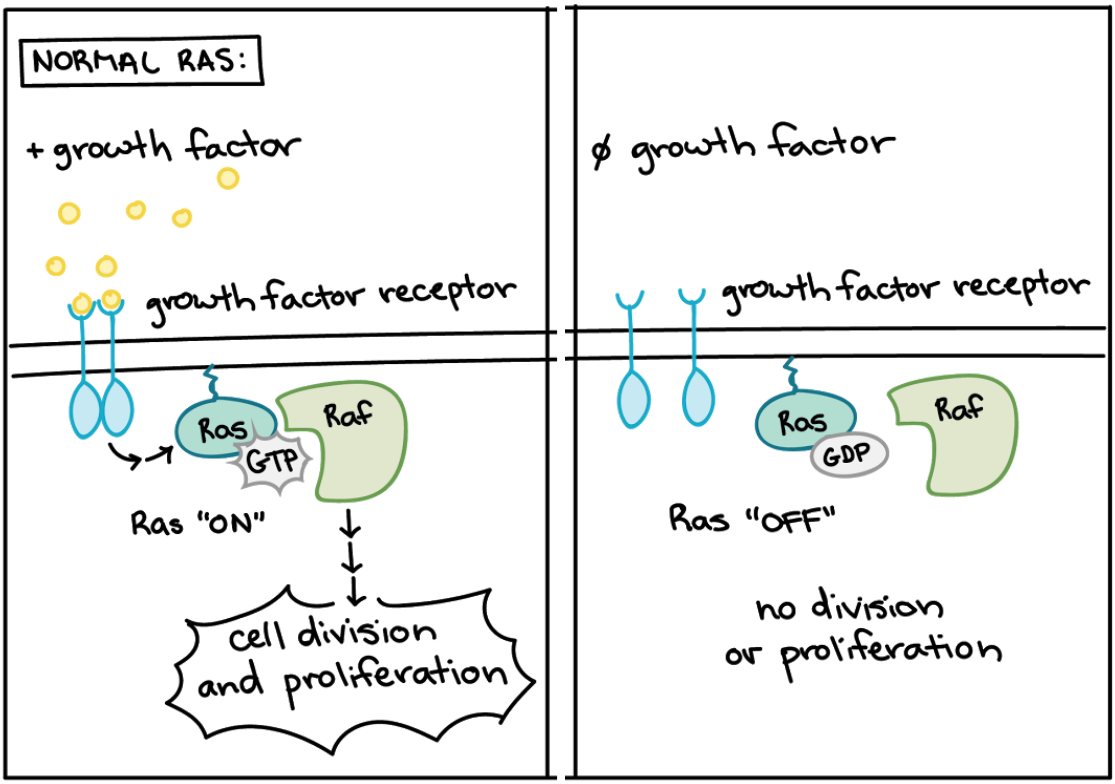
- Oncogenes is always turned **ON**

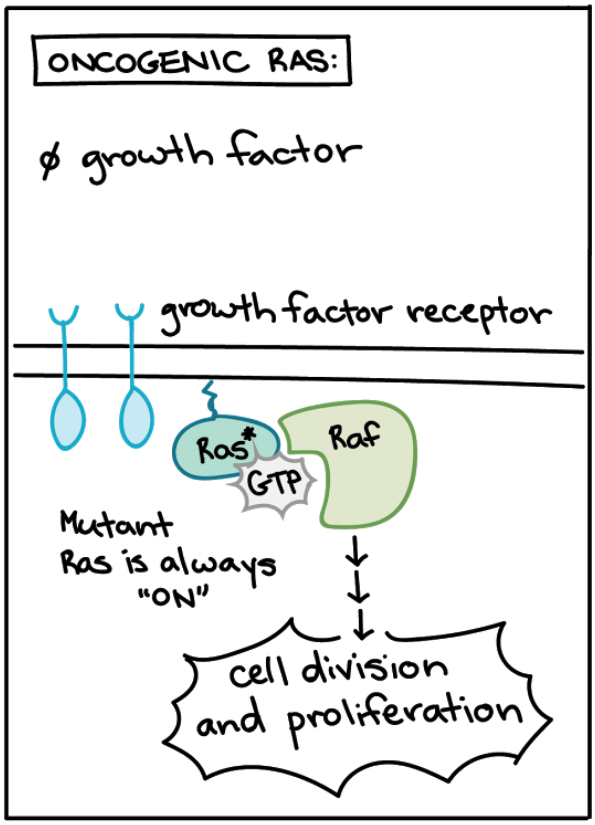
- Cell can continuously respond to growth factor

- OR growth factor receptor sends signals to the DNA even when growth factor is not present

- Uncontrolled cell growth = cancer

Oncogene = self-sufficiency to growth signals


NORMAL RAS:
+ growth factor
growth factor receptor
Ras
GTP
Raf
Ras "ON"
cell division and proliferation
ø growth factor
growth factor receptor
Ras
GDP
Raf
Ras "OFF"
no division or proliferation


ONCOGENIC RAS:
ø growth factor
growth factor receptor
Ras*
GTP
Raf
Mutant Ras is always "ON"
cell division and proliferation

(b) Tumour-suppressor genes (pg 520)

- Usually turned **ON**

- Prevents cell-division from going too quickly (**growth suppressor**)

- Causes older or defective cells to commit suicide (apotosis = programmed cell death)

- Each cell has two working copies of tumour-suppressor genes

Effect of mutation on Tumour-Suppressor genes

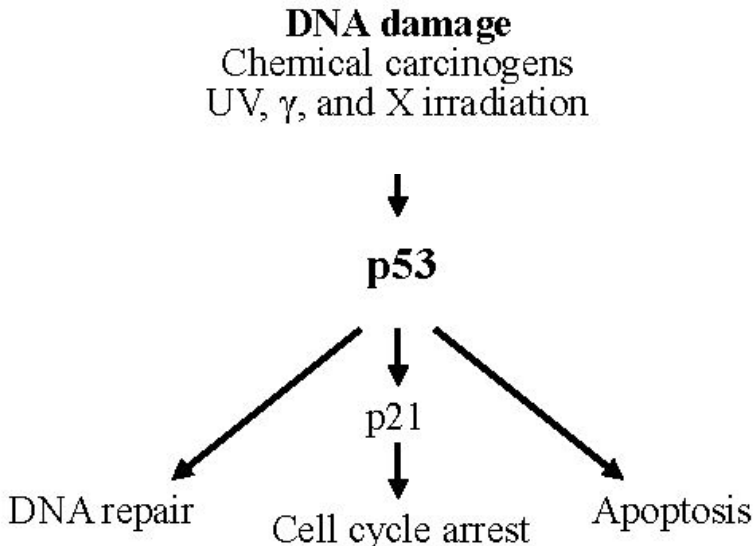
- A mutation in one allele has little effect on the phenotype (but increases risk for cancer)

- A mutation in the second allele results in both alleles now being non-functional

- Uncontrolled cell division = cancer

Examples:

TP53 gene, which codes for the **p53** protein. Many cancers are associated with a mutation in this gene.



BCRA1 and BCRA2 = linked to breast cancer

- Gene products help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material

BRCA1/2 Mutations: Cancer Risks

	BRCA1	BRCA2
• Breast cancer to age 80	50-85%	50-85%
• Ovarian cancer to age 80	20-60%	up to 27%
• Male breast cancer	Slight incr.	~6%
• Prostate cancer	Slight incr.	Slight incr.
• Pancreatic cancer	No incr.	1.5-5%
• Melanoma	No incr.	Slight incr.

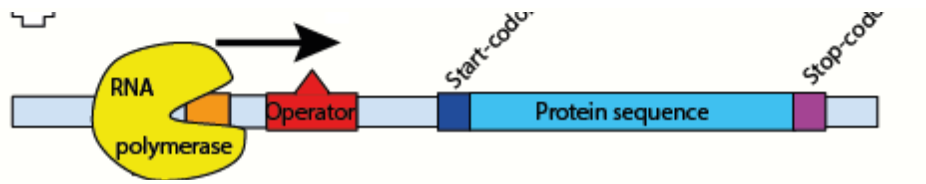
Daly MD: NCCN 2002 genetic/familial high-risk assessment clinical practice guidelines in oncology.

OHSU March of Dimes DHS

Cancer related to the regulation of gene expression

(pg 521)

- All genes have a promoter region
- Promoter is the part of DNA where the enzyme RNA Polymerase binds, to initiate transcription
- If the promoter is damaged, transcription fails



In some cancers,

- The promoter region of tumour-suppressor genes is modified by adding methyl groups (**hypermethylation**)
- This prevents RNA polymerase from binding to the promoter
- The gene is turned **OFF** (silenced) = cancer

Hypomethylation (removal of methyl groups) can turn ON oncogenes

Oestrogen and Breast cancer (pg 521)

- Oestrogen is a key hormone in the menstrual cycle
- It is normally produced by the ovaries

- After menopause,
    - Production by ovaries decreases
    - Production by fat cells in the breast tissue increases

- Increased levels of oestrogen in the blood

Oestrogen

- is a lipid-soluble hormone.
- It is also a gene regulator
- Turns on genes that would normally be off = uncontrolled growth = cancer

- These cells also produce extra oestrogen receptors

- 70% cases of breast cancer show increased sensitivity to oestrogen

- WBCs drawn to the site of tumour due to oestrogen production → inflammation due to chemicals released (cytokines) → increased growth of tumour

Soyabeans (and soya milk) contains phyto-oestrogens