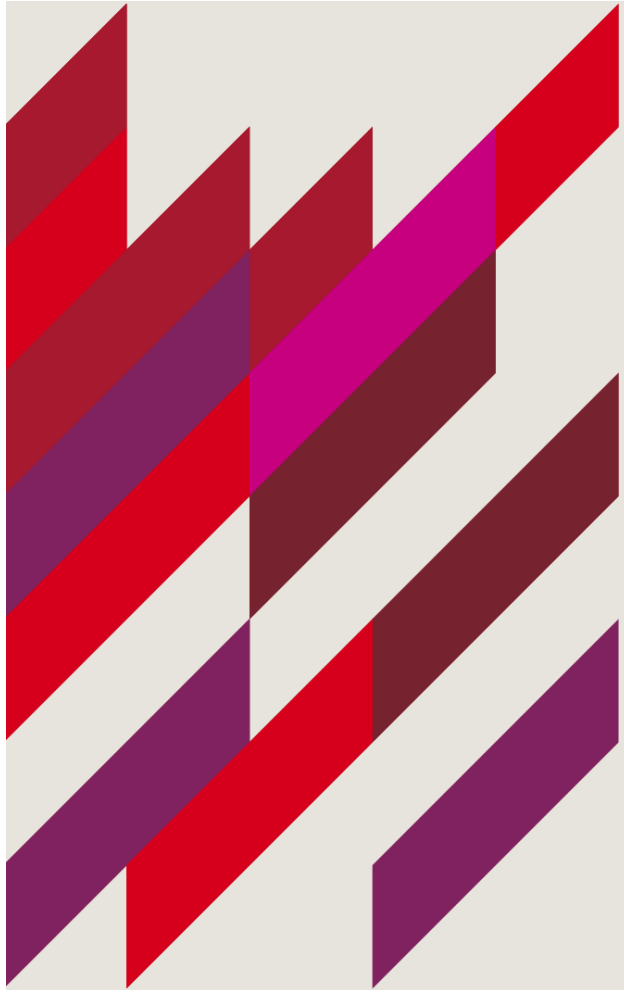
BIOL3120 –Human Genetics and Evolutionary Medicine

Chromosomal Mutations

3	The Human Genome Modes of Inheritance and Population Genetics	Problem Set 1	Problem Set 1 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
4	Heritability and Polygenics Chromosomal Mutations	Problem Set 2	Problem Set 2 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources
5	Nucleotide Mutations Human Genetic Diversity and Evolution	Problem Set 3	Problem Set 3 (5%)	Explain the principles of evolutionary biology and their role in human health and disease Solve problems in human genetics using appropriate analytical methods and a variety of up to date resources

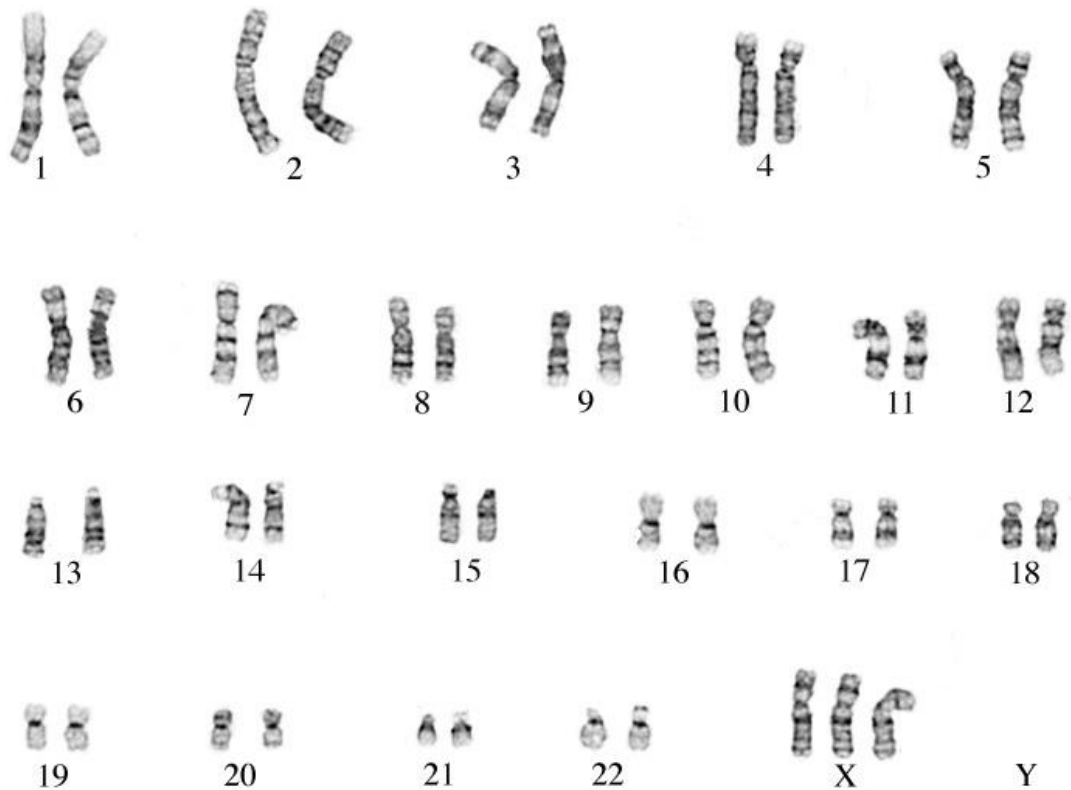
BIOL3120 –Chromosomal mutations

LEARNING OBJECTIVES



On successful completion of this lecture, you will be able to:

- Explain the different types of chromosomal mutations
- Use this knowledge to solve problems in human genetics relating to heritability, polygenic inheritance and chromosomal mutations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Chromosomal mutations overview

- Mosaicism
- Aneuploidy / other euploidies
- Uniparental disomy
- Translocations + Robertsonian translocations
- Changes within a chromosome

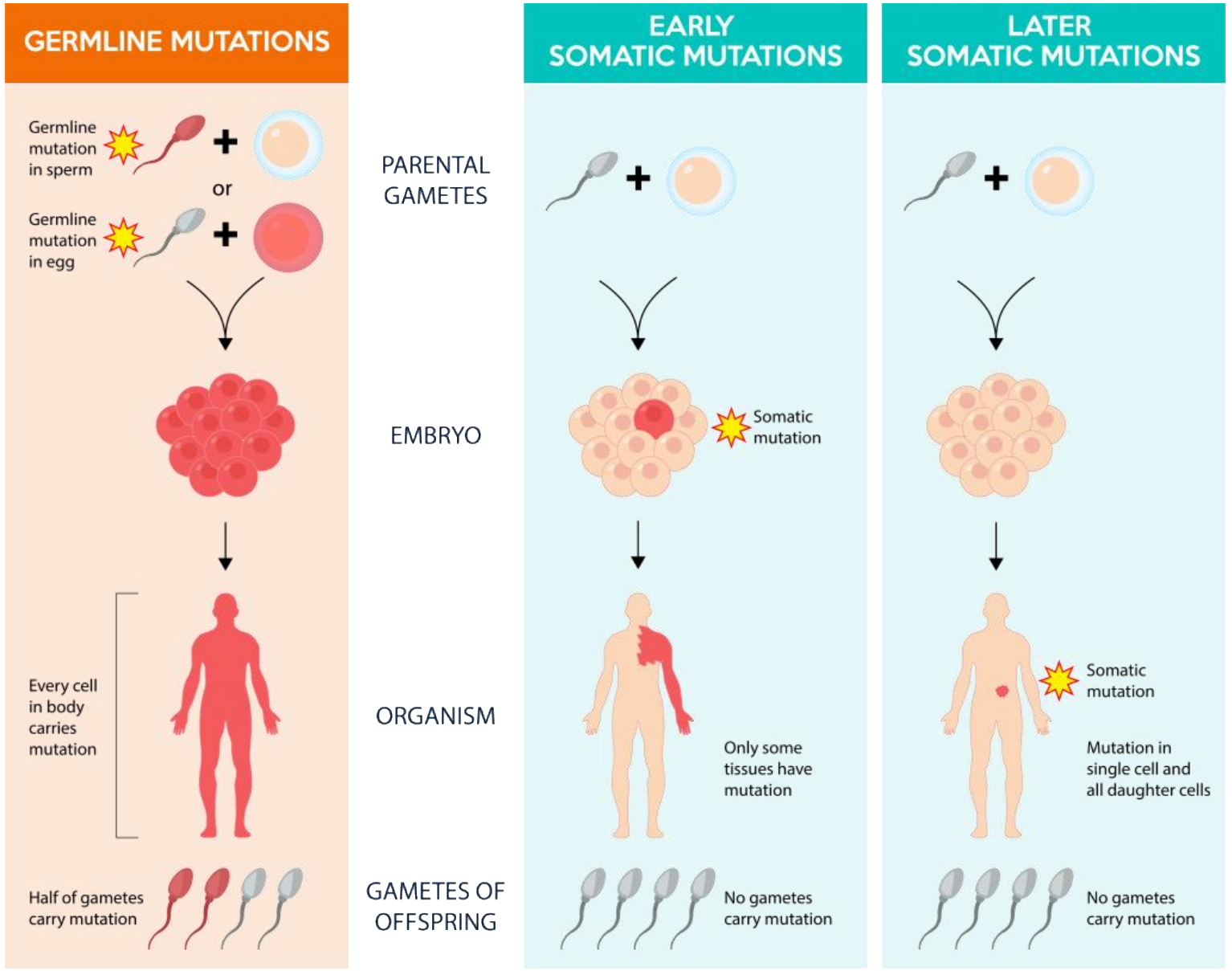
Chromosomal mutations

- Mosaicism
- Aneuploidy / other euploidies
- Uniparental disomy

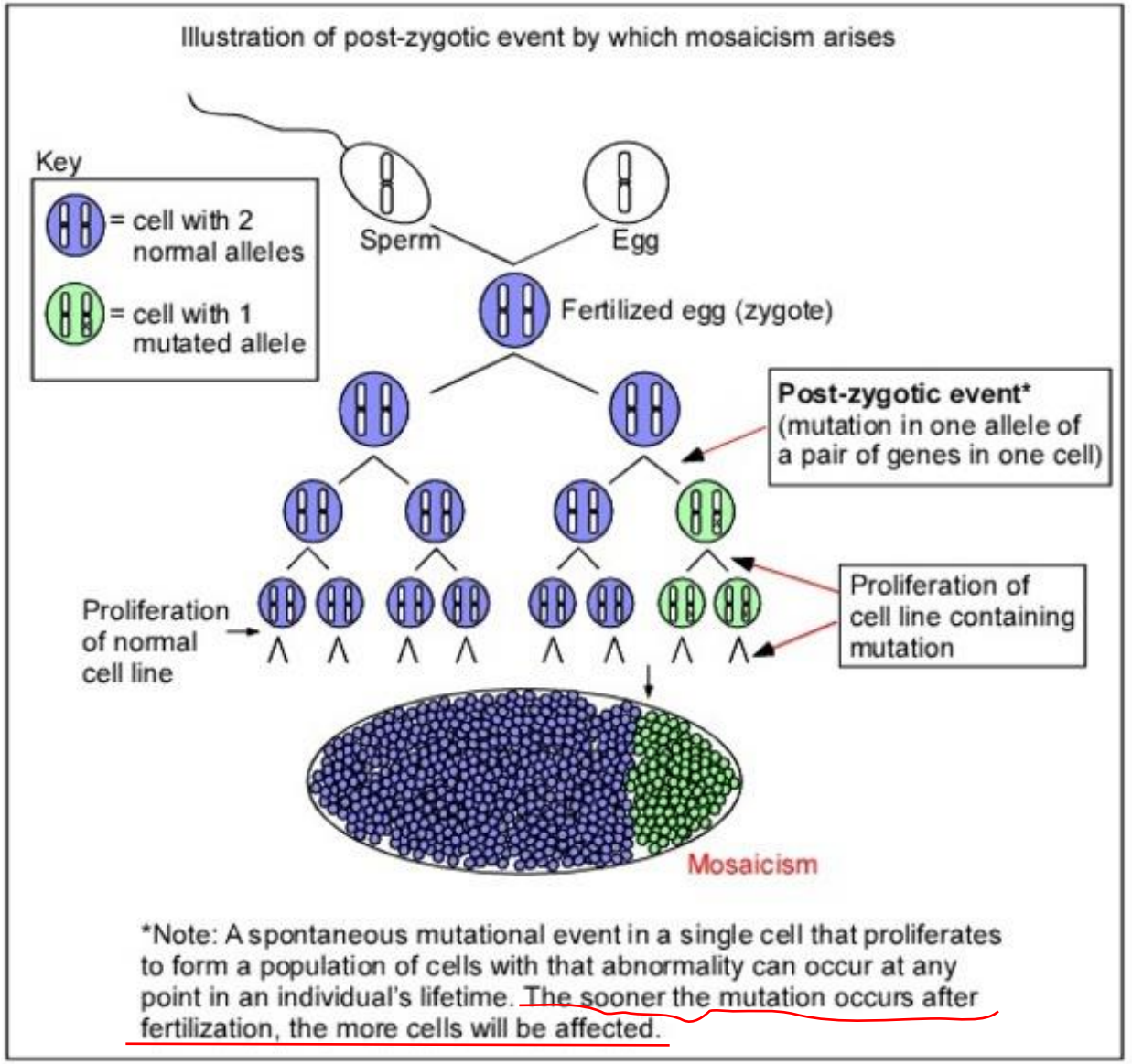
Mosaicism

- Mosaicism = two sets of genomes in an organism
- Somatic mosaicism refers to the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation.
- In contrast to inherited mutations, somatic mosaic mutations may affect only a portion of the body and are not transmitted to progeny.
- These mutations affect varying genomic sizes ranging from single nucleotides to entire chromosomes and have been implicated in disease, most prominently cancer.

What cell is a mutation happening in, and when?



Mosaicism = two sets of genomes in an organism

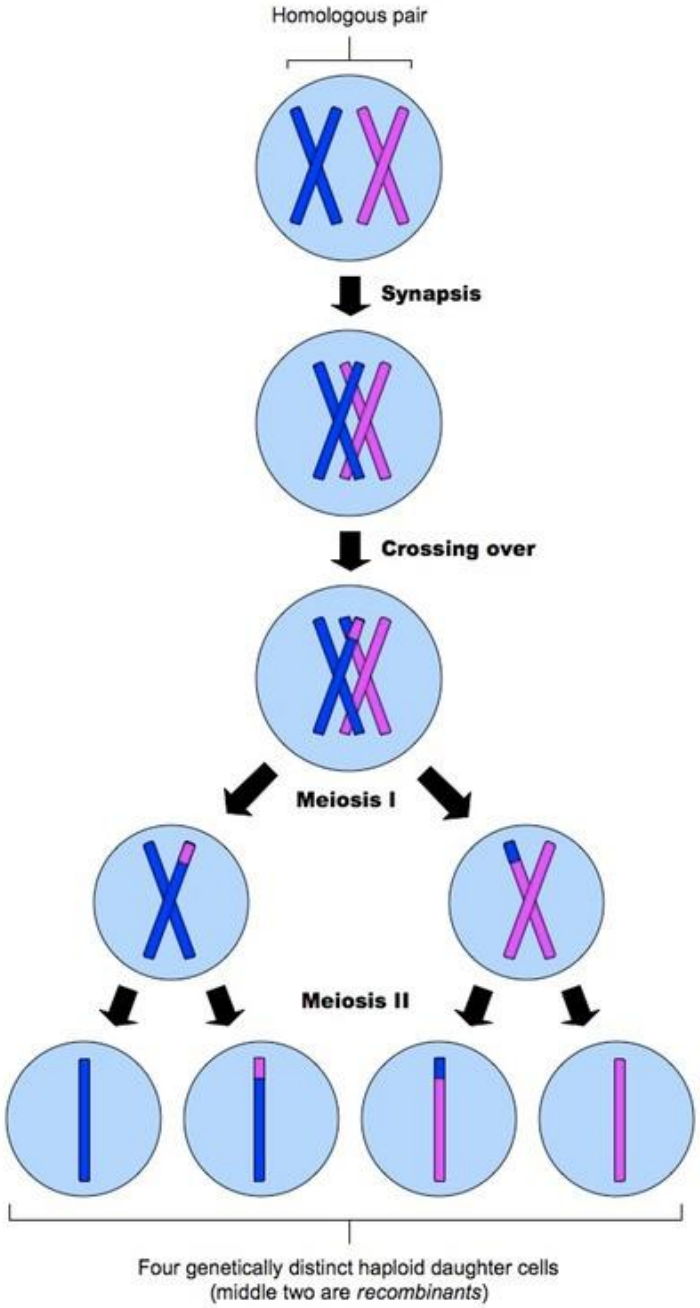


Aneuploidy

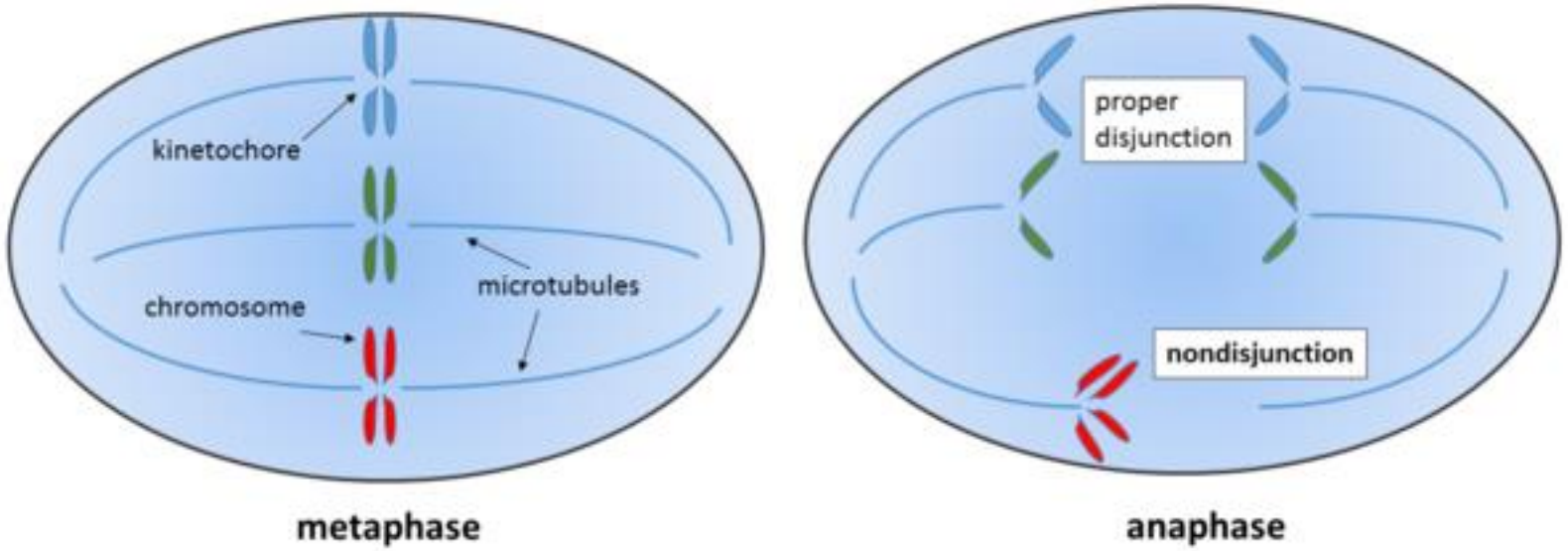
- Aneuploidy = abnormal number of chromosomes in a cell

- Aneuploidy usually caused by nondisjunction
  - Failure of homologous chromosomes to separate properly during cell division

Normal meiosis

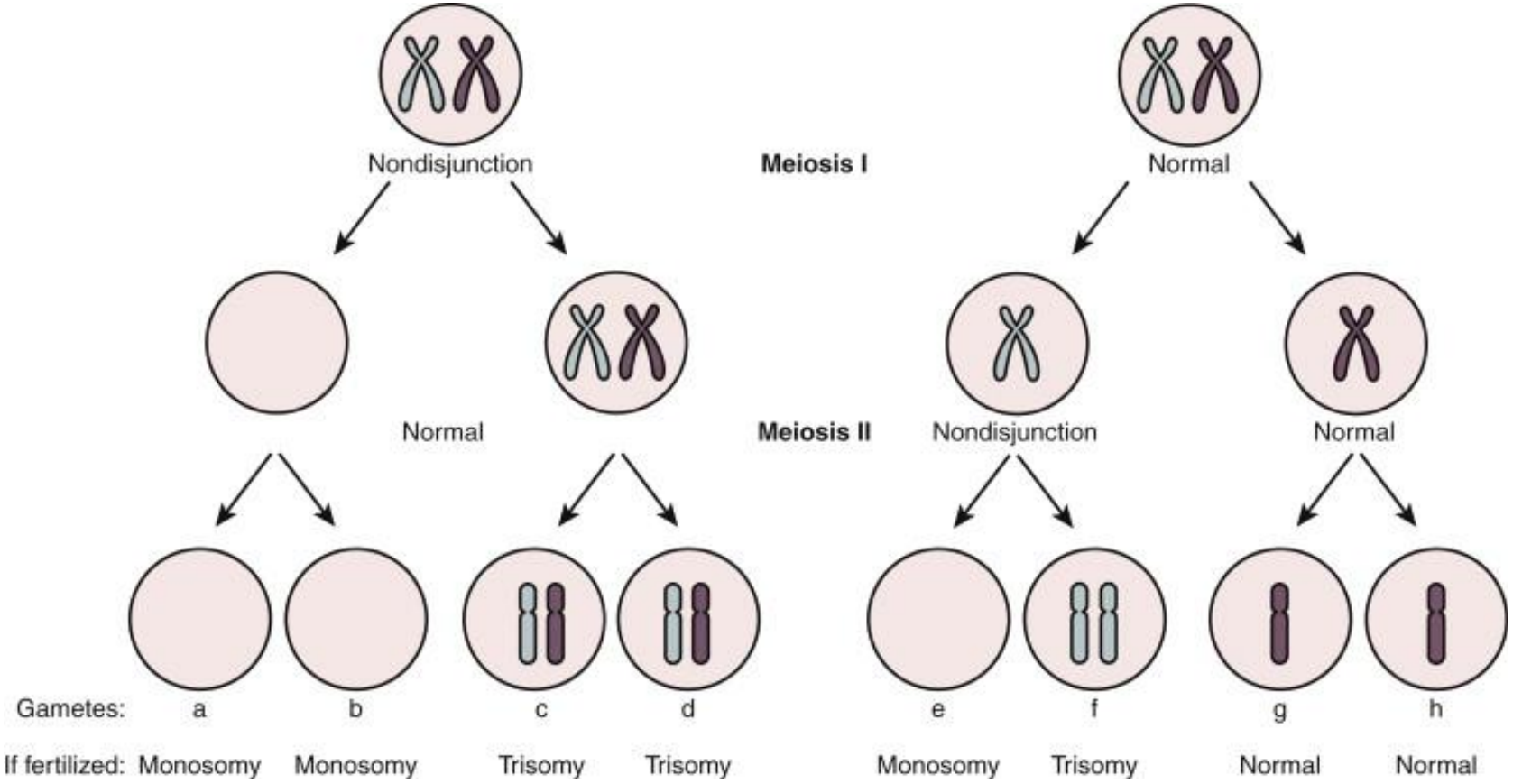


Nondisjunction



Can occur during mitosis, but only gets passed onto offspring if occurs during meiosis

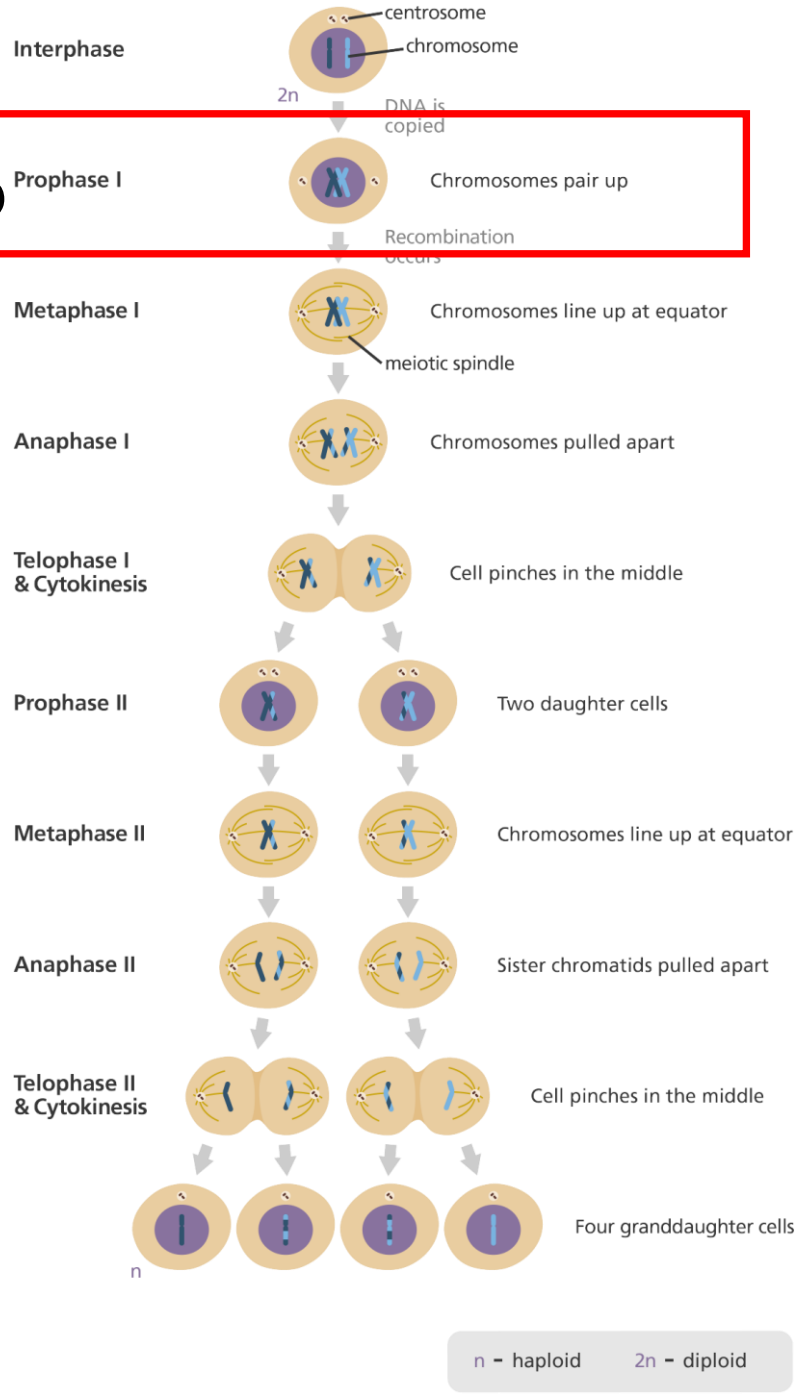
Aneuploidy usually caused by nondisjunction



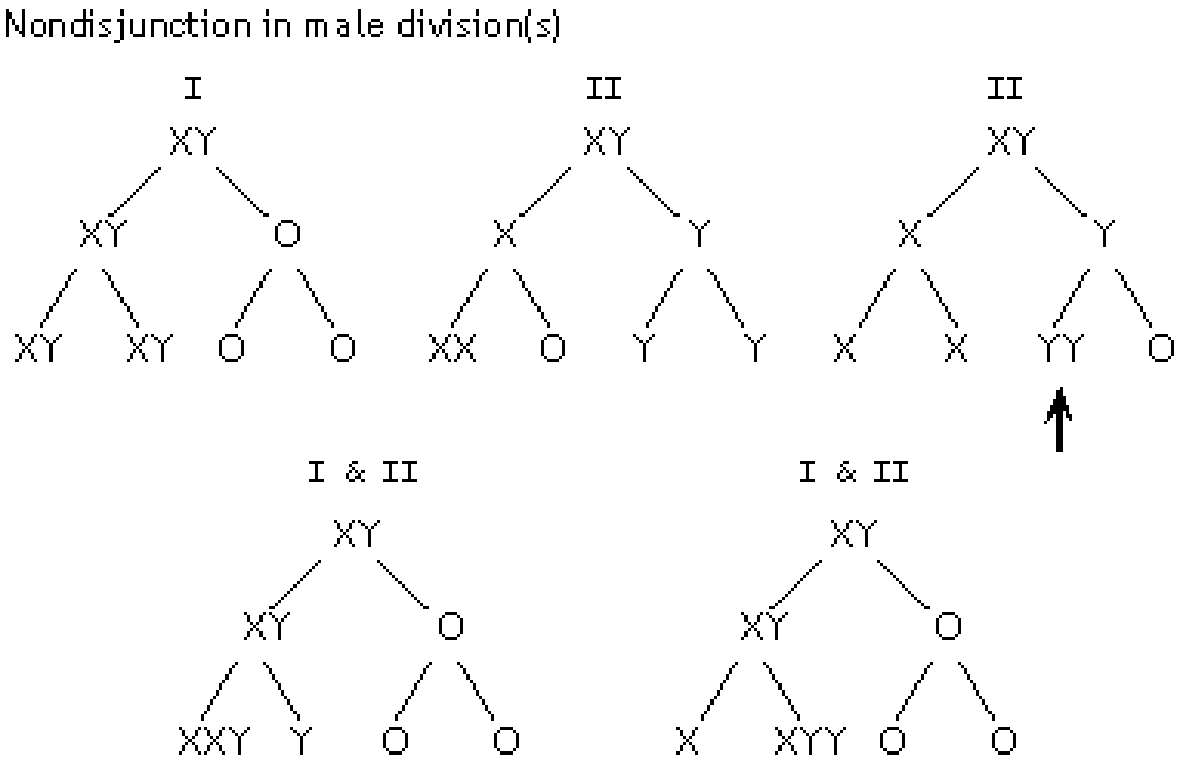
- Nondisjunction in meiosis 1 = pass on two different copies of chromosome
- Nondisjunction in meiosis 2 = pass on two same copies of chromosome

Why/how does non-disjunction happen?

- Happens more frequently in oocytes (egg cells)
  - Oocytes initially form before birth (at 3-4 months)
  - Arrested in prophase 1
  - Resume rest of meiosis after puberty as eggs are released
  - Cohesin which holds chromosomes together wears down over time?
  - Fewer crossover events in oocytes?
  - Spindle/centromere breakdown?



Male sex chromosome nondisjunction



- Also occurs in males:
  - 1 in 1,000 boys are XYY = nondisjunction had to occur in sperm

Aneuploidy = abnormal number of chromosomes in a cell

- Monosomy = 1 copy of a chromosome
  - Monosomy X (XO) = Turner syndrome
  - Short stature, delayed puberty, infertility, heart defects, learning disabilities
  - 1 in 2,000-2,500 live female births

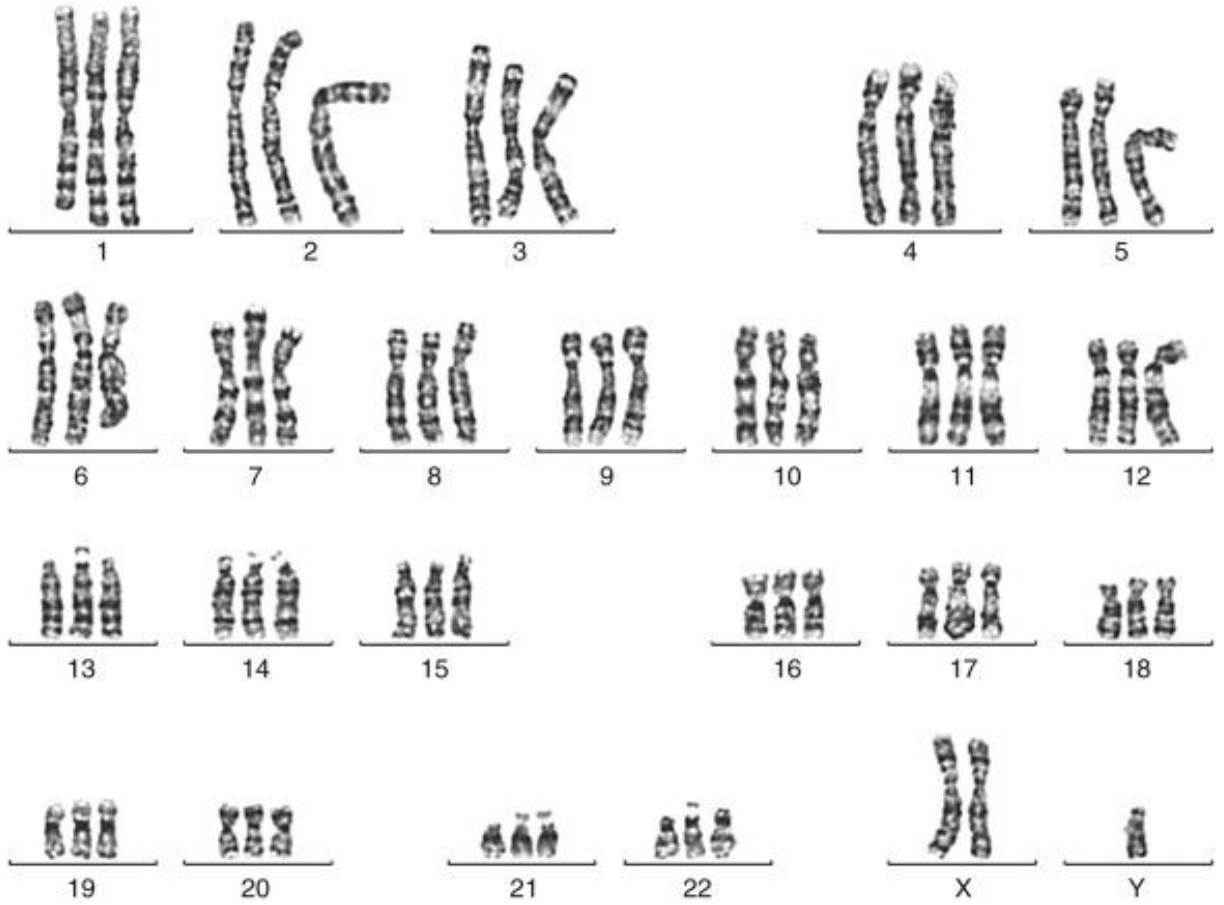
- Trisomy = 3 copies of a chromosome
  - Trisomy 21 = Down syndrome
  - Distinct facial appearance, intellectual disability, developmental delays
  - Maybe: thyroid/heart issues

- Others:
  - Trisomy X = Triple X syndrome 1 in 1,000 female births
  - XXY = Klinefelter syndrome = 1 in 500-1,000 males
  - XYY = XYY syndrome = 1 in 1,000 males
  - Trisomy 13 = Patau syndrome
  - Trisomy 18 = Edwards' Syndrome

Generally: deletion is more severe than duplication

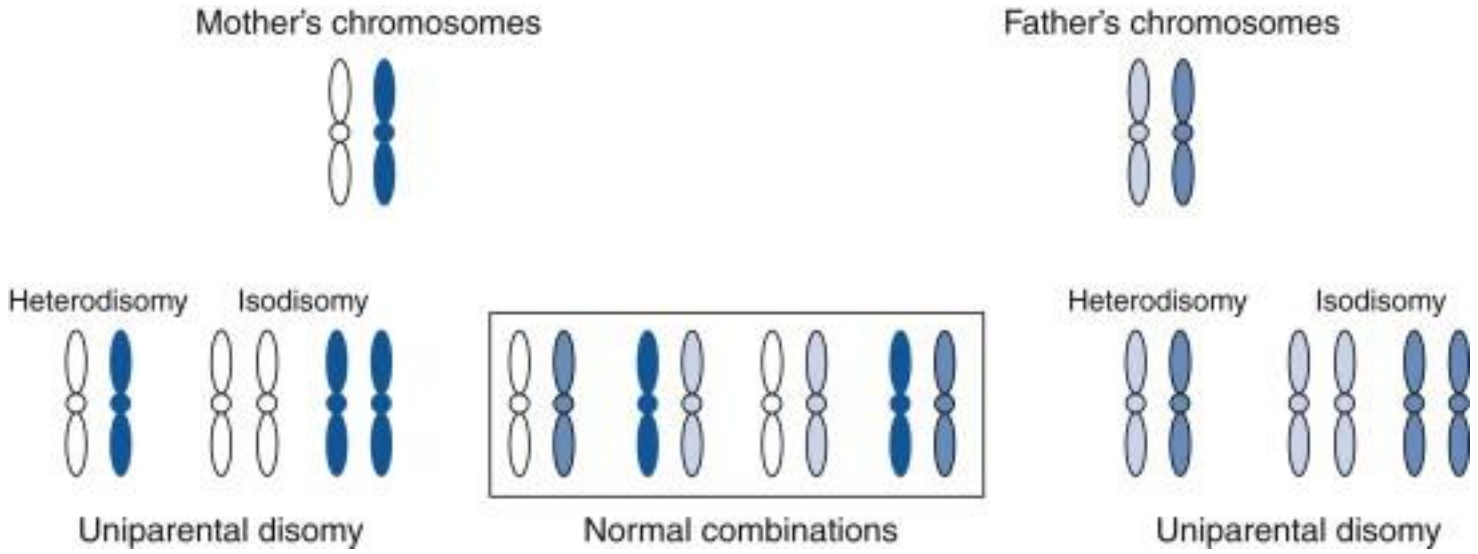
Triploidy

- 1-2% of all conceptions
- Usually early miscarriages but can survive to birth
- Euploid = an exact multiple of the haploid number of chromosomes
  - Monoploidy
  - Diploid
  - Triploidy
  - Tetraploid
  - etc



Uniparental disomy

- When two copies of a chromosome are inherited from the same parent
- **Heterodisomy** = inherited both of one parent's chromosomes
  - Error in meiosis I
- **Isodisomy** = inherited two identical copies of a chromosome from one parent
  - Error in meiosis II

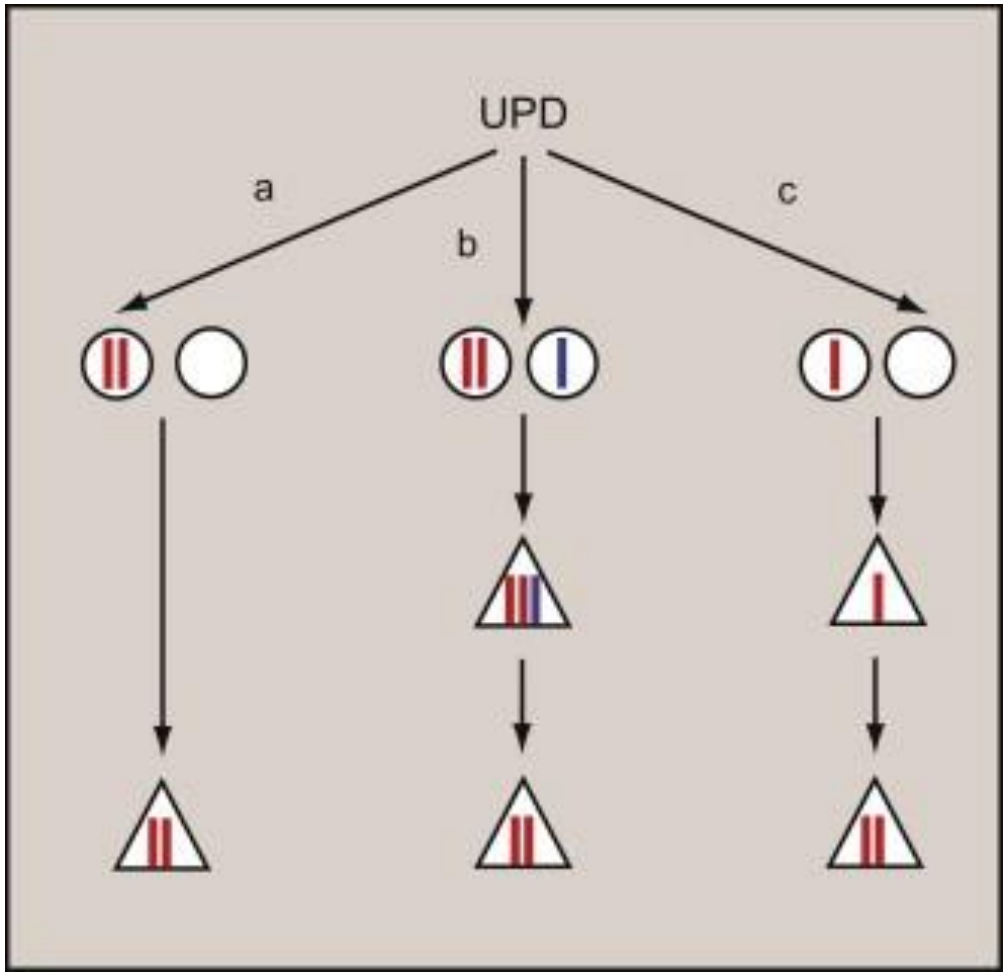


Uniparental disomy – how?

a) Errors in meiosis from both parents
(isodisomy or heterodisomy)

b) Trisomy rescue
(isodisomy or heterodisomy)

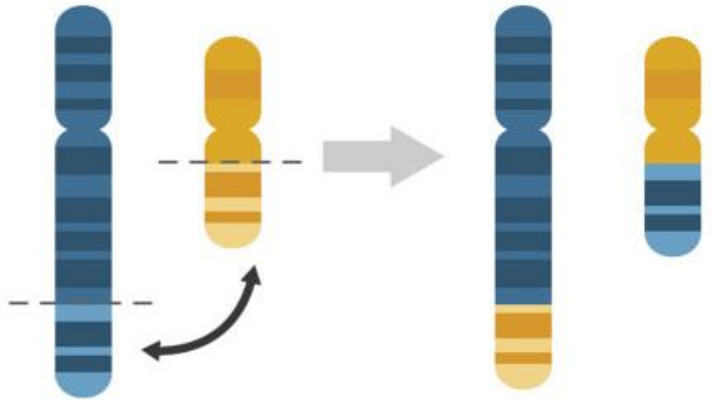
c) Duplication of single chromosome
(isodisomy only)



Abnormalities of Chromosome Structure

- Translocations + Robertsonian translocations
- Structural varients

Translocations



- Structural rearrangements of the chromosome

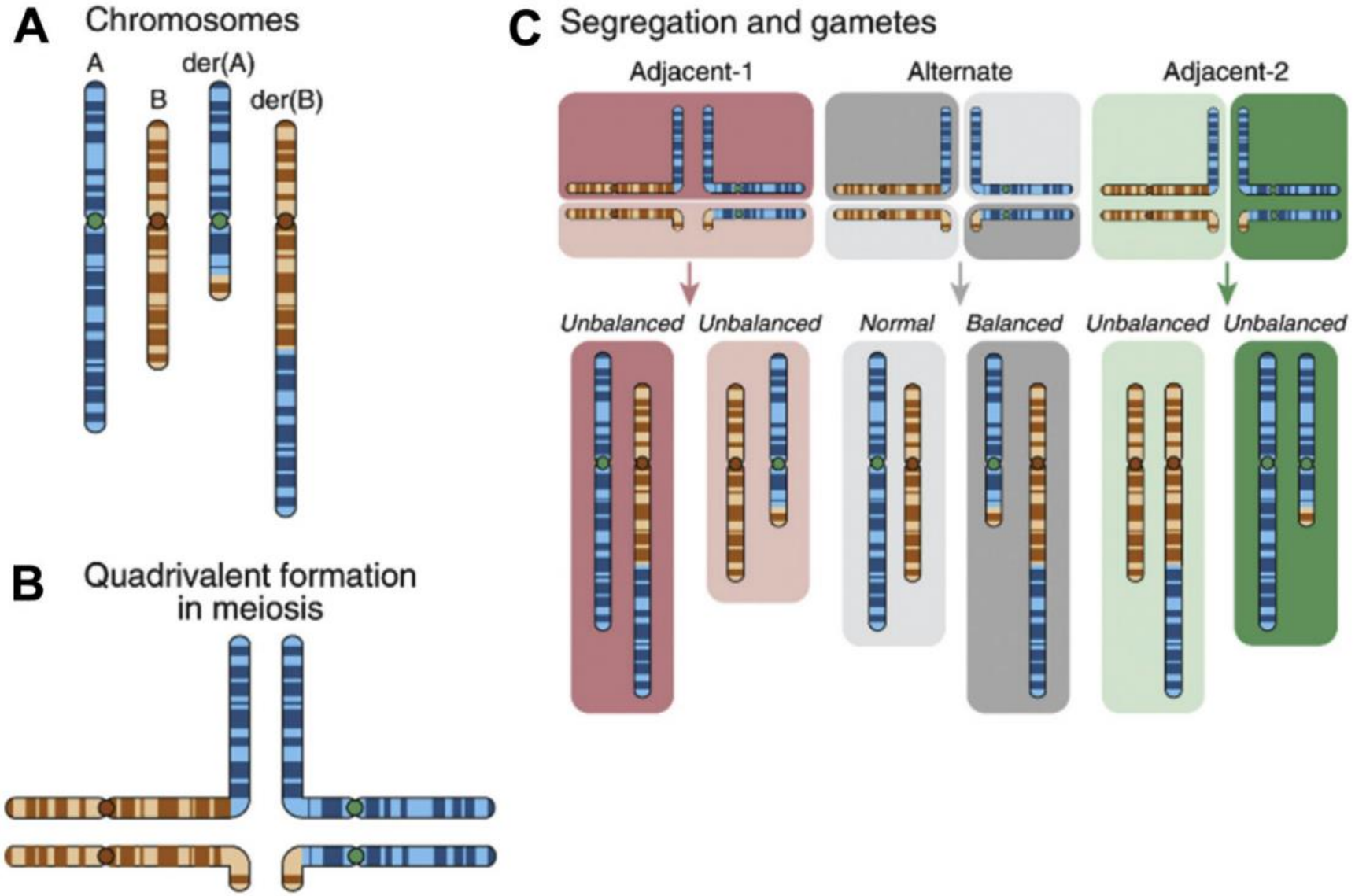
- Balanced
  - Normal complement of chromosomal material
- Unbalanced
  - Additional or missing material

- 1 in 375 newborns, most unaware until they try to have children

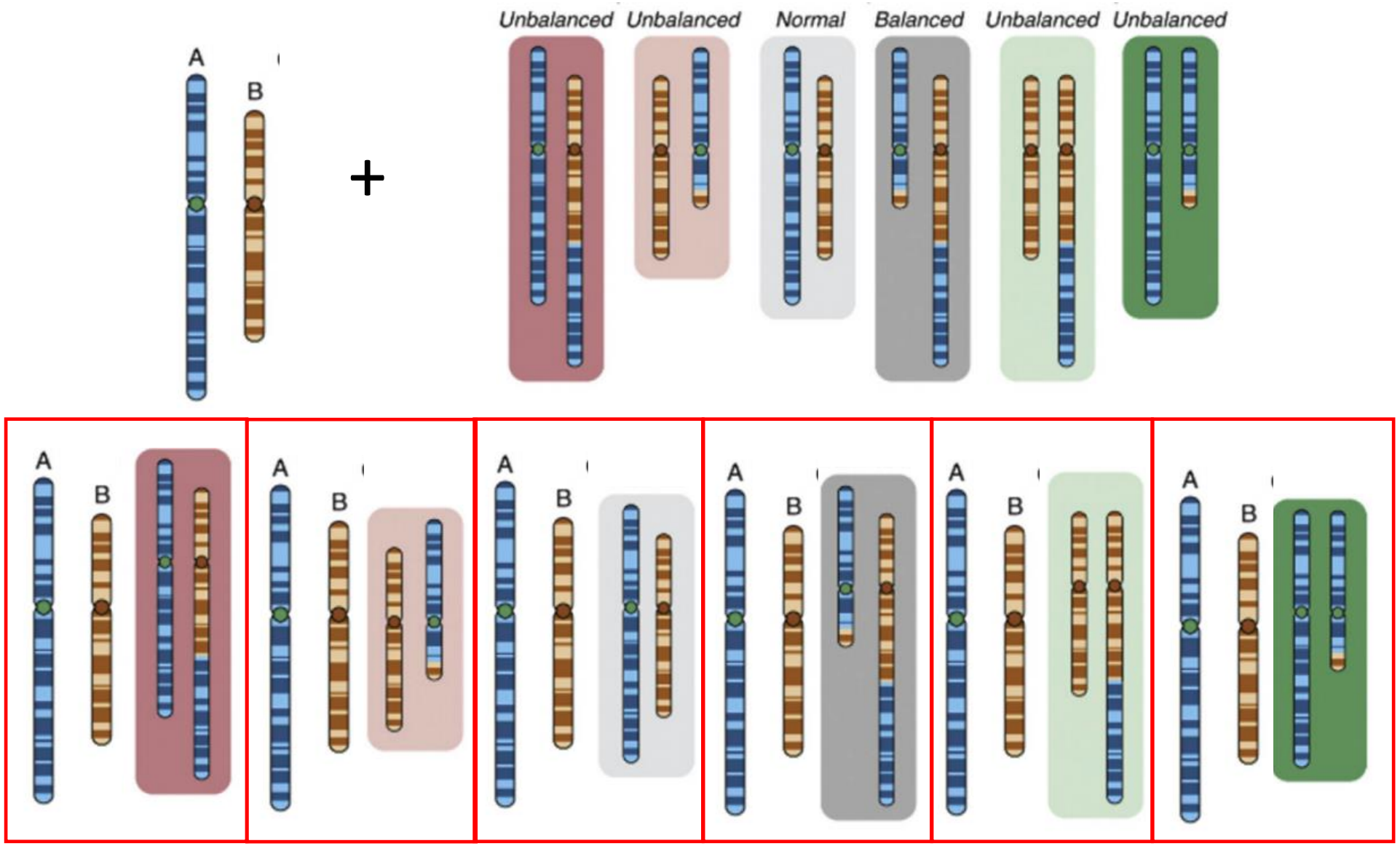
- Naming: **t(8;14)(q24;q32)** indicates a translocation between chromosomes 8 and 14
  - recombination points at 8q24 and 14q32

- Many specific translocations are seen more often, many linked with cancers

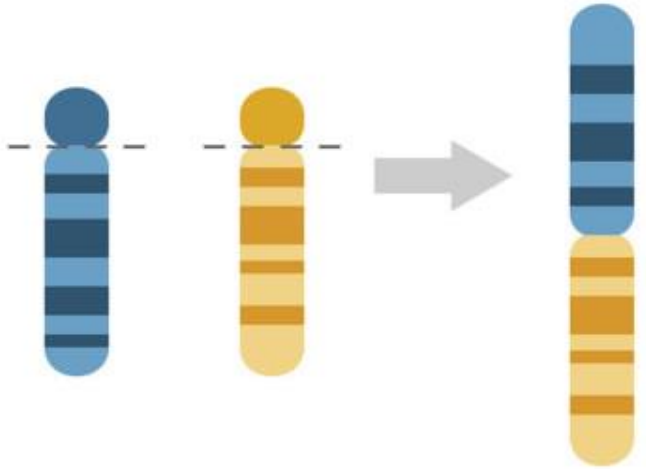
Meiosis with balanced translocations?



Fertilization with balanced translocations?



Robertsonian translocations



- Chromosomes 13, 14, 15, 21, 22 have only one functioning ‘arm’
- Robertsonian translocation = two of these chromosomes joining up into one chromosome, containing the long arm of both
- Balanced
- Individuals will have 45 chromosomes

Robertsonian meiosis/fertilization

If one parent is a Robertsonian translocation carrier

Mother has 13;21, 14;21, 15;21 or 21;22	10-15% risk of a baby with translocation Down's.
Mother has 13;14, 13;15, 13;21 or 13;22	1% chance of having a baby with trisomy 13.
Mother has 14;15, 14;22 or 15;22	Almost certainly no risk of having a baby with a trisomy, but possible risk of miscarriage or UPD.
Father with any Robertsonian combination	Low risk, below 1%, of any child being affected.

Images from rarechromo.org

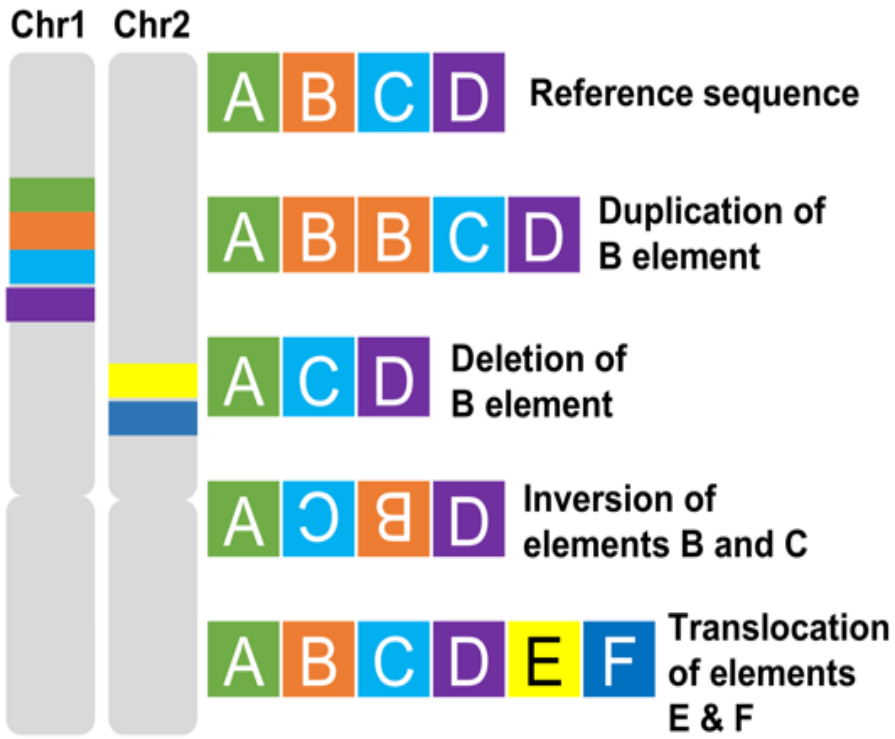
Notes on translocations

- A small number (~5%?) of down syndrome is caused by Robertsonian translocation.

- Some balanced translocations are causes of or associated with cancer types in **somatic** mutations (not germ line)

- Mechanism still under investigation, but happens more frequently at some known ‘breakage points’. Requires:
  - Double-stranded break
  - Non-homologous end joining

Structural variation (SV)



Jenn Fifita

What is it?

- Large genomic alterations affecting stretches of DNA >1000bp
- Affects chromosome structure
- Most prominent source of variation in the human genome
- Effects gene dosage and gene expression

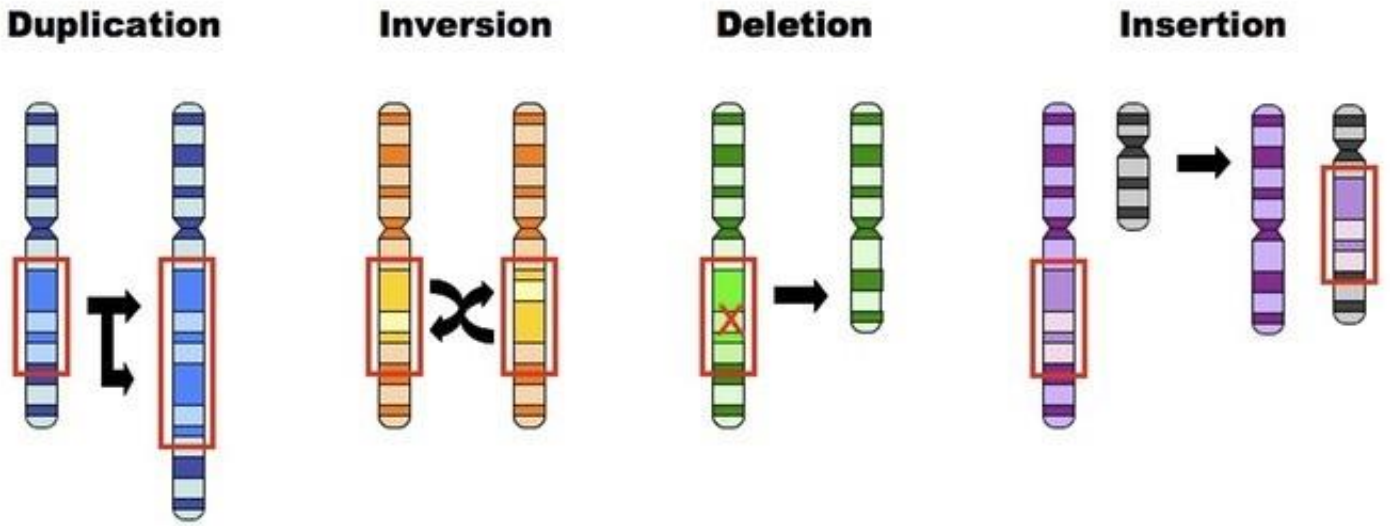
How to find it?

- Traditionally detected using laborious cytogenetic techniques
  - Multiplex ligation-dependent probe amplification (MLPA) or microarrays
- Recent development of bioinformatic tools for SV detection in NGS data now make high-throughput SV analysis possible

Relevance to ALS?

- Implicated in other neurodegenerative diseases
  - *incl. Parkinson's disease, Kennedy's disease, Spinocerebellar ataxias, Duchenne muscular dystrophy*
- ALS pathogenic *C9orf72* expansion is a similar phenomenon to copy number variation and is similar in size to SVs at up to 27,000bp long

Smaller/non-specific chromosome changes



- Insertion/Inversion similar to translocation
  - Maybe problems if gene interrupted, and in meiosis

- Duplications/deletions 5Mb or larger
  - <5Mb = microdeletion / microduplication
  - Can cause copy number variant (CNV)
  - Missing a gene copy more likely to cause problems than extra gene copy

Copy number variants (CNVs)

- In healthy population (Itsara et al., 2009):
  - 5-10% of people at least one del/dup larger than 500kb
  - 1-2% of people at least one del/dup larger than 1Mb

- What makes a CNV cause problems?
  - How many genes does it include? More = more likely to cause problem
  - Does it interrupt a gene?

- Extremely variable, even within same family

- Developmental delay / intellectual disability
  - 30% of unexplained cases had pathogenic duplication or deletion (2018 study)

- Many CNVs linked with Autism Spectrum Disorders (ASD), neurocognitive problems

Summary

- Mosaicism = mutation early in embryo development – person will have mutation in a certain % of their cells
- Aneuploidy = abnormal number of one chromosome set
  - Most trisomies/monosomies aren't survivable
- Uniparental disomy = both copies of a chromosome from one parent
- Translocations + Robertsonian translocations
- Changes within a chromosome = copy number variants
  - Deletions/duplications

- Next lecture: nucleotide mutations

BIOL3120 –Chromosomal mutations

LEARNING OBJECTIVES

On successful completion of this lecture, you will be able to:

- Explain the different types of chromosomal mutations
- Use this knowledge to solve problems in human genetics relating to heritability, polygenic inheritance and chromosomal mutations