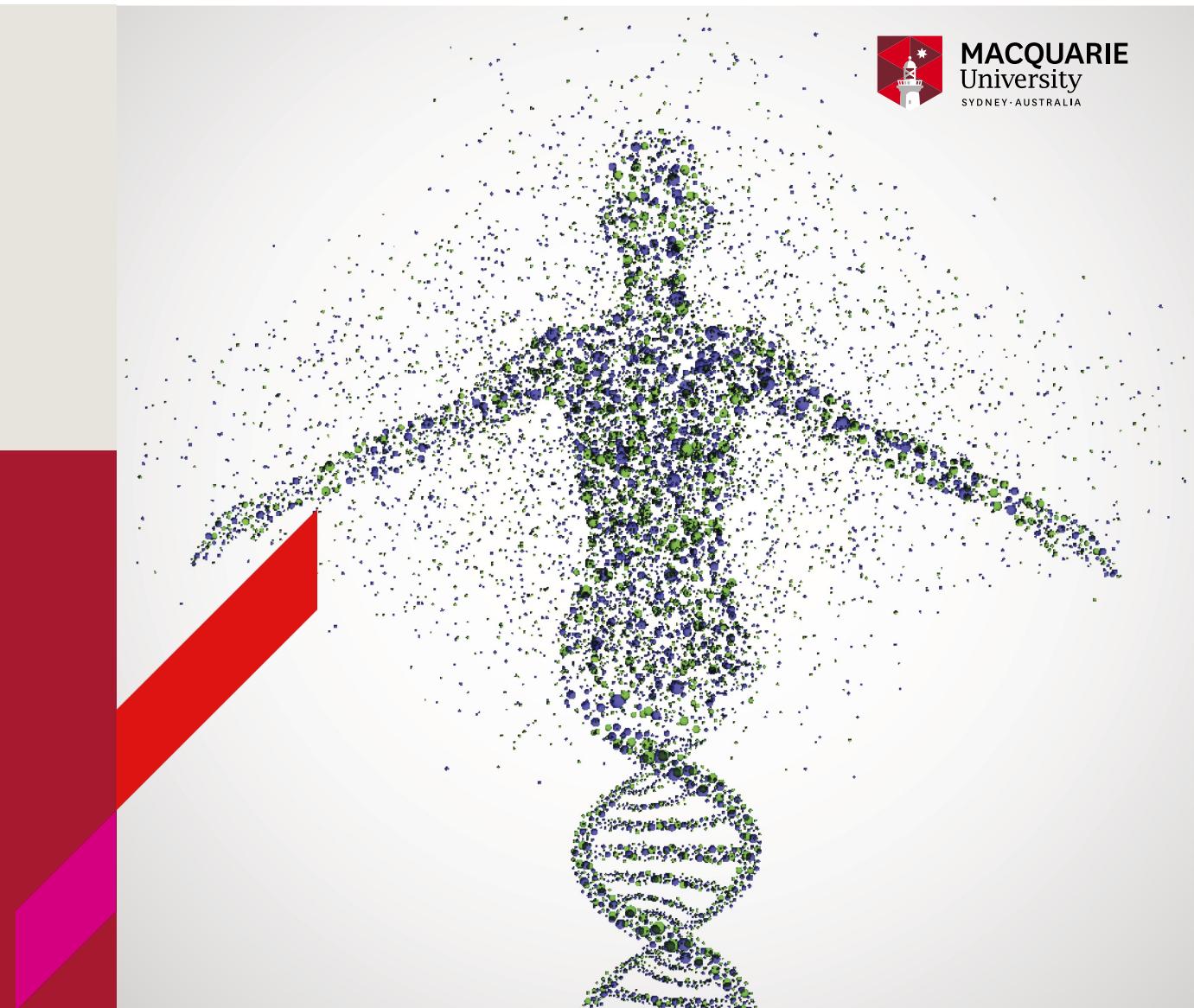


BIOL 3120

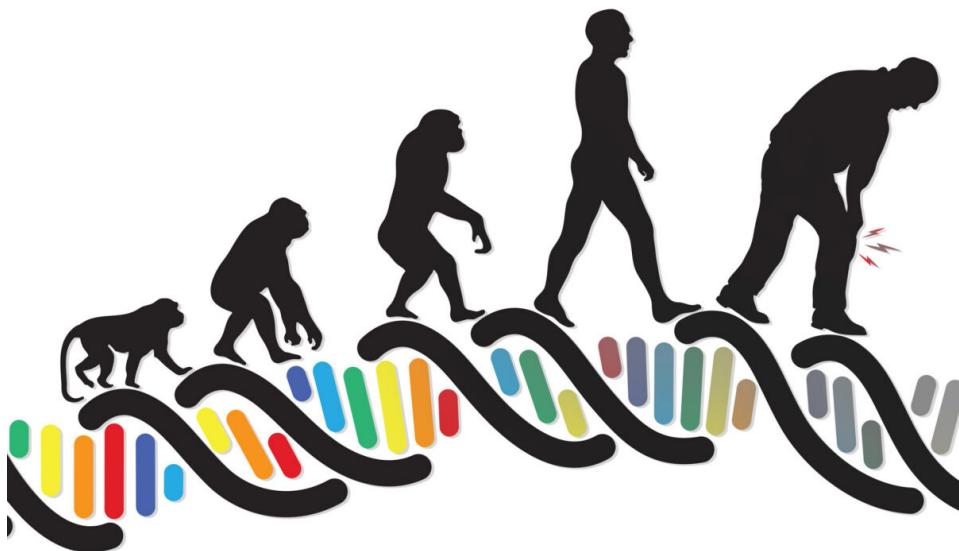
LECTURE 23 – UNIT REVISION



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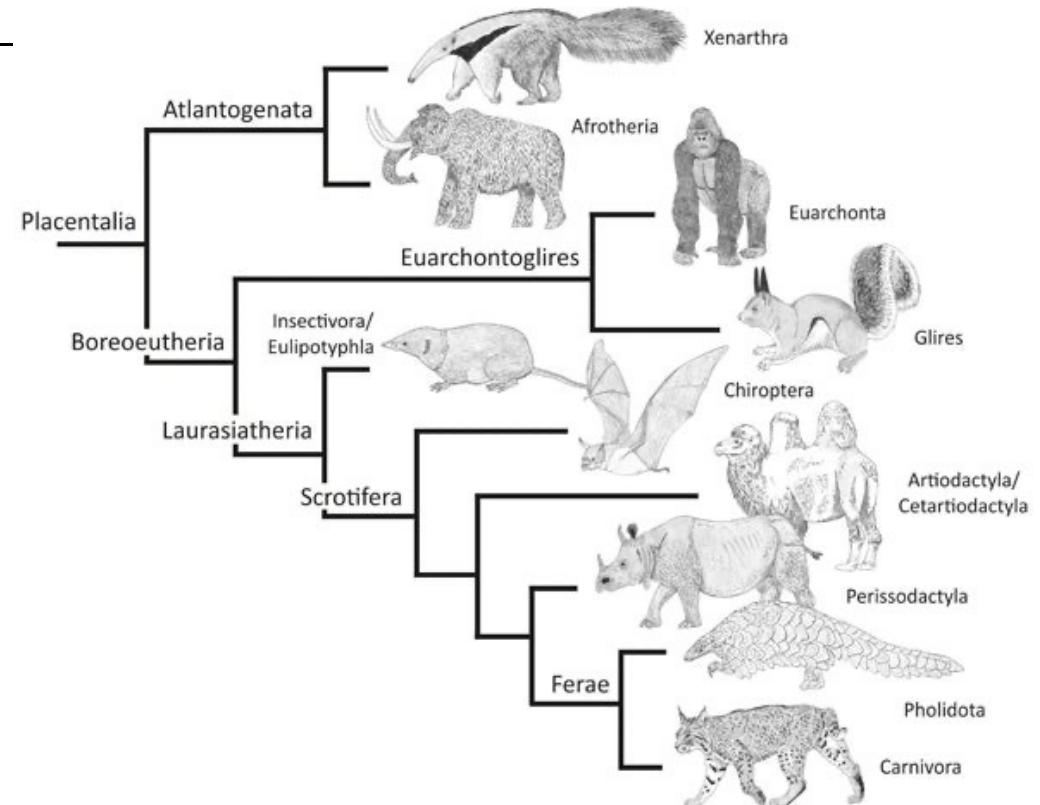
L2 -What is evolutionary medicine?



- Uses evolutionary biology to understand, prevent, and treat disease
- Evo Med, uses the knowledge that we and our pathogens are the product of evolution, to understand how we were put together, how we work, and how disease manifests

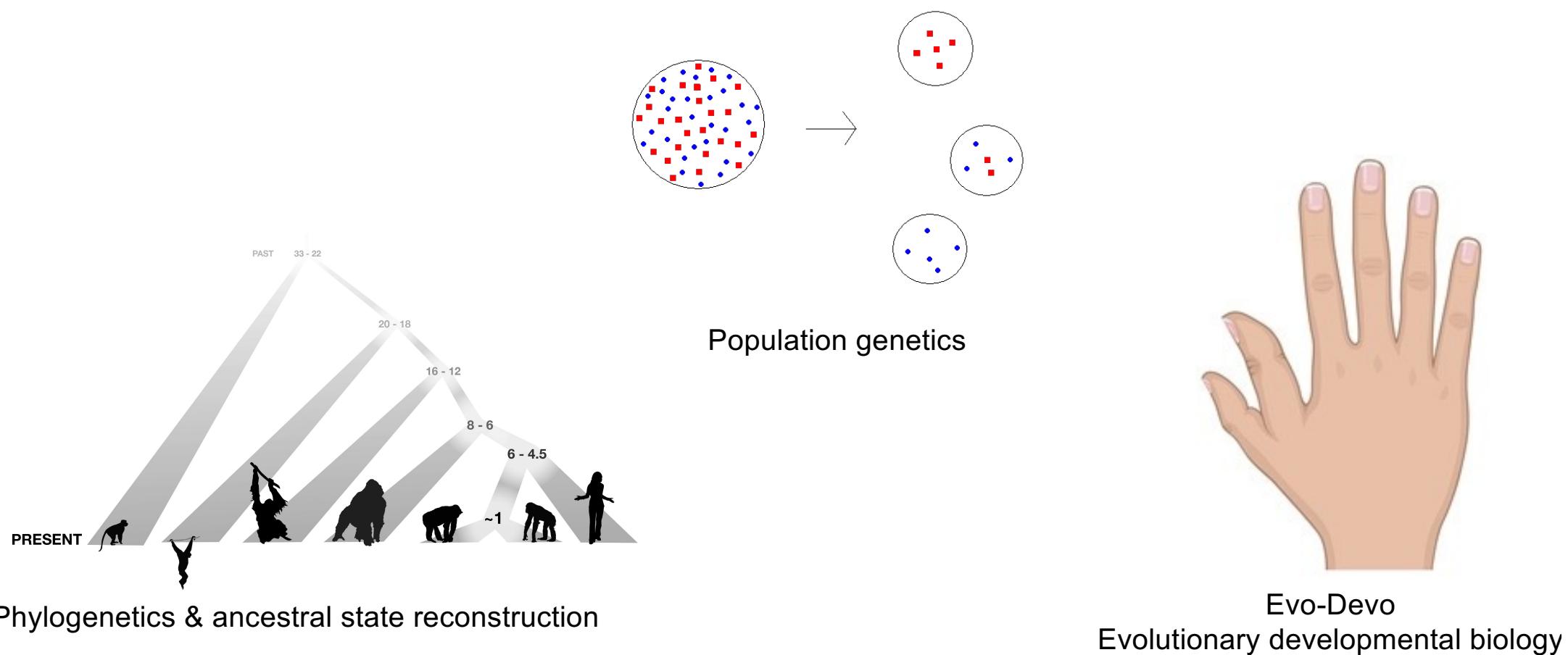
Core principles of evolutionary medicine

- Evolutionary understanding is required to fully understand traits including disease susceptibility
- Evolutionary processes shape traits and disease
- Natural selection maximises for reproductive success not health
- Evolution has trade offs
- Many signs and symptoms of disease are useful defenses (e.g. fever)



Darren Naish

Tools of evolutionary biology



Evolutionary comparisons allow us to understand how things were put together

- We can identify changes associated with the evolution of a trait
 - Identify candidate genes that underpin the process
- We can identify conserved components of a process
 - Most critical components for the physiological outcome
- We can identify how different animals do things differently
 - Alternative strategies for treatment

L4 -Emily's research lecture

- You should be able to:
 - Know which areas of research that can use zebrafish
 - Know the technologies that can be used in zebrafish
- In relation to the information presented in the lecture

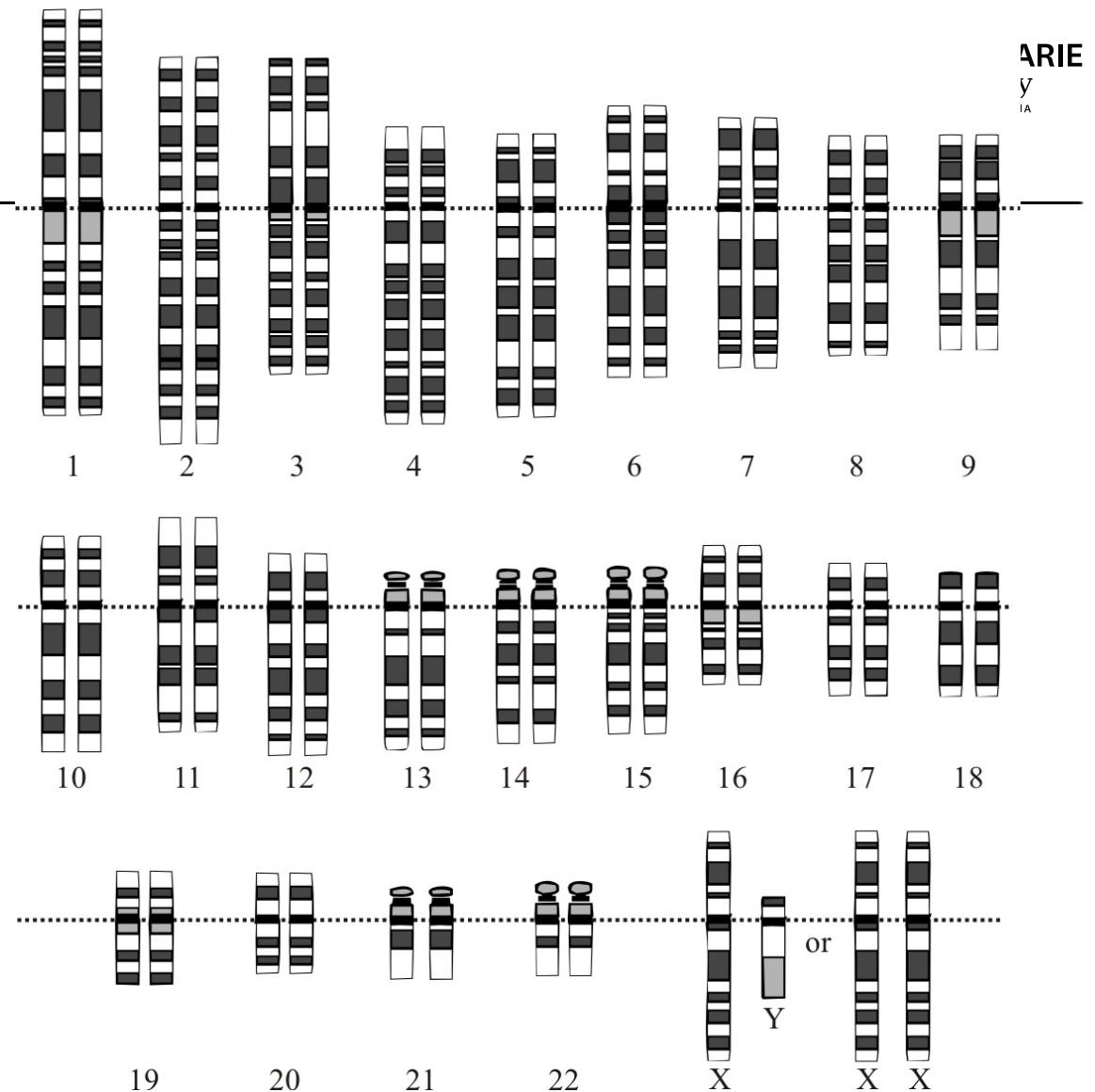
L5 – The human genome + gene structure

You should be able to:



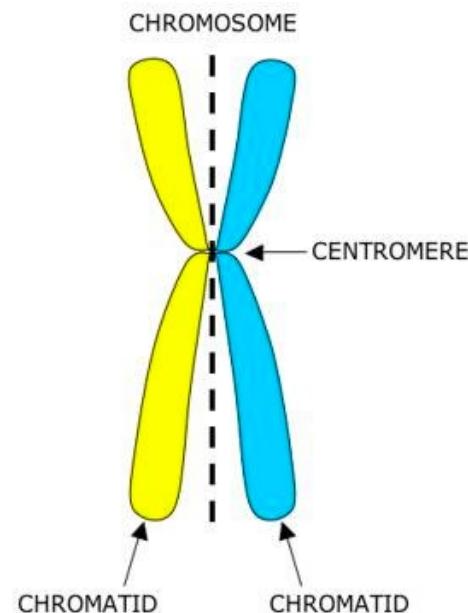
- Define the terms used to describe the human genome
- Understand the structure of chromosomes
- Understand the coding regions of the human genome

Chromosomes

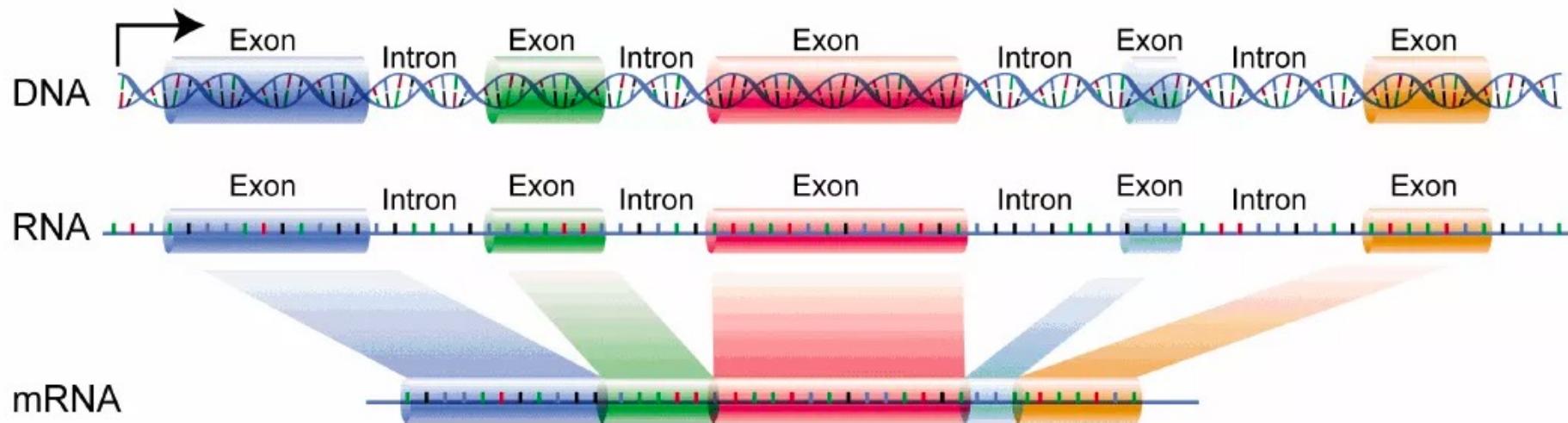


Chromosome related nomenclature

- Chromatin: the material of which chromosomes are made.
 - complex of DNA, and proteins (histones and non-histones)
- Chromatid: one of the two copies of a chromosome
 - joined at the centromere
 - two homologous chromatids are called sister chromatids.
- Centromere is DNA normally in a heterochromatin state
 - Site of spindle attachment to chromosomes (important in meiosis)



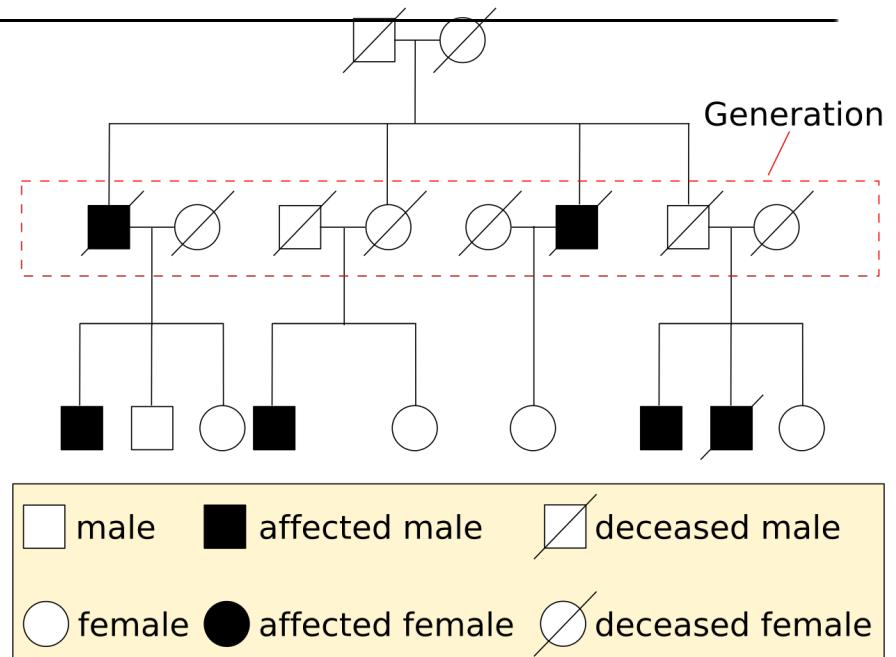
Exons and introns



- Exon: part of a gene that will encode a part of the final mature RNA
- Intron: any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product
- 1.1% of the genome is spanned by exons, whereas 24% is in introns, with 75% of the genome being intergenic DNA

L6 -Inheritance in humans

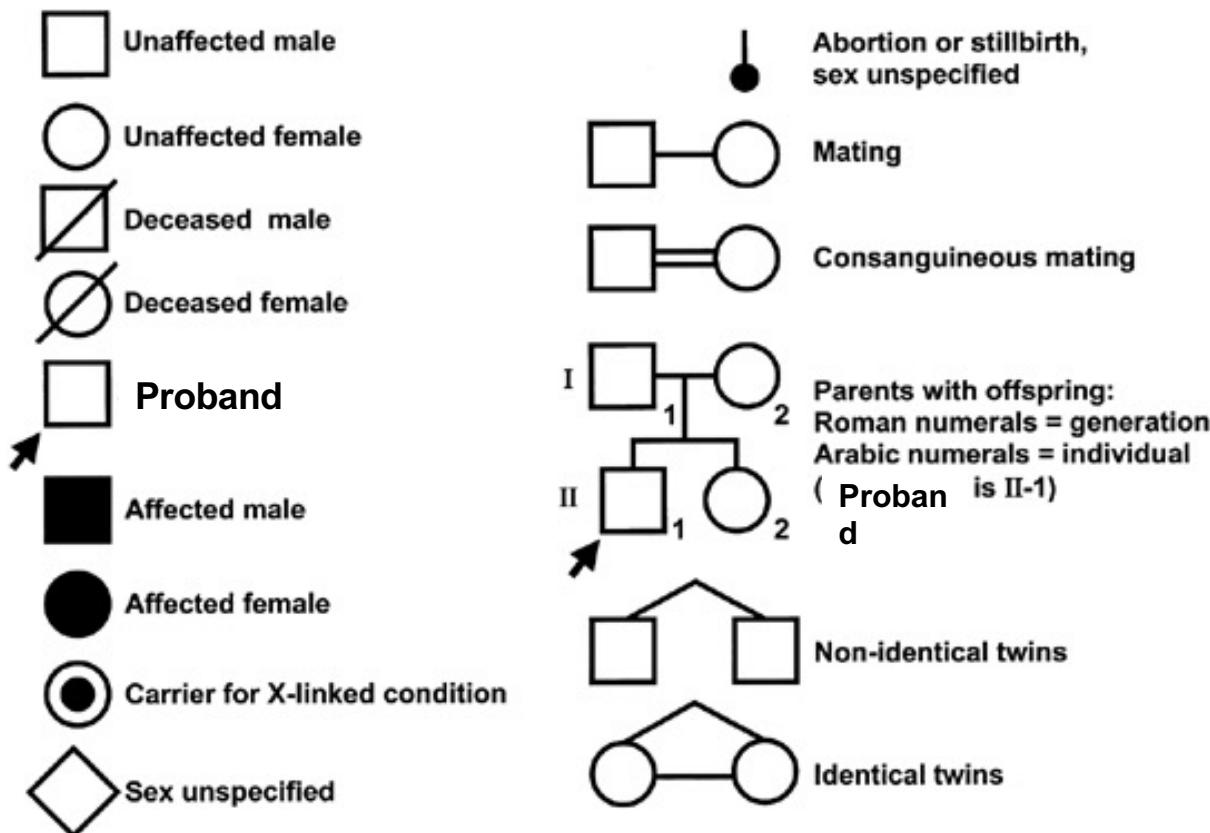
1. Autosomal dominant inheritance
2. Autosomal recessive inheritance
3. X-linked recessive inheritance
4. X-linked dominant inheritance
5. Y-linked inheritance
6. Mitochondrial inheritance



Human pedigree key



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Population genetics: Hardy Weinberg equilibrium

$$p + q = 1$$

Allele	A	a
Frequency	p	q

$$p^2 + 2pq + q^2 = 1$$

Genotype	AA	Aa	aa
Frequency	p^2	$2pq$	q^2

Assumptions of Hardy-Weinberg equilibrium

1. Large population (avoids random chance having a big impact on allele frequencies).
2. No selection (ie no allele is necessarily more likely to get passed on than another)
3. Mating is random (ie any individual has an equal chance of mating with any other individual).
4. Mutation either does not occur or is in equilibrium.
5. Immigration and emigration do not occur.

The consequences of abiding by the Hardy-Weinberg Law are that allele frequencies remain constant from generation to generation, so we can calculate allele/genotype frequencies

Do these assumptions fit for humans?

Recommended skills to practice



-
- Interpreting pedigrees
 - What is the most likely inheritance pattern? Justify/explain why it is the most likely
 - If another seems plausible/similarly likely, mention it and explain why it is less likely
 - Consider 'quirks' for each mode of inheritance:
 - Dominant – de novo mutation, reduced penetrance
 - Recessive – cis vs trans
 - X-linked – men pass on Y to sons, X to daughters
 - Mitochondrial - heteroplasmy level

Recommended skills to practice



-
- Hardy Weinberg
 - What info have you been given (p ? q^2 ? $2pq$? Etc)
 - What info have you been asked to provide?
 - All allele frequencies should add up to 1 ($p+q=1$)
 - All genotype frequencies should add up to 1 ($p^2 + 2pq + q^2 = 1$)
 - You might need to convert allele counts, or genotype counts into a frequency, or vice versa

Recommended skills to practice



- Answer the question!
 - Read the question fully
 - Underline what you are asked to do
 - Are you asked to give an allele frequency or counts, a genotype frequency or counts, or a proportion of the population

L7 – Heritability and Polygenics

You should be able to:



- Define heritability & understand it's limitations
- Discuss factors that indicate a possible genetic basis for a condition
- Discuss and calculate polygenic inheritance

How to tell how ‘genetic’ a disease is: Relative risk ratio

$$\lambda_r = \frac{\text{Prevalence of the disease in the relatives of an affected person}}{\text{Prevalence of the disease in the general population}}$$

TABLE 8-2 Risk Ratios λ_s for Siblings of Probands with Diseases with Familial Aggregation and Complex Inheritance

Disease	Relationship	λ_s
Schizophrenia	Siblings	12
Autism	Siblings	150
Manic-depressive (bipolar) disorder	Siblings	7
Type 1 diabetes mellitus	Siblings	35
Crohn disease	Siblings	25
Multiple sclerosis	Siblings	24

Value of 1 = no more likely to develop condition if you have an affected relative

Value higher than 1 = relative of affected person more likely to develop the condition

What is Heritability?



- A measure of how well differences in people's genes account for differences in their traits
 - Popularly referred to as 'nature versus nurture' debate
- Heritability is a statistical concept that describes how much of the variation in a given trait can be attributed to genetic variation
- Used in reference to the resemblance between parents and their offspring. In this context, high heritability implies a strong resemblance between parents and offspring with regard to a specific trait, while low heritability implies a low level of resemblance.
- An estimate of the heritability of a trait is specific to one population in one environment, and it can change over time as circumstances change.

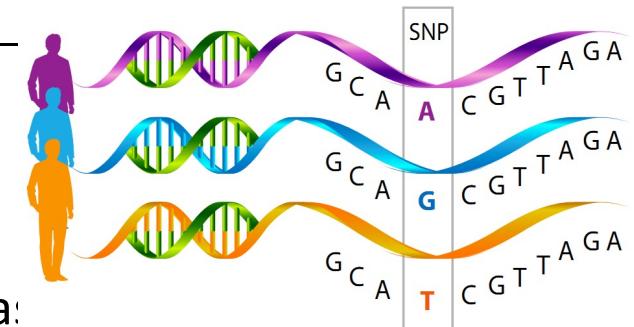
What is Heritability?

- Heritability estimates range from zero to one.

- A heritability close to zero indicates that almost all of the variability in a trait among people is due to environmental factors, with very little influence from genetic differences.
 - Characteristics such as religion, language spoken, and political preference have a heritability of zero because they are not under genetic control.
- A heritability close to one indicates that almost all of the variability in a trait comes from genetic differences, with very little contribution from environmental factors.
 - Many disorders that are caused by mutations in single genes, such as phenylketonuria (PKU), have high heritability
- Most complex traits in people, such as intelligence and multifactorial diseases, have a heritability somewhere in the middle, suggesting that their variability is due to a combination of genetic and environmental factors.

Polygenic Inheritance

- It's not just genes that you can inherit in a polygenic fashion
 - Disease risk alleles are also inherited polygenically
 - **Complex disease:** Most medical problems such as heart disease, Alzheimer's disease, asthma, Parkinson's disease, multiple sclerosis, osteoporosis, and sporadic MND, do not have a single genetic cause—they are likely associated with the effects of **multiple genes** in combination with lifestyle and environmental factors. These are called complex or multifactorial disorders.
 - **Susceptibility (risk) alleles:** an allele, usually inherited, that increases the likelihood of developing a complex disease. The combination of multiple susceptibility alleles and environmental factors may be additive or synergistic, leading to disease.
 - On their own, they are neither necessary nor sufficient to cause disease
- Ian Blair

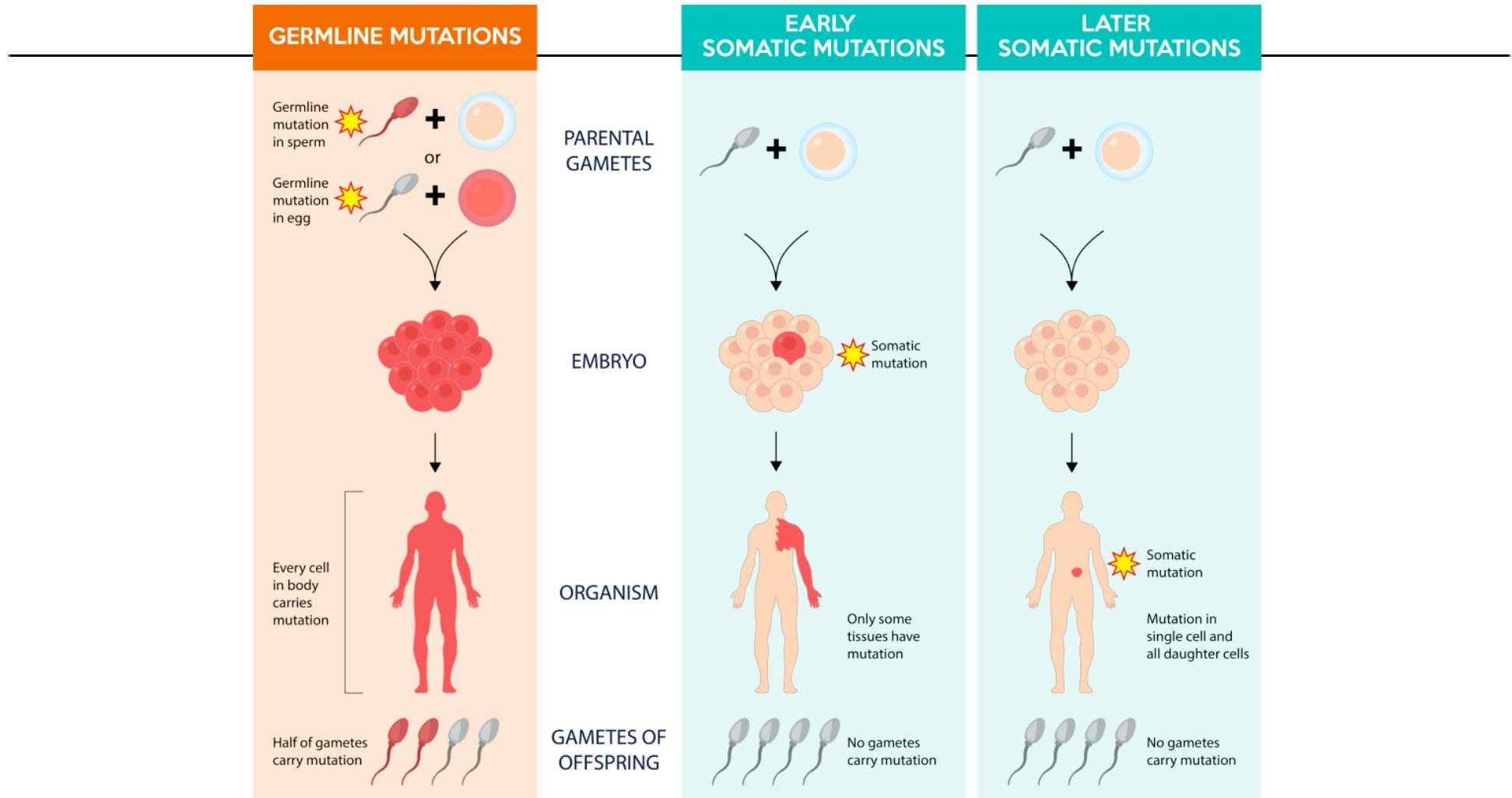


L8 – Chromosome mutations

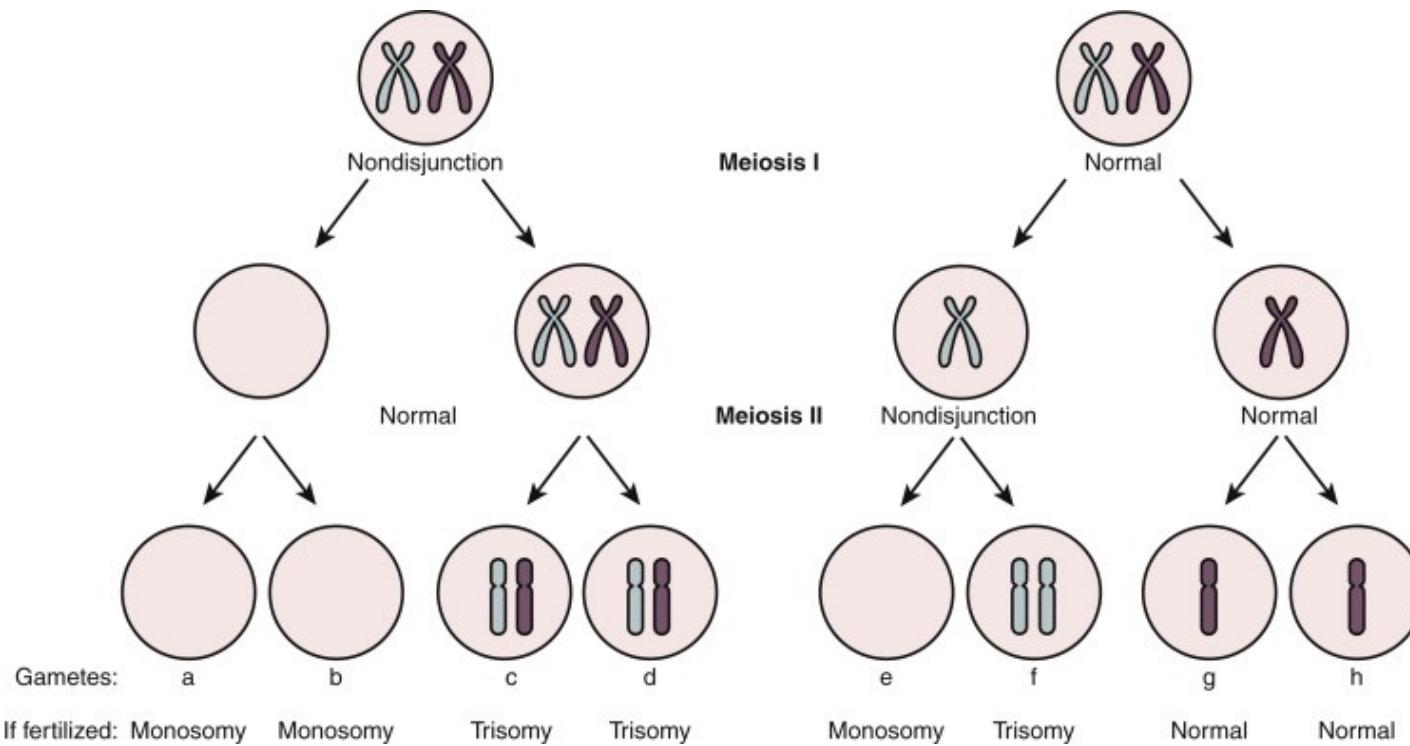
You should be able to:

- Explain the different types of chromosomal mutations
- Describe aneuploidy and uniparental disomy including causes and possible effects
- Describe balanced and robertsonian translocations, including impacts on gamete production/reproduction
- Discuss copy number variants (CNVs) and smaller chromosomal changes
- Use this knowledge to solve problems in human genetics relating to heritability, polygenic inheritance and chromosomal mutations

What cell is a mutation happening in, and when?

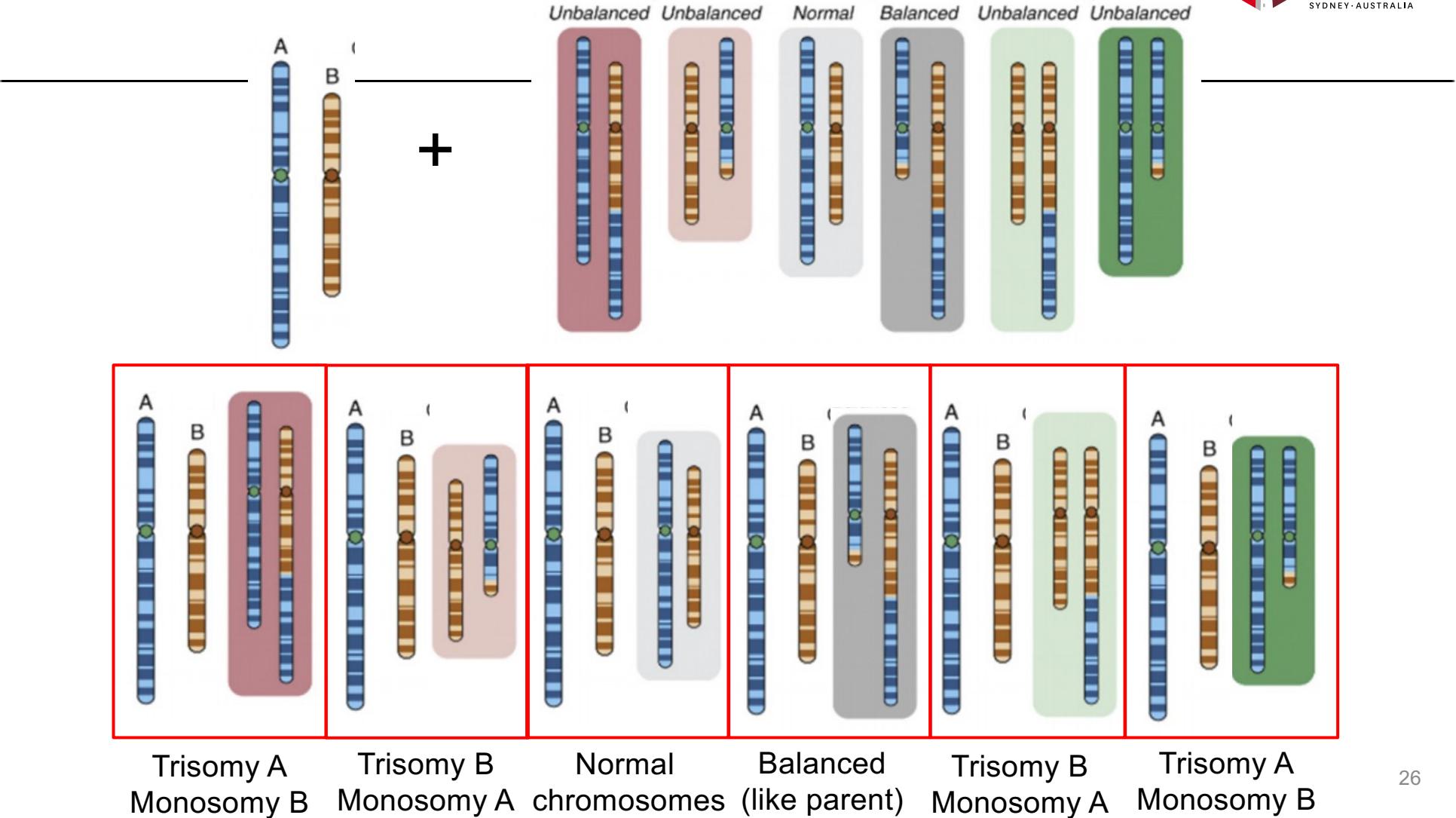


Aneuploidy usually caused by nondisjunction

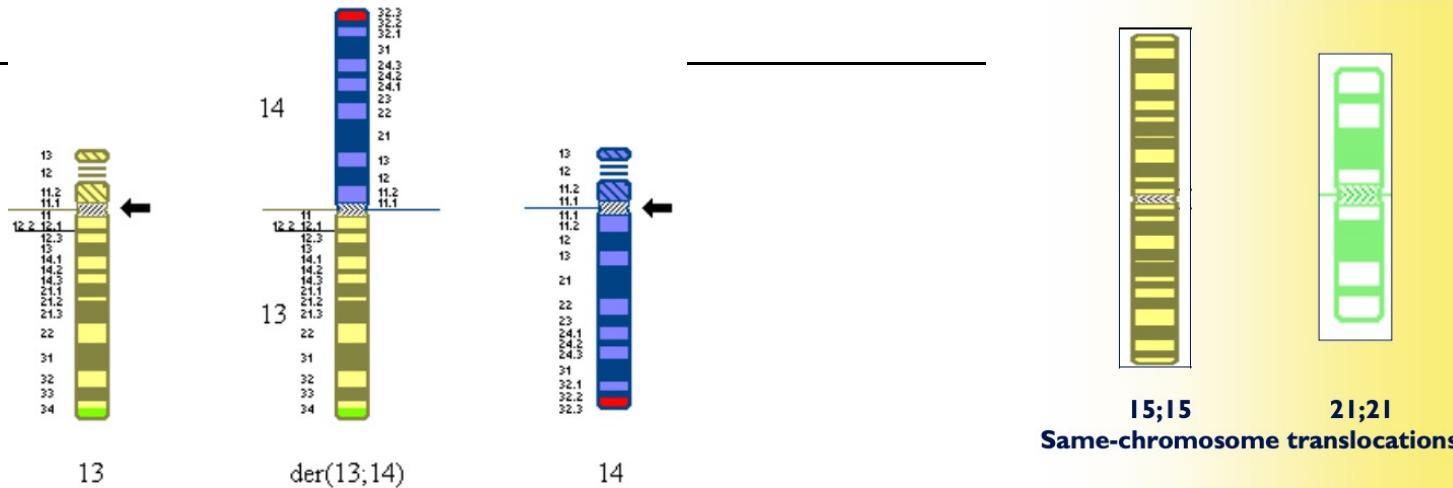


- Nondisjunction in meiosis 1 = pass on two different copies of chromosome
- Nondisjunction in meiosis 2 = pass on two same copies of chromosome

Fertilization with balanced translocations?



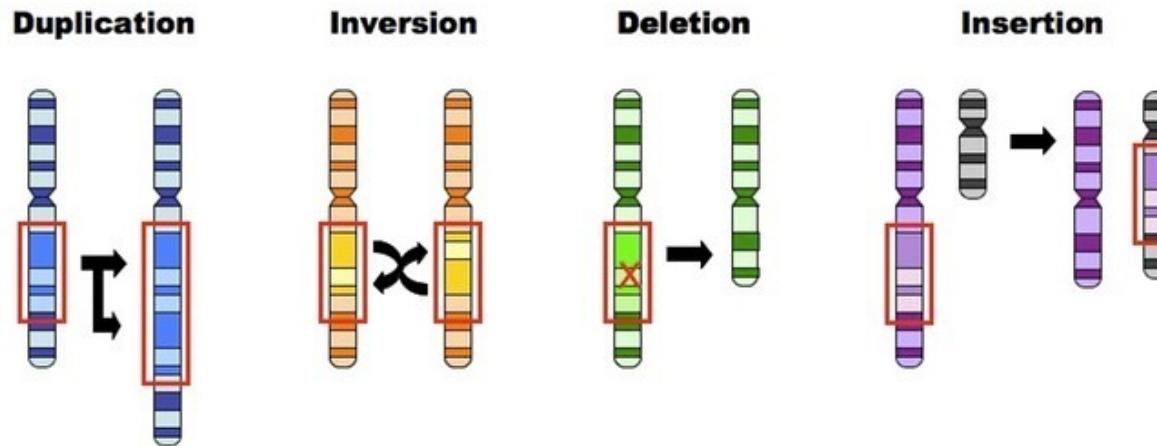
Robertsonian translocations



Robertsonian translocation	Approximately how common are carriers?
13;14	1 : 1,300
14;21	1 : 12,500
14;15	1 : 20,000
13;13, 13;15, 13;22, 14;22	1 : 50,000
13;21, 15;22	1 : 100,000
15;21, 21;21, 21;22	1 : 200,000

Images from rarechromo.org

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

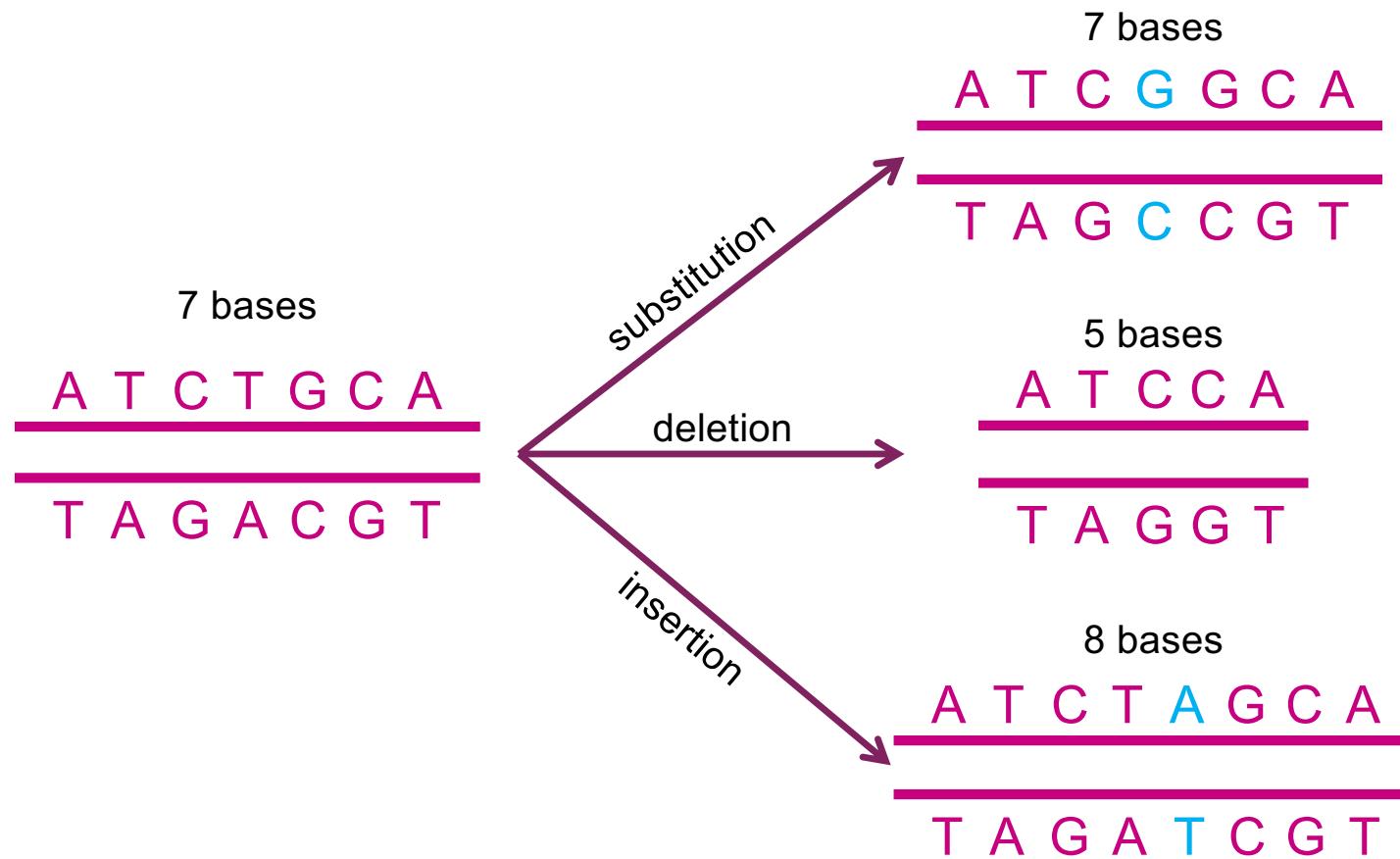
L9 – Nucleotide mutations

You should be able to:

- Identify and name nucleotide mutations
- Interpret nucleotide variations
- Understand repeat expansions

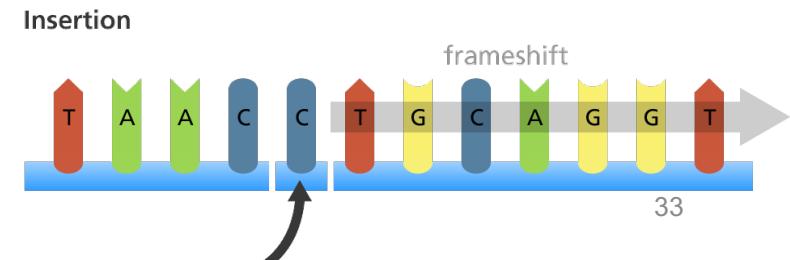
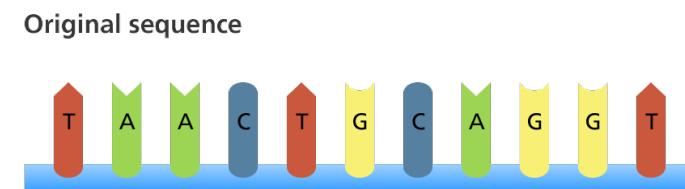
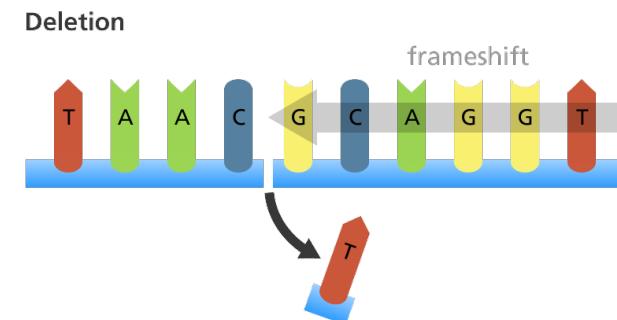
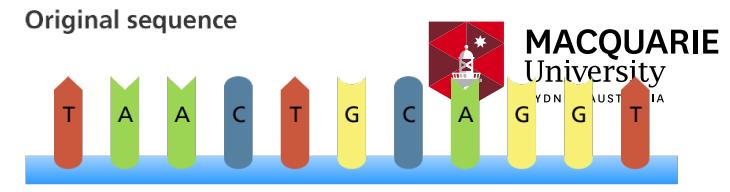
Nucleotide level variation

SINGLE NUCLEOTIDE AND INSERTION/DELETION VARIATION



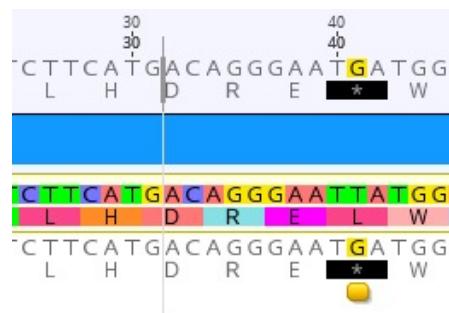
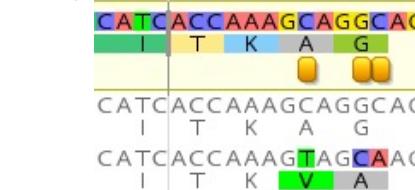
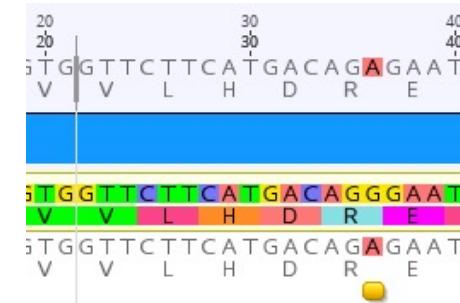
Deletions/Insertions

- Insertion or deletion of basepairs = Frameshift = all amino acids from there on affected
- Most likely a stop codon soon
 - 3/64 codons are stop codons = expect 1/23 codons to be a stop codon
- Very likely to impact function of protein
- Insertion/deletion of multiple of 3bp = no frameshift, extra or missing amino acids. May not impact function



Substitutions/Point Mutations

- Silent or synonymous mutation
 - No change to amino acid
 - In some cases can cause disease
- Missense mutation
 - Changes to another amino acid
 - Many possibilities
- Nonsense mutation
 - Changes to stop codon
 - How much is the protein getting shortened?



Nomenclature for the description of sequence variations



- First, describe the reference sequence
 - DNA, RNA or Protein
- Then describe the location
 - State the basepair or amino acid where the mutation has occurred
- Then describe the kind of mutation
 - Was is a substitution, deletion, stop codon, frameshift, etc.

Indicate the reference sequence:

DNA		
	coding DNA	c.
	genomic DNA	g.
	mitochondrial DNA	m.
RNA		r.
Protein		p.

Code:

substitution (for bases)	>
range	-
more change in one allele	:
more transcripts / mosaicism	:
uncertain	0
allele	[]
deletion	del
duplication	dup
insertion	ins
inversion	inv
conversion	con
extension	ext
stop codon	X
frame shift	fsX
opposite strand	o
translocation	t



Type of variation/mutation:

Substitution	
c.123A>G	on cDNA, A in 123 is replaced by G
p.P252R	on protein, proline (P) replaced by arginine (R)
Deletion	
c.546delT	deletion of T in 546
c.586_591del	for six bases deleted
p.F508del	deletion of phenylalanine (F) in 508
Duplication	
c.546dupT	duplication of T in 546
c.586_591dup	duplication of the segment 586 to 591
p.G4_Q6dup	duplication of the segment from glycine (G) in 4 to glutamine (Q) in 6
Insertion	
c.546_547insT	insertion of T between 546 and 547
c.1086_1087insGCGTGA	insertion of GCGTGA
p.K2_L3insQS	insertion of glutamine serine between lysine (K) in 2 and leucine (L) in 3
Inversion	
c.546_2031inv	segment 546 to 2031 inverted
Frameshift	
p.R83SfsX15	arginine (R) is the first amino acid changed, it is in position 83, it makes serine (S) instead, the length of the shift frame is 15, including the stop codon (X)



Recessive variants in *trans* or *cis*? The phase of the variants



- ie within the same allele or on different alleles
- Might be able to tell from sequence data but often no
- Check parents for variants
 - What if parents not available?
 - Same allele probably not an issue

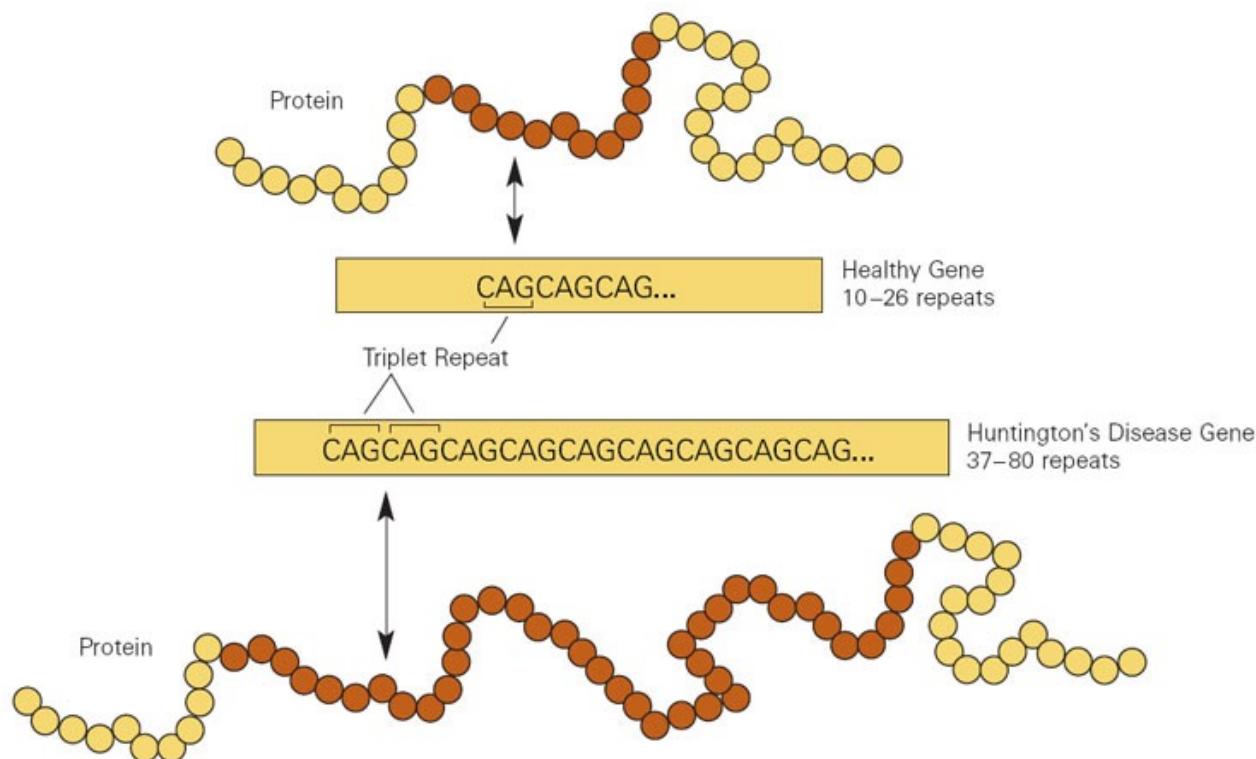
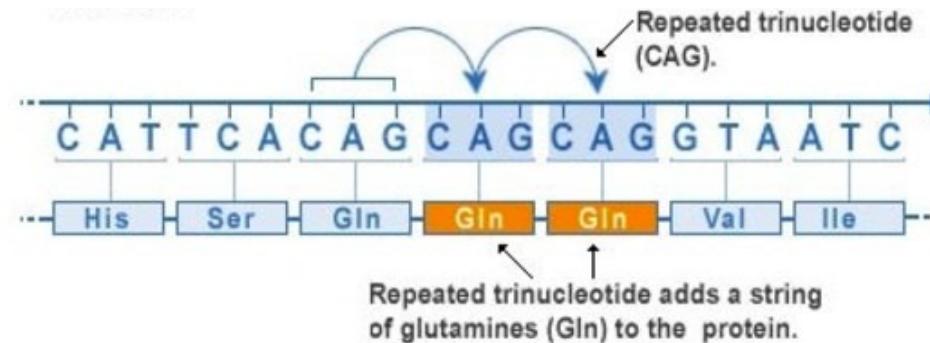
Variant classification

Questions to ask:

- Where in the gene is the change?
- If in an exon, what is the amino acid change? Bioinformatics predictions of the outcome on protein function
- Has this variant been reported in literature? Has a similar variant been reported (same residue?)
- Is this variant seen in healthy populations? What's the frequency?
- Is this residue conserved across other species' version of this protein?

Repeat expansions

- Some genes contain short repetitive sequences
- These repetitive sequence can expand and cause disease
 - >40 diseases, primarily affecting the nervous system
- Expanded trinucleotide repeat diseases were the first discovered and most frequent
 - Tetra-, penta-, hexa- and dodeca-nucleotide repeat expansions exist
- Can experience anticipation
 - Decreasing age of onset or increased severity of disease across generations



L11 – Genetic Testing Techniques

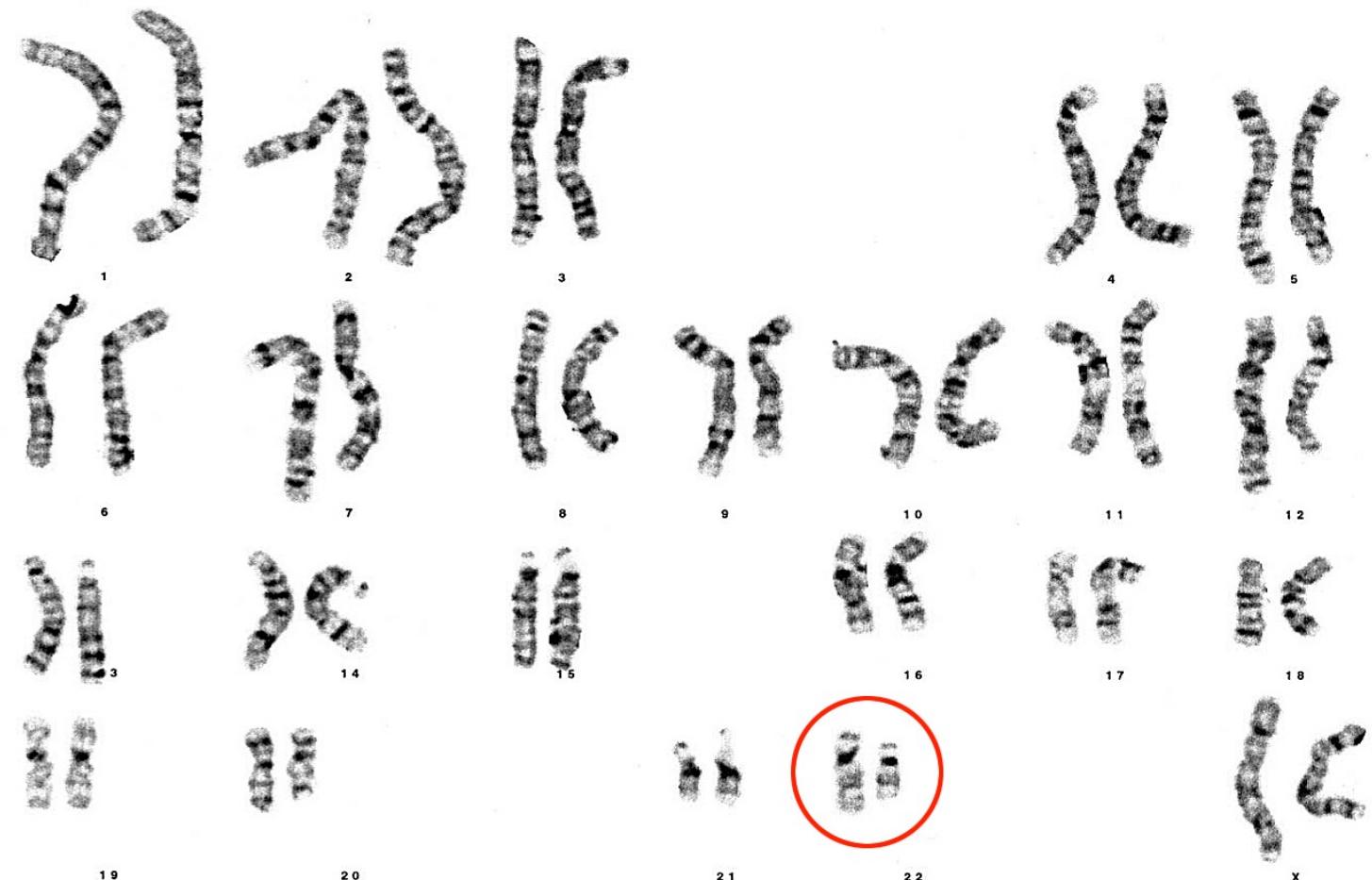
You should be able to:



- Identify and understand the technologies that detect chromosomal mutations
- Identify and understand the technologies that detect nucleotide mutations

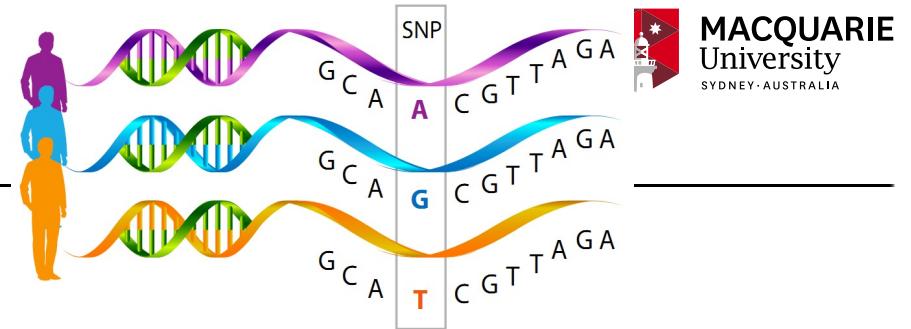
Karyotype

- ~5Mb and larger deletions/duplications detectable
- Can detect Translocations
- Mosaicism for detectable changes (count cells)



Microarray

- CGH / SNP
- Detects
 - Copy Number Variants over ~50kb
 - Homozygosity / uniparental disomy
- Can't detect
 - Balanced translocations
 - Inversions etc
 - Don't know where duplications are



A Targeted



B Targeted with Backbone

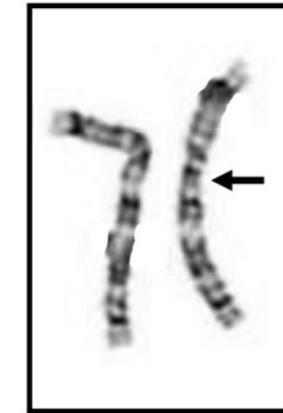
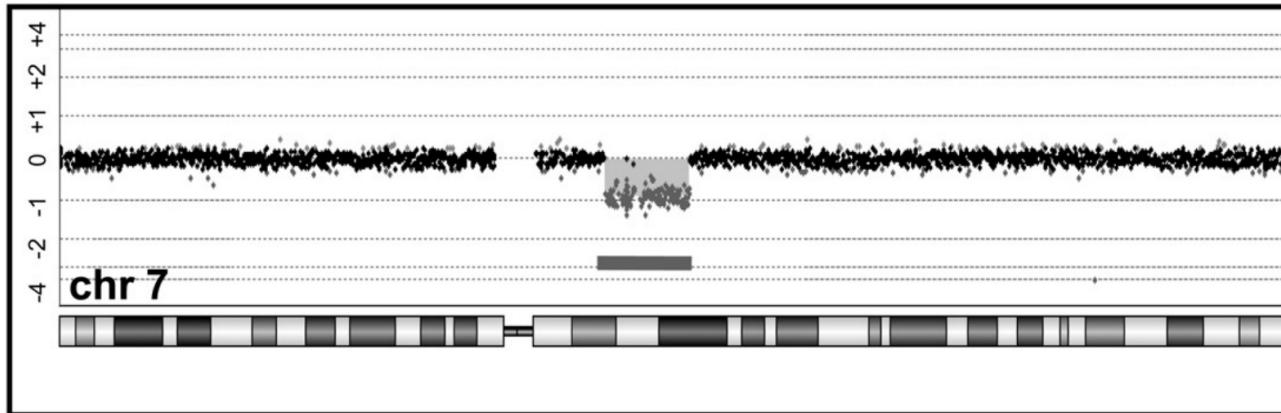


C Whole Genome

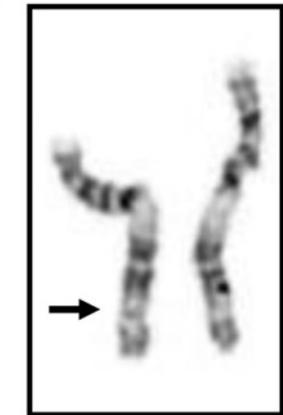
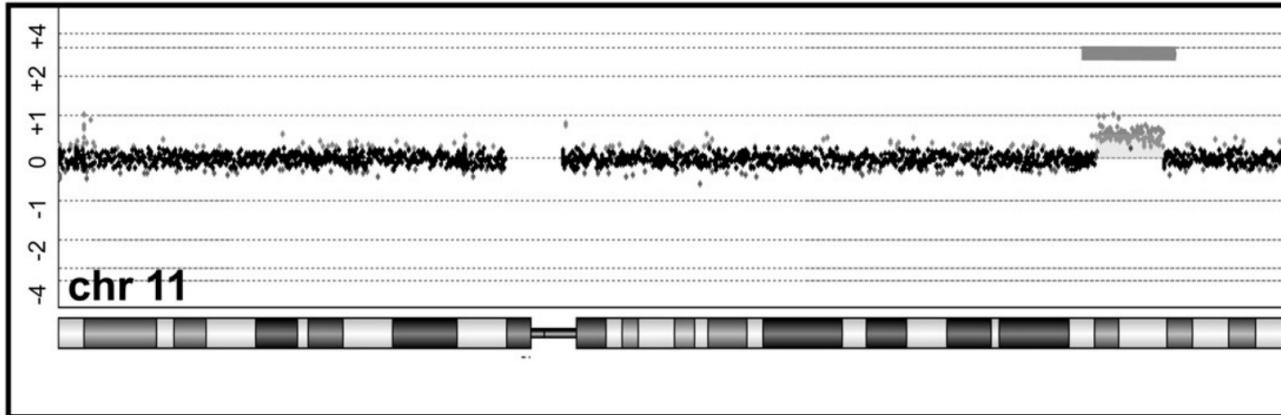


Initial analysis results

A

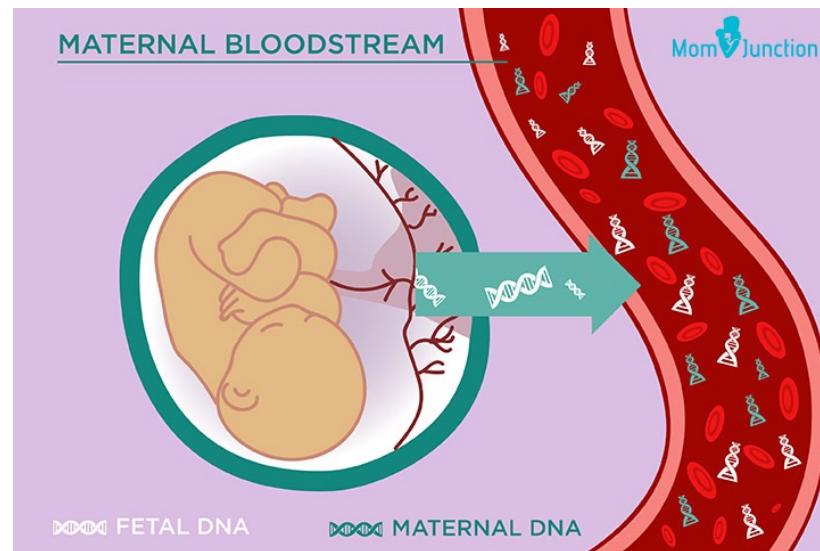


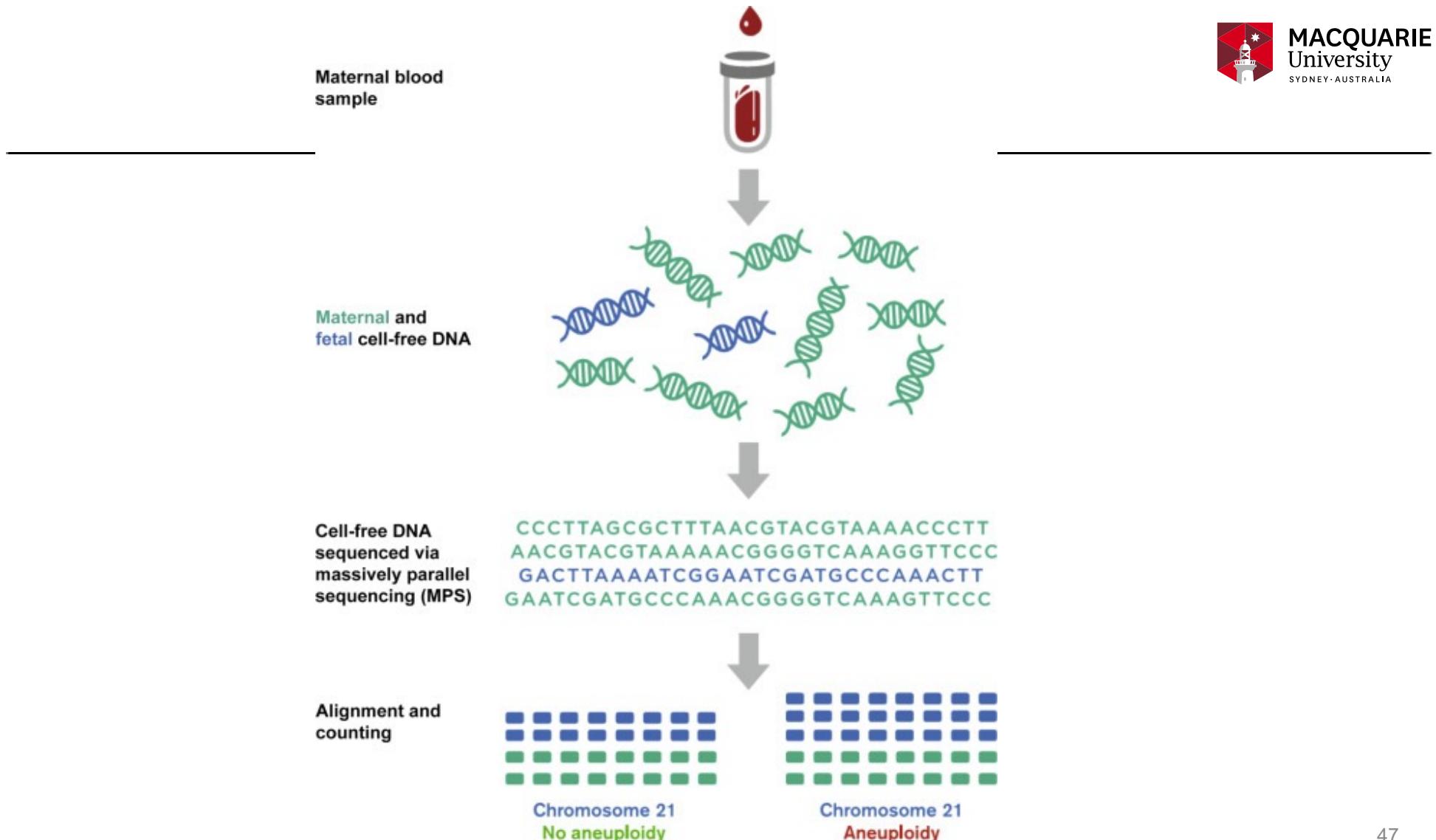
B



Non-Invasive Prenatal Testing (NIPT)

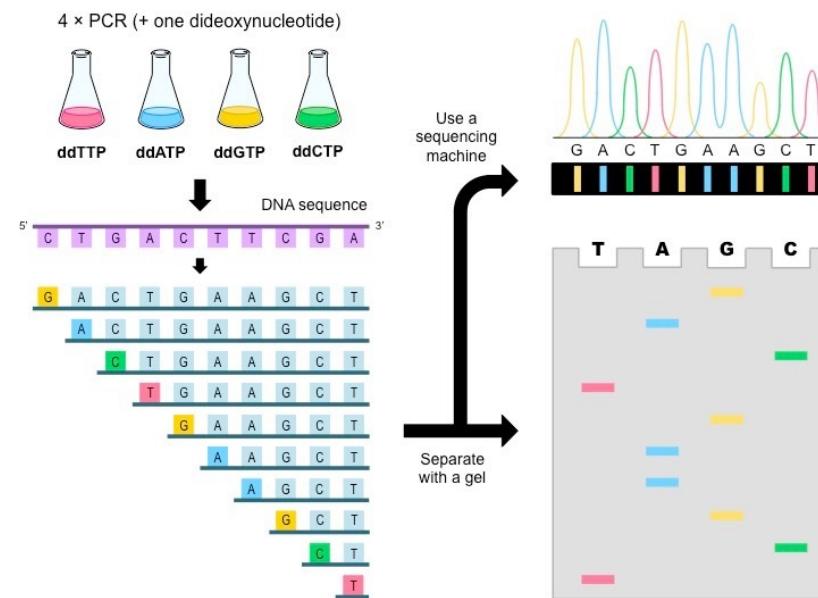
- Also called Non-invasive prenatal screening (NIPS)
- Fetal DNA present in mother's bloodstream cfDNA = cell-free DNA
- From 10 weeks
- Issues with high BMI mothers
 - Fetal fraction >4% required
- Find out baby's sex





Sanger sequencing

- Requires target region amplified by PCR – can be picky
- ~1kb limit per sequence – can build up overlapping reads to cover larger area



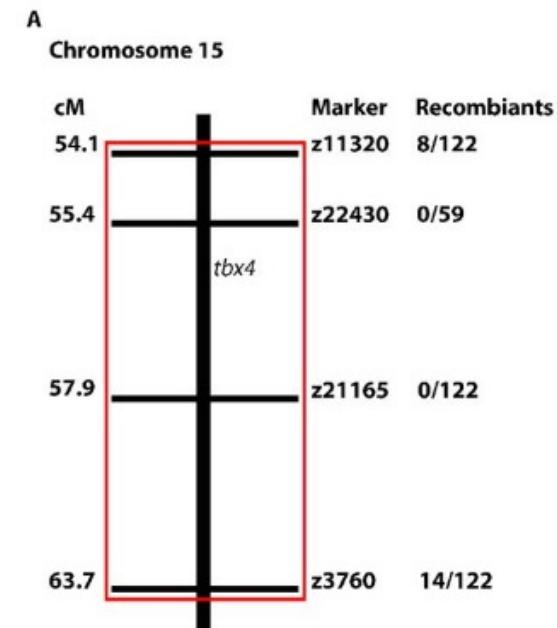
Next-generation sequencing (NGS)



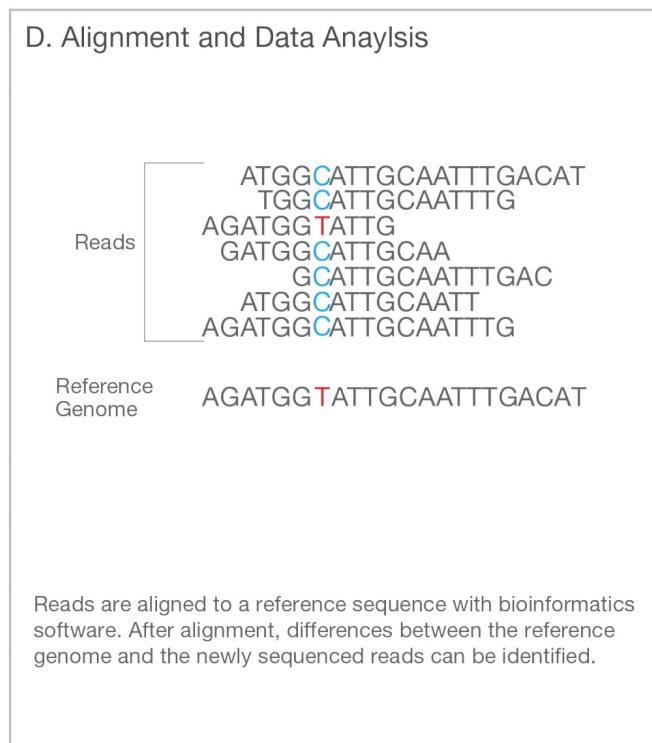
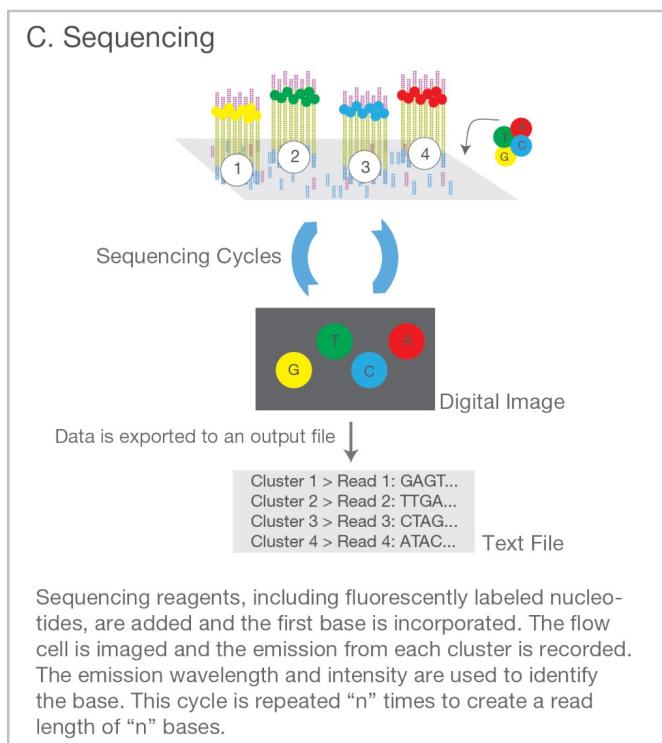
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- Sequence large regions of or entire genome
 - Often cheaper than sequencing individual genes
 - Means we are more likely to test multiple genes at once (up to hundreds)
 - Means we are more likely to find variants

Next-generation sequencing

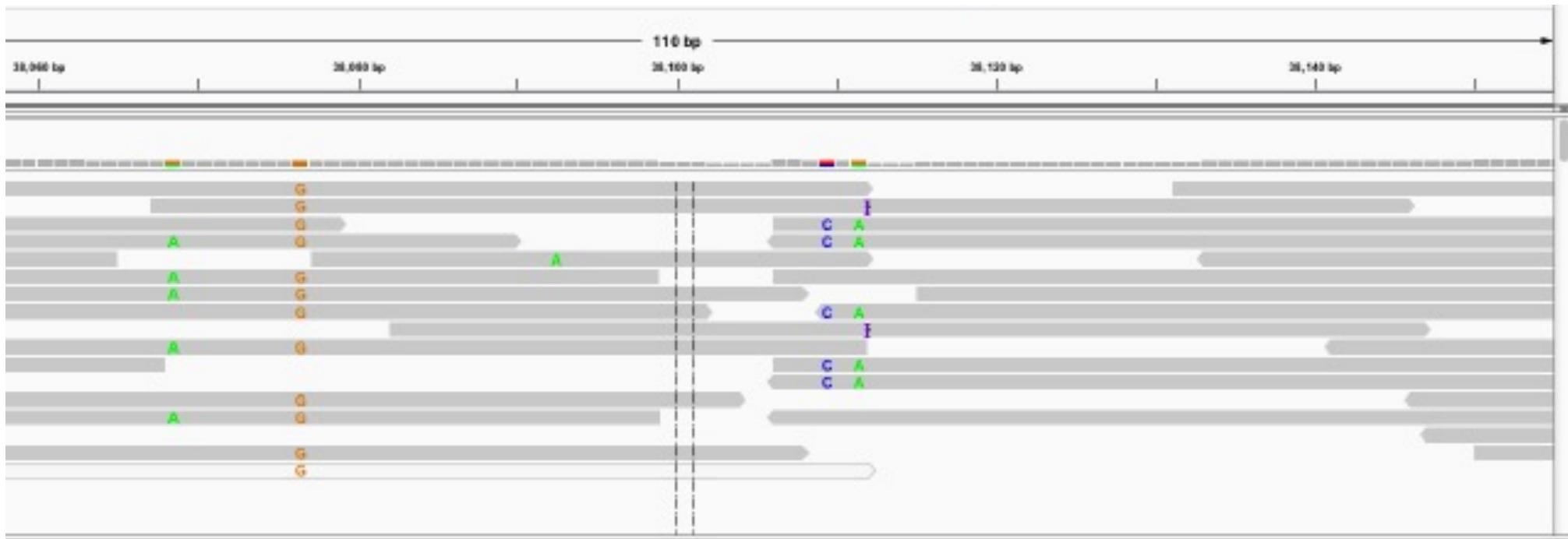
- Whole genome sequencing (WGS) = entire genome
- Whole exome sequencing (WES) = every known exon, usually with 10 base pairs either side
- Panel sequencing = selection of target genes (tens to hundreds)
- Targeted-enrichment next generation sequencing



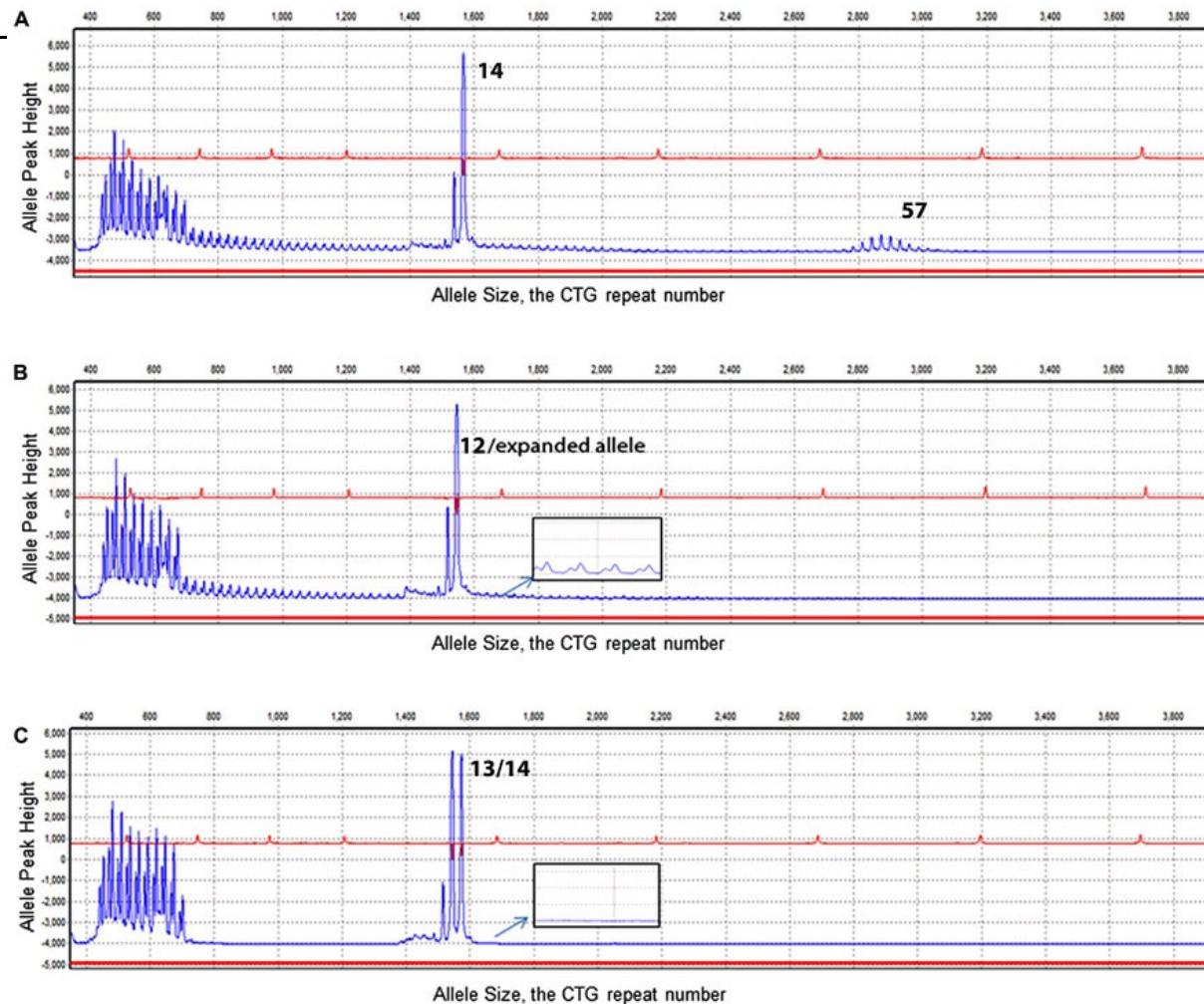
Next-generation sequencing: generation of reads



Next-generation sequencing: alignment of reads

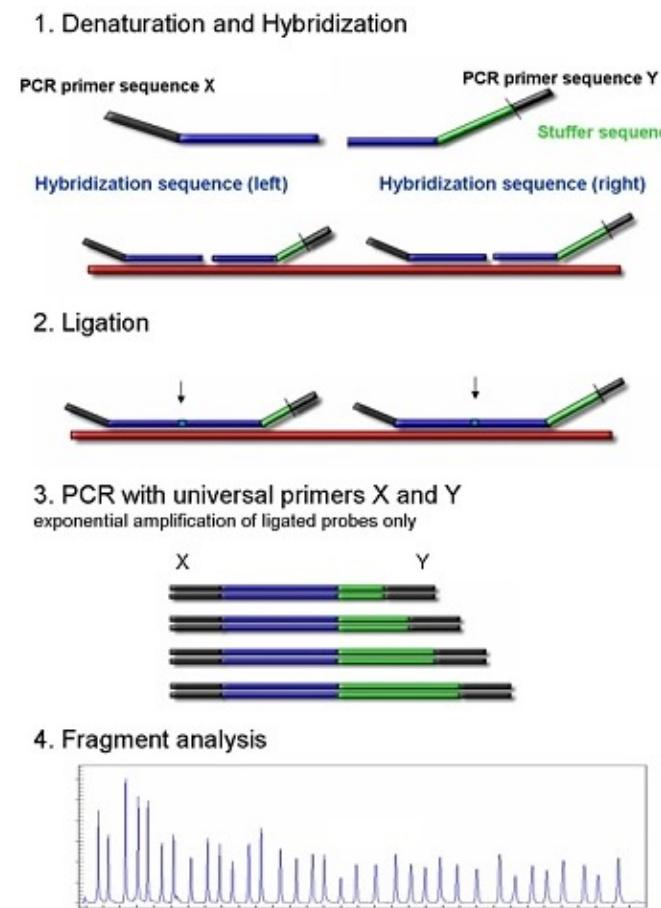


Triplet repeat primed PCR: Electropherogram results



Multiplex ligation-dependent probe amplification (MLPA)

- Detects deletions/duplications in a target gene (often complements NGS)
- Between next gen sequencing and microarray in deletion/duplication, sizewise
- Small probes throughout gene, amplification will only work if exact sequence is present
- Extra or missing regions show up as higher/lower amplification for that particular probe

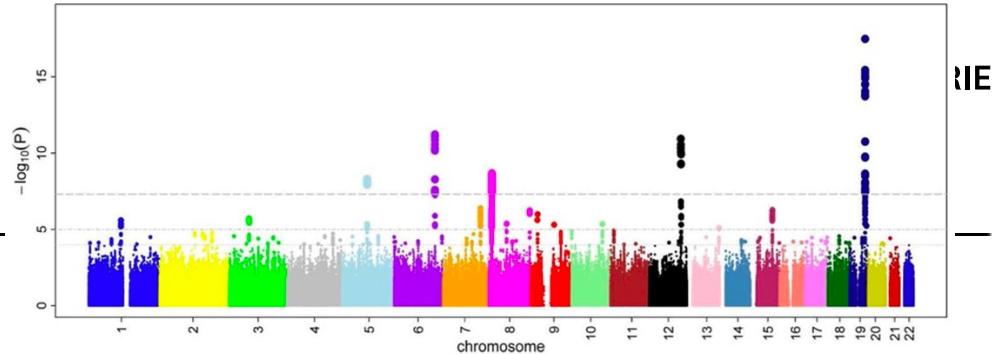


L12 – GWAS

You should be able to:

- Understand the difference between a candidate gene approach and GWAS
- Describe genome wide association studies
- Understand the limitations of GWAS

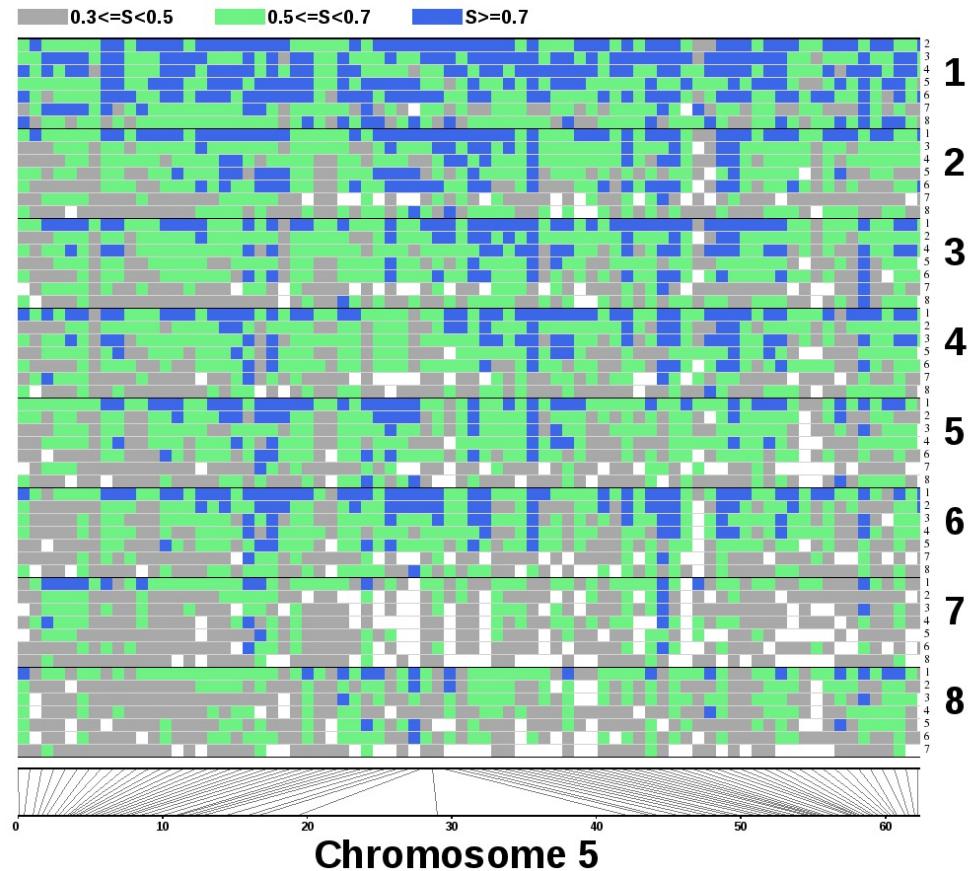
Genome-wide association studies (GWAS)



- A genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait (disease)
- GWAS studies compare the DNA of participants having varying phenotypes for a particular trait or disease
- Each person gives a sample of DNA, from which millions of genetic variants are read using SNP arrays
- If one type of allele is more frequent in people with the disease, the variant is said to be *associated* with the disease
- The associated SNPs are then considered to mark a region of the human genome that may influence the risk of disease

High-throughput genotyping

- Genome-wide association approaches have identified statistically significant evidence supporting relationships between complex human diseases and hundreds of common genetic variants in the human population
- However, finding disease-associated alleles is only the first step on the path to identifying those variants that directly contribute to disease risk
- A major challenge inherent in these studies is moving from identification of a genetic variant via association studies to determination of actual causal variants through functional genomics experimentation



Limitations of GWAS

- Despite the success of GWAS in enhancing understanding of disease mechanisms, the variants identified by this approach represent only a fraction of the overall genetic contribution to common disease risk
- While many disease-associated variants have been identified through GWAS, they have mostly been common variants with moderate to high (i.e., >0.1) allele frequencies
- Assumption that common genetic variation plays a large role in explaining the heritable variation of common disease
- The question of whether common or rare variants underlie the majority of risk for common diseases continues to remain an open one

L13 -Treatment for Genetic Conditions: What you should be able to do

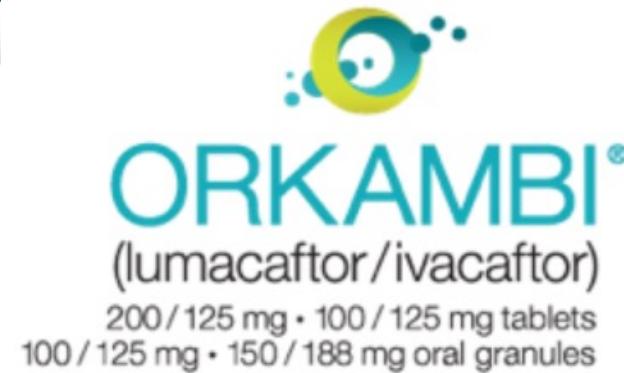


- Discuss medication use for genetic conditions, linking the mechanism / details of the disease with treatment
- Discuss approaches to gene therapy with examples of their current uses

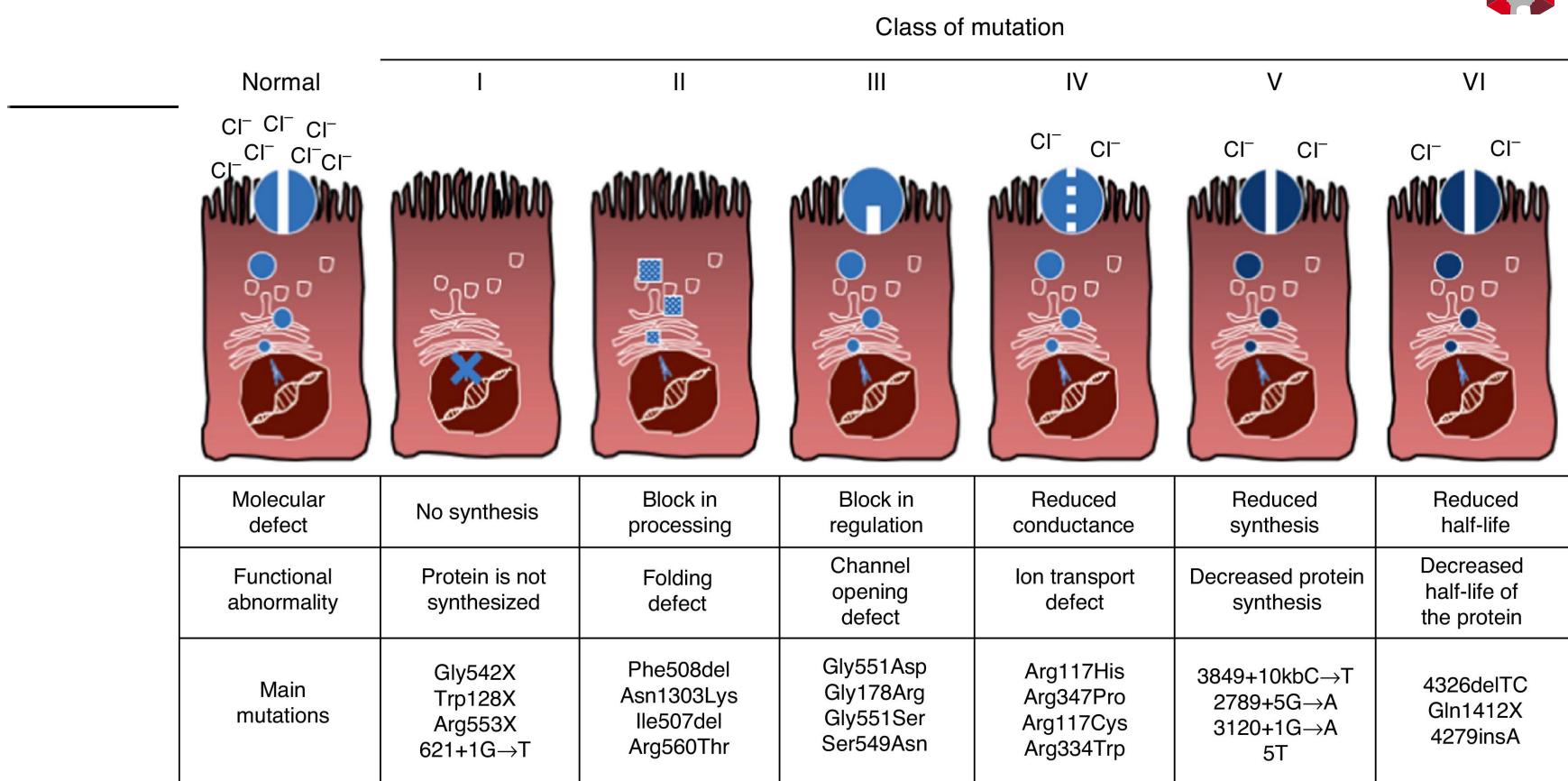
Three treatments for cystic fibrosis



Ivacaftor = helps CFTR channels stay open



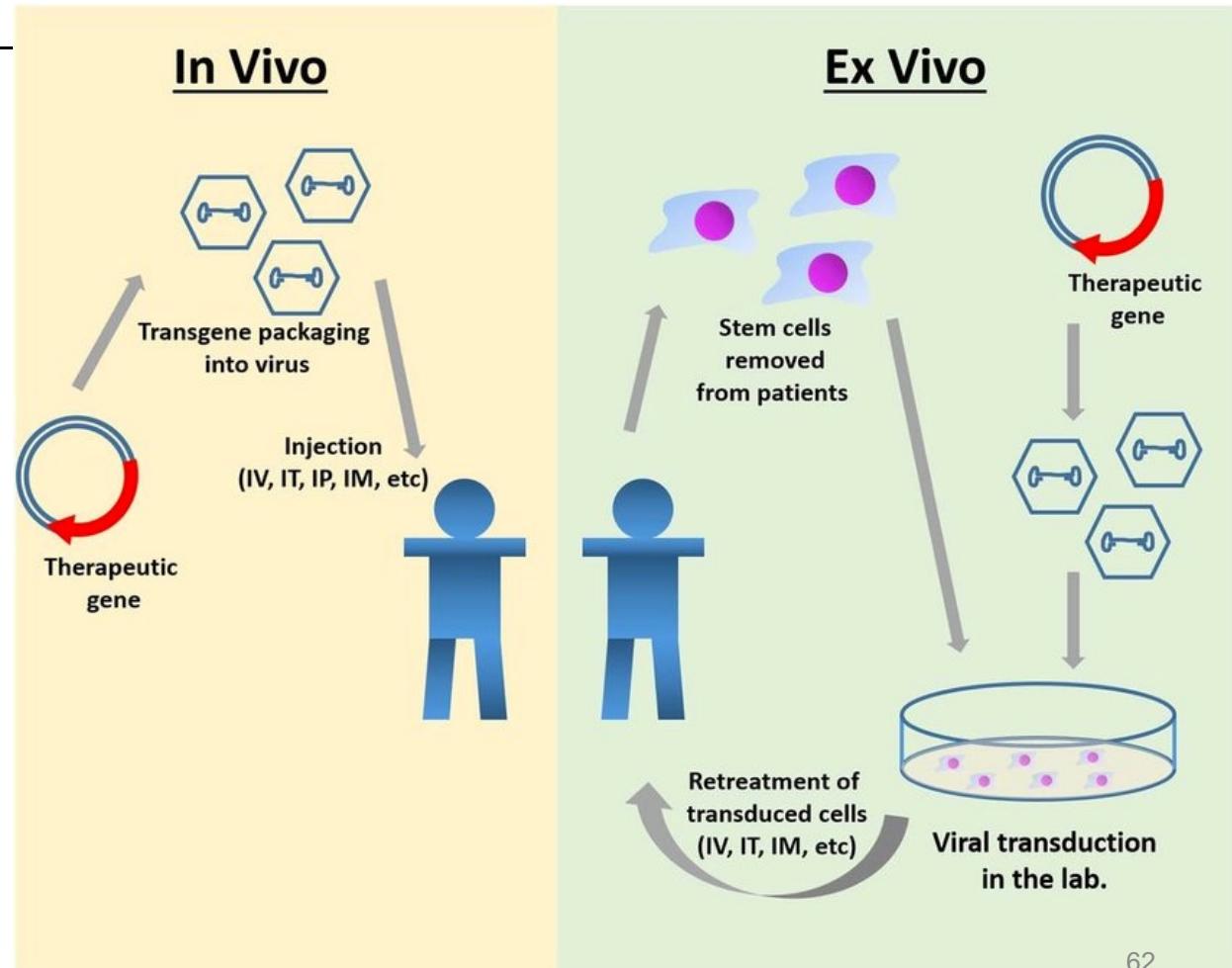
Lumacaftor and tezacaftor = helps bring more CFTR proteins to cell surface



Gene therapy

Challenges of gene therapy:

- Gene delivery
- Immune response
- Off target effects
- Cost / feasibility



L14 -Epigenetics and imprinting



1. Epigenetics

- Subtle layer of gene regulation
- Can persist over time/generations

Objective: Describe the importance of epigenetic processes in human health and disease

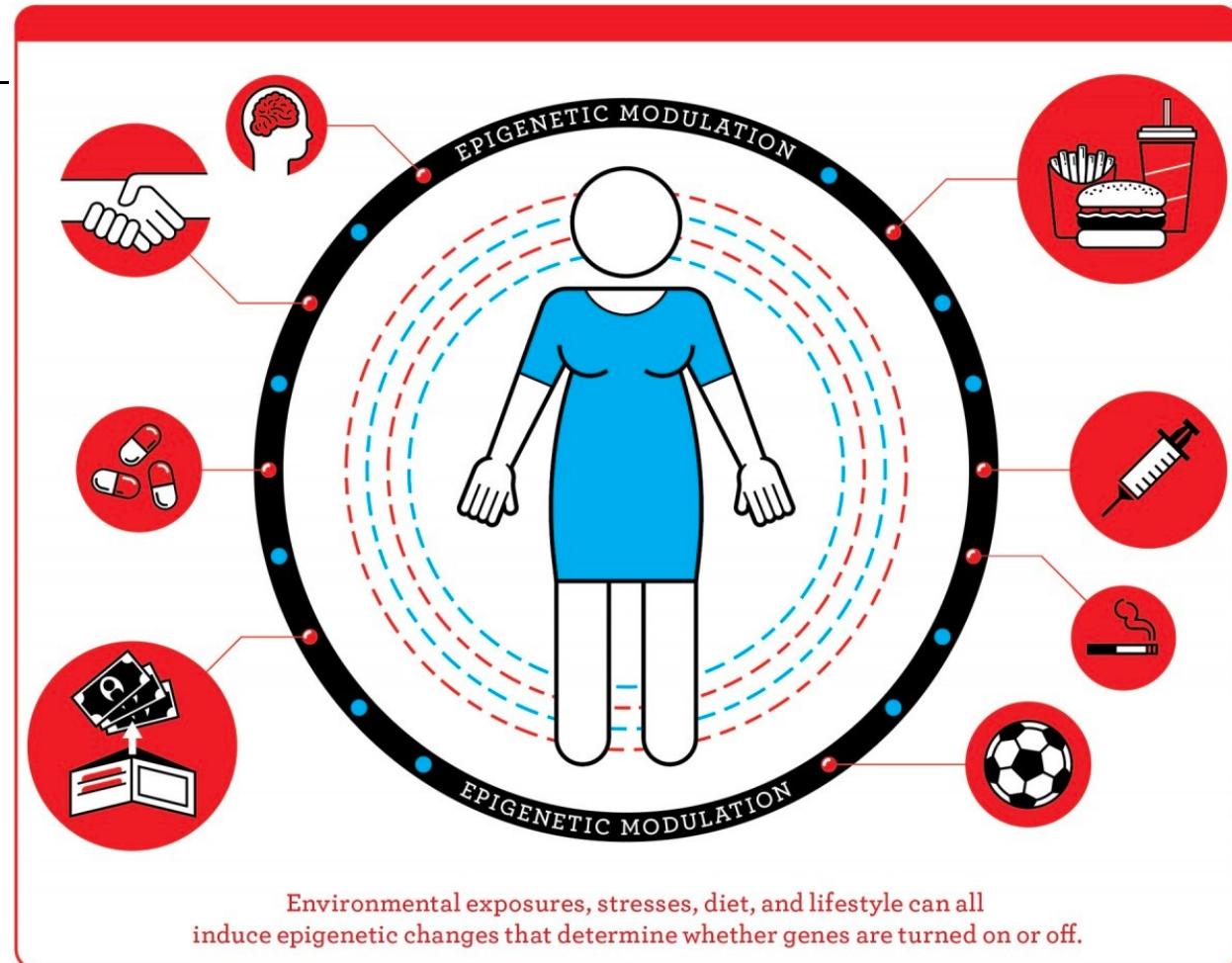
2. Imprinting

- Differential expression of genes based on parent of origin
- methylation of CpG islands
- Angelman / Pader Willi syndromes as example conditions

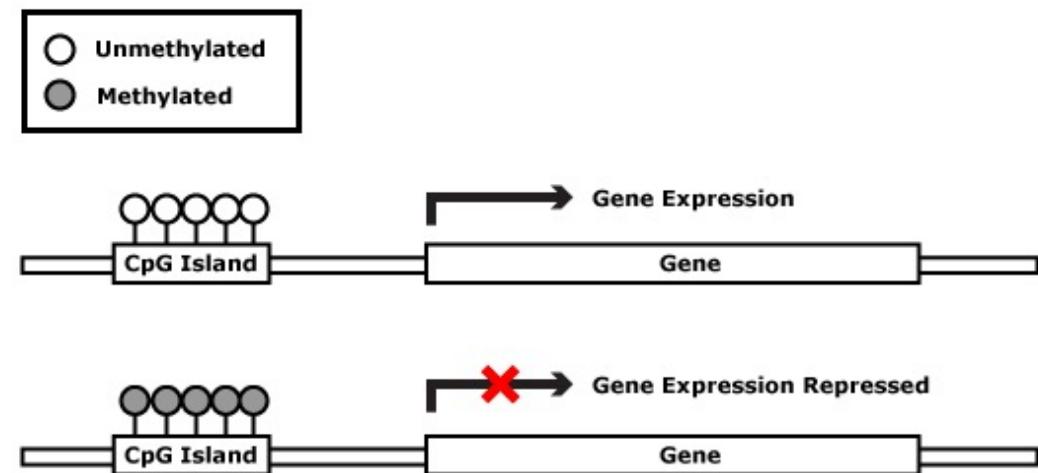
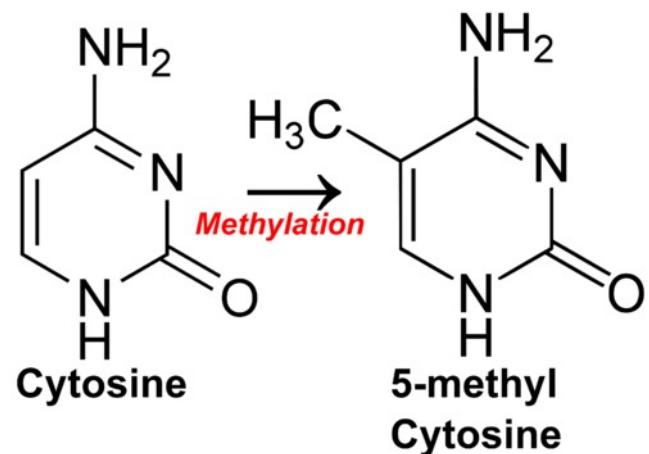
Objective: Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases

Epigenetics

- Epi = over or upon
- Changes in gene expression that do not involve changes in DNA sequence
 - But can be inherited
- Changes due to our environment/experiences
- Mechanisms
 - Methylation on DNA at 'CpG islands'
 - Histone modifications / chromatin changes
 - microRNAs (associated with CpG islands)
 - more



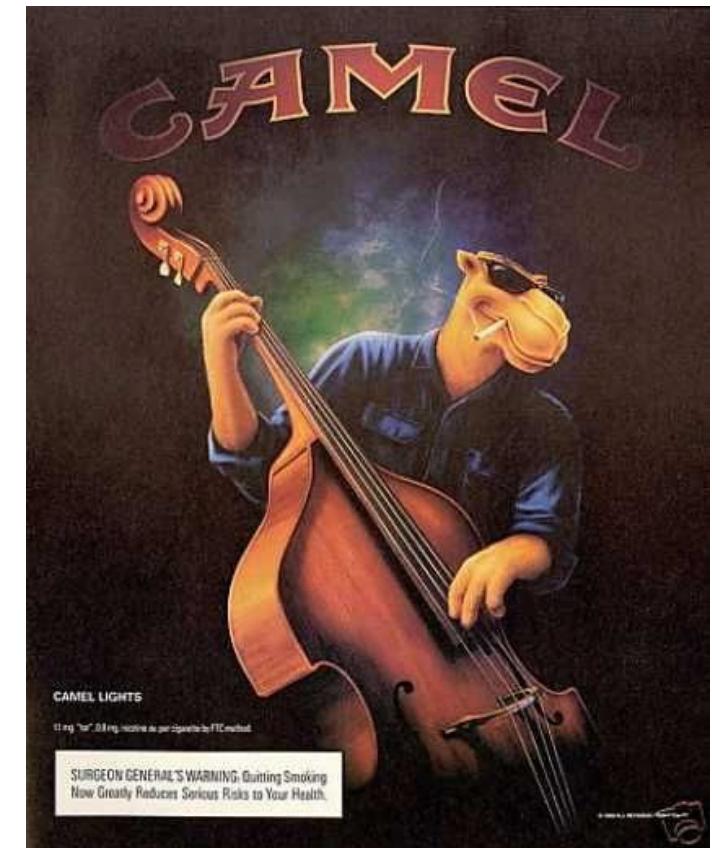
Methylation



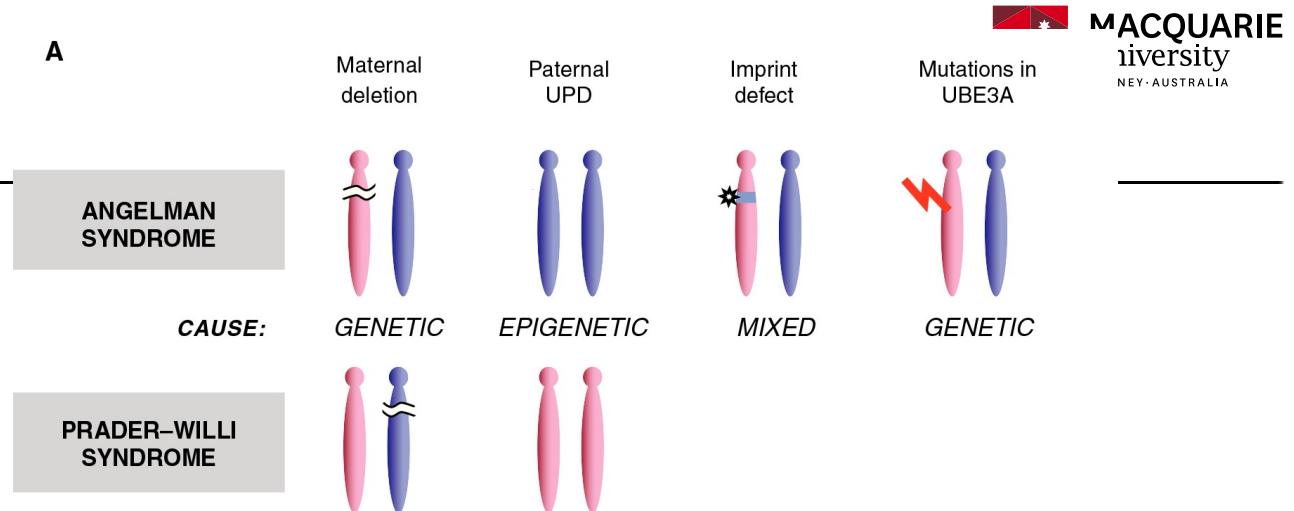
Epigenetic signatures of cigarette smoking

Joehanes et al., 2016 compared methylation of:

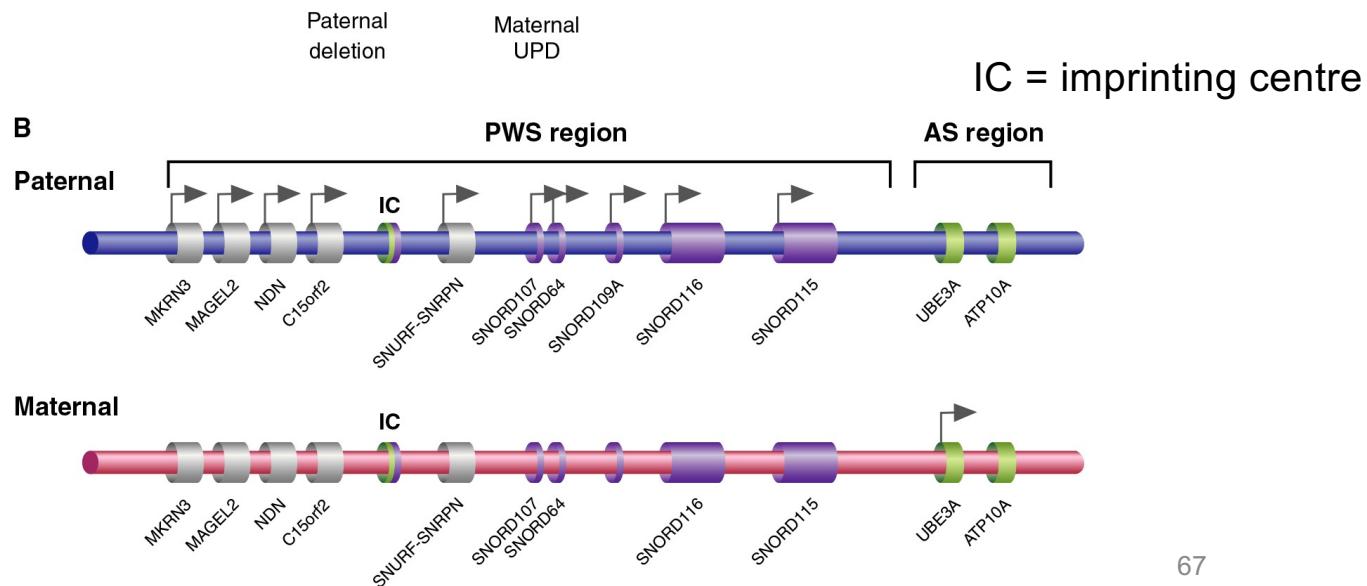
- 2,433 current smokers
- 6,518 former smokers
- 6,956 never smokers
- Comparing current to never smokers: 2,623 significantly different methylation sites linked to 1,405 genes.
- These genes more likely to be linked to pulmonary function, cancer, inflammatory disease, heart disease
- Comparing former vs. never smokers, 185 of these remained significantly different = “persistent altered methylation”



Diseases associated with imprinting: 15q11-13 region



- Loss of paternal expression of 11 genes = **Prader-Willi syndrome**
- Loss of maternal expression of UBE3A = **Angelman syndrome**



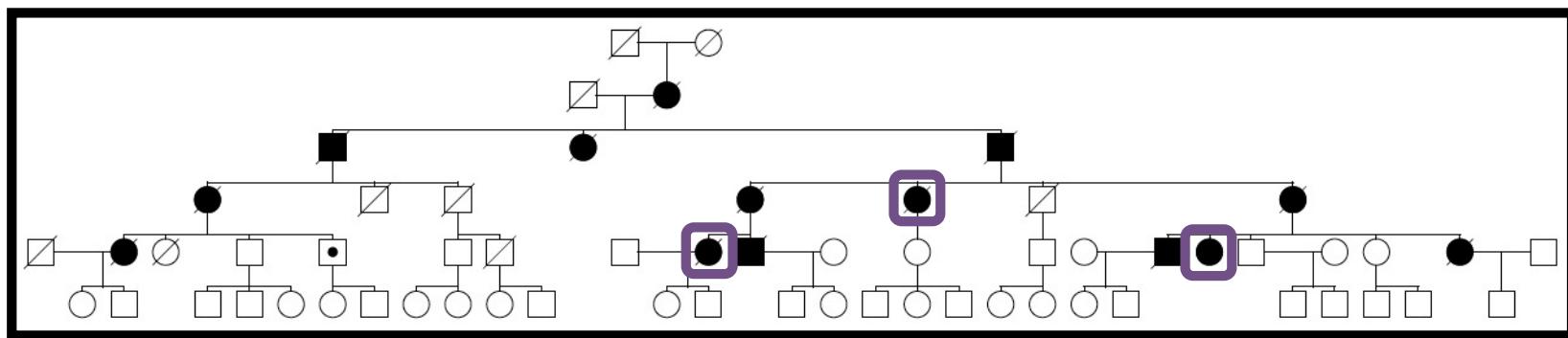
L15 – MND / FTD gene discovery

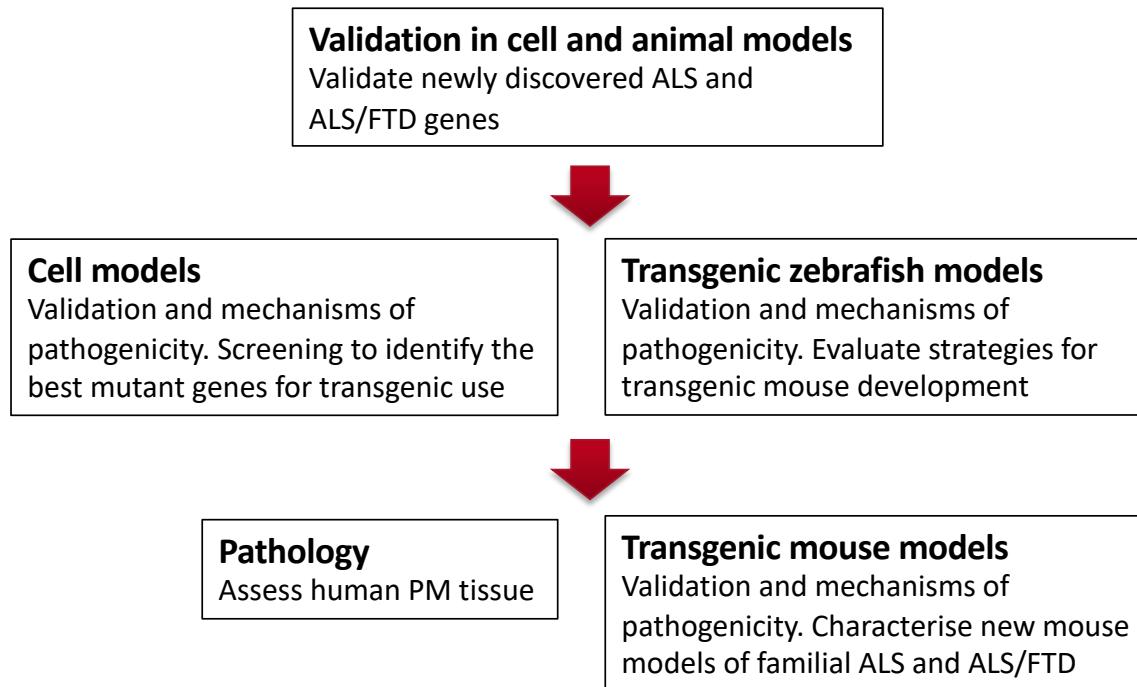
You should be able to:



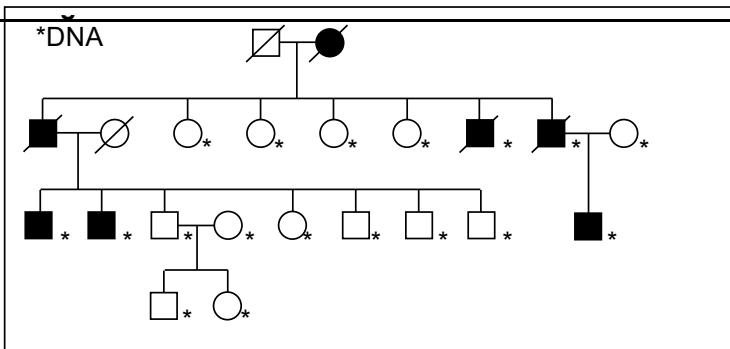
- Identify and understand the technologies that detect nucleotide mutations
- Understand the different approaches to disease gene discovery in MND/ALS
- Describe how these technologies can be used together to discover genes

Power of combining family-based studies with next-generation sequencing

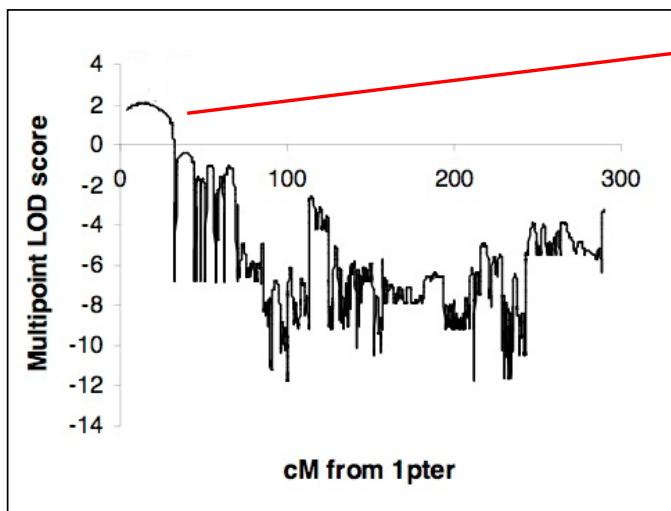




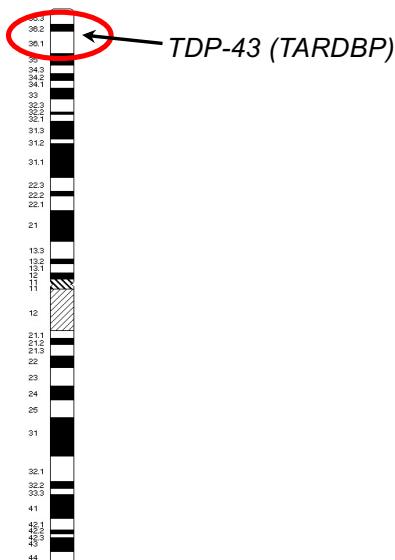
MND gene discovery by *sampling the genome* – linkage analysis

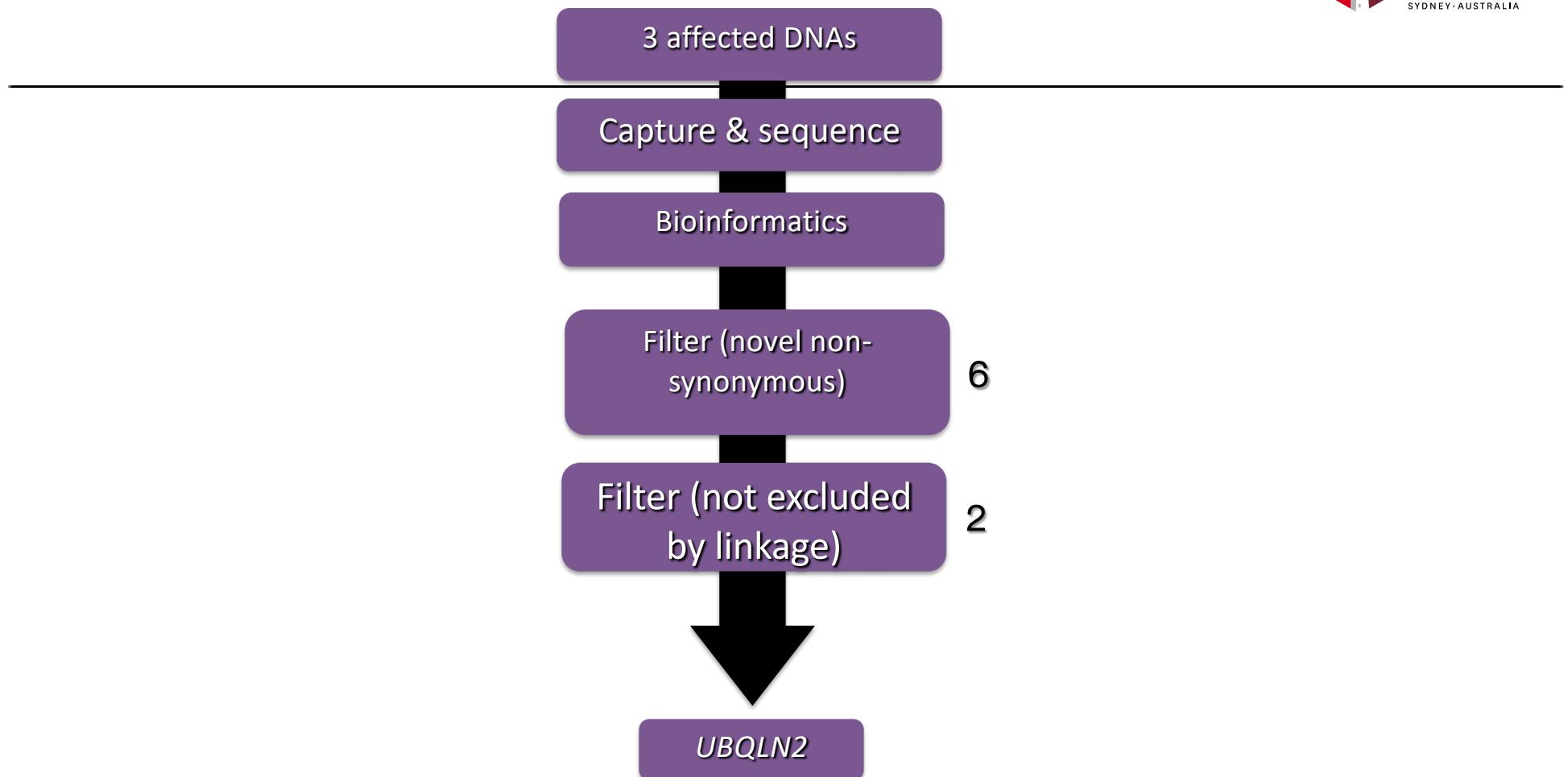


Genotyped SNPs in families – SNP array



Chromosome
1p36

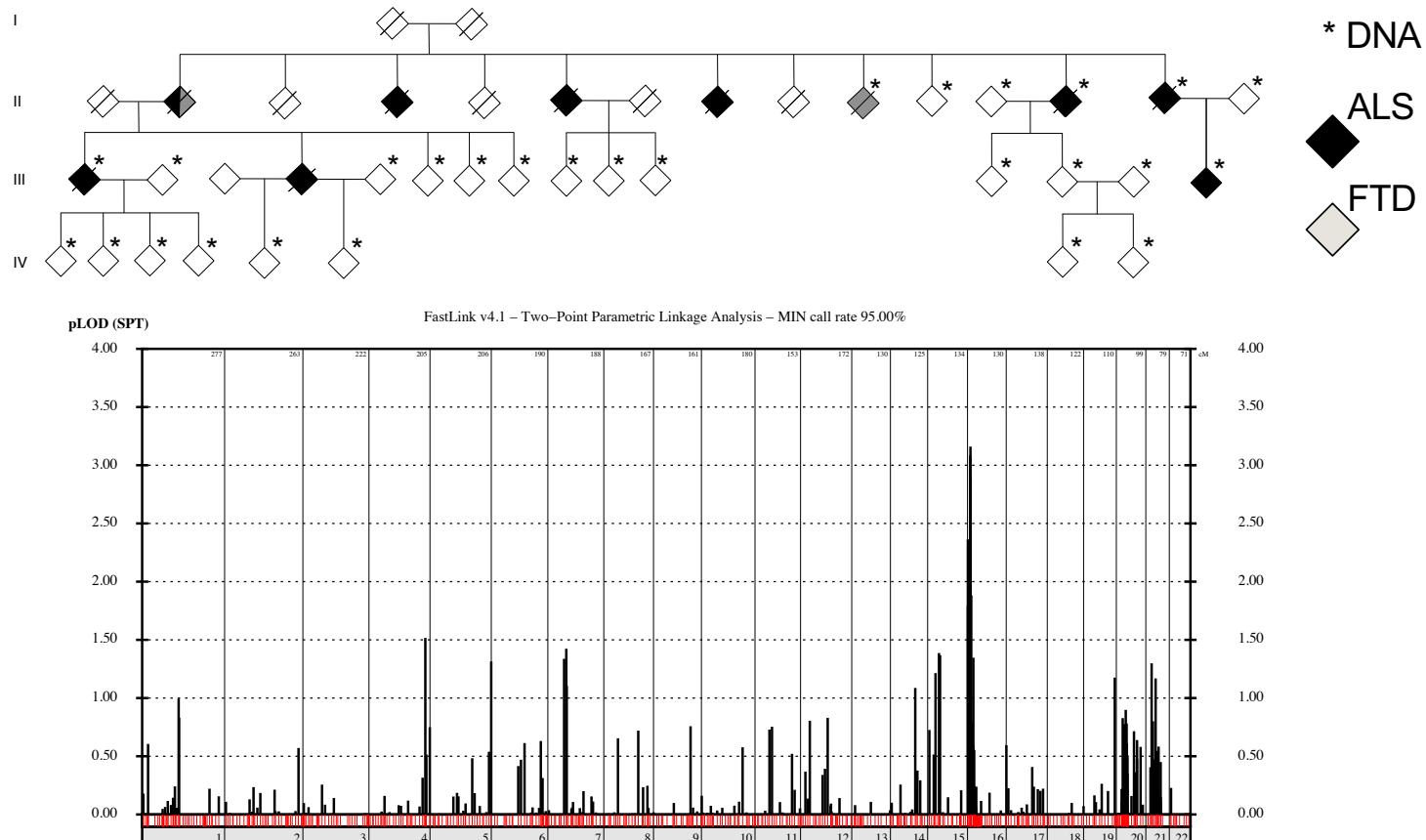




Power of combining family-based studies with next-generation sequencing



Unbiased genome wide scan for linkage

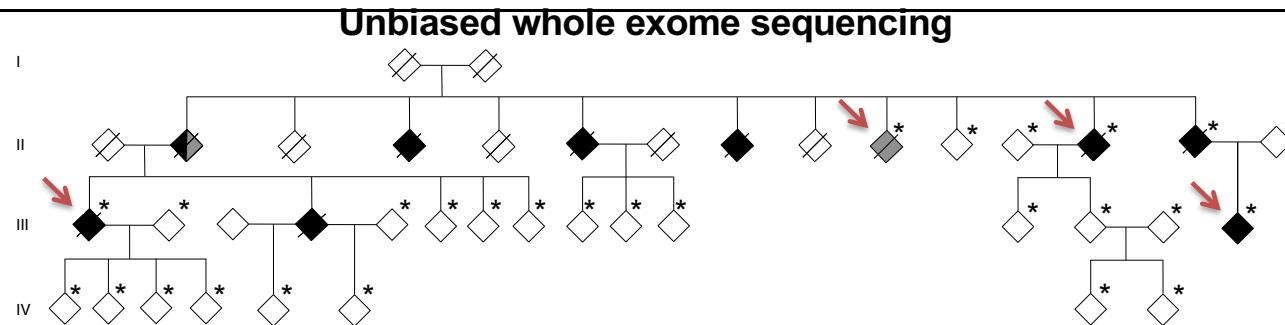


Analysis time: 31.07.2013 – 18:00:14
 Time elapsed: 4 min 45 s
 Path: C:\Users\Kelly Williams\Desktop\easyLINKAGE input files
 Pedigree structure file: p_ALS10_4affected.ped

Marker coverage and chromosomes

Copyright ©, Tom H. Lindner & Katrin Hoffmann
 easyLINKAGE Plus v5.08, January 12, 2007

Power of combining family-based studies with next-generation sequencing



Filter	Variants
Total variants identified	292,989
Present in all affected	35,930
Alters amino acid sequence	5,109
Novel variants	2
Within linkage region 16p13.3	1

L16 – Cancer genetics

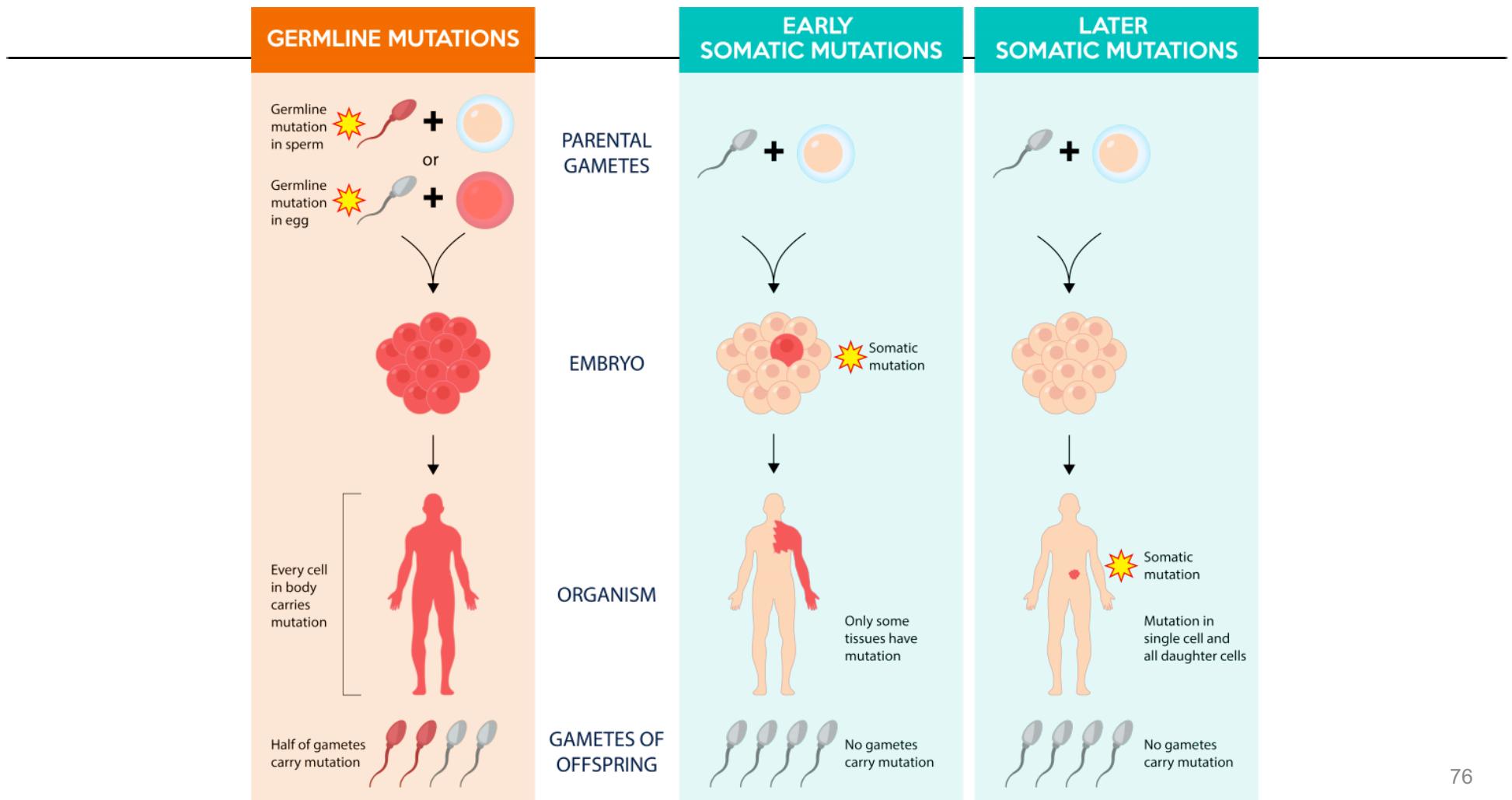
You should be able to:

- Understand the dynamic role of mutation selection in cancer development
- Analyse different types of mutations and their role in cancer development
- Describe the contribution of tumour suppressor genes and oncogenes in cancer

Germline mutation = cancer predisposition

Later somatic mutation = development of cancer

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Some genes associated with cancer

NAME	FUNCTION	EXAMPLES of Cancer/Diseases	TYPE of Cancer Gene
APC	regulates transcription of target genes	Familial Adenomatous Polyposis	tumor suppressor
BCL2	involved in apoptosis; stimulates angiogenesis	Leukemia; Lymphoma	oncogene
BLM	DNA repair	Bloom Syndrome	DNA repair
BRCA1	may be involved in cell cycle control	Breast, Ovarian, Prostatic, & Colonic Neoplasms	tumor suppressor
BRCA2	DNA repair	Breast & Pancreatic Neoplasms; Leukemia	tumor suppressor
HER2	tyrosine kinase; growth factor receptor	Breast, Ovarian Neoplasms	oncogene
MYC	involved in protein-protein interactions with various cellular factors	Burkitt's Lymphoma	oncogene
p16	cyclin-dependent kinase inhibitor	Leukemia; Melanoma; Multiple Myeloma; Pancreatic Neoplasms	tumor suppressor
p21	cyclin-dependent kinase inhibitor		tumor suppressor
p53	apoptosis; transcription factor	Colorectal Neoplasms; Li-Fraumeni Syndrome	tumor suppressor
RAS	GTP-binding protein; important in signal transduction cascade	Pancreatic, Colorectal, Bladder, Breast, Kidney, & Lung Neoplasms; Leukemia; Melanoma	oncogene
RB	regulation of cell cycle	Retinoblastoma	tumor suppressor
SIS	growth factor	Dermatofibrosarcoma; Meningioma; Skin Neoplasms	oncogene
XP	DNA repair	Xeroderma pigmentosum	DNA repair

Proto-oncogenes

- produce protein products that normally regulate cell growth & differentiation. The mutated forms of these genes are called **oncogenes**

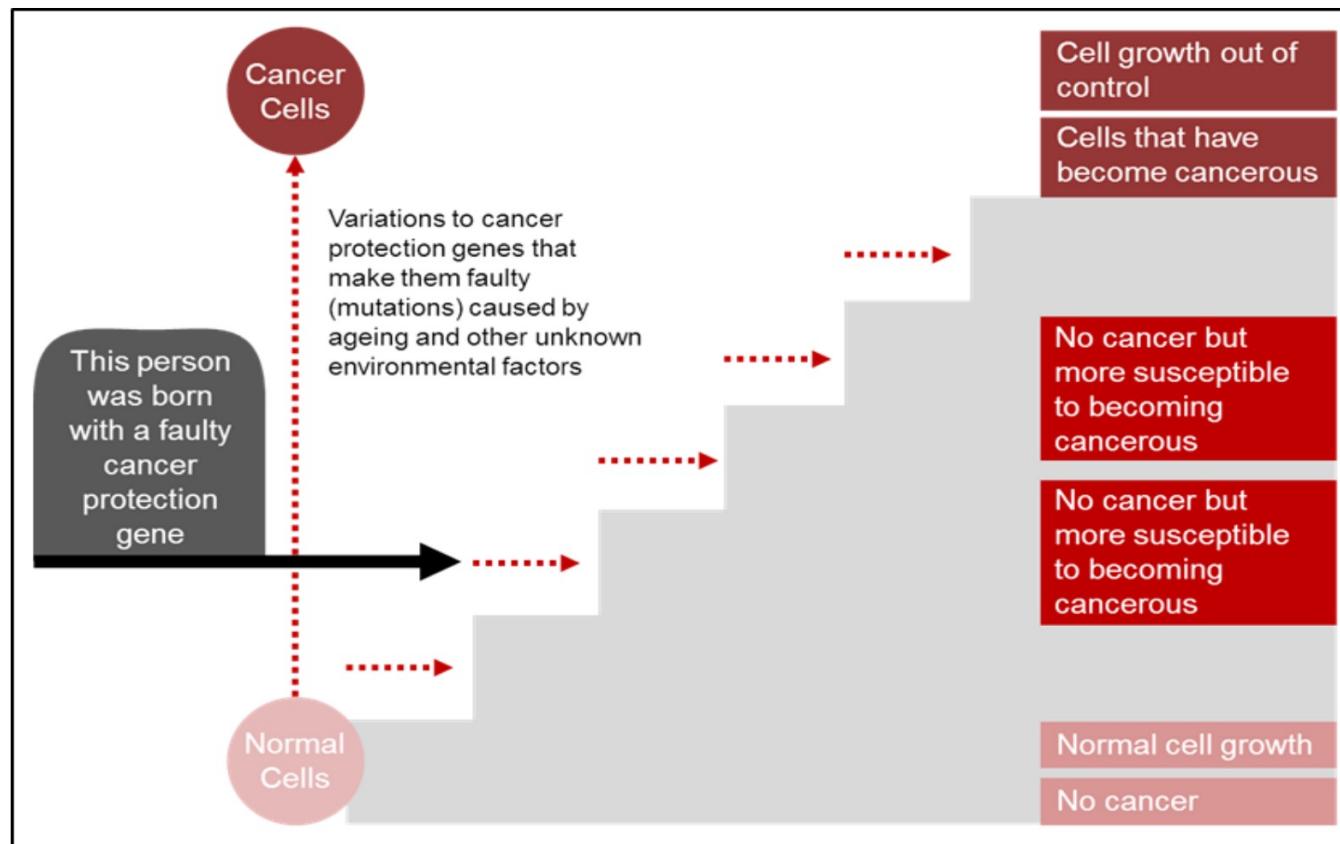
Tumour suppressors

- make proteins that normally prevent cell division or cause cell death

DNA repair genes

- help prevent mutations that lead to cancer

Cancer predisposition in germ line = shortcut to cancer development

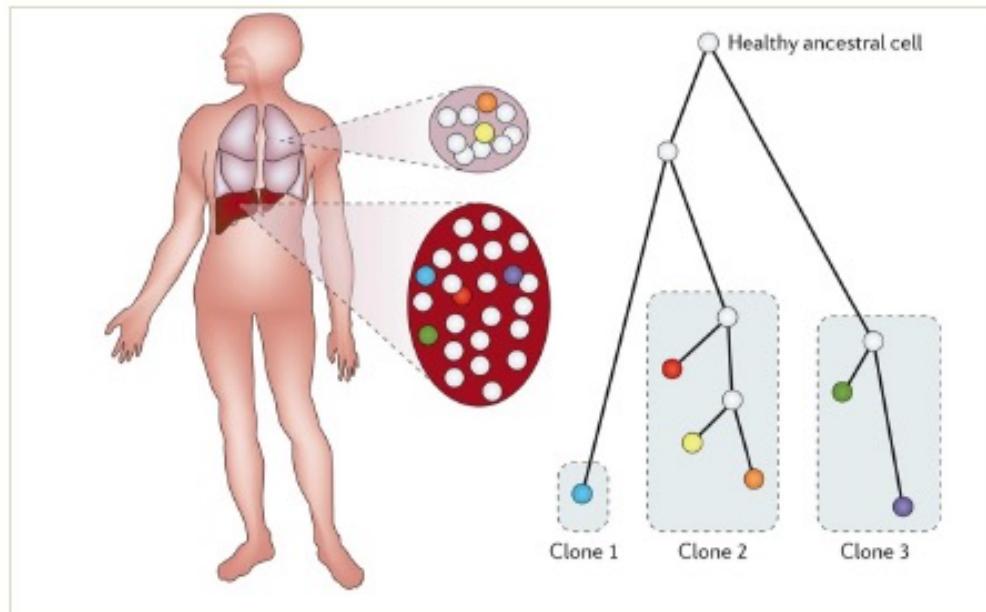


CANCER MUTATIONS

- Most acquired (or somatic) mutations are **neutral passenger** mutations (no direct role in cancer)
- A fraction of these mutations (**driver mutations**) confer a selective advantage to the cell – leading to growth or survival of a clone. These mutations are in **cancer genes**
- More than **500 cancer genes** have been identified so far
 - 90% are altered by somatic mutation and ~20% by germline mutations (occurs in germ cells) that predispose to cancer (familial cancers).

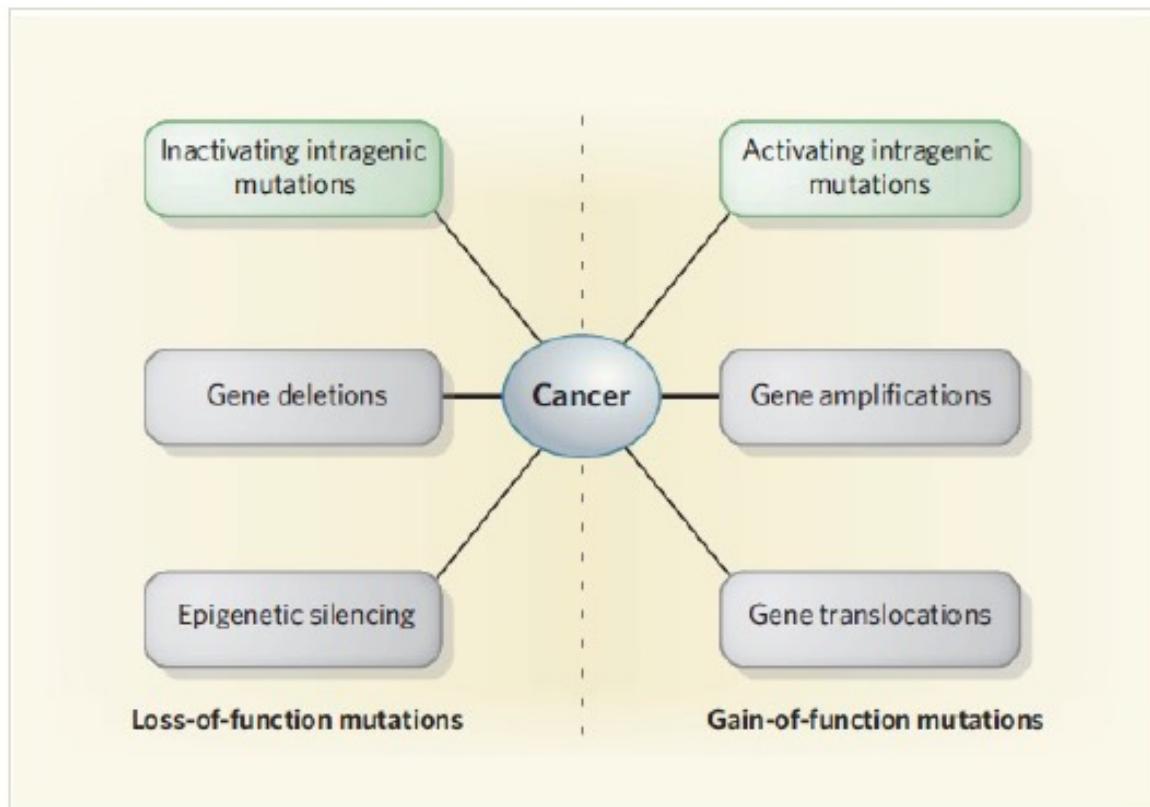
CANCER EVOLUTION

- Dynamic selection of mutations – in response to microenvironment and therapy
- Multiple cancer subclones exists
- Cancer show substantial intra-patient and intra-tumoural heterogeneity



Shwartz and Shaffer *Nat. Rev. Genet.* 18, 213-229 (2017)

CANCER GENES



- **Loss-of-function** mutations
- **Gain-of-function** mutations

Haber and Settleman *Nature* 446:145 (2007)

Human microbiota

You should be able to:

- Give an overview of the presence of microorganisms in/on humans
- Describe factors which have altered/can alter the makeup of bacteria in our bodies
- Describe the proposed effects that microbiota can have on a human

What aspects of modern life might affect our microbiota?



Caesarean birth



Bottle feeding

Antimicrobials

Diet

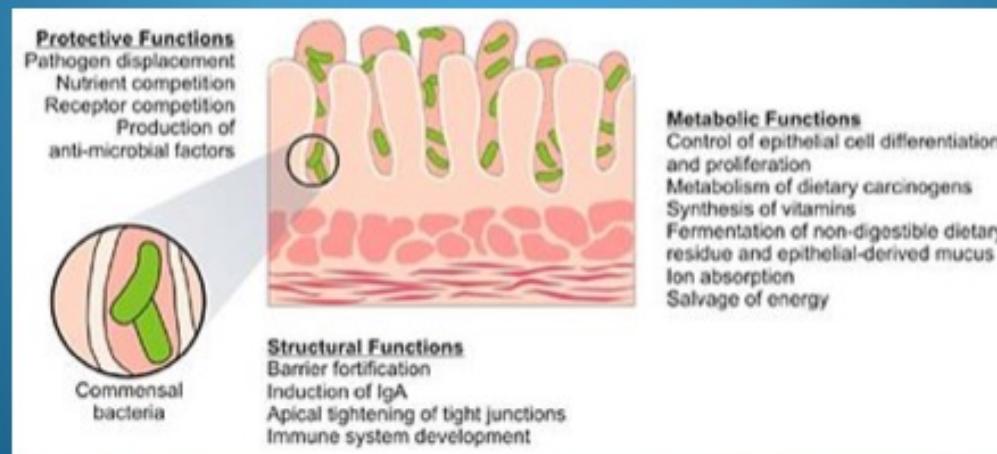
Host genetics



Dominguez-Bello et al. 2016 *Nature medicine* 22: 250-253; Gillings et al. 2015 *Genes*, 6: 841-857;
Ardesir et al. 2014 *Science Translational Medicine* 6: 252ra120; Dethlefsen & Relman 2011 *PNAS*, 108: 4554-4561

Why should we care about the microbiota?

The more we learn about the microbiota, the more we appreciate its central role in metabolism, immune function and protection against pathogens



19 - HIV

You should be able to:

- Give a brief overview:
 - How HIV was transmitted to humans
 - How HIV enters and retains a presence within a human cell, and a human in general (note mechanisms not required)
 - Genetic changes that interfere with HIV's normal functioning
 - Our success in treatment/management of HIV

19 - HIV

- Take Home Message

- No cure but if treated HIV positive people can live a normal life
- No transmission with undetectable viral load
- HIV-1 (at least 3) cross-species transmission from SIVcpz in the early 20ths century
- HIV-2 (at least 4) cross-species transmission from SIVsm
- No positive selection in inter-patient evolution

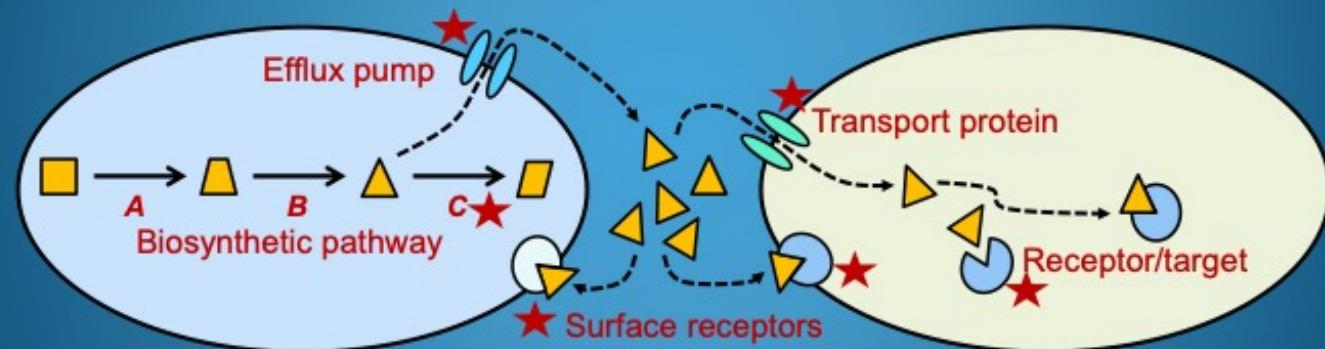
22 – Antibiotic resistance you should be able to:



- Define antibiotics, and describe how bacteria can survive their presence
- Describe antibiotic resistance, the genetics behind it, and how it is built and maintained by both bacteria and humans

Antibiotic resistance genes

Genes for synthesis of small molecules, efflux pumps, receptors, and transport proteins are all potential resistance genes★



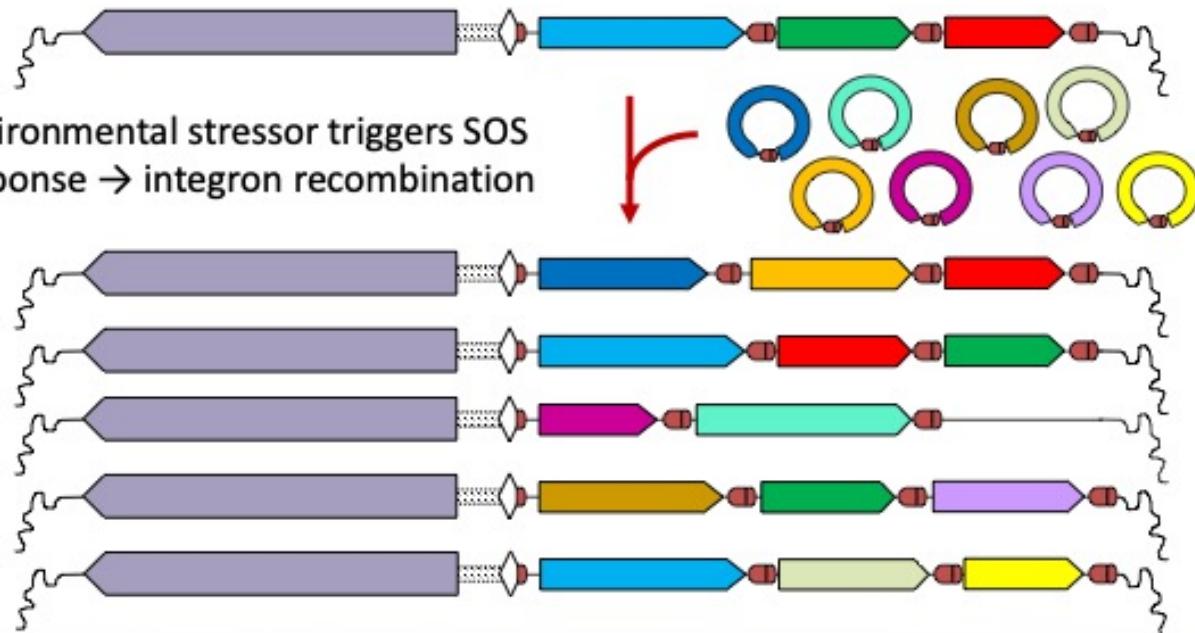
Resistance can be acquired by **Mutation**, or by **Lateral gene transfer**. The collection of genes that can be co-opted to confer resistance is called the **Resistome**.

D'Costa *et al.* 2011 *Nature* 477: 457-461; Bhullar *et al.* 2012 *PLoS ONE* 7: e34953; Gillings 2013 *Frontiers in Microbiology* 4: 4.

Integrons generate genomic diversity

Environmental perturbations trigger integron recombination. This generates populations of diverse cells upon which selection can act.

Chromosomal integron



Environmental stressor triggers SOS response → integron recombination

L21 – Ethics in human genetics

You should be able to:

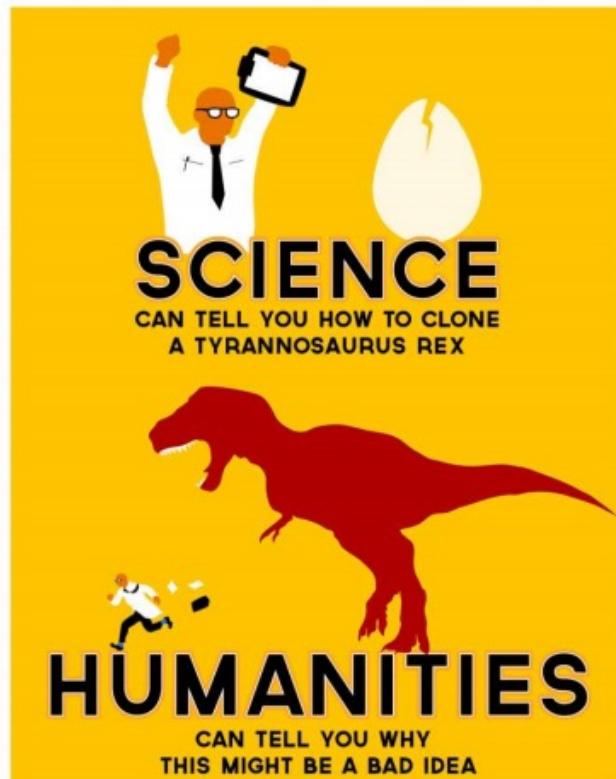
- Identify the principles of bioethics
- Identify ethical dilemmas in genetics
- Practice ethical decision making

Foundations in Ethics and Society

BLENDING SCIENCE AND HUMANITIES

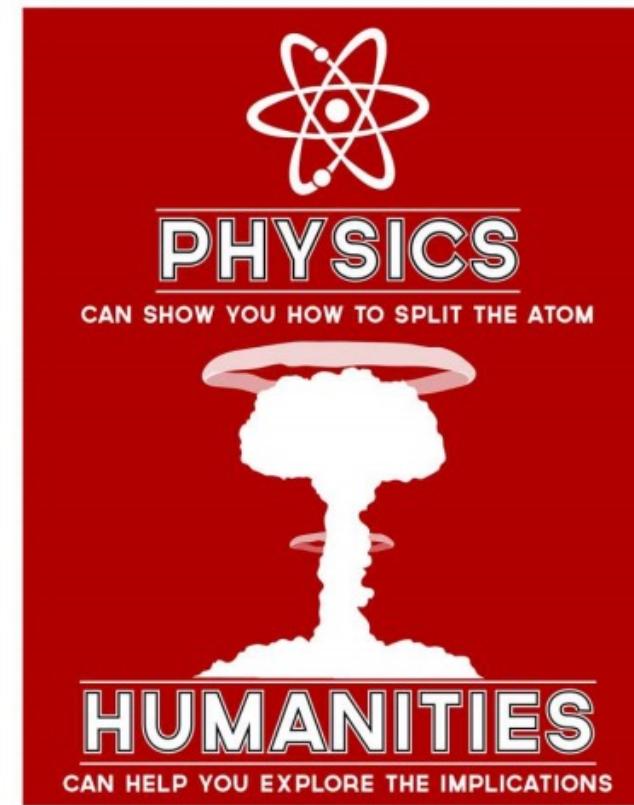


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Principles of ethics in medical practice and research



-
- **Autonomy:** respect autonomy - educate, communicate, consult, respect and empower.
 - **Justice:** Promote fair distribution of resources, respect for rights and respect for morally acceptable laws.
 - **Beneficence:** provide net benefits
 - **Non-maleficence:** do no avoidable harm, to individuals or groups.
 - Reflected throughout medical/research policies etc.

How to answer?



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Ethical Dilemma:

Central Issue: What is the over-riding ethical dilemma?

Competing Considerations: What other aspects should be taken into account?

Decision making process: Which principle(s) of bioethics did you apply and what was the decision?

CRISPR in the 21st Century

Learning objectives

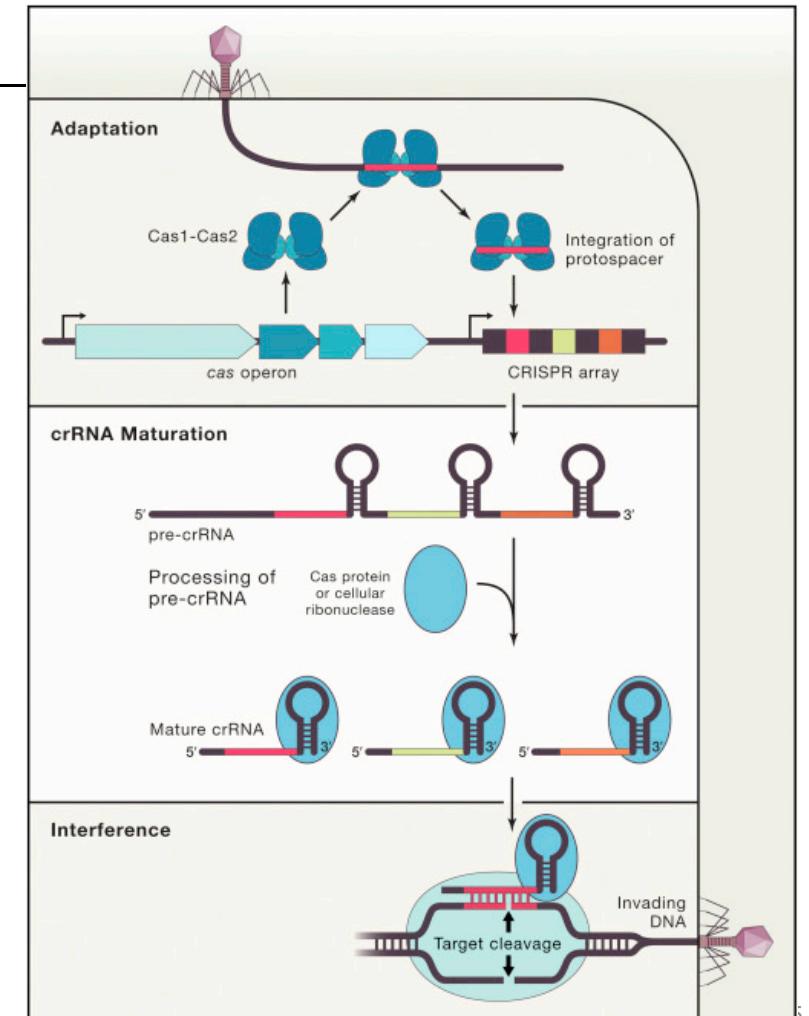


1. Understanding the basics of CRISPR-Cas9
2. What led to the discovery of CRISPR-Cas9 for molecular biology
3. How can CRISPR-Cas9 be used to genetically modify organisms
 1. Knock-out (NHEJ)
 2. Knock-in (HDR)
 3. Base editing
 4. Challenges
4. Uses of CRISPR

Where did CRISPR-Cas9 come from?

CRISPR is a primitive bacterial immune system

- After infection, bacteriophages release their genome into a host bacteria
- A small piece of DNA is cut out of the virus's genome with Cas1 and Cas2 endonucleases
- This piece of DNA can then be incorporated into the **CRISPR** array of the bacterial genome as a form of memory
- The **CRISPR** array is transcribed and processed to form guide RNA that can be used by Cas9 endonuclease to cut the genome of invading viruses



How can CRISPR-Cas9 be used to genetically modify organisms?



- Knock out genes
 - Non-homologous end joining (NHEJ)
- Knock in DNA sequences
 - Homology directed repair (HDR)
- Base editing

Thanks and good luck!



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