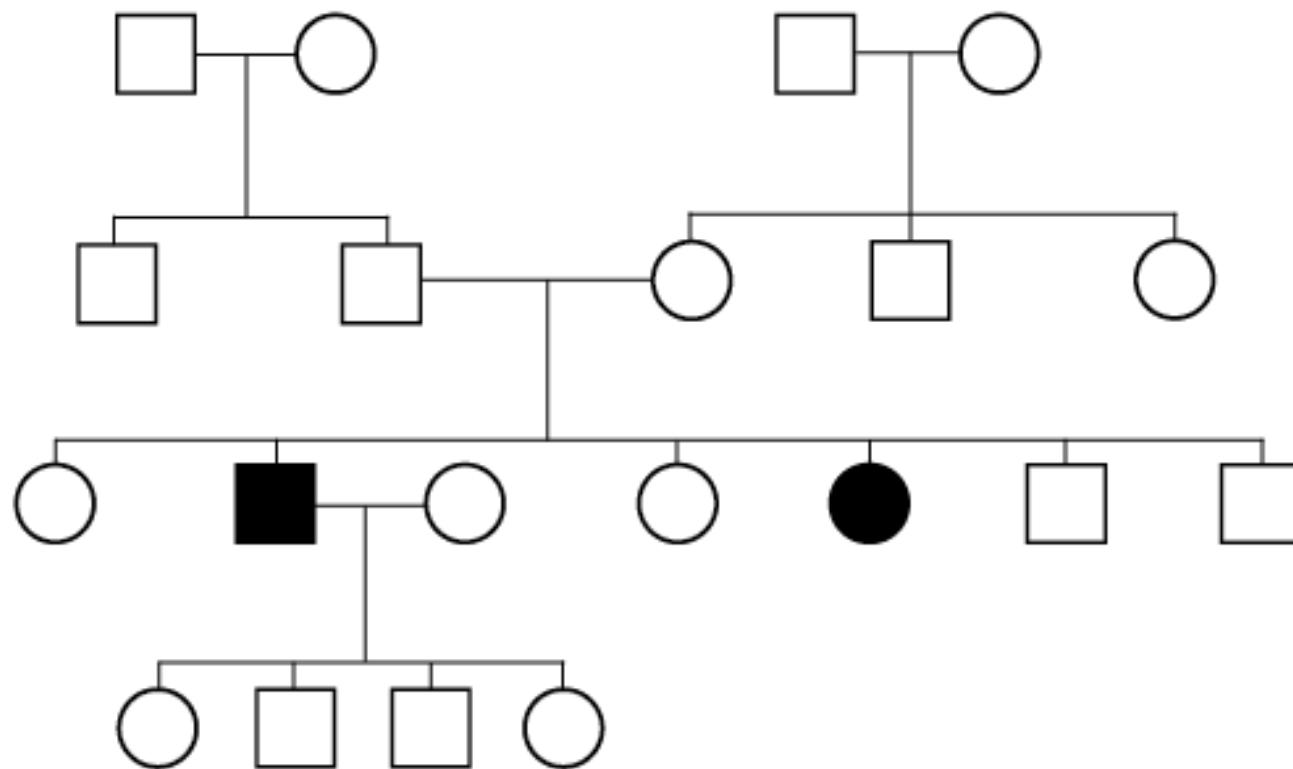


# BIOL3120

## Lecture 4: Modes of Inheritance and Population genetics



# Some terms/ideas to recall

- **Gene** = many different meanings depending on context.
  - In genetics we might talk about the gene for a specific trait. i.e. The gene associated with red hair.
  - In genomics we talk about genes as being a part of the genome associated with a specific transcribed unit of genetic information
  - In evolutionary biology we talk about genes as a unit of inheritance
- **Locus** = specific, fixed position on a chromosome where a particular gene or genetic marker is located
- **Allele** = a variant of a particular gene locus

# Some terms/ideas to recall

- **Dominant** = Having one copy of particular allele will show this condition/trait
- **Recessive** = Need two copies of recessive alleles for condition/trait to show
- **Genotype** = the alleles (versions of gene) you have at a particular gene or locus (genetic location)
  - Often shown with upper and lower case letters
  - **A** = dominant allele
  - **a** = recessive allele
  - Humans have two copies of most genes: **AA** or **Aa** or **aa**
- **Homozygote** = having two copies of the same allele at a particular gene/locus
- **Heterozygote** = having two different alleles at a particular gene/locus
  - **AA** is homozygous dominant genotype
  - **aa** is homozygous recessive genotype
  - **Aa** is heterozygote genotype
  - Homo = same, hetero = different, zygote = things coming together

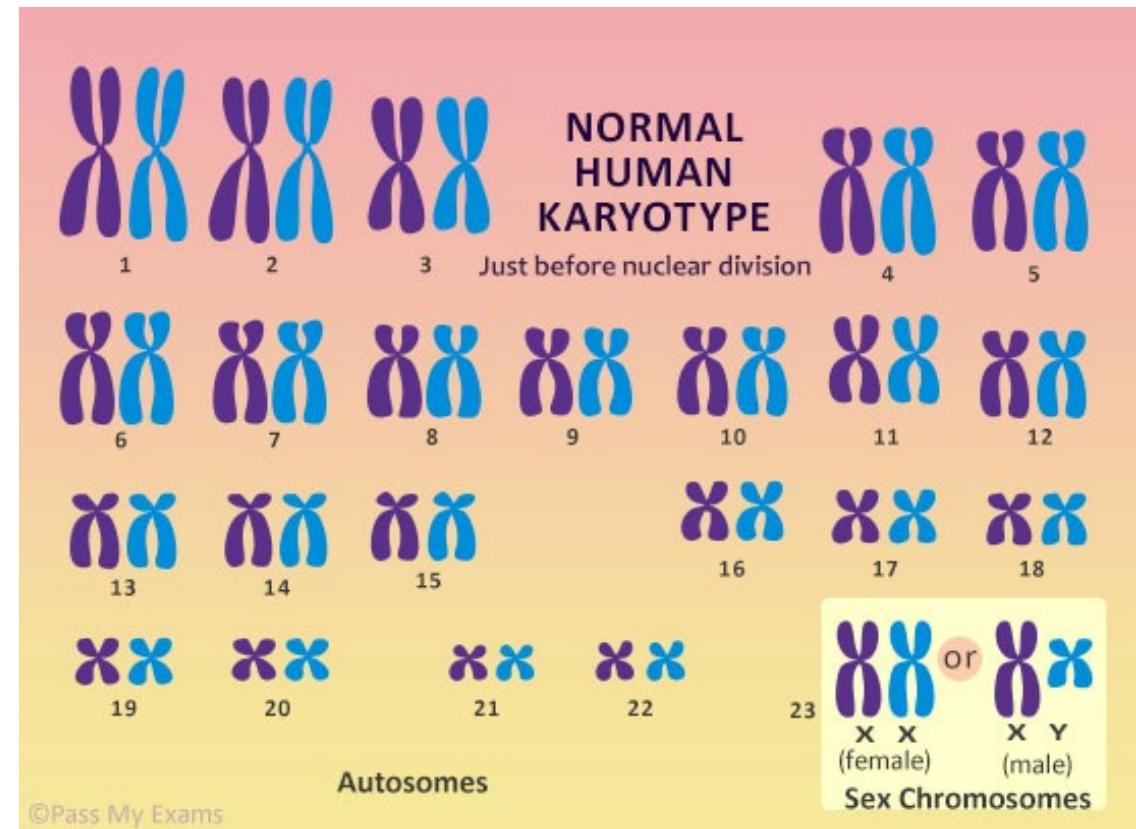
# More terms/ideas to recall

**Autosomal** = on a ‘normal’ chromosome (chromosomes 1-22)

- ie not X or Y chromosomes which determine your sex
- Generally affects males/females equally

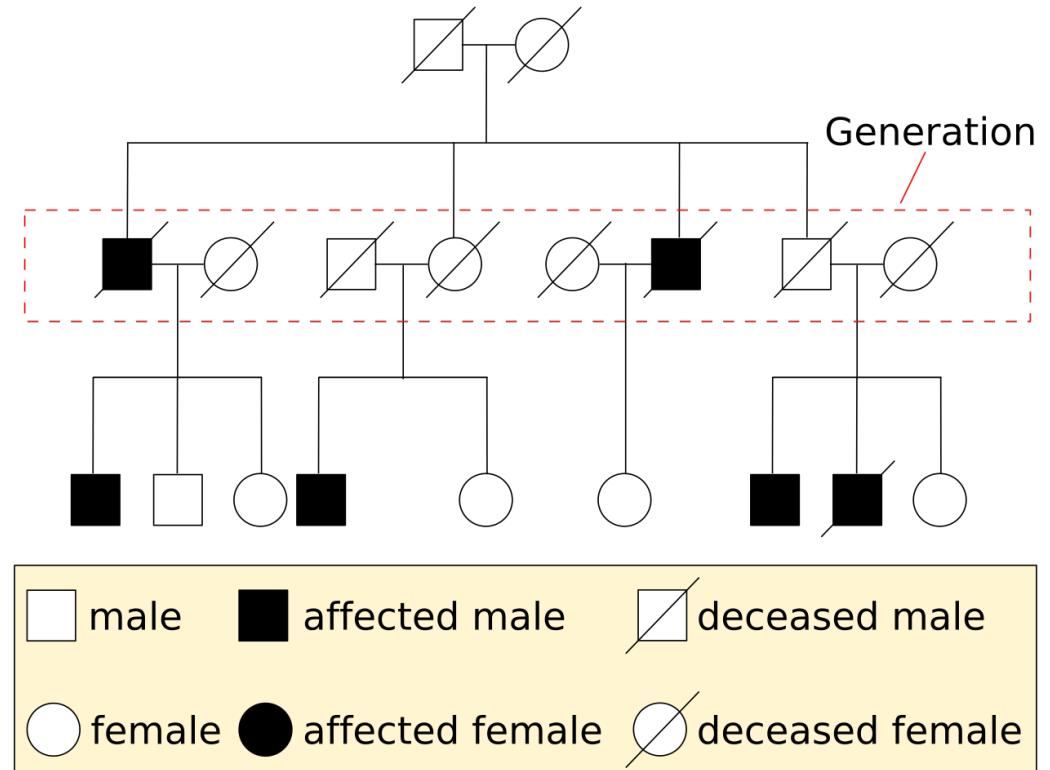
**Sex-linked** = on the X or Y chromosome

- Will affect males/females differently
- Female karyotype =  $22^*2 + XX$
- Male karyotype =  $22^*2 + XY$

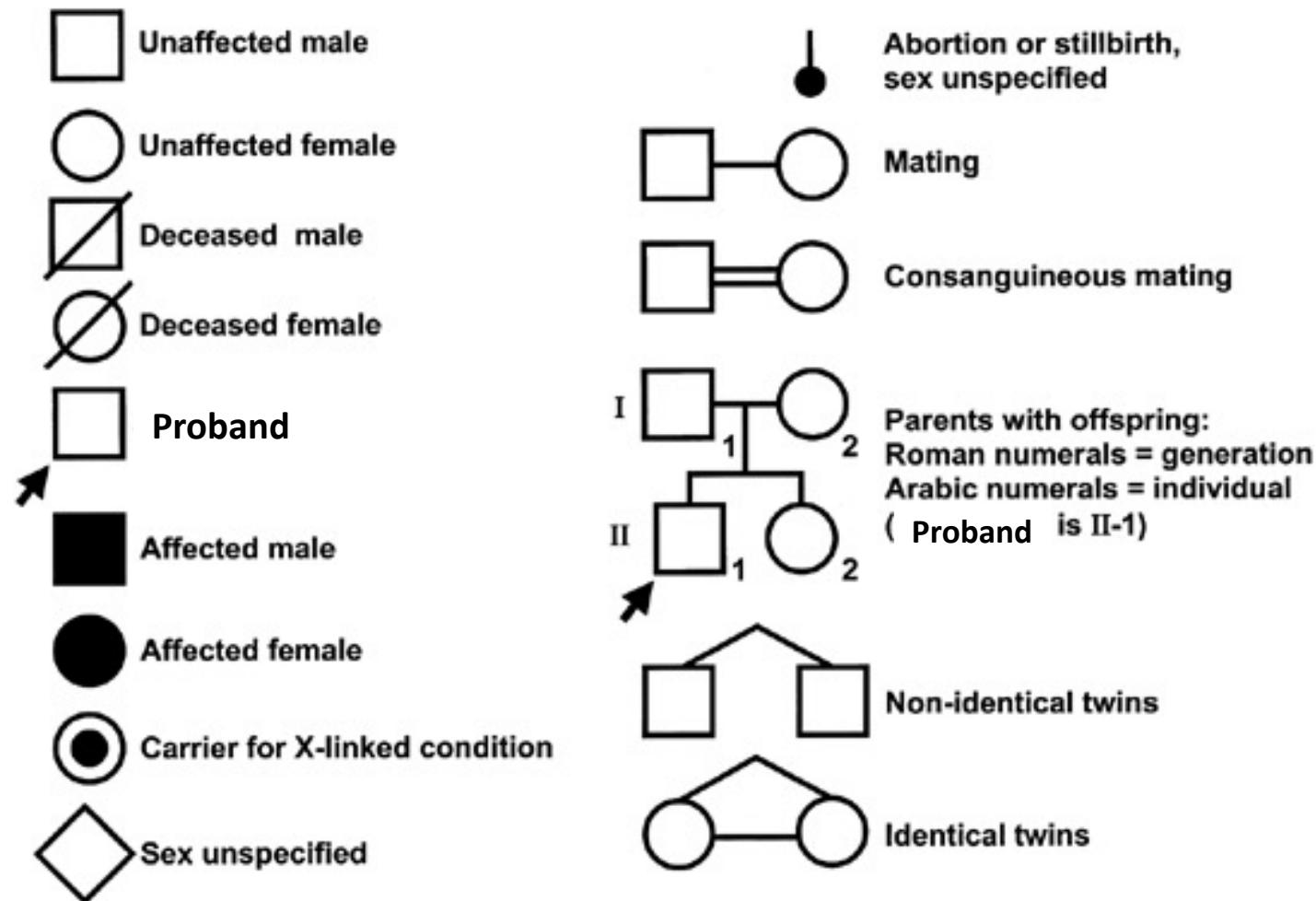


# Inheritance in humans

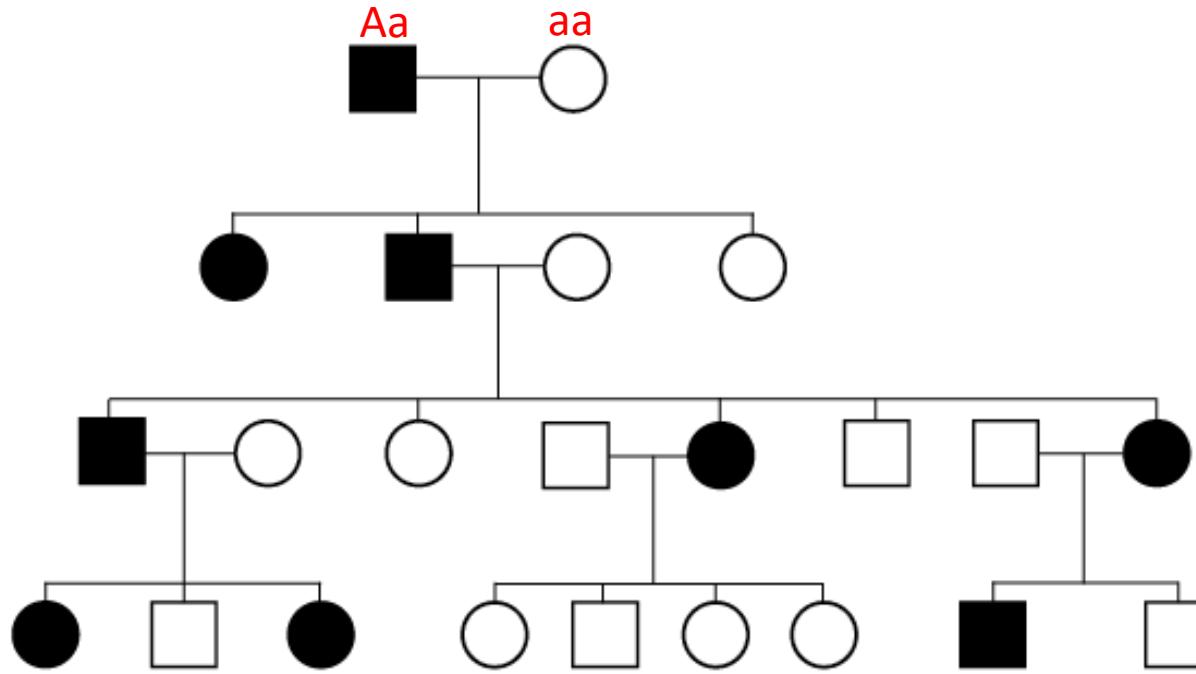
1. Autosomal dominant inheritance
2. Autosomal recessive inheritance
3. X-linked recessive inheritance
4. X-linked dominant inheritance
5. Y-linked inheritance
6. Mitochondrial inheritance



# Human pedigree key

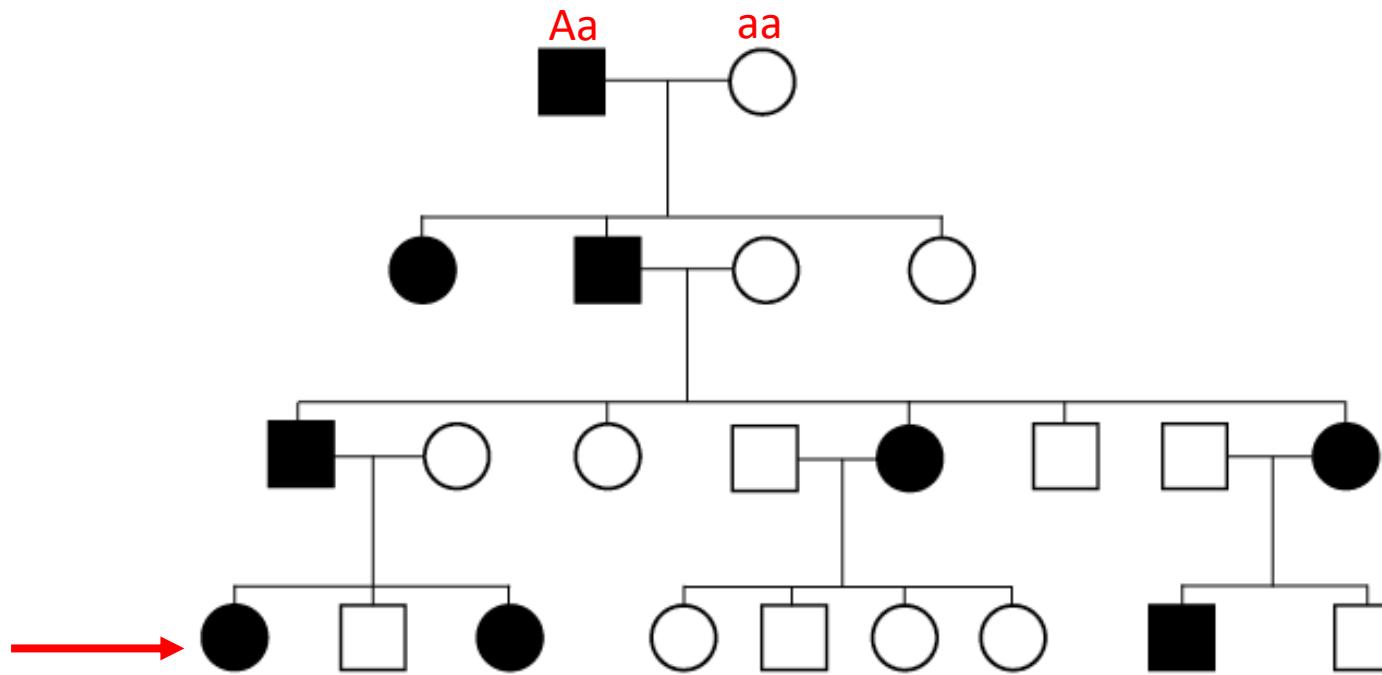


# Autosomal dominant inheritance



- One faulty copy of gene causes the condition/trait
- 50% chance of passing on to each child
- An affected person has at least one affected parent
- Approximately half the offspring of an affected parent will be affected
- Affects both genders evenly

# Autosomal dominant inheritance



- If this woman has children with an unaffected man, what are the chances of their first child being affected?
- Her genotype Aa, therefore 50% chance child would be affected

# Autosomal dominant inheritance

Exceptions to autosomal dominant pattern of inheritance:

## Incomplete penetrance

- When person carries mutant gene but does not show signs of disease
- Example: mutations in BRCA1 gene → 80% risk of breast cancer
- Pedigrees show skipping generations

## Variable Expression

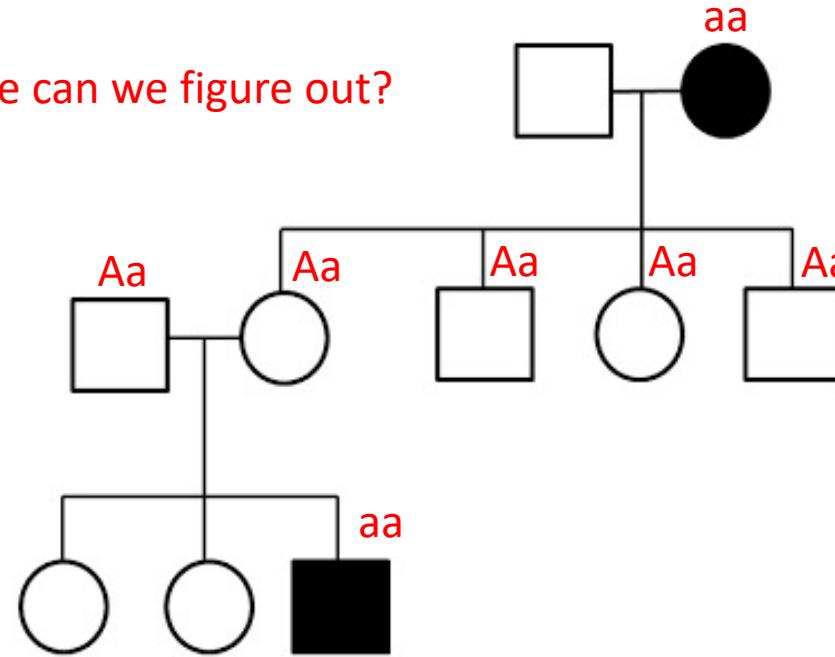
- Severity and manifestations of phenotype vary between individuals
- Example: mutation in FBN1 gene → Marfan syndrome is highly variable (disorder of connective tissue)

## Other situations that might not look dominant

- De novo (new) mutation: sporadic cases without affected parents
- Delayed onset: appears to skip a generation, consider an early death

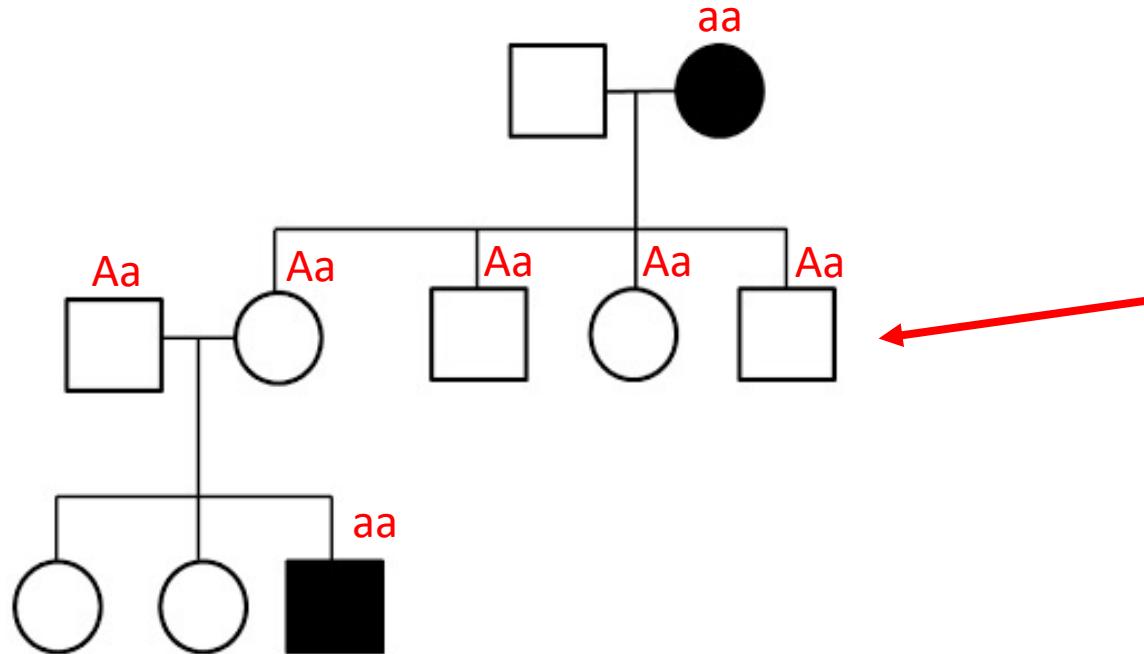
# Autosomal recessive inheritance

Who else's genotype can we figure out?



- Two copies of gene required for the condition/trait (homozygous recessive)
- Can skip generations
- Two unaffected parents can have an affected child (indicates parents are carriers)
- Affects genders equally

# Autosomal recessive inheritance



- If this person has a child with a carrier woman, what are the chances their child would be affected?
- If both parents carriers
  - $\frac{1}{4}$  of offspring affected  $aa$
  - $\frac{2}{4}$  of offspring carriers  $Aa$
  - $\frac{1}{4}$  of offspring normal  $AA$

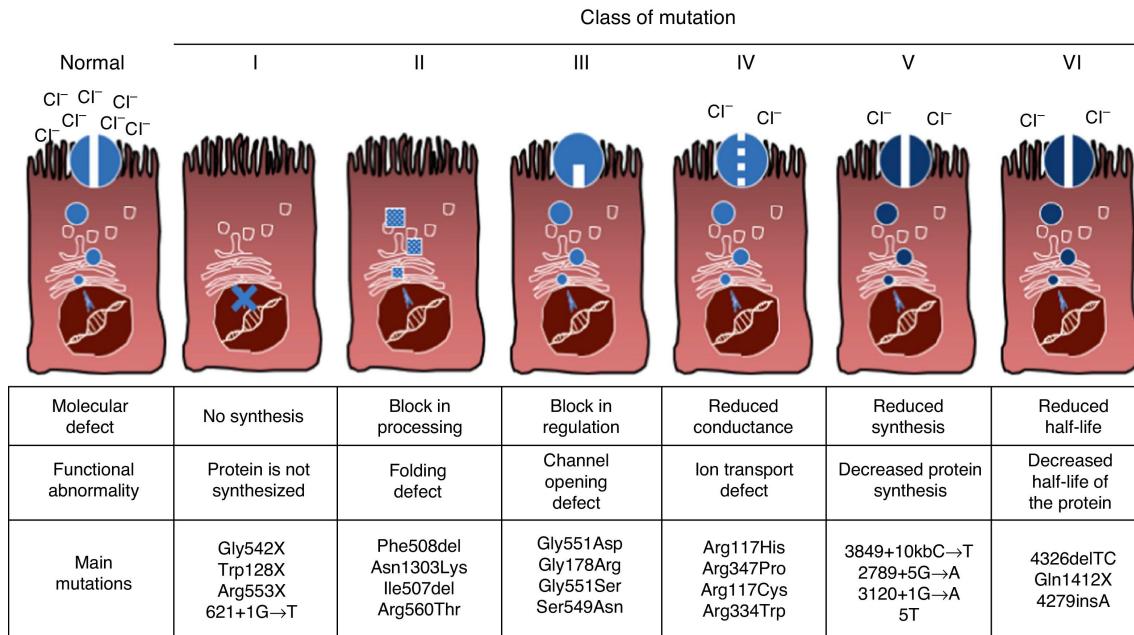
	A	a
A	AA	Aa
a	Aa	aa

# Allelic heterogeneity =

## Usually many mutations in a gene which can cause a condition

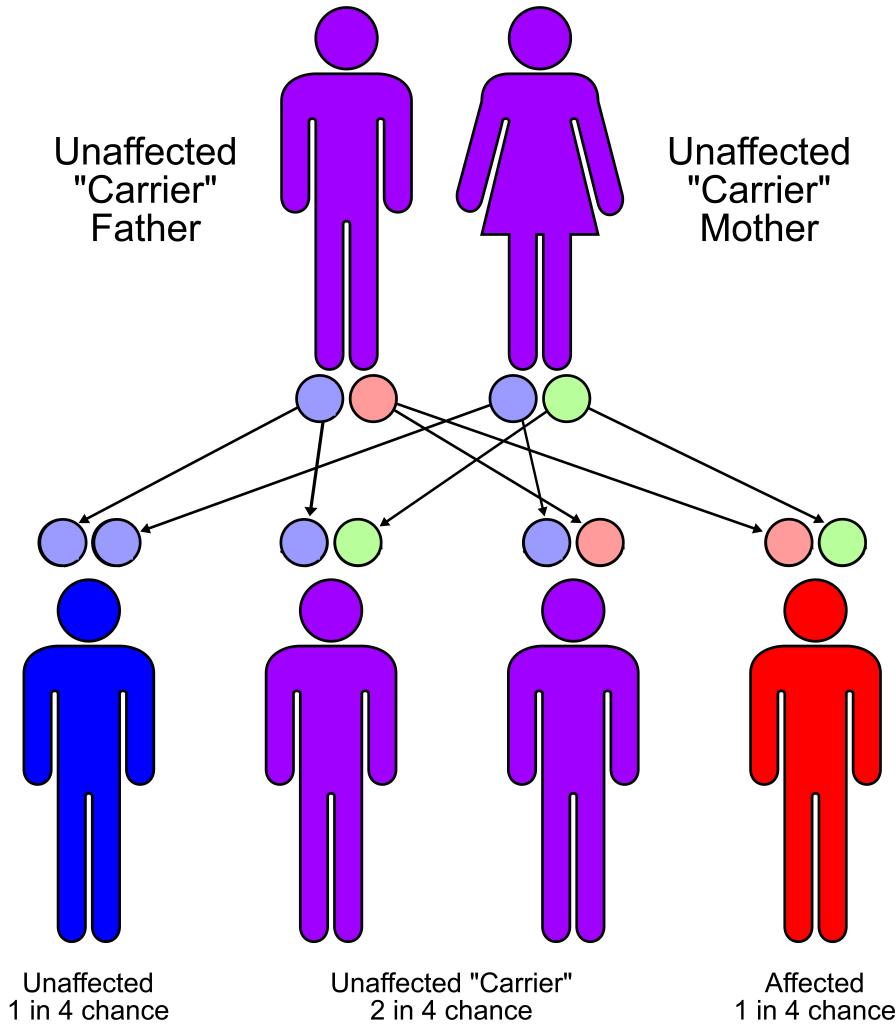
**Cystic fibrosis** = autosomal recessive genetic disorder

- Caused by mutations in CFTR gene (cystic fibrosis transmembrane conductance regulator)
- over 2,000 mutations in the CFTR gene associated with cystic fibrosis disease
- varying degrees of frequency within the disease carrying population
- different mutations produce varying degrees of disease phenotypes
- can also work in combinations to produce additive phenotypic effects.

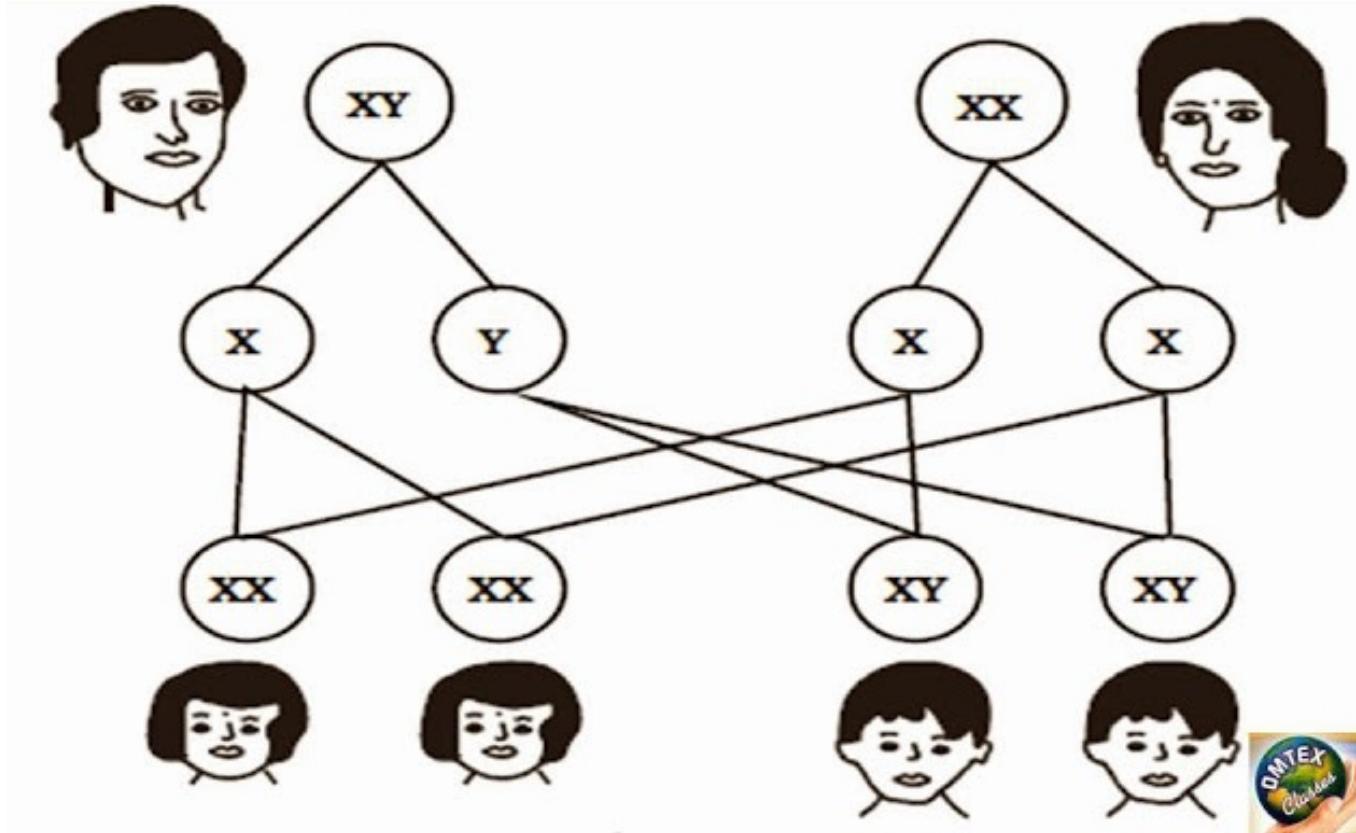


# Compound heterozygote

- The presence of two different mutant alleles at a particular gene locus
- Both are ‘recessive’



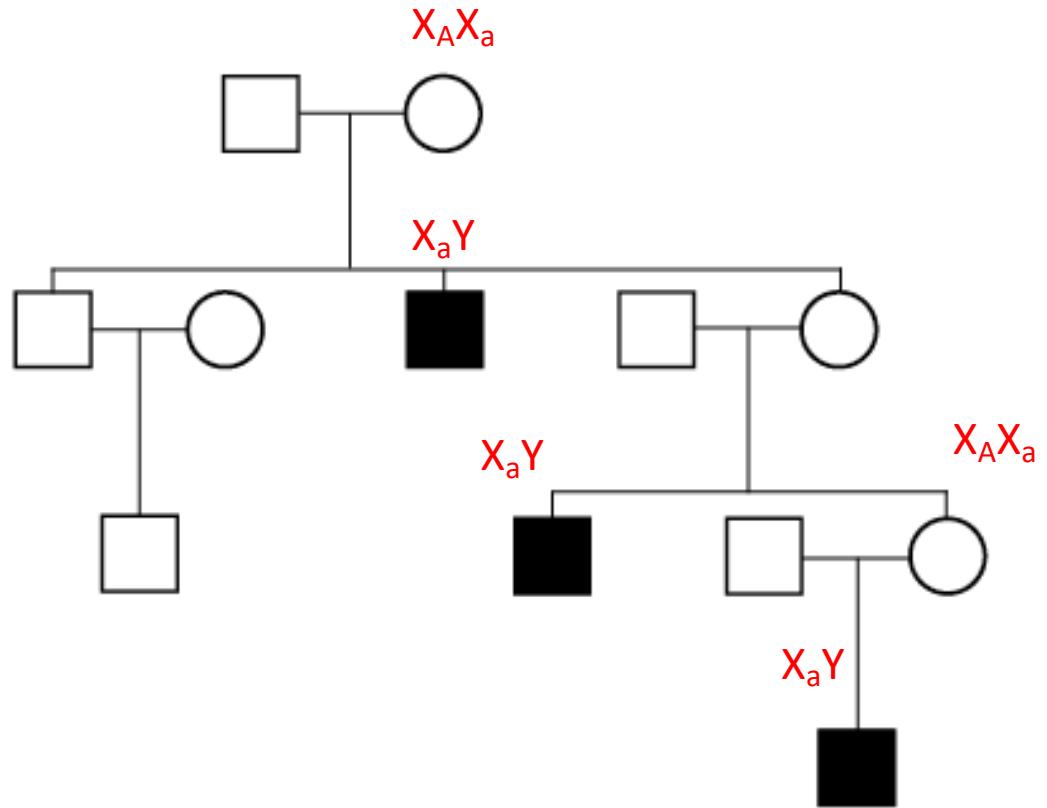
# Quick revision of sex determination



- Mothers always pass on one of their two X chromosomes
- Fathers pass on:
  - Y to sons
  - X to daughters

# X-linked recessive inheritance

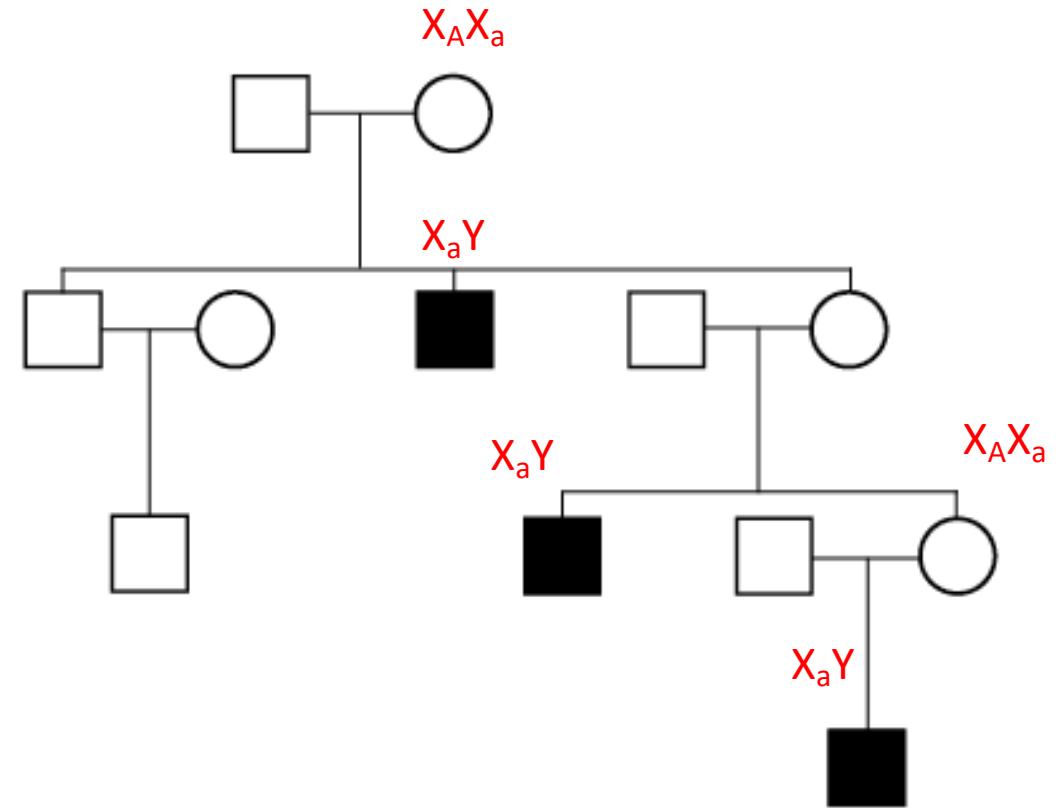
- Males hemizygous (only one copy) = affected or not, can't be carriers
  - Males more often affected by X-linked conditions
  - Males get their X from mother, so affected males have carrier mothers
- Females can be carriers, affected females much lower frequency since two copies of X
- Carrier mothers pass on either healthy X or mutant X
  - 50% of sons of carrier mothers will be affected
  - 50% of daughters of carriers mothers will be carriers
- Affected fathers pass on either X or Y
  - Y = boy – affected males can't pass condition onto a son
  - X = girl – all daughters of affected males will be carriers



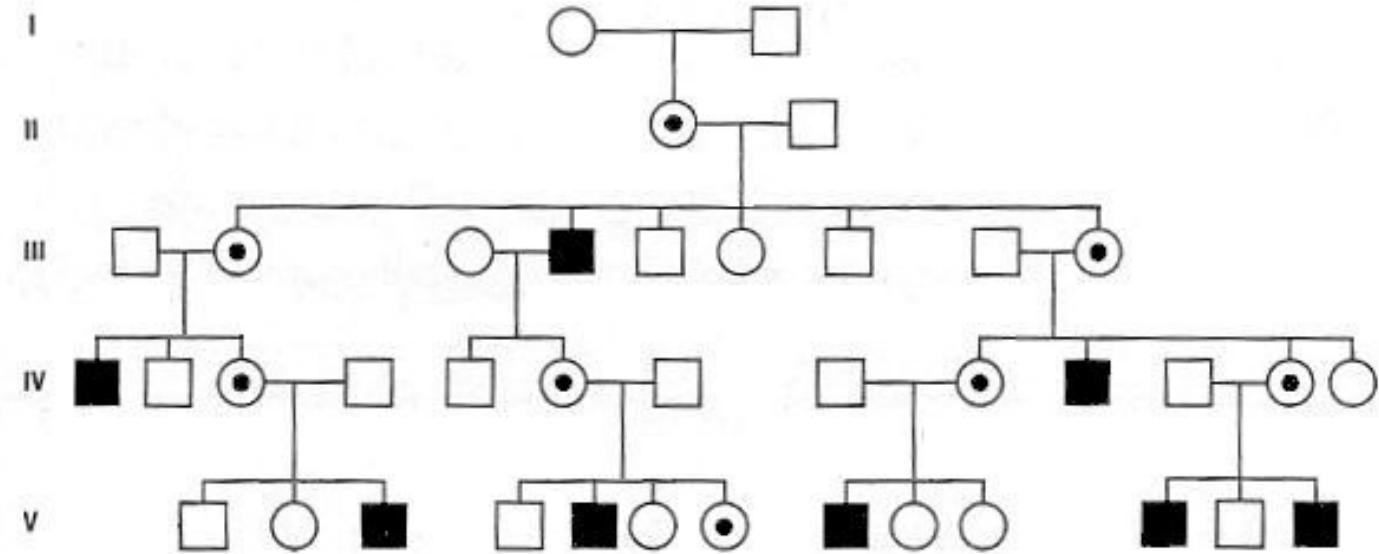
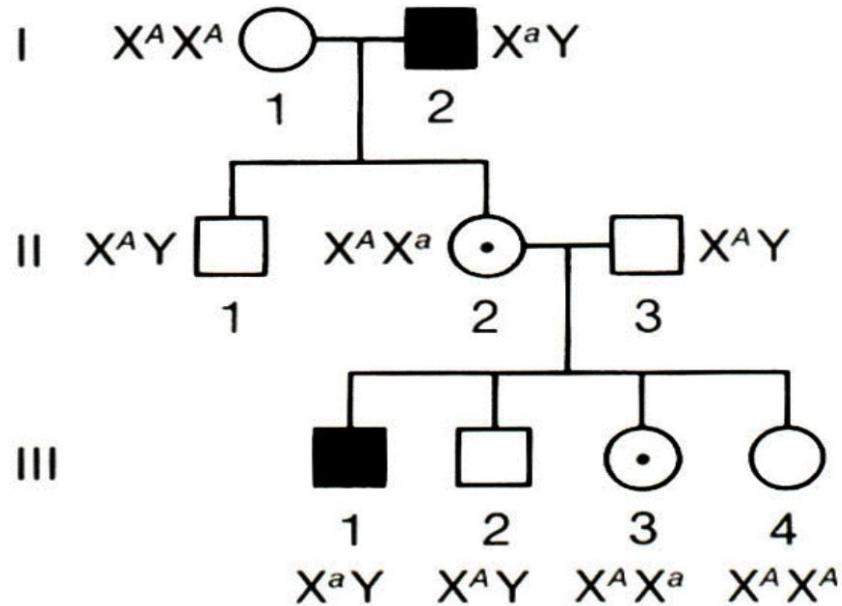
# X-linked recessive inheritance

End result of all this:

- Only / mostly males affected
- Can skip generations

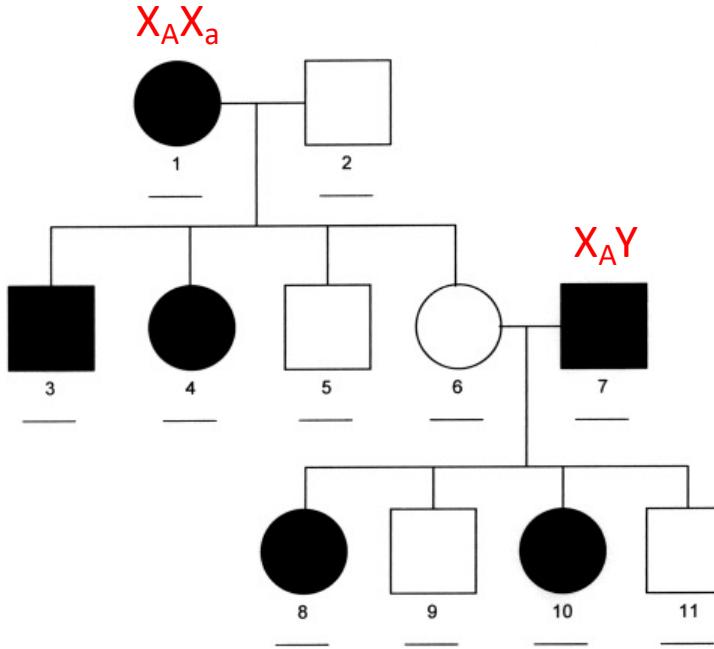


# X-linked recessive inheritance



- Sometimes dots or circles used to indicate carrier women in X-linked
- But don't assume you will get this information

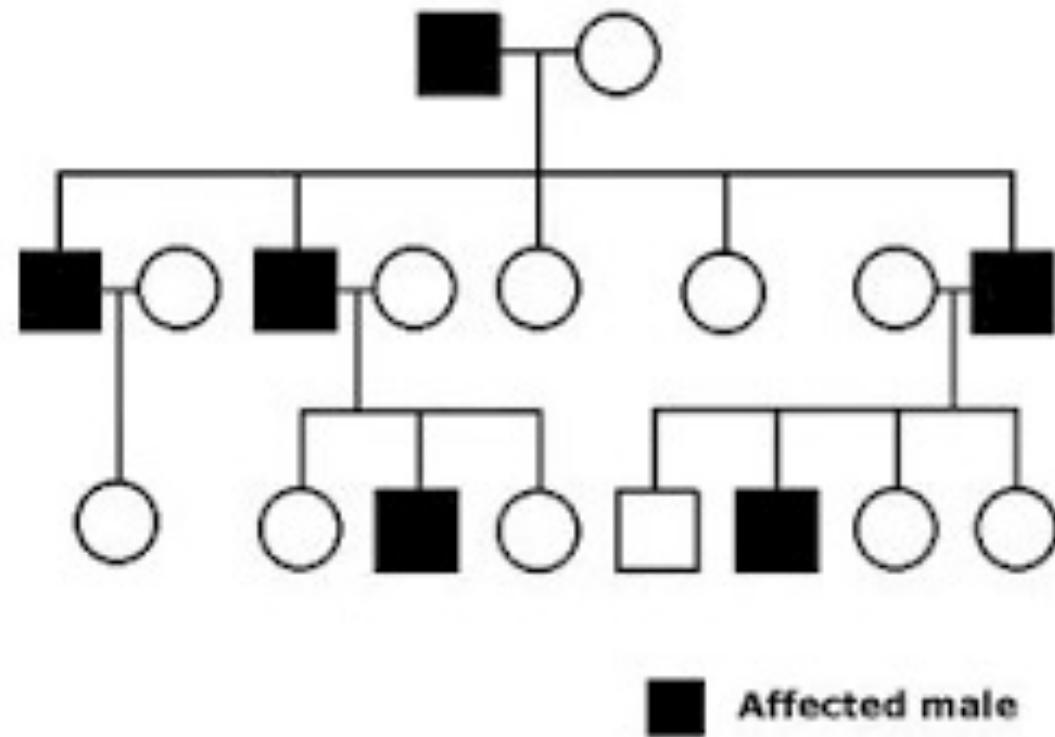
# X-linked dominant inheritance



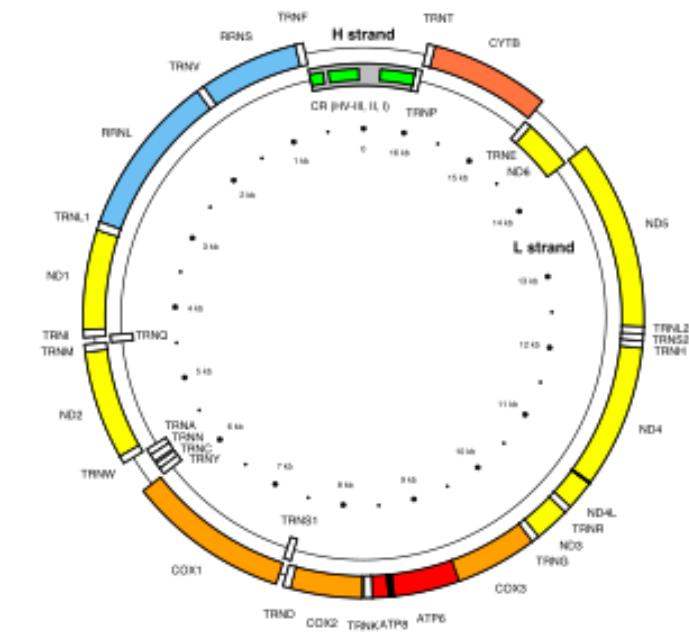
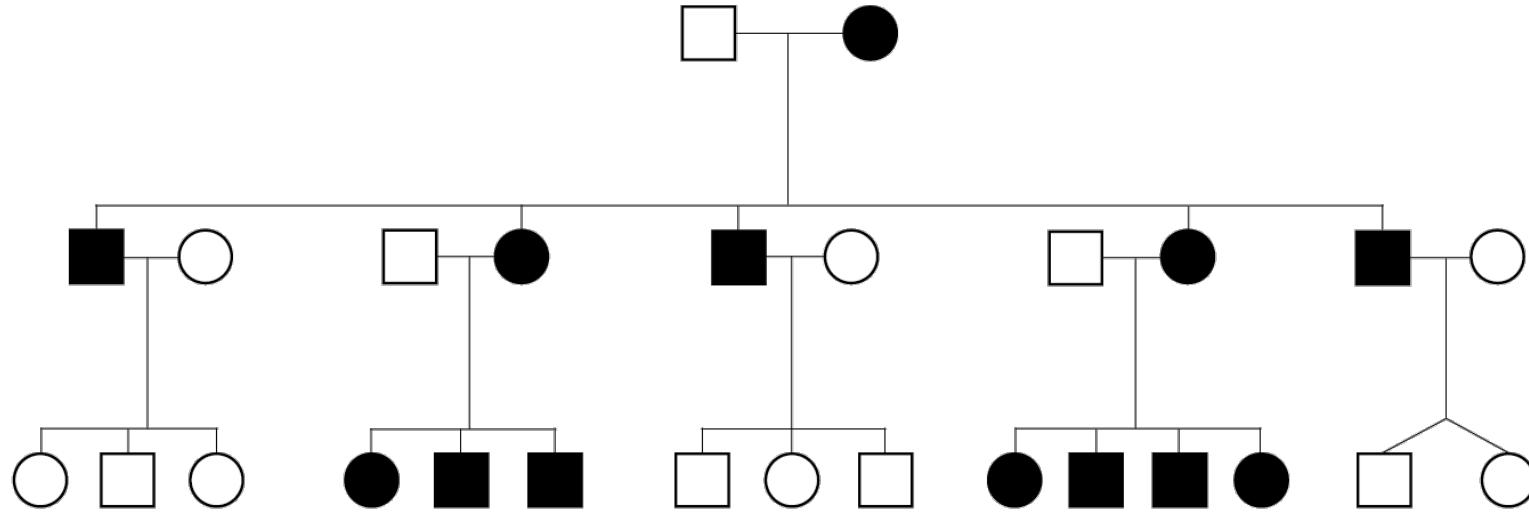
- No male-to-male inheritance since Y being passed on
- Affected males transmit to 100% of daughters but 0% of sons
- Affected females transmit to 50% of their offspring, regardless of sex
  - ratio = 2 affected females : 1 affected male

# Y-linked inheritance

- All sons of an affected father are affected
  - Very rare for expressed traits
  - Only males can be affected
  - Dominance is irrelevant
- 
- Far fewer Y-linked genetic disorders compared to X-linked
  - Y chromosome smaller and fewer genes compared to X
  - The SRY (sex determining region of the Y-chromosome) develops the testes and can be associated with Y-linked disorders

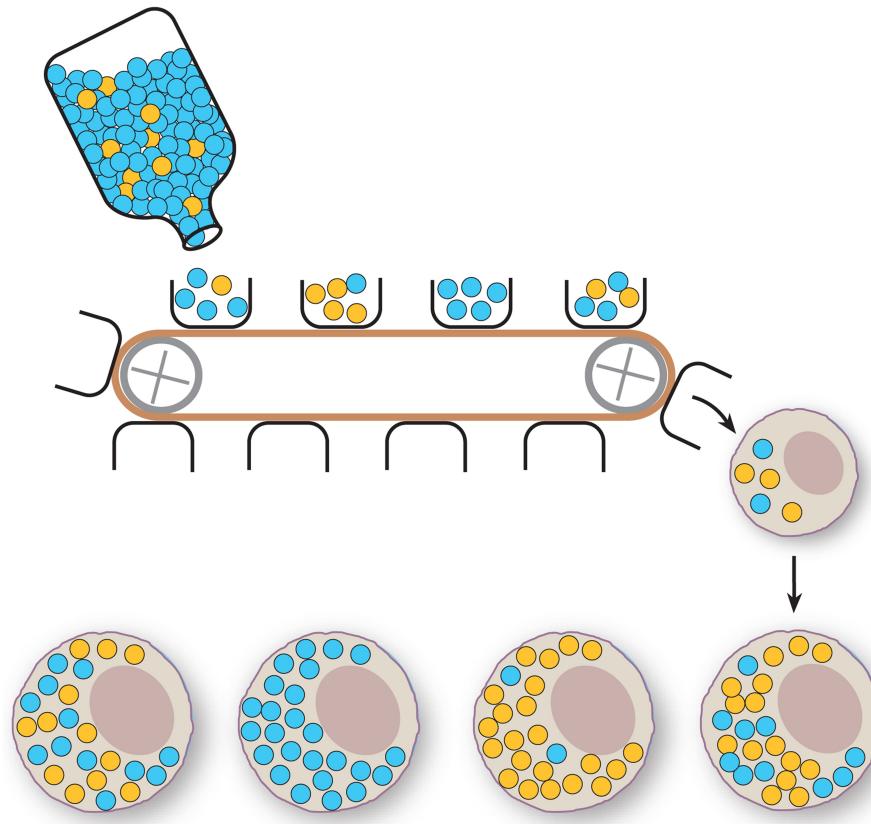


# Mitochondrial inheritance



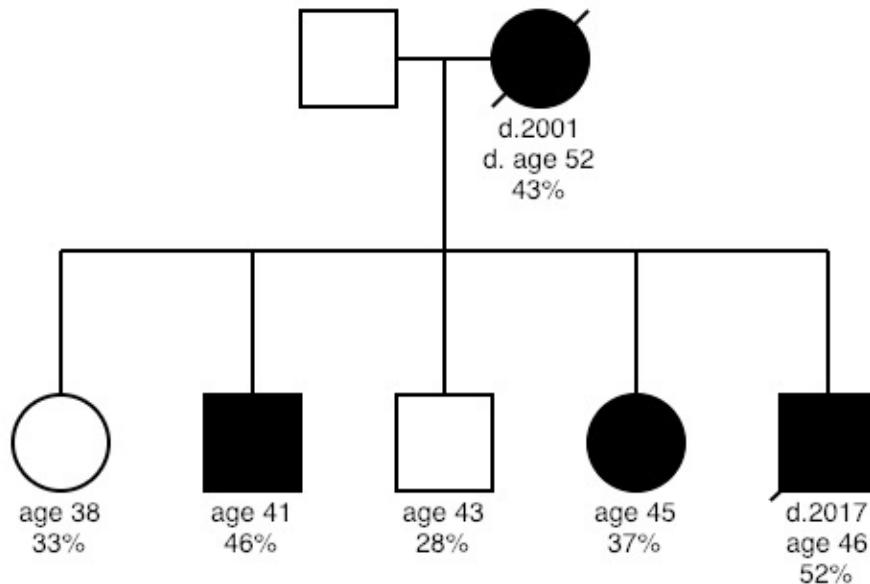
- Mitochondrial genome (16,569 base pairs) encodes genes of mitochondrial oxidative phosphorylation pathway and mitochondrial tRNAs
- Mutations can cause structurally and functionally abnormal mitochondria
- Usually maternally inherited (mitochondria in egg cell, not sperm cells)
- Rare evidence of father passing on mitochondrial disease
- Theoretically: every child of affected mother is affected

# Reality: Mitochondrial heteroplasmy



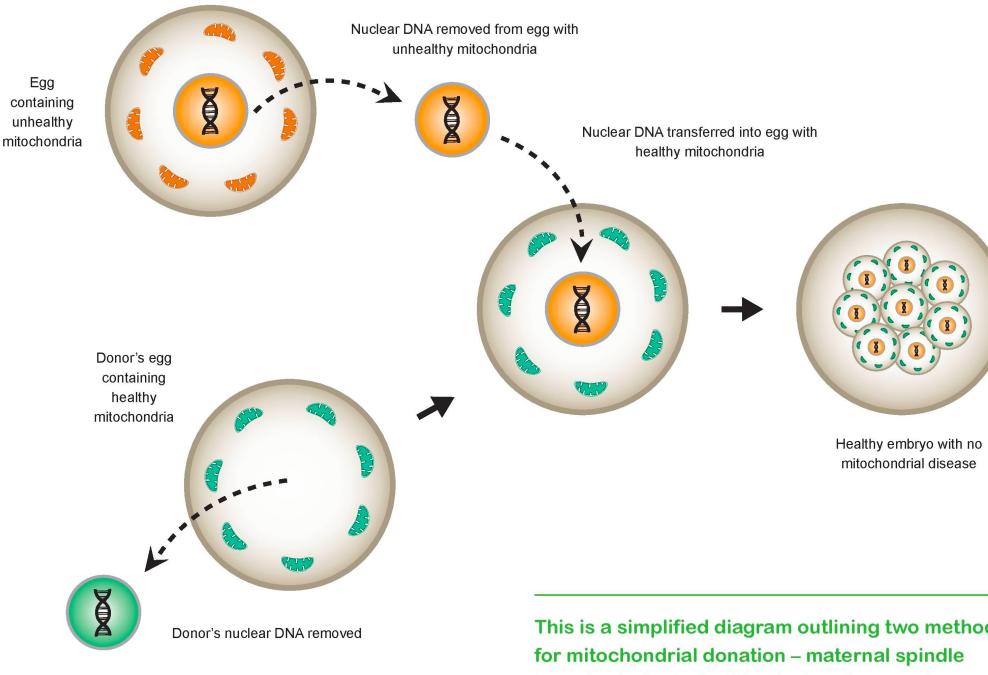
- Heteroplasmy = having a mix of mitochondrial genomes within cells/organism
- Heteroplasmy levels vary for each child of affected mum

# MELAS: Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like episodes



- m.3243A>G in majority of affected people
- Can be a ‘threshold level’ before disease onset
- Severity and age of onset often vary with heteroplasmy level

# Mitochondrial Replacement Therapy



- Nuclear DNA removed from a fertilised egg of affected mother
- Transplanted into the fertilised egg of a female donor whose nuclear material has been removed
- Legal in UK from 2018, legal in Australia soon?

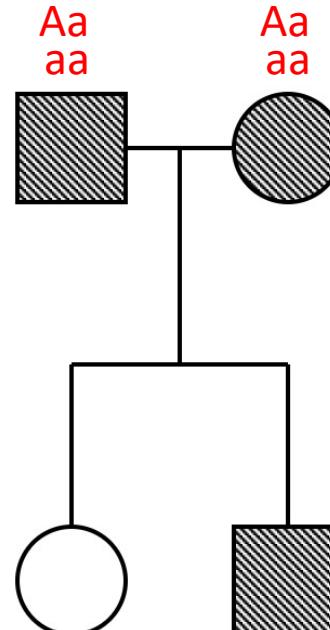
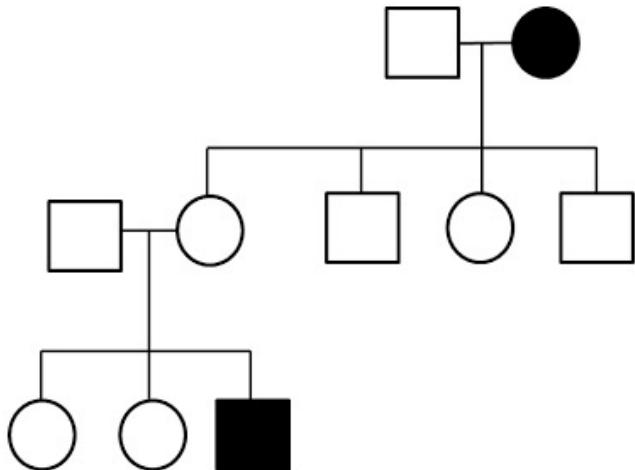
# Multiple modes of inheritance for same disease:

Kallman syndrome / normosmic isolated gonadotrophin-releasing hormone deficiency

	Gene <sup>1, 2</sup>	% of IGD Attributed to Pathogenic Variants in This Gene <sup>3</sup>
X-R	<i>ANOS1</i> ( <i>KALI</i> )	5%-10% (KS)
AD	<i>CHD7</i>	5%-10% (KS or nIGD)
AD	<i>FGFR1</i>	~10% (KS or nIGD)
AD or AR	<i>GNRHR</i>	5%-10% (nIGD)
AR	<i>IL17RD</i>	2%-5% (KS or nIGD)
AR	<i>PROKR2</i>	~5% (KS or nIGD)
AD	<i>SOX10</i>	2%-5% (KS)
AR	<i>TACR3</i>	~5% (nIGD)

Pedigrees help on a family by family basis, not necessarily a disease by disease basis

# General pedigree tips



- If you know the mode of inheritance, you know the genotype of anyone who is affected
  - You might be able to infer the genotypes of an affected person's parents
- You may be able to rule out a particular mode of inheritance
  - Father passing onto son = can't be X-linked (though mum may be a carrier)
  - Two affected people having an unaffected child = can't be recessive
  - Try to genotype everyone assuming a particular mode of inheritance – it just won't work for some modes

# 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?

# Hardy Weinberg equilibrium

$$p + q = 1$$

Allele	A	a
Frequency	p	q

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

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

In Caucasian populations, approximately 1 in 2,500 people are affected with cystic fibrosis

Theoretically, what is the carrier rate in this population?

$$q^2 = 1/2500$$

$$q = \text{square root } 1/2500 = 0.02$$

$$p = 1 - q = 0.98$$

$$\text{Carrier rate} = 2pq = 2 * .02 *.98 = .0392$$

# One more...

Consider two alleles A and a for sickle cell disease

	AA	Aa	aa
Observed:	25,374	5,482	67

Allele frequencies  $p = 0.91$  and  $q = 0.09$

Expected:	25,562	5,106	255
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Chi-squared = 167.7, p-value < 0.001 (very significantly different)

Excess of heterozygotes, deficiency of homozygotes

$d$	0.05	0.01	0.001
1	3.841	6.635	10.828
2	5.991	9.210	13.816
3	7.815	11.345	16.266
4	9.488	13.277	18.467
5	11.070	15.086	20.515
6	12.592	16.812	22.458
7	14.067	18.475	24.322
8	15.507	20.090	26.125
9	16.919	21.666	27.877

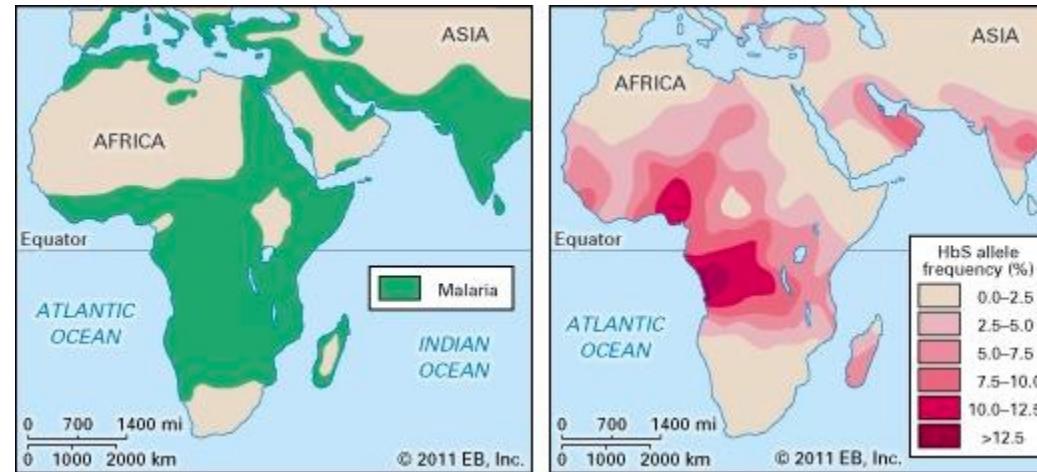
Why might this population be so different from HWE?

# Positive selection in humans

AA – no sickle cell, but relatively susceptible to malaria

Aa – sickle cell carrier, not clinically important

aa – die early because of sickle cell anaemia



in equatorial Africa, up to 40% of people are carriers of this mutated gene

Read a recent paper to find out more:

<http://science.sciencemag.org/content/334/6060/1283.full>