

Inheriting variants

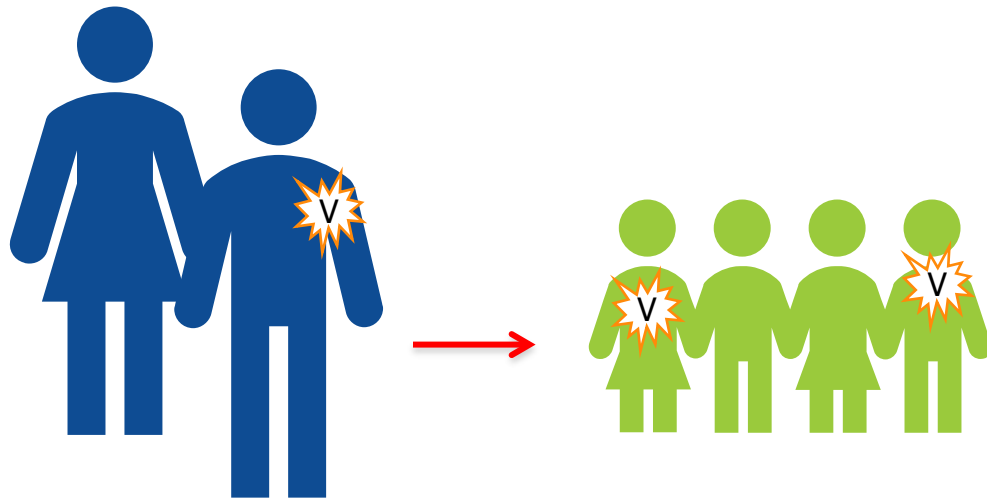
Germline variants and Mendelian Inheritance



Germline vs Somatic variants

Germline variants are heritable

- Present in somatic cells and
- Present in egg or sperm
- Some cause family cancer syndrome



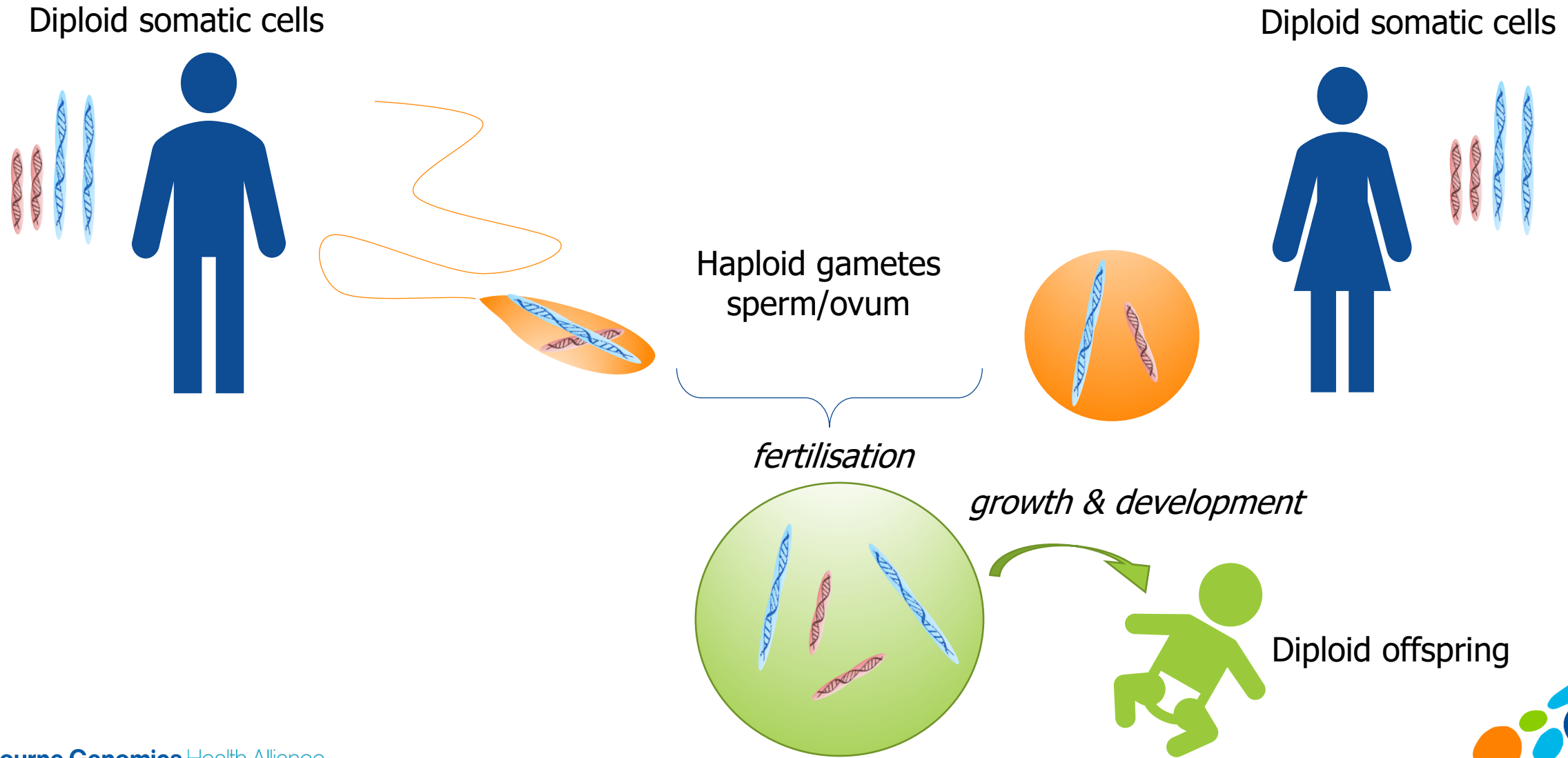
Somatic variants are not heritable

- Occur in somatic cells
- Present in the daughter cells
- May cause cancer



Diploid and haploid cells

◆ Inheriting one of each chromosome from each parent



Terminology

Autosomes and sex chromosomes

Autosomes – human chromosomes 1-22; do not determine sex
Sex chromosomes – the sex-determining chromosomes X and Y

Genotype

Genetic constitution

- an individual's alleles & variants

Phenotype

Physical and molecular characteristics

- e.g. morphology, biochemistry, behaviour

Allele

Alternative sequence for a gene

- a gene with a variant sequence

Polymorphism

Common alleles (variants) in the population (>1%)



Terminology

Autosomes and sex chromosomes

Autosomes – human chromosomes 1-22; do not determine sex
Sex chromosomes – the sex-determining chromosomes X and Y

Monosomy
Trisomy

Number of copies of a whole chromosome
▪ Monosomy – one copy; Trisomy – 3 copies

Genotype

Genetic constitution
▪ an individual's alleles & variants

Phenotype

Physical and molecular characteristics
▪ e.g. morphology, biochemistry, behaviour

Allele

Alternative sequence for a gene
▪ a gene with a variant sequence

Polymorphism

Common alleles (variants) in the population (>1%)



Describing phenotype as dominant or recessive

Dominant One copy of the allele is enough to show the trait

Recessive An individual needs two copies of the same allele to show the trait

Codominant When the trait of two alleles is expressed equally in the phenotype

Dominant negative The protein product of a variant allele alters the action of the protein from the 'normal' allele



Zygoty

Homozygoty

- Two identical alleles for the gene
 - same sequence, same variant(s)

Heterozygoty

- Two different alleles for the gene
 - different variants

Hemizygoty

- One allele for the gene, e.g.
 - XY males are hemizygoty for all genes on X chromosome and all genes on Y chromosome
 - Monosomy – chromosome deletion
 - Deletion of one allele



e.g. male hemizygoty for 'A' variant on X chromosome



Genotypes

Compound heterozygous

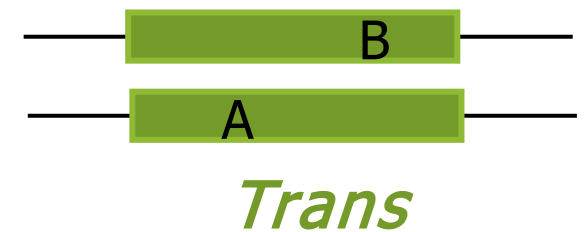
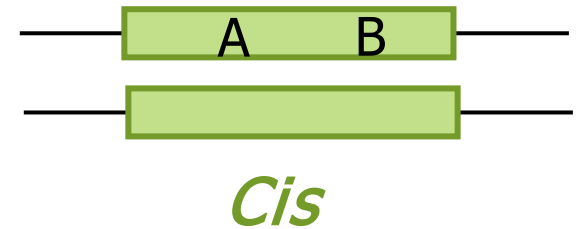
- Two different variants for the gene
 - both variants different to reference sequence

Variants in *cis* – variants are on same allele

- If a parent is affected with same as the child, predict variants in *cis*

Variants in *trans* – variants on different alleles

- If neither parent is affected but child is affected, predict variants in *trans*

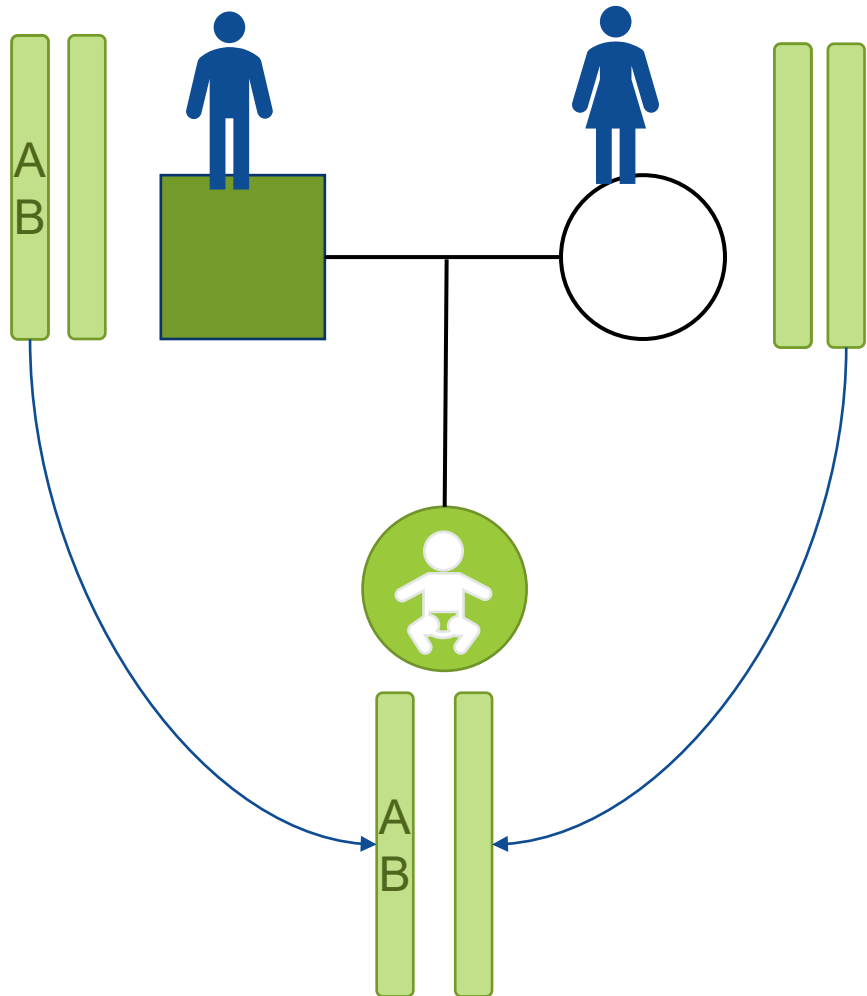


*Inheritance of compound het
illustrated on next page*

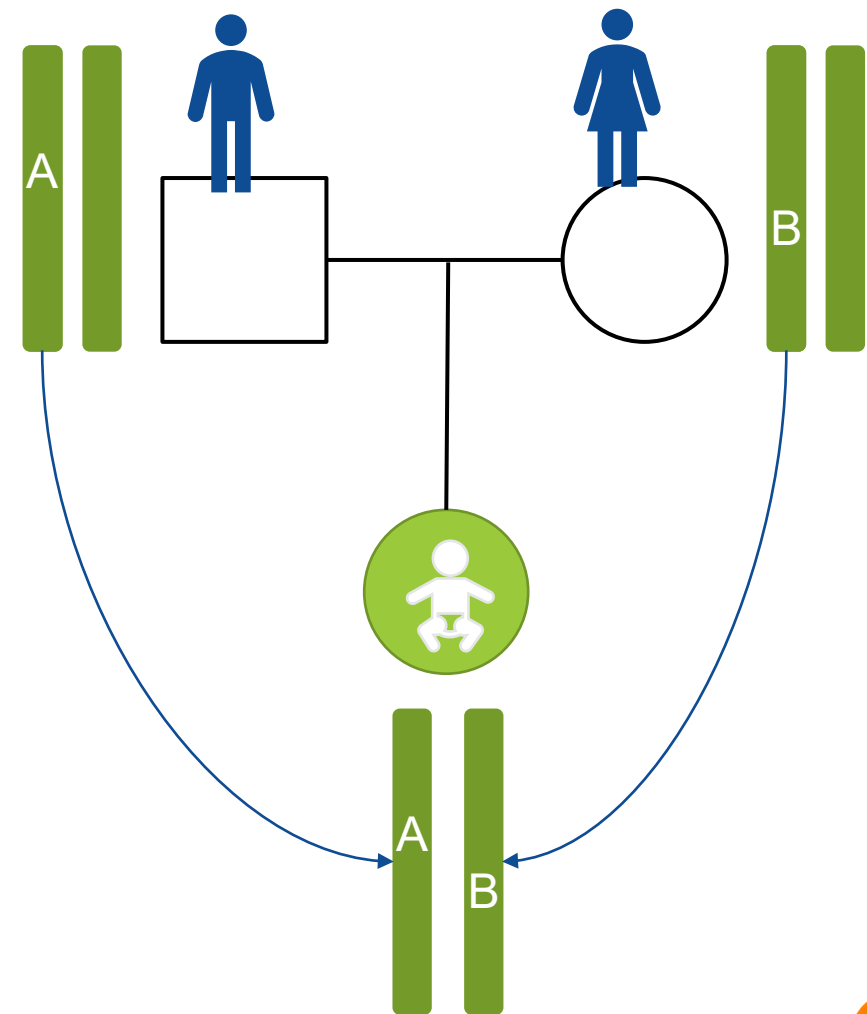


Inheriting...

Variants in *cis*



Variants in *trans*



Other concepts you might encounter relating to phenotypes and inheritance...

Are you familiar with:

- Penetrance
- Expressivity
- Chimerism
- Genetic anticipation
- Gonadal mosaicism

If not, read on...



Factors affecting phenotypic expression

Penetrance

The chance that the phenotype will become evident.

Some people with the variant display the phenotype, others don't.

[analogy – on/off switch]

Expressivity

Variable expressivity - a range of signs and symptoms can occur in different people with the same genetic condition

[analogy – dimmer switch]

Genetic anticipation

When the signs and symptoms of an inherited condition tend to appear earlier and become more severe in successive generations. Frequently seen with trinucleotide repeat disorders



Factors affecting phenotypic expression

Genetic Mosaicism

When cells in an individual have different genotypes, e.g. a mutation occurs in one cell of an early embryo and is passed on only to its daughter cells, so is present in only some cells in the adult. May not be present in germline cells or gametes.

Germline (gonadal) mosaicism

When the germline cell population has differences in the genetic information: e.g. a nucleotide variant may be present in only some gametes; epigenetic modification may affect genes in only some gametes

Chimerism

When an individual has two or more genotypes resulting from fusion of more than one fertilised embryos very early in embryo development



Genetic Pedigrees

Drawing and interpreting family history
and genetic pedigree charts

Here we use terminology such as male, female, mother and father to explain genetic inheritance concepts. We recognise that not everyone will identify with these terms.



Family history

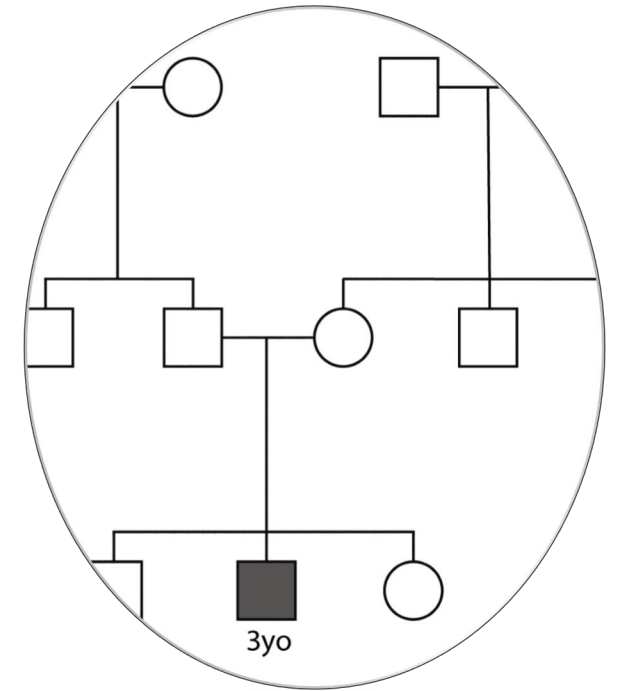
Inheritance of traits or disease can be followed through families by looking at family trees or pedigrees

Dominant and recessive phenotypes have characteristic pedigrees

- Examples on the following pages

Mutations/variants can arise *de novo* in an individual

- the condition would not be seen in previous generations



Pedigree charts

Symbols

□ ■ Male (unaffected/affected)

○ ● Female (unaffected/affected)

◇ Gender unspecified

◇₂ Number of siblings

◻ ◯ Deceased

◼ ◉ Proband (person presenting with condition)

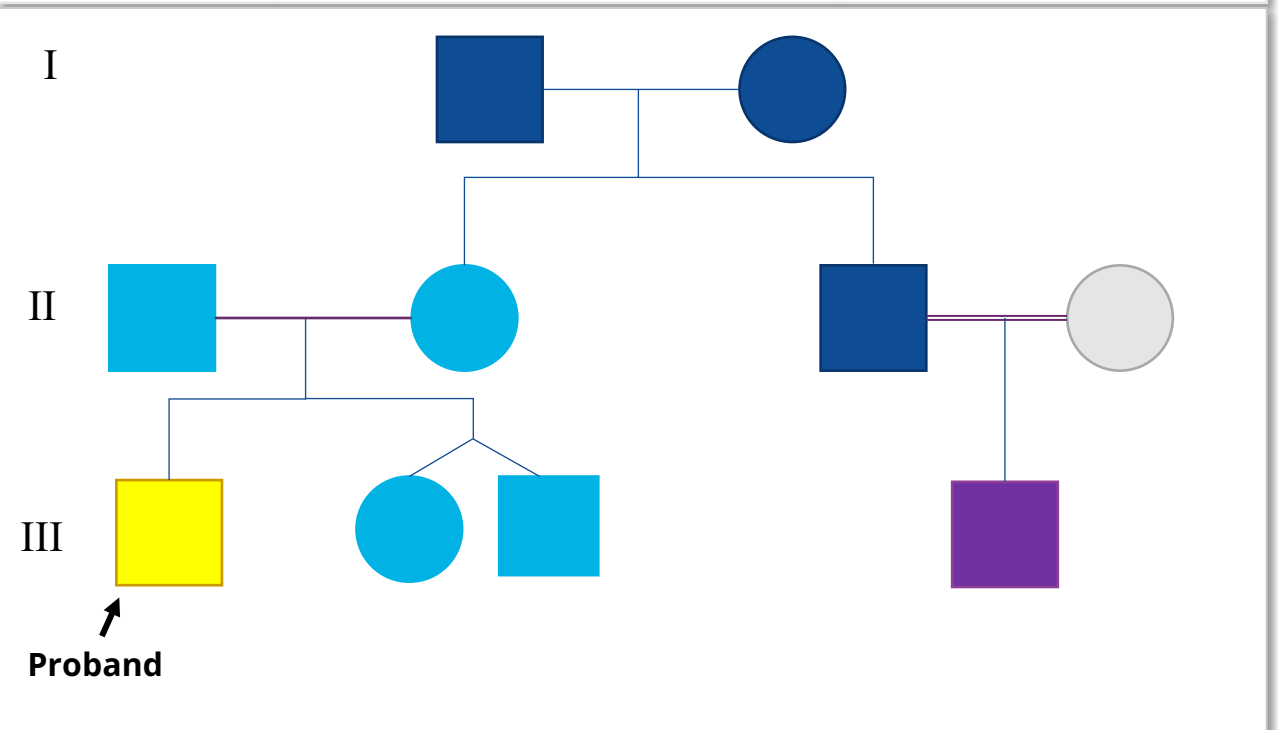
◉ ◻ Carrier

Relatedness to proband (yellow):

1° = first degree relative – shares 50% genetic material

2° = second degree relative – shares 25% genetic material

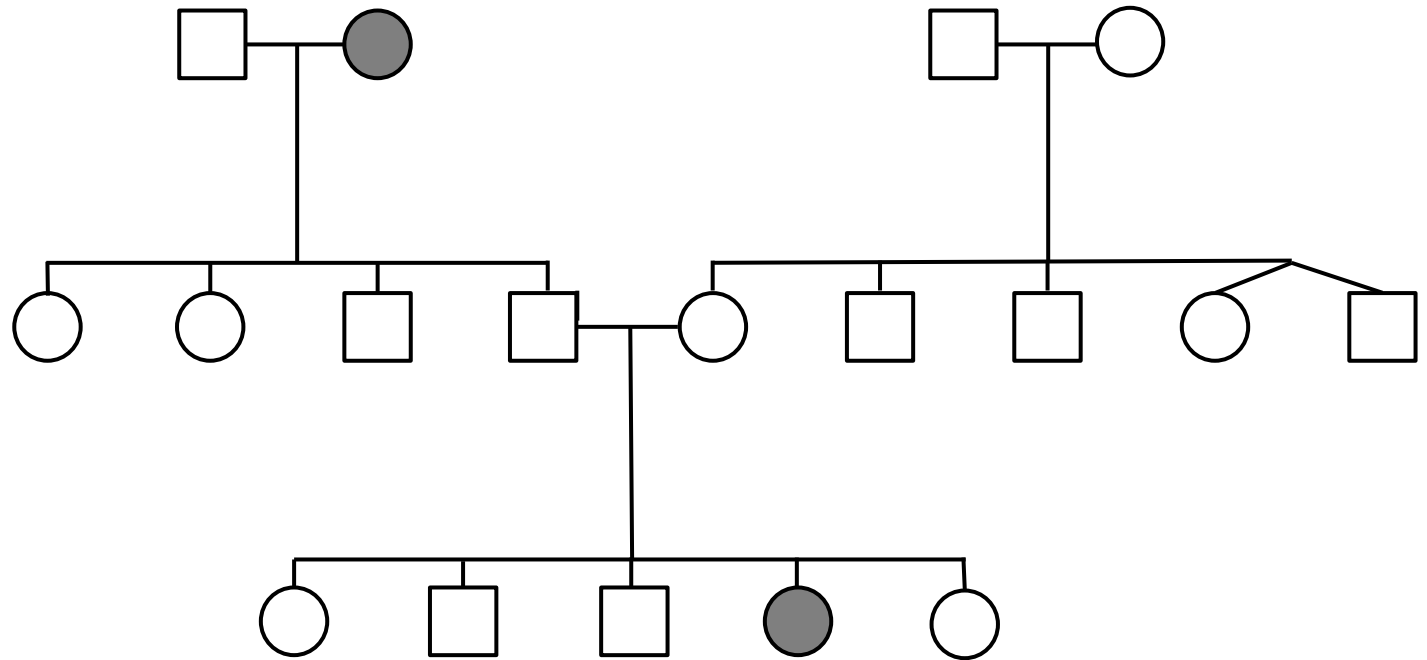
3° = third degree relative – shares 12.5% genetic material



Autosomal Recessive

The phenotype is seen only when two identical alleles are present

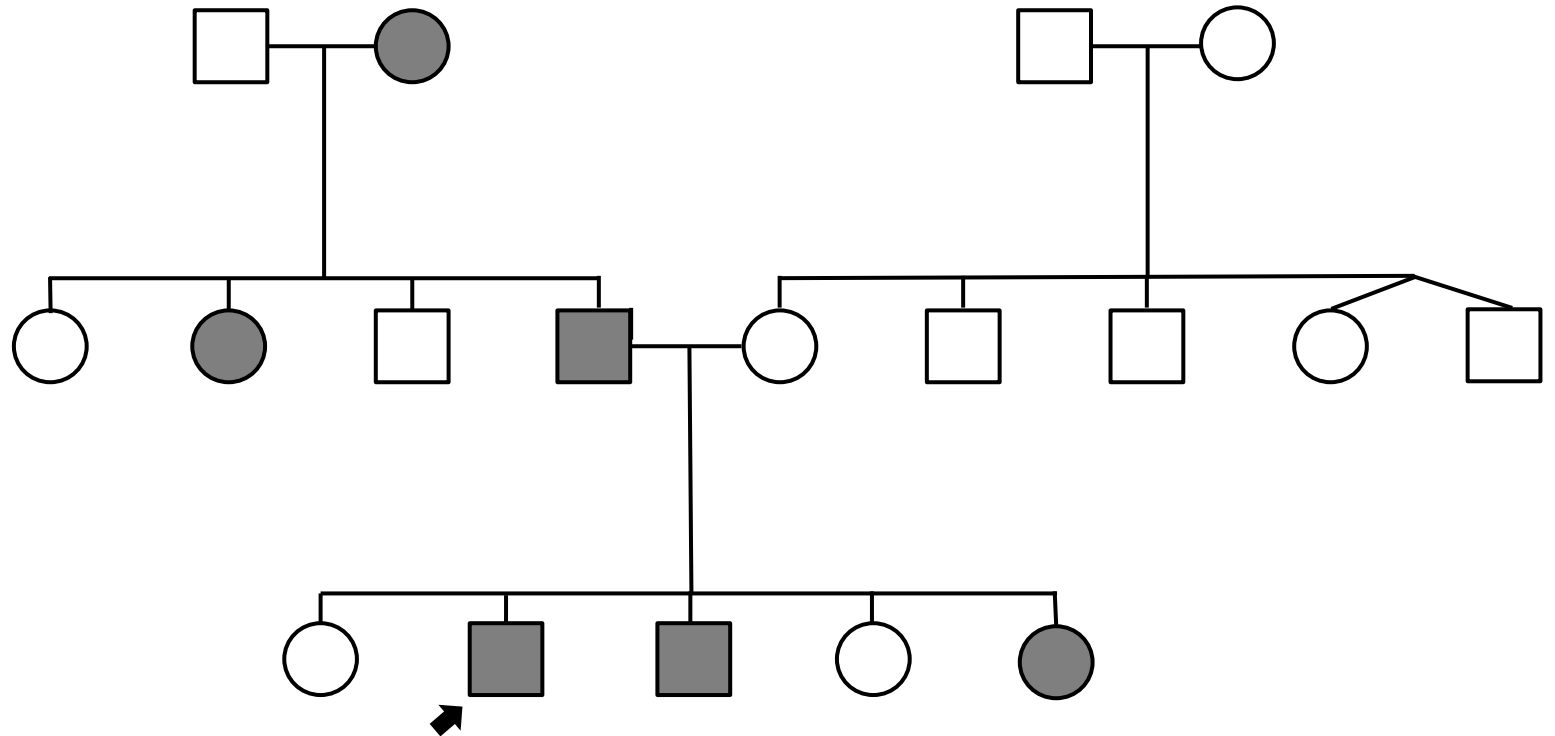
- Trait seen only in homozygous individuals
- Two unaffected parents can have an affected child
- Unaffected individuals with one variant allele are heterozygous 'carriers'
- Trait may 'skip' generations



Autosomal Dominant

The phenotype is seen in the presence of only one allele

- Trait can appear in each generation
- Individuals heterozygous and homozygous for the variant show the trait



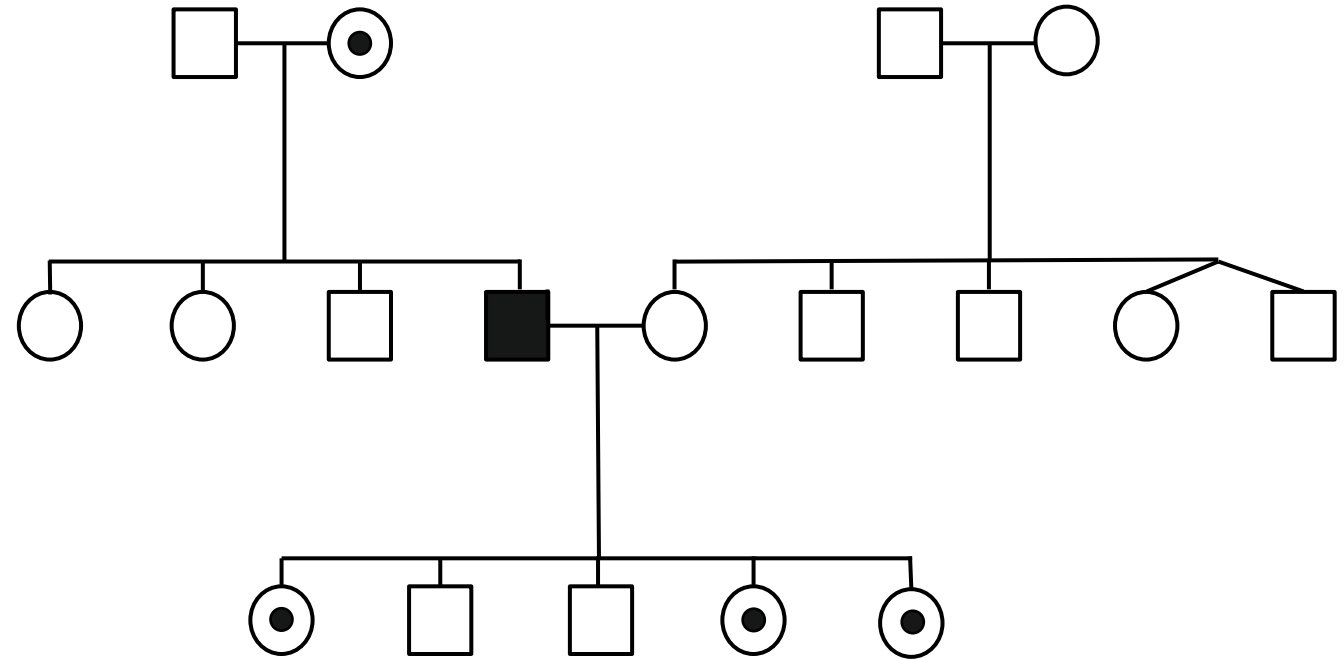
Sex linked: X-linked recessive

The variant is on the X-chromosome

Recessive X-linked traits expressed more often in boys
(one X chromosome)

Heterozygous females are 'carriers'

- Heterozygous 'carrier' mother can pass allele to sons or daughters, but
 - males show the trait
 - females are unaffected carriers
- Affected fathers pass the allele/variant to all daughters, but not to sons



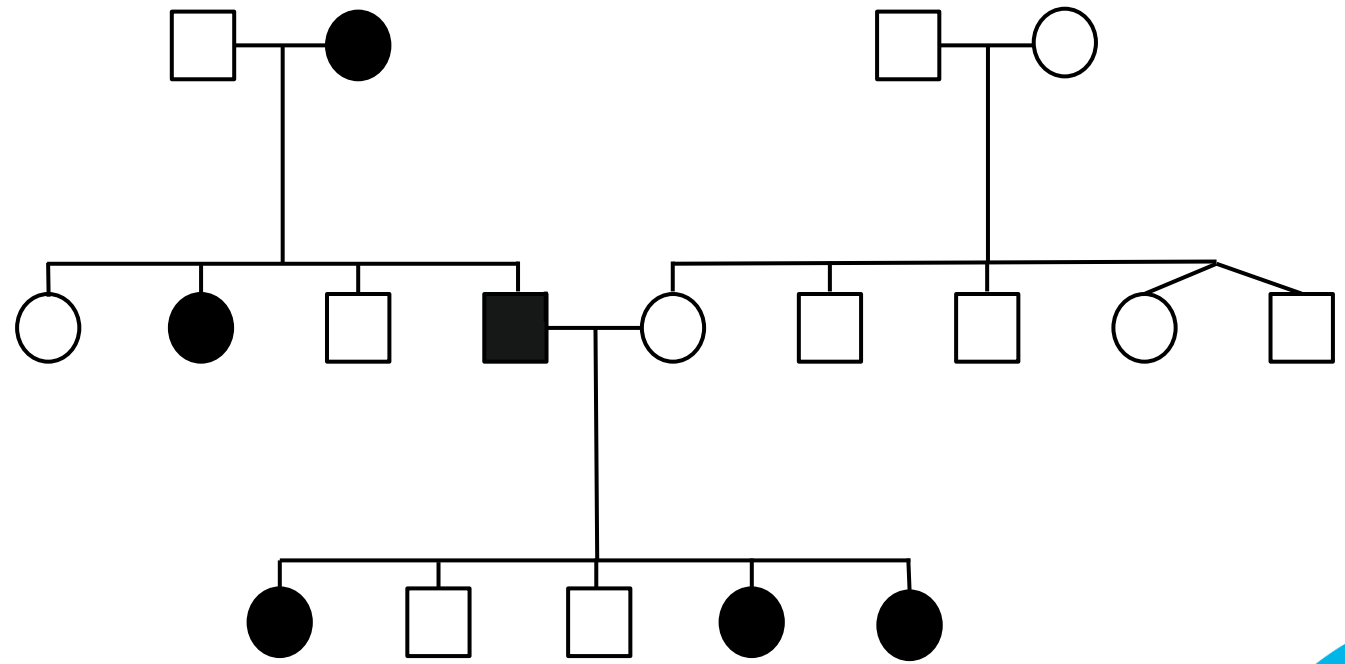
Sex linked: X-linked dominant

The variant is on the X-chromosome

Individuals are affected or not (no carriers)

Dominant X-linked traits expressed in males or females inheriting the X-chromosome with the variant

- Condition may appear in each generation
- Mothers pass allele to sons or daughters
- Fathers pass allele to daughters, not sons

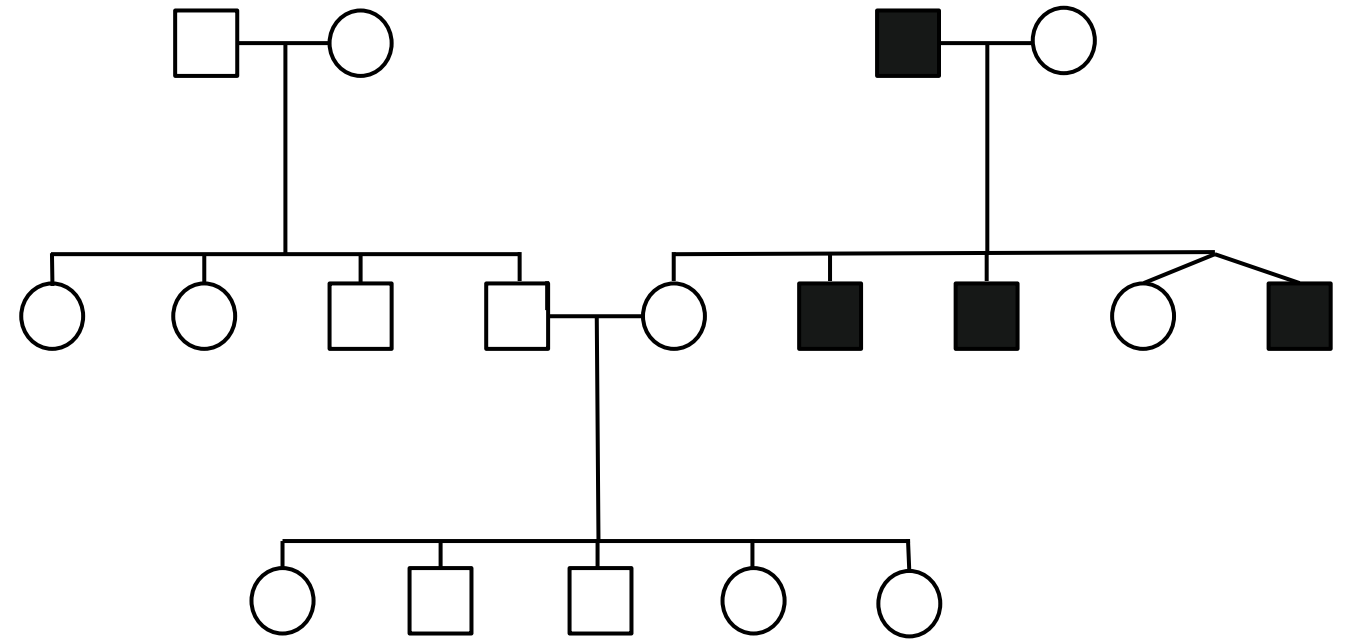


Sex-linked: Y-linked

The gene is on the Y chromosome

All males with the variant are affected

Inherited only by males



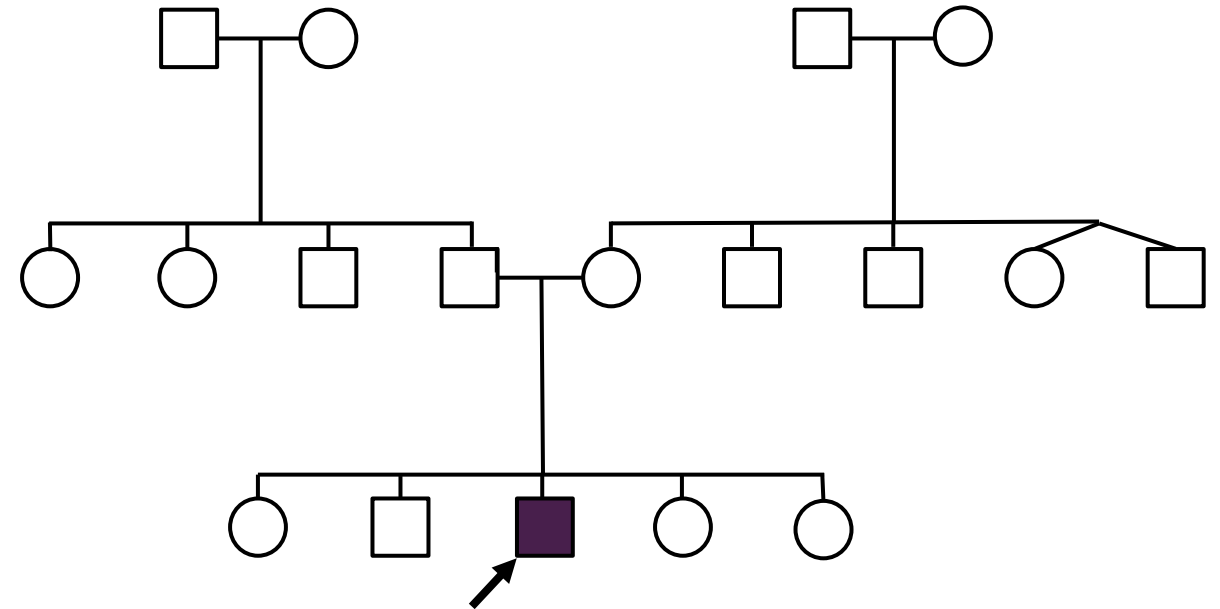
De novo (dominant trait)

New variant, not present in parents

Causes dominant trait

Arises during gamete formation or early development – parent unaffected

- Inheritance resembles autosomal recessive
- Inheritance resembles compound heterozygous (*in trans*)



Thanks for viewing

