Melbourne Genomics
Health Alliance

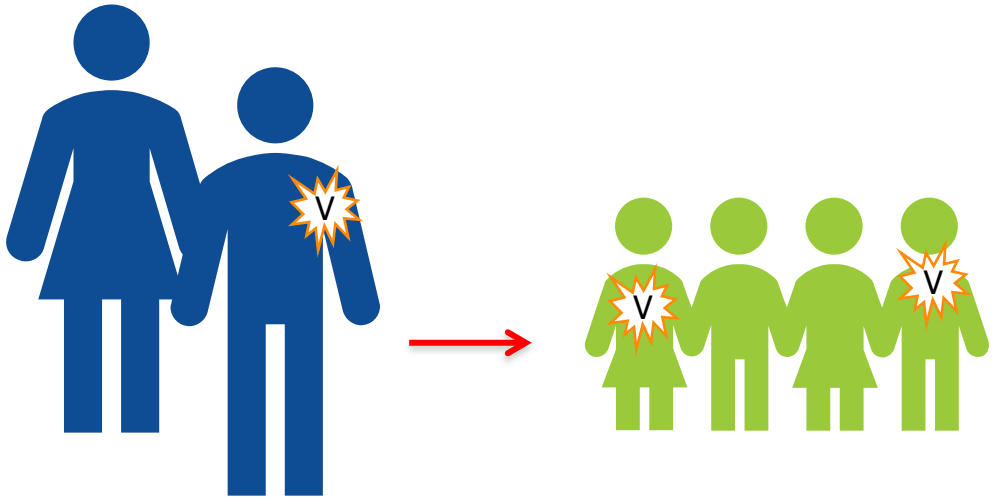
Inheriting variants

Germline variants and Mendelian Inheritance

Germline vs Somatic variants

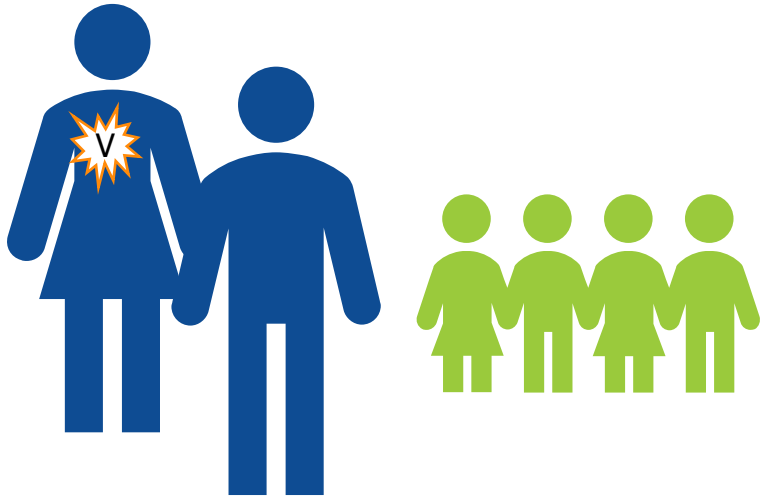
Germline variants are heritable

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



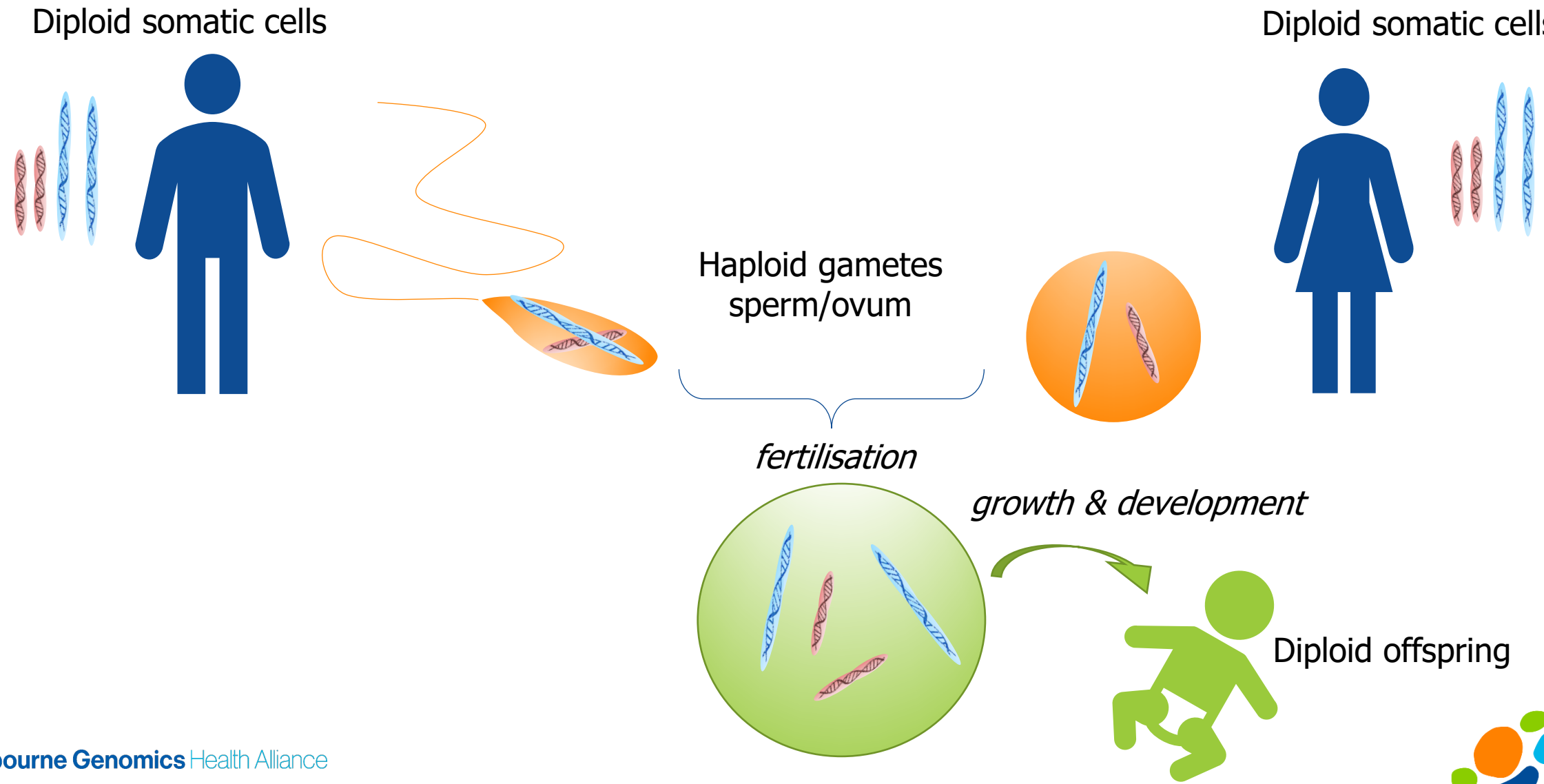
Somatic variants are not heritable

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



Diploid and haploid cells

- Inheriting one of each chromosome from each parent



Definitions

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%)

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

Genotypes

Homozygous

- Two identical alleles for the gene
  - same variant

Heterozygous

- Two different alleles for the gene
  - different variants

Hemizygous

- One allele for the gene, e.g.
  - all genes on X chromosome in a male
  - all genes on Y chromosome (except in XYY male)
  - Monosomy – chromosome deletion
  - Deletion of one allele

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

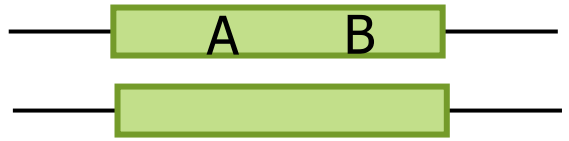
Genotypes

Compound heterozygous

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

Variants in c*is* – variants are on same allele

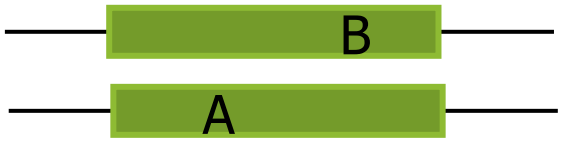
- If a parent is affected with same as the child, predict variants in *cis*



Cis

Variants in *trans* – variants on different alleles

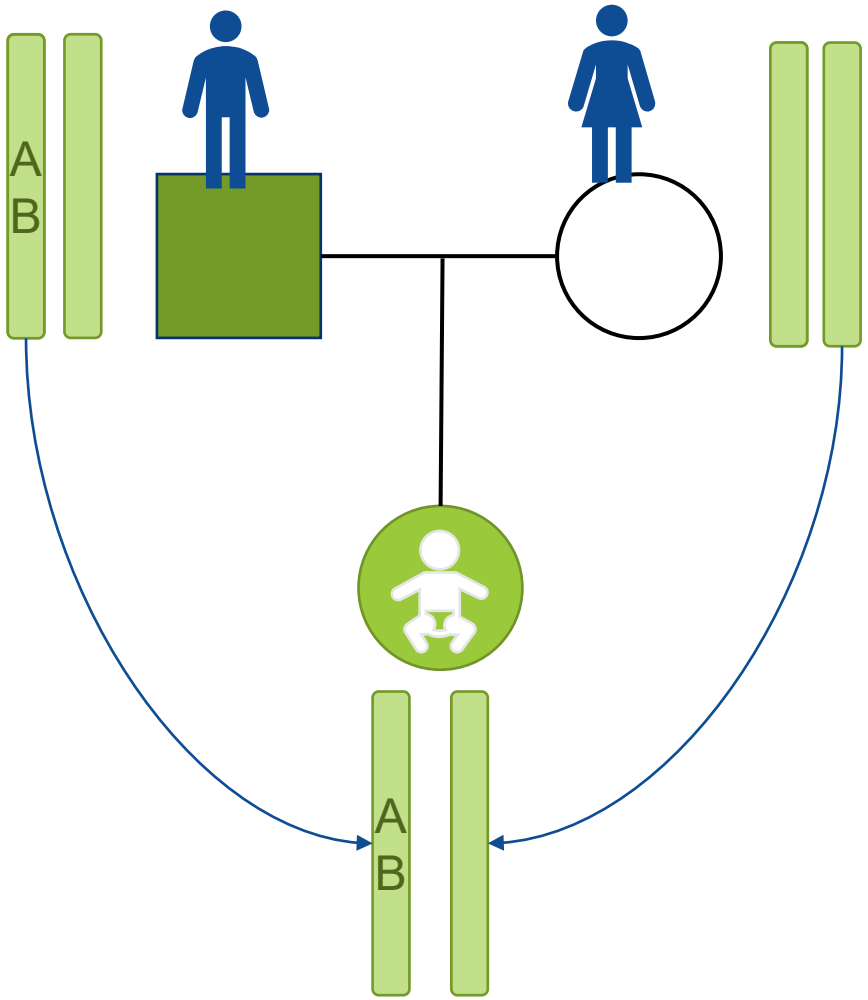
- If neither parent is affected but child is affected, predict variants in *trans*



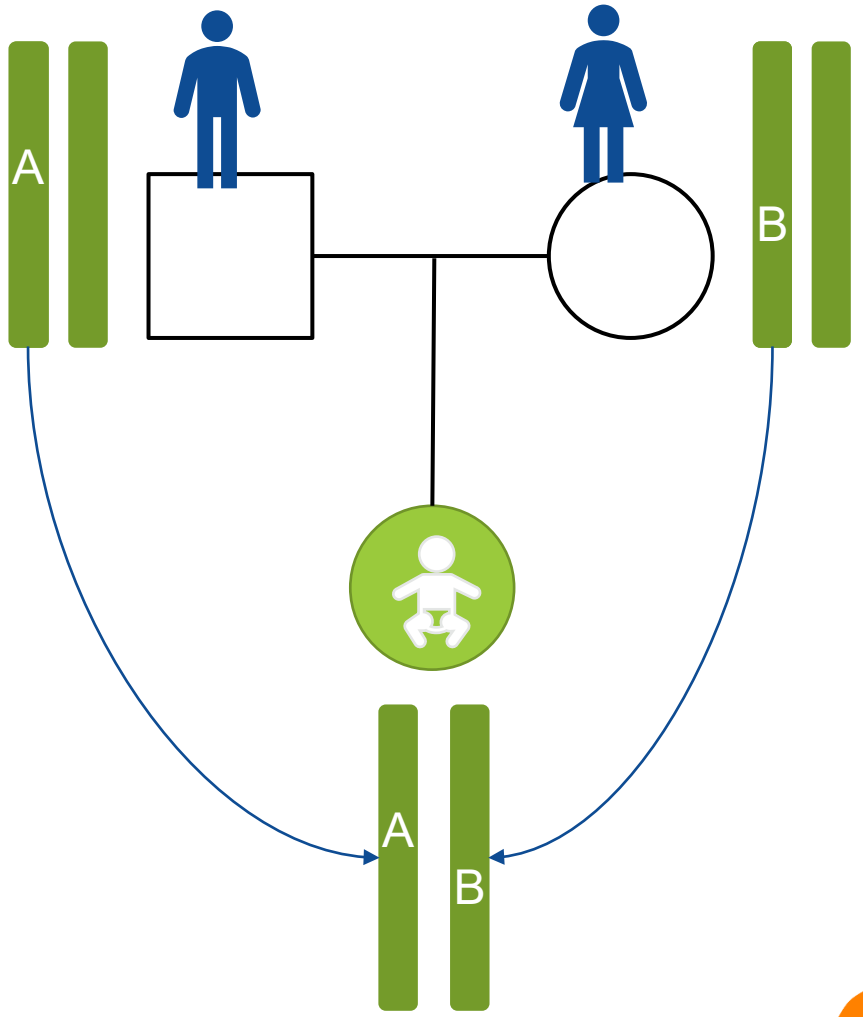
Trans

Inheritance of compound het illustrated on next page

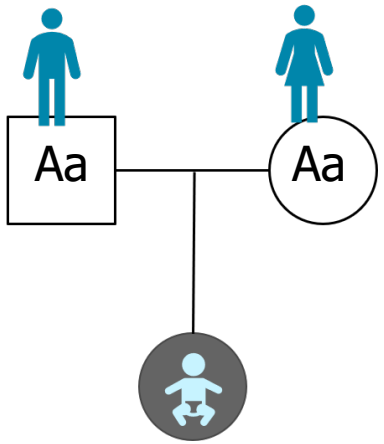
Variants in *cis*



Variants in *trans*

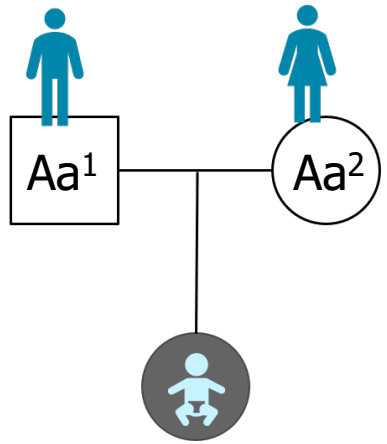


Unaffected parents can have an affected child



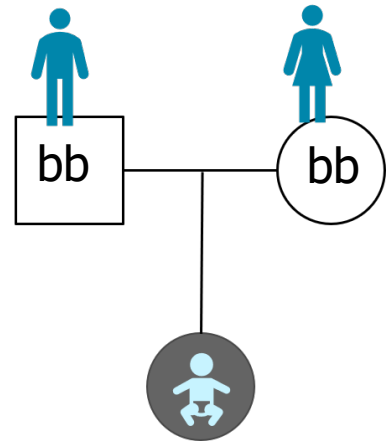
Autosomal Recessive

Each parent is a heterozygous carrier of the same variant in the gene



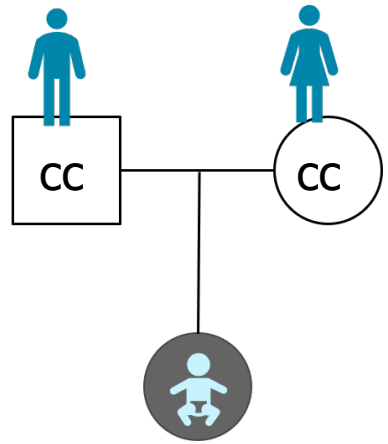
Compound Heterozygous

Each parent is a heterozygous carrier of different variant in the gene



Germline Mosaicism

B = dominant pathogenic variant present in a portion of a parent's germline cells. The parent not affected.



De novo variant

C = dominant pathogenic variant arising in a gamete or early embryo

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 [analogy – on/off switch]
Expressivity	Variable expressivity - the range of signs and symptoms that 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

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Genetic Pedigrees

Drawing and interpreting family history and genetic pedigree charts

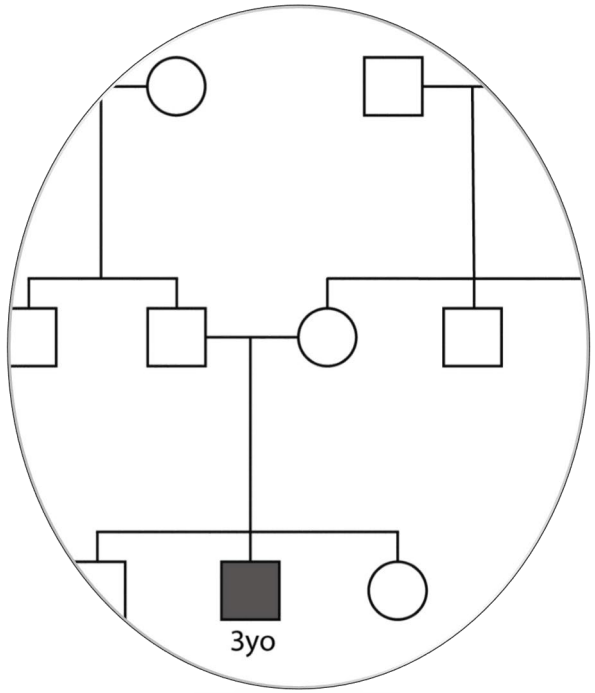
Useful link: **Genomics Education UK tutorial**
Taking and drawing a family history

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

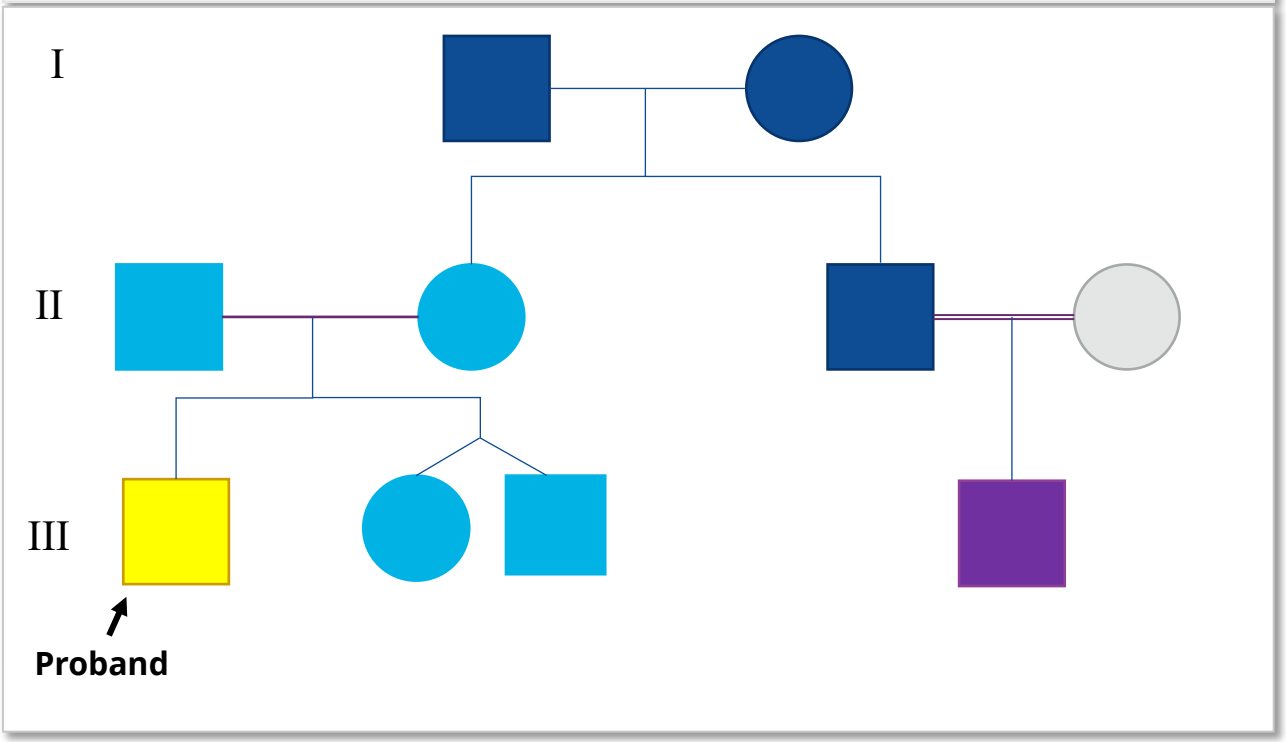


Pedigree charts

Symbols

- Male (unaffected/affected)
- Female (unaffected/affected)
- Gender unspecified
- Number of siblings (2)
- Deceased
- Proband (person presenting with condition)
- Carrier

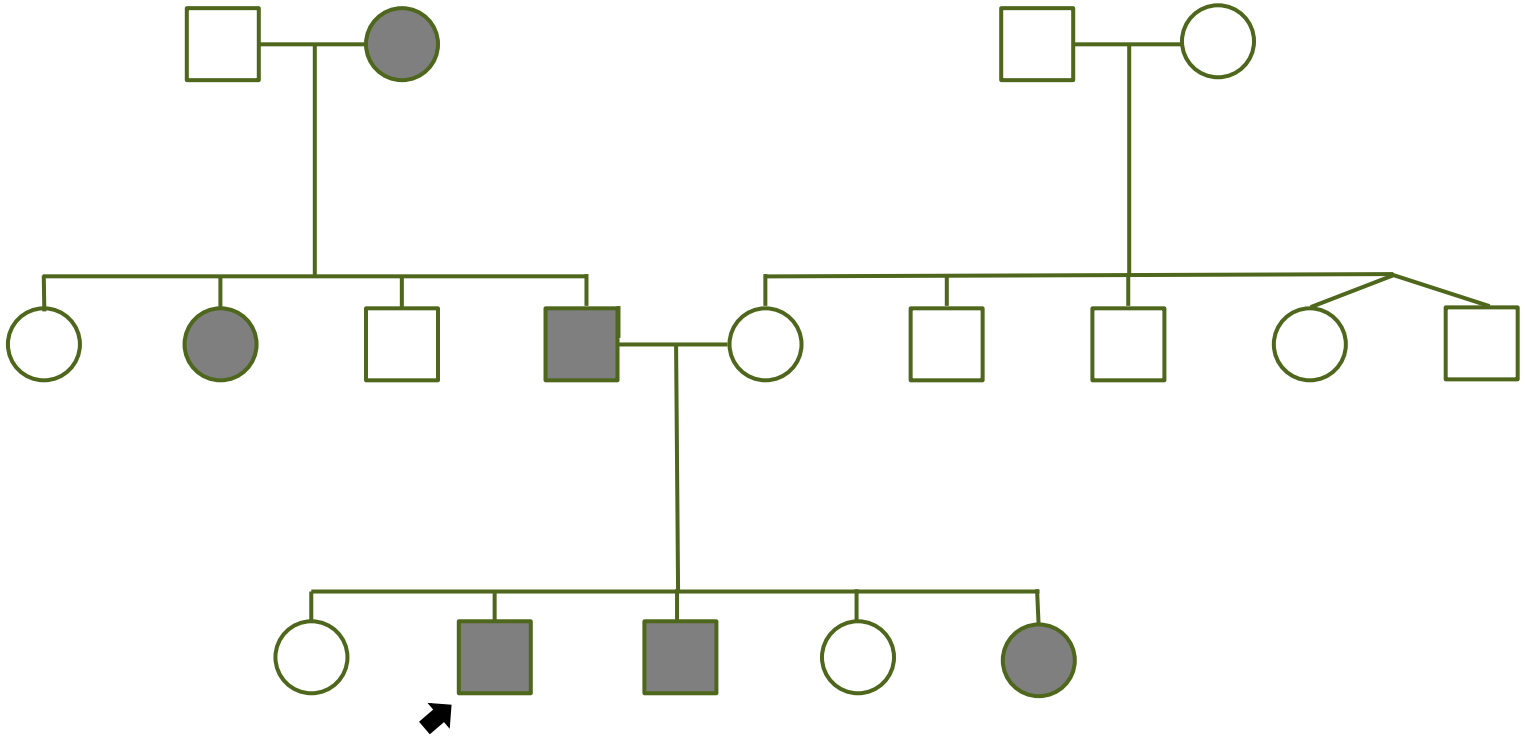
Relatedness to proband (yellow):
1° = first degree relative – shares 50% genetic material
2° = second degree relative – shares 25% genetic material
3° = third degree relative – shares 12.5% genetic material



Autosomal Dominant

The phenotype is seen in the presence of only one allele

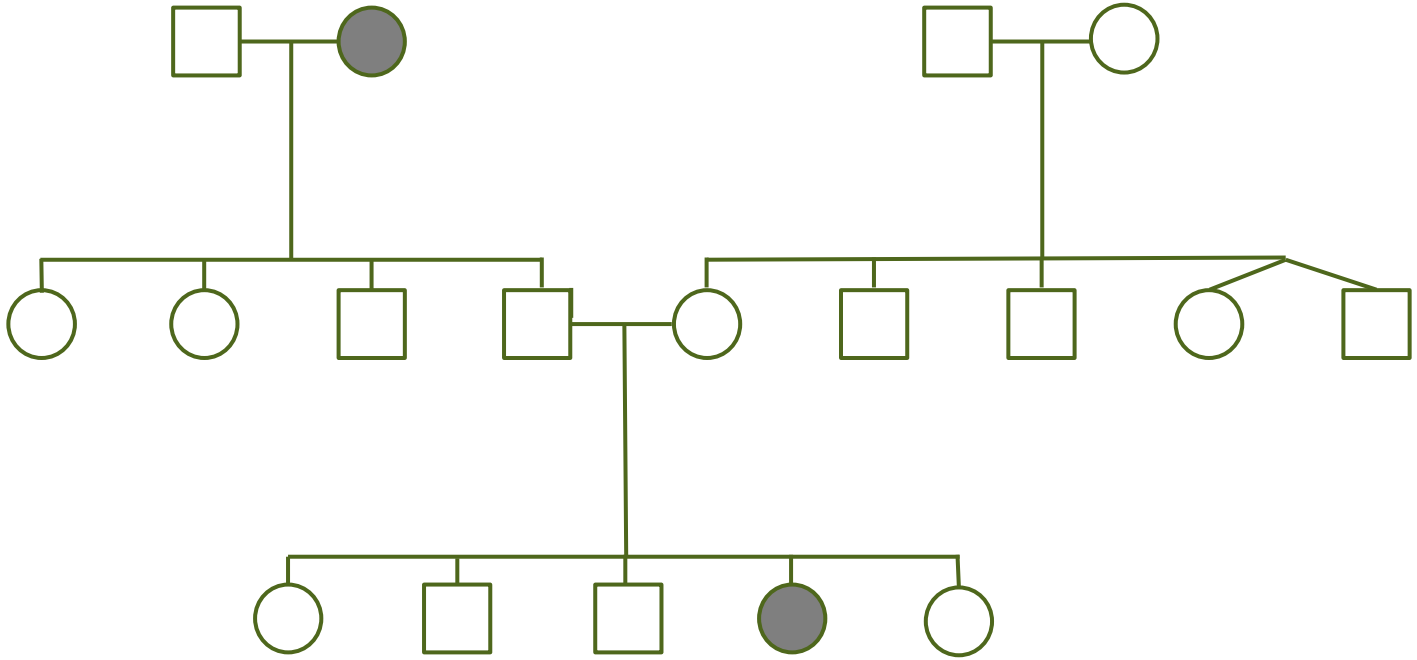
- Trait can appear in each generation
- Individuals heterozygous and homozygous for the variant show the trait



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



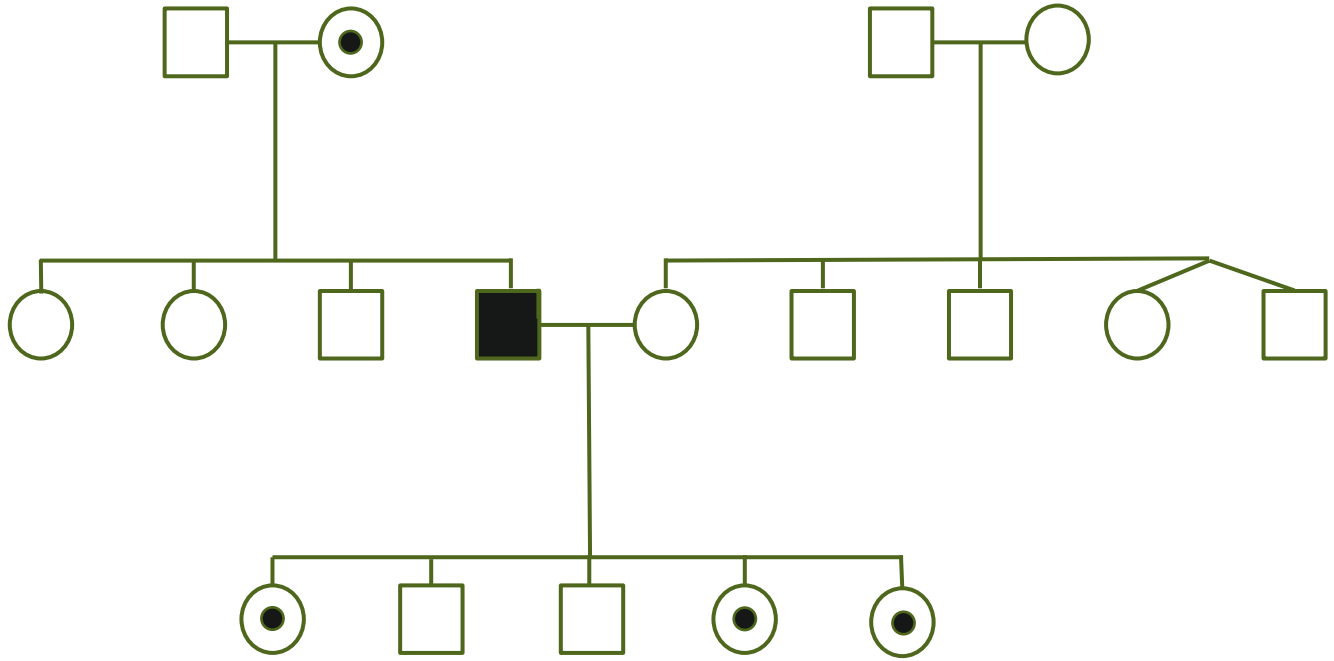
Sex linked: X-linked recessive

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



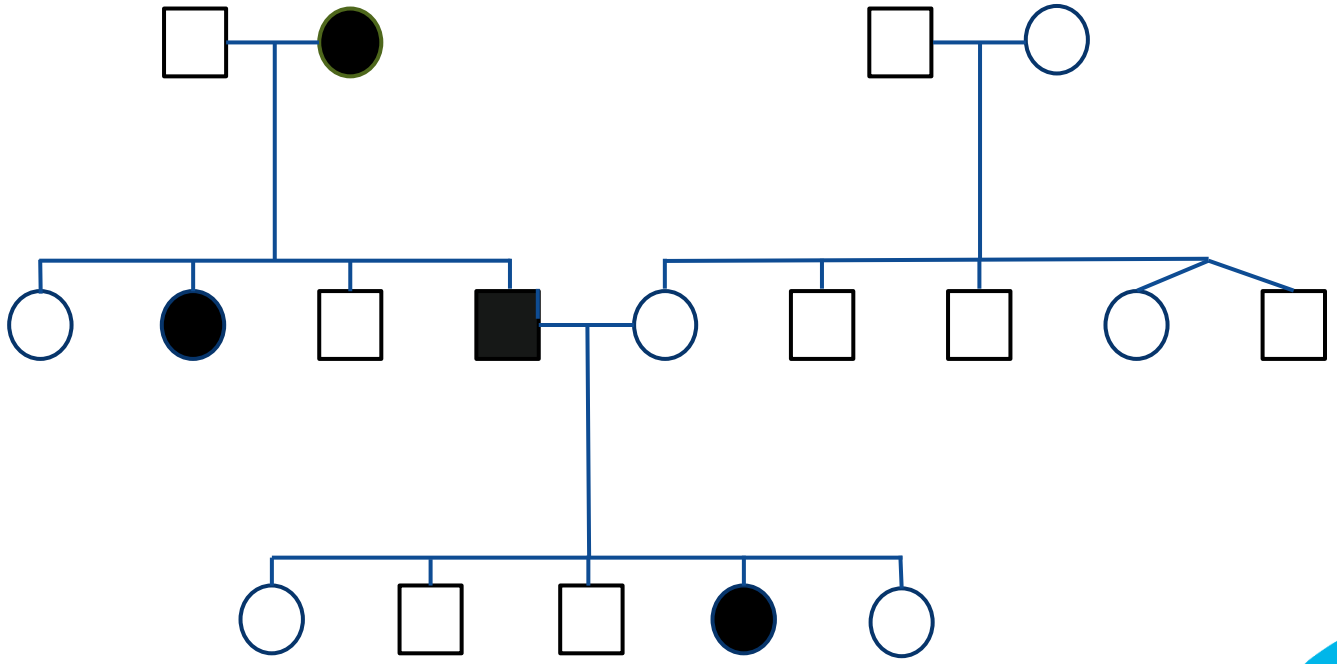
Sex linked: X-linked dominant

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

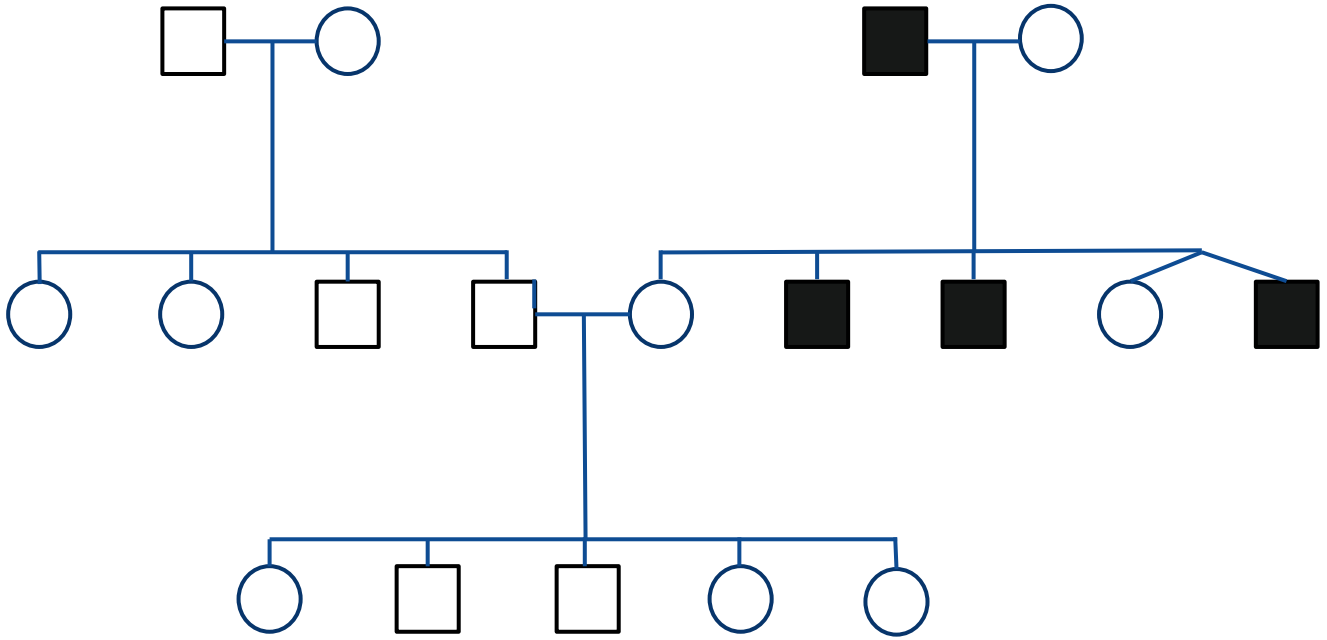


Sex-linked: Y-linked

The gene is on the Y chromosome

All males with the variant are affected

Inherited only by males



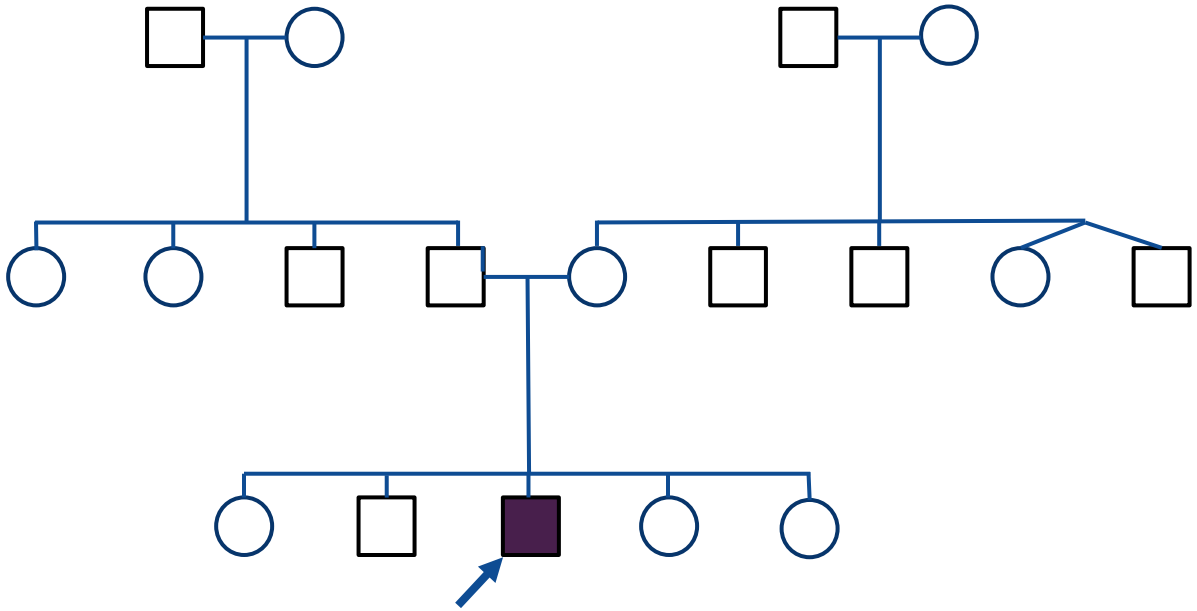
De novo (dominant trait)

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*)



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Thanks for viewing