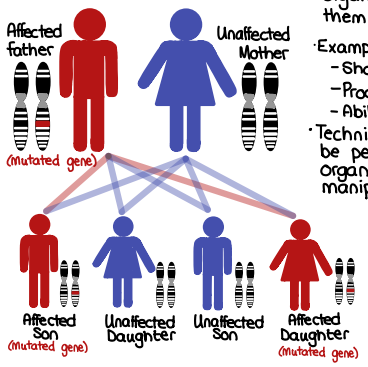
Chapter 4 ~ Pedigree Analysis

Introduction:



Model Organisms:

- Organisms w/ characteristics that make them useful for genetic analysis
- Example of Characteristics:
  - Shorter generation time
  - Production of numerous progeny
  - Ability to be reared in laboratory
- Technique like test crosse can ONLY be performed w/ model organism/ organisms that can be experimentally manipulated

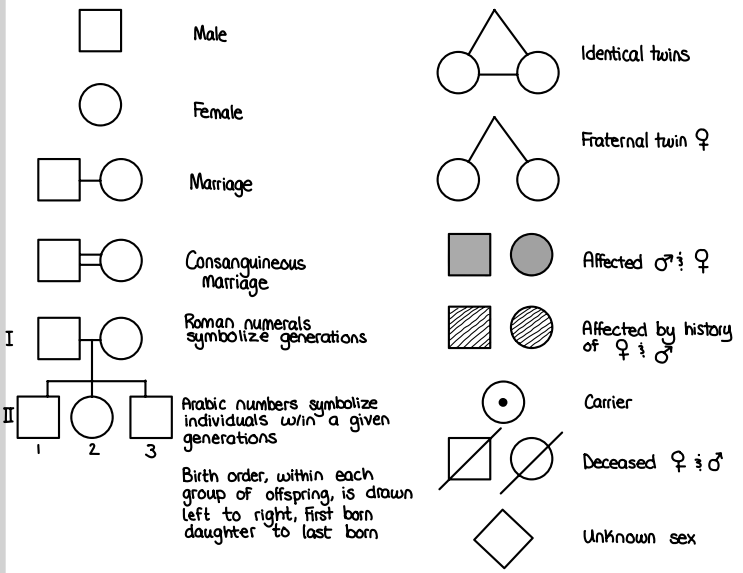
*HUMANS ARE NOT MODEL GENETIC ORGANISMS B/C
- No pre-breeding lines
- Controlled mating is NOT possible
- Longish generation time
- Small progeny number

*To study pattern of inheritance of traits in humans we look either at a large number of families or several generations w/in a large family

Pedigrees

- A pictorial representation of a family history or a family tree, which outlines the inheritence of one or more characteristics
- Many traits which run in families do NOT exhibit a simple pattern of Mendelian Inheritance, usually b/c these traits are coded for by MORE than one gene
- Traits that ARE governed by ONE gene are typically an abnormality that is life-threatening/debilitating
  - ↳ ex:
    - Huntington's Disease (via dominant allele)
    - Cystic Fibrosis (via ressesive allele)

Symbols used in Pedigree Charts



Pedigree Charts

- Diagrams that show the phenotypes and/or genotypes for a particular organism, its ancestors & descendants
- Signs & symboles must be properly recognized & interpreted
- Diagrams are used to determine the mode of inheritance of a particular disease/trait and to predict the probability of it's appearance among offspring
- Pedigree analysis is an important tool in basic research, agriculture & genetic counselling
- Pedigree chart is drawn using phenotypic information, but there is always some possibility of error in this info
  - In real pedigree further complications can arise due to incomplete penetrance (including age of onset) and variable expressivity of disease alleles

Proband (or Propositus)

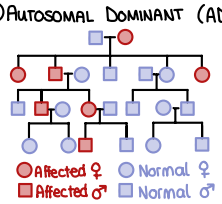
- Affected individual that brings the family to the attention of a geneticist

Consultand

- An unaffected individual
- If the individual is known to have symptoms of the disease (affected) then the symbol is filled in
- Half filled in = carrier
  - Someone who does NOT have symptoms of the disease but is someone who passed the disease on to subsequent generations because they are heterozygote
- Female carriers of an X-linked trait is indicated by a circle w/ a dot in the center

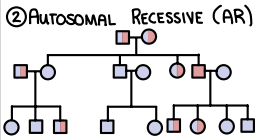
Modes of Inheritance

① Autosomal Dominant (AD)



When a disease is caused by a dominant allele of a gene, every person w/ that allele will show symptoms of that disease
- Only 1 disease allele need to be inherited for an idividual to be affected
- Every affected person had an affected parent
- If affected parent is heterozygous they can have unaffected children

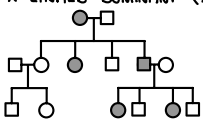
② Autosomal Recessive (AR)



Diseases that are inherited in a autosomal recessive pattern require that BOTH parents of an affected individual carry at least one copy of the disease allele
- Many individuals can be carriers
- AR pedigrees tend to show fewer affected individuals and are likely to spik a generation

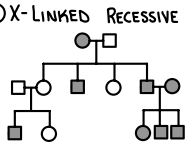
*Major Distinguisher...
- unaffected individuals can have affected offspring

③ X-Linked Dominant (XD)



The gene responsible for the disease is located on the X-chromosome and the allele that causes the disease is dominant to the normal allele in females
- Females have twice as many X chromosomes as males
- Females tend to be more frequently affected than males

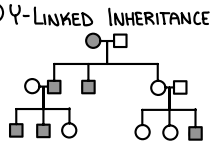
④ X-Linked Recessive (XR)



Males only have one x-chromosome so any male that inherits an x-linked recessive disease allele WILL be affected by it
- Males tend to be affected more frequently than females

*AD trait if an affected father passes on the disease to his son

⑤ Y-Linked Inheritance (Y)



Only males are affected in human Y-linked inheritance
- There is ONLY father-son transmission
- It is the easiest mode of inheritance to identify BUT is also the rarest b/c there are so few genes located on the Y-chromosome

2 Assumptions:

① Complete penetrance - an individual in the pedigree will be affected (express the phenotype associated w/ a trait) when the individual carriers at least one dominant trait or 2 recessive alleles of a recessive trait

② Rare-in-Population - generally, the trait in question is rare in the general population

Hints For Pedigee Charts

- An unaffected individual cannot have any alleles of a dominant trait (because a single allele of a dominant trait causes an individual to be affected)
- Individuals marrying into the family are assumed to have NO disease alleles - They will never be affected or be carriers of a recessive trait
- An unaffected individual can be a carrier (have one allele) of a recessive trait (because 2 alleles of a recessive trait are required for an individual to be affected
- When a trait is X-linked, a single recessive allele is sufficient for a male to be affected (because a male is hemizygous - he only has one allele of an x-linked trait)
- A father transmits his allele of X-linked genes to his daughters but NOT his sons whitel a mother transmits an allele of X-linked genes to both her daughters & sons

Sporadic & Non-Heritable Diseases

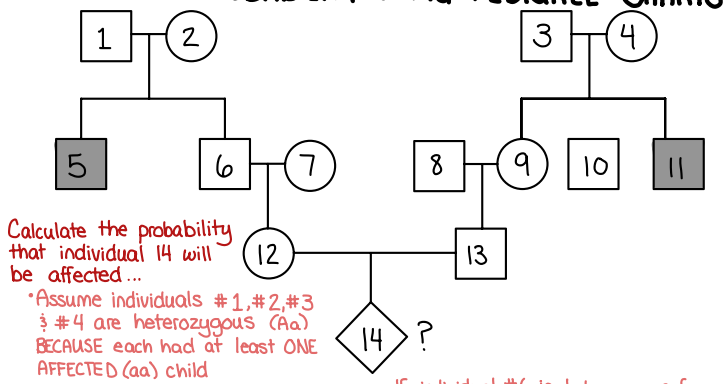
- Not all characterized human traits and diseases are attributed to mutant alleles at a single gene locus
- Many diseases that HAVE a HERITABLE component, have more complex inheritance due to...
  1. The involvement of MULTIPLE genes
  2. Environmental factors
- Some non-genetic diseases may appear to be heritable b/c they affect multiple members of the SAME family... this is due to:
  - Family members being exposed to the SAME TOXINS or other environmental factors
- Diseases with SIMILAR SYMPTOMS may have different causes, some of which may or may NOT be genetics
  - ex: Amyotrophic lateral sclerosis (ALS)

5-10% of cases are INHERITED

THE REST of cases are SPORADIC

We now know that different genes or proteins are affected in the inherited & sporadic forms of ALS

Calculating Probability using Pedigree Charts



Calculate the probability that individual 14 will be affected...

- Assume individuals #1, #2, #3 & #4 are heterozygous (Aa) BECAUSE each had at least ONE AFFECTED (aa) child
  - $\frac{2}{3}$ Chances #6 & 9 are ALSO "Aa" b/c

	A	a
A	AA	Aa
a	Aa	aa

1 : 2 : 1
AA : Aa : aa

#6 is unaffected so CAN'T be "aa" but could be AA or Aa but the probability of Aa is 2x more likely

- IF individual #6 is heterozygous for the disease allele then there is $\frac{1}{2}$ chance #12-13 will be heterozygote

	A	a
A	AA	Aa
A	AA	Aa

1 : 1
AA : Aa

*we assume that #7 (unrelated) does NOT carry the diseased alleles

Probability #12-13 is heterozygous $= \frac{2}{3} \times \frac{1}{2} = \frac{1}{3}$

Therefore probability of #14 being affected...

$$\frac{1}{3} \times \frac{1}{3} \times \frac{1}{4} = \frac{1}{36}$$

	A	a
A	AA	Aa
a	Aa	aa

1 : 2 : 1
AA : Aa : aa