

Lecture 36: Human Genetics

Human Genetics:

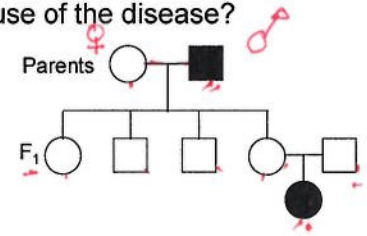
- Cannot do well controlled crosses (Mendel had pea plants)
- Genotypes are generally unknown (Mendel had homozygous, pure breeding, lines).
- Small number of progeny → poor statistics (Mendel counted thousands of peas).

Goals:

1. Can we predict the pattern of inheritance?
2. Given a pattern of inheritance, can we deduce the most likely cause of the disease?

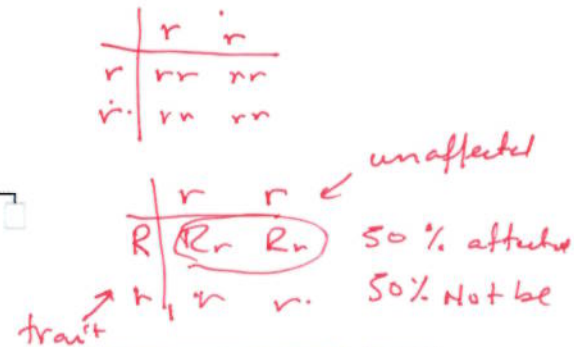
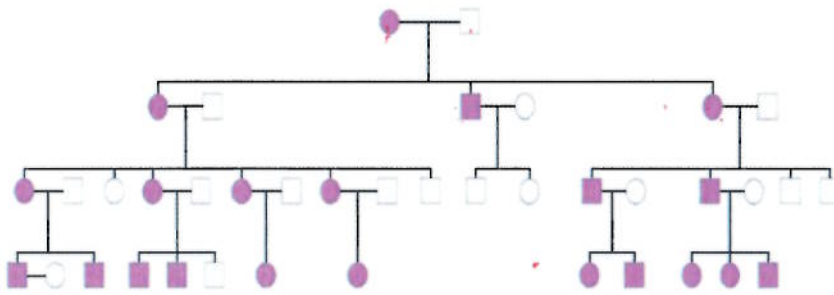
Pedigrees:

- Circles – female, 1/2 filled circle – carrier female Rr
- Squares – male, 1/2 filled square – carrier male Rr
- Filled = presence of the disease.
- F_1 – first filial generation
- F_2 – second filial generation $RR Rr$



1. Autosomal Dominant - Males and females equally affected.

- Affected people will have at least one affected parent (dominant allele from parent)
- Unaffected parents cannot produce affected children.
- Mating of an affected individual with a normal person will usually produce 50% affected children.



Marfan syndrome – error in a gene that codes for connective protein. Single defective copy is sufficient to “poison” good copy. One of many symptoms are long limbs. Serious complications can arise from this disease.

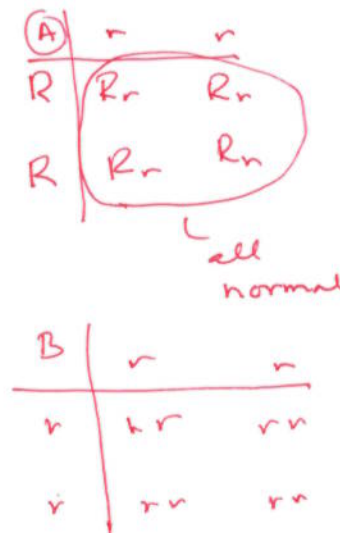
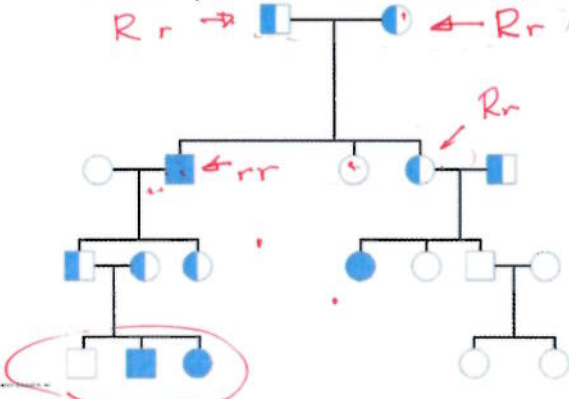
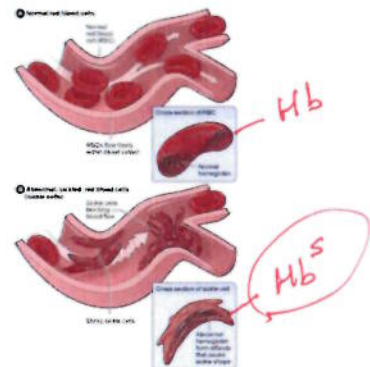
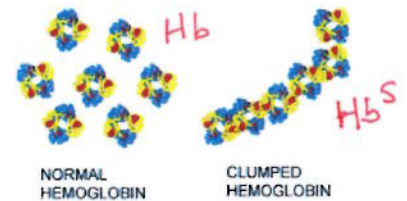


2. Autosomal Recessive - Males and females equally affected.

- Can have unaffected parents (skip a generation)
- Mating of affected individuals with a normal person will usually produce all normal offspring (rare allele) (A)
- If both parents are affected, all of their children will be affected. (B)

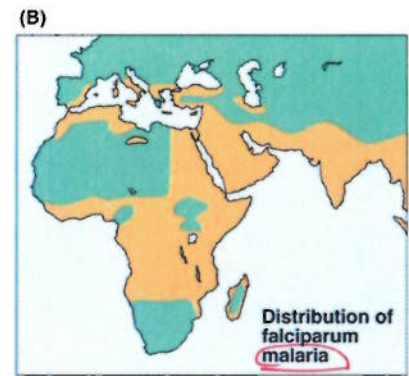
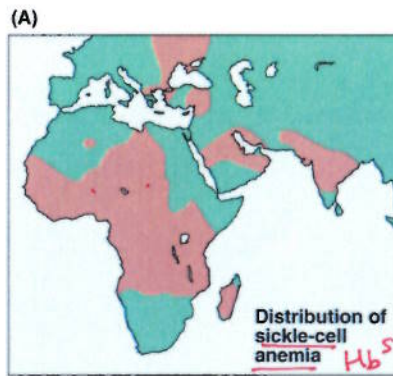
Sickle Cell Anemia.

- Mutation in hemoglobin, Glu6 (Hb) to Val6 (Hb^s) causes hemoglobin to form polymers (clumped) when deoxygenated.
- Presence of one copy of normal gene greatly reduces polymer formation (therefore Hb^s is recessive, not co-dominant).



If the recessive allele for Hb S causes problems with blood circulation, and therefore reduces the fitness of the individual, why has it persisted in the human population?

Hb^S poor food for malaria parasite.



3. X-Linked Recessive Disease

- Affects males *mostly* (all affected males have carrier mothers). This assumes the recessive allele is relatively rare, so it is unlikely for females to inherit two negative alleles.
- Carrier mothers have 1:1 ratio of affected and unaffected sons (A)
- Cannot be transmitted from father to son (son's X is from the mother) (B)
- All daughters of affected males are unaffected (unless they have a carrier mother) (B)

Hemophilia – mutation in clotting factor, gene is on X-chromosome. One good copy is sufficient, therefore recessive.

heterozygote does not show phenotype ∴ recessive

♀ $X^R X^R$ Common
 ♂ $X^R Y$

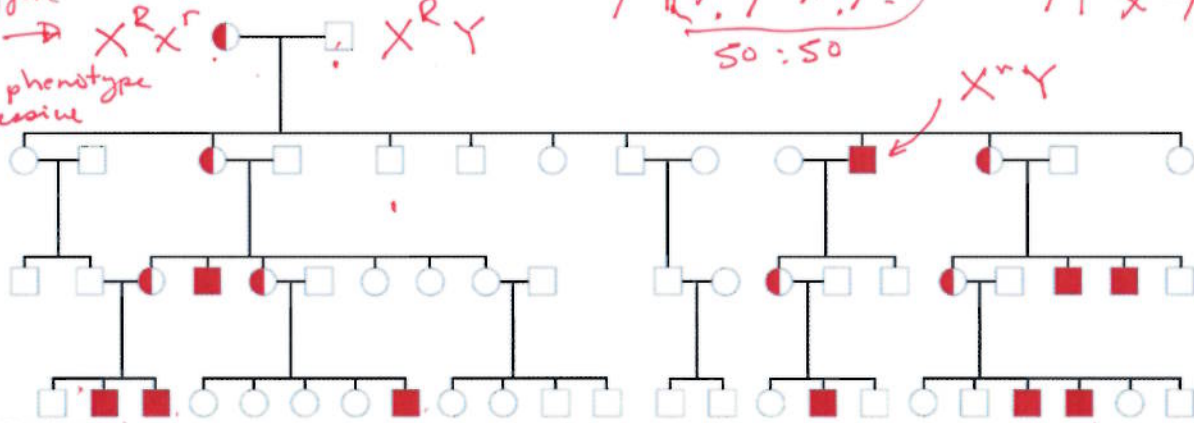
Example: 10% r 90% R

♀ $X^R X^r$ rare carrier
 ♂ $X^r Y$ affected male

1:10 males affected
 1:100 females affected (0.1 x 0.1 = 0.01)

(A) $X^R X^r$ x $X^R Y$
 $X^R X^R$ $X^R Y$
 $X^r X^R$ $X^r Y$
 50:50

(B) $X^R X^R$ x $X^R Y$
 $X^R X^R$ $X^R Y$
 $X^R X^R$ $X^R Y$



only males tend to be affected

Expectations:

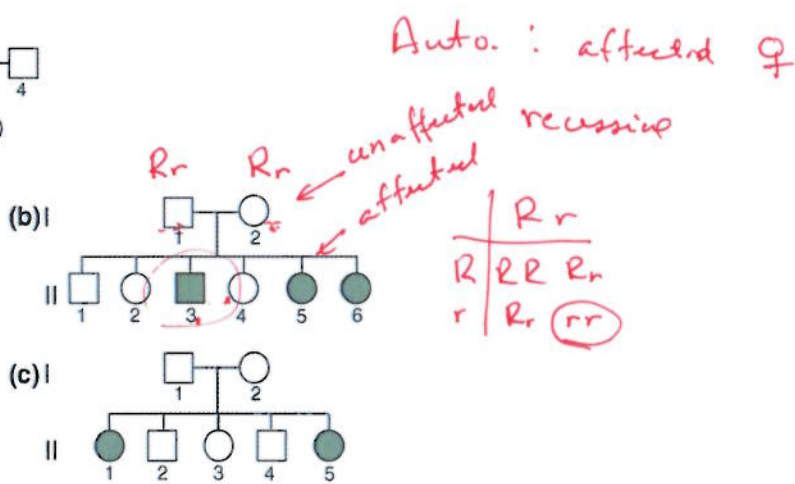
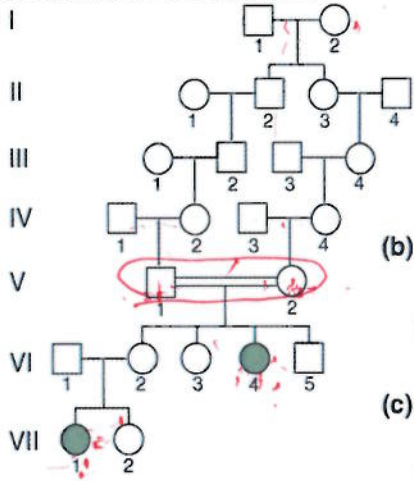
- Understand the definitions: trait, phenotype, genotype, allele, dominant, recessive, codominance, unlinked and linked alleles.
- Be able to predict the outcome for monohybrid and dihybrid crosses, given the genotype of the parents.
- Understand that DNA recombination during meiosis I can generate new combinations of alleles that were not present in the parents.
- Be able to explain blood group incompatibilities in blood transfusions, effect of Rh factor health of the fetus with an Rh- mother.
- Be able to determine the inheritance pattern of autosomal dominant, autosomal recessive, and sex linked recessive from a pedigree.

Analyzing Pedigrees: Assume recessive allele is relatively rare, heterozygotes are more likely.

Cystic fibrosis – non-functional CF channel in membrane – thick mucus in lung.

Note: Carriers not indicated.

(a)



Effect of in-breeding – consanguineous mating ($\square=\bigcirc$).

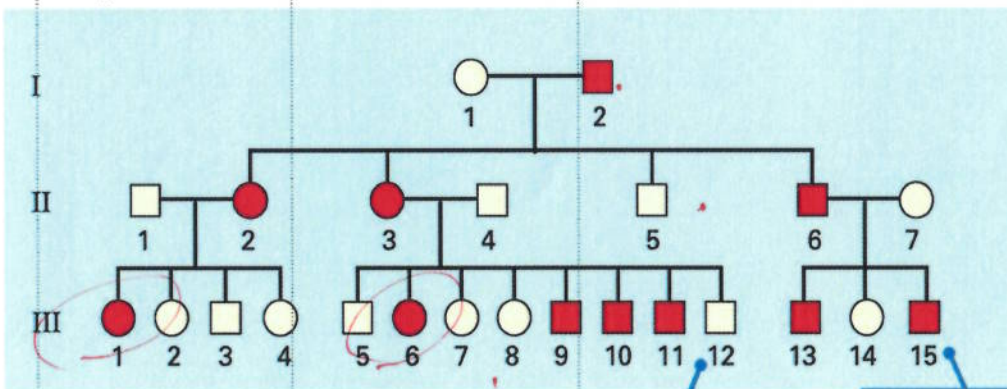
- In-breeding generates homozygous individual at a higher frequency.
- Makes it likely that rare recessive alleles will become homozygous.

Going back to Mendel's peas. What happens if we cross two heterozygous peas (F1 self-cross): $Yy \times Yy$ (yellow x yellow).

	Y	y
Y	YY	Yy
y	Yy	yy

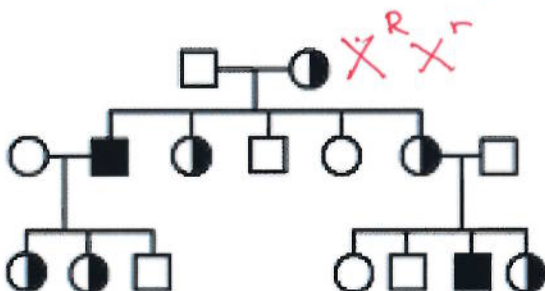
inbreeding between heterozygotes produces homozygotes, showing disease phenotype

Huntington's Disease – triplet repeat disease – poly glu residues in Huntington protein → neurological disease.



Autosomal (♀ affected) dominant affected parents - next generation

Severe combined immune disorder (SCID) – Individual cannot make any B or T-cells.



Sex linked, recessive

An example from flies: Fly wings can be long or short. The following crosses were done (parents are not necessarily homozygous).

1) Is this trait sex linked? Why or why not?

Yes, diff outcome for reciprocal cross.

2) Assume long is dominant (L) and short is recessive (l). What are the genotypes of the parents in both crosses?

Cross 1:

♀ $X^{Ll} X^{Ll}$, $X^{Ll} X^{Ll}$
 ♂ $X^{Ll} Y$

both possible, try this one first

Cross 2:

♀ $X^{ll} X^{ll}$
 ♂ $X^{Ll} Y$

3) Does your answer to 2 explain the outcomes?

<p>Cross 1: long ♀ X short ♂:</p> <p>50% long, equal number of ♀ and ♂ 50% short, equal number of ♀ and ♂</p>	<p>Cross 2: short ♀ X long ♂:</p> <p>50% long, ♀ only ✓ 50% short, ♂ only ✓</p>
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	♀	
	X^L	X^l
♂	X^l	$X^L X^l$
	X^l	$X^l X^l$
	Y	$Y X^L$
		$Y X^l$
		↑ long
		↑ short

	♀	
	X^l	X^l
♂	X^L	$X^L X^l$
	X^l	$X^l X^l$
	Y	$Y X^l$
		$Y X^L$
		← long
		← short

agrees with observed outcome ∴ parental genotypes are correct.