

Marcello Cherchi's notes for

GENETICS

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(Please let me know of any errors! mchercl@uic.edu)

References

- GE GELEHRTER, Thomas D., Francis S. COLLINS and David GINSBURG, *Principles of Medical Genetics*, 2nd ed. Baltimore: Williams & Wilkins, 1998.
- WY WYNGAARDEN, James B, Llohd H. SMITH, Jr., *Cecil Textbook of Medicine*, 16th ed. Philadelphia: W.B. Saunders Co., 1982.

Type of inheritance	“Vertical,” i.e. patterns across generations	“Horizontal,” i.e. patterns within a generation	Recurrence	Sex	Notes
Autosomal dominant (GE 26)	<ul style="list-style-type: none">• Every affected individual has an affected biological parent.• There is no “skipping of generations.”• Normal siblings of affected individuals do not transmit the trait to their offspring.		The recurrence risk of each child of an affected parent is 1/2.	Males and females have an equally likely probability of inheriting the mutant allele and being affected.	<ul style="list-style-type: none">• The defective product of the gene is usually a structural protein, not an enzyme.• Variable penetrance is only associated with autosomal dominant inheritance (GE 26).• Variable expressivity is only associated with autosomal dominant inheritance (GE 29).

Autosomal recessive	The trait (phenotype) is not found in the parents of the affected, nor is it found in the offspring of the affected. Rather, it is found in the siblings of the affected.	The trait (phenotype) is characteristically found in siblings, not in the parents of the affected nor in the offspring of the affected.	On the average, the recurrence risk to the unborn sibling of an affected individual is 1/4.	Males and females are equally likely to be affected.	<ul style="list-style-type: none"> • The trait (phenotype) may appear as an isolated (sporadic) event in small sibships. • Parents of affected children may be related. The rarer the trait in the general population, the more likely a consanguinous mating is involved.
X-linked dominant	<ul style="list-style-type: none"> • The trait (phenotype) is never passed from father to son. (If the affected male has an affected son, then the disease is not X-linked.) • All daughters of an affected male and a normal female are affected. (If the affected male has any normal daughters, then the disease is not X-linked.) • All sons of an affected male and a normal female are normal. (If the affected male has an affected son, then the disease is not X-linked.) • Matings of affected females and normal males produce 1/2 the sons affected and 1/2 the daughters affected. 				<ul style="list-style-type: none"> • Males are usually more severely affected than females. The trait may be lethal in males. • In the general population, females are more likely to be affected than males, even if the disease is not lethal in males.
X-linked recessive	<ul style="list-style-type: none"> • The trait (phenotype) is never passed from father to son. (If the affected male has an affected son, then the disease is not X-linked.) • All affected males in a family are related through their mother (who is a carrier). • The trait (phenotype) is typically passed from an affected grandfather, through his carrier daughters, to half of his grandsons. 				Males are much more likely to be affected than females. If affected males cannot reproduce, then only males will be affected (??).

Mitochondrial (non-Mendelian!)	<ul style="list-style-type: none"> • Affected fathers produce no affected offspring. • The offspring of an affected mother are all affected. 				
Multi-factorial (non-Mendelian!)	Most affected children have normal parents.		<ul style="list-style-type: none"> • Recurrence risk increases with the number of affected children in a family. • Recurrence risk increases with severity of the defect. (A more severely affected parent is more likely to produce an affected child.) • Risk of affected relatives declines rapidly with the degree of relationship. 	If the two sexes have a different probability of being affected, then the least likely sex, <i>if affected</i> , is the most likely sex to produce an affected offspring.	Consanguinity slightly increases the risk for an affected child.

Variable penetrance: The clinical expression of the phenotype is “all or none” (GE 27, 28). A person who displays the phenotype is said to exhibit “complete penetrance,” while a person who does not display the phenotypes (but is a carrier) is said to exhibit “incomplete penetrance.” Variable penetrance is only associated with autosomal dominant traits. An example of such a disease is erythromegalia (GE 27).

Variable expressivity: The expressivity of a trait refers to the nature and severity of the phenotype. Examples of diseases exhibiting variable expressivity are Marfan syndrome and neurofibromatosis (GE 29).

Note that variable penetrance, variable expressivity and late onset only occur in diseases which are inherited in an autosomal dominant fashion.

Genomic imprinting, or “**uniparental disomy**”: This is an abnormal, *non-Mendelian* form of inheritance. For a given autosomal chromosome, a person usually inherits one paternal chromosome and one maternal chromosome. In uniparental disomy, the person inherits *both* chromosomes from a single parent. Although such an individual is euploid (i.e. has the correct number of chromosomes), such inheritance still results in clinical symptoms, which indicates that “maternal and parental genetic contributions of autosomal genes are not necessarily equivalent, and that genetic contributions from both parents are necessary for normal development” (GE 175).

Two examples of uniparental disomy were discussed in class. **Prader-Willi** syndrome results when both chromosomes 15 are inherited from the mother (and there is no paternal contribution to chromosome 15). **Angelman** syndrome results when both chromosomes 15 are from the father (and there is no maternal contribution to chromosome 15) (GE 174).

Stages of cell division and results of nondisjunction

Stage of cell cycle	Results of nondisjunction
MEIOSIS (germline cell division, GE 20)	<p><i>Down syndrome</i> (47,XY,+21) results from meiotic nondisjunction (GE 171), usually in the mother (WY 20).</p> <p><i>Turner syndrome</i> (45,X) can arise from meiotic nondisjunction (GE 186), either maternal or paternal (WY 20).*</p> <p><i>Triple X syndrome</i> (47,XXX) is thought to arise from maternal meiotic nondisjunction (WY 20).</p>
Meiosis I (“reductional division”)	<p>If nondisjunction occurs during the first meiotic division, then the resulting gametes can contain either (GE 163):</p> <ul style="list-style-type: none"> • Both parental chromosomes, or • Neither parental chromosome. <p><i>Klinefelter syndrome</i> (47,XXY) is due to nondisjunction in the first meiotic division (GE 185) either in the mother (61%) or father (39%) (WY 20).</p>
Meiosis II (“equatorial division”)	<p>If nondisjunction occurs during the second meiotic division, then the resulting gametes can contain either (GE 163):</p> <ul style="list-style-type: none"> • Two copies of one parental chromosome (maternal or paternal), or • Neither. <p><i>XYY syndrome</i> (47,XYY) results from meiotic nondisjunction during paternal meiosis (GE 186-7), specifically in the second meiotic division (WY 20).</p>
Gametes → Fertilization	
MITOSIS (somatic cell division, GE 19)	<p>The result of mitotic nondisjunction is mosaicism (GE 162).</p> <p><i>Turner syndrome</i> (45,X) can result from mitotic nondisjunction, in which case the result is also a mosaic (GE 186).*</p>

* Turner syndrome (45,X) can arise from disjunction either in meiosis or in mitosis.

Math pertaining to Hardy-Weinberg equilibrium (see GE 43 ff.)

Assume that: **A** = wild-type (normal) allele
a = mutant allele

p = frequency of allele “A”
q = frequency of allele “a”

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

Frequencies of the genotypes must add up to one, so $1 = p^2 + 2pq + q^2$.

Also, frequencies of the alleles must add up to one, so $1 = p + q$.

An individual who is affected with an autosomal recessive disease has genotype “aa.”
The prevalence of genotype “aa” in the population is q^2 .

If such a disease has a prevalence of $1/2500$ (i.e. if $q^2 = 1/2500$), then the frequency of allele “a” is $q = \sqrt{\frac{1}{2500}} = \frac{1}{50}$.

Since $p + q = 1$, we also know that the frequency of allele “A” is $p = \frac{49}{50} \approx 1$.

We know then that the frequency of heterozygous carriers (genotype “Aa”) is $2pq = 2\left(\frac{49}{50}\right)\left(\frac{1}{50}\right) \approx 2\left(\frac{1}{50}\right) = \frac{1}{25}$.

Fitness calculations

Biological fitness is a measure of fertility and therefore of the contribution to the gene pool of the succeeding generation (GE 47).

t = fitness of the dominant allele (= 1 - selection against the dominant allele)

s = fitness of the recessive allele (= 1 - selection against the recessive allele)

At equilibrium:

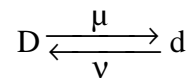
$$\text{Frequency of the dominant allele} = p = \frac{s}{s + t}.$$

$$\text{Frequency of the recessive allele} = q = \frac{t}{s + t}.$$

Moreover, if μ is the mutation rate, then the following equation holds at equilibrium: $\mu = sq^2$.

Mutation rate

If “D” is the functional allele, and “d” is the non-functional (or dysfunctional) allele, mutation can occur either in the “forward” direction (that is, $D \rightarrow d$) or in the “reverse” direction (that is, $D \leftarrow d$). Each direction of mutation has its own rate of occurrence:



Under these conditions, the frequency of the non-functional allele is $q = \frac{\mu}{\mu + \nu}$.

Concordance rates

For a pair of twins (monozygotic or dizygotic), a particular phenotype may appear in one or in both. If a trait appears in both twins, then that pair of twins is said to be **concordant** for that trait. If the trait only appears in one twin but not in the other, then the pair of twins is said to be **discordant** for that trait. Under these conditions, the concordance rate (CR) is given by the following equation:

$$\text{Concordance rate} = \frac{\text{concordant}}{\text{concordant} + \text{discordant}}$$

The concordance rate can be calculated for monozygotic twins (CR_{MZ}) or for dizygotic twins (CR_{DZ}). Under these conditions, the **heritability** (H) of a given trait can be calculated from the following equation:

$$H = \frac{CR_{MZ} - CR_{DZ}}{100 - CR_{DZ}}$$