

Genetics Cardio Block:

Inheritance of Complex Disorders:

- Complex Disease//Trait: results from complex interactions between genes and environmental exposures; transmission is “Non-Mendelian”
 - o Factors to consider when counseling complex disorders:
 - Reduced Penetrance: frequency of expression of genotype (not always expressed)
 - Variable Expressivity: different clinical expression or severity due to same gene
 - Heterogeneity: different loci produce clinically indistinguishable phenotypes
 - Interlocus: more than one locus causes disease
 - Intralocus: more than one allele can cause the disease
 - Phenocopies: environmental exposure causes a phenotype that mimics a phenotype that is usually determined by a specific genotype; ex) prion diseases
 - Age-dependent penetrance: younger siblings may not yet express phenotype
 - Modifying genes: many genes of small effect can modify the phenotype of a single major gene
 - Genotype-environment interaction: differences between genotypes with respect to risk factors variability or genotype/risk association depend on presence or absence of environmental factors
 - o Polygenic Inheritance: many genes of small effect acting together with possible environmental risk factors; large number of genetic loci are postulated to contribute an equal and additive effect in trait expression (not actually realistic)
 - o Multifactorial Inheritance: mixture of many genes of small effect acting together with environmental risk factors
 - **Threshold Model:** distribution of liability for a trait or disease determined by both genes and the environment; when all factors reach a certain threshold, the person will be affected - “perfect storm” of sorts
 - **Criteria for Multifactorial Inheritance:**
 - **Correlation between relatives is proportional to # of genes in common** (higher correlation with first degree relatives)
 - o Risk/% Affected should drop by $\frac{1}{2}$ in Second degree family members since they share $\frac{1}{2}$ the genome
 - **Recurrence risk is higher when >1 family member is affected or the disorder is severely expressed (genome/environment is pushing threshold, points to increased liability)**

- **Occurrence may differ based on gender** (different genders have different thresholds, makes gender a risk factor)
 - o Doesn't mean one sex is protective, just means it has a higher threshold
 - **Cosanguinity increases recurrence risk** (increases baby's liability, closer to threshold)
 - How do you know its genetic?
 - o Heritability: populational study (not specific to individual); proportion of the total phenotypic variation of a trait that is due to genetics
 - o Familial aggregation studies: are relatives of an affected person at a higher risk than someone in the gen pop?
 - $\lambda = (\text{disease prevalence in sibs of affected pt}) / (\text{disease prevalence in pop})$
 - if caused by genetics, $\lambda > 1$
 - **Correlation Coefficient for quantitative traits: if fully genetic, correlation coefficient between relatives is proportional to number of genes they have in common**
 - o Twin studies, linkage studies, association studies
 - Dx of Complex Disorder: TAKE FAMILY HX,

Population Genetics:

- Hardy-Weinberg Principle: relates gene (or allele) frequencies to disease frequencies;
 - o ASSUMES:
 - no selection
 - no migration
 - no mutation
 - population in infinite
 - random mating
 - LOL, OKAY
 - o The frequency of the "A" allele = P, The frequency of the "a" allele = q and $p+q=1$
 - $AA = p^2$
 - $aa = q^2$
 - $Aa = 2pq$
 - $P^2 + 2pq + q^2 = 1$
- Hardy-Weinberg Equilibrium: when the gene frequencies do not change from one generation to the next
 - o gene frequencies does NOT equal genotype frequencies; have to count alleles
- Autosomal Recessive Disorders: you assume that since the recessive allele is very rare (q is small enough), the dominant allele is so common that $p \approx 1$ (makes calculations easier)
 - o Ex) Incidence of CF = 1/1600, must be qq for CF
 - q allele frequency? $q^2 = 1/1600$ and $q = 1/40$

- carrier frequency? $2pq$, $p \approx 1$ and $q = 1/40$ so $2(1)(1/40) = 1/20$
- o Need to know incidence of disorder for calculations
 - When determining if the child of a potential carriers you must first: calculate parent with affected siblings risk, calculate other parents risk based on population (if no affected siblings), multiply them together with the risk of having an autosomal recessive disorder ($1/4$) to get probability of affected child
- Autosomal Dominant Disorders: incidence of an AD disorder is approximately twice the gene (allele) frequency
 - o Ex) Incidence of Dentogenesis imperfecta = $1/8000$
 - What is the frequency of the DI gene? for all practical purposes the incidence rate equals the heterozygous rate = $2pq$ and the allele frequency for the recessive allele is $q \approx 1$ (AA doesn't often survive)
 - $2pq = 1/8000$, $q = 1$ so $2p = 1/8000$, $p = 1/16000$
 - **so for AD, incidence = $2p$**
- X-linked Recessive: two genders must be considered separately
 - o Incidence of red-green colorblindness = $1/12 = q$ for males
 - o Incidence in females = $q^2 = (1/12)^2 = 1/144$ (q is very small)
 - o Incidence of carrier females? since q is very small, $p \approx 1$, $2pq = 2(1)(1/12) = 1/6$
- Can be applied with more than 2 alleles, but the allele frequencies should add to 1 and the genotype frequencies will sum to 1.
- **Factors that Affect HWE:**
 - o **Assortative mating: non random mating** (as in what actually occurs, people mate with similar IQs, height preference, etc.)
 - o **Inbreeding:** cousins marrying- effect on prevalence of genetic disorders is surprisingly low and only increases homozygotes so does not change allele frequencies
 - o **Mutation:** an inheritable change
 - o **The raw material of evolution upon which selection works to produce new combinations of genes.**
 - o **Selection:** change in the gene or genotype frequency from one generation to the next due to differential survival and/or reproduction (natural selection accumulates and maintains favorable genotypes)
 - o **Migration:** individuals from outside the population contribute to the gene pool or individuals from a population take genes away via migration
 - o **Genetic Drift:** chance fluctuations from generation to generation which occur, in small population, as a result of random sampling among gametes (sampling = selection by chance)
 - o **Founder Effect:** example of severe genetic drift; in isolated populations certain genes may be very common because they were present in the founders of that population; different allele frequencies in a subpopulation that may be different from the frequencies in the population from which it originated

Looking for Genes