Genetics Cardio Block:

Inheritance of Complex Disorders:

- Complex Disease//Trait: results from complex interactions between genes and environmental exposures; transmission is "Non-Mendelian"
    - Factors to consider when counseling complex disorders:
        - Reduced Penetrance: frequency of expression of geneotype (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 geneotypes with respect ot risk factors variability or genotype/risk association dpdnt on presence or absence of environmental factors
    - 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)
    - 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)
        - Risk/% Affected should drop by ½ in Second degree family members since they share ½ 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)
    - Doesn't mean one sex is protective, just means it has a higher threshold
- **Cosanguinity increases recurrence risk** (increases baby's liability, closer to threhold)

- How do you know its genetic?
    - Heritabilty: populational study (not specific to individual); proportion of the total phenotypic variation of a trait that is due to genetics
    - Familial aggregation studies: are relatives of an affected person at a higher risk than someone in the gen pop?
        - λ= (disease prevalence in sibs of affected pt)/(disease prevalence in pop)
        - if caused by genetics, λ >1
        - Correlation Coefficient for quantitative traits: if fully genetic, correlation coefficient between relatives is proportional to number of genes they have in common
    - 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;
    - ASSUMES:
        - no selection
        - no migration
        - no mutation
        - population in infinite
        - random mating
        - LOL, OKAY
    - 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
- Hardy-Weinberg Equilibrium: when the gene frequencies do not change from one generation to the next
    - 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=~1 (makes calculations easier)
    - 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=~1 and q = 1/40 so 2(1)(1/40)=1/20

    - 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
    - Ex) Incidence of Dentigenesis 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 = ~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
    - Incidence of red-green colorblindness = 1/12 = q for males
    - Incidence in females = $q^2 = (1/12)^2 = 1/144$ (q is very small)
    - Incidence of carrier females? since q is very small, p = ~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 genetoype frequencies will sum to 1.
- **Factors that Affect HWE:**
    - **Assortative mating: non random mating** (as in what actually occurs, people mate with similar IQs, height preference, etc.)
    - **Inbreeding:** cousins marrying- effect on prevalence of genetic disorders is surprisingly low and only increases homozygotes so does not change allele frequencies
    - **Mutation:** an inheritable change
    - **The raw material of evolution upon which selection works to produce new combinations of genes.**
    - **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)
    - **Migration:** individuals from outside the population contribute to the gene pool or individuals from a population take genes away via migration
    - **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)
    - **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 alleles frequencies in a subpopulation that may be different from the frequencies in the population from which it originated

Looking for Genes