LECTURE 5

Pedigree analysis

Symbols: circles (females), squares (males) — open (normal), filled-in (affected)
small circles/squares (stillborns) — dashed or double lines (consanguinity)

A. *Autosomal dominant pedigree* [OVERHEAD]

1. Evidence suggests is autosomal dominant

   a) presence in almost every generation
   b) mating of affected parents generating unaffected offspring
   c) occurrence of stillborns

2. Two major questions

   a) What about individual VI-2?

   b) Why, given that deleterious, autosomal-dominant alleles should be rare, are there so many affected individuals and in virtually every generation?

Answer to a): $P = G + E$

(i) penetrance: the relationship of phenotype to genotype; the proportion of individuals of a given genotype that display the associated phenotype

(ii) expressivity: degree of expression of a trait

(iii) thus, for individual VI-2, most likely explanation is that trait is <100% penetrant and that individual V-2 carries the gene but does not display the trait

(iv) another possibility might be a newly arisen mutation; this possibility is unlikely given that the trait is in the kindred

Answer to b):

(i) the population from which the kindred was drawn represents a (sub)population that was foundered by a small number of individuals and where religious (and other) factors have minimized exchange of genes with external subpopulations or populations

(ii) because of the small number of founders, alleles at some genes may be (by chance) in higher frequencies in the "foundered" subpopulation than in the population from which the founders came

(iii) the effect of minimizing gene exchange with the outside maintains these (sometimes deleterious) alleles is comparatively high frequency

3. Probability in pedigrees of dominant genes straightforward; can even factor in penetrance value(s) if known; should note that penetrance values (estimates) typically have very large standard errors

Autosomal recessive pedigree [OVERHEAD]

1. Circumstantial evidence suggests the trait is due to an autosomal recessive

   a) rare occurrence
   b) two unaffected parents with an affected child
   c) two instances of consanguinity, both leading to an affected child
   d) probability: e.g., estimate chance (assuming dominant with complete penetrance) that all six children of marriage between IV-4 x IV-5 would be homozygous for the normal, recessive allele

   $p = (1/2)^6 = 1/64$

2. Assuming the trait is due to an autosomal recessive, next step is to fill in all <u>known</u> genotypes

   a) this is fairly straightforward, allowing one (ultimately) to estimate the probability that any phenotypically normal individual carries the allele and the probability that any two individuals (of the opposite) could produce an affected offspring

   b) this can be demonstrated by using individuals from different generations of this pedigree

      (i) III-6? What is the probability that he carries the recessive allele? 2/3

      (ii) IV-6? What is the probability that he carries the recessive allele? 1/3

      (iii) V-7? What is the probability that he carries the recessive allele? 1/6

   Now try some putative matings (marriages):

      (iv) V-7 x III-1?What is the probability they could have an affected child?

probability that V-7 is heterozygous	1/6		
probability that III-1 is heterozygous	1/2		
probability of an affected child (from two hets)	1/4	=	1/48

      (v) V-8 x V-2? What is the probability they could have an affected child?

probability that V-8 is heterozygous	1/6		
probability that V-2 is heterozygous	1		
probability of an affected child (from two hets)	1/4	=	1/24

(vi) IV-6 x IV-1? What is the probability they could have an affected child?

probability that IV-6 is heterozygous	1/3		
probability that IV-1 is homozygous (aa)	1		
probability of an affected child (homo x het)	½	=	1/6

3. Consider one last pedigree that represents a fairly typically encountered situation

   a) two individuals who have full sibs afflicted with the same (presumably genetic) syndrome wish to marry. Both have "normal" parents. What is the probability they might have a child afflicted with the same syndrome as their sibs?

Introduction to Gene Interaction

Up to now, we've considered the interaction between alleles at one gene. In reality, very few individual genes are responsible for a single trait, i.e., in most instances phenotypic traits are the result of interactions among numerous genes.

This is most easily understood by considering biochemical pathways, each step of which is catalyzed by an enzyme, the primary product of a single gene.

This was suggested in 1902 by Sir. A. Garrod in his book 'Inborn Errors of Metabolism'

A. Consider a simple pathway:

Substrate A → Product A (Substrate B) → Product B (Substrate C) → End Product

1. Given that many enzymes are the primary products of genes, one can understand straightforwardly how 3:1 phenotypic ratios (and others) in an F_2 population arise

B. The first trait discussed by Garrod was alkaptonuria, a simple Mendelian trait (as we now know) that is inherited as an autosomal recessive

1. A-; normal
   aa: alkaptonuria

   alkaptonurics (aa) excreted in their urine a substance called "alkapton" (*homogentisic acid*) that turns black upon exposure to air (oxidized)

2. In normal individuals, homogentisic acid does not accumulate because it is broken down into fumaric acid and acetoacetic acid by an enzyme called *homogentisic acid oxidase*

3. Garrod surmised correctly that the responsible enzyme was absent or inactive in affected individuals

4. In further experiments, Garrod found that if alkaptonurics were fed excesses of the amino acids *phenylalanine or tyrosine*, the amount of homogentisic acid was increased significantly. This led to the suggestion (hypothesis) that…

   phenylalanine, tyrosine → → homogentisic acid → → fumaric acid + acetoacetic acid

   a) "genes" are enzymes (or at least catalysts in biochemical pathways)
   b) can use "mutants" to construct biochemical pathways
   c) origin of the "one gene-one-enzyme" hypothesis

5. Further study on phenylalanine/tyrosine metabolism showed that

   phenylalanine → tyrosine by phenylalanine hydroxylase

   a) defects in phenylalanine hydroxylase result in accumulation of phenylketones (notably phenylpyruvic acid) that produce severe mental retardation in humans

   b) the syndrome is known as *phenylketonuria* and is inherited as a simple recessive, i.e., pk^+, pk;

   c) because only developing neural systems are affected, the syndrome can be "medically" alleviated by diet

6. The tyrosine metabolic pathway demonstrates *pleiotropy* [OVERHEAD]