Lecture 31: Genetic Heterogeneity and Complex Traits

- Allelic heterogeneity
- Nonallelic heterogeneity
- r
- Twin studies
- Sib-pair analysis

Each of the heritable human traits that we have discussed in recent weeks is **monogenic**

invariably caused by mutation in the same gene.

Each of these traits was quite straightforward from a Mendelian perspective:

Sickle cell disease: autosomal recessive

Phenylketonuria: autosomal recessive

Huntington's disease: autosomal dominant

genetic homogeneity

all affected individuals have the same mutation in the same gene

ALLELIC HETEROGENEITY

cystic fibrosis (CF):

- autosomal recessive disorder affecting 1/2500 newborns in populations of European origin

- phenotype: sticky viscous secretions → obstruction of pancreas and airways → pancreatic insufficiency (treated with enzyme supplements) + lung infections
- mapped to chromosome 7 by genetic linkage analysis in 1985
- gene identified at molecular level in 1989: encodes a chloride channel protein
- > 600 mutant alleles in the gene have been identified

allelic heterogeneity

Would such allelic heterogeneity affect the outcome of combining LOD scores from multiple families with affected children?

No, because all such families would show linkage to the same chromosomal locus.

TWO MUSCULAR DYSTROPHIES

DUCHEYNNE

BECKER

retinitis pigmentosa (RP):

- degeneration of retina (accompanied by deposits of pigment in retina) → progressive visual impairment → blindness
- population prevalence of 1/3,000
- one of most common causes of blindness among middle aged in developed countries
- autosomal recessive inheritance in 84% of affected families
- autosomal dominant inheritance in 10% of affected families
- X-linked recessive inheritance in 6% of affected families
- At least 66 different genetic loci implicated

but RP appears to be result of a single gene mutation in any given family, at least in most cases

NON-ALLELIC HETEROGENEITY

How could one begin to genetically dissect a trait like RP that shows nonallelic heterogeneity?

Approach 1: Linkage analysis on large families with many affected individuals.

Different families with RP may show linkage to different loci, combining LOD scores from different families might obscure rather than clarify the situation. However, this trap can be avoided if one can identify a family with sufficient numbers of affected individuals (and informative meioses) to provide, by itself, a LOD score of 3.

Approach 2: Direct search for mutations in candidate genes.

In some diseases, one can make good guesses as to the biochemical structures or pathways that are likely sites of causative mutations. In such cases, a direct search for mutations at the DNA sequence level in "candidate genes" -- can be an effective strategy -- even in the absence of any prior genetic linkage analysis.

This "candidate gene" approach will become increasingly prominent given:

- Complete sequence of human genome

Complete sequence of human genome (rough draft published in 2001; reference grade sequence expected in 2003)

- Falling cost of sequencing

Perhaps 10 years from now, scientists will routinely sequence the entire genomes of individuals with unexplained phenotypes.

r = **coefficient of relationship** between two individuals

= likelihood of sharing by descent a given allele at a given locus

= expected proportion of all alleles (at all genes) that two individuals share by descent

coefficient of relationship, r ➡ **inbreeding coefficient, F**

(likelihood that an individual is homozygous by descent at a given locus)

Relationship	degree	r
Parent-child	1st	1/2
Siblings	1st	1/2
Aunt/niece	2nd	1/4
First cousins	3rd	1/8

Cleft lip is a common birth defect. Its incidence in the general population is about 0.001, but relatives of affected children are at higher risk:

Relatives of affected child	degree	% affected	Risk (relative to general population)
Sibs	1st	4.1	x40
Children	1st	3.5	x35
Aunts and uncles	2nd	0.7	x7
Nephews and nieces	2nd	0.8	x8
First cousins	3rd	0.3	x3

Are these findings consistent with autosomal dominant inheritance of cleft lip?

No, because the percentages of 1st and 2nd degree relatives who are affected are too low (would expect 50% and 25%, respectively).

Are these findings consistent with autosomal recessive inheritance of cleft lip?

No, because the percentage of affected siblings is too low (would expect 25%) and because the risk in children is nearly as high as that in siblings.

Phenotypic concordance in monozygotic (MZ; identical) and dizygotic (DZ; fraternal) twins

MZ twins arise when a developing embryo (derived from one zygote; fertilization of one egg by one sperm) splits into two parts, each giving rise to a baby

DZ twins arise from two separate, but nearly simultaneous fertilization events.

Relationship	degree	r
Parent-child	1st	1/2
Siblings	1st	1/2
Aunt/niece	2nd	1/4
First Cousins	3rd	1/8
MZ twins	0	1
DZ twins	1st	1/2

Twin studies:

Concordance = both twins display phenotype in question

Discordance = one twin displays phenotype in question, other does not

	Concordance Rates in MZ twins	DZ twins	Interpretation
Huntington's disease	100%	50%	autosomal dominant
Sickle cell disease	100%	25%	autosomal recessive
Cystic fibrosis	100%	25%	autosomal recessive
Measles	97%	94%	environmental (contagious)
Cleft lip	40%	4%	environment + multiple genes
Insulin-dependent diabetes	30%	6%	environment, ≥1 gene
Coronary heart disease	46%	12%	environment, ≥1 gene
Schizophrenia	46%	14%	environment, ≥1 gene

male homosexuality

Concordance Rates	
MZ twins	57%
DZ twins	24%
Non-twin brothers	13%

In early 1990's, Dean Hamer and colleagues at NIH embarked on genetic studies of male homosexuality. They phenotyped the individuals by asking them to answer a number of questions about their sexuality: self-identification, attraction, fantasy, and behavior → bimodal distribution of scores.


Pedigree figures removed due to copyright considerations

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Hamer and colleagues then employed **concordant sib-pair analysis**, variation on conventional genetic linkage analysis that

1. requires no knowledge of mode of inheritance

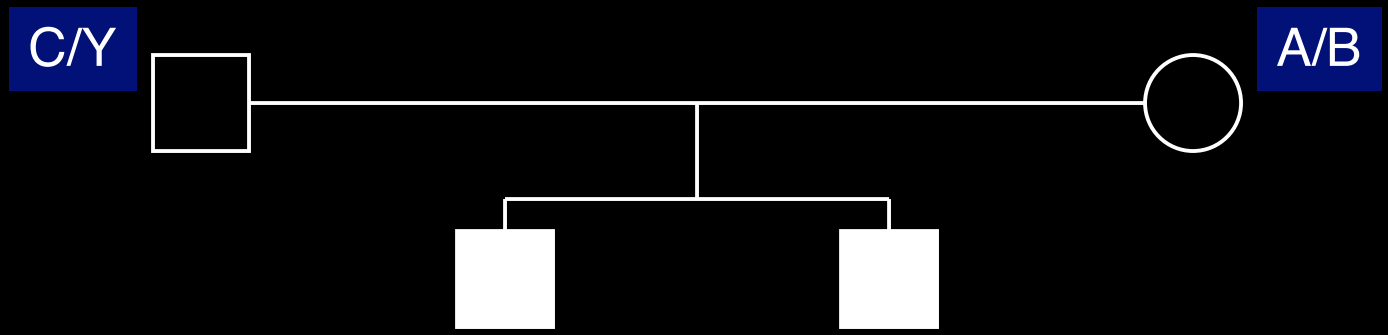
2. unaffected by incomplete penetrance

3. can tolerate some degree of non-allelic heterogeneity

Sib-pair analysis =

search for nonrandom sharing of alleles between phenotypically concordant sibs

Hamer and colleagues (Science 261:321-327 [1993]) identified 40 nuclear families in which there were two homosexual brothers. In each of the 40 families, they studied the transmission of X-linked SSRs from the mother to the homosexual sons. For an X-linked SSR, there are two possible genotypes in each son, and thus there are four possible combinations of genotypes in the two sons:



A/Y	A/Y	Identical by descent (IBD)
B/Y	B/Y	
A/Y	B/Y	Nonidentical
B/Y	A/Y	

If the region of the X chromosome being tested plays no causal role in male homosexuality, then the four possible combinations should be equally likely, and identity by descent and nonidentity should be equally likely.

	IBD	Nonidentical
Expected	20	20

On the distal long arm of the X chromosome, Hamer and colleagues observed a dramatic departure from random expectations among the 40 families:

	IBD	Nonidentical
Observed	33	7

Chi-square = $\sum \frac{(O-E)^2}{E}$ = $\frac{(33\text{-}20)^2}{20} + \frac{(7\text{-}20)^2}{20}$ = 16.9

The table of critical values of the X^2 distribution has been removed due to copyright considerations.

p = probability, given the null hypothesis, of observing the data (or data even more diverged from the null expectations)

$p <<< 0.005$

Suggests that a gene on distal long arm of X chromosome contributes to the development of male homosexuality -- in some but not all cases.