Biostatistics 666 Statistical Models in Human Genetics

Instructor

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Course Logistics

Grading

Office Hours

Class Notes

Course Objective

- Provide an understanding of statistical models used in gene mapping studies
- Survey commonly used algorithms and procedures in genetic analysis

Assessment

- Weekly Assignments
  - About 60% of the final mark
- 2 Half Term Assessments
  - About 40% of the final mark

Academic Integrity

- All assignments are made on an individual basis – the solutions you provide must represent your own work.
- Cheating, plagiarism and aiding and abeting these acts constitutes academic misconduct and is a serious offense.
- See also the School policy on academic conduct.

Office Hours

- Please cross out times for which you are unavailable in the sheet going around
- Room M4132
  School of Public Health II

Class Website

- PDF versions of notes and problem sets

  http://genome.sph.umich.edu/wiki/666

- It is a wiki, so you should be able to add comments, notes and discussion to each lecture.

Course Contents

Brief Overview

Genetic Mapping

"Compares the inheritance pattern of a trait with the inheritance pattern of chromosomal regions"

Positional Cloning

"Allows one to find where a gene is, without knowing what it is."

Some of the Topics Covered

- Maximum Likelihood
- Modeling Genes in Populations
- Modeling Genes in Pedigrees

Modeling Genes in Populations

- Hardy Weinberg Equilibrium
- Linkage Disequilibrium
- The Coalescent
- Methods for Haplotyping
- Methods for Handling Shotgun Sequence Data

Modeling Genes within Pedigrees

- Elston-Stewart algorithm
- Lander-Green algorithm
- Checking Genetic Data for Errors
- Genetic Linkage Tests
- Genetic Association Tests

Let's Get Started!

The Basics

Today – Primer In Genetics

- How information is stored in DNA
- How DNA is inherited
- Types of DNA variation
- Common designs for Genetic studies

DNA – Information Store

- Encodes the information required for cells and organisms to function and produce new cells and organisms.

- DNA variation is responsible for many individual differences, some of which are medically important.

Human Genome

- Multiple chromosomes
  - 22 autosomes
    - Present in 2 copies per individual
    - One maternally and one paternally inherited copy
  - 1 pair of sex chromosomes
    - Females have two X chromosomes
    - Males have one X chromosome and one Y chromosome
- Total of ~3 x 10^9 bases (each A, C, T or G)

Inheritance of DNA

- Through recombination, a new “DNA string” is formed by combining two parental DNA strings
- Thus, each chromosome we carry is a mosaic of the two chromosomes carried by our parents
- Only a small number of changeovers between the two parental chromosomes
  - On average ~1 per Morgan (~10^8 bases)
- Copying of DNA sequences is imperfect and, for typical sequences, the error rate is about 1 per 10^8 bases copied

Human Variation

- Every chromosome is unique …
- … but when two chromosomes are compared most of their sequence is identical
- About 1 per 1,000 bases differs between pairs of human chromosomes

DNA Sequences That Vary…

- Genes (protein coding sequences, which total <2% of all DNA)
  - ~20,000-25,000 in humans
- Pseudogenes
  - Ancient genes, inactivated through mutation
- Promoters and Enhancers
  - Sequences which control gene expression
- Repeat DNA
  - Often more variable than other types of sequences
  - Useful for tracking DNA through families or populations
- Packaging sequences, “spacer” DNA, etc.

Important Vocabulary ...

- Locus
- Polymorphism
- Allele
- Mutation
- Linkage
- Genetic Marker
- Genotype
- Phenotype
  - Mendelian Traits
  - Complex Traits
- Chromosomal landmarks
  - Centromeres
  - Telomeres
- Gene
- RNA
- Protein

Data for a Genetic Study

- Pedigree
  - Set of individuals of known relationship
- Observed marker genotypes
  - SNPs, VNTRs, microsatellites
- Phenotype data for individuals

Genetic Markers

- Genetic variants that can be measured conveniently
- Typically, we characterize them by:
  - Number of Alleles
  - Frequency of Each Allele
  - These are summarized by the heterozygosity
- The most commonly used genetic markers are microsatellites and SNPs

Phenotypes

- Measured characters of individuals

- Mendelian Phenotypes
  - Completely determined by genes
  - e.g. Cystic Fibrosis, Retinoblastoma
- Complex Phenotypes
  - Controlled by multiple genes and environmental factors
  - eg. Diabetes, Inflammatory Bowel Disease

Ultimate Aim of Gene-Mapping Experiments

- Localize and identify variants that control interesting traits
  - Susceptibility to human disease
  - Phenotypic variation in the population
- The difficulty…
  - Testing several million variants is impractical…

3 Common Questions

- Are there “genes” influencing this trait?
  - Epidemiological studies
- Where are those “genes”?
  - Linkage analysis
- What are those “genes”?
  - Association analysis

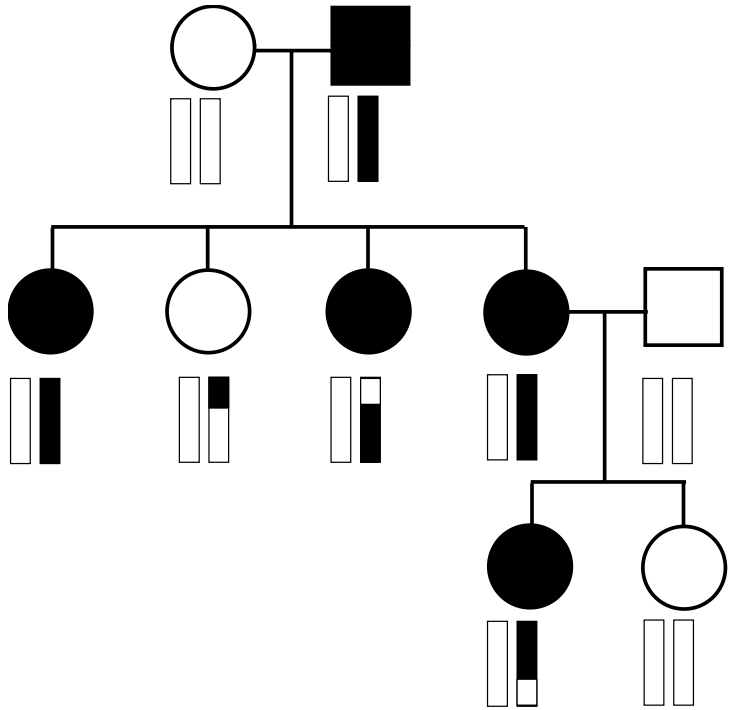
Is a trait genetic?

- Examine distribution of trait in the population and among relatives

- E.g. Inflammatory Bowel Disease (Crohn's)
  - General population
    - 1-3 cases per 1,000 individuals
  - Twins of affected individuals
    - 44% of monozygotic twins also have Crohn's
    - 3.8% of dizygotic twins also have Crohn's

Where are those genes?

- Find genetic markers that co-segregate with disease
- E.g. D16S3136 co-segregates with Crohn's



What are those genes?

- Identify genetic variants that are associated with disease…
- E.g. Mutations which disrupt NOD2 are much more common in Crohn's patients

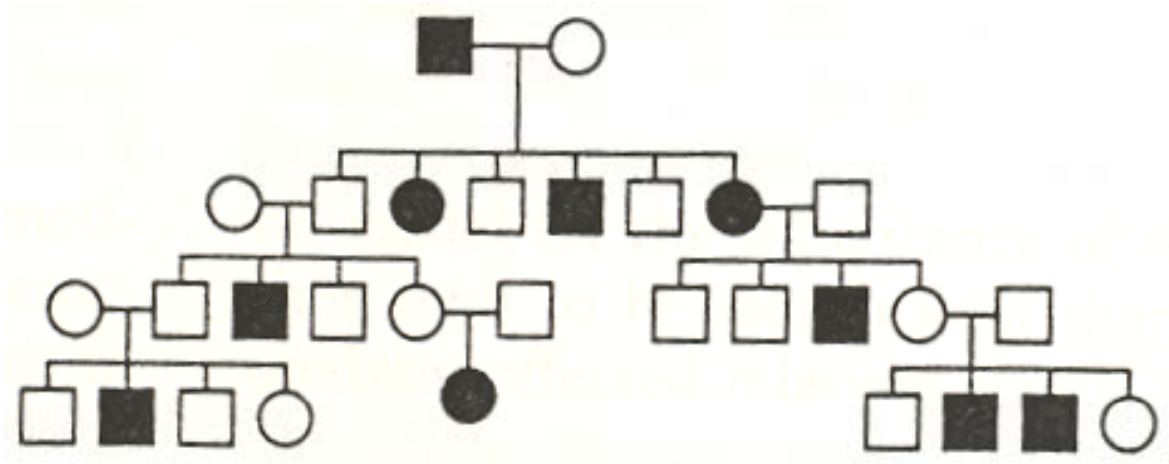
	Crohn's	Controls
Arg702Trp:	11%	4%
Gly908Arg:	4%	2%
Leu1007fs	8%	4%

Common Designs for Genetic Studies

- Parametric Linkage analysis
- Allele-sharing methods
- Association analysis

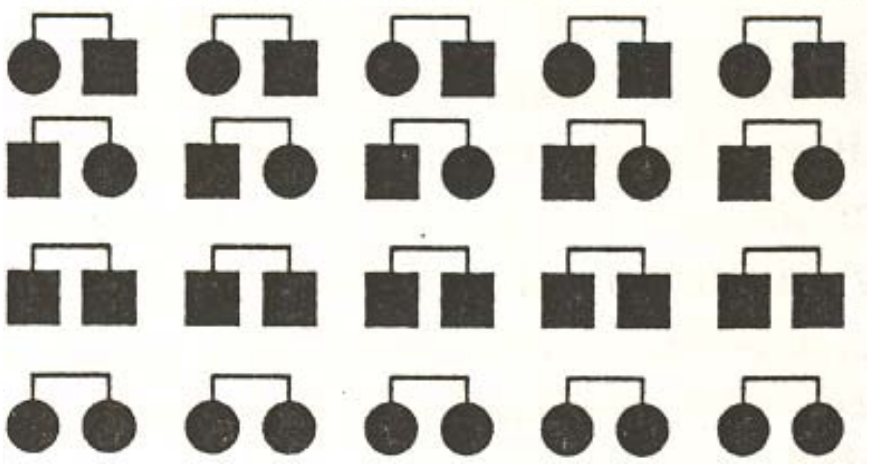
Parametric Linkage Analysis

- Evaluate a specific model and location
  - Allele frequencies at disease loci
  - Probability of disease for each genotype
- Potentially very powerful
- Vulnerable to heterogeneity, model misspecification



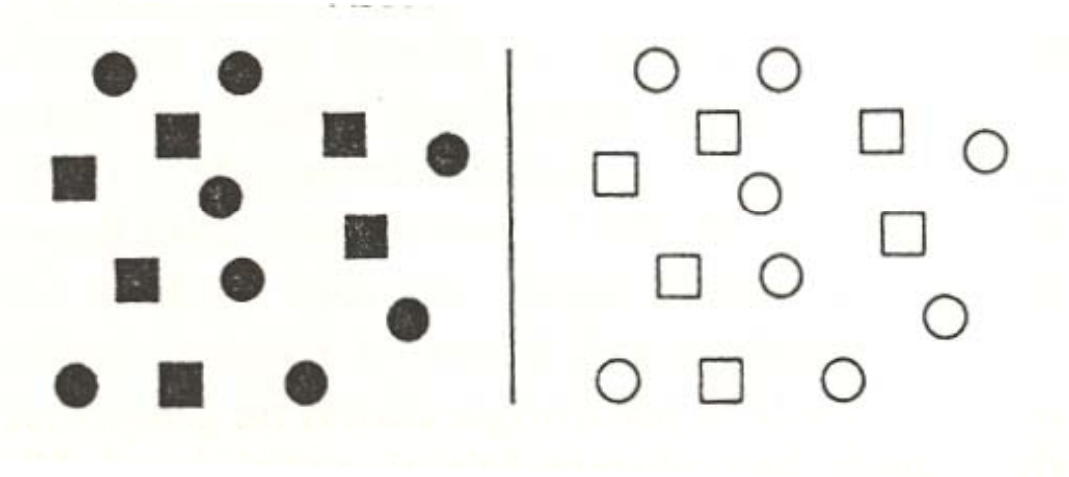
Allele Sharing Analysis

- Reject null hypothesis that sharing is random at a particular region
- Less powerful, but more robust
- Quantitative trait extensions exist



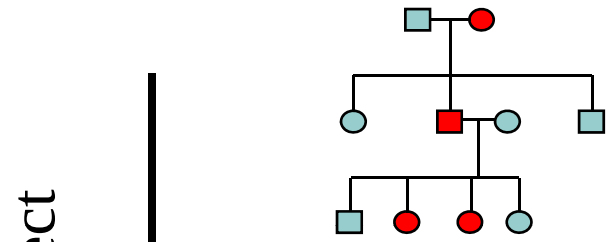
Association Analysis

- Simplest case compares frequency of allele among cases and controls
- Genome-wide search requires hundreds of thousands of markers
- Typically, focuses on candidate genes



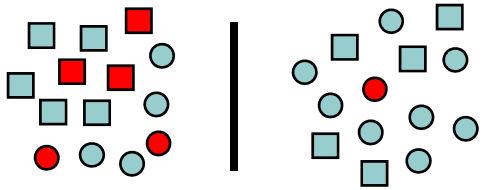
Which Design to Choose?

The Right Choice Depends on the Alleles We Seek…



Rare, high penetrance mutations – use linkage

Common, low penetrance variants – use association



Magnitude of effect

Frequency in population

Genetic Linkage Studies

- Identify variants with relatively large contributions to disease risk
- Require only a coarse measurement of genetic variation
  - 400 – 800 microsatellites can extract most of the linkage information in typical pedigrees
  - Until recently, the only option for conducting whole genome studies
- High-throughput SNP genotyping has already sped up and facilitated these studies
  - Data analysis methods must select subset of independent SNPs or model disequilibrium between markers

Genetic Association Studies

- Identify genetic variants with relatively small individual contributions to disease risk
- Require detailed measurement of genetic variation
  - > 10,000,000 catalogued genetic variants, so …
  - Until recently, limited to candidate genes or regions
    - A hit-and-miss approach…
- SNP resources and decreasing assay costs now make it possible to examine 100,000s of markers

Recommended Reading

- An introduction to important issues in genetics:
  - Lander and Schork (1994)
    Science **265:**2037-48
- A good reference on molecular genetics:
  - Human Molecular Genetics
    Tom Strachan and Andrew Read

Reading for Next Lecture

- Will be discussing Hardy-Weinberg equilibrium
  - A basic feature of genotypes in human populations

- Wigginton, Cutler, Abecasis (2005)
  A note on exact tests of Hardy-Weinberg equilibrium.
  Am J Hum Genet **76**:887-93

- This paper describes an efficient method for testing Hardy-Weinberg equilibrium and includes many important historical references