GGSB 2015 Prelim

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Required

1-8: General Genetic Principles

9-12: Mapping

39-50: Study Design and Statistical Data Analysis

Choice between

13-17: Genetic Architecture of Human Phenotypes

or

18-28: Population and Evolutionary Genetics

29-32: Molecular Mechanisms and Model Organisms in Human Genetics

or

33-38: Gene Regulation and Human Phenotypes

A good answer would show in escalating order:

- Basic understanding via descriptions and definition of basic terms and concepts
- Knowledge of biology/literature via empirical examples of concepts in action,
- Engagement of critical thinking by highlighting well-known limitations or novel critiques of a concept or its common application
- Recognition of open problems and novel research opportunities.

Contents

General Genetic Principles

1. Explain the distinction between allelic heterogeneity, genetic (locus) heterogeneity, and clinical heterogeneity. Give examples of each.

Great review of this topic:
Genetic Heterogeneity in Human Diseases

Overview
Each of the following topics have implications in the type of studies which can or cannot be used. Overall, heterogeneity ensures that large-scale association tests or case-control studies will be poorly powered to detect causal variants or genes. See the review linked above for more detail.

Definition Allelic Heterogeneity - *In a given population, different mutations in the same gene result in a similar phenotype.*

Example

Cystic Fibrosis is caused by defective cystic fibrosis transmembrane conductance regulator proteins (CFTR). Many mutations in the CFTR gene can give rise to non-functioning proteins, which all lead to the same CF phenotype.

Two-thirds of all CF mutations are a 3bp deletion at position 508, resulting in a loss of phenylalanine. 1,500 other mutations also exist which lead to CF. However, this disease is haplosufficient..

Unknown alleleic heterogeneity can affect GWA results[1] when LD methods are used.

[1] http://hmg.oxfordjournals.org/content/11/20/2417.short

Sources
http://hmg.oxfordjournals.org/content/20/20/4082.short

Definition Genetic (locus) heterogeneity - *Mutations in different genes result in a similar phenotype.*

Example - *The BRCA1 and BRCA2 genes are a good example of how mutations in different genes lead to the same phenotype.*

Definition Clinical Heterogeneity - *Variability in clinical manifestations, or phenotypes, with the same underlying mutation/genetic disorder.*

Mutations in several genes can lead to familial hypercholesterolemia, high level of LDL cholesterol. Mutations in LDLR (LDL receptor), Apolipoprotein B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and the ARH/LDLRAP1 genes can all lead to familial hypercholesterolemia.

2. What is the relationship between the inbreeding coefficient, kinship coefficient, and coefficient of relatedness? How are they calculated in pedigrees? Can they be estimated in the absence of pedigree information?

Definition Identity by descent - *Two alleles at the same locus that are descended from the same ancestral allele within the recent past. Can be 0, 1, or 2 depending on how many ancestral alleles shared between individuals.*

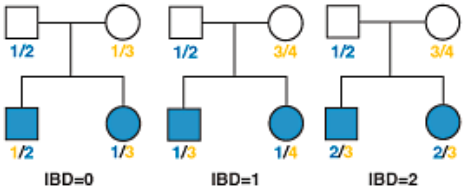
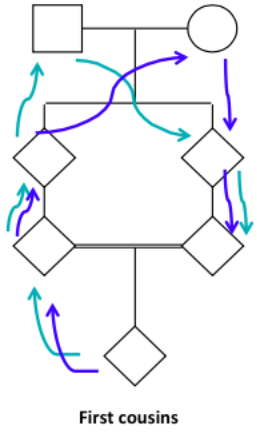


Figure 1: IBD Pedigree Example

Definition Coefficient of Kinship - f_{xy}*: The probability that two alleles, one from X and the other from Y, are IBD.*

Calculating F

- $F = \Sigma\ (½)^n$
  - n = number of connections between inbred offspring and each common ancestor
  - Summed over all "loops" (or common ancestors)



$F = (½)^5 + (½)^5 = (1/16)$

Definition Coefficient of Relatedness - R_n*, the probability of sharing* $n \in \{0, 1, 2\}$ *IBD alleles. Mean relatedness,* $\bar{r} = 0 \times r_0 + 1 \times r_1 + 2 \times r_2$.

Relationship between Coefficients

$$f_{xy} = \frac{1}{2}\bar{r}$$

Relationship	Kinship coefficient	Coeffcient of relatedness
Self	0.5000	1.000
Monozygotic twins	0.5000	1.000
Parent-child	0.2500	0.500
Full siblings	0.2500	0.500
Half siblings	0.1250	0.250
First cousins	0.0625	0.1250
Unrelated	0.0000	0.0000

Figure 2: Relationship between Kinship and Relatedness coefficients

3. What are the key distinguishing characteristics of pedigrees segregating autosomal dominant, autosomal recessive, X-linked, Y-linked, and mitochondrial diseases?

Autosomal Dominant

On average, half of offspring of affected-nonaffected parents will be affected.

Autosomal Recessive

If both parents are carriers, then $\frac{1}{4}$th of offspring will show a disease phenotype.

X-linked Dominant

Affected men always pass disease to daughters. Affected women have $\frac{3}{4}$ths chance of passing disease to daughters and same chance to sons.

X-linked Recessive

Women can be either affected or carriers. Men always affected.

4. Explain the "non-Mendelian" concepts of uniparental disomy and imprinting. How would these be manifested in pedigrees and how are they demonstrated at the cellular or molecular levels?

5. What evidence is there for the presence of modifier loci? How is this related to the concept of epistasis and how is it distinct (or not) from polygenic and other models of inheritance?

6. What are distinctions among the concepts linkage, linkage disequilibrium, and association? Under what circumstances would each be preferable for genetic mapping? Consider both sample composition and types of diseases.

Definition Linkage - *Two loci tend to be inherited together due to lack of recombination.*

Linkage Mapping

Useful when samples are from large and informative pedigrees. Informative indicates that each allele can be assigned to

7. Define epistasis. Describe approaches that allow epistasis to be detected or quantified. Describe some biological mechanisms that can produce epistasis. Discuss the implications of epistasis for efforts to map the genetic causes of phenotypes. Discuss the potential implications of epistasis for the evolutionary process.

8. Define heritability. Describe methods used to quantify the heritability of a phenotype. Discuss the value and limitations of heritability as a descriptor of the extent to which a phenotype has genetic causes. Describe the "missing heritability problem" and its potential explanations.

Mapping

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Population and Evolutionary Genetics

Molecular Mechanisms and Model Organisms in Human Genetics

Gene Regulation and Human Phenotypes

Study Design and Statistical Data Analysis