GGSB 2015 Prelim

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Required

Questions 1-8: General Genetic Principles
Questions 9-12: Mapping
Questions 39-50: Study Design and Statistical Data Analysis

Choice between

Questions 13-17: Genetic Architecture of Human Phenotypes
or
Questions 18-28: Population and Evolutionary Genetics

Questions 29-32: Molecular Mechanisms and Model Organisms in Human Genetics
or
Questions 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.*

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

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?

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

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.

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.