Lecture 1: Introduction

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Personal Introduction

• Biostatistics (post-doctoral fellowship)
  – Harvard School of Public Health
• Epidemiology (doctoral)
  – Harvard School of Public Health
• Public Health (master’s)
  – University of Washington School of Public Health
• Neuroscience (bachelor’s)
  – University of Colorado Boulder
What I do

• “Big Data Epidemiology”
• Risk Factors
  – Molecular and genetic factors
  – Traditional epidemiological factors
• Health and behavioral outcomes
  – Behavioral and Psychiatric outcomes
  – Cardio-metabolic outcomes (obesity)
Course Overview – Day 1

• Lecture 1: Introduction
  – Tutorial 1: Getting Started

• Lecture 2: Quality Control Procedures
  – Tutorial 2: Data Cleaning and Genetic Ancestry
Course Overview – Day 2

• Lecture 3: Genome-Wide Association Approaches
  – Tutorial 3: Genome-Wide Association Analysis

• Lecture 4: Aggregation of GWAS Data
  – Tutorial 4: Heritability and Polygenic Scores
Course Overview – Day 3

• Lecture 5: Family-Based Approaches
  – Tutorial 5: Family-Based Association Testing

• Lecture 6: Meta-Analysis
  – Tutorial 6: Conducting a meta-analysis
Course Objectives

• Have a working knowledge of the steps necessary to carry out a genome-wide analysis
• Appreciate the inherent limitations to genome-wide analysis
• Gain hands-on experience working with genome-wide data
Background
Measurable Genetic Variation

- DNA
  - Frequencies of alleles at base-pair locations
- Gene Expression
  - Amount of gene product being expressed
- Epigenetics
  - Methylation patterns, etc.
DNA Variation

- DNA
  - Adenine (A)
  - Guanine (G)
  - Cytosine (C)
  - Thymine (T)

- DNA double helix
  - A pairs with T and G pairs with C

- Codons
  - Triplets of bases
  - 64 possible codons
    - 20 amino acids
Mutations: A Source of DNA Variation

• Point
  – Substitute one base for another

• Deletions
  – Base removed entirely

• Insertions
  – Base inserted

• Duplications
  – Base and/or sequence duplicated
Point Mutations:

*A Source of Single Nucleotide Polymorphisms*

- Base pair substitution
  - (e.g. replication error)
- Synonymous
  - *No change* in amino acid
- Nonsynonymous
  - Amino acid change
- Transitions
  - Between A and G or C and T
  - Change within same base (purines and pyrimidines)
- Transversions
  - All others
  - Change between bases
Population Genetics

• Infinite Sites Model
  – Each mutation creates a unique polymorphic site
  – Mutation rate $\sim 10^{-6}$
Life After Mutation

• Mutation is neutral
  – Random Genetic Drift
    • Eventually, the allele will “drift” out

• Mutation is harmful
  – Selective Pressure
    • Allele may quickly disappear

• Mutation is beneficial
  – Selective Pressure
    • Allele frequency may increase rapidly
Beneficial Mutation

- Lactase Persistence (~7500 years)
Beneficial Mutation

- Thriving at Altitude (~3000 years)
Common Ancestry

Sequences

Time
Common Ancestry

Sequences

Time
Common Ancestry

MRCA
Ancestry and Genetic Variation

• All DNA sequences are derived from others
  – Every sample has a genealogy
• Eventually, all lineages coalesce
  – Most Recent Common Ancestor (MRCA)
• Mutations may become polymorphisms
Measuring the Genome
Rapid pace of technology

• Advantages
  – Unprecedented look into biological systems
  – Efficiency is up
  – Cost is down

• Disadvantages
  – Technology is driving the bus
  – We do things because we can
  – We often have no idea what we’re looking for
Measuring the Genome

Molecular Precision

Family Data

Microsatellite Markers

Single Polymorphism

Traditional Heritability

Traditional Linkage

Genome-Wide Association
Traditional Heritability

• Objective
  – “Does it run in families?”

• Design
  – Family, twin and adoption studies

• Molecular data
  – None

• Desired outcome
  – Gives us a clue that genetics might be important
Traditional Linkage

• Objective
  – Find **genomic loci** linked to disease

• Design
  – Family-based

• Molecular information
  – 300 - 600 markers (often short tandem repeats)

• Desired outcome
  – Find genetic variation linked to disease
Genome-Wide Association

• Objective
  – Find **common alleles** associated with disease

• Design
  – Cohort, case-control, family-based

• Molecular information
  – 500,000 – 2.5M single nucleotide polymorphisms

• Desired outcome
  – Find genetic variation associated with disease
Why Genome-Wide Association?

• Molecular precision
  – Measure the genome on a more refined scale
• More powerful to detect common alleles
  – Common disease, common variant
• A result of the human genome project effort
Approaches to Genetic Research

• Genome-Wide
  – Linkage Analysis
  – Genome-Wide Association Analysis
  – Whole Genome Sequence Analysis

• Targeted
  – Candidate Gene(s) Association Analysis
Gene Hunters

• By definition, “integrative”
  – Combines epidemiological, sociological, statistical, clinical, genetic and molecular approaches

• The Goal...
  – FIND GENES INVOLVED WITH DISEASE
Why Hunt for Genes?
Why Hunt for Genes?

• Disease etiology

• Refined diagnosis and/or prognosis

• Drug development

• Disease prediction
Gene-Mapping

• Monogenic ‘Mendelian’ Diseases
  – Rare disease
  – Rare variants
    • Highly penetrant

• Complex Disease
  – Rare/Common disease
  – Rare/Common variants
    • Variable penetrance
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Linkage!
Gene-Mapping

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Association
Disease and DNA Variation

Penetrance: \( P(D \mid G) \)

2012 Nature Reviews | Genetics
“Where in the genome...?”

• 1980s - 2005
  – Linkage (LOD Scores, etc.)

• 2006 -
  – Association
Why Now?
The “-omics” Age

c. 2000
  – Pre-genomic era
  – 100’s of Markers
    • STRs
  – Genome-wide linkage

c. 2016
  – Post-genomic era
  – 1M+ markers
    • SNPs
  – Genome-wide association
 Genetic Information

• Human Genome Project
  – One human genome (3B base pairs)

• HapMap Project
  – 100s of human genomes (millions of base pairs)

• ENCODE Project
  – 100s of human genomes (functional data)

• 1000 Genomes Project
  – 1000s of human genomes (12M base pairs)

• Large-Scale Whole Genome Sequencing
  – 1000s of human genomes (3B base pairs)
Next up...

• Tutorial 1
  – Getting started