The Promise of Personalized Medicine

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Individualizing Medicine

• We are all different

• Some of our differences lead to differences in
  
  disease susceptibility
  
  drug response

• Aim is to tailor healthcare to the individual
Questions

• Why do some people get a disease and others don’t?

• Why isn’t the same drug dosage effective for everyone?

• Why do some patients experience adverse side-effects of drug therapy, and some do not?
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• Why do some people get a disease and others don’t?

• Why isn’t the same drug dosage effective for everyone?

• Why do some patients experience adverse side-effects of drug therapy, and some do not?

How can we explain this variation?
Individual Characteristics

- To manage a patient’s health based on their characteristics must consider
  
  Gender
  Age
  Diet
  Environment
Individual Characteristics

- To manage a patient’s health based on their characteristics must consider:
  - Gender
  - Age
  - Diet
  - Environment
  - ...and more recently genetics

2001: Sequence of the human genome
You Are Your DNA

Organism

A human body is made up of trillions of cells.

Each cell nucleus contains an identical complement of chromosomes in two copies. Each copy is a genome.

One specific chromosome pair

Each chromosome is one long DNA molecule, and genes are functional regions of this DNA.

DNA is a double helix.
Genetic Transmission

Maternal grandparents × Paternal grandparents

Mother × Father

You
The Variable Human Genome

- 3 billion basepairs long
- ~15 million sites differ between a pair of genomes (0.5%)
- ~1/2 of the 20,500 genes show at least 1 alteration between genomes
Genetic Variation and Disease

• **Single Nucleotide Polymorphisms (SNPs)**
  
e.g., sequence alters from: AAGGCTAC
to: AAGACTAC

• Typically have no effect on cell function

• BUT some predispose individual to disease or influence their response to drugs
A Malfunctioning Enzyme Leads to Albinism

[Diagram showing the process of melanin production and its relation to albinism]
Sickle-cell Anemia

- Due to a mutation in a gene forming hemoglobin
- Single nucleotide change causes mutant hemoglobin protein to form fibers

“sickle” shaped red blood cell
Huntington’s Disease is Caused by Mutation in a Single Gene

Individual’s without HD: 28 CAG repeats

Individual’s with HD: 40 CAG repeats

Nonaffected individuals have two normal copies of HTT gene

Affected individuals have one defective copy of HTT gene
Rare Single-gene Diseases

- Cystic fibrosis: 1 in 4,000
- Huntington’s: 1 in 10,000
- Phenylketonuria (PKU): 1 in 15,000 births

While devastating, most of the population are not directly affected by these diseases
Common Complex Diseases

- Diabetes affects 7.8% of the US population
- Alzheimer’s affects 5.3 million Americans
- Heart disease and cancer are the leading causes of death in the US

Multiple environmental and genetic factors increase the risk for complex disease
Diabetes is Very Common

2005
Percent of adults ≥ 20 years old with diabetes

- 0 - 6.5
- 6.6 - 8.0
- 8.1 - 9.4
- 9.5 - 11.1
- 11.2 - 15.0
Risk

- **Risk**
  
  Chance that some event will happen

- **Risk factor**
  
  Any factor that *increases* the chance the event occurs

- For many diseases there are a number of proven *environmental* risk factors
  
  e.g., 80-90% of lung cancer deaths are due to smoking
Genetic Variants as Risk Factors
Genetic Variants as Risk Factors

- Lifetime risk of breast cancer in general population is 13.2%
• Lifetime risk of breast cancer in general population is 13.2%

• In women with altered BRCA1 or BRCA2 genes 36-85% will develop breast cancer
The Complexity of Complex Disease

Environment

Genetics
The Complexity of Complex Disease

- Environment
- Genetics
- Age
- Gender
- Height/weight
- Activity level
- Other
The Complexity of Complex Disease

Environment
- Age
- Gender
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Genetics
- SNP 1
- SNP 2
- SNP 3
- SNP 4
- SNP 5
- Combined effects of other SNPs
Finding Genetic Risk Factors

Locate sites in the genome that influence disease susceptibility
Finding Genetic Risk Factors

Locate sites in the genome that influence disease susceptibility

Case-control study
Do patients share any characteristics that differ from the controls?
Querying Genomes

• Still too expensive to sequence the genome of all the 1,000s of patients and controls

• Instead specifically genotype ~1 million common SNPs

Spot intensity gives a readout of SNP genotype
Are any sites associated with disease state?
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## Type 1 Diabetes Associations

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>SNP</th>
<th>Risk Variant</th>
<th>Frequency</th>
<th>Controls</th>
<th>Cases</th>
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<tr>
<td>1p13</td>
<td>rs6679677</td>
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</tr>
</tbody>
</table>

All risk variants have higher frequency in affected individuals.

Location of the 5 SNPs implicated in a genomewide study of T1D.
Genes for Addictive Behavior
Genes for Addictive Behavior

SNP in nicotinic acetylcholine receptor gene

SNP associated with number of cigarettes smoked per day
Genes for Addictive Behavior

SNP in nicotinic acetylcholine receptor gene

SNP associated with number of cigarettes smoked per day

...and also linked to risk for lung cancer!
Success Stories

All from single issue of Nature Genetics

- Genome-wide association study identifies eight loci associated with blood pressure
- Multiple loci associated with indices of renal function and chronic kidney disease
- Loci at chromosomes 13, 19 and 20 influence age at natural menopause
- Narcolepsy is strongly associated with the T-cell receptor alpha locus
- Genome-wide association study of blood pressure and hypertension
- Genome-wide and fine-resolution association analysis of malaria in West Africa
- Common variations in BARD1 influence susceptibility to high-risk neuroblastoma
Can Find Large Effect Risk Genes

- *CCR5 Δ32* variant - strongly protective against HIV
  
  ~1% of individuals of European ancestry

- Individuals with the risk allele at the complement factor H gene have 8-fold higher chance of macular degeneration
Modest Effects

• Identified risk variants typically have modest effects
  
  Each increases risk by ~1%

• And collectively explain only a fraction of the genetic risk to disease
  
  e.g., the 18 SNPs associated with T1D explain just 6% of genetic risk
Predicting Disease From Genetic Data?

- Genetic tests for these subtle risk variants not currently routine in health screenings
  - Genetic testing is costly
  - Few risk variants known for most diseases
  - Risk associated with each variant is tiny