The Impact of Genomics on Drug Development, Clinical Research, and Medical Practice
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NIH Introduction to the Principles and Practice of Clinical Research
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Outline of Talk

Definitions
The Human Genome Project and its successors
Genome-wide association studies
Pharmacogenomics and personalized medicine
Drug development based on the genome
When can we expect the impact from the HGP to be realized?

Improved understanding of biology, diseases, and evolution: 0-3 years
New diagnostic tests for common diseases: 2-5 years
New therapeutics bases on genomic knowledge: 4-10 years
Geneic Disease

Single gene sequence variant *causes* disease
- Modifier genes and environment lesser contributors
  - e.g., Huntington’s disease, cystic fibrosis
6000 rare genetic diseases, but each is individually uncommon (<200,000 U.S. prevalence)
Most people not directly affected
Therefore genetics has traditionally played a “niche” role in health care and clinical research
Genomic Disease

Variants in multiple genes changes *predisposition to disease* (∆ risk 5-50%)
a.k.a., 'polygenic', 'common', 'complex'
Environmental contributions generally larger
e.g., hypertension, obesity, Alzheimer’s disease
   ApoE (Alzheimer’s disease)
   BRCA1 & 2 (breast & ovarian cancer)
   PPARγ (Type 2 diabetes)

Virtually all diseases have heritable component
Thus, most people directly affected
Thus, genetics is playing an increasingly large role in health care and clinical research
Stages of Deciphering the Genome

Pictures showing the stages of deciphering the genome.
Article on the International HapMap Project
Haplotypes and Tag SNPs

Graph showing Haplotypes and tag SNPs

**Genome-Wide Association Studies (GWAS)**

- Method for interrogating all 10 million variable points across the human genome
- Variation inherited in groups, or blocks, so not all 10 million points have to be tested
- Blocks are shorter (so need to test more points) the less closely people are related
- Technology now allows studies in unrelated persons, assuming ~10,000 base pair lengths in common (300,000 – 500,000 markers)
SNP-trait associations detected in GWA studies

genetic chart
Screenshot of the National Human Genome Research Institute website
Screenshot of the National Human Genome Research Institute website
Article: How to Interpret a Genome-wide Association Study
Genes, Environment and Health Initiative (GEI)

- NIH-wide initiative of the Secretary, HHS
- Aims to accelerate understanding of genetic and environmental contributions to health and disease
- Two components:
  - Genetic analyses of case-control studies of common disease ($26M per year for four years)
  - Development of innovative technologies to measure environmental exposures, diet, and physical activity ($14M per year for four years)
Screenshot: Genes, Environment and Health
Screenshot: NCBI website
Screenshot: NCBI website
Screenshot:  http://www.genetests.org
Screenshot:  http://www.pharmgkb.org
Pharmacogenomics

Use of genetic differences among individual patients to
  - Identify new disease genes/targets of intervention
  - Improve specificity of diagnosis
  - Improve likelihood of response to a drug
  - Customize drug dose
  - Decrease likelihood of adverse reaction to a drug

SNPs most useful type of genetic difference
  - Frequency ~1/300 base pairs (10M total)
  - Easily assayed
  - With HapMap, all common SNPs among individuals can be assessed with much less effort/cost than previously
Pharmacogenomics extends established concepts of “Personalized Medicine”

Clinical history
Physical examination
Blood examination
  - Chemistry
  - Hematology
Body fluids
  - Urine
  - CSF
Organism culture and sensitivity to antibiotics
Protein examination
  - Albuminuria in DM
mRNA examination
  - Microarray differentiation of histologically similar lymphomas
  - Oncotype DX in breast cancer
DNA examination
  - Somatic: Her2/neu amplification in breast cancer
  - Germline: Mutation testing for monogenic disorders (e.g., HD, CF)
SNPs in drug targets can affect drug response

Chart showing Gene polymorphism and Drug Response Affected
Customizing medication dosage, avoiding dose-related toxicity

CYP2C19 SNP genotype produces 10-fold variation in Prilosec blood levels
Chart showing hours after single dose application
Customizing medication dosage, avoiding dose-related toxicity

Screen shot of product detail.
Personalizing diagnosis and treatment

Screenshot: Herceptin brochure
Print layout: breast cancer drug treatment
Companies and individuals are often ahead of medicine in their use of genetic association data

Screenshots: Drug company advertisements
Website: Health & DNA
Drug Reaction Testing
The Genetic Information Nondiscrimination Act of 2008 (GINA)

- A federal law that prohibits health insurers and employers from discriminating based on an individual’s genetic information
- Intended to allow Americans to take advantage of the benefits of genetic testing without fear of losing their health insurance or their jobs
GINA prohibits health insurers from...

- Requesting or requiring genetic information from an individual or their family members
- Using genetic information for decisions regarding coverage, rates, or preexisting conditions
GINA prohibits employers from…

• Using genetic information in decisions regarding hiring, firing, promotion or any other terms of employment (e.g., benefits)

• Limits the permitted scope of post-offer, pre-employment physical examinations and employer wellness programs

• Retaliating against employees who file a complaint under GINA
What GINA will not do

- Affect underwriting regarding manifest disease – someone who is already sick is not protected by GINA

- Restrict discriminatory use of genetic information in regard to life, long-term care, or disability insurance

- Extend to members of the military
The best of times, the worst of times

How to translate the genome into biological insights and therapeutics?
Developing Drugs from the Genome

Numbers
- Human genes ~20,000
- Human proteins (targets) > 250,000
- Current drug targets: <500
  >95% remain

Gene identification only start to determining function and any therapeutic potential

“Validation”
- Definition of sequence function, role in disease
- Demonstration of manipulability of gene product
- Transforms gene product into drug target
The “Non-Druggable” Genome Problem

Pie Chart #1: Drug Target Classes
Pie Chart #2: Human Genome
The Rare and Neglected Diseases Problem

• 7,000 diseases affect humankind
• Only a very small fraction are common enough to support commercial development
• Two types of neglected diseases
  – Low prevalence
    • a.k.a., “rare”, “orphan”
    • 6000 different diseases
    • Cumulative prevalence in U.S. = 25 million
    • Most are single-gene diseases
    • e.g., ALS, cystic fibrosis, rare cancers.....
  – High prevalence in developing world
    • Population cannot pay for medicine
    • Most are infectious diseases
    • e.g., schistosomiasis, leishmaniasis, trypanosomiasis.....
Creating a Human Genome Translation Toolbox

Different pictures that show the translation of human genome.
Screenshot:
NIH Roadmap
Genome Technology
Molecular Libraries and Imaging
Chart: Steps and NIH involvement in current drug development
Screenshot:

U.S. Food and Drug Administration
FDA’s Critical Path Initiative
Genomics is changing how drugs are developed in the clinic

Genetically defined subpopulations for clinical trials
  greater power with reduced $n$

Smaller patient populations eligible for treatment upon drug approval
  Better efficacy data improves chance of formulary acceptance
  Financial success of drugs for genetically defined populations suggests more “targeted” drugs
  will be entering trials
    Herceptin
    Gleevec
    Avastin
    Cerezyme

ALL diseases may eventually be “rare”!
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