

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 based on genomic knowledge: 4-10 years

Genetic 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* (Δ 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)

PPAR γ (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

Manolio et al., J. Clin. Invest. 118:1590, 2008

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

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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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