Implications of the Human Genome Project for Medical Research

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The Human Genome will be completed in April 2003

- All clonable euchromatin (>95% of the total genome) with error rate < 1/10,000 bp
- Sequencing will cease as of this time and all “draft” sequence will have been converted to “finished” sequence
- Sequencers will move on to finish mouse, rat, honeybee, chicken, and chimpanzee
- Next organisms to have their genomes sequenced will be cow, dog, sea urchin, and several fungi
Wasn’t the human genome completed before?

June 26, 2000: First Draft

April 2003: Full finished sequence

February 15, 2001: Working Draft
April 2003

50 Years of DNA: From Double Helix to Health
Big Events in April 2003

- 50th Anniversary of discovery of DNA structure by Watson and Crick
- Completion of the sequence of all the human chromosomes
- Announcement of bold new research plan for genomics
Genome Celebration Public Events

April 14-15
From Double Helix to Human Sequence - and Beyond
Scientific Symposium at The National Institutes of Health

April 15
Bringing the Genome to You
Public Symposium at The National Museum of Natural History

April 25
National DNA Day
A teachable moment for educators & students across the nation

www.genome.gov/About/April2003
Public Symposium – April 15

- Opening Remarks
  - James Watson
  - Francis Crick
    (recorded)

- The Human Genome Project
  - Eric Lander

- HGP to Medicine
  - Wylie Burke

- Media’s View of the Genome
  - Robert Krulwich
Public Symposium – April 15

- The Human Genome Project to Society
  Moderator: Robert Krulwich
  - Genetic Policy: Members of Congress
  - Ethics: Tom Murray
  - A Consumer’s View: Kay Jamison
  - Health Disparities: Harold Freeman
  - Disabilities: Paul Miller
  - Historical issues: Vanessa Gamble

- The Human Genome Project and the Future
  - Francis Collins
What now for the Human Genome?

- “A Vision for Genome Research” to be published April 2003
- Genome to Biology
  - structural and functional components, networks and pathways
  - heritable variation
- Genome to Health
  - genetic contributions to disease and drug response
  - genome-based diagnostic approaches
  - new therapeutic approaches to disease
- Genome to Society
  - how genetic risk information is conveyed and used in clinical settings
  - genetic discrimination, privacy – HIPAA
  - ethical boundaries
Genetics vs Genomics

- Critical and often misunderstood difference between single gene and multiple gene diseases
  - Single gene: mutation *causes* disease (100%)
    - e.g., Huntington’s disease, cystic fibrosis, thalassemias
    - Are of great importance to individuals and families with them
    - But, even when added together, are relatively rare
    - Most people not directly affected
    - Thus, genetics played small role in health care (and in society)
Genetics vs Genomics

- Multiple genes: mutation *predisposes to* disease (5-50%)
  - a.k.a., ‘polygenic’, ‘common’, ‘complex’, ‘genomic’ diseases
  - e.g., heart disease, hypertension, diabetes, obesity, cancer, Alzheimer’s disease, schizophrenia
    - ApoE (Alzheimer’s disease)
    - BRCA1 & 2 (breast & ovarian Ca)
    - CCR5 (HIV/AIDS resistance)

- Most common diseases have heritable (genetic) component
- Other part of disease susceptibility is environmental (e.g., diet, exercise, smoking)
- Most people directly affected
- Thus, genomics will play a large role in health care (and in society)
The Human Genome

- 3 billion nucleotide base pairs
  - Adenine (A)
  - Cytosine (C)
  - Guanine (G)
  - Thymine (T)
  - on a sugar-phosphate backbone

- 99.9% identical in all humans
  - 1/1000 bp variant between individuals (3 million total)
  - 1/300 bp variant among population (10 million total)

- A single variant can cause disease
Great (Genomic) Expectations

- Genomics holds great promise for improving human health, but short term expectations are outsized.
- “Genomics (will) lead to short-term increases in R+D spending and little increase in productivity…the industry could go bankrupt trying to innovate”
- Issue is mismatch between data and information.
Where and when can impact on medicine from the HGP be expected to begin?

- Improved understanding of biology, disease, and evolution: 0-3 years
- New diagnostic tests for common diseases: 2-5 years
- New therapeutics based on genomic knowledge: 4-10 years
Development of a novel drug

The Human Genome Project
30,000 genes/100,000 proteins

Years

Development

Phase I
Phase II
Phase III
Phase IV-V

Product Surveillance
Clinical Tests (Human)
Preclinical Tests (Animal)

Research

500,000 Compounds

500 Compounds

1

2

2-5

5 cmpds

0

15

Introduction
Registration

Target validation
Assay
HTS
MedChem
DNA Sequences vs. Drug Targets

- Total number of human genes ~30,000
- Total number of human proteins ~100,000 (?)
- Current drug targets: ~500
- Gene identification is only the start to determining function and any therapeutic potential
- Total number of targets estimated at 10% of total, or ~3,000 ⇒ 90% of potential remains
- “Validation”
  - Definition of sequence function, role in disease
  - Demonstration of manipulability of gene product
  - Transforms gene product into drug target
Turning a Gene into a Drug Target

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<th>DRUG TARGET</th>
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<td>Secreted Proteins</td>
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Druggable Gene Products: GPCRs, Ion Channels, Proteases, Nuclear Receptors, Kinases/Phosphatases, Secreted Proteins
Genomic Medicine

- Molecular, rather than historical/clinical, taxonomy of disease
- Individual prospective risk assessment will allow:
  - Individualized screening, e.g., mammography schedule, colonoscopy, prostate specific antigen
  - Presymptomatic medical therapies, e.g., antihypertensive agents before hypertension develops, anti-colon cancer agents before cancer occurs
Drug development in the genome era

- "Parts list" of human development and function will allow
  - More intelligent choosing of targets for therapeutic development
  - Choosing among all possibilities rather than taking what’s available
  - Comprehensive definition of gene interactions and pathways, critical to understanding common polygenic diseases

- Magnitude of task of functioning the genome will require
  - Shift in tasks undertaken by public vs private sectors, with more target evaluation being done in public sector
  - Better community-wide understanding of the value of early research findings
  - Resolution of IP issues surrounding gene and other research tool patents
Applications of genetic variation to drug development

- **Target Identification/Prioritization**
  - Association of SNPs in potential targets with disease
    - β2 adrenergic receptor – Asthma, Heart failure
    - Angiotensin II receptor - Hypertension
    - PPARγ - Diabetes
    - ACE - Peripheral/Carotid artery disease, LVH

- **Target Biology**
  - characterization of variability in novel targets
    - predict variability in clinical response/safety

- **Screening**
  - determination of correct/most prevalent allele for HTS
Genetic variation influencing drug metabolism

*Improved DMPK studies, dose finding*

- CYP2C19 SNPs affect Prilosec levels: AUCs vary 10-fold with genotype
- CYP2C9 SNPs predict warfarin and phenytoin levels
Applications of genetic variation to clinical research

- Drug Metabolism/Clinical Pharmacology
- Clinical trials
  - Improved uniformity of subjects by characterizing genetic markers → increased power
  - Post-hoc analysis of non-responders, subjects with adverse events
  - Fragmenting of markets is holding back utilization
  - Examples now in medical
    - Herceptin for breast cancer (somatic mutation)
    - Ziagen for HIV/AIDS (viral mutation)
    - 6-Mercaptopurine for pediatric leukemia (TPMT test)
Genetic variation associated with drug response

Focus drug treatment, avoid AEs

Gene polymorphism
- LTC₄ synthase
- β2 adrenergic receptor
- ACE
- Cholesterol ester transfer protein
- Potassium channels

Drug Response Affected
- montelukast, zafirlukast
- albuterol
- ACE inhibitors
- pravastatin
- AF, drug-induced QT prolongation
Applications of genetic variation to clinical practice

- Improved diagnosis, “splitting” of diseases
- Customization of medication dose, therapy
  - Bring into line with other consumer products
  - Decrease AE rates/costs, increase compliance (?)
- Being promoted with little regulation

Body Benefits - nutrition

Sciona’s 'Body Benefits - nutrition' is a personalised report describing your lifestyle results and genetic results, together with further informative sections on food groups, vitamins & minerals and an easy to understand guide to the science behind the service. The entire report is presented in a compact, high quality A5 binder and cover.

Your DNA sample is obtained in an easy and completely painless way that can be performed in the home. Simply rub a brush swab on the inside of your cheek, complete the lifestyle questionnaire and return them for assessment.