Genomics in Medicine

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Bioscience in the 21st Century
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Genomics Recap:

Human Genome Project (HGP) at TEN Transcriptomics

Insights from other Genomics Projects

Impact of the HGP

Focus on Genomics and Medicine

Genes and Disease
Mapping the Cancer Genome
Molecular Basis of Disease
SNPs and Diagnostics
Pharmacogenomics
Targeted Drug Therapy, Imantinib
What have we learned about ourselves from the genomes of other model organisms?
Just how genetically unique are humans?

Large numbers of genes are in common with other organisms:

- ~50% of our genes are also found in fruit flies
- ~40% of our genes are also found in roundworms
- ~30% of our genes are also found in yeast
- ~80% of our genes are shared with the mouse and ~96% of our genes are shared with chimpanzees
- ~100 of our genes are even shared with bacteria
What else have we learned from the analysis of model organism genomes?

Many human genes determining body plan, organ development, and aging are nearly identical to genes in the fruit fly.

~61% of genes mutated in nearly 300 human disease conditions are found in the fruit fly.

Genes include those involved in prostate cancer, pancreatic cancer, cardiac disease, cystic fibrosis, leukemia, and many other human genetic disorders.
http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml
NCBI Home ➤ Genomic Biology ➤ Human

Web Resources

BLAST. Compare your sequence to the genome or its gene products.

Cytogenetics. A cytogenetic resource of FISH-mapped, sequence-tagged clones.

dbSNP. Database of SNPs and other genetic variations.

e-PCR. Check your sequence for STTs and view in genomic context.

GEO. Gene Expression Omnibus, a public repository for expression data.


Homology Map. Blocks of conserved synteny between mouse and human.

LocusLink. Focal point for genes and associated information.

Building an information infrastructure

A challenge facing researchers today is the ability to piece together and analyze the multitudes of data currently being generated through the Human Genome Project. NCBI's Web site serves an an integrated, one-stop, genomic information infrastructure for biomedical researchers from around the world so that they may use this data in their research efforts.

More...

Working Draft Analysis Published

- NLM Press Release
- NHGRI Press Release
- Interactive Tour of the Genome
- NCEI Genome Analysis Pipeline
- Nature (2/15/01) Human Genome Issue
- Science (2/16/01) Human Genome Issue

Genes & Disease

G&D. Selected gene stories for students and the public.

RB1. Complex of

Impact of the Human Genome Project: Opportunities to

• understand the molecular basis of disease

• understand biochemical pathways and metabolism

• design novel molecular diagnostics

• develop novel and personalized therapeutics (e.g., drug target discovery, gene therapy)
**Anemia, Sickle Cell**

Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 72,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood.

SCA is an autosomal recessive disease caused by a point mutation in the hemoglobin beta gene (HBB) found on chromosome 11p15.4. Carrier frequency of HBB varies significantly around the world, with high rates associated with zones of high malaria incidence, since carriers are somewhat protected against malaria. About 8% of the African American population are carriers. A mutation in HBB results in the production of a structurally abnormal hemoglobin (Hb), called HbS. Hb is an oxygen carrying protein that gives red blood cells (RBC) their characteristic color. Under certain conditions, like low oxygen levels or high hemoglobin concentrations, in individuals who are homozygous for HbS, the abnormal HbS clusters together, distorting the RBCs into sickled shapes. These deformed and rigid RBCs become trapped within small blood vessels and block them, producing pain and eventually damaging organs.

Though, as yet, there is no cure for SCA, a combination of fluids, painkillers, antibiotics and transfusions are used to treat symptoms and complications. Hydroxyurea, an antitumor drug, has been shown to be effective in preventing painful crises. Hydroxyurea induces the formation of fetal Hb (HbF)—a Hb normally found in the fetus or newborn—which, when present in individuals with SCA, prevents sickling. A mouse model of SCA has been developed and is being used to evaluate the effectiveness of potential new therapies for SCA.
Mapping Human Disease Genes

• Approximately 12 disease genes mapped by 1989

• Thousands of human disease genes have been identified and mapped as a result of the Human Genome Project (completed in 2003)
Disease genes on chromosomes 13 and 21

From *Understanding the Human Genome Project* by M. Palladino
Mapping the Cancer Genome

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

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Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient’s skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

Nature 456 (November 6, 2008), 66-72.
Major findings of AML study

- Comparison of genome from normal skin compared to tumor cell from same patient

- 10 protein-coding gene differences: 2 already identified genetic alterations and 8 previously unknown mutations

- Alterations also noted in non-coding DNA

- Differences noted in genes from other AML patients suggests complex and diverse pathways to cancer onset and progression

- Prospect for personalized treatment strategies over time
**Molecular basis of disease**

**Chronic myeloid leukemia:**
Specific chromosomal abnormality called the Philadelphia (Ph) chromosome contained within affected cells.

Ph chromosome results from translocation (exchange of genetic material) between chromosomes 9 and 22.

This exchange brings together two genes: the *BCR* (breakpoint cluster region) gene on chromosome 22 and the proto-oncogene *ABL* (Ableson leukemia virus) on chromosome 9 to produce a hybrid gene called *BCR-ABL*.

Hybrid gene encodes a fusion protein with tyrosine kinase activity, which activates signal transduction pathways, leading to uncontrolled cell growth.

Developing Novel Diagnostics and Predicting Disease Predisposition
Single Nucleotide Polymorphisms (SNPs)

GATCTGTATGCCTACTAGAAGATCGAT
GATCTGTATGCCTACGAGAAGATCGAT

Genomes from different individuals may differ from each other by 0.1%.

There are 3 million polymorphic sites in the human genome.

SNPs can distinguish individuals from one another.

SNPs can be used to diagnose disease.
SNPs can be used to diagnose disease

Single Nucleotide Polymorphisms (SNPs)

• Most SNPs have no known effect

• Rarely is a single SNP is responsible for the disease state

• Some SNPs predispose an individual to disease

• Some SNPs can be used to determine drug efficacy

• Some SNPs can be used to determine adverse drug effects (want to choose the right medicine for the right patient)
PHARMACOGENOMICS

Welcome to PharmGKB!

PharmGKB is an integrated resource about how variation in human genes leads to variation in our response to drugs. Genomic data, molecular and cellular phenotype data, and clinical phenotype data are accepted from the scientific community at large.

Categories of Pharmacogenetic Knowledge

- Genotype
  - molecular & cellular functional assays
  - pharmacokinetics
  - pharmacodynamics & drug response
  - clinical outcome

Search the PharmGKB Knowledge Base: [Search]

Genomics and the Law

H.R.5440 - Genomics and Personalized Medicine Act of 2010

To secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments, and for other purposes.

Originally introduced in 2006 by then Illinois Senator Barack Obama. Reintroduced for 4th time this year.
Designing Novel Therapeutics

Go to ascb.org

American Society for Cell Biology
iBioSeminar by Dr. Brian Druker

"Imatinib (Gleevec) as a Paradigm of Targeted Cancer Therapies"
Much about human health and the genetic basis of diseases will be learned from functional studies in model organisms.

The Human Genome Project will continue to have an impact on technologies and strategies to improve human health.