



# Pharmacogenomics

Individualized Care:  
Efforts and Effects

By:

Minal Mehta

Biochem118

Spring, 2001



# Current Scene

- ☞ People expect individual treatment in all spheres of life
- ☞ The “one-size-fits-all” approach to provision of drugs is clumsy
- ☞ Inter-patient variability in response to drugs is the rule and not the exception

# Facts and Figures

- Only a third of patients taking prescriptive medicines actually derive their intended benefit
- Adverse drug reaction (ADR) is one of the top six leading causes of death in the U.S.
- Serious ADRs – 6.7% (2,216,000 people in 1994)
- Fatal ADRs – 0.32% (106,000 people in 1994)

# What Next?

- Inter-individual variation in the efficacy and toxicity of drugs is largely determined by genetic factors
- Understanding the molecular basis of drug action and genetic determinants of drug response should enlighten our use of many medications
- The ultimate goal is to give the right drug at the right dose to the right patient at the right time





# Pharmacogenomics

- Field of new drug development based on rapidly increasing knowledge of all genes in the human genome
- Study of the impact of genetic variation in the efficacy and toxicity of drugs
- Represents the genetic basis of a drug's absorption, distribution, metabolism, excretion and receptor-target affinity
- Delivers 3 main genomics-based products: therapeutics, diagnostics and information




# Growth of Pharmacogenomics

- Systematic discovery of genetic variance can provide important, achievable opportunities for developing new therapeutic and diagnostic products from genomics
  - Emergence of appropriate methods for discovery and analysis of genetic variation in human populations
  - The emergence of managed care as an economic incentive for the use of pharmacogenomics
- 



We need to analyze the effort in pharmacogenomics from several perspectives: ethical, legal, practical, financial and commercial



# Uses of Pharmacogenomics

- Analgesic effect from codeine (and other effects) that relate to the six major families of cytochrome P450 enzymes
- Relation of effect of tacrine on patients with Alzheimer's based on APO E4
- Effect of a polymorphism in the B-adrenergic receptor gene on asthma



## ...and More

- Trastuzumab in the treatment of breast cancer
- Polymorphisms in dopamine receptors and migraine symptoms

# Methods

- SNPs. Single SNPs and positioning and interaction of several SNPs in haplotypes
- Pharmacogenomic candidate gene validation relies on:
  - Identification of candidate pharmacogenomic target genes
  - Identification of all potential alleles for these
  - Genotyping of a clinically relevant population for the set of relevant alleles
  - Application of robust statistical methods to establish linkage between any allele and a selected response/nonresponse phenotype

# Tools

- Subtractive cloning
- Differential display
- EST sequencing
- cDNA Microarray Hybridization
- Serial Analysis of Gene Expression

# Management

- The Pharmacogenetics Research Network and Knowledge Base
- Has the capacity to collect genetic information, detect polymorphic variants, identify the functional consequences of variation, and correlate this information with drug responses
- The network consists of research groups that receive funding from NIH to contribute to the development of and add data to a database



# Knowledge Base (PharmGKB)

- Being developed by Russ B. Altman, Stanford University
- Interlink genomic, molecular, cellular and clinical information about gene systems important for modulating drug responses
- Flexibility, security and stability
- Absolute confidentiality

# Analysis

- Bioinformatics has been key in development of pharmacogenomics
- Software has been developed that captures the experimental data and compares results with existing genome databases, generates dendrograms for sequence homology, and recognizes patterns
- Spawned the field of *in-silico* biology, in which mining of computer databases for genomic information is performed without laboratory experimentation

# Challenges (Scientific)

- Identification of new disease-related genes -> new targets to pursue
- Improvement of technology

# Challenges (Non-scientific)

- Financial Viability
- Ethical Issues



# Financial Viability (for Pharmaceutical Firms)

- Opportunities for the development of customized drugs
- Reintroduction of older drugs which are effective in certain individuals
- However, reduced market from which to regain investment
- Difficult to predict how many NCEs might be approved on the basis of pharmacogenomic studies

# Ethical Considerations


- If drugs are tested against the common polymorphisms of the USA or Europe, should the results be applied to people who for reasons of their own refuse genetic testing?
- Would it be illegal or unethical to try it in patients who do not match the genetic profile of the trial participants who achieved benefit?
- Are genetics even likely to be the major determinant of treatment response given that environmental and social factors play such a large role on disease response?

# Ethical Considerations

- Will people with rare genetic profiles simply not be studied to cut down on costs?
- Genotyping in both clinical research trials and eventually, clinical practice will become routine. The genotype could be misused
- Risk-benefit analysis: to be justifiable ethically, clinical research must produce benefits and either prevent or minimize possible risks



# Ethical Considerations

- Should pharmaceutical companies conducting a clinical trial or marketing a particular drug be obliged to offer genotyping to patients given the doing so might lead to reductions in their potential markets?
  - Serious consequences if drugs are given to the wrong group of people
  - Less ethical controversy than other applications of genetics
- 



# The Future ...


- Optimistic view:

“In the future, before a doctor prescribes a medicine, the doctor will take some blood, have it analyzed at a nearby lab and identify which of, let’s say, 12 drugs are most likely to treat the patient effectively with minimum side effects,”


- Allan D. Roses, vice president and worldwide director of genetics research at Glaxo-Wellcome.

# The Future ... a More Realistic View

- Enormous promise, but will have the greatest initial benefit in developed countries, owing to expense, availability of resources and the focus of initial research
- Most likely, it will take 3 or 4 examples before the regulatory agencies feel comfortable issuing guidelines. In the meantime, companies will have to work closely with regulatory bodies to work out where genetic data is going to be useful.



- “At present drugs are picked out on the basis of whether they are not going to put people at risk”, says Jerry Colins of the FDA. “One day, we will be picking out drugs on the basis that they are going to treat people effectively.”



# Acknowledgements

- Professor Douglas Brutlag  
Department of Biochemistry
- Professor Teri Klein  
Project Director, PharmGKB



# References

- 1) Freeman TR. "Pharmacogenetics and pharmacogenomics: using genetic information to guide therapeutic decision making." J Am Pharm Assoc (Wash). 2001 May-Jun;41(3):475-6.
- 2) Peet NP, Bey P. "Pharmacogenomics: challenges and opportunities." Drug Discov Today. 2001 May 1;6(10):495-498.
- 3) McLeod HL, Evans WE. "Pharmacogenomics: unlocking the human genome for better drug therapy." Annu Rev Pharmacol Toxicol. 2001;41:101-21.
- 4) Rusnak JM, Kisabeth RM, Herbert DP, McNeil DM. "Pharmacogenomics: a clinician's primer on emerging technologies for improved patient care." Mayo Clin Proc. 2001 Mar;76(3):299-309.
- 5) "Pharmacogenomics." Nat Biotechnol. 2000 Oct;18 Suppl:IT40-2.
- 6) Becker C. "The DNA Rx. Advances in genetics give physicians ability to tailor drugs to patients' unique makeup." Mod Healthc. 2000 Aug 28;30(36):24-8, 30, 33.
- 7) Weinstein JN. "Pharmacogenomics--teaching old drugs new tricks." N Engl J Med. 2000 Nov 9;343(19):1408-9.

# References

- 8) Destenaves B, Thomas F. "New advances in pharmacogenomics." *Curr Opin Chem Biol.* 2000 Aug;4(4):440-4.
- 9) Issa AM. "Ethical considerations in clinical pharmacogenomics research." *Trends Pharmacol Sci.* 2000 Jul;21(7):247-9.
- 10) Carrico JM. "Human Genome Project and pharmacogenomics--implications for pharmacy." *J Am Pharm Assoc (Wash).* 2000 Jan-Feb;40(1):115-6.
- 11) Coats AJ. "Pharmacogenomics: hope or hype?" *Int J Cardiol.* 2000 Oct;76(1):1-3.
- 12) Evans WE, Relling MV. "Pharmacogenomics: translating functional genomics into rational therapeutics." *Science.* 1999 Oct 15;286(5439):487-91.
- 13) Ledley FD. "Can pharmacogenomics make a difference in drug development?" *Nat Biotechnol.* 1999 Aug;17(8):731.
- 14) Bailey DS, Bondar A, Furness LM. "Pharmacogenomics - it's not just pharmacogenetics." *Curr Opin Biotechnol.* 1998 Dec;9(6):595-601.
- 15) Persidis A. "Pharmacogenomics and diagnostics." *Nat Biotechnol.* 1998 Aug;16(8):791-2.

# References

16) Housman D, Ledley FD. "Why pharmacogenomics? Why now?" Nat Biotechnol. 1998 Jun;16(6):492-3.

17) Hodgson J, Marshall A. "Pharmacogenomics: will the regulators approve?" Nat Biotechnol. 1998 Mar;16(3):243-6.]

18) Park BK, Pirmohamed M. "Toxicogenetics in drug development." Toxicol Lett. 2001 Mar 31;120(1-3):281-91.

19) Jeanette J. McCarthy, Rolf Hilfiker. "The use of single-nucleotide polymorphism maps in pharmacogenomics". Nature Biotechnology 18, 505 - 508 (May 2000).

20) Andrew Marshall. "Laying the foundations for personalized medicines". Nature Biotechnology 16, 6 - 8 (October 1998).

21) Andrew Marshall. "Getting the right drug into the right patient." Nature Biotechnology 16, 9 - 12 (October 1998)

22) Bonnie E. Gould Rothberg. "Mapping a role for SNPs in drug development". Nature Biotechnology 19, 209 - 211 (March 2001).

23) <http://pharmGKB.org>





Thank-you!

