Pharmacogenomics

Individualized Care: Efforts and Effects

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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 takings 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 an 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

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References


References


References


23) http://pharmGKB.org
Thank-you!