Pharmacogenetics and individual variation of drug response - basic concepts
Outline

• Introduction and definitions
• Very Basic concepts
• **Pharmacogenomics**
  – The science of how genes affect the way people respond to drugs
  – How genes affect...
    ...the way our body processes drugs (pharmacokinetics)
    ...the interaction of drugs with receptors (pharmacodynamics)
    ...the treatment efficacy and adverse side effects

• **Pharmacogenetics**
  – A subset of ‘pharmacogenomics’
  – The study of how *inherited variation* affects drug response and metabolism
Pharmacogenetic versus Pharmacogenomic

- No universally accepted definitions of either
- Often used interchangeably
- *Pharmacogenetics* used for more than 40 years to denote the science about how heritability affects the response to drugs.
- *Pharmacogenetics* involves both pharmacokinetics and pharmacodynamics
- *Pharmacogenetics*: The study of the role of inheritance in the individual variation in drug response.
- *Pharmacogenetics*: The role of genetics in drug responses.
- *Pharmacogenetics*: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)
- “*Pharmacogenetics* is the study of how *genetic variations* affect the *disposition* of drugs, including their *metabolism and transport* and their *safety and efficacy*”
- **Pharma** = drug or medicine
- **Genomics** = the study of genes

**Pharmacogenomics** is a new science about how the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function over time affects drug response/metabolism etc.

- **The term pharmacogenomics was coined in connection with the human genome project**
- **Pharmacogenomics:** The science that allows us to predict a response to drugs based on an individual's genetic makeup.
- **Pharmacogenomics:** Uses genome-wide approaches to elucidate the inherited basis of differences between persons in the response to drugs
- **Pharmacogenomics:** Study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics - COMPLEX interactions)
- **Pharmacogenomics** - The effects of an individual’s genotype on the pharmacokinetics and pharmacodynamics of drug action.
- **Pharmacogenomics:** Study of variability in drug response determined by multiple genes within the genome.
Most use pharmacogenetics to depict the study of single genes and their effects on interindividual differences in (mainly) drug metabolising enzymes, and pharmacogenomics to depict the study of not just single genes but the functions and interactions of all genes in the genome in the overall variability of drugs response.
• The main goal of Pharmacogen(etics)omics is Personalized Medicine

• There is an emerging goal among ‘translational scientists’ to make medical practice more personalized

• Pharmacogenetics is an important step towards that goal
The Goals of Pharmacogen(etics)omics

• The Hope/goal of Pharmacogenomics is that individuals genetic makeup with allow selective use of medications such that
  – Drug efficacy is maximized, and
  – Drug Side effects and toxicity rare minimized
  – Scientists can predict patients who will respond to drug intervention
  – Such studies will aid in new drug development
The Goal of Personalized Medicine is

• The **Right** Dose of
• The **Right** Drug for
• The **Right** Indication for
• The **Right** Patient at
• The **Right** Time.
“therapy with the right drug at the right dose in the right patient”
Pharmacogenomics: advancing personalized medicine
The Opportunity: To Deliver on the Promise of Individualized Medicine

U.S. News and World Report, January 24, 2003
Why Personalized Medicine?

• Medicine is personal:
  – We are all different.
  – Some of our differences translate into how we react to drugs as individuals.
  – This is why personalized medicine is important to everyone.

• Important questions to be considered include.
• Why does someone need twice the standard dose to be effective?
• Why does this drug work for you but not me?
• Why do I have side-effects and you don’t?
• Why do some people get cancer and others don’t?
• Why is anecdotal information irrelevant to your own health and treatment?
Pharmacogenomics

Will allow:

• individualized medication use based on genetically determined variation in effects and side effects
• use of medications otherwise rejected because of side effects
• More accurate methods of determining appropriate dosage
The utility of pharmacogenetics:
- Determining appropriate dosing
- Avoiding unnecessary toxic treatments
- Ensuring maximal efficacy
- Reducing adverse side effects
- Developing or choosing novel treatments
- Can also explain variable response to illicit drugs
Your DNA Affects Your Response to Drugs

DNA Test

Safe, effective
Safe, not effective
Unsafe, not effective
Unsafe, effective
Due to individual variation in our DNA...

- 20-40% of patients benefit from an approved drug
- 70-80% of drug candidates fail in clinical trials
- Many approved drugs removed from the market due to adverse drug effects

• One hopes that the use of DNA sequence information to measure and predict the reaction of individuals to drugs, will lead to:
  - Personalized drugs
  - Faster clinical trials
  - Less drug side effects

**Pharmacogenetics**
Pharmacogenomics

Personalized medicine tailored to your genes
Using people’s genetic information for the right drug at the right dose at the right time!
This is the hope/hype

"Here's my sequence..."

New Yorker, 2000
Today We have One-size-fits-all drugs

• Current drug development system develops drugs for the average patient
• No simple way to determine who will respond well and who will respond poorly
• Because genetic variation leads to phenotypic differences and differences in how we all react to drugs.
• One size does NOT fit all!
• What’s the solution?
  Pharmacogenomics (PGx)
  Personalized Medicine
This is the hope/hype

TODAY versus TOMORROW

Respond to Drugs: 30-60%

Does Not Respond To Drugs: Everyone Else

Respond To Drugs: 100%

Does Not Respond To Drugs: 0%

(made according to specific genes)
April, 2050

You wake up feeling terrible, and you know it's time to see a doctor. In the office, the physician looks you over, listens to your symptoms, and decides to prescribe you a drug.

But first, the doctor takes a look at your DNA.

**TODAY vs. FUTURE**

*Today = Drugs are One-Size-Fits-All*
*Future = Drugs Specific for You!*

More effective & minimizes side effects
Pharmacogenetics

• “Study of interindividual variation in DNA sequence related to drug absorption and disposition (Pharmacokinetics) and/or drug action (Pharmacodynamics) including polymorphic variation in genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins.”

• “The study of how people respond differently to medicines due to their genetic inheritance is called pharmacogenetics.”

• “Correlating heritable genetic variation to drug response”

• An ultimate goal of pharmacogenetics is to understand how someone's genetic makeup determines, how well a medicine works in his or her body, as well as what side effects are likely to occur.
  
  • **“Right medicine for the right patient”**
WHY DO DRUGS ACT DIFFERENTLY IN DIFFERENT PEOPLE?

How do we know if a patient will respond (or have an adverse response) to a drug?

(we don’t)

Because drug responses are genetic!

Variation in drug response is hereditary!
Drug responses are genetic!

• Drug metabolism/response can be monogenic
  – alteration of the key metabolizing enzyme can alter drug’s effect

• Drug responses are polymorphic
  – Drugs trigger downstream events that can vary among patients
Variation in drug response is hereditary

- Variations in absorption rates
- Variations in drug metabolism
- Variations in drug inactivation/elimination
- Variation in target receptors
- We can see then that
- Pharmacogenomics is the effects of an individual’s genotype on the pharmacokinetics and pharmacodynamics of drug action.