Pharmacogenomics

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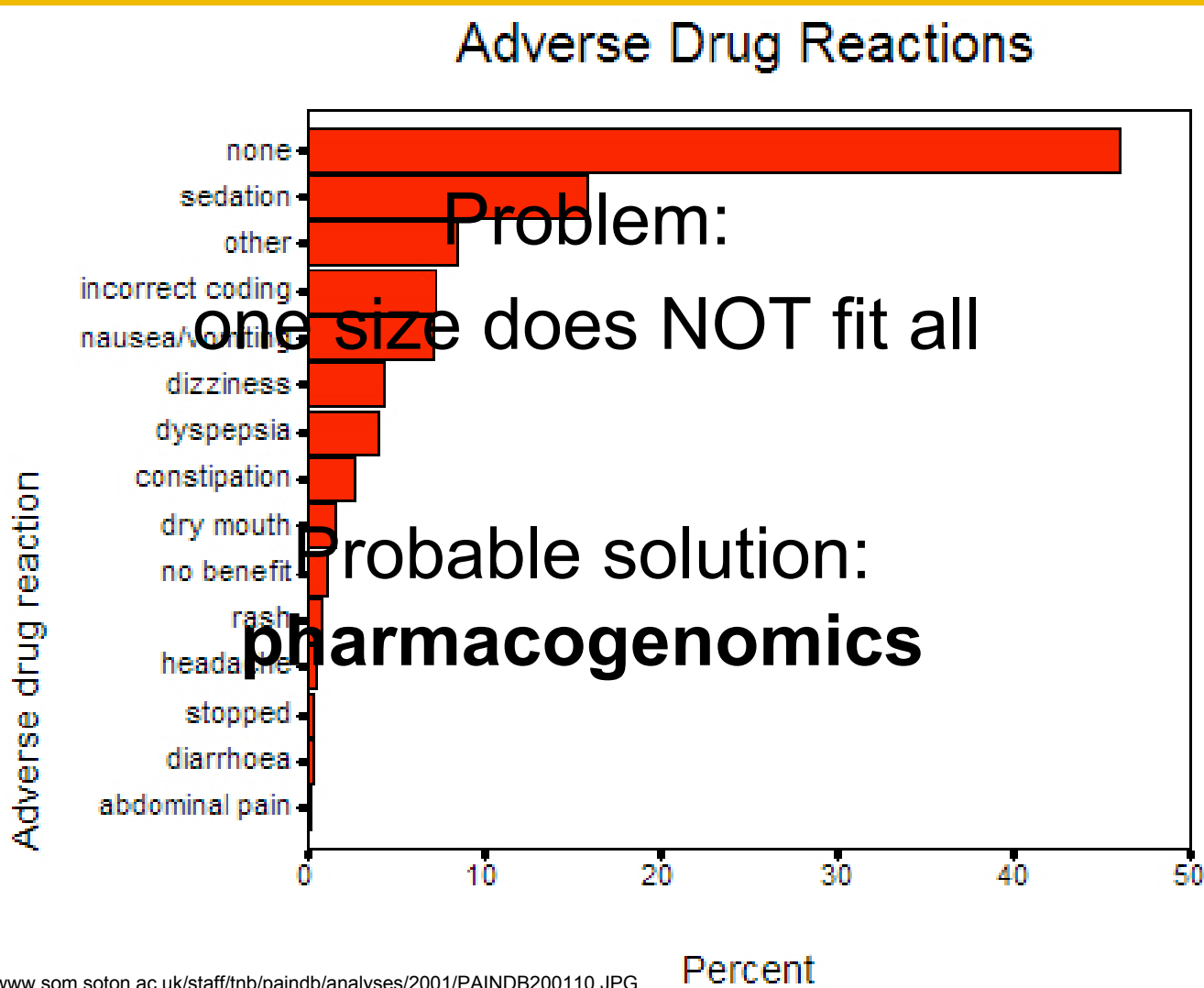
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Biochem118

Adverse Drug Reaction

- Severe negative reaction to a prescribed drug
- 1994: more than 2.2 million serious cases and over 100,000 deaths by ADR
  - Made ADRs one of the leading causes of hospitalization and death in the U.S.
- Can't determine how each individual will respond to a medication
  - Drugs use the "one size fits all" system
  - Suits only the "average" patient

Adverse Drug Reaction

Adverse Drug Reactions

Problem:
one size does NOT fit all

Probable solution:
pharmacogenomics

http://www.som.soton.ac.uk/staff/tnb/paindb/analyses/2001/PAINDB200110.JPG

Background

- Responses to drugs (positive and negative) are complex traits influenced by many different genes
  - Hard to develop genetic tests to predict drug response without knowing all the genes
  - People's gene show small variations in their nucleotide content → made genetic testing for predicting drug response possible
- Most of human genome are identical, varies in single nucleotide polymorphisms (SNPs or "snips"): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered
  - Occurs once every 1,000 base pairs along the 3-billion-base human genome

Definitions

- **Pharmacogenomics**: general study of all the genes that determine drug behavior

- **Pharmacogenetics**: study of inherited differences in drug metabolism & response
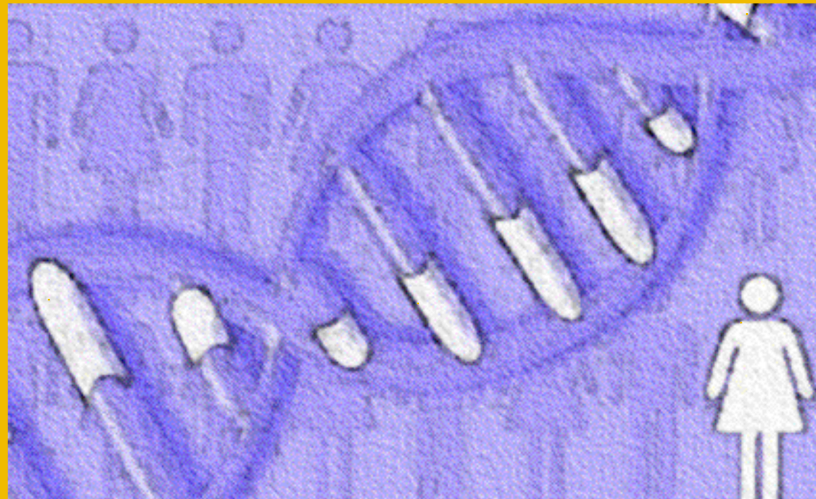
What is Pharmacogenomics?

- Combination of human genome knowledge (genes, proteins, SNPs) and pharmaceutical sciences (biochemistry, medicines)

- Examines inherited variations in genes that dictate drug response

- Explores ways these variations can be used to predict whether a patient will have a good/bad/no response to a drug

- Ultimately, researchers hope to be able to customize drug therapies for specific patient populations or even individuals

Current Uses

- Cyto... ...enzymes
  - R... ...0 different
    cla...
  - D... ...lize drugs
  - In... ...ug overdose
  - Cl... ...for variations
    in... ...onitor
    pa...
  - Pl... ...l compounds
    → ... ...y variant
    fo...

http://quanta.synchem.kyoto-u.ac.jp/bioquant/images/p450.jpg

Current Uses

- **TPMT (thiopurine methyltransferase)**
  - Important in chemotherapy treatment of a common childhood leukemia → breaks down a class of therapeutic compounds called thiopurines
  - Some Caucasians have genetic variances that prevent them from producing an active form of thiopurines
    - Since the inactive form of TMPT cannot break down the drug, thiopurines elevate to toxic levels in the patient
  - Doctors use this genetic test to screen for this deficiency → TMPT activity is monitored to determine appropriate thiopurine dosage levels

Current Uses

- Cardiovascular pharmacogenetics
  - Goals:
    - to guide cardiovascular drug development and selection
    - to optimize therapeutic benefit
    - to minimize the potential for toxicity
  - Researchers are exploring differences in the efficacy and efficiency of these cardiovascular drugs (regardless of drug concentration) based on common genetic variations (polymorphisms) → will become prominent in the future
    - e.g. antiarrhythmic, reninangiotensin, beta-blocker, lipid-lowering, and antithrombotic classes

Benefits

- **More effective medicines**
  - Can create drugs based on proteins, enzymes, and RNA molecules
  - Facilitated drug discovery
  - Therapy targeted to specific diseases
    - Decrease damage to healthy cells
- **"Right" drugs the first time:**
  - No more trial-and-error; process:
    - analyze patient's genetic profile
    - prescribe best available drug therapy
  - Speedy recovery; increase in safety

Benefits

- **More appropriate drug dosages**
  - Current bases for appropriating dosage:
    - Weight and age
  - With pharmacogenetics:
    - Based on genetics
  - Maximizes therapy value; decreases over dosage
- **Advanced screening for diseases**
  - Decide on lifestyle and adapt to environmental changes early on → to avoid and/or lessen the seriousness of genetic diseases
  - Allows for careful monitoring; treatments at right age ("optimal" age)

Benefits

- Better vaccines
  - Vaccines made of DNA/RNA → existing vaccines in our bodies without risks
  - Activation of the immune system without causing infections
  - Inexpensive, stable, easy to store and engineer
- Improvements in drug discovery
  - Using genome targets → more easily discover potential therapies
  - Previously failed drug candidates can be revived

Benefits

- Improves approval process
  - Drug approval process will be facilitated
    - Trials are targeted for specific genetic population groups
    - Greater degrees of success
  - Cost/risk of clinical trials will be reduced because of the individual-target basis
- Decreases overall cost of health care
  - Decreases in ADR, failed drug trials, time to get drug approval, medication times, number of trial medications, effects of disease on body
  - Increase in range of possible drug targets

Issues

- Still a complicated method of finding the SNPs that affect a specific drug response
- Limited drug alternatives
- Disincentives for drug companies for make multiple pharmacogenomic products
- Educating healthcare providers
- Economic issues
- Ethical issues

Now → Future

- **Current:**
  - Researchers are now trying to catalog as many genetic variances (SNPs) in the human genome as possible
  - DNA must be sequenced for presence of SNPs
  - Problem: traditional gene sequencing technology = slow and expensive
- **Future:**
  - DNA microarrays (DNA chips) can make it possible for doctors to examine patients for specific SNPs quickly and affordably
    - Takes only a couple of hours to screen 100,000 SNPs
  - SNP screening in the doctor's office to determine drug response prior to drug prescription