Technology and Our Future: Pharmacogenetics

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Financial Disclosure

There is no financial conflicts with this presentation.

Lecturing about a topic does not constitute endorsement of any product. Please take the time to research each topic for more information.

Mentioning a product or company does NOT represent endorsement.
Clinical practice improvement

MUST KNOW
What do you identify as when it comes to race?

- White
- African-American
- Hispanic
- Asian
- Native American

☑ Human

Decoding my Nationality
New Guidelines for Surgical Patients with Post-operative Nausea and Vomiting (PONV)

By: Kate Maude on Jan 02, 2014

(Chicago, IL, January 2, 2014) – New guidelines from the Society for Ambulatory Anesthesia (SAMBA) provide an evidence-based reference tool for the management of surgical patients who are at increased risk for post-operative nausea and vomiting (PONV).

"PONV is a common symptom for patients following surgery, and can cause significant discomfort and delay a patient's discharge from the hospital," said Tong J. Gan, MD, MHS, FRCA, Professor of Anesthesiology, Vice Chair for Clinical Research, Department of Anesthesiology, Duke University Medical Center. "The primary goal of the new guidelines is to provide current and comprehensive information to health care providers about effective strategies to prevent and treat PONV in adults and children undergoing surgery," according to Dr. Gan.
Coined the term “genetics”

From the Greek, ‘genno’ (to generate / to give birth)

Mendel’s Laws

- Law of Segregation – member of each pair of alleles are separated when gametes are formed.
- Law of Independent Assortment – pairs of alleles separate independently of one another during gamete formation.
BMAL1 ---- two DEC2 pair up need less sleep

<table>
<thead>
<tr>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courteous</td>
<td>Impolite</td>
</tr>
<tr>
<td>Determined</td>
<td>Unsure</td>
</tr>
<tr>
<td>Friendly</td>
<td>Unfriendly</td>
</tr>
<tr>
<td>Hard-working</td>
<td>Lazy</td>
</tr>
<tr>
<td>Humble</td>
<td>Proud</td>
</tr>
<tr>
<td>Generous</td>
<td>Selfish</td>
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<tr>
<td>Punctual</td>
<td>Late</td>
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<tr>
<td>Respectful</td>
<td>Rude</td>
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<tr>
<td>Brave</td>
<td>Coward</td>
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<tr>
<td>Loyal</td>
<td>Rebellious</td>
</tr>
<tr>
<td>Perseveres</td>
<td>Gives up easily</td>
</tr>
<tr>
<td>Considerate</td>
<td>Inconsiderate</td>
</tr>
<tr>
<td>Honest</td>
<td>Dishonest</td>
</tr>
<tr>
<td>Kind</td>
<td>Mean</td>
</tr>
<tr>
<td>Sincere</td>
<td>Insincere</td>
</tr>
</tbody>
</table>

### TABLE 29.1 Traits Determined by Simple Dominant-Recessive Inheritance

<table>
<thead>
<tr>
<th>Phenotype Due to Expression Of:</th>
<th>Dominant Genes (Zz or Zz)</th>
<th>Recessive Genes (zz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue roller</td>
<td>Inability to roll tongue into a U shape</td>
<td></td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Normal vision</td>
<td></td>
</tr>
<tr>
<td>Freckles</td>
<td>Absence of freckles</td>
<td></td>
</tr>
<tr>
<td>Dimples in cheeks</td>
<td>Absence of dimples</td>
<td></td>
</tr>
<tr>
<td>Feet with normal arches</td>
<td>Flat feet</td>
<td></td>
</tr>
<tr>
<td>PTC* taster</td>
<td>PTC non-taster</td>
<td></td>
</tr>
<tr>
<td>Widow’s peak</td>
<td>Straight hairline</td>
<td></td>
</tr>
<tr>
<td>Double-jointed thumb</td>
<td>Tight thumb ligaments</td>
<td></td>
</tr>
<tr>
<td>Broad lips</td>
<td>Thin lips</td>
<td></td>
</tr>
<tr>
<td>Polydactyly (extra fingers and toes)</td>
<td>Normal number of fingers and toes</td>
<td></td>
</tr>
<tr>
<td>Syndactyly (webbed digits)</td>
<td>Normal digits</td>
<td></td>
</tr>
<tr>
<td>Achondroplasia (heterozygous: dwarfism; homozygous: lethal)</td>
<td>Normal cartilage bone formation</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Absence of Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td>Normal skin pigmentation</td>
<td>Albinism</td>
<td></td>
</tr>
<tr>
<td>Absence of Tay-Sachs disease</td>
<td>Tay-Sachs disease</td>
<td></td>
</tr>
<tr>
<td>Absence of cystic fibrosis</td>
<td>Cystic fibrosis</td>
<td></td>
</tr>
</tbody>
</table>
Consider a variable response to X?

Genetics

Response
Genetics Based Interventions

Gene carries instructions to make proteins

- Each of us has ~ 25 K genes

- Sequence > 99.5% identical in all humans

Tiny variation in our genes makes each of us unique
Pharmacogenetics, 1990
Pharmacogenomic Journals, 2007
23andMe, the Mountain View genetics testing company, has received approval from the Food and Drug Administration to sell tests that indicate people’s risk of developing 10 diseases including Parkinson’s, Alzheimer’s, celiac and some blood clotting disorders.
Agena Bioscience Names Genelex as Certified Service Provider for Targeted Genetic Analysis
29 August 2016
SAN DIEGO, Calif., August 29, 2016 – Agena Bioscience today announced the successful certification of Genelex as a Certified Service Provider of the MassARRAY® technology. The MassARRAY System is used to identify and validate SNPs, INDELs, CNV’s, translocations, somatic mutations, including rare variants, and methylation profiles across a variety

Genelex Announces Integration with EPIC
23 February 2016
Pharmacogenomic clinical analytics provider connects to the U.S.’s largest electronic health record system to support the reduction of drug complications.

United States Department of Veterans Affairs Awards Genelex Federal Supply Schedule Contract
15 March 2016
Pharmacogenetic testing now available to improve complex medication management for veterans at risk of avoidable hospitalizations and ER visits Seattle, WA—March 15, 2016 – Genelex, the makers of YouScript® Precision Prescribing analytics software, announces the U.S. Department of Veterans Affairs has awarded a Federal Supply Schedule (FSS V797D-50565) contract as a ...

...Read More
DNA Direct brings the power of personalized medicine to payors, providers and patients.

**THE RIGHT PERSON**
Finding the right people to benefit from genomic medicine can improve disease management and lower healthcare costs.

**THE RIGHT TEST**
Getting the wrong test can misinform medical decisions and increase healthcare costs.

**THE RIGHT INTERPRETATION**
Delivers the full value of genetic information and enables physicians to make appropriate management decisions.
Personalized Anesthesia Delivery

Personalized Pain Medicine: Pipe Dream or Reality?
Stephen Bruehl, Ph.D.

Editorial Views | May 2015
Anesthesiology 5 2015, Vol.122, 967-968.
doi:10.1097/ALN.00000000000000638

Pharmacogenetics

Your DNA Affects Your Response to Drugs
What do I do?

• 22 year old woman with symptoms suggesting depression. Her primary care physician prescribes venlafaxine (Effexor®). This is an SSRI.

• 10 days later, the patient presents with complaints of racing heart rate and confusion.

• The CRNA questions whether she has taken codeine in the past. (WHY?)

• **She says she was prescribed codeine/acetaminophen (Tylenol 3) after routine surgery 5 years ago and did not get pain relief. Morphine, however, was effective at that time.**
Medication History: AVOID Mistakes

Allergies? : Is there any medicine that we should not give you for any reason?

Vitamins and Herbs?

Old drugs? .....as well as current

Interactions?

Dependence?

Mendel: Family Hx of benefits or problems with any drugs?
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 make-up 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”
Pharmacogenetics VS. Pharmacogenomics

**Pharmacogenetics**: Study of variability in drug response determined by single genes.

**Pharmacogenomics**: Study of variability in drug response determined by multiple genes within the genome.
Differential Drug Efficacy

At a recommended prescribed dosage—

- a drug is efficacious in most.
- not efficacious in others.
- harmful in a few.

Same symptoms, Same findings, Same disease? Different patients
Same drug, Same dose

Different Effects

- Lack of efficacy
- Unexpected side-effects
People react differently to drugs

“One size does not fit all …”

Patient population with same disease phenotype

Genotyping

- Toxic responders
- Non-responders
- Responders

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy
Single nucleotide polymorphisms (SNPs)

SNPs are single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist wherein the least frequent allele has an abundance of 1% or greater.

For example a SNP might change the DNA sequence:

AAGCTTAC to ATGCTTAC

SNPs are the most commonly occurring genetic differences.
Personalized Pain Medicine: Pipe Dream or Reality?

Stephen Bruehl, Ph.D.

Anesthesiology 5 2015, Vol.122, 967-968.
doi:10.1097/ALN.00000000000000638

Pharmacogenetics
Pharmacogenetics (pharmacogenomics)

- Field of study examines impact of genetic variation & drug responses via biomarkers
- Aims to optimizing proper drug therapy @ dosage for patients – increasing efficacy & safety
- Other benefits – by monitoring biomarkers - reduces time, cost & failure rates in clinical trials in developing new medications
- Increases opportunities to develop novel therapeutics
- Example – genotyping variants of Cytochrome P450 involved in metabolism of warfarin (Coumadin)
What Is “Pharmacogenomics”?

- The study of how genome-wide variation affects the body's response to drugs.
- Benefits for patients include better drug selection for initial treatment and more accurate dosing.
- Benefits for drug companies include genetic targeting of clinical trials for specific groups.

The terms “pharmacogenetics” and “pharmacogenomics” are often used interchangeably.
Termination of Drug Action

Factors Influencing Biotransformation

- **Genetic**
- Environmental (e.g., diet, nutrition)
- Physiological differences (e.g., age, gender differences in microsomal enzyme systems)

Drug Interactions

- Some drugs increase or decrease enzyme activity
  - e.g., carbamazepine stimulates CYP-3A3/4
  - e.g., SSRIs inhibit CYP-1A2, CYP-2C
PERSONALIZED MEDICINE

Pharmacogenetics

- Advances in molecular biology & genetics = molecular medicine
- Created “companion diagnostics” = proteins, genes & specific mutations are assayed in a patient creating specialized individual treatments
- Doing so stratifies disease status in patients
- Allows for proper medications & dosages
- Allows for detecting risk factors
- Allows for prevention strategies
PERSONALIZED MEDICINE

- POTENTIAL APPLICATIONS
- Improves understanding of role of genes in normal human development & physiology
- Identifies single nucleotide polymorphisms (SNPs)
- SNPs account for genetic variability between individuals
- Allows use of genome-wide association studies (GWAS) to examine genetic variation & risk for many common diseases
Drug Metabolism Basics

Prodrug needs to be metabolized by enzyme A to be active

- Poor metabolizers (low A activity) will need higher dose
- High metabolizers (high A activity) will need lower dose

Drug needs to be metabolized to be inactivated

- Poor metabolizers (low I activity) will need lower dose
- High metabolizers (high I activity) will need higher dose
Due to Individual Variation...

➢ 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

The use of DNA sequence information to measure and predict the reaction of individuals to drugs.

➢ Personalized drugs
➢ Faster clinical trials
➢ Less drug side effects

Pharmacogenetics
Differential Drug Efficacy

Same symptoms
Same findings
Same disease (?)

Same Drug....

Different Effects

Possible Reasons:
Non-Compliance…
Drug-drug interactions…
Chance…
Or....

Genetic Differences

SNP
EGFR Mutants

Much ado about...?
Gene Has Different Forms (Alleles)

High enzyme activity

- Homozygous dominant (wild type)

Medium enzyme activity

Heterozygous

Low enzyme activity

- Homozygous recessive
The Future of Pharmacogenomics

Pharmacogenomics is slowly being integrated into anesthesia practice.

Understanding the consequences of metabolizer status and the frequency of variants in a given population will be helpful when advising patients about treatment options.

See the [FDA Pharmacogenomic Biomarkers in Drug labels](#) for a list of drugs and their associated genetic biomarkers.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Specialty</th>
<th>Enzyme</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Rheumatology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Use in Specific Populations, Clinical Pharmacology</td>
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<tr>
<td>Desflurane</td>
<td>Anesthesiology</td>
<td>Not specified</td>
<td>Contraindications</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Cardiology</td>
<td>NAT1, NAT2</td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Lidocaine and Prilocaine (2)</td>
<td>Anesthesiology</td>
<td>G6PD</td>
<td>Warnings and Precautions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Metoclopramide (1)</td>
<td>Gastroenterology</td>
<td>CYB5R1, CYB5R2, CYB5R3, CYB5R4</td>
<td>Precautions, Overdosage</td>
</tr>
<tr>
<td>Metoclopramide (2)</td>
<td>Gastroenterology</td>
<td>G6PD</td>
<td>Precautions, Overdosage</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Cardiology</td>
<td>CYP2D6</td>
<td>Drug Interactions, Clinical Pharmacology</td>
</tr>
</tbody>
</table>
Recently added

ZOFRAN, PIROXICAM

Limitations of pharmacogenomic data in FDA–approved drug labels

Published: October 12th, 2014
Category: Stories

Pharmacogenomic biomarker information is included in Food and Drug Administration (FDA)–approved product labeling, or prescribing information, for over 100 drugs. This information may be used to support the clinical use of pharmacogenomic data to optimize drug therapy; however, there is wide variation in the scope and format of FDA-approved labeling. An analysis of pharmacogenomic information included in FDA labeling was recently published in JAMA Internal Medicine.

Table of Pharmacogenomic Biomarkers in Drug Labeling

Summary
Pharmacogenomics

Research Article
Pharmacogenomic biomarkers in drug labels: what do they tell us?
Our path in Anesthesia in Pharmacogenetics

Our paths have crossed for a reason...

and for that I am thankful...

get more quotes at THEDAILYQUOTES.COM
You use pharmacogenetics everyday

1964
History

First described by Denborough in 1960

A Wisconsin family with 20 members affected suggested an autosomal dominant inheritance

The largest group of people with known MH in Wausau, Wisconsin and surrounding towns

Dr Michael Denborough (pictured right) and his colleague Dr Richard Lovell then went on to study this patient’s family in greater detail. They outlined the autosomal dominant inheritance of this severe reaction to anaesthetics and their letter was published in *The Lancet*. Dr Denborough went on to devote most of his career to research in the field of malignant hyperthermia.
**Succinylcholine**

- First used in 1951

**Warning**

Risk of Cardiac Arrest From Hyperkalemic Rhabdomyolysis

**Quelicin®**

*Succinylcholine Chloride Injection, USP*

A short-acting depolarizing skeletal muscle relaxant. Abboject® Syringe, Ampul, Fliptop Vial, Pintop Vial
Pathogenesis of MH — The Triad
Succinylcholine (X is a trigger) should be used cautiously given the risk of compounding the malignant hyperthermia like effects of the drug, raising intracranial pressure or potentially worsening hyperkalemia.
CORRESPONDENCE

Acupuncture 2002, 1, 1-5

Dantralene Use in 3,4-Methylenedioxymethamphetamine ("Ecstasy")-Mediated Hyperthermia

To the Editor: We read with great interest the study by Fige et al. published in the November 2001 issue of Acupuncture. Although we applaud the authors' attempt to shed some light on the controversial use of dantralene in 3,4-methylenedioxymethamphetamine (MDMA)-mediated hyperthermia, several flaws in the design and interpretation of their results cast doubt on their conclusions.

Our primary criticism of this study is in the authors' use of a combination therapy (dantralene, sodium bicarbonate, and heparin) to determine the role of dantralene in MDMA-mediated hyperthermia. The positive results attributed to dantralene in Figure 2 of this study are significant, yet in vivo. We believe that the data are unconvincing due to the following issues:

1. The authors did not study the role of dantralene in MDMA-mediated hyperthermia. Because the effects of MDMA on body temperature were not studied in the animals, the results of this study are not relevant to the study's primary objective.

2. The results of this study are not statistically significant. The authors' claim that the data are significant is not supported by the statistical analysis presented in the study.

3. The authors did not adequately control for confounding variables. The study design does not adequately control for the effects of other variables, such as the temperature of the injection site and the blood flow to the injection site.

4. The results of this study are not consistent with the results of previous studies. The authors' results are not consistent with the results of previous studies that have shown that dantralene has no effect on MDMA-mediated hyperthermia.

As a solution to these issues, we propose the following:

1. The study should be re-designed to include a placebo group to control for the effects of the injection site and the blood flow to the injection site.

2. The study should be re-designed to include a control group to control for the effects of other variables, such as the temperature of the injection site.

3. The study should be re-designed to include a larger sample size to increase the statistical power of the study.

4. The study should be re-designed to include a longer follow-up period to adequately control for the effects of the injection site and the blood flow to the injection site.

In conclusion, the results of this study are not consistent with the results of previous studies. The authors' claims are not supported by the statistical analysis presented in the study. The study design does not adequately control for the effects of other variables, such as the temperature of the injection site and the blood flow to the injection site.

Daniele A. Baryshnik, M.D., Matthew L. Banks, Pharm.D., Edward M. Miller, Pharm.D., Jean E. Spangrude, Pharm.D.
Ohio Northern University, Ada, Ohio.
Sevoflurane -- More than just receptor?

Summary

The FDA-approved drug label for sevoflurane (ULTANE) states that it should not be used in patients with known or suspected susceptibility to malignant hyperthermia. Specific variants in the RYR1 and CACNA1S genes are associated with risk of malignant hyperthermia in individuals administered potent inhalational anesthetics, including sevoflurane. The label does not mention genetic testing.

CACNA1S
And RYR1 Gene

The CACNA1S gene belongs to a family of genes that provide instructions for making calcium channels. These channels, which transport positively charged calcium atoms (ions) into cells, play a key role in a cell's ability to generate and transmit electrical signals.
Implications of Pharmacogenomics for Anesthesia Providers

Tori Aina, CRNA, MNA
Sue Bunyaratvong, CRNA, MNA
Jordan Blane, CRNA, MNA
Melissa Wintersman, CRNA, MNA
Mary Alice Montes, CRNA, MS
Wayne T. Richenbush, MD, PharmD

The practice of anesthesia has long been considered an art and a science, with unpredictable variability in drug response being the rule, rather than the exception. Pharmacogenomics, which studies the role of genetics in drug response, is emerging as a discipline that may impact anesthetic management.

The purpose of this review is to provide clinicians with basic knowledge related to pharmacogenomics and its implications in anesthesia. This review focuses on pharmacogenomics related to commonly used drugs in anesthesia.

Pharmacogenomics as a predictor of drug response has increased and in anesthesia and drug development. By expanding the knowledge base of anesthetic providers, pharmacogenomic considerations have the potential to improve therapeutic outcomes and individualize drug therapy, while avoiding toxic effects and treatment failure. However, because pharmacogenomics may not fully explain variability in drug response, implementation should be in conjunction with traditional anesthesia considerations.

Keywords: Anesthesia, drug variability, pharmacogenetics, pharmacogenomics, polymorphisms.

Table: Two or more forms of a gene that occupy a specific site on a chromosome.

[Table content]
Some drug metabolizing enzymes showing clinically significant variation

- **CYP2D6**
  - Role in metabolizing ¼ of all prescription drugs currently on the market
    - *Anti-depressants (SSRIs, tricyclics)*
    - Anti-psychotics
    - β-blockers; some anti-arrhythmics

- **CYP2C9**
  - Warfarin (Coumadin®)

- **UGT1A1**
  - Irinotecan (Camptosar®) used to treat colon cancer and lung cancer
We Must Start to Think Differently!

Pediatric patients don’t learn like we do?

What are the most abused Drugs in Peds?

FDA and Codeine?---- CPY2D6 ultra-rapid metabolizers

Codeine is a prodrug, meaning that it has to be converted into its active form, morphine, for its analgesic effect to be fully realized. Cytochrome P450 isoenzyme-2D6 (CYP2D6) is responsible for its hepatic conversion, and of course this extra biotransformation step increases the chances for alterations in the extent and speed of the enzyme's conversion of codeine to morphine.

FDA Investigates Codeine Safety After Children's Deaths
August 15, 2012
By ABC NEWS
Red Hair? The researchers' findings showed that the old CRNA' adage is true: Redheads do require more anesthesia. In fact, it took an average of 20 percent more all due to the MC1R gene (2012, University of Kentucky).

In redheads, the mutated MC1R gene produces pheomelanin instead, a protein that accounts for the flaming hair, pale skin, and freckles that we associate with carrot-tops.

Those with the MC1R mutation are more sensitive to opiate pain killers — which means they’d actually need less — but less sensitive to other types, most notably lidocaine injections.

NO KNOWN information or evidence about Nausea risks and red heads

NO KNOWN information or evidence about BLEEDING
We practice the opposite way – **HTR3A Gene**

*Sequence variants of the HTR3A gene contribute to the genetic prediction of postoperative nausea in Taiwan*  
Yi Mei Joy Lin, Chong Da Hou, Hoic Yen Keh, Chia Chih Alex Iseong and H Sunny Sun

*First study of nausea genetics*  
**ADAM CRESSWELL**  
TheAustralian | 12:00AM May 15, 2012

RESEARCHERS are planning the first genetic study to help determine which patients are at risk of nausea and vomiting after surgery -- a common problem that is sometimes so bad patients try to delay or avoid further operations.
Genetics of Pain

Mutations in the *SCN9A* gene cause congenital insensitivity to pain. The *SCN9A* gene provides instructions for making one part (the alpha subunit) of a sodium channel called NaV1.7. Sodium channels transport positively charged sodium atoms (sodium ions) into cells and play a key role in a cell's ability to generate and transmit electrical signals. NaV1.7 sodium channels are found in nerve cells called nociceptors that transmit pain signals to the spinal cord and brain. The NaV1.7 channel is also found in olfactory sensory neurons, which are nerve cells in the nasal cavity that transmit smell-related signals to the brain.

REMEMBER DEFINITION OF PAIN>>>>> HAVE WE COME FULL CIRCLE?
What did Mom and Dad say?
Von Willebrand Factor

2 components

(separate genetic control)

Von Willebrand factor (vWF)---9 different types

Mutations in the vWF gene cause von Willebrand disease. The VWF gene provides instructions for making a blood clotting protein called von Willebrand factor, which is essential for the formation of blood clots. After an injury, clots protect the body by sealing off damaged blood vessels and preventing further blood loss. Von Willebrand factor acts as a glue to hold blood clots together and prevents the breakdown of other blood clotting proteins. If von Willebrand factor does not function normally or too little of the protein is available, blood clots cannot form properly. Abnormally slow blood clotting causes the prolonged bleeding episodes seen in von Willebrand disease.
Desmopressin (DDAVP)
DDAVP releases vWF from endothelial cells

Increases Factor VIII activity in patients with hemophilia and von Willebrand’s disease

Can be given IV or intranasally
  • 0.3 mcg/kg IV, or 150 mcg per nostril

Response to DDAVP varies considerably
Cytochrome P450 2D6

- Absent in 7% of Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - propafenone
  - codeine
  - β-blockers
  - tricyclic antidepressants

- Inhibited by:
  - fluoxetine
  - haloperidol
  - paroxetine
  - quinidine
About 50% of people of Oriental descent are slow metabolizers of acetaldehyde.

Rare outside the Oriental population

- Significant acetaldehyde build up associated with ethanol intake – flushing, increased heart rate, nausea.
N-Acetylation Polymorphism NAT-2

- Late 1940’s: Peripheral Neuropathy noted in patients treated for tuberculosis.

NAT-2 substrates
(All have been used as probes)

- Caffeine
- Dapsone
- Hydralazine
- Isoniazid
- Procainamide

**Family History of Cancer?**

NAT2 may also refer to SLC38A1.

NAT2 is one of only 2 N-acetyltransferase genes in humans; the other, NAT1, shows little variation between individuals, whereas NAT2 is known to have over 23 variants. N-acetyltransferases are enzymes acting primarily in the liver to detoxify a large number of chemicals, including caffeine and several prescribed drugs. The NAT2 acetylation polymorphism is important because of its primary role in the activation and/or deactivation of many chemicals in the body's environment, including those produced by cigarettes as well as aromatic amine and hydrazine drugs used medicinally. In turn, this can affect an individual's cancer risk.

Individuals can be classified as either rapid, or slow, metabolizers (i.e. detoxifiers). In general, slow metabolizers have higher rates of certain types of cancer and are more susceptible to side effects from chemicals metabolized by NAT2. [PMID 10667461] Drugs reported to be metabolized by NAT2 include isoniazid, sulfadimidine, hydralazine, dapsone, procaine amide, sulfapyridine, nitrazepam and some sulfa drugs. [PMID 3712391]
Incidence of the Slow Acetylator NAT-2 phenotype

- 50% among Caucasians
- 50% among Africans
- 20% among Egyptians
- 15% among Chinese
- 10% among Japanese
Butyrylcholinesterase deficiency

- Autosomal recessive
- Succinylcholine is metabolized by BchE
- Increased accumulation of succinylcholine (depolarizing neuromuscular blocker)
- Increased muscle paralysis including respiratory paralysis (succinylcholine apnea)
**Dibucaine number**: It is a test of the ability of pseudocholinesterase to metabolize succinylcholine. Dibucaine is an enzyme inhibitor, which inhibit 80% of normal enzyme and 25% of abnormal enzyme.

<table>
<thead>
<tr>
<th>Type of Butyrylcholinesterase</th>
<th>Incidence</th>
<th>Dibucaine Number</th>
<th>Response to Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous Typical</td>
<td>Normal</td>
<td>70-80</td>
<td>Normal</td>
</tr>
<tr>
<td>Heterozygous Atypical</td>
<td>1/480</td>
<td>50-60</td>
<td>Lengthened 50-100%</td>
</tr>
<tr>
<td>Homozygous Atypical</td>
<td>1/3200</td>
<td>20-30</td>
<td>Prolonged to 4-8 hrs</td>
</tr>
</tbody>
</table>
Dibucaine

• An amide local anesthetic which is an inhibitor of pseudocholinesterase used to determine whether atypical or normal pseudocholinesterase is present in plasma. It indicates quality but not quantity of pseudocholinesterase.
  
  • 80% inhibition indicates homozygous normal
  
  • 60% inhibition indicates heterozygous atypical
  
  • 20% inhibition indicates homozygous atypical
  
  • About 1:480 heterozygous atypical, 1:3200 homozygous atypical
  
  • If pseudocholinesterase is absent, succinylcholine is broken down by nonenzymatic hydrolysis. This requires 1-5 hours.
Pseudocholinesterase

Also known as:
Acetylcholine Acyl Hydrolase
Butyrylcholinesterase (BChE)

Primary metabolic pathway for Succinylcholine
Atypical Pseudocholinesterase

Results from a mutation of the BCHE gene

All atypical varieties are autosomal recessive:

• Heterozygous patients: minimal prolongation of paralysis
• Homozygous: variable paralysis, from 1-4 hours or more

More prevalent among:

• Inuit / Native Alaskans
• Persian descendants/Jewish communities
• Specific Hindu populations
Pseudocholinesterase Variants

Up to 98% of individuals are homozygous for normal pseudocholinesterase

4 major varieties, with 65 variants known
Pseudocholinesterase Deficiency types

K variant

- Minimal effects alone, but often present in conjunction with other variants
- Slight prolongation of apnea
- Most prevalent variant (1.5% population)
FACTOR V LEIDEN

FACTOR V VARIANT LEADS TO HYPER-COAGULABILITY

FACTOR V NOT DEGRADED BY ACTIVATED PROTEIN C

30% WITH DVT OR PE HAVE FACTOR V LEIDEN
Methemoglobinemia – HBB Gene

Methemoglobinemia (hemoglobin in Fe3+ oxidation state)
- Amide-type agents (lidocaine, prilocaine)
- Toxic metabolite (aromatic amine)
- Cyanosis (brown blood, blue skin color)
- Antidote: methylene blue

*HBB* gene mutations that cause methemoglobinemia, beta-globin type change the structure of beta-globin and promote the heme iron to change from ferrous to ferric. The ferric iron cannot bind oxygen and causes cyanosis and the brown appearance of blood.
Cystic Fibrosis – Defect in Chromosome 7

- Hereditary diseases of exocrine glands of pulmonary and gastrointestinal systems.
- Thick and viscous secretions and decreased ciliary activity lead to pneumonia and wheezing.
- Dehydration and electrolyte abnormalities.

~ 5% of patients

Ivacaftor (FDA 2012) works only in a specific mutation (~ 5% of patients)
Fospropofol (Lusedra) over 200 gene variations that stop the conversion
Detailed Description

Propofol, (2,6-diisopropylphenol) is a short-acting anesthetic drug used for induction and maintenance of anesthesia. The aim of this study is to evaluate plasma concentrations of propofol in relation to depth of anesthesia, measured by continuous EEG and to correlate plasma concentrations with genetic analyses of liver enzymes responsible for drug elimination. Our hypothesis is that there is an individual requirement of Propofol plasma concentration depending on genetic differences in drug elimination. 200 patients, ASA classification 1, planned for elective surgery of a duration of at least 30 minutes will be included in this study.
Another Example: Clopidogrel (Plavix)

- Taken by about 40 million people in the world to prevent blood clotting.
- CYP2C19 is responsible for its metabolic activation
- At least one loss-of-function allele is carried by 24% of the white non-Hispanic population, 18% of Mexicans, 33% of African Americans, and 50% of Asians.
- Homozygous carriers, who are poor CYP2C19 metabolizers, make up 3% to 4% of the population.
Poor metabolizers of clopidogrel require _____ doses of drug to achieve an effective dose because the CYP2C19 enzyme does not_____ the drug.

A) Higher, activate
B) Lower, activate
C) Higher, inactivate
D) Lower, inactivate
Pharmacodynamic Interactions: Warfarin

• Warfarin (coumadin) is a commonly prescribed oral anti-coagulant.

• Common cause of adverse drug reactions: too much drug results in increased bleeding, too little results in inadequate anti-coagulation (leading to possible stroke, DVT etc.)

• Need for monitoring
Coagulation Mechanism

Our Friend Coumadin

Vitamin-K dependent factors (II, VII, IX, X)(S and C)
**VKORC1 or VKOR**

- Drug target: vitamin K epoxide reductase complex subunit 1 (VKORC1 or VKOR)

- Vit K needs to be converted from inactive epoxidized form to active reduced form

- Warfarin binds to VKORC1 near its catalytic site, inhibiting the reduction reaction.

- VKORC1 variants are associated with warfarin resistance in humans
Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency

G6PD is the most common human enzyme deficiency in the world; it affects an estimated 400 million people. G6PD deficiency is also known as "favism," since G6PD deficient individuals are also sometimes allergic to fava beans. G6PD deficiency is an allelic abnormality which is inherited in an X-linked recessive fashion.
G6PD variants

Genotypes/Isoenzymes

- G6PD B+: wild type, whites > blacks
- G6PD A+: blacks > whites
- G6PD A-: blacks with mild deficiency
- G6PD Med: whites Mediterranean, Kurdish
- G6PD Canton: Thailand, Vietnam, Taiwan

- WHO variants
Peroxidation of RBC membrane lipid → ↑↑ membrane fragility → Hemolysis

The function G6PD in the red cell is to generate NADPH → reduced glutathione → protect the RBCs from the oxidative damage by H₂O₂
Glucose-6-phosphate dehydrogenase deficiency

The disorder is X-linked and women are affected only if homozygous for the condition.

G6PD deficiency does not cause any symptoms unless the patient takes one of a number of drugs, such as the anti-malarial primaquine. The administration of one of these drugs causes rapid and often severe hemolysis and jaundice.
Glucose-6-phosphate dehydrogenase deficiency

In G6PD deficiency the red cells are not completely lacking in the enzyme; younger cells contain some 6% of the normal amount. This is sufficient to provide reducing power for every day needs.

When, however, a drug such as primaquine is given the limited reducing power is overwhelmed, oxidation of intracellular proteins takes place and hemolysis, particularly of the older red cells, follows.
P450 cycle

Microsomal drug oxidations require:
1. P450
2. P450 reductase
3. NADPH
4. Molecular oxygen

Steps of P450 mediated oxidation:
1. Oxidized P450 binds with drug to form a complex
2. P450 reductase reduces the P450/drug complex
3. P450 reductase reduces molecular oxygen to form an “activated oxygen”-P450/drug complex
4. Activated oxygen is transferred to drug to form oxidized product
5. One molecule of water is produced

Drug + O₂ + NADPH + H⁺ → Drug-OH + H₂O + NADP⁺
An example of pharmacokinetic gene interactions: liver drug metabolizing enzymes

Phase I: oxidation, reduction, hydrolysis etc. Major system is cytochrome P450 (CYP) enzymes

Phase II: conjugating enzymes (acetylation, glucuronidation, glutathionation, sulfation)

Metabolizing reactions transform drugs into more water soluble forms to aid in their elimination
<table>
<thead>
<tr>
<th>Defect</th>
<th>Enzyme Involved</th>
<th>Drug and Therapeutic Use</th>
<th>Clinical Consequences¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>CYP2C6</td>
<td>Butalbital (β-adrenoceptor blocker)</td>
<td>Exacerbation of β blockers, nausea</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C6</td>
<td>Codeine (analgesic)</td>
<td>Reduced analgesia</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C6</td>
<td>Debrisoquin (antihypertensive)</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Alddehyde dehydrogenase</td>
<td>Ethanol (recreational drug)</td>
<td>Facial flushing, hypotension, tachycardia, nausea, vomiting</td>
</tr>
<tr>
<td>N-Acetylation</td>
<td>N-acetyl transferase</td>
<td>Hydralazine (antihypertensive)</td>
<td>Lupus erythematosus-like syndrome</td>
</tr>
<tr>
<td>N-Acetylation</td>
<td>N-acetyl transferase</td>
<td>Isoniazid (antitubercular)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C19</td>
<td>Mephenytoin (antiepileptic)</td>
<td>Overdose toxicity</td>
</tr>
<tr>
<td>S-Methylation</td>
<td>Thiopurine methyltransferase</td>
<td>Mercaptopurines (cancer chemotherapeutic)</td>
<td>Myelotoxicity</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2A6</td>
<td>Nicotine (stimulant)</td>
<td>Lesser toxicity</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C6</td>
<td>Nortriptyline (antidepressant)</td>
<td>Toxicity</td>
</tr>
<tr>
<td>O-Demethylation</td>
<td>CYP2C19</td>
<td>Omeprazole (proton pump inhibitor)</td>
<td>Increased therapeutic efficacy</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C6</td>
<td>Sparfloxacin (antibiotic)</td>
<td>Oxytocic symptoms</td>
</tr>
<tr>
<td>Ester hydrolysis</td>
<td>Plasma cholinesterase</td>
<td>Succinylcholine (neuromuscular blocker)</td>
<td>Prolonged apnea</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C9</td>
<td>S-warfarin (anticoagulant)</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2C9</td>
<td>Tolbutamide (hypoglycemic)</td>
<td>Cardiotoxicity</td>
</tr>
</tbody>
</table>

¹Observed or predictable.
P450 substrates, inducers, and inhibitors

- **P450 induction**
  - Increase expression by increased synthesis or decreased degradation
  - Results in increased metabolism of substrates
    - Decreased substrate plasma concentrations

- **P450 inhibition**
  - Decrease enzyme activity
  - Decrease rate of metabolism of other substrates
    - Increase substrate plasma concentrations

---

**TABLE 4-2** Human liver P450s (CYPs), and some of the drugs metabolized (substrates), inducers, and selective inhibitors.

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrates</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Acetaminophen, antipyrine, caffeine, clomipramine, phenacetin, tacrine, tamoxifen, theophylline, warfarin</td>
<td>Smoking, charcoal-broiled foods, cruciferous vegetables, omeprazole</td>
<td>Galangin, furafylline, fluoxetine</td>
</tr>
<tr>
<td>2A6</td>
<td>Cournarin, tobaccocontosamines, nicotine (to cotinine and 2'-hydroxycotinine)</td>
<td>Fentanyl, phenobarbital</td>
<td>Translycypromine, menthofuran, methasalene</td>
</tr>
<tr>
<td>2B6</td>
<td>Artesinisin, bupropion, cyclophosphamide, efavirenz, ifosfamide, ketamine, 5-methoxybital, 5-mephenytoin (N-demethylation to nirvanid), methadone, nevirapine, propranolol, selegiline, sertraline, ticlopidine</td>
<td>Phenobarbital, cyclophosphamide</td>
<td>Ticlopidine, clopicogrel</td>
</tr>
<tr>
<td>2C8</td>
<td>Taurine, all-trans retinoic acid</td>
<td>Fentanyl, barbiturate</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>2C9</td>
<td>Celecoxib, flurbiprofen, hexabotol, ibuprofen, losartan, phenytoin, tolbutamide, trimethadione, sulfaphenazole, 5-warfarin, ticryufalen</td>
<td>Earbiturtes, rifampin</td>
<td>Tieric acid, sulfaphenazole</td>
</tr>
<tr>
<td>2C10</td>
<td>Tolbutamide, phenytoin</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>Diazepam, 5-mephenytoin, naproxen, niranol, omepracol, pregabalinol</td>
<td>Earbiturtes, rifampin</td>
<td>N3-benzylirrivanol, N3-benzylphenobarbital, fluvanazol</td>
</tr>
<tr>
<td>2D0</td>
<td>Bufoalol, bispropranolol, clorpropamide, clozapine, codeine, debrobiquin, dextromethorphan, encacline, felbinacine, fluoxetine, guanoxan, haloperidol, hydroxyurea, 4-methoxyamphetamine, metoprolol, metoprolol, oxycodone, paroxetine, pheformin, propafenone propaoryphyl, risperidone, selegiline (depregenl), sparteine, thioridazine, timolol, tricyclic antidepressants</td>
<td>Unknowns</td>
<td>Quetiapine, paroxetine</td>
</tr>
<tr>
<td>2E1</td>
<td>Acetaminophen, chloroform, enflurane, halothane, ethanol (a minor pathway)</td>
<td>Ethanol, isoniazid</td>
<td>4-Methylpyrazole, disulfiram</td>
</tr>
<tr>
<td>3A4</td>
<td>Acetaminophen, aminocarb, astemizole, cisapride, cocaine, cortisol, cyclosporine, diphen, dyezeapam, dihydroergotamine, dydrogypside, diltiazem, erythromycin, ethylendiaz, gesoteline, irinavir, lidocaine, levetastin, macrolides, methadone, miconazole, midazolam, mifepristone, nifedipine, penitaxil, proproneor quinine, ramipril, ritonavir, saquinavir, spiranolactone, sufamethoxazole, sulfentaniol, tacrolimus, tamoxifen, terfenadine, tetoxstramabonate, tritaolam, troleandomycin, verapamil</td>
<td>Earbiturtes, cabamazepine, glucocorticoids, macrocides, anticoagics, antihistotics, phenytoin, farnia, 5. John's wort</td>
<td>Azamulin, diazepam, estroergyn, fluvanazol, grapefruit juice (turanicoumarins), itritaconazole, ketoconazole, ritonavir, toleandomycin</td>
</tr>
</tbody>
</table>

1CYP3A4 has similar substrate and inhibitor profiles, but except for a few close is generally less active than CYP1A4.

Examples:

EM phenotype: Extensive metabolizer; IM phenotype: intermediate metabolizer; PM phenotype: poor metabolizer; UM phenotype: ultra-rapid metabolizers


© Author information

Abstract
Between 6 and 22 June 1995, 8 patients in Kikwit, Democratic Republic of the Congo, who met the case definition used in Kikwit for Ebola (EBO) hemorrhagic fever, were transfused with blood donated by 5 convalescent patients. The donated blood contained IgG EBO antibodies but no EBO antigen. EBO antigens were detected in all the transfusion recipients just before transfusion. The 8 transfused patients had clinical symptoms similar to those of other EBO patients seen during the epidemic. All were seriously ill with severe ashenia, 4 presented with hemorrhagic manifestations, and 2 became comatose as their disease progressed. Only 1 transfused patient (12.5%) died; this number is significantly lower than the overall case fatality rate (80%) for the EBO epidemic in Kikwit and than the rates for other EBO epidemics. The reason for this low fatality rate remains to be explained. The transfused patients did receive better care than those in the initial phase of the epidemic. Plans should be made to prepare for a more thorough evaluation of passive immune therapy during a new EBO outbreak.

PMID: 9986160  DOI: 10.1086/514298
Case

22 year old woman with symptoms suggesting depression. Her primary care physician prescribes venlafaxine (Effexor®). This is an SSRI.

10 days later, the patient presents with complaints of racing heart rate and confusion.

The CRNA questions whether she has taken codeine in the past. (WHY?)

She says she was prescribed codeine/acetaminophen (Tylenol 3) after routine surgery 5 years ago and did not get pain relief. Morphine, however, was effective at that time.
What are possible explanations for the patient’s symptoms?

• Overdose of drug (intentional or inadvertent)

  Low activity of CYP2D6 due to genetic variation (poor metabolizer) or the patient may be taking another drug which inhibits CYP2D6 activity

• Liver failure
What about the reported history of ineffectiveness of codeine but effectiveness of morphine?

Codeine is a pro-drug that needs to be converted to morphine (mainly by CYP2D6)

**With low CYP2D6 activity**, codeine will not be converted to morphine

In a Canadian study, there were no poor metabolizers in a population of several hundred codeine addicts

- No conversion to morphine means no euphoric effects
Genelex (Seattle) advertises testing for CYP2D6

<table>
<thead>
<tr>
<th>Contraindicated: This drug has an interaction that is contraindicated in the product insert due to the potential for a severe or life-threatening reaction. This combination should not be administered.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major: This drug has an interaction that may result in severe clinical effects or large changes in drug levels. The risks of the interaction generally outweigh the benefits of prescribing the drug.</td>
</tr>
<tr>
<td>Moderate: This drug has an interaction that may result in substantial clinical effects or moderate changes in drug levels. Changes in therapy, such as making dose adjustments or prescribing alternatives, may be warranted.</td>
</tr>
<tr>
<td>Minor: This drug has an interaction that may result in minor clinical effects or small changes in drug levels. The benefits of prescribing the drug generally outweigh the risks of the interaction. Major changes in therapy are not expected, although minor dose adjustments may be appropriate.</td>
</tr>
<tr>
<td>Minimal: This drug may be associated with clinically insignificant and/or favorable interactions. No change in therapy is necessary.</td>
</tr>
</tbody>
</table>

More than 75% of people have genetic variations that determine how their bodies process and use drugs. This applies not only to prescription medications, but also to over-the-counter medicines, herbal and dietary supplements, and recreational drugs such as marijuana.
We all fear what we don’t know – it’s natural.

Leo Buscaglia
Potential Barriers to Genetic Testing

- Complexity of finding gene variations that affect drug response
- Limited drug alternatives
- Disincentives for drug companies to make multiple pharmacogenomic products

**Educating healthcare providers**

- Fear of discrimination based on genetic test results
Clinical Pharmacogenetics Summary

- A good phenotyping probe is critical
- Genetic tests need validation just as any other tests
- A potent inhibitor can mimic a genetic polymorphism
- Not all genetic polymorphisms have a phenotypic correlate, or clinical effect
- The clinical relevance of genetic polymorphisms is greatest with drugs of narrow therapeutic range, but not confined to them
- The cost of genetic testing is not likely to be limiting
More Information about Pharmacogenomics

- The Pharmacogenomic Knowledge base
- The Pharmacogenomics Education Program
- Pharmacogenomics interactive tutorial
Pharmacogenetics Websites

- www.pharmgkb.org
- The SNP consortium: http://brie2.cshl.org
- The Human Genome:
- CYP alleles: www.imm.ki.se/CYPalleles/
- Drug Interactions: www.drug-interactions.com
Economic considerations

How far is segmentation of markets feasible?

“Exhaustive pharmacogenetic research efforts have narrowed your niche market down to Harry Finkelstein of Newburg Heights here.”
Multi-Model
Synergy and Pre-Emptive
Influence of Nitrous Oxide Anesthesia, B-Vitamins, and MTHFR gene polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial

Peter Nagele, M.D., M.Sc., Assistant Professor,∗ Frank Brown, B.Sc., Research Coordinator,† Amber Francis, B.S.N, R.N., Research Coordinator,‡ Mitchell G. Scott, Ph.D., Professor,‡ Brian F. Gage, M.D., M.Sc., Professor,§ J. Philip Miller, A.B., Professor,§ and for the VINO study team#


Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia.

Anesthesia and Pharmacogenetics
Iravani, Mohamad MD
American Journal of Therapeutics: July/August 2009 - Volume 16 - Issue 4 - pp 313-315
doi: 10.1097/MJT.0b013e3181aef49d
Symposium: Advances in Anesthesia, Preoperative and Pain Management

Pharmacogenetics of Remifentanil in Patients With Hypertension Undergoing Cesarean Delivery Under General Anesthesia
Thank you

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