Pharmacogenetics and Personalized Anesthesia

Precision Anesthesia

LTC Peter Strube
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Assistant Professor Rosalind Franklin University
Associate Academic Faculty, University of Wisconsin Oshkosh
Have you ever wondered WHY?

This patient is driving Crazy, why won’t he get numb?

Keep calm and call a nurse anesthetist.
They don’t get numb with Local? Also: MC1R Gene

Missense Mutation – One amino acid in the protein is different

A genetic defect relating to a specific sodium channel in the body, known as sodium 1.5.

The affected gene, called SCN5A, produces a protein called NaV1.5, which is a major component of this channel.

Ehrler's Danlos Syndrome

Hawkins 2005, Clendenen 2010

Genetic Variations Associated With Red Hair Color and Fear of Dental Pain, Anxiety Regarding Dental Care and Avoidance of Dental Care

Catherine J. Binkley, DDS, MSPH, PhD, [1] Abbie Beacham, PhD, William Neace, PhD, Ronald G. Gregg, PhD, Edwin B. Lien, MD, Daniel I. Sessler, MD

2 RHC Alleles at the MC1R variant
Genetics are Powerful!
Genetics of Who we Are!

Life Long Learning = Better Patient Care!
Life Long Learning = Better Patient Care!
Life Long Learning = Better Patient Care!
can't stop laughing 😂
BMAL1 ---- Two DEC2 Pair up -- Need Less Sleep
Life Long Learning = Better Patient Care!

FUTURE OF PERSONALIZED MEDICINE

GIVE ME MY DATA!

TEST BEFORE YOU TREAT

CHART YEARS IN MEDICINE ARE JUST AROUND THE CORNER!

GET TO THE RIGHT DRUG THE FIRST TIME!

ALL OF THE DATA FROM THE INTERNET CAN BE ENTERED IN DAYS IN A SMALL TEST TUBE

Trollway Anesthesia
www.DiscoveryDoodles.com
Our Path in Anesthesia and Pharmacogenetics
bias

NOUN
1. prejudice in favor of or against one thing, person, or group compared with another, usually in a way considered to be unfair:
   "there was evidence of bias against foreign applicants" · [more]
   synonyms: prejudice · partiality · partisanship · favoritism · [more]
2. in some sports, such as lawn bowling, the irregular shape given to a ball.
3. a steady voltage, magnetic field, or other factor applied to an electronic system or device to cause it to operate over a predetermined range.

VERB
1. cause to feel or show inclination or prejudice for or against someone or something:
   "readers said the paper was biased toward the conservatives" · [more]
   synonyms: prejudice · influence · color · sway · weight · predispose · [more]
2. give a bias to:
   "bias the ball"
Cauda equina syndrome

Is a rare condition but has serious consequences if not treated promptly. It is most often caused by a large disc herniation in the lower back that compresses the nerve roots at the end of the spinal cord that causes bowel and bladder dysfunction.
Advances in Susceptibility Genetics of Intervertebral Degenerative Disc Disease

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Abstract

The traditional view that the etiology of lumbar disc herniation is primarily due to degenerative biomechanical changes has dominated much of the last century. Recent research indicates that heredity may be largely responsible for the development of spinal degenerative diseases. The role of genetic influences in the etiology of spinal degeneration is likely to be increasingly recognized.

How environmental and hereditary influence, each with a part of contribution at different stages of the disease, will be integrated with the current understanding of the pathobiology of the intervertebral disc degeneration.

Keywords: Intervertebral disc Disease, Degeneration, Candidate Genes, Familial Aggregation
Collagens are a family of proteins that strengthen and support connective tissues, such as skin, bone, cartilage, tendons, and ligaments. Collagens form a network of fibers that create structure and stability within the intervertebral discs.
Gene Has Different Forms (Alleles)

High enzyme activity

- Homozygous dominant (wild type)

Medium enzyme activity

- Heterozygous

Low enzyme activity

- Homozygous recessive
The Basics of Genetics

45 human chromosomes
3 billion DNA subunits
  The bases: A, T, C, G

Approximately 30,000 genes code for proteins that perform most life functions.

**Variant alleles**
Genetic polymorphisms
The search is on to identify variant alleles that yield polymorphisms.

It may be that a single nucleotide polymorphism or “SNP” can be associated with a specific drug or group of drugs.

Opioid receptors – encoded by the OPRM1 gene – has lots of polymorphisms.

They cause differences in pain perceptions and responses to opioids.

An association between opioid mu receptor genotypes, specifically A118G and C17T and their postoperative pain responses in orthopedic trauma.


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.
What Is “Pharmacogenomics”? 

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.
Pharmacogenetics

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

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”

Identification of gènes conferring to individuals who carry them a better sensitivity to the therapeutic action of a medicine or a better tolerance (drug metabolizing enzymes, disease susceptibility factors)
I am allergic to codeine but morphine works?

What did the patient say? Crazy?
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.
**TABLE 4-4** Some examples of genetic polymorphisms in drug metabolism.

<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>CYP2D6</td>
<td>Bufuralol (β-adrenoceptor blocker)</td>
<td>Exacerbation of β blockade, nausea</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2D6</td>
<td>Codeine (analgesic)</td>
<td>Reduced analgesia</td>
</tr>
<tr>
<td>Oxidation</td>
<td>CYP2D6</td>
<td>Debrisoquin (antihypertensive)</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Aldehyde 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>CYP2D6</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>CYP2D6</td>
<td>Sparteine</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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Specialty</th>
<th>Enzyme(s)</th>
<th>Details</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>
</tr>
<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>
Personalized Anesthesia Delivery

Pharmacogenetics

Pharmacogenetic workup of perioperative serotonin syndrome

Nicole C. Beatty, MD (Anesthesiology Resident), Wayne T. Nicholson, MD, PharmD (Assistant Professor of Anesthesiology and Pharmacology), Lorrie J. Langman, PhD (Associate Professor of Laboratory Medicine and Pathology), Timothy B. Curry, MD, PhD (Associate Professor of Anesthesiology), Assistant Professor of Physiology), John H. Eisenach, MD (Associate Professor of Anesthesiology; Assistant Professor of Physiology)
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 provider 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.
Life Long Learning = Better Patient Care!

Miller or Mac?
What is your Allele Variation?

Cranwall       Parrott
Jackson        Phillips
Janeway        Wisconsin
Reduced Flange Robert-Shaw
Macintosh      Siker
Magill         Soper
Miller         Wisconsin-Hipple
Life Long Learning = Better Patient Care!
You use pharmacogenetics everyday

1964

Review Article

Pharmacogenetics and Anesthesia

Werner Kalow, M.D.

The Affordable Care Act – Pre-excising Conditions
Pharmacogenetics of analgesic drugs

Roman Cregg¹², Giovanna Russo³, Anthony Gubbay², Ruth Branford² and Hiroe Sato⁴
Implications of Pharmacogenomics for Anesthesia Providers

Tori Ama, CRNA, MNA
Sou Bounmythavong, CRNA, MNA
Jodee Blaze, CRNA, MNA
Melissa Weismann, CRNA, MNA
Mary Shirk Marienau, CRNA, MS
Wayne T. Nicholson, MD, PharmD
Pharmacogenetics, 1990

Slide adapted from; Chuck Biddle PhD, CRNA Virginia Commonwealth University
Pharmacogenomic Journals, 2007

Slide adapted from; Chuck Biddle PhD, CRNA Virginia Commonwealth University
Life Long Learning = Better Patient Care!

Compare; Pharmacogenetics

How do we practice now?

Evidenced-Based Practice
People tend to pick and choose this!

What if?
Support for Multi-Model

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

By: Kate Maude on Jan 02, 2014

For additional information, contact: SAMBA headquarters at 312-321-6872
A Solution on the Horizon...

Pharmacogenetics!

Pharmacogenetics and Obstetric Anesthesia

Ruth Landau, MD, PD
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Life Long Learning = Better Patient Care!

People react differently to drugs

“One size does not fit all …”

Patient population with same disease phenotype

Genotyping

- Patients with drug toxicity
- Patients with non-response to drug therapy
- Patients with normal response to drug therapy
- Toxic responders
- Non-responders
- Responders

"One size does not fit all …"
Is it Really Necessary?

30% of patients are not benefitting from prescribed medications they are currently taking.

Every year in the US 2.2 million adverse reactions to drugs occur.

Over 100,000 deaths per year are attributed to reactions to prescription drugs.

Genetics are estimated to account for 20-95% of variation in individual responses to drugs.
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
Why Should Anesthesia Providers Test their Patients?

Eliminate trial and error:

“Right Drug, Right Dose, Right Indication, Right Patient, Right Time”

Enhance Patient Satisfaction

Enhance Patient Care

Eliminate “One Size Fits All” medication management

Enhance Compliance

Risk Management: Reduce liability to the anesthesia provider
What about ME?
Life Long Learning = Better Patient Care!
FDA approves 23andMe tests showing risk of developing 10 diseases

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.
Chromosome pair 6

Carriers for a rare condition called ARPKD have a variant in the PKHD1 gene.

View your ARPKD report

Your Information

- Ancestry: 5 reports
- Genetic Health Risk: 6 reports
- Wellness: 8 reports
- DNA Relatives: Click to participate

What you can do

New report: Age-Related Macular Degeneration.

AMD is an eye disease affecting older adults that can cause irreversible vision loss. Genetics is one of many factors that influences whether someone develops AMD.

See your report

Life Long Learning = Better Patient Care!

Or browse by chromosome:

My genetic sequence and detections or non-detection of variants

- **Age-Related Macular Degeneration**
  - Variant detected, not likely at increased risk

- **Hereditary Hemochromatosis (HFE-Related)**
  - Variant detected, not likely at increased risk

- **Late-Onset Alzheimer's Disease**
  - Variant not detected

- **Parkinson's Disease**
  - Variants not detected

- **Alpha-1 Antitrypsin Deficiency**
  - Variants not detected

- **Hereditary Thrombophilia**
  - Variants not detected
Peter, you have one of the two genetic variants we tested.

However, you are not likely at increased risk of developing AMD based on your genetic result. Lifestyle and other factors may also influence your risk.
What do you identify as when it comes to race?

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

Human

Decoding my nationality
Consider a variable response to X?

Genetics

Response
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
Many nonsteroidal anti-inflammatory drugs (NSAIDs) are metabolized by the cytochrome enzyme CYP2C9.

Individuals with the CYP2C9*3 allele metabolize celecoxib, naproxen, piroxicam, ibuprofen, and flurbiprofen more slowly than those without this allele.
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

Average Life Expectancy now 39
Sneezing with peribulbar Injection


Photic sneeze reflex

Autosomal Dominate Compelling Helio-Ophthalmic Outburst reflex

25% of population evoked by the bright light.

Trigeminal


Red Hair? The researchers' findings showed that the old anesthesia provider 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.


Xing Y, Sonner JM, Eger EI 2nd, Cascio M, Sessler DI. Mice with a melanocortin 1 receptor mutation have a slightly greater minimum alveolar concentration than control mice. *Anesthesiology*. 2004;101:544-546.
Women with Red Hair Report A Slightly Increased Rate of Bruising, but Have Normal Coagulation Tests

Edwin B. Liem, M.D.,* Sandra C. Hollensead, M.D.,† Teresa V. Joiner, B.S.N., ‡ and Daniel I. Sessler, M.D.¶**

Author information ►, Copyright and License information ►

Red for danger: the effects of red hair in surgical practice

BMJ 2010; 341 doi: https://doi.org/10.1136/bmj.c6931 (Published 09 December 2010)
Cite this as: BMJ 2010;341:c6931

Kumar VV, Kumar NV, & Isaacson G (2004). Superstition and post-tonsillectomy hemorrhage. The Laryngoscope, 114 (11), 2031-3 PMID: 15510037
Liem EB, Hollensead SC, Joiner TV, & Sessler DI (2006). Women with red hair report a slightly increased rate of bruising but have normal coagulation tests. Anesthesia and Analgesia, 102 (1), 313-8 PMID: 16368849
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.

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.

**CACNA1S**

And RYR1 Gene

Mutation of CACNA1S is responsible for 1% of all cases of MH susceptibility.
Succinylcholine

First used in 1951

MH is associated with more than 30 mutations, and 30% of patients with known MH have one of these mutations.
Side Effects: MDMA--Ecstasy

**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.**

**2012**


3,4-Methylenedioxymethamphetamine (Ecstasy) increases the sensitivity of the contractile apparatus to calcium ions in both malignant hyperthermia-susceptible and normal skeletal muscle fibres.

Gerbershagen MU, Missler G, Schütte JK, Starosse A, Graf BM, Wappler F, Zink W.
Dantrolene Use in 3,4-Methylenedioxyamphetamine ("Ecstasy")-Mediated Hyperthermia
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 -- 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.
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**
Double Homozygous MTHFR Mutation

MTHFR gene mutation have a highly reduced ability **to convert folic acid or even folate into a usable form**. Converting folate into a useable form is essential for DNA synthesis and repair, neurotransmitter production, detoxification, and immune function, thus not being able to do so has many different implications for the body.

**Anesthesia to Avoid by Someone with MTHFR:**
- Nitrous Oxide (Laughing Gas)
- Anesthesia containing adrenaline (epinephrine)
- Propofol – can be toxic to mitochondria.
  - Lactated ringers – can elevate blood lactate levels, contributing to mitochondrial dysfunction

**Safer Anesthesia for a Person with MTHFR:**
- Carbocaine
- Sevoflurane without Nitrous Oxide
- Versed
- Fentanyl
Influence of Nitrous Oxide Anesthesia, B-Vitamins, and MTHFR gene polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial

Peter Nagole, 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.

In vivo study of hepatic oxidative stress and mitochondrial function in rabbits with severe hypotension after propofol prolonged infusion

Sónia Campos, Luís Félix, Carlos Venâncio, Maria de Lurdes Pinto, Francisco Peixoto, Paula Guedes de Pinho, and Luís Antunes

Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy

Schenkman, Kenneth A. MD, PhD; Yan, Shiluo MS

Critical Care Medicine: January 2000 - Volume 28 - Issue 1 - p 172-177
Laboratory Investigations
Sequence variants of the HTR3A gene contribute to the genetic prediction of postoperative nausea in Taiwan

Yi-Mei Joy Lin, Cheng-Da Hsu, Hsiao-Yen Hsieh, Chia-Chih Alex Tseng and H Sunny Sun

Postoperative nausea (PON) is a common complication, and therefore, it is important to identify the associated genetic factors and the candidate predictive markers. Current clinical and basic research suggests that the 5-hydroxytryptamine type 3A receptor (HTR3A) may be important in the occurrence of PON. The association between three single nucleotide polymorphisms (SNPs) of the HTR3A gene and PON was examined to determine whether this can be used to predict the incidence of PON in a unique Taiwanese population without any reported postoperative nausea and vomiting (PONV) risk factors associated with PON occurrence.

One thousand adult surgical patients who received general anesthesia were included in this analysis. A total of 369 patients were finally selected for a two-stage association study. Significant single-locus associations for all three HTRA3 SNPs and PON were identified in both stages. In addition, two of the most common haplotypes, CTG and TAG, showed both a significant risk for and a protective effect against PON, respectively. Our findings support the notion that different haplotypes of HTR3A have reciprocal effects in the etiology of PON. Therefore specific haplotypes of HTR3A may be useful as predictors of PON for 24h immediately after surgery in our population.
Recently added

ZOFRAN, PIROXICAM

Limitations of pharmacogenomic data in FDA-approved drug labels

Summary

Pharmacogenomics
(doi:10.2217/pgs.13.198)

Research Article

Pharmacogenomic biomarkers in drug labels: what do they tell us?

Table of Pharmacogenomic Biomarkers in Drug Labeling
What did Mom and Dad say?

Clinical and genetic risk factors of self-reported penicillin allergy

Andrea J. Apter, MD, MSc\textsuperscript{a,b,c}, Hedi Schelleman, PhD\textsuperscript{b}, Amy Walker, BS\textsuperscript{b}, Kathakali Addya, PhD\textsuperscript{d}, Timothy Rebbeck, PhD\textsuperscript{b}

http://doi.org/10.1016/j.jaci.2008.03.037

Referred to by Jean-Louis Guéant, Rosa-Maria Guéant-Rodriguez, Jose-Antonio Cornejo-Garcia, Marinella Viola, Miguel Blanca, Antonino Romano

Gene variants of IL13, IL4, and IL4RA are predictors of β-lactam allergy

Journal of Allergy and Clinical Immunology, Volume 123, Issue 2, February 2009, Page 509
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
NAT-2 substrates

- Caffeine
- Dapsone
- Hydralazine
- Isoniazid
- Procainamide

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
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

A particular mutation in the F5 gene causes factor V Leiden thrombophilia. The F5 gene provides instructions for making a protein called coagulation factor V. This protein plays a critical role in the coagulation system, which is a series of chemical reactions that forms blood clots in response to injury.
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

Classical drug causes of methemoglobinaemia include antibiotics (trimethoprim, sulfonamides, and dapsone), local anesthetics (especially articaine, benzocaine, and prilocaine), and aniline dyes, metoclopramide, rasburicase, chlorates, and bromates. Celecoxib, Acetaminophen, Ibuprofen

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.
Propofol over 200 gene variations that stop the conversion
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.
Pharmacogenetics of Anesthesia: An Integrative Review
Aroke, Edwin N.; Dungan, Jennifer R.

Nursing Research: July/August 2016 - Volume 65 - Issue 4 - p 318–330
doi: 10.1097/NNR.0000000000000164
Biology Review Series

Abstract

Background Monitoring a patient's response to drug therapy and early identification of an adverse reaction are important responsibilities of nurses. Despite the relative safety of anesthesia practice, 1 in 20 perioperative medication administrations includes a medication error and/or adverse drug reaction. Although several factors contribute to an individual's response to medications, genetic predisposition accounts for over 50% of that response.

Objective The purpose of this review is to explore the evidence of genetic variability associated with response to volatile and intravenous anesthetics.

Methods A comprehensive search of published literature in PubMed, INAH, and Cochrane databases from 1960 to May 30, 2015, was performed. Iterative reading of the primary articles was performed to ensure congruence between the extracted data and the primary article and reduce the data to draw conclusions.

Results The analysis revealed that most anesthetics are metabolized by enzymes in the CYP2 and UGT1 family. CYP2B6 catalyzes propofol and ketamine metabolism. CYP2B6*6 allele is associated with decreased propofol and ketamine metabolism and increased adverse effects. Genetic variants in the UGT1A9 enzyme are associated with the need for higher induction dose and increased clearance of propofol.

Discussion Despite the significant gaps in the literature, current evidence suggests that close monitoring is required when administering anesthetics to individuals with the CYP2B6*6 allele. Future research to address identified gaps in this review may have the potential to identify underlying genetic contribution to anesthetic response and prevent significant adverse events during anesthesia delivery and perioperative nursing care.
Most anesthetics are metabolized by enzymes in the CYP2 and UGT1 family.

CYP2B6 catalyzes propofol and ketamine metabolism.

CYP2B6*6 allele is associated with decreased propofol and ketamine metabolism and increased adverse effects.

Genetic variants in the UGT1A9 enzyme are associated with the need for higher induction dose and increased clearance of propofol.
Another Example: Clopidogrel (Plavix)

Prodrug $\rightarrow$ Drug $\rightarrow$ Inactive

enzyme A $\rightarrow$ enzyme I

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. (FDA has warning)
Pharmacodynamic Interactions: Warfarin

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

Genetics of Warfarin Response


Genetic Determinants of Response to Warfarin during Initial Anticoagulation

Ute I. Schwarz, M.D., Marylyn D. Ritchie, Ph.D., Yuki Bradford, M.S., Chun Li, Ph.D., Scott M. Dudek, B.S., Amy Frye-Anderson, R.N., Richard B. Kim, M.D., Dan M. Roden, M.D., and C. Michael Stein, M.D.

**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**
Beta-Blockers

ADRB variants

Pharmacogenetics of β-Blockers

Jaekyu Shin, Pharm.D. and Julie A. Johnson, Pharm.D.
Beta-Blockers

Areas of study: genes involved in the synthesis of proteins for the adrenergic receptors and that code for G proteins involved in signal transduction.

Possibilities:

1. SNP of gene for angiotensinogen could result in better blood pressure control with atenolol

2. Substitution of Arg instead of Gly at site 389 of the gene for protein of the β1 adrenergic receptor linked to increased affinity for receptor agonist binding

3. Silent polymorphism on exon 5 of gene for α-subunit of Gs-protein, which pairs β-adrenergic receptor activation to cAMP production
ACE-Inhibitors

SNP’s altering RAAS function could lead to enhanced response to ACE-inhibitors

Insertion/deletion polymorphisms of angiotensin converting enzyme; similar responses to ACE-inhibitors
Angiotensin II Blockers

6 possible SNP’s isolated in one study

Angiotensin converting enzyme and angiotensinogen gene
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 an allelic abnormality which is inherited in an X-linked recessive fashion.

The G6PD gene provides instructions for making an enzyme called glucose-6-phosphate dehydrogenase. This enzyme, which is active in virtually all types of cells, is involved in the normal processing of carbohydrates. It plays a critical role in red blood cells, which carry oxygen from the lungs to tissues throughout the body. This enzyme helps protect red blood cells from damage and premature destruction.
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

What is G6PD?

- G6PD is an metabolic enzyme is involved in pentose phosphate pathway, especially important in red blood cell metabolism
- It also protects red blood cells from the effects of potentially harmful molecules called REACTIVE OXYGEN SPECIES
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
Genetics of pain, opioids, and opioid responsiveness

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.
What if?

What if in our life time narcotics are a thing of the past?

SCN9A Which provides instructions for making the sodium channel NaV1.7
Steve Pete has congenital insensitivity to pain

Millius’ Family Erythromelalgia “Man on Fire Syndrome”

In 2004 erythromelalgia became the first human disorder in which it has been possible to associate an ion channel mutation with chronic neuropathic pain; when its pathophysiology was initially published in the Journal of Medical Genetics.

Conversely, in December 2006 a University of Cambridge team reported an SCN9A mutation that resulted in a complete lack of pain sensation
5

Genetics and implications in perioperative analgesia

Andrea M. Trescot, MD, Medical Director *

Pain and Headache Center, Anchorage, AK 99654, USA
Genelex (Seattle) advertises testing for CYP2D6

<table>
<thead>
<tr>
<th>Contraindicated</th>
<th>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>
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<tbody>
<tr>
<td>Major</td>
<td>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>
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<tr>
<td>Moderate</td>
<td>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>
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<tr>
<td>Minor</td>
<td>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</td>
<td>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.
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, hospitalizations and ED visits Seattle, WA—February 23, 2016 – Genelex the makers of YouScript® Precision Prescribing analytics software announces enhanced connection with Epic, the U.S.’s most widely used electronic health...

Life Long Learning = Better Patient Care!
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.
Life Long Learning = Better Patient Care!

BCA Gene

At $149, Color's new at-home BRCA gene test is the cheapest on the market, making gene testing accessible to... more +
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
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

No conversion to morphine means no euphoric effects
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](https://www.fda.gov) for a list of drugs and their associated genetic biomarkers.
Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients

K. Mupapa, M. Massamba, K. Kibadi, K. Kuvula, A. Bwaka, M. Kipasa, R. Colebunders and J. J. Muyembe-Tamfum on behalf of the International Scientific and Technical Committee

Transfusion-Associated Microchimerism in Combat Casualties

CDR James R. Dunn, MD, Tsang-Hoe Lee, MD, PhD, Christopher Barns, MD, Lisa J. Condo, MD, Kathleen Curry, RN, and Michael P. Bara, MD

Background: Fresh whole blood (FwB) is routinely used in the resuscitation of combat casualties in Operation Enduring Freedom and Operation Iraqi Freedom. However, studies have shown high risks of transfusion-associated microchimerism (TAMC) in civilian trauma patients receiving allogeneic red blood cell (RBC) transfusions. We explored the incidence of TAMC in combat casualties receiving FwB compared with patients receiving stored RBC transfusions.

Methods: Prospective data on TAMC at ±4 days posttransfusion were collected from 26 severely injured combat casualties admitted to the National Naval Medical Center between December 2006 and March 2007. Demographic variables included age, sex, injury Severity Score, and transfusion history. Data are expressed as mean ± SD.

Results: The mean age of the study cohort was 24 ± 7 years. Injury Severity Score was 17 ± 2. All were men and suffered penetrating injury. Average hospital length of stay was 46 ± 35 days. TAMC was present in 4% (10 of 22) patients who were transfused at least 1 unit of blood. The four nontransfused patients all tested negative for TAMC. Among six patients who received 4 to 40 units of FwB, five also received RBCs and one apheresis platelets. The remaining 16 transfused patients who received RBCs (11 FwB) included seven who also received platelets in their units. The presence of TAMC was 58% (3 of 6) in FwB patients, 56% in patients given platelets (4 of 8), and 56% (4 of 8) in those given only RBCs in a cellular component (p = 0.1).

Conclusions: Although these preliminary data do not demonstrate a significantly increased rate of TAMC in FwB or apheresis platelets recipients compared with RBC recipients, the overall 56% (10 of 22) rate of TAMC in transfused soldiers warrants further study to ascertain possible clinical consequences such as graft-versus-host or autoimmune disease syndromes.

Key Words: Microchimerism, Transfusion, Combat, Blood, Allogenic, Autoimmune, T cell.

J Trauma. 2008;65:552-554.
One Person, Two Sets of DNA (Chimera)

People that have two different sets of DNA are called human chimeras.

It can happen when a woman is pregnant with fraternal twins and one embryo dies very early on. The other embryo can "absorb" its twin's cells.

It can also happen after a bone marrow transplant, and (in a smaller scale) during normal pregnancy.
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

Pharmacogenetic testing costs
The price of testing ranges from $250 to $500. The cost of pharmacogenetic testing required by FDA is generally reimbursed by most insurance plans.
# The ethics of DNA databasing

*This house believes that people's DNA sequences are their business, and nobody else's.*

### Opening statements

<table>
<thead>
<tr>
<th>Defending the proposition</th>
<th>Against the proposition</th>
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<td>Professor Arthur Caplan</td>
<td>Mr. Craig Venter</td>
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Economist Debates

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In 7 hours...a statement from guest speaker Professor Soren Holm.

1. Get alerts!
More Information about Pharmacogenomics

http://www.pharmgkb.org/

http://pharmacogenomics.ucsd.edu

http://www.phgfoundation.org/tutorials/pharmacogenomics/index.html
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
**SAMPLE REPORT**

**MENTAL HEALTH DNA INSIGHT®**

**Protected Health Information**

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Test Results Reviewed & Approved by:
Laboratory Director,
Nilesh Dharajiy, M.D.

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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.”
CYP2C19 G681A Benzo's
We all fear what we don’t know – it’s natural.
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.
Chronic Cough
Life Long Learning = Better Patient Care!

Thank you

pstrube3000@yahoo.com

608-469-1750