Introduction
Academic Background
Academic Background
Academic Background
Academic Background
Research Trajectory
Research Trajectory

Genetics!

Using Model Organisms in Genetics

Human Genetics
Genetics of Chronic Disease

Using Model Organisms in Genetics

Human Genetics

Research Trajectory
Research Trajectory

- Genetics
- Using Model Organisms in Genetics
- Genetics of Chronic Disease
- Human Genetics
- Pharmacogenomics
Research Trajectory

- Genetics!
- Using Model Organisms in Genetics
- Genomics of Chronic Disease
- Pharmacogenomics
- Human Genetics
- Molecular System of Precision Medicine
Research Trajectory

- Genetics!
- Genetics of Chronic Disease
- Pharmacogenomics
- Using Model Organisms in Genetics
- Human Genetics
- Molecular System of Precision Medicine
Research Trajectory

1. Genetics
2. Using Model Organisms in Genetics
3. Human Genetics
4. Genetics of Chronic Disease
5. Pharmacogenomics
6. Molecular System of Precision Medicine
A Bit of Genetics

- Single Nucleotide Polymorphism (SNP) refers to a single base change
- ~10 Million SNPs in human genome
- ~3 Million SNPs between any 2 random people
What is Pharmacogenomics?

- The study of how genes affect a person’s response to drugs
- Combines the fields of pharmacology and genomics
Figure 1. Trends in the percentage of persons using prescription drugs: United States, 1999–2008

- **Use of 1 or more drugs**: 43.5% in 1999–2000, 46.2% in 2001–2002, 47.6% in 2003–2004, 46.8% in 2005–2006, 148.3% in 2007–2008


NOTE: Age adjusted by direct method to the year 2000 projected U.S. population.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.
Prescription Drug Use

2.6 billion drugs ordered/provided in the U.S. in 2010
Why Pharmacogenomics?

Reasons for Drug-Related Emergency Department (ED) Visits, by Year: 2004 to 2011

*The estimate for ED visits involving adverse reactions in 2004 was suppressed due to low statistical precision.
Pharmacogenomic Successes
Pharmacogenomic Successes
Pharmacogenomic Successes

Clinical Pharmacogenetics Implementation Consortium Guideline for \textit{SLCO1B1} and Simvastatin-Induced Myopathy: 2014 Update

LB Ramsey$^1$, SG Johnson$^{2,3}$, KE Caudle$^1$, CE Haida$^1$, D Voora$^4$, RA Wilke$^{5,6}$, WD Maxwell$^7$, HL McLeod$^8$, RM Krauss$^9$, DM Roden$^{10,11}$, Q Feng$^{10,11}$, RM Cooper-DeHoff$^{12}$, L Gong$^{13}$, TE Klein$^{13}$, M Wadelius$^{14}$ and M Niemi$^{15,16}$

Simvastatin is among the most commonly used prescription medications for cholesterol reduction. A single coding single-nucleotide polymorphism, rs4149056T>G, in \textit{SLCO1B1} increases systemic exposure to simvastatin and the risk of muscle toxicity. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for simvastatin based on \textit{SLCO1B1} genotype. This article is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium guideline for \textit{SLCO1B1} and simvastatin-induced myopathy.

Implementation Consortium guideline for \textit{SLCO1B1} and simvastatin-induced myopathy have not changed and are included here. However, this updated guideline also provides a brief review regarding \textit{SLCO1B1} genotype and risk of myopathy for other statins. Furthermore, the accompanying supplementary material has been updated, including the addition of resources to facilitate incorporation of \textit{SLCO1B1} pharmacogenetics into an electronic health record with clinical decision support.

**DUG: SIMVASTATIN**

**Background**

In 2012, simvastatin was the most commonly prescribed generic statin formulation in the United States (http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012). The most common statin-related adverse drug reaction (ADR) is skeletal muscle toxicity. Statin-related muscle problems include muscle pain, weakness, and myalgia.

**FOCUSED LITERATURE REVIEW AND UPDATE**

Simvastatin is the most commonly used prescription medication for cholesterol reduction and is associated with the development of muscle pain, weakness, and myalgia. The prevalence of this ADR varies by dose and is generally low (less than 10%). The most common ADRs associated with simvastatin are muscle pain, weakness, and myalgia. The prevalence of these ADRs is generally low (less than 10%). The most common ADRs associated with simvastatin are muscle pain, weakness, and myalgia. The prevalence of these ADRs is generally low (less than 10%).

**Abstract**

Simvastatin is one of the most commonly prescribed medications for cholesterol reduction. A single coding single-nucleotide polymorphism, rs4149056T>G, in \textit{SLCO1B1} increases systemic exposure to simvastatin and the risk of muscle toxicity. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for simvastatin based on \textit{SLCO1B1} genotype. This article is an update to the 2012 Clinical Pharmacogenetics Implementation Consortium guideline for \textit{SLCO1B1} and simvastatin-induced myopathy. This update to the 2012 guideline provides information that enables the interpretation of \textit{SLCO1B1} genotype tests so that the results can be used to guide dosing of simvastatin. Detailed guidelines for the use of simvastatin are beyond the scope of this article. Although polymorphisms in \textit{SLCO1B1} affect multiple statins, the strength of the evidence is highest for simvastatin.

**Conclusions**

Simvastatin is the most commonly used prescription medication for cholesterol reduction and is associated with the development of muscle pain, weakness, and myalgia. The prevalence of this ADR varies by dose and is generally low (less than 10%). The most common ADRs associated with simvastatin are muscle pain, weakness, and myalgia. The prevalence of these ADRs is generally low (less than 10%). The most common ADRs associated with simvastatin are muscle pain, weakness, and myalgia. The prevalence of these ADRs is generally low (less than 10%).

**References**

Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis


Summary
Background. Clopidogrel and prasugrel are subject to efflux via Pglycoprotein (encoded by ABCB1, also known as MDR1). ABCB1 polymorphisms, particularly 3435C>T, may affect drug transport and efficacy. We aimed to assess the effect of this polymorphism by itself and alongside variants in CYP2C19 on cardiovascular outcomes in patients treated with clopidogrel or prasugrel in TRITON-TIMI 38. We also assessed the effect of genotypes on the pharmacodynamic and pharmacokinetic properties of these drugs in healthy individuals.

Methods. We genotyped ABCB1 in 2,932 patients with acute coronary syndromes undergoing percutaneous intervention who were treated with clopidogrel (n=1,471) or prasugrel (n=1,461) in the TRITON-TIMI 38 trial. We evaluated the association between ABCB1 3435C>T and rates of the primary efficacy endpoint (cardiovascular death, myocardial infarction, or stroke) until 30 months. We then assessed the combined effect of ABCB1 3435C>T genotype and reduced-function alleles of CYP2C19. 321 healthy individuals were also genotyped, and we tested the association of genetic variants with reduced in maximum platelet aggregation and plasma concentrations of active drug metabolites.

Findings. In patients treated with clopidogrel, ABCB1 3435C>T genotype was significantly associated with the risk of cardiovascular death, myocardial infarction, or stroke (p=0.0064). TT homozygotes had a 72% increased risk of the primary endpoint compared with CC/TG individuals (Kaplan-Meier event rates 12.9% [95% CI 8.8-17.0%] vs 7.8% [95% CI 4.0-12.4%]). In patients treated with prasugrel, ABCB1 3435C>T and CYP2C19 genotypes were significant independent predictors of the primary endpoint, and 48% of the US genotyped patients taking clopidogrel who were either CYP2C19 reduced-function allele carriers, ABCB1 3435TT homozygotes, or both were at increased risk of the primary endpoint (HR 1.97, 95% CI 1.38-2.82, p=0.002). In healthy participants, 3435 TT homozygotes had an absolute reduction in maximum platelet aggregation with clopidogrel that was 7.3 percentage points less than for CC/TG individuals (p=0.0127). ABCB1 genotypes were not significantly associated with clinical or pharmacological outcomes in patients with an acute coronary syndrome or healthy individuals treated with clopidogrel, respectively.
Genetics Research with Tangible Population Benefits

• Cannot change DNA but we can:
  – Help prevent ADRs
  – Rescue previously withdrawn products/failed pharmacologic targets
  – Inform clinical administration
The Pharmacogenomics of QT-Prolonging Medications
Study Aims

Identify genetic variants that modify the association between QT-prolonging medications and QT interval
What is in a Heart Beat
Ventricular Conduction on the Electrocardiogram
Ventricular Conduction on the Electrocardiogram

Depolarization
Ventricular Conduction on the Electrocardiogram
Ventricular Conduction on the Electrocardiogram

Depolarization

Repolarization

QT Interval
QT INTERVAL

- **QRS = Depolarization = Contracting Muscle**

- **JT = Repolarization = Relaxing Muscle**

- **QT = Ventricular Conduction = QRS + JT**
Risks of QT Prolongation

- Cardiac arrhythmias
- Coronary heart disease
- Chronic heart failure
- Stroke
- Cardiovascular and all-cause mortality
Drug-Induced QT Prolongation

- Drug-induced QT prolongation is the most common cause of medication withdrawal/relabeling
- Currently 170+ medications known to prolong QT
- FDA begins considering regulation of drugs after just 5 ms increase in QT
Genetics of QT Interval

• QT is between 25-50% heritable

• Currently 40+ genetic loci associated with QT duration
Pharmaceuticals Under Study

- Thiazide Diuretics
- Sulfonylureas
- Tri and Tetra-Cyclic Antidepressants
CHARGE Populations
Exposed Participants Compared to Total Participants
Statistical Analysis

• Genome-wide analysis
  – Linear regression
    \[ Y = a_1x_1 + a_2x_2 + a_3x_3 \ldots \]

• Adjusted for
  – Heart rate
  – Clinical covariates
  – Principal components of ancestry
Statistical Analysis

• Genome-wide analysis
  – Linear regression
    \[ Y = a_1x_1 + a_2x_2 + a_3x_3. \]

• Adjusted for
  – Heart rate
  – Clinical covariates
  – Principal components of ancestry

- Surveys most of the genome
- Enables testing of multiple, genome-wide (~2.5+ million) variants without any prior hypothesis
SULFONYLUREAS

MANHATTAN PLOT OF QT INTERVAL RESULTS IN EUROPEANS

Floyd, J. S., et al. (2016). "Large-scale pharmacogenomic study of sulfonylureas and the QT, JT and QRS intervals. CHARGE Pharmacogenomics Working Group." Pharmacogenomics J.
SULFONYLUREAS

Manhattan Plot of QT Interval Results in Europeans

Sulfonylureas

But the Result that is Really Interesting is only Suggestive

Sulfonylureas

But the Result that is Really Interesting is only Suggestive

SULFONYLUREAS

But the Result that is Really Interesting is only Suggestive

---

But what about other race/ethnic groups?
Exposed Participants Compared to Total Participants
Exposed Participants Compared to Total Participants
Diversity is Critical in Genomics Research

Genetic analyses of diverse populations improve discovery for complex traits

Genevieve L. Wojcik1,25, Mariaelisa Graf2,25, Katherine K. Nishimura3,25, Ran Tao4,5,25, Jeffrey Haessler1,25, Christopher R. Ginogou1,3,25, Heather M. Highland1,25, Yesha M. Pare1,25, Elena P. Sorokin1, Christy L. Avery2, Gillian M. Belbin3,25, Stephanie A. Bien3, Iona Cheng6,7, Sinead Cullinan8,9, Chani J. Hodonsky2, Yao Hu2, Laura M. Huckins11, Janina Jeff8,9, Anne E. Justice1, Jonathan M. Kocarnik1, Unhee Lim12, Bridget M. Lin1, Yingchang Lu9, Sarah C. Nelson13, Sung-Shim L. Park1, Hannah Poisner8,9, Michael H. Preuss1, Melissa A. Richard14, Claudia Schurmann7,15,16, Veronica W. Setiawan7, Alexandra Sockell1, Karon Vah1, Marie Verbanck1, Abhishek Vishnu1, Ryan W. Walker9, Kristin L. Young2, Niha Zubaib1, Victor Acuna-Alonso15, Jose Luis Ambite17, Kathleen C. Barnes8, Eric Boerwinkle18, Erwin P. Bettinger9,19, Carlos D. Bustamante12, Christian Caberto12, Samuel Canizales-Quinteros20, Matthew P. Conomos11, Ewa Deelman12, Ron Do19, Kimberly Doheny10, Lindsay Fernández-Rhodes22,25, Myrram Fornage14, Benyam Halli12, Gerardo Heiss8, Brenna M. Henn9, Lucia A. Hindorff25, Rebecca D. Jackson26, Cecelia A. Laurie13, Cathy C. Laurie13, Yuqing Li10,27, Dan-Yu Lin1, Andres Moreno-Estrada28, Girish Nadkarni19, Paul J. Norman8, Loreal C. Pooler1, Alexander P. Reiner23, Jane Romm27, Chiara Sabatti1, Karla Sandoval29, Xin Sheng1, Eli A. Stahl25, Daniel O. Stram7, Timothy A. Thornton13, Christina L. Wassel30, Tynne R. Wilkens15, Cheryl A. Winkler30, Sacha Yoneyama30, Steven Buyske31,36, Christopher A. Haiman24,26, Charles Kooperberg1,36, Loic Le Marchand12,36, Ruth J. Loos4,11,36, Tara C. Matise13,36a, Karl E. North2,36, Ulrike Peters3,36, Eimic E. Kenny9,31,34,36a & Christopher S. Carlson3,36a

Genome-wide association studies (GWAS) have laid the foundation for investigations into the biology of complex traits, drug development and clinical guidelines. However, the majority of discovery efforts are based on data from populations of European ancestry1-3. In light of the differential genetic architecture that is known to exist between populations, bias in representation can exacerbate existing disease and healthcare disparities. Critical variants may be missed if they have a low frequency or are rare in the United States—where minority populations have a disproportionately higher burden of chronic conditions13— resulting in inequitable access to precision medicine for those with the highest burden of disease. We strongly advocate for continued, large genome-wide efforts in diverse populations to maximize genetic discovery and reduce health disparities.

The P4CE study was developed by the National Human Genome...
This is Particularly Important in Pharmacogenomics
Do these differences really matter?
Simulating the Importance of Diversity in Pharmacogenomics

We will simulate a population, based on real-world data, to quantify the benefits of pharmacogenomics testing and determine if these benefits are disproportionately gained by European-descent populations.
How will we do this?

• Simulate a population of patients who are all taking warfarin
  – Use real world data to help define the characteristics of this population
  – This is done by running SAS on the UNC Longleaf computing cluster
How will we do this?

• Consider 3 different scenarios
  1. No pharmacogenomics
  2. Use a warfarin pharmacogenomics dosing formula based only on research from European descent populations
  3. Use a warfarin pharmacogenomics dosing formula based on research from both European and African American populations
Project Pieces

- Lit Review

- Use SAS to simulate variables

- Use Longleaf to run the simulation 10,000 times
Project Pieces

- Lit Review

- Use SAS to simulate variables

- Use Longleaf to run the simulation 10,000 times

LITERATURE REVIEW

- We want our simulated population to resemble the real world as much as possible

- Need to answer questions like
  - How many people on warfarin develop a bleed?
  - Are chronic disease states (e.g. diabetes, hypertension, etc.) common among warfarin users?
  - What percentage of warfarin users are male and female?
Project Pieces

• Lit Review

• Use SAS to simulate variables

SIMULATION CODE IN SAS

• We use SAS to simulate each needed variable for each individual patient in our simulated population

*Coding Genotype (x1);
probMinorAlleleHomo = &minorallelefreq.**2;
probMajorAlleleHomo = (1-&minorallelefreq.)*2;

x1 = 1;
if z >= 1-probMajorAlleleHomo then x1 = 0;
if z <= probMinorAlleleHomo then x1 = 2;

z=ranuni(&i+2000000);

*Coding Age (x2);

x2 = &meanage. + &sdage. * rannor(&i+3000000);
Project Pieces

• Lit Review

• Use SAS to simulate variables

• Use Longleaf to run the simulation 10,000 times

Using Longleaf to Run the Simulations
• Once we have our code written we will need to run it on the UNC Longleaf computing clusters because it might crash our local machines
Questions?