African American Pharmacogenomics: Challenge Accepted

Minoli Perera PharmD, PhD
Minorities in Pharmacogenomics

- More studies in European descent populations
- Most of the clinical studies in African Americans involve SNPs found in other populations
- Correct for race
- What are we missing
  - Variation unique to African Americans
  - Effect of genetic architecture on association.

- African are the oldest population – more genetic variation
- African Americans are admixed (a mix between Europeans and Africans)
- Disparities in disease (breast cancer)
- Difference in drug metabolism (CYP3A5)
Warfarin Pharmacogenomics

- Previous genomic and GWAS studies were done almost exclusively in Whites and Asians.
  - Major genes: CYP2C9, VKORC1, CYP4F2

- African Americans
  - Warfarin dose variability less well explained by VKORC1 and CYP2C9.
  - Suggested other genes/SNPs may be important.

- Genetic determinants of high dose requirement.
  - Current genetic predictors help explain low dose requirements.
  - African Americans require higher doses than other populations.
A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing


A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohrke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group

Results

EU-PACT - European population

COAG - Ethnically diverse population

Courtesy of Larisa Cavallari
African Americans

COAG - African American subgroup

Courtesy of Larisa Cavallari
African American GWAS

Genotyped the top 15 independent signals (found after conditioning) in replication cohort.

Only SNP to replicate is rs12777823 (p = 5.04E-05)

MAF = 25% - 47% carry one allele

Previously been found to be associated with Clopidogrel response in Amish

R² = 0.87 in Amish with CYP2C19*2 (rs4244285)


R² = 0.5 in AA with CYP2C19*2 (p = 0.001 in GWAs meta-analysis)

Unable to pinpoint the function of this SNP using gene expression data.

Perera et al. Lancet 2013
Exome Study (N = 100)

- Sequence the extremes of the dose distribution
- Exome-wide significant hit in FPGS
  - Replicate in a second cohort
  - potential splice variants
  - completely absent in European Ancestry populations.

Daneshjou et al. Blood 2014
African Americans and VTE

- African Americans are disproportionately affect by this disease.
- Secondary phenotypes from the Warfarin study added additional healthy African Americans.
- Our cases were younger and there was significantly association with African ancestry

## GWAS Results

<table>
<thead>
<tr>
<th>Chr.</th>
<th>SNP</th>
<th>MAF</th>
<th>OR</th>
<th>p-value</th>
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<tbody>
<tr>
<td>7</td>
<td>rs73692310</td>
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<td>1.73 x 10^{-9}</td>
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<td>18</td>
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<td>rs1998081</td>
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<td>2.28</td>
<td>5.17 x 10^{-7}</td>
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Hernandez et.al. *Blood*, in press
GWAS Results

Novel biomarker:

<table>
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<tr>
<th>Chr</th>
<th>SNP</th>
<th>Allele</th>
<th>Discovery Cohort</th>
<th>Previous Studies</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>AF</td>
<td>OR (95% CI)</td>
</tr>
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<td>NA</td>
</tr>
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<tr>
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<tr>
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</tbody>
</table>
Our newest study – bleeding risk

- African American suffer from a higher rate of warfarin related bleeding than other populations.
- Many bleed at therapeutic INRs
  - A majority were INR<4
- Genetic predictors of adverse event
  - Improve anticoagulant selection

Poster PT-03, for our newest work by Dr. De
Understanding Gene Regulations Drug Metabolizing Enzymes

- New directions
  - Several phenotypes and several transcriptomes
  - First in-depth evaluation African American drug metabolism

GWAS Genotyping

Baseline and after Enzyme induction

RNA-seq

eQTLs

Absorption Phase
Elimination Phase
AUC
To those that make it possible

- Perera Lab
- Mentors
  - Nancy Cox
  - Mark Ratain
  - Julie Johnson
  - Russ Altman
- Collaborators (too many to list)
- Funding
  - NIH
  - AHA
  - PGRN, RIKEN
- Patients
To my Support System.
QUESTIONS?

GOD... THE HUMAN GENOME CODE'S BEEN UNRAVELLED

DAMN HACKERS!!! NOW, I HAVE TO CHANGE THE PASSWORD