African American Pharmacogenomics: Challenge Accepted

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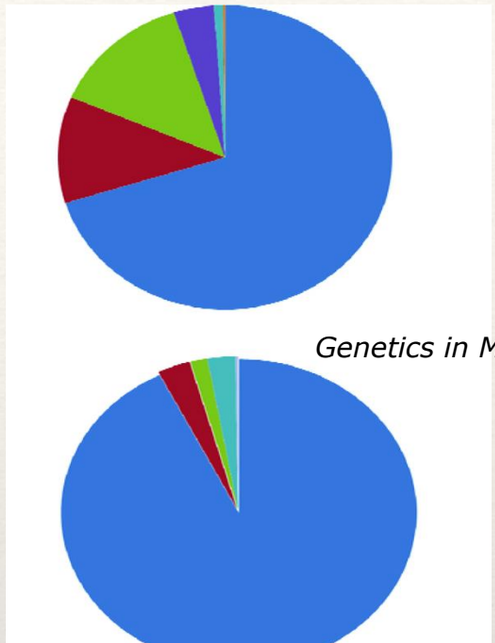
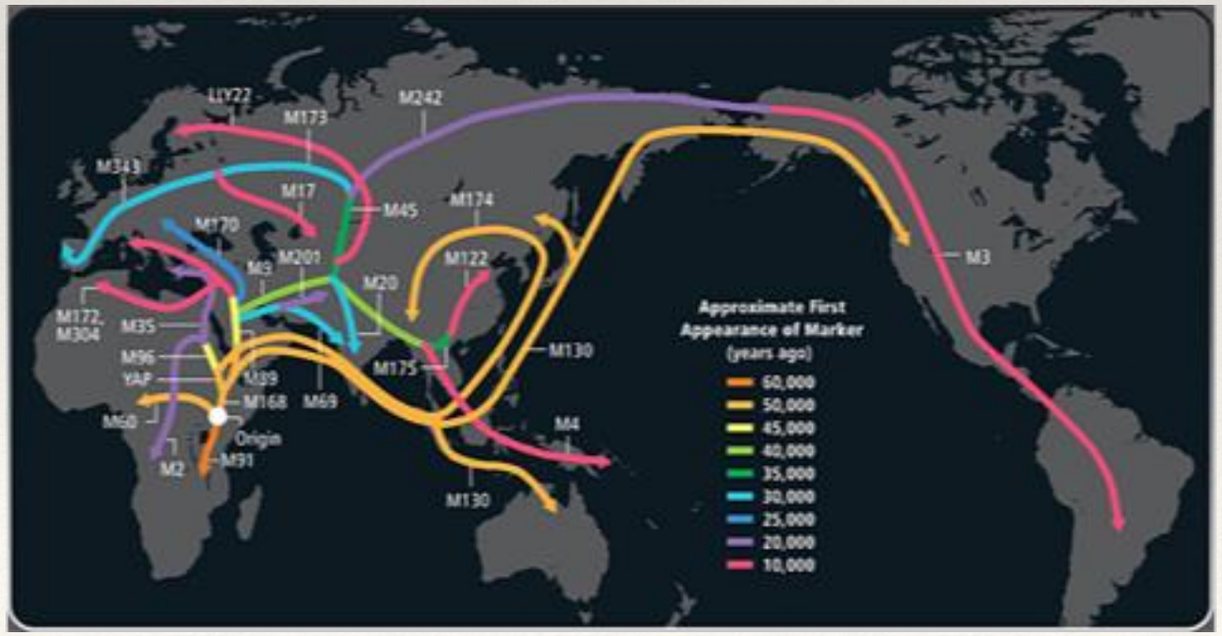
Minorities in Pharmacogenomics

- 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.



Genetics in Medicine (2010) **12**, 81–84



- 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.

The NEW ENGLAND JOURNAL of MEDICINE

COAG trial

ORIGINAL ARTICLE

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Stephen E. Kimmel, M.D., Benjamin French, Ph.D., Scott E. Kasner, M.D., Julie A. Johnson, Pharm.D., Jeffrey L. Anderson, M.D., Brian F. Gage, M.D., Yves D. Rosenberg, M.D., Charles S. Eby, M.D., Rosemary A. Madigan, R.N., M.P.H., Robert B. McBane, M.D., Sherif Z. Abdel-Rahman, Ph.D., Scott M. Stevens, M.D., Steven Yale, M.D., Emile R. Mohler, III, M.D., Margaret C. Fang, M.D., Vinay Shah, M.D., Richard B. Horenstein, M.D., Nita A. Limdi, Pharm.D., Ph.D., James A.S. Muldowney, III, M.D., Jaspal Gujral, M.B., B.S., Patrice Delafontaine, M.D., Robert J. Desnick, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Henny H. Billett, M.D., Robert C. Pendleton, M.D., Nancy L. Geller, Ph.D., Jonathan L. Halperin, M.D., Samuel Z. Goldhaber, M.D., Michael D. Caldwell, M.D., Ph.D., Robert M. Califf, M.D., and Jonas H. Ellenberg, Ph.D., for the COAG Investigators*

N Engl J Med 2013; 369:2283-2293 | December 12, 2013 | DOI: 10.1056/NEJMoa1310669

EU-PACT trial

ORIGINAL ARTICLE

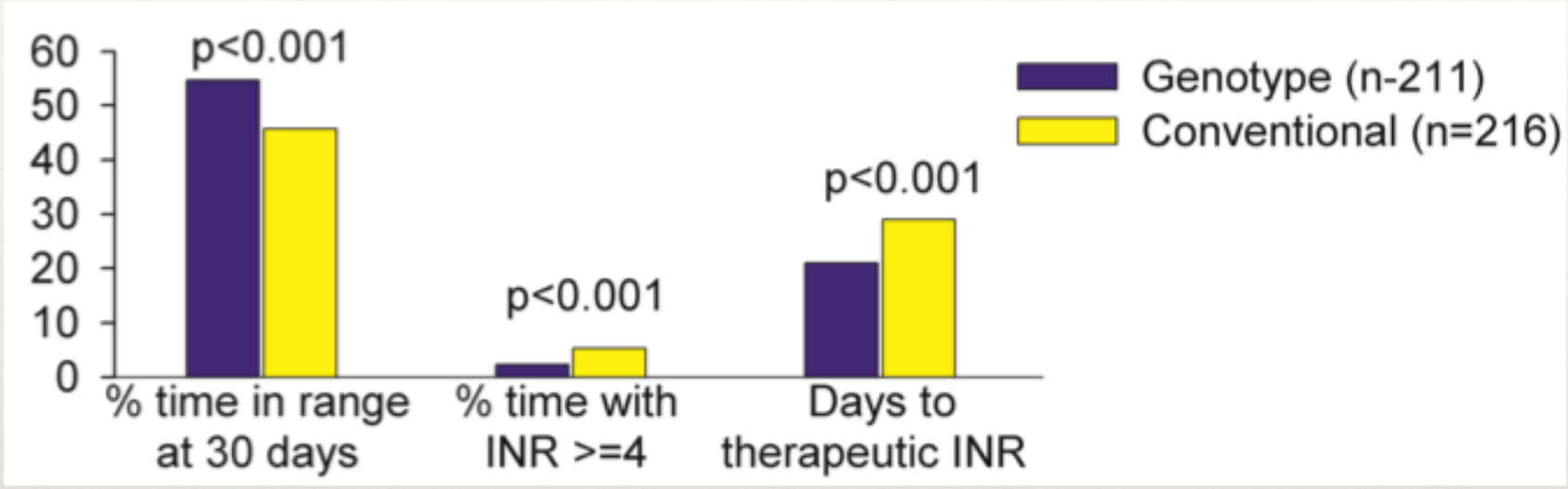
A Randomized Trial of Genotype-Guided Dosing of Warfarin

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 Kohnke, 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*

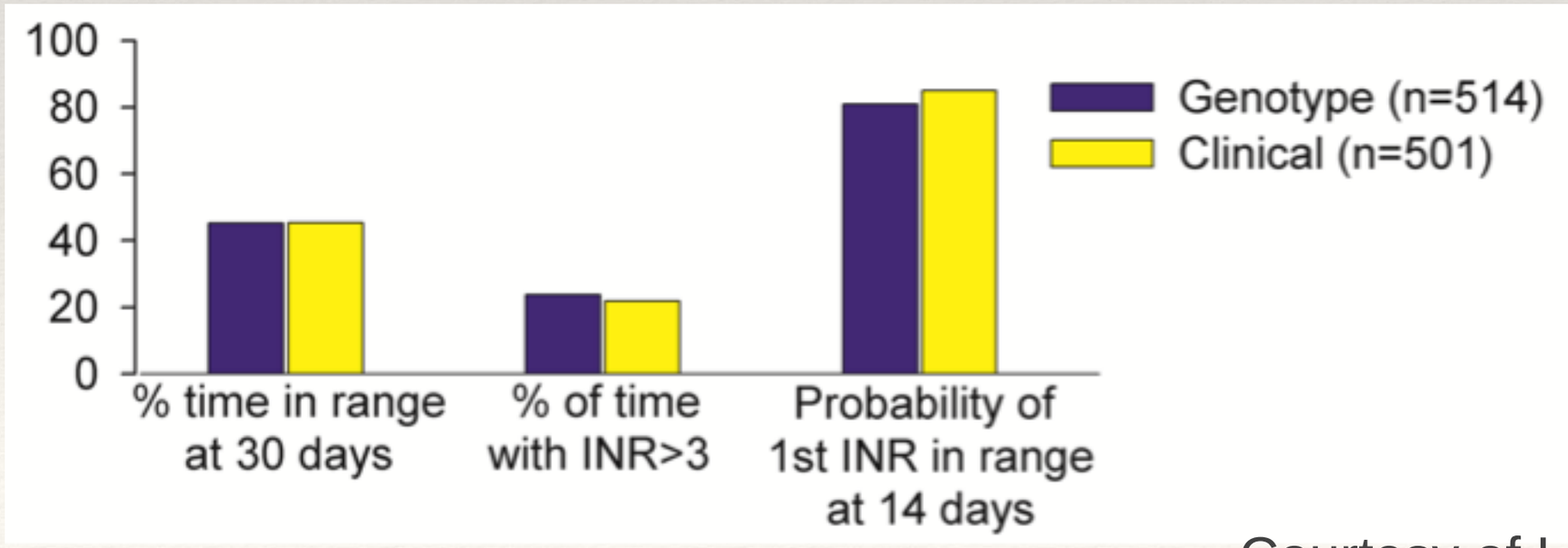
N Engl J Med 2013; 369:2294-2303 | December 12, 2013 | DOI: 10.1056/NEJMoa1311386

Results

EU-PACT - European population



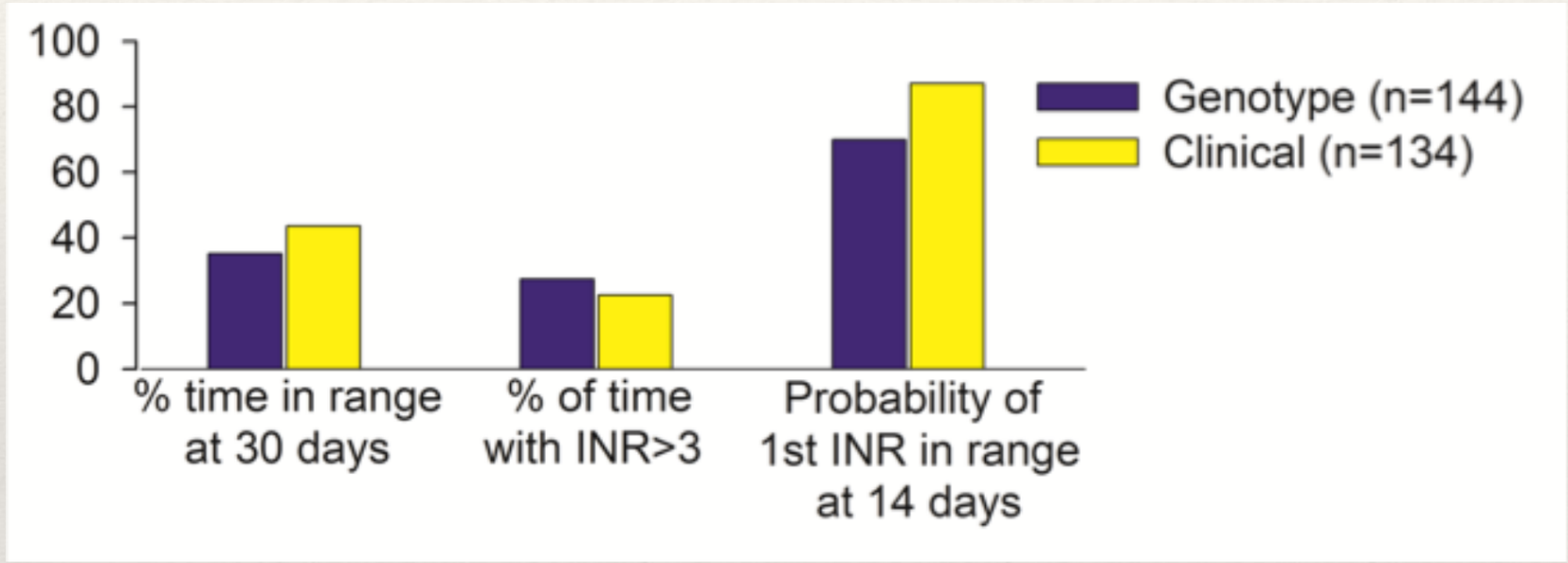
COAG - Ethnically diverse population



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)

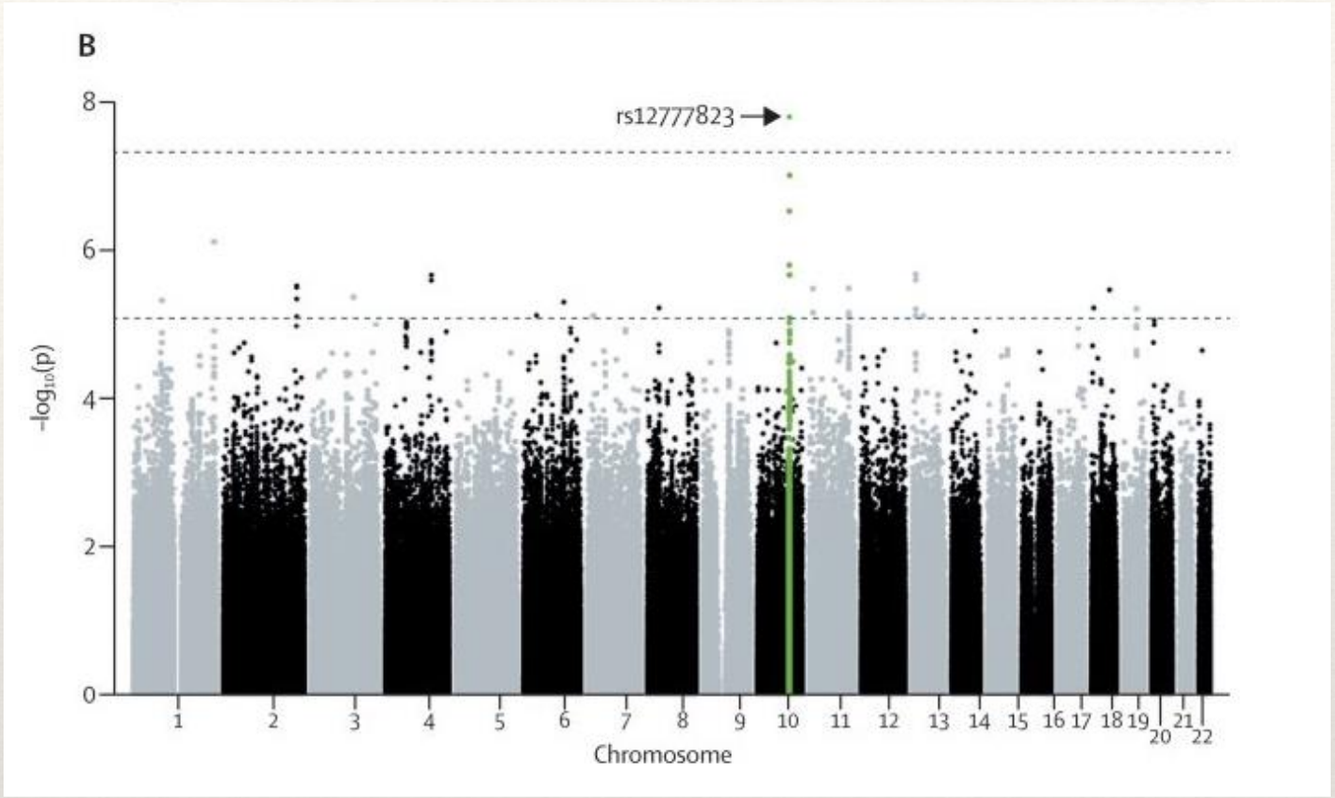
MAF = 25% - 47% carry one allele

Previously been found to be associated with Clopidogrel response in Amish

R^2 = 0.87 in Amish with CYP2C19*2 (rs4244285)

JAMA. 2009 Aug 26;302(8):849-57.

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



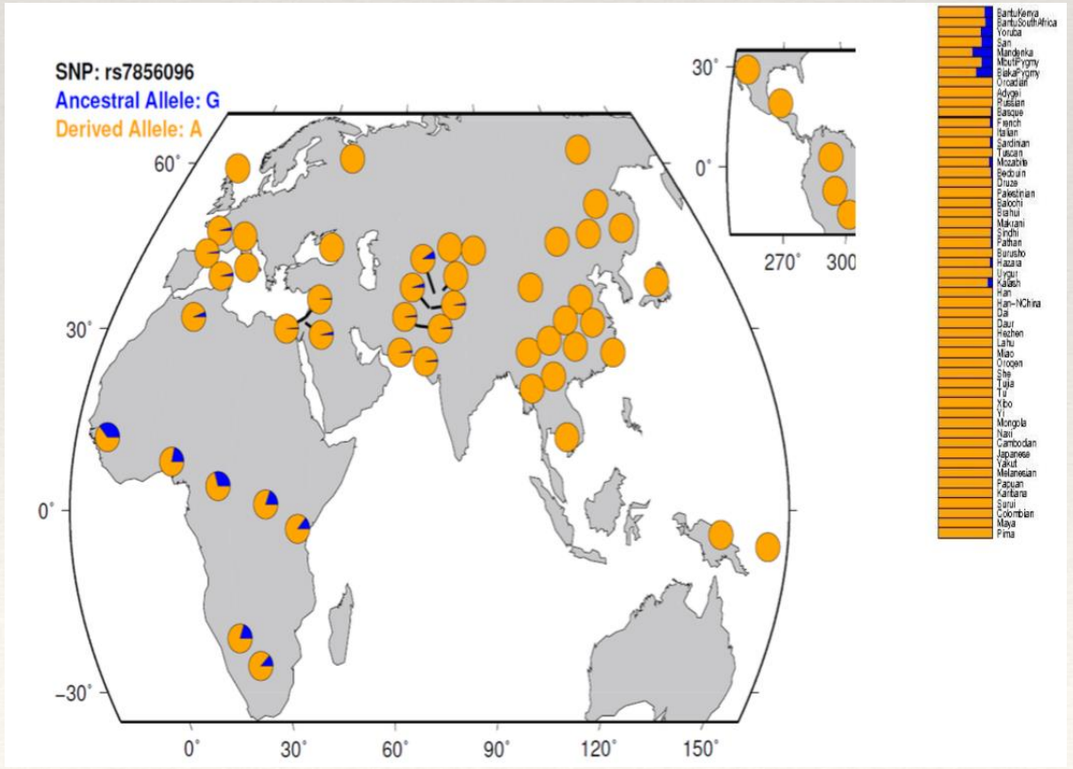
Variant	Coefficient	p-value	Adjusted R-squared
IWPC Dosing Equation Predicted Dose	1	<2e-16	0.2193
rs12777823 AG	-6.9175	6.76E-06	–
rs12777823 AA	-9.3388	0.000502	–
IWPC Dosing Equation + rs1277823			0.2666

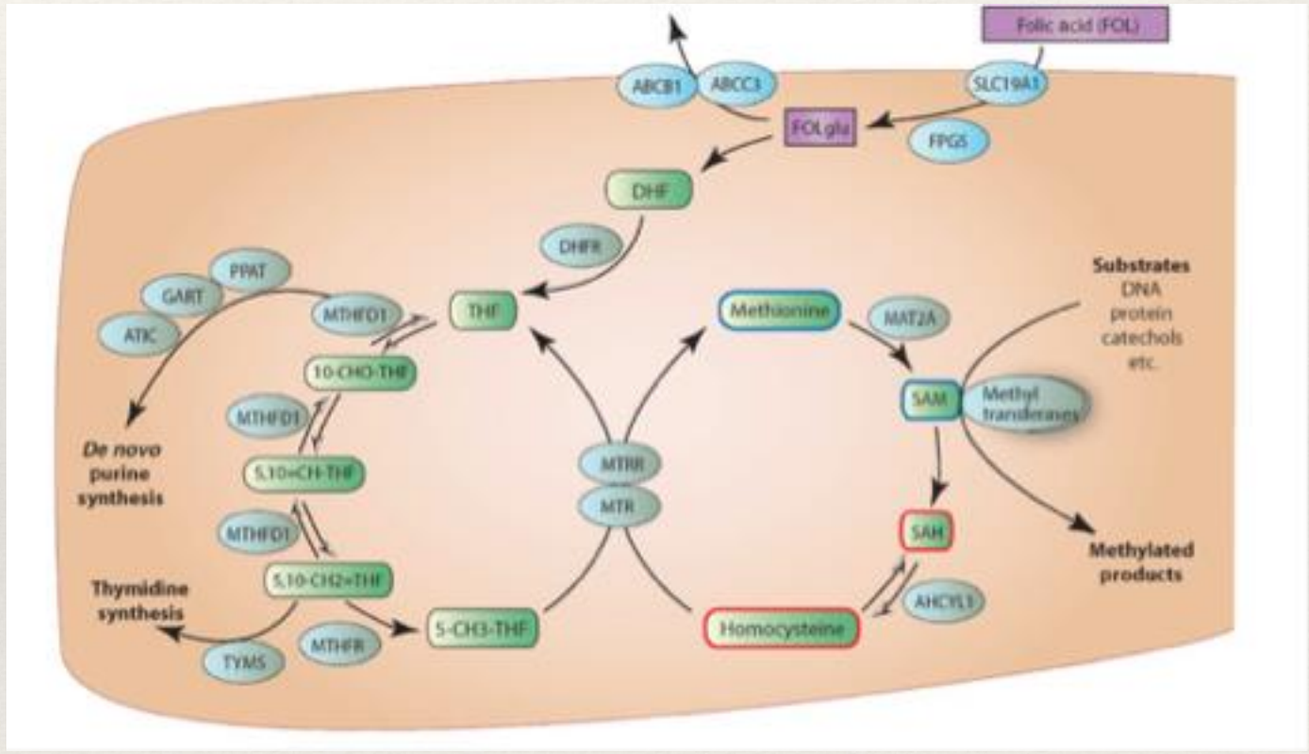
Unable to pin point the function of this SNP using gene expression data.

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.

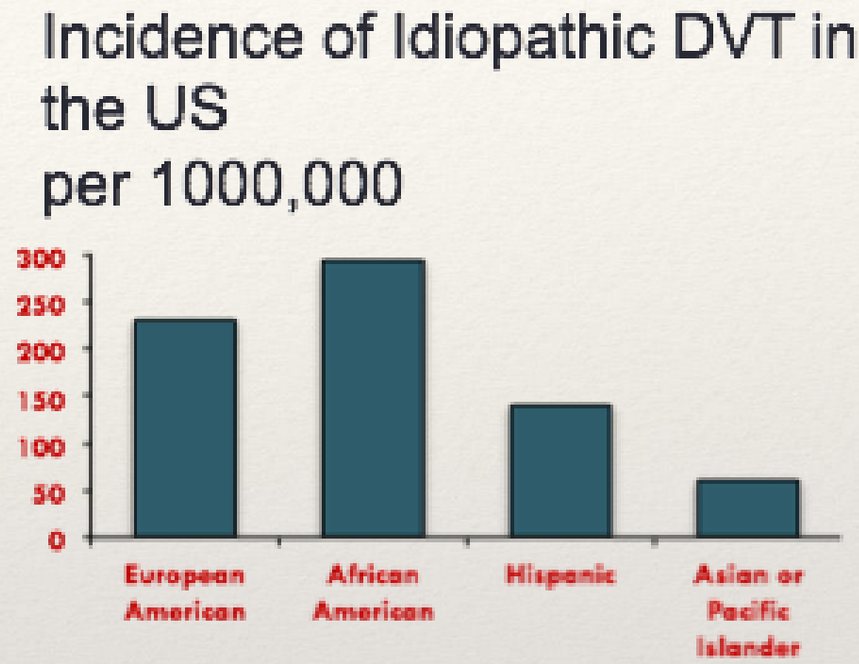


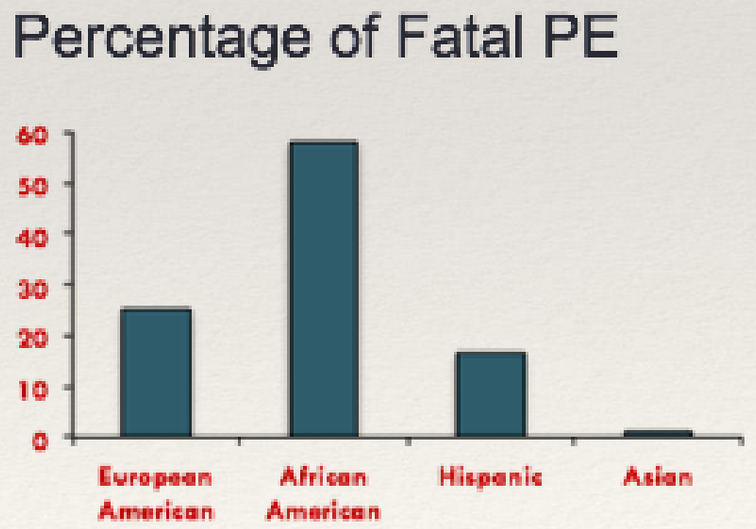


Daneshjou et al. *Blood* 2014

African Americans and VTE

- African Americans are disproportionally 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

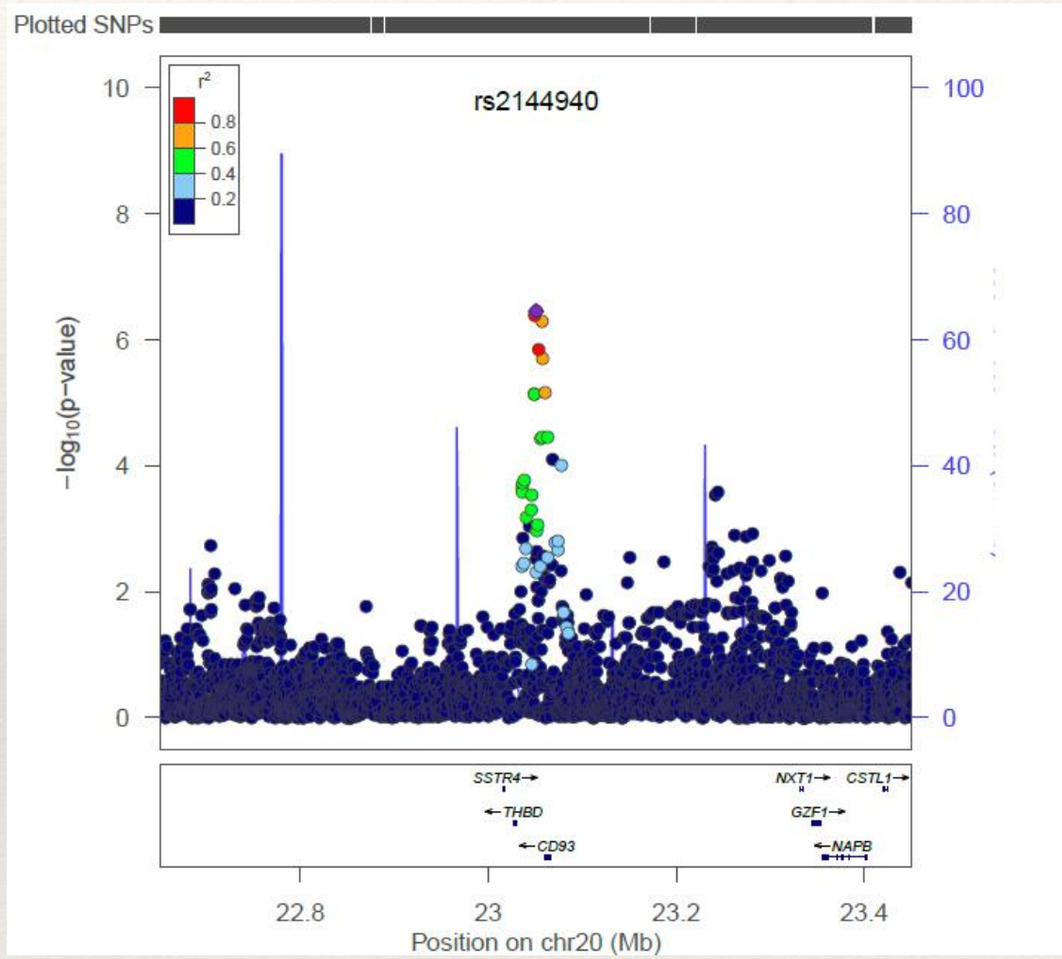




White RH et al. *Ann Intern Med*, 1998

GWAS Results

Chr.	SNP	MAF	OR	p-value
7	rs73692310	0.08	3.04	1.73×10^{-9}
18	rs28496996	0.11	2.48	1.73×10^{-8}
18	rs58952918	0.10	2.44	1.07×10^{-8}
20	rs2144940	0.21	2.18	3.52×10^{-7}
20	rs2567617	0.21	2.17	4.01×10^{-7}
4	rs62322307	0.08	2.79	2.25×10^{-7}
20	rs1998081	0.17	2.28	5.17×10^{-7}



Hernandez et.al. *Blood*, in press

GWAS Results

Novel biomarker:

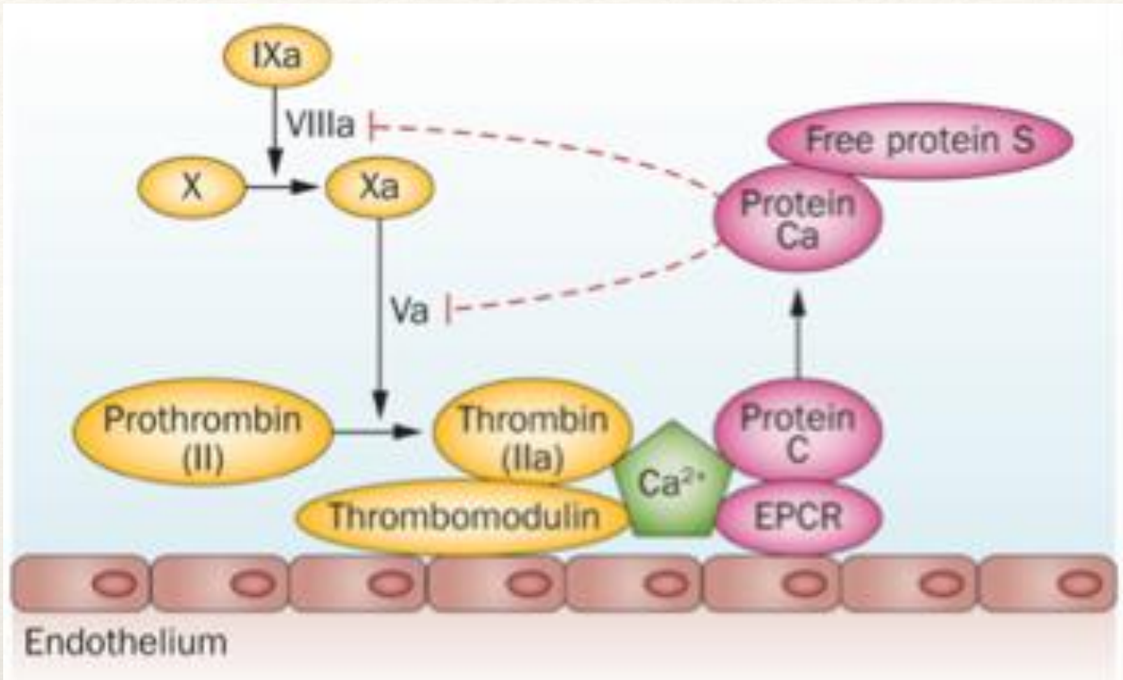


Table 4. Comparison of previously identified VTE risk alleles between the Discovery Cohort and Caucasians

			Discovery Cohort			Previous Studies			
Chr	**SNP**	**Allele**	**AF**	**OR (95% CI)**	**P**	AF	OR	P	Reference
1	rs6025 (*F5*)	T	0.0	NA	NA	0.06♦	2.56♦	1.40×10^{-12}	(11)
11	rs1799963 (*F2*)	A	0.0	NA	NA	0.02♦	1.69♦	3.00×10^{-2}	(11)
9	rs687621 (*ABO*)	G	0.43	1.55 (1.2-2.0)	0.002	0.43‡	1.84‡	6.69×10^{-22}	(10)
9	rs505922 (*ABO*)	C	0.36	1.52 (1.2-2.0)	0.002	0.43‡	1.85‡	1.84×10^{-22}	(10)
9	rs657152 (*ABO*)	A	0.44	1.39 (1.1-1.8)	0.03	0.45‡	1.7‡	2.00×10^{-17}	(10)
10	rs78707713 (*TSPAN15*)	T	0.97†	NA	NA	0.88•	1.28•	5.74×10^{-11}	(28)
19	rs2288904 (*SLC44A2*)	G	0.93	0.90 (0.5-1.5)	0.75	0.79•	1.19•	1.07×10^{-9}	(28)

Our newest study – bleeding risk

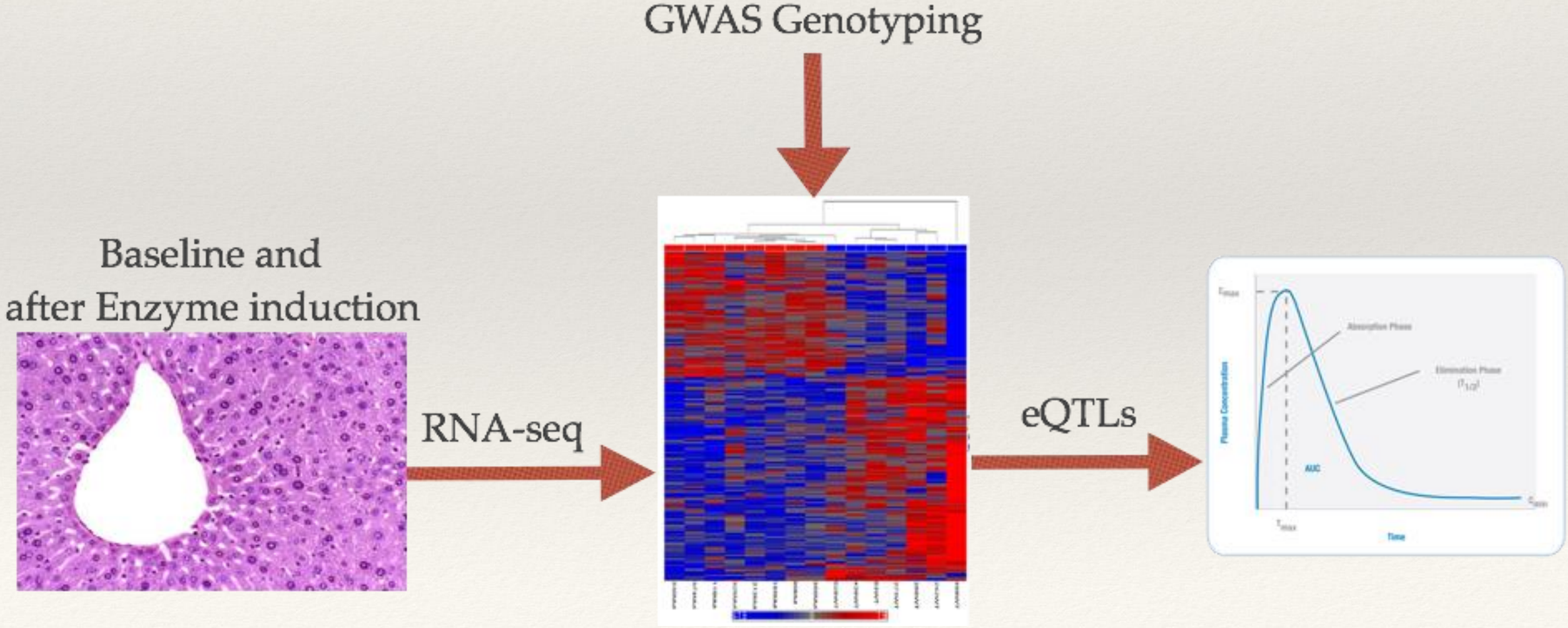
- African American suffer from a higher rate of warfarin related bleeding than other populations.
- Many bleed at therapeutic INRs
  - A majority were INR<4
- Genetic predictors of adverse event
  - Improve anticoagulant selection

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



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