

MULTI-SITE INVESTIGATION OF GENETIC
DETERMINANTS OF WARFARIN DOSE VARIABILITY
AMONG LATINOS

Nihal El Rouby, Ph.D.
Postdoctoral Associate

Mentor: Dr. Larisa Cavallari, Pharm.D.

Department of Pharmacotherapy and Translational Research
University of Florida College of Pharmacy

Background and introduction

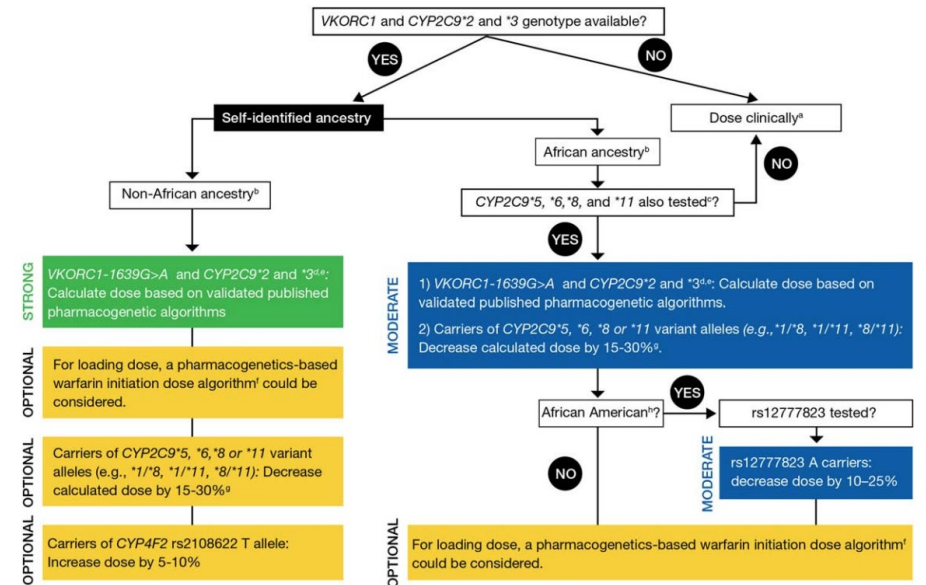
Warfarin remains a widely used anticoagulant medication

Dosing guidance exists for African and Non-African Ancestry

Large Inter-Patient Variability in dose

Narrow Therapeutic Index

Adverse events related to **over anticoagulation** or **under-anticoagulation**



Aims of the research

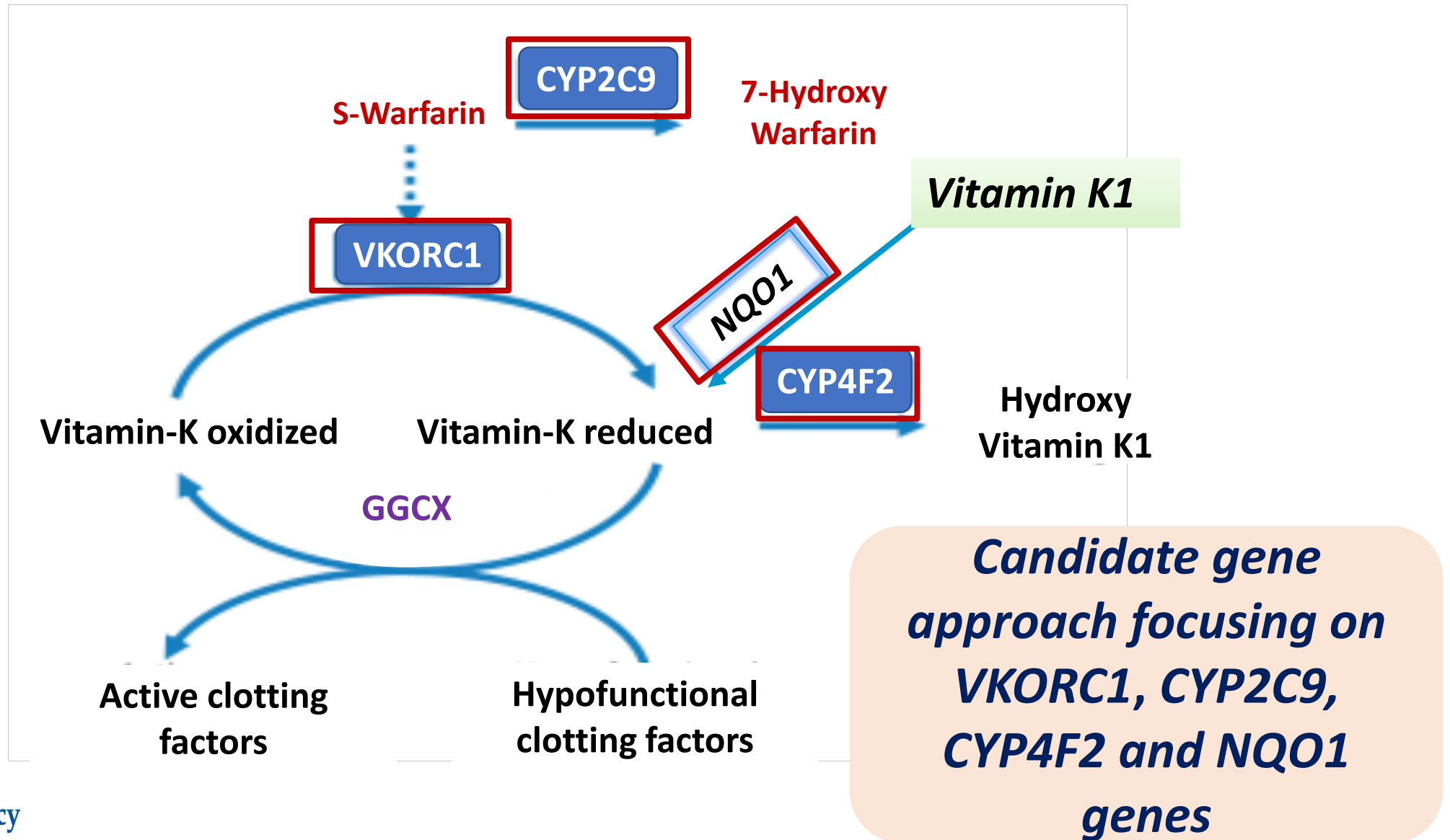
With Limited data on Pharmacogenetics- Guided Warfarin Dosing in Hispanics

Investigate the contribution of genetic factors to warfarin dose variability among largest cohort of patients with Hispanic ancestry across US and Brazil

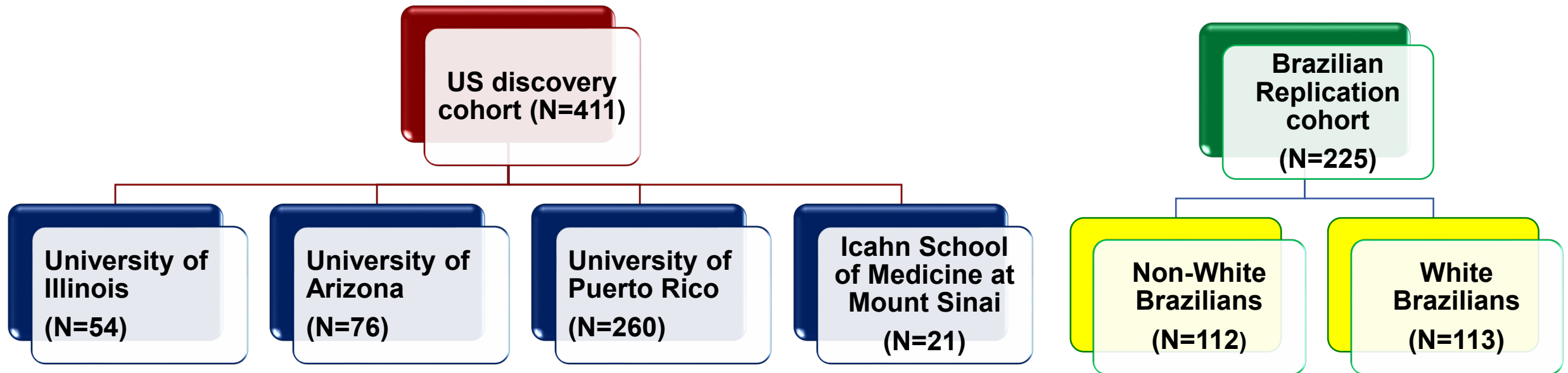


***Research goal:* Individualize warfarin dosing in Hispanics**

Candidate gene approach



Participating cohorts



Participating sites contributed clinical and genetic data with genotypes for variants in *VKORC1*, *CYP2C9*, *CYP4F2*, and *NQO1*

Analysis steps

1

- DNA was genotyped at each site for variants in *VKORC1* (rs9923231), *CYP2C9* (*2,*3,*8,*11), *CYP4F2* (rs2108622), *NQO1*(rs1800566)

2

- Stable warfarin dose was defined as a dose that resulted in therapeutic INR for two-three consecutive visits

3

- Univariate analysis of log transformed warfarin dose was tested against each SNP in the combined US cohort

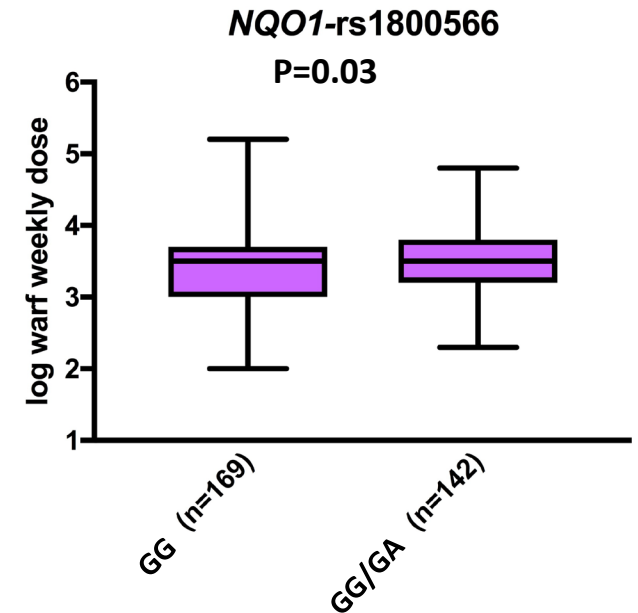
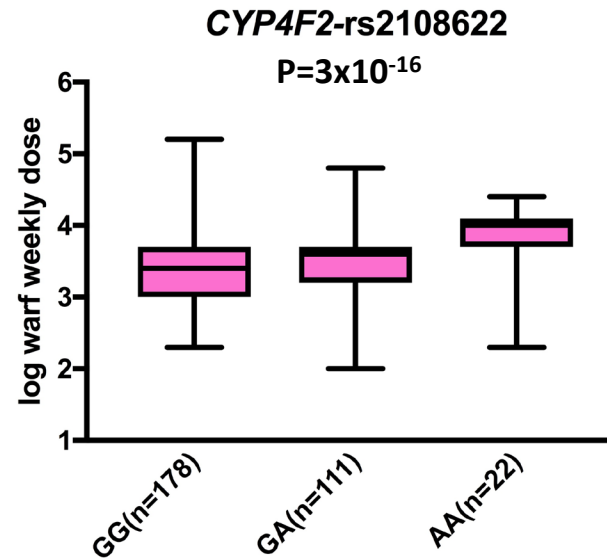
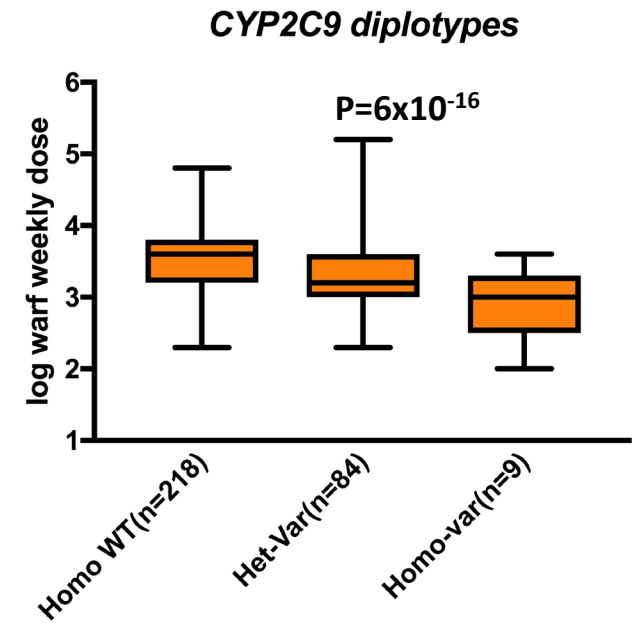
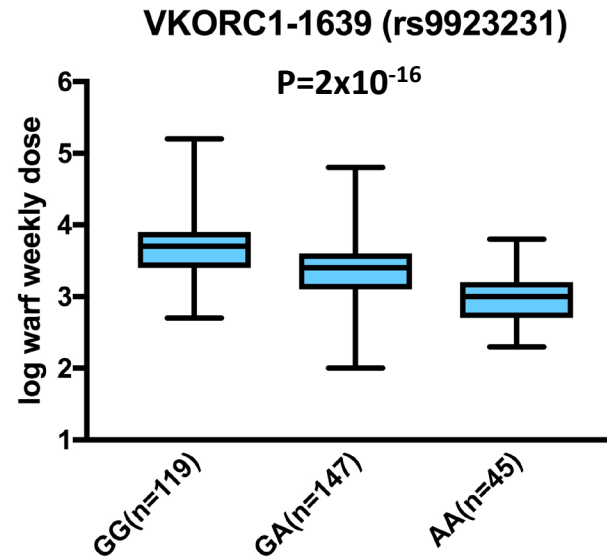
4

- Stepwise linear multiple regression was performed in the combined US cohort including clinical predictors and genotypes

5

- Model association was tested in Brazilian cohorts

Univariate analysis of SNPs with warfarin dose



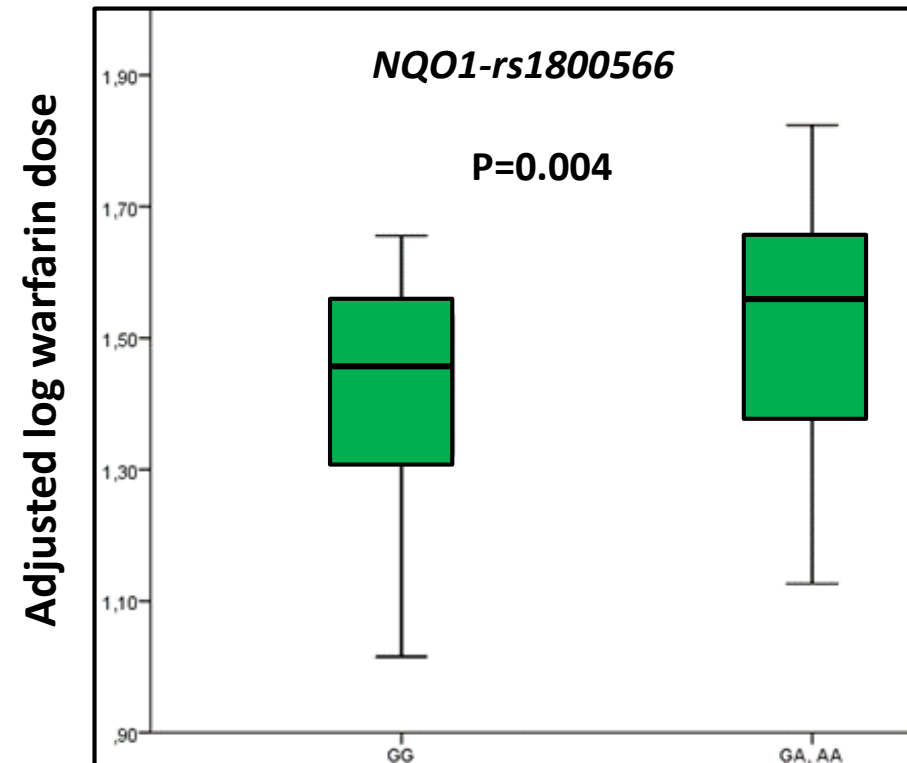
Multiple linear regression in US cohorts

	Model 1		Model 2		Model 3	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Intercept	3.1 (0.3)	3×10^{-35}	3.5 (0.2)	9×10^{-51}	3.5 (0.2)	3×10^{-42}
Age	-0.01 (0.002)	4×10^{-9}	-0.01 (0.002)	1×10^{-9}	-0.01 (0.002)	5×10^{-8}
BSA	0.5 (0.1)	8×10^{-6}	0.34 (0.08)	1×10^{-5}	0.36 (0.08)	6×10^{-5}
Carbamazepine	0.5 (0.3)	0.05	0.6 (0.2)	0.006	0.6 (0.2)	0.005
VKORC1-1639	-	-	-0.3(0.03)	2×10^{-23}	-0.3(0.03)	6×10^{-19}
CYP2C9	-	-	-0.2(0.03)	2×10^{-9}	-0.2(0.04)	2×10^{-7}
CYP4F2	-	-	-	-	0.1 (0.03)	4×10^{-4}
NQO1	-	-	-	-	0.13 (0.04)	0.01
Adjusted R ²	17%		41%		45%	

BSA: Body Surface Area; CYP2C9: variant carrier; CYP4F2:rs2108622; NQO1:rs1800566

Warfarin association in non-whites Brazilians

	Non-white Brazilians	
	β (SE)	p-value
Age	0.1(0.04)	0.001
BMI	0.009 (0.003)	0.001
<i>VKORC1-1639</i>	-0.2(0.02)	<0.001
<i>CYP2C9</i>	-0.004(0.001)	<0.0001
<i>NQO1</i>	0.05 (0.03)	0.01
Adjusted R ²	53.5%	



Summary and Future Direction

- * Warfarin association with clinical characteristics, *VKORC1* and *CYP2C9* genotypes was confirmed in Hispanics among US sites and Brazil
- * We were able to explain 45-53% of warfarin dose variability by including the four genes in the model
- * Warfarin association with the missense *NQO1* SNP in the non-white patients of Brazil is intriguing
- * Dissecting the association of *NQO1* and understanding the mechanistic underpinning is warranted

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