PHARMACOGENETICS IN ADMIXED POPULATIONS:

Brazil as a model case

Guilherme Suarez-Kurtz
Instituto Nacional de Câncer
Rio de Janeiro - Brazil

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Brazilian population

Highly heterogeneous and admixed,

the result of 500 years of inter-ethnic mating between

Native Amerindians, Europeans and sub-Saharan Africans

Sources of the tri-hybrid Brazilian population

1500	~ 2.5 M	Amerindians
1500 - 1808	~ 0.5 M	Portuguese colonizers
1872 - 1975	~ 5.0 M	European immigrants

Portugal	1.6 M
Italy	1.8 M
Spain	0.8 M
Germany	0.25 M

1551 - 1880	~ 3.6 M	enslaved Sub-Saharan Africans

"... the combinations of marriage (in Brazil) between white, indian and black are so manifold that the nuances of flesh color are countless."

Gobineau, French Minister, Rio de Janeiro, 1869

Tarsila do Amaral
***Operários*, 1933**

Data from Brazilian Census 2010

Color/"race" Categories		Individuals	
		N	%
White	(*Branco*)	92.003	48,43
Brown	(*Pardo*)	83.196	43,80
Black	(*Preto*)	12.987	6,84
Amerindian	(*Indígena*)	1.101	0,58
Yellow	(*Amarelo*)	536	0,28
Undeclared		130	0,07

99%

Source: www.ibge.gov.br

The Pharmacogenomics Journal (2004) 4, 347–348

EDITORIAL

G Suarez-Kurtz

Pharmacogenomics in admixed populations: the Brazilian pharmacogenetics/pharmacogenomics network—REFARGEN

www.refargen.org.br

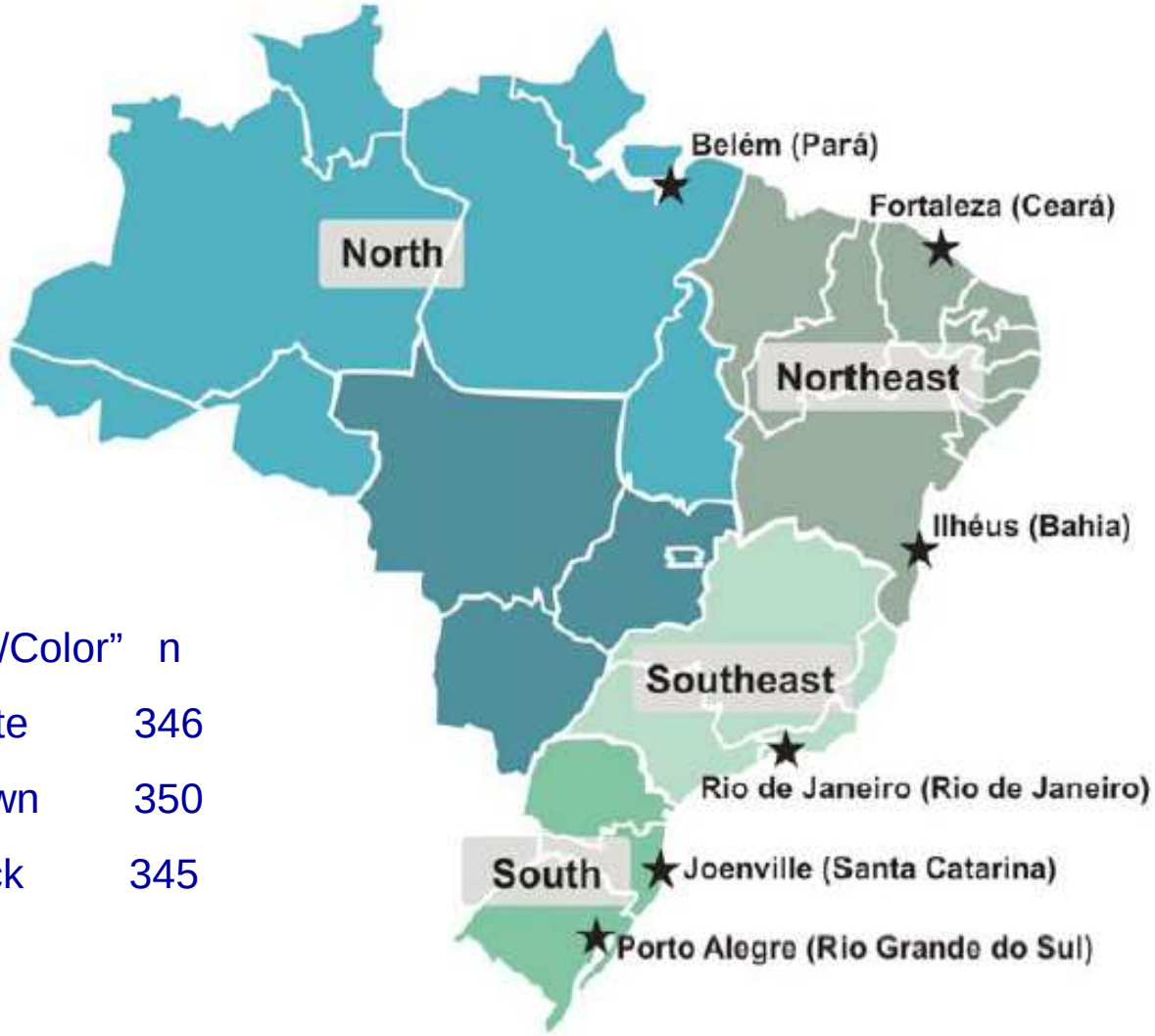
Pharmacogenetic polymorphisms among Brazilians

REFARGEN Study Cohort

★Recruitment sites

Region	n
NO	254
NE	265
SE	264
SU	258

"Race/Color"	n
White	346
Brown	350
Black	345



Pharmacogenetic polymorphisms among Brazilians (1)

REFARGEN-Finep project

Frequency data for PGx polymorphisms in

CYPs 1A2, 2C8, 2C9, 2C19, 2D6, 3A5

GSTM1, GSTT1, COMT, TPMT, NAT2

ABCB1, SLCO1B1, SLCO1B3 and *VKORC1*

may be assessed at

http://www.refargen.org.br//rubrique.php3?id_rubrique=28

Data are presented for White, Brown and Black individuals

in the North, Northeast, Southeast and South regions,

and for the overall Brazilian population.

Pharmacogenetic polymorphisms among Brazilians (2)

REFARGEN-PGENI project

Frequency data for 1,936 genetic variants in 231 genes

included in the DMET-Plus platform

may be assessed at

http://www.refargen.org.br//rubrique.php3?id_rubrique=28

Data are presented for White, Brown and Black individuals

from the Southeast region

Biogeographical ancestry of Brazilians

Panels of ancestry-informative markers have been used

to estimate the individual proportions of the

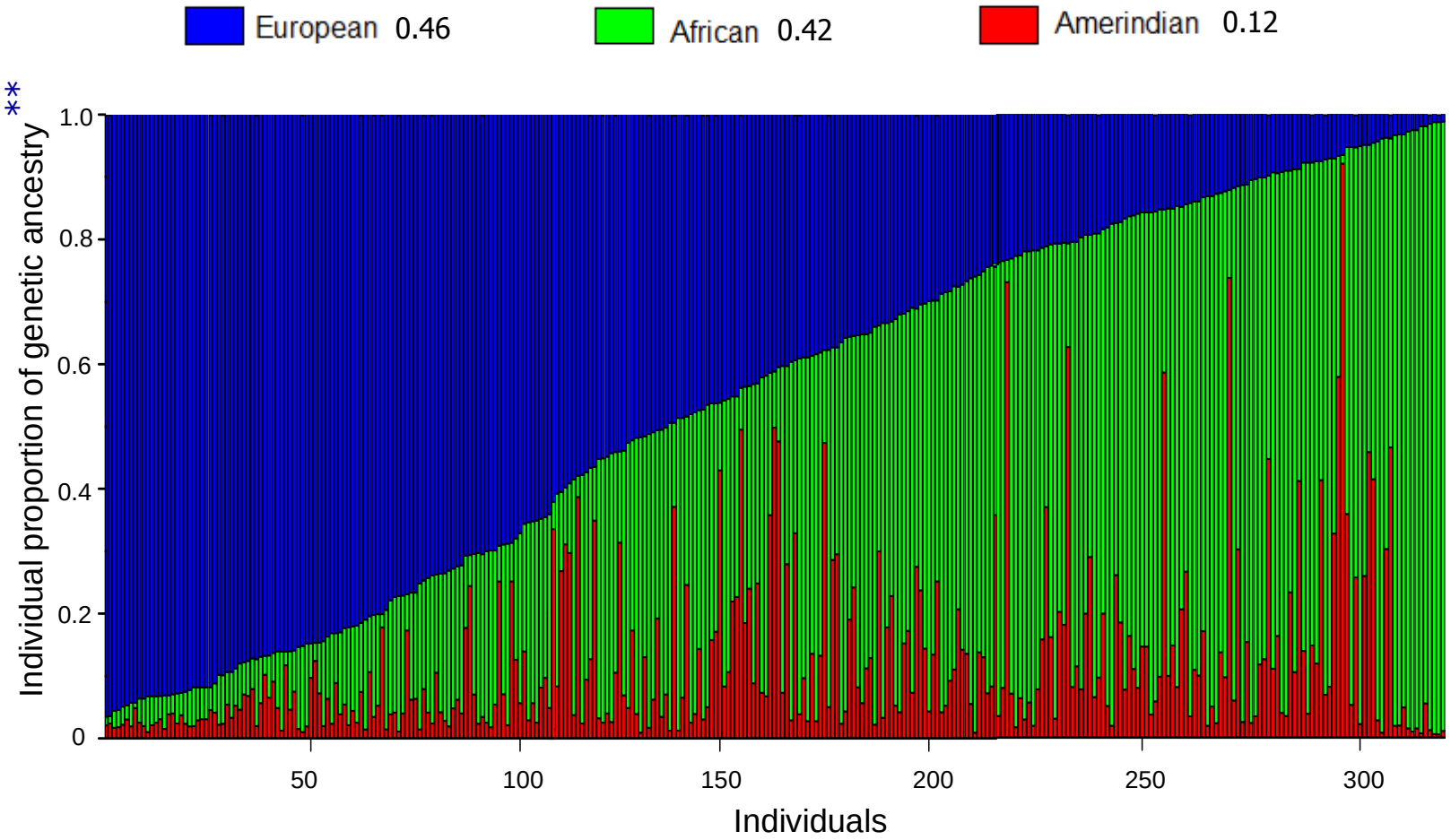
three major ancestral roots of Brazilians, namely

- Native American
- European
- Sub-Saharan African

Biogeographical ancestry of BLACK Brazilians

Suarez-Kurtz *et al*., *Pharmacogenomics J,* 2010

Average proportions of biogeographical ancestry *



Zoom in for better visualization.

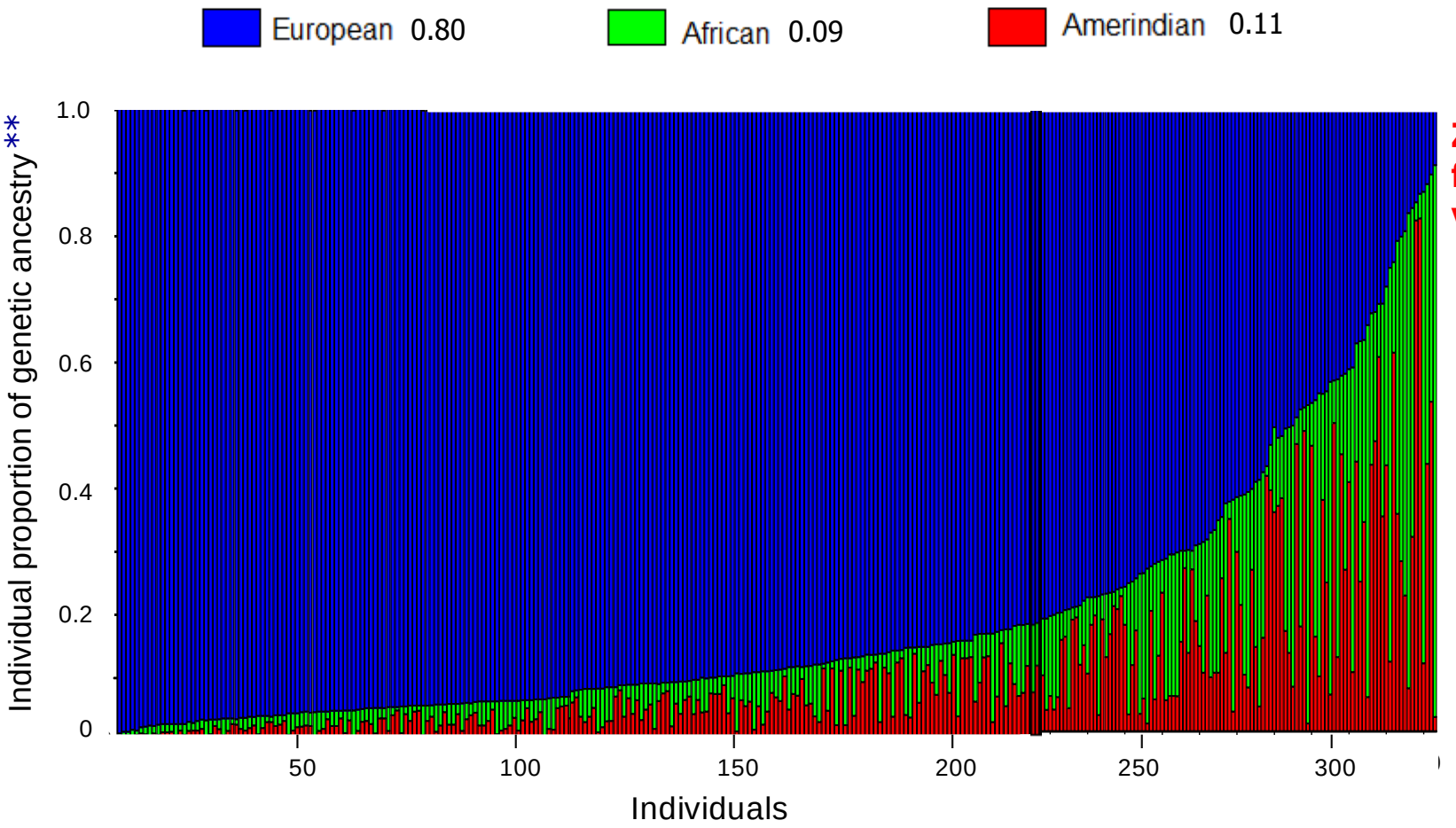
* Data obtained with a panel developed and validated by Bastos-Rodrigues *et al.* 2003.

** Each column represents estimates of individual biogeographical ancestry.

Biogeographical ancestry of WHITE Brazilians

Suarez-Kurtz *et al*., *Pharmacogenomics J*, 2010

Average proportions of biogeographical ancestry *



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* Data obtained with a panel developed and validated by Bastos-Rodrigues *et al.* 2003.

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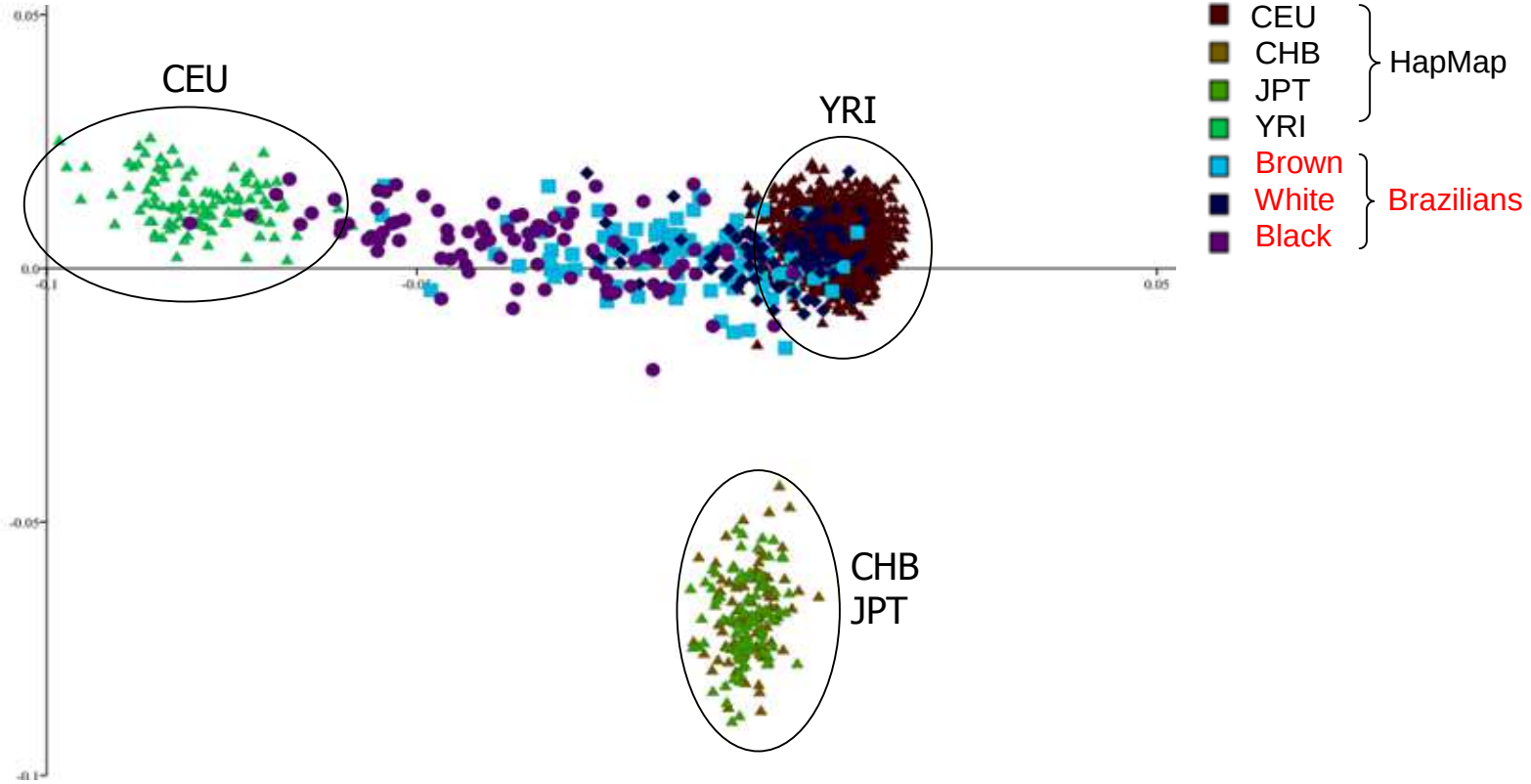
Principal component analysis of biogeographical ancestry in Brazilians*

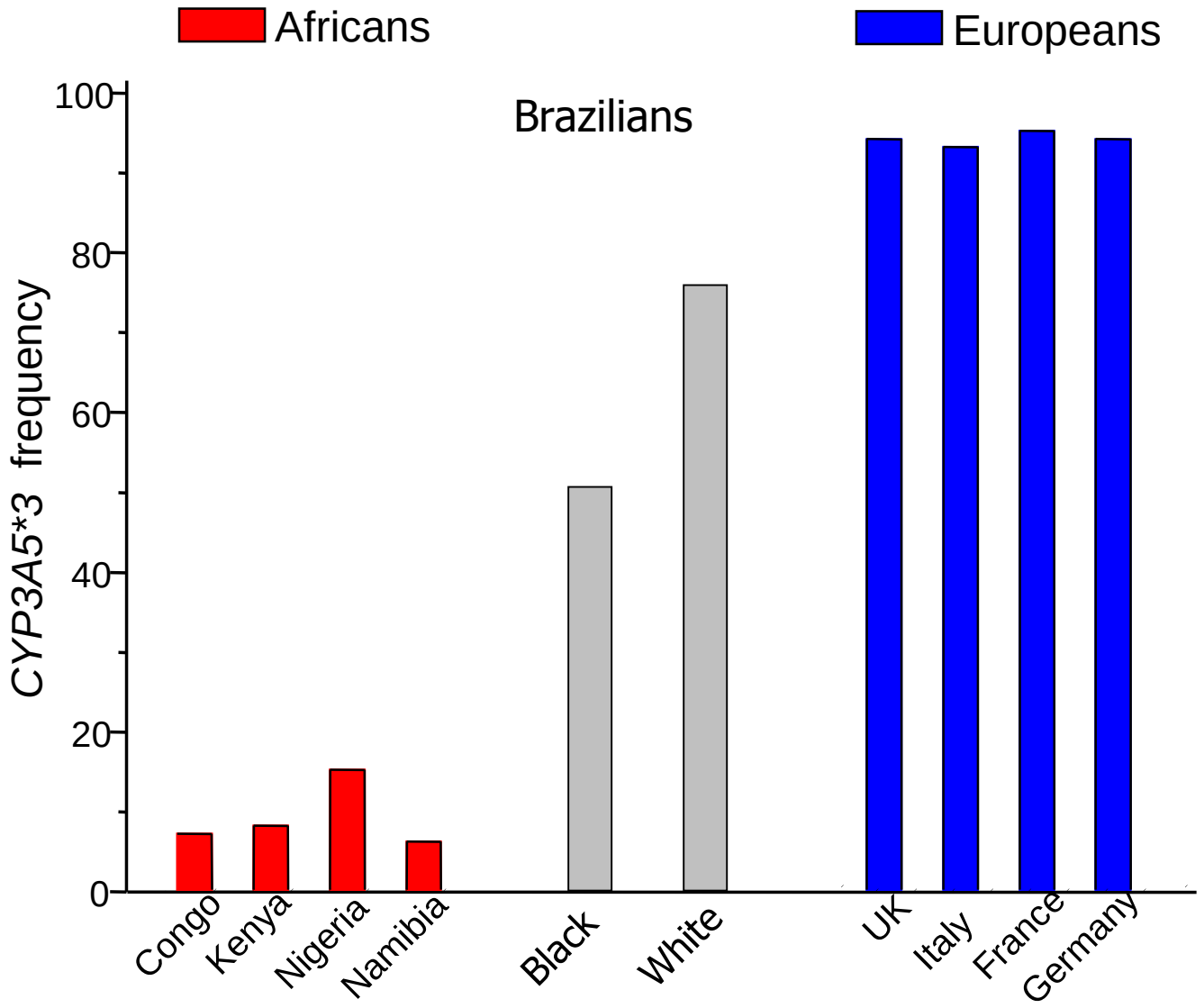
Bonifaz-Peña *et al*., PLoS One , 2014



* Data obtained with a set of markers included in the DMET-Plus chip

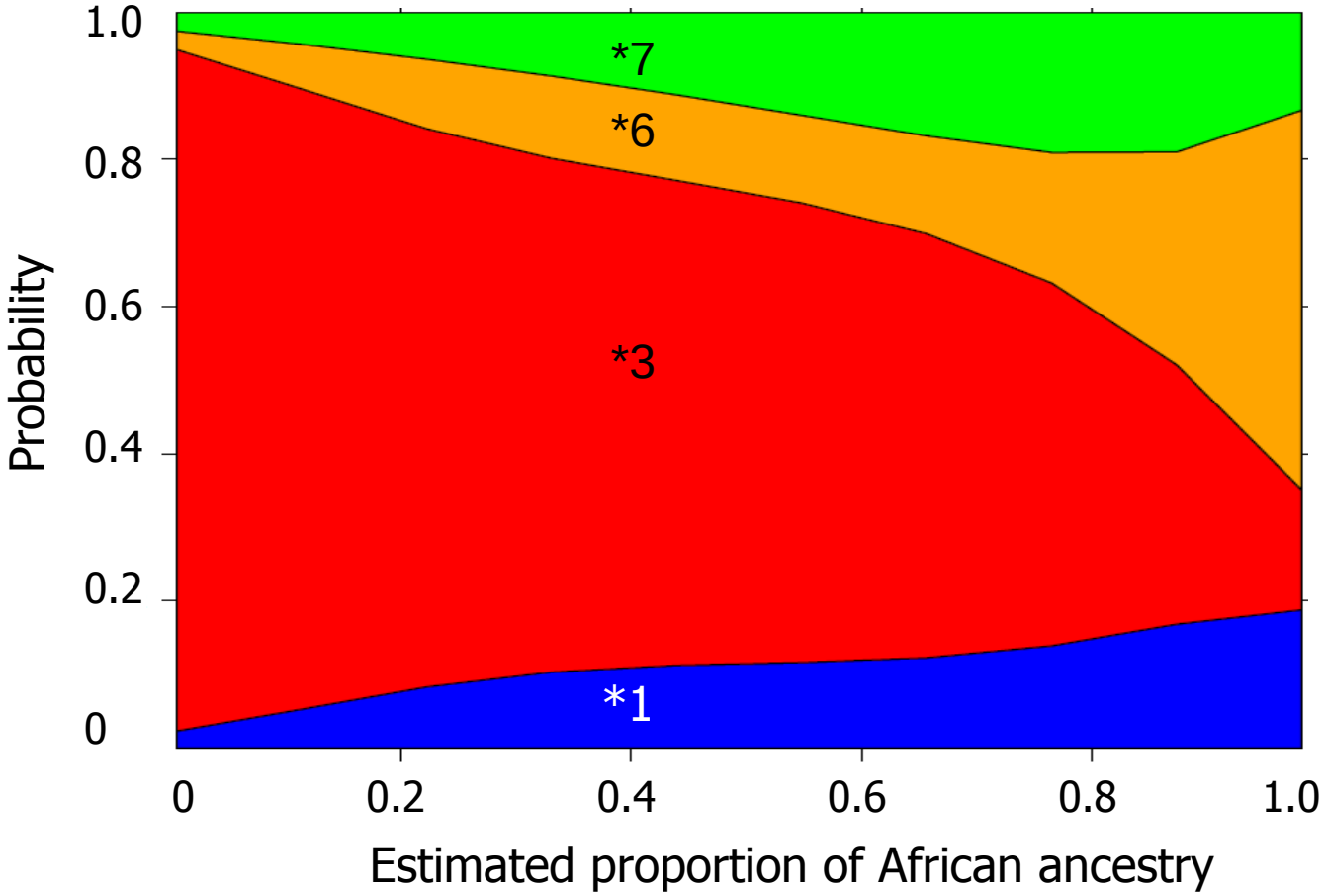
Admixture impacts the distribution of polymorphisms: *CYP3A5*3* as an example

Suarez-Kurtz *et al.* PLoS One 2014



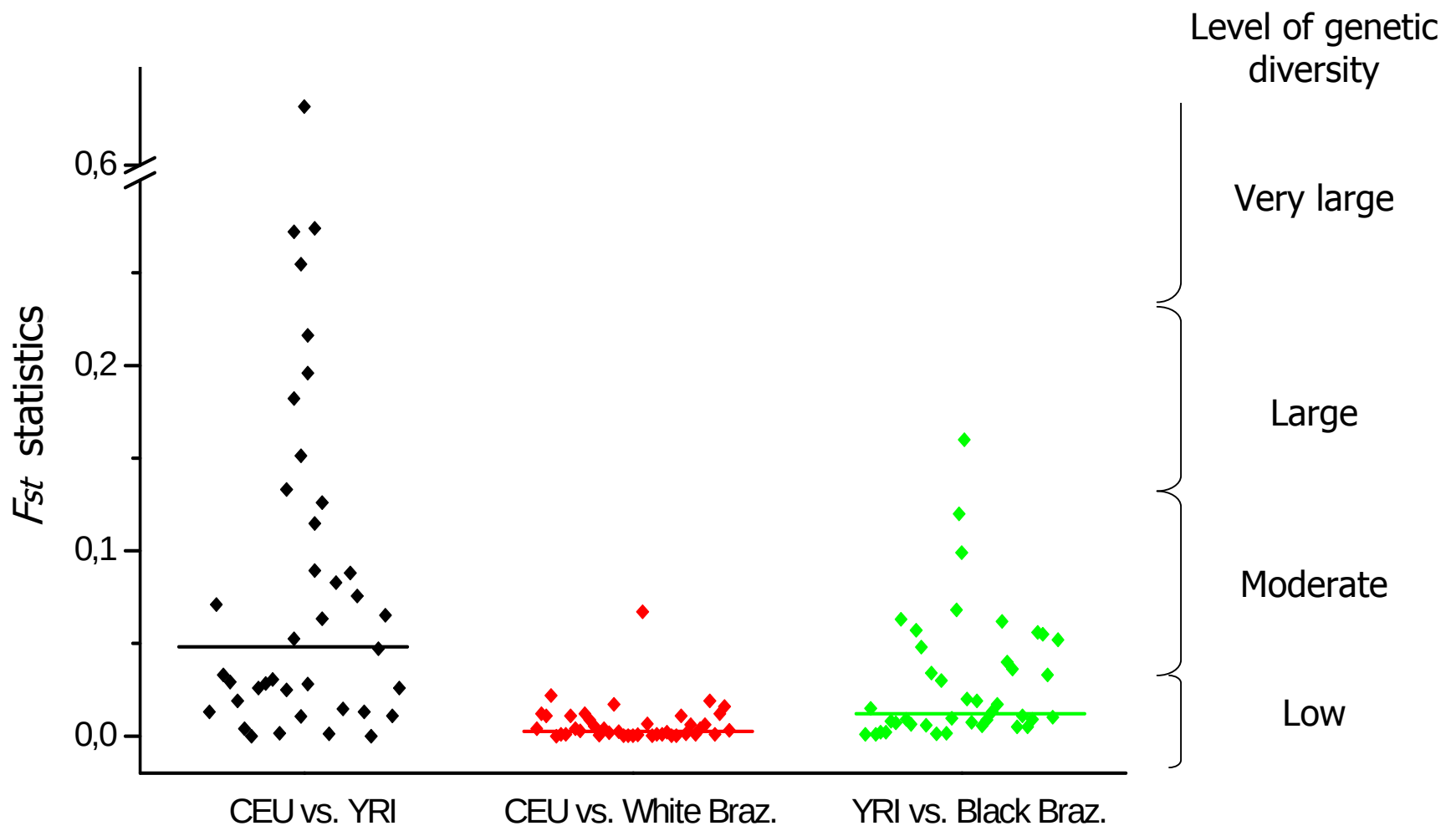
Modeling the impact of African ancestry on the distribution of *CYP3A5* alleles

Suarez-Kurtz *et al.* PLoS One 2014



PGx diversity: Brazilians *vs.* HapMap populations

Data for 42 pharmacogenetic polymorphisms examined in the Refargen-Finep project



Suarez-Kurtz *et al.* Pharmacogenomics, 2012

Admixture impacts the clinical implementation of PGx: Warfarin as an example

Warfarin, a "model" PGx target:

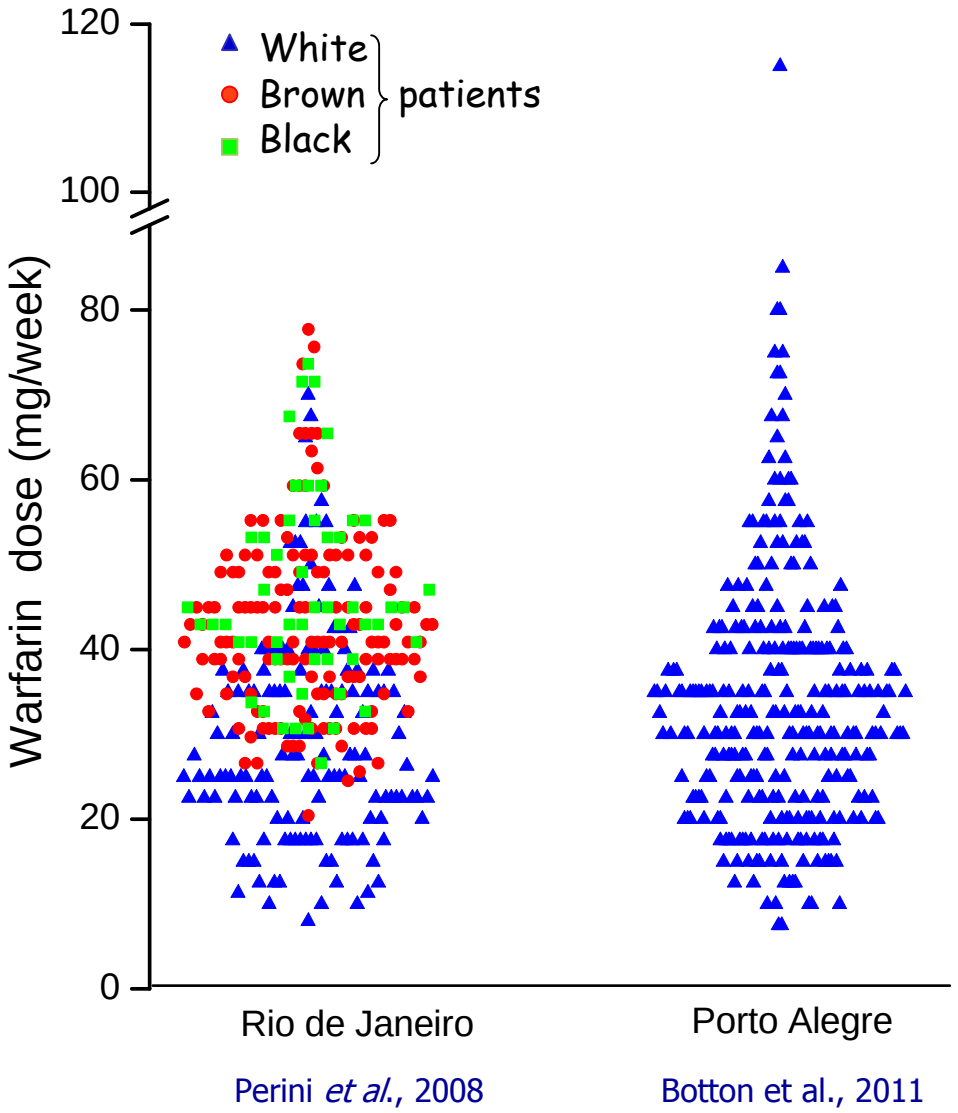
Widely used anticoagulant

- Large inter-individual dose range
- Narrow therapeutic index

  insufficient dose: thrombosis

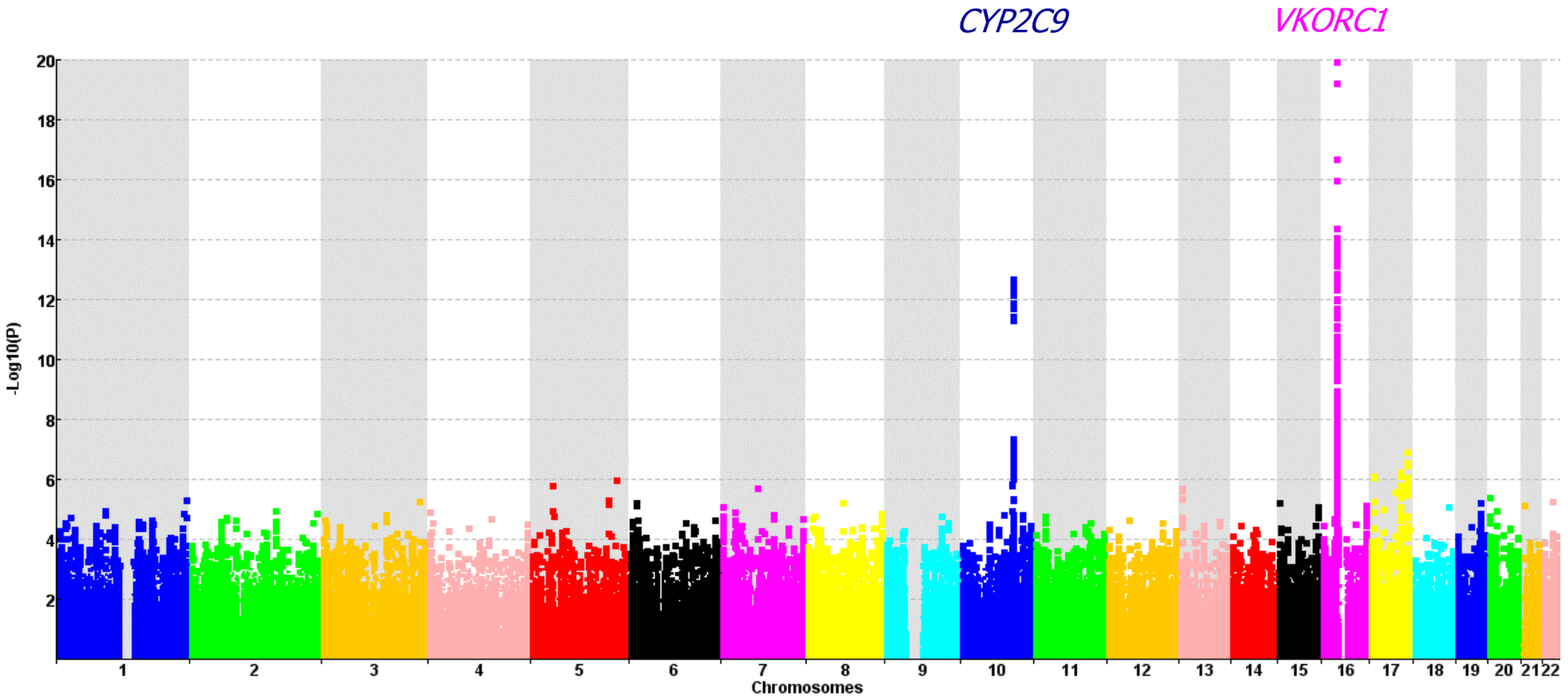
  excessive dose: haemorrhage/bleeding
- INR = biomarker of anticoagulant effect
- Oligogenic modulation of clinical response

PGx of warfarin in Brazilians:
Inter-individual variability of maintenance dose



Genome-Wide Association Study (GWAS) of warfarin in Brazilians

Parra *et al.* Pharmacogenomics, 2015



Development of a warfarin PGx dosing algorithm

Perini *et al.*, Clin Pharmacol Ther 2008

Variables

Pharmacogenetic
VKORC1, CYP2C9

Demographic
age, sex
weight, height, BSA
"*race/color*"

Clinical
indication
concomitant drugs

Two-step procedure

Univariate analysis

↓

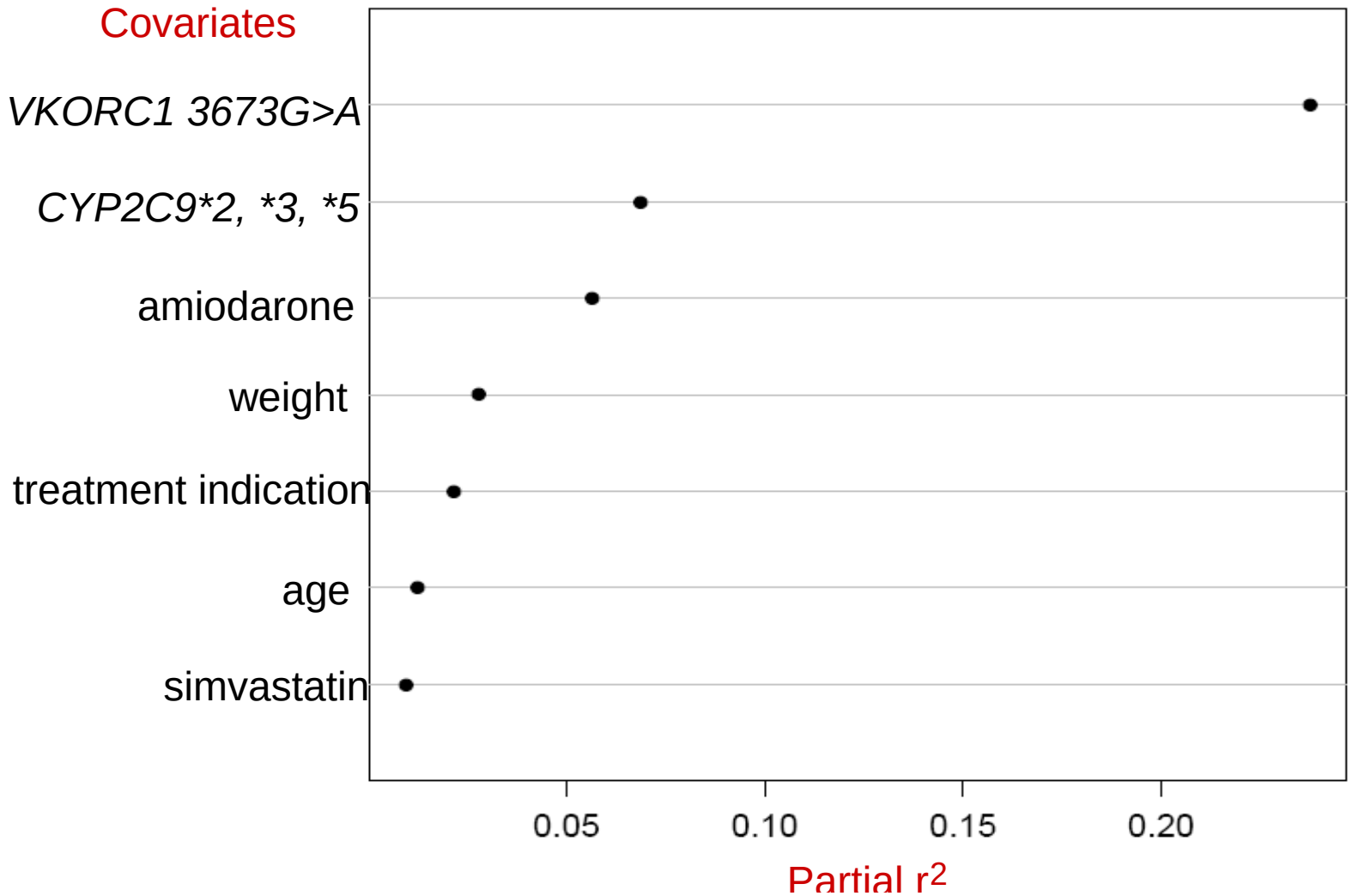
Multivariate analysis

↓

Dosing algorithm

Covariates associated with warfarin dose in Brazilian patients

Perini *et al.*, Clin Pharmacol Ther 2008



A warfarin PGx dosing algorithm for Brazilians

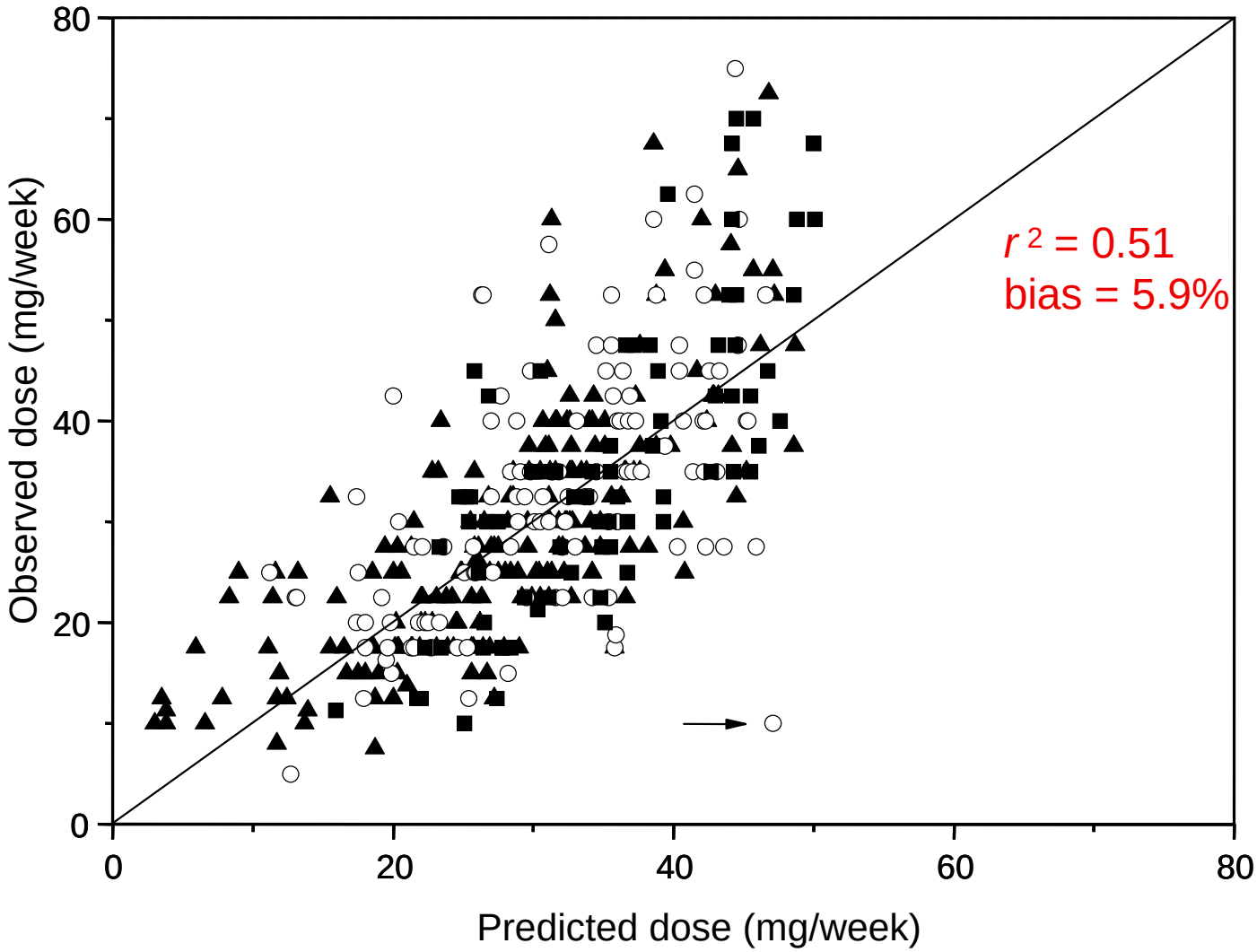
Perini *et al.*, Clin Pharmacol Ther 2008

Warfarin weekly dose (mg)

= square root of 3.8548 – 0.0103 × (age in years) + 0.0159 × (weight in kg) + 0.4284 × (1, if patient has heart valve prosthesis, else 0) + 0.3983 × (1, if patient has thromboembolic disease, else 0) – 0.4387 × (1, if prescribed simvastatin, else 0) – 0.7903 × (1, if prescribed amiodarone, else 0) – 0.6179 × (1, if patient has one *CYP2C9* variant allele, else 0) – 1.0726 × (1, if patient has two *CYP2C9* variant alleles, else 0) – 0.8516 × (1, if *VKORC1* 3673GA genotype, else 0) – 1.7856 × (1, if *VKORC1* 3673AA genotype, else 0).

A warfarin PGx dosing algorithm for Brazilians

Perini *et al.*, Clin Pharmacol Ther 2008



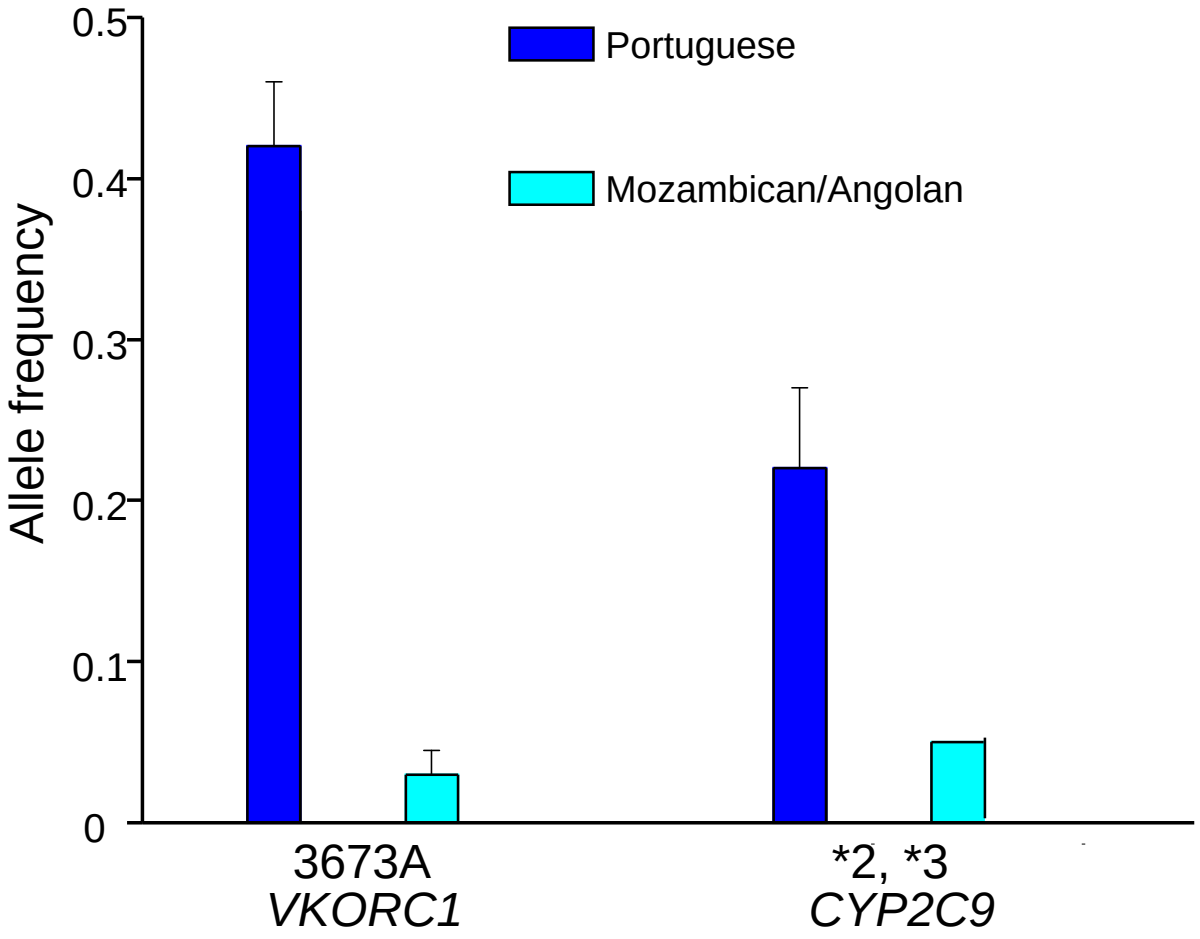
Comparison of warfarin PGx algorithms

Population	Age	Sex	Wt/BSA	Race	Drugs	Treat Ind	*VKORC1* *CYP2C9*	INR	R^2	Reference
IWPC - White	■		■	■	■		■		0.45	IWPC Consortium
IWPC - Asian	■		■	■	■		■		0.33	
IWPC - Black/AA	■		■	■	■		■		0.26	
Brazilian	■		■		■	■	■		0.51 White 0.52 Black	Perini , 2008
North American	■		■	■	■	■	■		0.51 White 0.31 Black	Gage , 2008
North American	■		■			■	■		0.37 Black	Cavallari , 2010

The warfarin dosing algorithms developed by Perini *et al.* (Clin Pharmacol Ther, 2009) and by Suarez-Kurtz *et al* . (Blood, 2009) perform equaly well in self-reported White and Black Brazilian patients.

Why warfarin PGx algorithms perform poorly in Africans and African-Americans ?

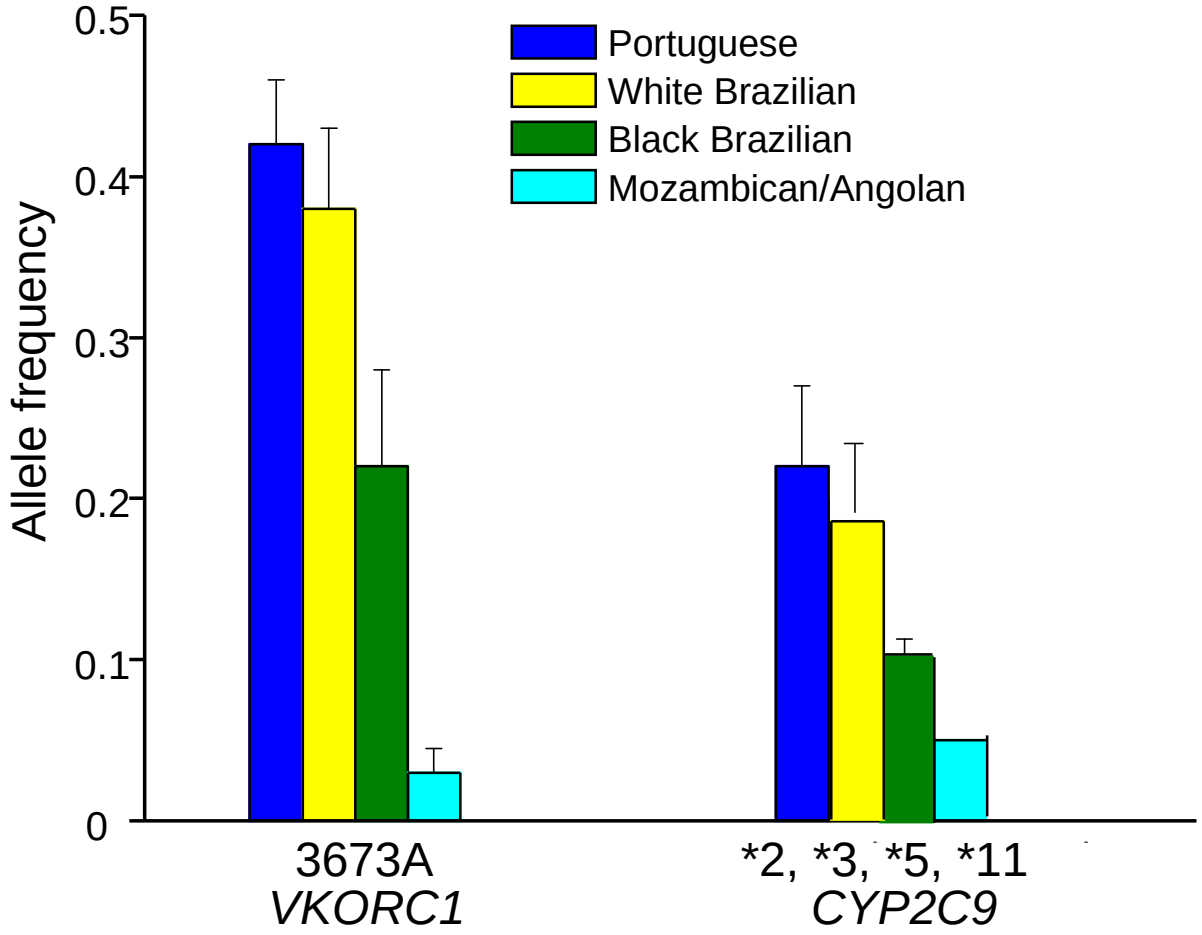
The major PGx terms in warfarin algorithms, i.e. polymorphisms in *CYP2C9*2 and *3* and *VKORC1* –3673G>A, occur at much lower frequencies in African- than in European-derived populations.



Suarez-Kurtz *et al.*,
Pharmacogenomics, 2010

Why warfarin PGx algorithms perform poorly in Africans and African-Americans, but perform equally well in white and black Brazilians ?

The difference in frequency of relevant polymorphisms in *CYP2C9* and *VKORC1,* between Europeans and Africans is markedly attenuated in the admixed Brazilian population.

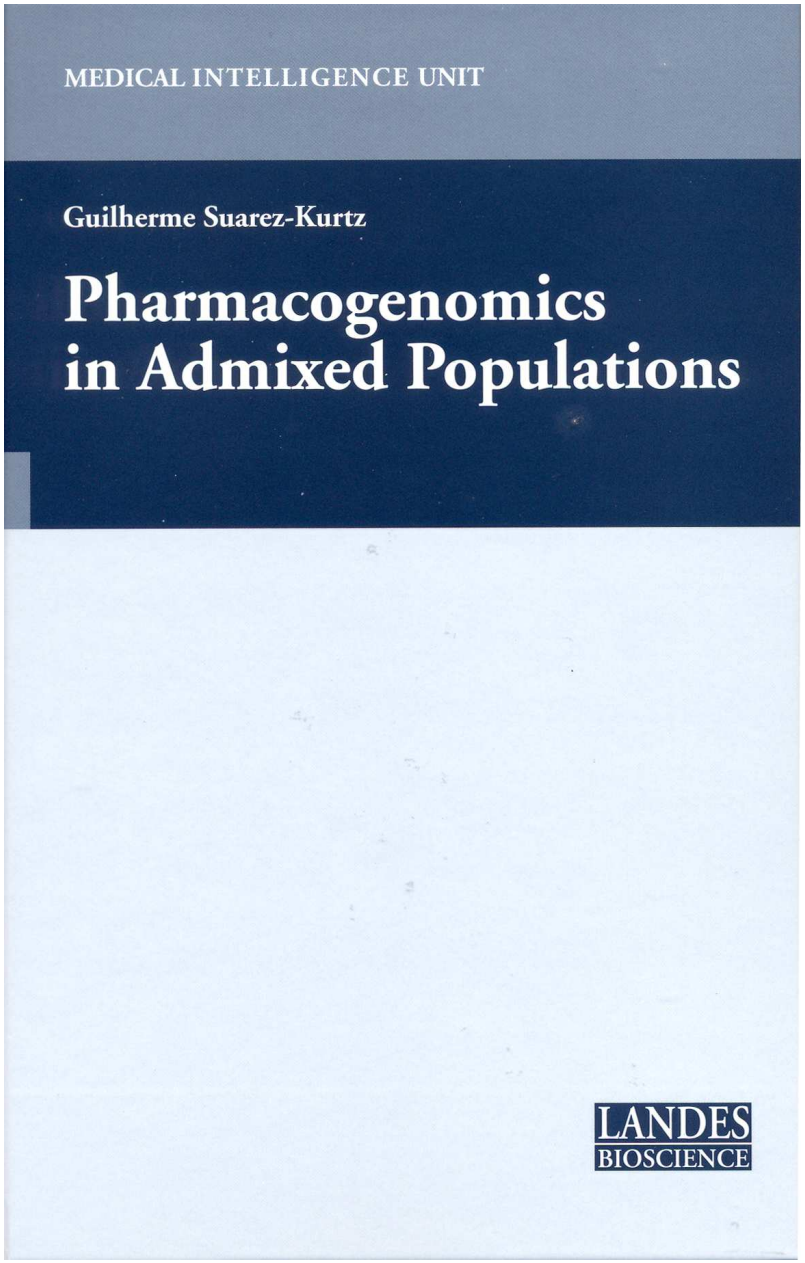


Suarez-Kurtz *et al.,* Pharmacogenomics, 2010

POPULATION DIVERSITY/ADMIXTURE: PGx implications

- "Racial", ethnic or biogeographical categories do not capture human genetic diversity.
- Admixture/heterogeneity must be recognized in the design, analysis and reporting of PGx data…and dealt with as a continuous variable.
- To impact positively on global health, PGx must broaden its scope of investigation, with respect to both target and population diversity, and avoid the risk of contributing to the creation of a genomics divide between regions or nations".

Suarez-Kurtz, *Trends Pharm. Sci.*, 2005



"Da miscigenação nasce uma raça
de tanto talento e resistência, tão poderosa,
que supera a miséria e o desespero
na criação quotidiana da beleza e da vida."

Jorge Amado, *Tenda dos Milagres*

"From admixture, a race is born
of so much talent and resilience, so powerful,
that it overcomes misery and despair
in the daily creation of beauty and life."

Jorge Amado, *Tent of Miracles*