Admixture in the Puerto Rican Population: Physiogenomic Analysis and Implications for Personalized Medicine

1st Latin-American Pharmacogenomics Congress

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Outlines

• PG analysis of Puerto Ricans
• Implication for Personalize Warfarin in Puerto Ricans
• Concluding Remarks
• Future Work
Population Admixture in Drug Prescription

Dr. Suarez-Kurtz pointed out:

“…personalized medicine must take into account individual genetic variability and that intra-group differences challenge the practice of using categories of race and ethnicity [as a proxy] in genetic association studies…..”
Ancestry in Puerto Rican: A tri-Hybrid Model

- AlMs (53.3% Eur/29.1% West-Afr./17.6% Natives)
- mtDNA (12.5% Eur/26% West-Afr./61% Natives/ ~53% Amerindians)
- Blood markers (45% Eur/ 37% West-Afr./ 18% Natives)
- Y-Chr (~ 80% Eur/ ~ 20% Afr.)
- Others (60% Eur/25% Afr./15% Natives-Simulated)

- Pharmacological meanings?...........PG markers
  - Pop stratification/confounding surrogates
Physiogenomic Technology

PhysioGenomic PG Array
222 Genes  384 SNPs
SINGLE NUCLEOTIDE POLYMORPHISMS
STABLE, INHERITED DNA MARKERS
DNA OBTAINED FROM BLOOD SAMPLE

Novel Platform for DNA-guided Medicine: System Analysis of Physiological Pathways

Ruaño G, Windemuth A. Physiogenomic Method for Predicting Clinical Outcomes of Treatments in Patients. 2006; 20060278241, USA patent.
Representative sampling (N=100) per geographic regions based on percentage of birth at each region around the Puerto Rican Island according to the 2004 National Births Registry.
Admixture of the PR population

Ancestry-based STRUCTURE triangle plot. Bayesian algorithm (K=3)

Pharmacogenomics, 2009 Apr; 10(4):565-77
Genetic Heterogeneity of the PR population

Hierarchical clustering algorithm was blind as to ethno-geographic ancestry

Pharmacogenomics, 2009 Apr; 10(4):565-77
Population dissimilarity between the 3 clusters found by STRUCTURE compared to 3 International HapMap reference populations

Pharmacogenomics, 2009 Apr; 10(4):565-77
Genetic Admixture of the PR population

Judge Sonia Sotomayor

Boricua, Hispanic or Latino, but what does it really mean?

Pharmacogenomics, 2009 Apr; 10(4):565-77
The Challenge
Variability in warfarin dose requirement

GWAS of Warfarin Anticoagulation Dose-Response

Takeuchi et al. PLoS Genetics 2009; 5(3)
ORIGINAL REPORTS: CARDIOVASCULAR DISEASE

PREVALENCE OF COMBINATORIAL CYP2C9 AND VKORC1 GENOTYPES IN PUERTO RICANS: IMPLICATIONS FOR WARFARIN MANAGEMENT IN HISPANICS

Abstract: Polymorphisms in the cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes significantly alter the effective warfarin dose. We determined the frequencies of alleles, single carriers, and double carriers of single nucleotide polymorphisms (SNPs) in the CYP2C9 and VKORC1 genes in a Puerto Rican cohort and gauged the impact of these polymorphisms on warfarin dosage using a published algorithm. A total of 92 DNA samples were genotyped using Lumines® x-MAP technology. The polymorphism frequencies were 6.5%, 5.43% and 28.8% for CYP2C9*2, *3 and VKORC1-1639 C>A polymorphisms, respectively. The prevalence of combinatorial genotypes was 16% for carriers of both the CYP2C9 and VKORC1 polymorphisms, 9% for carriers of CYP2C9 polymorphisms, 35% for carriers of the VKORC1 polymorphisms, and 11% for non-carriers.

INTRODUCTION

Warfarin is an oral anticoagulant considered as the standard-of-care therapy for many thromboembolic disorders.1-2 More than 24 million prescriptions for warfarin were written in United States in 2007.3-4 Warfarin is frequently prescribed at stable maintenance dosages and increased bleeding complications.8-10 Polymorphisms of CYP2C9 include CYP2C9*2 and CYP2C9*3, which are associated with reduced enzyme activity to 70% and 5% of the normal level, respectively.8,11-13 The result is warfarin accumulation and possible hemorrhagic...
Individual VKORC1 genotypes (N=52), overlaid on the genetic distance dendrogram.
Green: G/G genotype; Blue: G/A genotypes; Red: A/A genotypes.
P-values were calculated by a chi-squared test comparing observed allele frequencies with expected frequencies given the overall allelic ratios.

Clinica Chimica Acta, 2010, in press
Admixture Matching

Green: *1/*1 genotype; Blue: *1/*2 genotypes; Red: *1/*3 genotypes.
CYP2C9*2: 0%; 7.7%; 18.8% // CYP2C9*3: 11.1%; 7.6%; 0%

Clinica Chimica Acta, 2010, in press
IWPC-derived Warfarin Dosing Algorithm

$R^2 = 0.3633$
AD = 7.9 mg/week
25% mean bias
Stepwise Regression Model (n=127)

$R^2 = 0.382$
SEE=1.49 mg/day
$p=0.018$

Variables:
- VKORC1 Code
- AGE
- CYP2C9*3 Code
- CYP2C9*2 Code

Dosing Algorithm for Puerto Rican Warfarin Patients
(San Juan & Hartford)
Vectors A $(1,0,0)$; B $(0,1,0)$; C $(0,0,1)$
Conclusions

• Three-way mixture in PR calls for markers that distinguish among all three ancestral populations.
• Our results demonstrated that pop analysis can be performed with a PG-array to facilitate the translation of genome diversity into personalized medicine.
• Early published warfarin dosing algorithms performed poorly in PR patients→ customized equation/rare alleles/admixture vector.
• Need to adjust by IA (admixture-matching) due to pop stratification.
Study Limitations

• Lack of database of markers with freq known in Native Americans (i.e., Tainos*).
• Sample size*
• Structure (clustering) analysis bias
• Cubic clustering criterion, pseudo Fstat
• Lack of admixture estimates on warfarin patients
Future Work

• Very high density of markers (Illumina iScan + Infinity Hap1M Duo BeadChip™: whole genome)
• Increase sample size & mining multiple databases w/Amerindians markers
• Identify markers that best represent the Native American–ancestry contribution of Hispanics
• Develop DNA-guided PerSoma model for warfarin dosing in PR
• Incorporate Admixture as a continuum variable
• Other cardio-vascular and neuro-endocrine conditions/drugs (Plavix, Statins, AAP-induced adverse events, etc)
Partners in PGx Research

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