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

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Background and introduction

Warfarin remains a widely used anticoagulant medication

Large Inter-Patient Variability in dose

Narrow Therapeutic Index

Dosing guidance exists for African and Non-African Ancestry

Adverse events related to over anticoagulation or under-anticoagulation

PMID: 28198005
Aims of the research

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

With Limited data on Pharmacogenetics- Guided Warfarin Dosing in Hispanics

Research goal: Individualize warfarin dosing in Hispanics
Candidate gene approach focusing on VKORC1, CYP2C9, CYP4F2 and NQO1 genes
Participating cohorts

US discovery cohort (N=411)

University of Illinois (N=54)
University of Arizona (N=76)
University of Puerto Rico (N=260)
Icahn School of Medicine at Mount Sinai (N=21)

Brazilian Replication cohort (N=225)

Non-White Brazilians (N=112)
White Brazilians (N=113)

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DNA was genotyped at each site for variants in VKORC1 (rs9923231), CYP2C9 (*2,*3,*8,*11), CYP4F2 (rs2108622), NQO1(rs1800566)</td>
</tr>
<tr>
<td>2</td>
<td>Stable warfarin dose was defined as a dose that resulted in therapeutic INR for two-three consecutive visits</td>
</tr>
<tr>
<td>3</td>
<td>Univariate analysis of log transformed warfarin dose was tested against each SNP in the combined US cohort</td>
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<tr>
<td>4</td>
<td>Stepwise linear multiple regression was performed in the combined US cohort including clinical predictors and genotypes</td>
</tr>
<tr>
<td>5</td>
<td>Model association was tested in Brazilian cohorts</td>
</tr>
</tbody>
</table>
Univariate analysis of SNPs with warfarin dose

- **VKORC1-1639 (rs9923231)**
  - P = 2 × 10^{-16}

- **CYP2C9 diplotypes**
  - P = 6 × 10^{-16}

- **CYP4F2-rs2108622**
  - P = 3 × 10^{-16}

- **NQO1-rs1800566**
  - P = 0.03
Multiple linear regression in US cohorts

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (SE)</td>
<td>p-value</td>
<td>$\beta$ (SE)</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.1 (0.3)</td>
<td>$3 \times 10^{-35}$</td>
<td>3.5 (0.2)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01 (0.002)</td>
<td>$4 \times 10^{-9}$</td>
<td>-0.01 (0.002)</td>
</tr>
<tr>
<td>BSA</td>
<td>0.5 (0.1)</td>
<td>$8 \times 10^{-6}$</td>
<td>0.34 (0.08)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.5 (0.3)</td>
<td>0.05</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>VKORC1-1639</td>
<td>-</td>
<td>-</td>
<td>-0.3(0.03)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-</td>
<td>-</td>
<td>-0.2(0.03)</td>
</tr>
<tr>
<td>CYP4F2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NQO1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adjusted $R^2$</td>
<td>17%</td>
<td></td>
<td>41%</td>
</tr>
</tbody>
</table>

BSA: Body Surface Area; CYP2C9: variant carrier; CYP4F2:rs2108622; NQO1:rs1800566
Warfarin association in non-whites Brazilians

<table>
<thead>
<tr>
<th>Non-white Brazilians</th>
<th>β (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.1(0.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.009 (0.003)</td>
<td>0.001</td>
</tr>
<tr>
<td>VKORC1-1639</td>
<td>-0.2(0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-0.004(0.001)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NQO1</td>
<td>0.05 (0.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td></td>
<td>53.5%</td>
</tr>
</tbody>
</table>

Adjusted log warfarin dose

NQO1-rs1800566

P=0.004
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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University of Arizona
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- Heidi Steiner

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