Pharmacogenomic Investigations in the Hmong: CYP2C19 Single Nucleotide Polymorphisms (SNPs) as Predictors of Drug Response

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Introduction

Pharmacogenomic investigations have enhanced our understanding of drug response variability and disease susceptibility.1 Such pharmacogenomic investigations are lacking for the Hmong (~60,0002 within Minnesota). Lack of pharmacogenetic knowledge within this unique Asian population represents a health disparity, especially since cardiovascular diseases (CVD) and associated risks (DM, BMI, and dyslipidemia)3,4 are on rise for Hmong. CVD is leading cause of death nation wide3 with acute coronary syndromes (ACS) at top of the list. ACS standard of care is dual antiplatelet therapy (aspirin and clopidogrel).

Genetic polymorphisms in CYP2C19, an enzyme required for clopidogrel bioactivation, have been linked to variable PD and PK responses (figure 1).1 Specifically, CYP2C19 loss of function (*2, *3) or gain of function (*17) alleles have shown to be associated with clopidogrel’s antiplatelet effectiveness and clinical outcomes.5

Knowledge of an individual’s genotype can be used to optimize antiplatelet selection.

Central research question: With possibility of minor allele frequencies (MAFs) differing between Asian groups6, we sought to quantify MAFs for three CYP2C19 SNPs in Hmong. Our central research question was whether prevalence of CYP2C19*2 (rs42442825), *3 (rs49868693), and *17 (rs12248560) differ for White non-Hispanics (WNH) and Han-Chinese (CHI) cohorts.

Aims of Project: Determine MAFs for each SNP (CYP2C19*2, *3, and *17) in Hmong and compare MAFs for each SNP between Hmong vs WNH and Hmong vs CHI.

Table 1a. Hmong Data (N=236)

<table>
<thead>
<tr>
<th>SNP Alleles</th>
<th>CYP2C19*2 (rs42442825)</th>
<th>CYP2C19*3 (rs49868693)</th>
<th>CYP2C19*17 (rs12248560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major G</td>
<td>288</td>
<td>461</td>
<td>461</td>
</tr>
<tr>
<td>Minor A</td>
<td>172</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>460</td>
<td>461</td>
<td>461</td>
</tr>
</tbody>
</table>

Table 1b. Hmong Data (N=236)

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Mean</th>
<th>SD</th>
<th>Gender</th>
<th>MAF female (%)</th>
<th>Gender</th>
<th>MAF male (%)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.3</td>
<td>18</td>
<td>85</td>
<td>0.017</td>
<td>46</td>
<td>0.775</td>
</tr>
<tr>
<td>Weight</td>
<td>164</td>
<td>33</td>
<td>73</td>
<td>0.017</td>
<td>156</td>
<td>0.775</td>
</tr>
<tr>
<td>BMI</td>
<td>33.3</td>
<td>25</td>
<td>45.9</td>
<td>0.017</td>
<td>33.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Male</td>
<td>36.6</td>
<td>26</td>
<td>51.5</td>
<td>0.017</td>
<td>34.8</td>
<td>35.9</td>
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</tbody>
</table>

Table 2. MAF comparisons between Hmong vs WNH and Hmong vs CHI

<table>
<thead>
<tr>
<th>SNP Alleles</th>
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Methods

Study Population: Salivary DNA collected from 236 Hmong adults from Minnesota or Wisconsin DNA Extraction: Genomic DNA samples extracted via Oragene® kit.

Genotyping: Genomic DNA samples genotyped by Sequenom iPLEX Gold assay through the Biomedical Genetics Center (BMGC) for three SNPs CYP2C19*2, *3, and *17.

Reference Cohorts: Published White Non-Hispanics (WNH) and Han-Chinese (CHI) MAFs for each SNP from HGDP-CEPH database.8

Statistical Analysis: MAFs for each SNP were compared by Chi-squared or Fisher’s exact test (Hmong vs WNH, Hmong vs CHI).

Translation

Knowledge of loss/gain of function allele frequencies for Hmong versus WNH or CHI populations would validate the importance of genotyping individuals both between and within racial classifications.

Knowledge of genotype can guide optimal drug selection for ACS patients to improve outcomes, reduce cost of care, and avoid adverse drug reactions.

Figure 1. Post-delivery of drugs, PK and PD involve sets of genes that lead to both efficacious and toxic effects. Variability in response can be due to genetic variation in PK and PD genes.1

Results

Hmong participant data summarized in Tables 1a and b. MAFs for Hmong and reference cohorts summarized in Table 2; Hmong CYP2C19 phenotypes summarized in Table 3. Table 1 revealed that MAFs for both loss of function alleles (*2, *3) were significantly different compared to both WNH and CHI. MAFs for *2 were significant lower for both *2/2 and *2/3 compared to both WNH and CHI. MAFs for *3 were significant lower for *3/3 compared to both WNH and CHI. Bonferroni correction (α = 0.017) used for comparisons (Table 2). Table 3 revealed 56.3% of Hmong participants were IMs or PMs (Table 3).

Conclusion

Hmong had higher prevalence of CYP2C19*2 loss of function allele compared to both WNH and CHI.

Hmong had same prevalence of CYP2C19*3 loss of function allele compared to both WNH and CHI.

Hmong had lower prevalence of CYP2C19*17 of gain function allele compared to both WNH and CHI. Results in Hmong cannot be extrapolated to other populations (Fig. 2).

Thus, MAF differences may have significant implications for dose and/or drug selection for ACS.

MAFs for both loss of function alleles (*2, *3) were significantly different compared to both WNH and CHI suggesting those with ACS standard of care is dual antiplatelet therapy (aspirin and clopidogrel).

Knowledge of genotype can guide optimal drug selection for ACS patients to improve outcomes, reduce cost of care, and avoid adverse drug reactions.

Figure 2. CPIC algorithm for antiplatelet therapy based on CYP2C19 phenotypes in ACS patients9

Acknowledgements

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4US Census Bureau; 2010 SF2, Table PCT1; American FactFinder; http://factfinder2.census.gov; 01 Aug 2013.
10US Census Bureau; 2010 SF2, Table PCT1; American FactFinder; http://factfinder2.census.gov; 01 Aug 2013.

References