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

CENTER FOR HEALTH EQUITY

Jenny Xiong[1], Youssef Roman[1], Kathleen Culhane-Pera[2], Robert Straka[1]

[1]Experimental and Clinical Pharmacology Department, College of Pharmacy, University of Minnesota, Minneapolis MN; [2]East Side Family Clinic, West Side Community Health Services, St. Paul MN

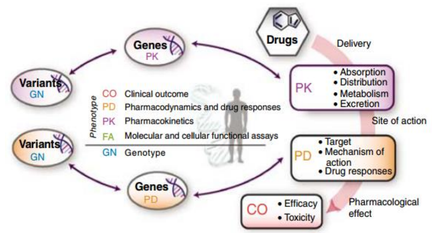
Introduction

- Pharmacogenomic investigations have enhanced our understanding of drug response variability and disease susceptibility.[1] Such pharmacogenomic investigations are lacking for the Hmong (~60,000[2] 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 nationally[5] 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 outcome.[6]
- 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 groups[7], we sought to quantify MAFs for three *CYP2C19* SNPs in Hmong. Our central research question was whether prevalence of *CYP2C19*2* (rs4244285),**3* (rs4986893), 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.

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]



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)

Table 1a. Hmong Data (N=236)

	Mean	Min	Max
Age (yrs)	30.3	18	85
Height (in)	61.8	44	73
Weight (lbs)	150.9	90	300
Female waist (in)	33.3	24.5	50
Male waist (in)	35.6	26	51.5

Table 1b. Hmong Data (N=236)

Gender no. (%)	Female	131 (55.5)
	Male	105 (44.5)
BMI no. (%)	Underweight (<18.5)	3 (1.3)
	Normal (18.5 to 24.9)	88 (37.2)
	Overweight (25-29.9)	76 (32.2)
	Obese (30 to 39.9)	54 (22.9)
	Morbidly Obese (≥40)	15 (6.4)

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

SNP Alleles	Hmong Allele Copies	Hmong Allele Frequency	WNH Allele Copies	WNH Allele Frequency	P-value£
***CYP2C19*2* (rs4244285)**					
Major G	288	0.626	2173	0.867	
Minor A	**172**	**0.374**	**333**	**0.133**	**0.0001**
Total (n)	460 (230)	1	2506 (1253)	1	
***CYP2C19*3* (rs4986893)**					
Major G	461	0.998	2506	1	
Minor A	**1**	**0.002**	**0**	**0**	0.1557*
Total (n)	462 (231)	1	2506 (1253)	1	
***CYP2C19*17* (rs12248560)**					
Major C	469	0.998	1942	0.775	
Minor T	**1**	**0.002**	**564**	**0.225**	**0.0001***
Total (n)	470 (235)	1	2506 (1253)	1	

SNP Alleles	Hmong Allele Copies	Hmong Allele Frequency	CHI Allele Copies	CHI Allele Frequency	P-value£
***CYP2C19*2* (rs4244285)**					
Major G	288	0.626	602	0.753	
Minor A	**172**	**0.374**	198	0.247	**0.0001**
Total (n)	460 (230)	1	800	1	
***CYP2C19*3* (rs4986893)**					
Major G	461	0.998	774	0.967	
Minor A	**1**	**0.002**	26	0.033	**0.0001***
Total (n)	462 (231)	1	800 (400)		
***CYP2C19*17* (rs12248560)**					
Major C	469	0.998	787	0.984	
Minor T	**1**	**0.002**	**13**	**0.016**	0.0233*
Total (n)	470 (235)	1	800 (400)	1	

*p-values = Fisher's Exact Test; £Bonferroni correction.

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¥CPIC=Clinical Pharmacogenetics Implementation Consortium
PCI=percutaneous coronary intervention; EM=extensive metabolizer; IM = intermediate metabolizer; PM=poor metabolizer; UM, ultra-rapid metabolizer
HTN = Hypertension
BMI = Body-Mass Index
DM = Diabetes Mellitus

Results

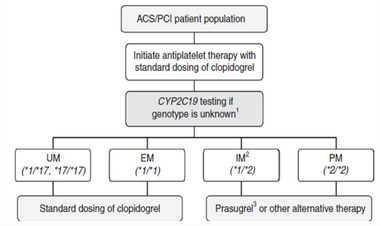
- Hmong participant data summarized in Tables 1a and b.
- MAFs for Hmong and reference cohorts summarized in Table 2; Hmong *CYP2C19* phenotypes summarized in Table 3.
- Hmong MAFs were SS higher for *2, lower for *17 compared to WNH; Hmong MAFs were SS higher for **2,* lower for **3* compared to CHI; Bonferroni correction (α = 0.017) used for comparisons (Table 2).
- 58.5% of Hmong participants were IMs or PMs (Table 3).

*SS = Statistically significantly

Table 3. Hmong Phenotypes

***CYP2C19* Phenotype**	**No. (%)**
UM (*1/*17, *17/*17)	1 (0.4)
EM (*1/*1)	90 (38.3)
IM (*1/*2, *1/*3)	104 (44.3)
PM (*2/*2, *2/*3, *3/*3)	34 (14.5)
Total (Missing Data)	**229 (6)**

Figure 2. CPIC¥ algorithm for antiplatelet therapy based on *CYP2C19* phenotype in ACS patients[8]



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 WNH but lower prevalence compared to CHI.
- Hmong had lower prevalence of *CYP2C19*17* gain of function allele compared to WNH but same prevalence compared to CHI cohorts.
- >50% Hmong had IM/PM phenotype suggesting those with ACS would benefit from Prasugrel or alternate antiplatelet therapy (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 for Hmong compared to CHI suggesting. that dose and drug selection cannot rely on race alone. Thus an individual's genotype may be a more useful tool for making such clinical decisions

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