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Differences in Predicted Warfarin Dose for Hmong vs East Asians Using Genotype-Based Dosing Algorithm

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Introduction: Warfarin is the world's most widely prescribed anticoagulant,[1] however, it exhibits a narrow therapeutic index and a large variability in dosage, in part due to genetics.[3] Several studies have demonstrated improved outcomes using genotyped-guided warfarin dosing compared to clinical-dosing.[5,6] The NIH driven "*All of Us*" initiative advocates for inclusion of under-served and under-studied populations. The Hmong are a unique Asian population numbering over 73,000 in Minnesota[3] whose participation in genetic-based research is virtually non-existent. Earlier findings[2] indicated allele frequencies for warfarin pharmacogenes differ between Hmong and other Asian populations**. Our goals** are to validate and translate these findings as they relate to predicted Hmong warfarin starting doses.

Methods: Salivary genomic DNA collected from two independent cohorts (N=219 and N=187) of self-identified Hmong adults were genotyped for single nucleotide polymorphisms (SNPs) including CYP2C9 (*2, *3), VKORC1 (G-1639A) and CYP4F2 (*3) by iPLEX® assays. Allele frequencies between the Hmong cohorts (N=406) and an East Asian cohort (N=1200) from the "1000 Genomes Project" were compared using a Chi-squared test. Mean warfarin starting doses and the prevalence of extreme starting doses* predicted from a warfarin dosing algorithm**,[5] were compared using a t-test and Chi-squared test respectively. (*p*-value < 0.05 for significance). Non-genetic variables required by the algorithm[5] were collected from our Hmong cohorts and simulated for the East Asian cohort using a bootstrapping method.

*Extreme dosage: Absolute difference between genetic and clinical (non-genetic) dose predicted by the algorithm[5] >= 1mg/day

Algorithm factors: Age, BSA, Drugs (Amiodarone, Azoles, Sulfas), Venous Thromboembolism (VTE), Race (AA), **CYP2C9, VKORC1, CYP4F2.

Table 1: Participant Data

	Cohort 1 (N=236)	Cohort 2 (N=198)
Age, years*	22 (20-39)	23 (20-37)
Gender		
Male	101 (43%)	77 (38.9%)
Female	134 (57%)	121 (61.1%)
Height, inches	61.7 ± 4.6 [44-73]	62.1 ± 3.5 [53.8-70]
Weight, lbs	151.5 ± 37.7 [90-300]	148.5 ± 32.3 [82-288]
Smoking	16 (6.8%)	16 (8.1%)

*Numerical variables: median (interquartile range) or mean ± SD [range] when appropriate; Categorical variables: count (%)

Table 2: Allele Count (Frequencies) for CYP2C9 *1, *2, *3, CYP4F2 *3 and VKORC1-1639 G>A

	Cohort 1	Cohort 2	*p*-value	Combined Hmong	East Asians	*p*-value
VKORC1-1639 G>A	390 (89%)	324 (86.6%)	0.29	714 (87.9%)	5281 (88.2%)	0.96
CYP2C9*1	346 (79%)	311 (83.2%)	0.13	657 (80.9%)	9916 (96.6%)	**<0.00001**
CYP2C9*2	0 (0%)	0 (0%)	>1	0 (0%)	4 (<0.1%)	0.47
CYP2C9*3	92 (21%)	63 (16.8%)	0.13	155 (19.1%)	369 (3.4%)	**<0.00001**
CYP4F2*3	NA	25 (9.8%)	NA	39 (9.8%)	879 (22.1%)	**<0.00001**

Table 3: Predicted Mean Warfarin Starting Dose (mg/day)*

	Cohort 1 (N=219)	Cohort 2 (N=187)		Combined Hmong, N=406	East Asians, N=1200	p (Combined vs East Asians)
		Without CYP4F2	With CYP4F2			
Dose (SD)	2.7 (0.73)	2.8 (0.77)	2.7 (0.8)	2.7 (0.81)	3 (0.62)	**<0.01**

*Target INR was input as 2 in the algorithm; Indications, related medication and medical histories were input as unknown.

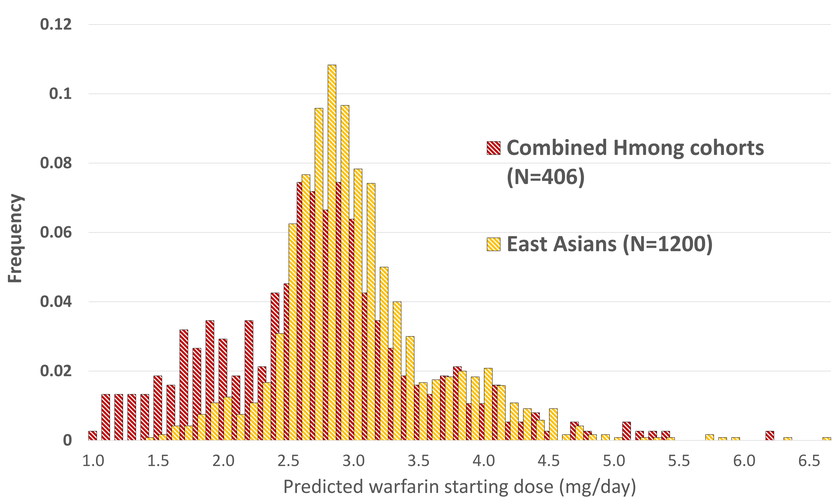

Figure 1: Frequency distribution of predicted warfarin starting doses

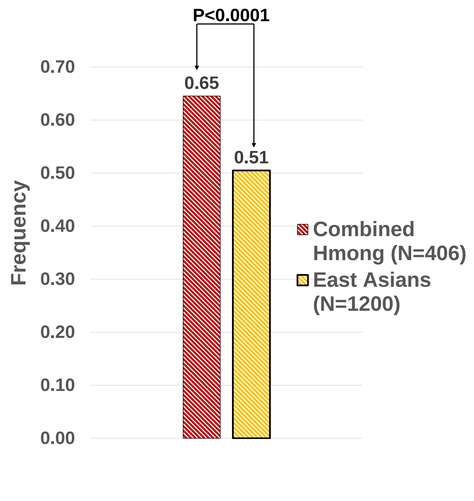

Figure 2: Prevalence of extreme warfarin doses

Results: Allele frequencies of CYP2C9*3 and CYP4F2*3 of Hmong cohorts (N=406) were significantly different than those in East Asians (19.1% vs 3.4%, p<0.00001 and 9.8% vs 22.1%, p<0.00001, respectively). Other SNPs were similar in prevalence. The mean predicted starting dose (2.7 vs 3mg/day, p<0.001) and prevalence of individuals predicted to need extreme starting doses (65% vs 51%, p<0.0001) differed between Hmong and East Asian cohorts.

Translation: Our findings suggest there may be clinically important risks to generalizing warfarin dosage requirements based on race/ethnicity classifications. Rather, our data illustrate the importance of individualizing drug dosage requirements regardless of race/ethnicity for drugs such as warfarin.

Conclusion: Differences in allele frequencies of CYP2C9*3 and CYP4F2*3 were consequential to the predicted warfarin starting dosages and the predicted extreme dosage requirements between Hmong and East Asians.

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