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Frequency of Genetic Polymorphisms of CYP2C19 in Native Hawaiian, and Asian and Pacific Islander Subgroups: Implications for Personalized Medicine

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The Frequency of Genetic Polymorphisms of *CYP2C19* in Native Hawaiian, and Asian and Pacific Islander Subgroups: Implications for Personalized Medicine

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BACKGROUND

- Genetic polymorphisms in drug-metabolizing enzymes have been linked to interindividual variabilities in the efficacy and toxicity of the most prescribed drugs.
- Pharmacogenomics (PGx) provides a stronger scientific basis for optimizing drug therapy based on each patient's genetic makeup.[1]
- The prevalence of Single Nucleotide Polymorphisms (SNPs) in very important pharmacogenes (VIPs) in some Asian subpopulations, Hawaiians, and Pacific Islanders are lacking.
- The cytochrome P450 (CYP) 2C19 is a major hepatic enzyme and a member of the CYP family that metabolizes ~ 10% of commonly prescribed drugs.
- Clopidogrel is a prodrug, converted by CYP2C19 to its active metabolite, which is required for its anti-platelet activity.
- Multiple studies linked adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent rethrombosis) to *CYP2C19* genotype in clopidogrel-treated ACS patients undergoing PCI.[3-4,6]
- Asian subgroups have substantially higher rates of being poor and intermediate CYP2C19 metabolizers, compared with Caucasians (allele frequencies: 29%-35% and 9%, and ~15% and 0.4%; respectively).[5,7,8]

OBJECTIVES

- To assess the prevalence of three *CYP2C19* SNPs in post-partum women self-reported of 100% Native Hawaiian (NT), Asian and Pacific Islander (PI) descent, compared with Europeans (EUR).
- To describe the clinical impact of *CYP2C19* genetic polymorphisms on treating Asian, NT, and PI patients with clopidogrel, using the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines.[5]

METHODS

- The Ensemble genome browser[7,8] was used to estimate the frequencies of 3 major SNPs in EUR for *CYP2C19, gene/SNP* pairs included: *CYP2C19* (*rs12248560, rs4244285, and rs4986893*).
- Data: De-identified DNA samples linked with limited clinical data procured from the University of Hawaii biospecimens' repository[9].
- Chi-square or Fisher's exact test was used, when appropriate, with $P < 0.05$ for significance to test the hypothesis that the genotype/allele frequencies between our study populations (i.e., Filipino, Japanese, Samoan, Korean, Marshallese, and Native Hawaiian differ from EUR.
- Quality control analysis: Genotypes that were not HWE ($p < 0.05$) in their respective population, and age < 18 years old were excluded.

RESULTS

Table 1: Participants Characteristics

Characteristics	n (%)
Sample size	1064 (100)
Age in years	
Mean	28.8
SD	± 6.3
Race/Ethnicity	
Filipino	230 (21.61)
Hawaiian	158 (14.84)
Japanese	210 (19.73)
Korean	104 (9.77)
Marshallese	161 (15.13)
Samoan	201 (18.89)

SD: Standard deviation

Figures 1 & 2: Bar plots of *CYP2C192 G>A (rs4244285) Genotype and Allele Frequencies**

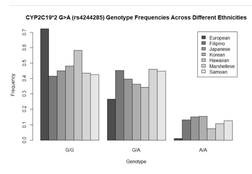

Figure-1

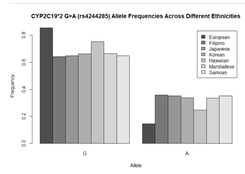

Figure-2

Figures 3 & 4: Bar plots of *CYP2C19* *3 G>A (rs4986893), Genotype and Allele Frequencies

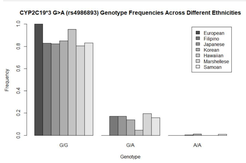

Figure-3

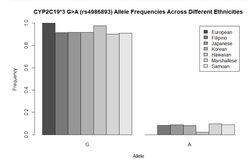

Figure-4

Figures-5 & 6: Bar plots of *CYP2C19*17* C>T (rs12248560) , Genotype and Allele Frequencies

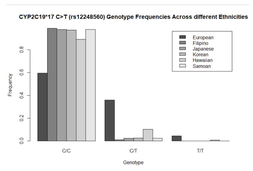

Figure-5

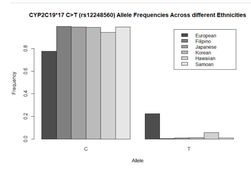

Figure-6

Table 2: CYP2C19*2, &*3 G>A (rs4244285) & (rs4986893), and CYP2C19*17 C>T (rs12248560) Genotype/Allele Frequencies Across different Ethnicities.

Genotype/ Allele		EUR (n= 503)	Filipino (n=190)	Japanese (n= 184)	Korean (n= 77)	Hawaiian (n= 146)	Marshallese (n= 122)	Samoan (n= 181)
CYP2C19*2 G>A (rs4244285) % (n), 95% Confidence Interval (CI)	Genotypes							
	G/G	72.2 (363)	41.6 (79), (34.2, 49.2)	45.1 (83), (37.5, 52.7)	48.1 (37), (37.7, 60.7)	58.2 (85), (50.7, 66.9)	43.4 (53), (34.4, 52.9)	42.5 (77), (35.4, 50.7)
	G/A	26.6 (134)	45.2 (86), (37.9, 52.9)	39.7 (73), (32.1, 47.3)	36.4 (28), (26, 50)	34.3 (50) (26.7, 43)	45.9 (56), (36.9, 55.3)	44.8 (81), (37.6, 52.9)
	A/A	1.2 (6)	13.2 (25), (5.7, 20.8)	15.2 (28), (7.6, 22.8)	15.5 (12), (5.2, 28.2)	7.5 (11), (0, 16.2)	10.7 (13), (1.6, 20.1)	12.7 (23), (5.5, 20.8)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	0.00004*	<0.0001*	<0.0001*
	Alleles							
	G	85.5 (860)	64.2 (244), (59.5, 69.3)	64.9 (239), (60.1, 70)	66.2 (102), (59.1, 74.1)	75.3 (220), (70.5, 80.3)	66.4 (162), (60.7, 72.6)	64.9 (235), (60, 70.1)
	A	14.5 (146)	35.8 (136), (31.1, 40.9)	35.1 (129), (30.2, 40.1)	33.8 (52), (26.6, 41.6)	24.7 (72), (19.9, 29.7)	33.6 (82), (27.9, 39.8)	35.1 (127), (30.1, 40.1)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	0.00004*	<0.0001*	<0.0001*

		EUR (n= 503)	Filipino (n=190)	Japanese (n= 184)	Korean (n= 77)	Hawaiian (n= 146)	Marshallese (n= 122)	Samoan (n= 181)
CYP2C19*3 G>A (rs4986893) % (n), 95% Confidence Interval (CI)	Genotypes							
	G/G	100 (503)	82.9 (160), (78.2, 88.4)	82.3 (153), (77.4, 88)	84.8 (67), (78.5, 93)	95.3 (141), (92.6, 98.5)	80.3 (98), (73.8, 87.2)	83.2 (153), (78.3, 88.5)
	G/A	0 (0)	17.1 (33), (12.4, 22.6)	17.2 (32), (12.4, 22.9)	13.9 (11), (14, 22.1)	4.7 (7), (2, 8)	19.7 (24), (13.1, 26.6)	15.8 (29), (10.9, 21.2)
	A/A	0 (0)	0 (0), (0, 5.5)	0.5 (1), (0, 6.2)	1.3 (1), (0, 9.4)	0 (0), (0, 3.3)	0 (0), (0, 6.9)	1.1 (2), (0, 6.5)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	0.00002*	<0.0001*	<0.0001*
	Alleles							
	G	100 (1006)	91.5 (353), (88.9, 94.1)	90.9 (338), (88.2, 93.7)	91.8 (145), (88.1, 95.7)	97.6 (289), (96.3, 99.3)	90.2 (220), (86.9, 93.9)	91 (335), (88.3, 93.8)
	A	0 (0)	8.5 (33), (6, 11.2)	9.1 (34), (6.5, 12)	8.2 (13), (4.4, 12.2)	2.4 (7), (1, 4)	9.8 (24), (6.6, 13.5)	9 (33), (6.3, 11.7)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.00002*	<0.0001*

		EUR (n= 503)	Filipino (n=190)	Japanese (n= 184)	Korean (n= 77)	Hawaiian (n= 146)	Samoan (n= 181)
CYP2C19*17 C>T (rs12248560) %(n), 95% Confidence Interval (CI)	Genotypes						
	C/C	59.6 (300)	98.9 (186), (97.9, 1)	97.8 (181), (96.2, 99.7)	97.4 (74), (94.7, 1)	89.2 (132), (85, 94.3)	97.8 (177), (96.1, 99.7)
	C/T	36 (181)	1.1 (2), (0, 2.2)	2.2 (4) (0.5, 4)	2.6 (2), (0, 5.4)	10.1 (15), (6.1, 15.2)	2.2 (4), (0.6, 4.1)
	T/T	4.4 (22)	0 (0), (0, 1.1)	0 (0) (0, 1.8)	0 (0), (0, 2.7)	0.7 (1), (0, 5.8)	0 (0), (0, 1.9)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
	Alleles						
	C	77.6 (781)	99.5 (374), (98.9, 1)	98.9 (366) (98.1, 99.8)	98.7 (150), (97.4, 1)	94.3 (279), (91.9, 96.7)	98.9 (358), (98.1, 99.7)
	T	22.4 (225)	0.5 (2), (0, 1.1)	1.1 (4) (0.3, 2)	1.3 (2), (0, 2.7)	5.7 (17), (3.4, 8.2)	1.1 (4), (0, 1.9)
	P-value	Reference	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

Results Cont.

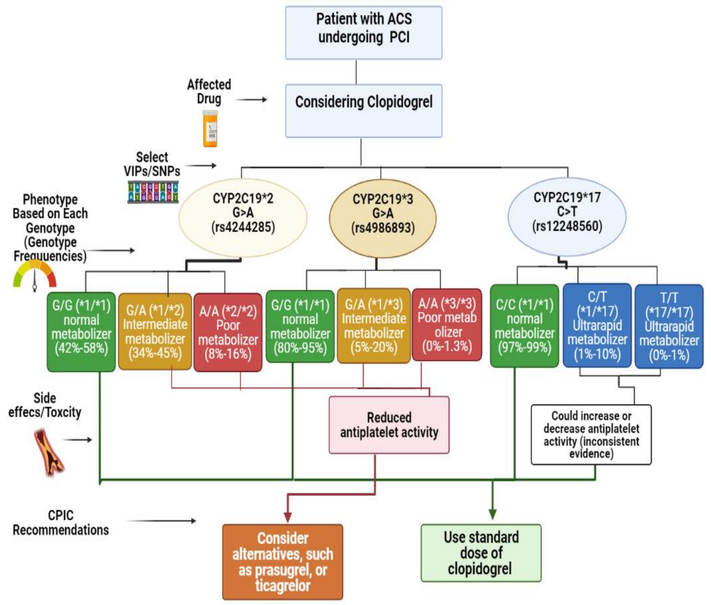

Figure 7: Algorithm to assist guiding the selection of the most appropriate treatment plan for patients in the population of interest using Clinical Pharmacogenetics Implementation Consortium (CPIC)[5] guidelines.

LIMITATIONs

- This was a retrospective data analysis of a study that used targeted sequencing; hence we were limited by the variants assayed.
- Race of participants was self-reported.
- Participants were post-partum women only.

CONCLUSION

- Significant differences in genotype and allele frequencies of variants in *CYP2C19* were found between Asians/Hawaiians/Pacific Islanders and Europeans.
- *CYP2C19 *2* and **3* variants were detected at higher frequencies in Asians, Hawaiians, and Pacific Islanders, compared with Europeans.
- Knowledge of individual's CYP2C19 metabolizer status may be useful in prescribing clopidogrel in our studied populations.
- Our results are consistent with published reports of Asian populations being enriched with the reduced or loss of function alleles of *CYP2C19* compared with Europeans.

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