Research Article

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Pharmacogenomics

The frequency of major *ABCG2*, *SLCO1B1* and *CYP2C9* variants in Asian, Native Hawaiian and Pacific Islander women subgroups: implications for personalized statins dosing

Khalifa Alrajeh[1,2], Ola AlAzzeh[1] & Youssef Roman*[,1]

[1]Department of Pharmacotherapy & Outcome Science, Virginia Commonwealth University School of Pharmacy, 410 N 12th Street, Richmond, VA 23298, USA

[2]Department of Pharmacy Practice, King Faisal University College of Clinical Pharmacy, PO Box 400, Hofuf, Eastern Province, 31982, Saudi Arabia

*Author for correspondence: romany2@vcu.edu

Aim: The frequencies of *SLCO1B1*5* and *CYP2C9*2* and **3* in specific Asian, Native Hawaiian and Pacific Islander (NHPI) subgroups are unknown. **Patients & methods:** Repository DNA samples from 1064 women self-identifying as Filipino, Korean, Japanese, Native Hawaiian, Marshallese or Samoan and aged 18 years or older were used for targeted sequencing of three genetic variants (rs4149056, rs1799853 and rs1057910). **Results:** *SLCO1B1*5* was significantly less frequent in NHPI women (0.5–6%) than in Europeans (16%). Except for Koreans, *CYP2C9*2* (0–1.4%) and **3* (0.5–3%) were significantly less frequent in all subgroups than in Europeans (8 and 12.7%, respectively). Prior reports showed that Asian and NHPI individuals have significantly higher *ABCG2* Q141K allele frequency (13–46%) than Europeans (9.4%). Combined phenotype rates for rosuvastatin and fluvastatin revealed that Filipinos and Koreans had the highest frequencies of statin-associated myopathy symptoms risk alleles. **Conclusion:** Differences in *ABCG2*, *SLCO1B1* and *CYP2C9* allele frequencies among different racial and ethnic subgroups highlight the need for increased diversity in pharmacogenetic research. Risk alleles for statin-associated myopathy symptoms are more prevalent in Filipinos, underscoring the importance of genotype-based statin dosing.

Plain language summary: Statins are medications used to lower low-density lipoprotein ('bad') cholesterol. Variation in genes for proteins which transport drugs (*SLCO1B1* and *ABCG2*) or metabolize drugs (*CYP2C9*) may significantly influence how much statin someone is exposed to. Genetic variants within *SLCO1B1* can affect exposure to all statins, while variants within *ABCG2* and *CYP2C9* can affect exposure to rosuvastatin and fluvastatin, respectively. The prevalence of the decreased or no-function genetic variants is unknown among Filipino and Native Hawaiian and Pacific Islander (NHPI) subgroups. The major racial categorization of 'Asians and NHPI' (ANHPI) can miss potential genetic and ancestral differences among population subgroups. Our study used biobank data from 1064 women of ANHPI descent to estimate the frequencies of four important variants within *SLCO1B1*, *ABCG2* and *CYP2C9*. Those of ANHPI ancestry were less likely to have variations in *SLCO1B1* and *CYP2C9* but significantly more likely to have nonfunctional *ABCG2* than Europeans. Our findings provide insight into *SLCO1B1* and *CYP2C9* genetic variations among under-represented subgroups. Specifically, Filipinos and Koreans have the highest rates of higher risk genetic variants linked to high rosuvastatin and fluvastatin exposure and muscle-related side effects. Estimating the frequency of genetic variations in under-represented subgroups is pivotal in reducing health disparities in treatment outcomes, diversifying pharmacogenetic research and advancing personalized medicine.

Tweetable abstract: Knowledge of allele frequencies in *SLCO1B1, CYP2C9* and *ABCG2* in under-represented population subgroups could help personalize statin dosing. Statin-associated muscle symptoms risk alleles affecting rosuvastatin and fluvastatin are highly prevalent in Filipinos and Koreans.

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The prevalence of clinically actionable genetic variants in statin transporters and major metabolizing enzymes is well established in individuals of European ancestry [1–4]. However, this information is either extrapolated or unknown among under-represented populations, such as Asians and Native Hawaiian and Pacific Islanders (ANHPIs). Determining the frequencies of these variants in statin-related genes (*SLCO1B1*, *CYP2C9* and *ABCG2*) [4] in population subgroups is critical for evaluating the impact of pharmacogenetic testing, diversifying the genetic research landscape, selecting appropriate lipid-lowering therapy and avoiding adverse drug reactions (ADRs) [5]. Replicating the prevalence of currently well-documented genetic variants in under-represented populations, such as ANHPIs, could uncover distinct population-specific genetic variants [5–7], leading to safe and effective statin dosing and optimal ADR risk predictions [6,8–11]. With the increasing racial and ethnic diversity in the US population, identifying these genetic variants for health equity and personalized medicine is increasingly important [5].

Atherosclerotic cardiovascular diseases (ASCVDs) affect 13.2 million US adults [12], with dyslipidemia, particularly elevated levels of low-density lipoprotein cholesterol (LDL-C), as a major risk factor [12,13]. The racial differences in LDL-C prevalence are prominent among the US population [12], with the highest rates in Filipinos (73% in men and 63% in women) compared with 63 and 57% in African–American men and women, and 62 and 53% in European men and women, respectively [12,14]. The rate of dyslipidemia-related deaths due to coronary heart disease is highest among Filipinos, Japanese individuals and Asian Indians compared with other Asians [12,15], highlighting the need for a better understanding of the etiology of dyslipidemia in impacted population subgroups to guide prevention, screening and treatment efforts.

Statins are highly effective lipid-lowering pharmacological treatments that reduce LDL-C levels, but with marked heterogeneity in response [13]. Statins exert their lipid-lowering effect by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the hepatocytes, leading to the upregulation of LDL-C receptors and increased LDL-C uptake by the liver [13,16,17]. Statins are commonly prescribed due to their significant positive effect on ASCVD-related mortality [13,16,17]. Approximately 13.7% of patients in the USA receive a statin prescription [18–20]. Atorvastatin is the most often prescribed drug in the country, with 7.5% of patients (24.5 million) receiving a prescription annually [18,19,21]. Despite the cardioprotective effects of statins, nearly one-half of all patients stop therapy within the first year, with interethnic differences in statin intolerance documented, particularly among those of Asian ancestry [22].

Adherence to statin therapy is crucial for optimal therapeutic outcomes [13,23]. However, common ADRs, and specifically myalgia, are a leading factor for stopping statin therapy [24,25]. Statin-associated musculoskeletal symptoms (SAMS) have been reported in controlled clinical trials and observational studies [26,27], with a higher risk among those with specific demographic and patient-specific factors such as female sex, hepatic or renal dysfunctions, hypothyroidism, advanced age (>75 years old), concomitant use of interacting drugs and specific genetic variants in drug transporters and drug-metabolizing enzymes [21,24,25]. Poor statin adherence (<80%) is associated with a 15% and 45% increase in the risks of ASCVD and all-cause mortality, respectively [28].

Individual statin drugs carry different levels of SAMS risks. The physicochemical and genetic variants associated with the pharmacokinetic and pharmacodynamic properties of statins will impact systemic exposure and the potential risks for ADR. While statins with a tendency toward hydrophilicity (e.g., rosuvastatin and pravastatin) allow lower penetration into myocytes due to low passive diffusion, others tend to be lipophilic (e.g., simvastatin and atorvastatin), permeating myocytes more thoroughly [29]. Efflux transporters eliminate hydrophilic statins into the bile, like the apical ATP-binding cassette transporter G2 (ABCG2; i.e., breast cancer resistance protein) [4,11,21,29]. The uptake transporters, like organic anion transporting polypeptides (OATP) family 1B1 (OATP1B1), facilitate the intake of most statins into hepatocytes [4,21,29]. Phase I metabolizing enzymes, such as the cytochrome P450 2C9 (CYP2C9), oxidize some statins, mainly fluvastatin [4,29].

Clinically actionable sequence variants caused by SNPs in transporters and drug-metabolizing enzymes can substantially influence the safety and efficacy of various statins [4]. SNPs within several candidate genes, such as *SLCO1B1* (encodes for OATP1B1), *ABCG2*, *CYP2C9*, *HMGCR*, *LDLR*, *APOE*, *APOA5*, *LPA* and *PCSK9*, were also found to influence the pharmacodynamics and pharmacokinetics of statins [30]. *SLCO1B1* encodes for a transmembrane transporter, mediating the influx of endogenous and exogenous compounds, including statins, into the liver [4,30,31]. The missense and defining variant for *SLCO1B1*5*, rs4149056 T>C (c.521T>C), can result

in decreased levels of OATP1B1 protein on the basolateral surface of human hepatocytes and decreased function, leading to diminished liver uptake of most statins [4,30,31].

Similarly, the Q141K (rs2231142 G>T) genetic variant within *ABCG2* has also been clinically relevant for rosuvastatin dosing [4]. The missense variant results in an amino acid change in the encoding sequence of *ABCG2*, changing the tertiary structure of ABCG2 protein, making it more prone to degradation and causing a 30–40% reduction in the transport function [4,11]. The most studied variants within *CYP2C9* are *CYP2C9*2* and **3*, defined by SNPs rs1799853 C>T and rs1057910 A>C, respectively [4]. The rs1799853 C>T SNP results in an Arg-to-Cys substitution at amino acid 144 of the CYP2C9 protein [4,32]. The rs1057910 A>C SNP results in an Ile-to-Leu substitution at amino acid position 359 of the CYP2C9 protein [3,4,33]. The respective functional allele statuses for *CYP2C9*2* and **3* are decreased and no function [4]. Both variants can result in decreased enzymatic activity, limiting the metabolism of fluvastatin and increasing exposure and potential risk for SAMS [4,32,34]. *CYP2C9*2* and **3* have been linked to 30–40% and 80% decreased CYP2C9 activity and increased exposure to fluvastatin, respectively [3,4,33] *SLCO1B1*5* can influence the systemic exposure to most statins, whereas Q141K and *CYP2C9*2* and **3* can specifically affect the exposure to rosuvastatin and fluvastatin, respectively [4].

Prevalence data for *SLCO1B1*5* and *CYP2C9*2* and **3* in select ANHPI subgroups are missing, and available findings for some Asians need further replication given the ethnogeographical differences in allele frequency. Therefore investigating the frequency of clinically actionable pharmacogenetic variants in special population groups provides critical information, highlighting population-specific variants for preemptive pharmacogenetic testing. The latter guides statin selection and prevents the likelihood of SAMS in high-risk population subgroups. Our study targeted genes implicated in the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on statins [2,4]. With the growing body of evidence that links the reduced-function genetic variants in *SLCO1B1, CYP2C9* and *ABCG2* to the systemic exposure to statins [4,21], the same variants could be contributing to the interethnic differences in pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid [21,30,35].

The 2022 CPIC guidelines for statin dosing highlighted the importance of considering single and combined (high-risk phenotype group) statin pharmacogenes before prescribing fluvastatin and rosuvastatin therapies [4]. In light of the most recent CPIC recommendations and the lack of information on the prevalence of important statin pharmacogenes in ANHPI individuals, the objective of this study was to investigate the frequencies of clinically actionable variants and genotypes for *SLCO1B1* and *CYP2C9* in each ANHPI subgroup compared with Europeans, and to estimate the combinatorial genotype risk based on the CPIC guidelines, using genetic information about *CYP2C9* and *SLCO1B1* and our previously reported *ABCG2* data [8]. Our approach can improve diversity in pharmacogenetic research and provide insights into high-risk individuals for increased statin exposure in minimally represented population subgroups.

Materials & methods

Study population

Deidentified DNA samples were made available via the University of Hawaii biospecimens repository, along with limited clinical information [36]. The original sample collection was coupled with routine prenatal and hospital labor and delivery procedures. Only postpartum women who donated their placenta, umbilical cord, excess cord blood and maternal blood were included in this study. Adults (≥18 years old) who self-identified as having full ancestry of Filipino, Japanese, Korean, Native Hawaiian, Marshallese or Samoan origin were considered eligible to be included in our analysis. 'Self-reported full ancestry' was defined as having biological parents and all grandparents identifying with the same race and ethnicity. An earlier publication provides study approval, sample procurement and genotyping information [37]. We then compared the frequencies of several major clinically actionable pharmacogenetic variants – *SLCO1B1*5* and *CYP2C9*2* and **3* – in our studied population subgroups, with Europeans as the reference group. We obtained genetic data of Europeans from publicly available genomic data repositories [1,2]. The rs2231142 C>A (Q141K) allele and genotype frequency data of the same population subgroups were obtained from a prior study by Alghubayshi *et al.* [8] (Supplementary Tables 1 & 2). The Human Studies Program at the University of Hawaii reviewed and exempted all study materials and methods (protocol no.: 2018-00225) [36].

DNA extraction & genotyping

DNA samples were extracted from postpartum women's peripheral blood and genotyped at the Genomics and Bioinformatics Shared Resources, Cancer Center (Honolulu, Hawaii). Genetic testing assays were performed on

the TaqMan® OpenArray® (Thermo Fisher Scientific, MA, USA), Format 32. Assay IDs C__30633906_10, C__25625805_10 and C__27104892_10 were used to detect the respective SNPs rs4149056, rs1799853 and rs1057910 (*SLCO1B1*5*, *CYP2C9*2* and *CYP2C9*3*, respectively). The customized TaqMan assay was run on the QuantStudio™ 12K Flex Real-Time PCR system (Thermo Fisher Scientific). Applied Biosystems (CA, USA) supplied the made-to-order, predesigned assays used for genotyping.

Diplotype-to-phenotype prediction

We used the CPIC *SLCO1B1* and *CYP2C9* allele definition tables [2] to translate the genotype in each SNP (using the rsID) to the star (*) allele (Supplementary Tables 3 & 4). The CPIC did not have a star nomenclature for *ABCG2*; instead, it used G and T for reference and variant alleles for the SNP rs2231142 G>T, respectively (Supplementary Table 5). Using the CPIC genotype translation approach, both reference alleles translate to *SLCO1B1*1* or *CYP2C9*1* (i.e., individuals without any of the variant alleles of *SLCO1B1*5* or *CYP2C9*2* and *CYP2C9*3*). Then we used the CPIC diplotype-to-phenotype translation tables [2] to characterize the phenotypes of SLCO1B1 and ABCG2 as normal, decreased or poor functions, and those of CYP2C9 as normal, intermediate or poor metabolizers (Supplementary Tables 6–8).

Combinatorial pharmacogenetic assessment

Counts and proportions of individuals with combined genotypes among ANHPI subgroups were identified using Microsoft Excel® 2019 (Microsoft Corp., WA, USA) and multinomial proportions using RStudio 1.4.1103 (R Core Team, 2020, Vienna, Austria.) [38]. Proposed SAMS risk scores among our sample subgroups were separately assessed for rosuvastatin and fluvastatin pharmacogenes (*ABCG2* and *SLCO1B1*, and *CYP2C9* and *SLCO1B1*, respectively) with a maximum score of 4 (Tables 6 & 8). The scores were calculated based on the number of risk alleles within rosuvastatin- and fluvastatin-relevant pharmacogenes. Assuming an additive effect model for rosuvastatin and fluvastatin exposure [4], individuals were classified into four groups: normal (no variant), low (one variant), intermediate (two variants) or high (three or more variants; Tables 6 & 8). The CPIC diplotype-to-phenotype translation approaches were used to define combined phenotypes for rosuvastatin- and fluvastatin-specific pharmacogenes, yielding nine possible combined phenotypes (Figures 1 & 2). The combined phenotype implications in rosuvastatin and fluvastatin starting doses are shown in Tables 7 & 9.

Statistical analysis

We summarized categorical and numerical data using descriptive statistics, including percentages, range, mean and standard deviation. χ^2 or Fisher's exact test with a Bonferroni corrected $p < 0.008$ for statistical significance was used to assess the Hardy–Weinberg equilibrium of each SNP within each population subgroup. We used Microsoft Excel 2019 to compare each SNP's observed and expected genotype frequencies. When appropriate, we also conducted a χ^2 or Fisher's exact test with an adjusted p-value ($p < 0.008$) for statistical significance to compare the allele and genotype frequencies between Asian subgroups (Filipino, Japanese, Korean), Native Hawaiian and Pacific Islander subgroups (Marshallese and Samoan) and Europeans. The 95% CIs of genotype and allele frequencies were calculated using multinomial proportions using the DescTools (v. 0.99.37; Sinforeli A, 2021) package. Statistical analyses were conducted using RStudio 1.4.1103 [38].

Results

Genotype and allele frequencies for our population subgroups were calculated using biobank DNA samples of 1064 participants. The population sample included complete self-identified Filipino (21.6%), Japanese (19.7%), Korean (9.8%), Native Hawaiian (14.8%), Marshallese (15.1%) and Samoan (18.9%) individuals. The demographic characteristics of these participants are summarized in Table 1. The genotype call rates for each SNP were 97.2% (912/939 participants) for *SLCO1B1*5*, 97.2% for *CYP2C9*2* (914/940 participants) and 96.1% for *CYP2C9*3* (903/940 participants). Across all population subgroups, all our tested SNPs were in Hardy–Weinberg equilibrium ($p > 0.008$; Supplementary Tables 9 & 11).

SLCO1B1 allele frequencies

Allele frequencies are presented in Table 2. In each sample subgroup of Native Hawaiian, Marshallese and Samoan individuals, the frequencies of the no-function *SLCO1B1*5* variant were significantly lower than in Europeans (15.5%; $p < 0.008$; Table 2). However, the frequencies of *SLCO1B1*5* in Asian subgroups (Filipino, Japanese

Table 1. Demographic characteristics of study participants.

Characteristic	n (%)[†]
Age (years), mean ± SD	28.8 ± 6.3
Sex	
Female	1064 (100)
Race (ethnicity)	
Native Hawaiian	158 (14.8)
Asian	
Filipino	230 (21.6)
Japanese	210 (19.7)
Korean	104 (9.8)
Pacific Islander	
Samoan	201 (18.9)
Marshallese	161 (15.1)

[†]Percentages are based on the total number of study participants without any missing data for the *SLCO1B1*5* and *CYP2C9*2* and **3* alleles.
SD: Standard deviation.

Table 2. *SLCO1B1*5* allele frequencies among different Asian, Native Hawaiian and Pacific Islander subgroups compared with Europeans.

***SLCO1B1* allele**[†]	**Sample population subgroups, % (95% CI)**						
	European (reference) (n = 4300)[‡]	**Filipino (n = 181)**	**Japanese (n = 187)**	**Korean (n = 92)**	**Native Hawaiian (n = 147)**	**Marshallese (n = 121)**	**Samoan (n = 184)**
****1***[§]	84.5 (84.5–85.2)	89 (86.5–92.5)	86.4 (83.2–89.8)	85.9 (81.5–91)	94.2 (91.8–96.7)	97.1 (95.5–99.1)	99.5 (98.9–100)
p-value	Reference	0.01	0.3	0.6	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]
****5***	15.5 (14.8–16.3)	11 (8–14)	13.6 (10.4–17)	14.1 (9.8–19.3)	5.8 (3.4–8.3)	2.9 (1.2–4.9)	0.5 (0–1.1)
p-value	Reference	0.09	0.3	0.6	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]

[†]The CPIC *SLCO1B1* allele definition table [2] was used to translate the genotypes of the SNP rs4149056 T>C to *SLCO1B1*5* (Supplementary Table 3).
[‡]Data taken from [1] for European Americans.
[§]*SLCO1B1*1* was inferred from the presence of reference allele (T) in the rs4149056 T>C genotype. Frequencies of *SLCO1B1*1* in our study sample subgroups were estimated by summing the variant alleles and subtracting the total from 100.
[¶]Bonferroni corrected p-value < 0.008 for significance.
Bold indicates the risk allele/haplotype.
CPIC: Clinical Pharmacogenetics Implementation Consortium.

and Korean; ~13%) were insignificantly lower than in Europeans (15.5%; $p > 0.008$). The respective overall ranges of *SLCO1B1*5* frequency were 11–14% in Asians and 0.5–5.8% in Native Hawaiians and Pacific Islanders (NHPIs). Among our sample subgroups, the lowest detected allele frequencies of *SLCO1B1*5* were in NHPIs, specifically Samoans (0.5%), followed by Marshallese (2.9%) and Native Hawaiian (5.8%) individuals (Table 2). The *SLCO1B1*5* variant was detected at a rate of 11% in Filipino, 13.6% in Japanese, 14.1% in Korean, 5.8% in Native Hawaiian, 2.9% in Marshallese and 0.5% in Samoan individuals.

SLCO1B1 diplotype frequencies

SLCO1B1 diplotype frequencies are presented in Table 3. The NHPI population subgroups had significantly lower *SLCO1B1*1/*5* frequencies and undetected *SLCO1B1*5/*5* ($p < 0.008$) compared with Europeans. The *SLCO1B1*1/*5* diplotype was detected at significantly lower rates in NHPI sample subgroups (1–11%) and slightly lower rates in Asian subgroups (20–25%) than in Europeans (25.5%). Among our sample subgroups, the lowest detected allele frequencies of *SLCO1B1*1/*5* were in NHPI individuals, specifically Samoans (1.1%), followed by Marshallese (5.8%) and Native Hawaiians (11.6%; Table 3); the rates among the Asian subgroups were 25.1% in Japanese, 24% in Korean and 20.4% in Filipino individuals. The *SLCO1B1*5/*5* diplotype frequency was insignificantly lower in Asians (0.6–2.2%) and undetected in NHPI (0%) subgroups, compared with 2.8% in Europeans. *SLCO1B1*5/*5* was more detected among Asian subgroups at a rate of 2.2% in Korean, 1.1% in Japanese, and 0.6% in Filipino individuals versus undetected among NHPI subgroups.

Table 3. *SLCO1B1*5* diplotype frequencies among different Asian, Native Hawaiian and Pacific Islander subgroups compared with Europeans.

***SLCO1B1* diplotype**[†]	**Sample population subgroups, % (95% CI)**						
	European (reference; n = 4300)[‡]	**Filipino (n = 181)**	**Japanese (n = 187)**	**Korean (n = 92)**	**Native Hawaiian (n = 147)**	**Marshallese (n = 121)**	**Samoan (n = 184)**
***1/*1**	71.7 (70.3–73.1)	79 (73.4–84.9)	73.8 (68–80.4)	73.9 (66–83.5)	88.4 (84.4–93.9)	94.2 (91–98.2)	98.9 (97.8–100)
***1/*5**	25.5 (24.2–26.9)	20.4 (15–26.4)	25.1 (19.3–31.7)	24 (16.3–33.5)	11.6 (7.4–17)	5.8 (2.5–9.8)	1.1 (0–2.2)
***5/*5**	2.8 (1.4–4.2)	0.6 (0–6.5)	1.1 (0–7.6)	2.2 (0–11.8)	0 (0–5.4)	0 (0–3.9)	0 (0–1.1)
p-value	Reference	0.04	0.4	0.9	7.3 e^{-06}[§]	9.6 e^{-09}[§]	2.2e^{-16}[§]

[†]*SLCO1B1* CPIC diplotype-to-phenotype translation table [2] (*SLCO1B1*1/*1* [normal function]; *SLCO1B1*1/*5* [decreased function]; and *SLCO1B1*5/*5* [poor function]).
[‡]Data taken from [1] for European Americans.
[§]Bonferroni corrected p-value < 0.008 for significance.
Bold indicates the risk allele/haplotype.
CPIC: Clinical Pharmacogenetics Implementation Consortium.

Table 4. *CYP2C9*2* and *3 allele frequencies among different Asian, Native Hawaiian and Pacific Islander subgroups compared with Europeans.

***CYP2C9* allele**[†]	**Sample population subgroups, % (95% CI)**						
	European (reference) (n = 1.3M)[‡]	**Filipino (n = 192)**	**Japanese (n = 186)**	**Korean (n = 79)**	**Native Hawaiian (n = 148)**	**Marshallese (n = 123)**	**Samoan (n = 183)**
***1**[§]	79.6 (79.4–79.7)	97.6 (96.7–99.2)	99.5 (98.9–100)	97.3 (95.5–99.6)	97.9 (96.7–99.6)	98.8 (97.9–100)	98.1–(97–99.3)
p-value	Reference	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]
***2**	12.8 (12.6–12.9)	0.5 (0–2)	0 (0–0.5)	0 (0–2.1)	1.4 (0.3–3)	0.4 (0–1.8)	0.3 (0–1.6)
p-value	Reference	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]	< 0.0001[¶]
***3**	7.6 (7.4–7.7)	1.9 (0.8–3.3)	0.5 (0–1.1)	2.7 (0.6–4.7)	0.7(0–2.3)	0.8 (0–2.2)	1.6 (0.5–3)
p-value	Reference	< 0.0001[¶]	< 0.0001[¶]	0.02	< 0.0001[¶]	0.00006[¶]	< 0.0001[¶]

[†]The CPIC "*CYP2C9* allele definition table" [2] was used to translate the genotypes in the SNPs rs1799853 C>T and rs1057910 A>G to *CYP2C9*2* and *3, respectively (Supplementary Table 4). *CYP2C9*1* was inferred from the presence of reference alleles (C and/or A) in both SNPs genotypes.
[‡]Data obtained from the CPIC *CYP2C9* taken from [2].
[§]Frequencies of *CYP2C9*1* in the European and sample subgroups were calculated by summing the variant alleles (*CYP2C9*2* and *3) and subtracting the total from 100.
[¶]Bonferroni corrected p-value < 0.008 for significance.
Bold indicates the risk allele/haplotype.
CPIC: Clinical Pharmacogenetics Implementation Consortium.

SLCO1B1 predicted phenotype frequencies

The Native Hawaiian and Pacific Islander subgroups had significantly higher rates of SLCO1B1 normal function predicted phenotype (88.4 and ~97%, respectively) compared with Europeans (72%; Table 3). Among the same population subgroups, the overall range of SLCO1B1 decreased, and poor function was significantly lower (1–11 and 0%, respectively) than in Europeans (26 and 2.8%, respectively). Although statistically insignificant, the overall range of the predicted SLCO1B1 normal function in the Asian subgroups (74–79%) was slightly higher than in Europeans (72%). Further, the prevalence of decreased and poor function SLCO1B1 in Asian subgroups (20–25 and 0.6–2.2%, respectively) was insignificantly lower than in Europeans (26 and 2.8%, respectively).

CYP2C9 allele frequencies

Allele frequencies are presented in Table 4. Except for *CYP2C9*3* allele frequency in Koreans, each ancestral subgroup had significantly lower frequencies of *CY2C9*2* and *3 variants than Europeans ($p < 0.008$; Table 4). The overall *CYP2C9*2* and *3 frequencies were either undetectable or markedly lower in all our population subgroups (0–1.4 and 0.5–2.7%, respectively) than in Europeans (12.7 and 7.6%, respectively). *CYP2C9*2* was undetected in Korean (0%) and Japanese (0%) individuals. Among our population subgroups, Koreans had the highest frequency of *CYP2C9*3* at 2.7%, followed by Filipinos at 1.9% (Table 4).

CYP2C9 diplotype frequencies

CYP2C9 diplotype frequencies are presented in Table 5. All our population subgroups were found to have significantly lower or undetectable *CYP2C9*1/*2, *1/*3* and *2/*2* diplotypes (0–8, 1.4–5 and 0–0.7%, respectively)

Table 5. *CYP2C9* diplotype frequencies among different Asian, Native Hawaiian and Pacific Islander subgroups compared with Europeans.

CYP2C9 diplotype†	Sample population subgroups, % (95% CI)							Phenotype predicted†
	European (reference; n = 1.3M)‡	Filipino (n = 192)	Japanese (n = 186)	Korean (n = 79)	Native Hawaiian (n = 148)	Marshallese (n = 123)	Samoan (n = 183)	
1*/*1	63.3 (63.1–63.4)	95.8 (93.8–98.6)	96.3 (94.1–98.8)	94.9 (91.1–99.2)	89.9 (85.8–94.6)	97.6 (95.9–100)	96.7 (95.1–99.4)	NM
1*/*2	20.1 (19.9–20.3)	0.5 (0–3.3)	0 (0–2.6)	0 (0–4.3)	8.1 (4.1–12.8)	0.8 (0–3.5)	0 (0–2.7)	IM
1*/*3	12 (11.9–12.2)	3.1 (1–5.9)	3.8 (1.6–6.3)	5.1 (0–9.1)	1.4 (0–6.1)	1.6 (0–4.4)	2.7 (1.1–5.4)	IM
2*/*2	2 (1.9–2.2)	0 (0–2.8)	0 (0–2.6)	0 (0–4.3)	0.7 (0–5.4)	0 (0–2.7)	0 (0–2.7)	IM
2*/*3	2 (1.9–2.2)	0.5 (0–3.3)	0 (0–2.6)	0 (0–4.3)	0 (0–4.7)	0 (0–2.7)	0.5 (0–3.2)	PM
3*/*3	0.6 (0.5–0.7)	0 (0–2.8)	0 (0–2.6)	0 (0–4.3)	0.7 (0–5.4)	0 (0–2.7)	0 (0–2.7)	PM
p-value	Reference	0.0005§	0.0005§	0.0009§	0.0005§	0.0005§	0.0005§	PM

†CPIC diplotype-to-phenotype translation table [2] (*CYP2C9*1/*1* [NM]; *CYP2C9*1/*2, *1/*3* and **2/*2* [IM]; and *CYP2C9*3/*3* and **2/*3* [PM]).
‡Data taken from [3]. The total number of genotyped subjects in this table is subtracting subjects who were genotyped for other SNPs within different haplotypes, such as **4* or **75*. It only included individuals who carried **1/*1, *1/*2, *1/*3, *2/*2, *3/*3* or **2/*3* diplotypes.
§Bonferroni corrected p-value < 0.008 for significance.
Bold indicates the risk allele/haplotype.
CPIC: Clinical Pharmacogenetics Implementation Consortium; IM: Intermediate metabolizer; NM: Normal metabolizer; PM: Poor metabolizer.

Table 6. Distribution of the statin-associated musculoskeletal symptoms risk classifications based on risk alleles within rosuvastatin pharmacogenes (*ABCG2* and *SLCO1B1*) among different ethnicities.

SAMS risk score for rosuvastatin†	Sample population subgroups, % (95% CI)						Overall prevalence (n = 895)‡
	Filipino (n = 174)	Japanese (n = 184)	Korean (n = 90)	Native Hawaiian (n = 147)	Marshallese (n = 117)	Samoan (n = 183)	
Normal (0)	21.3% (13.8–29.5)	43.5 (35.9–51.2)	38.9% (28.9–50.7)	66.7% (59.2–74.3)	65.8% (58.1–75.1)	48.7% (41.5–56.6)	46.6% (43–50)
Low (1)	45.9% (38.5–54.2)	36.4% (28.8–44.1)	38.9% (28.9–50.7)	29.3% (21.7–36.9)	29.1% (21.4–38.3)	39.3% (32.2–47.4)	36.9% (33.5–40)
Intermediate (2)	29.9% (22.4–38.1)	17.9% (10.3–25.6)	21.1% (11.1–32.9)	4% (0–11.7)	4.3% (0–13.5)	12% (4.9–20)	15.3% (11.8–18.9)
High (3)	2.9% (0–11)	2.2% (0–9.8)	1.1% (0–12.9)	0% (0–7.6)	0.8% (0–10.1)	0% (0–8)	1.2% (0–4.7)

†Based on the total number of variant alleles in the two statin pharmacogenes (*ABCG2* and *SLCO1B1*), the maximum number of alleles is three. The higher the number, the more SAMS risk alleles and the higher the risk of exposure to statins and development of statin-associated myopathy symptoms, where no variants indicates normal, one variant indicates low risk, two variants indicates intermediate risk and three variants indicates high risk.
‡The sample size represents the number of participants with genotype data for both *ABCG2* and *SLCO1B1* (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotyping data for either of the two or any other single-nucleotide polymorphisms were excluded from the final analysis (n = 169).
CPIC: Clinical Pharmacogenetics Implementation Consortium; SAMS: Statin-associated musculoskeletal symptoms.

than Europeans (20, 12 and 2%, respectively; Table 5). The frequency of CYP*2C9*1/*2* was 8.1% in Native Hawaiian, 0.5% in Filipino, 0.8% in Marshallese, and undetected in Japanese, Korean and Samoan subgroups. The frequency of *CYP2C9*1/*3* was 3.1% in Filipino, 3.8% in Japanese, 5.1% in Korean, 1.4% in Native Hawaiian, 1.6% in Marshallese and 2.7% in Samoan subgroups. Lastly, the frequency of *CYP2C9*2/*2* was 0.7% in Native Hawaiian individuals and absent in the remaining ethnic subgroups (Table 5). The overall ranges of frequencies of *CYP2C9*2/*3* and **3/*3* were significantly lower or undetected in our studied population subgroups relative to Europeans (0.6 and 2%, respectively; Table 5). The *CYP2C9*2/*3* diplotype was barely detected in Filipinos and Samoans (both 0.5%). Further, the *CYP2C9*3/*3* diplotype was only detected in Native Hawaiians at a rate of 0.7%. Among all diplotypes and across all sample subgroups, the most common diplotype was *CYP2C9*1/*1* (~95%), followed by *CYP2C9*1/*3* (~3%) and *CYP2C9*1/*2* (~1.5%), with the rest being undetected or falling below 1%.

CYP2C9 predicted phenotype frequencies

The Asian and Pacific Islander subgroups had a higher frequency of CYP2C9 normal metabolizer predicted phenotype (~96 and ~ 97%, respectively) compared with Native Hawaiians (90%) and Europeans (63%; Table 5). The frequencies of the CYP2C9 intermediate metabolizer phenotype were significantly higher in Europeans (34%) compared with Asian (4%), Native Hawaiian (10%) and Pacific Islander (~2.6%) subgroups. Noticeably, Native Hawaiians had the highest frequency of CYP2C9 intermediate metabolizer phenotype compared with other subgroups. Similarly, the CYP2C9 poor metabolizer predicted phenotype was rare in Filipinos, Native Hawaiians

Table 7. Distribution of combined *ABCG2* and *SLCO1B1* phenotypes among different ethnicities and implications for rosuvastatin dosing.

Combined ABCG2 and SLCO1B1 phenotypes[†]	Sample population subgroups, % (95% CI)						Overall prevalence (n = 895)[¶]	Rosuvastatin starting dose[‡]
	Filipino (n = 174)	Japanese (n = 184)	Korean (n = 90)	Native Hawaiian (n = 147)	Marshallese (n = 117)	Samoan (n = 183)		
Normal function	21.3% (13.7–28.8)	43.4% (36.4–51)	38.9% (28.8–49.5)	66.7% (59.8–74.6)	65.8% (58.1–74.9)	48.6% (41.5–56.6)	46.4% (43.1–50)	Standard starting dose
Normal ABCG2 and decreased SLCO1B1 functions[§]	5.7% (0–13.3)	12% (4.8–19.6)	15.5% (5.5–26.2)	8.8% (2–16.8)	3.4% (0–12.5)	0% (0–8)	7% (3.8–10.6)	
Normal ABCG2 and poor SLCO1B1 functions	0.6% (0–8.1)	0.5% (0–8.1)	2.2% (0–12.9)	0% (0–7.9)	0% (0–9.1)	0% (0–8)	0.4% (0–3.9)	Starting dose adjustment (≤20 mg/day)
Decreased ABCG2 and normal SLCO1B1 functions	40.2% (32.8–47.8)	24.5% (17.4–32)	23.4% (13.3–34)	20.4% (13.6–28.4)	25.6% (17.9–34.8)	39.4% (32.2–47.3)	30% (26.6–33.5)	Standard starting dose
Decreased ABCG2 and decreased SLCO1B1 functions[§]	12.1% (4.5–19.6)	11.4% (4.3–19)	7.8% (0–21.8)	2.8% (0–10.7)	1.7% (0–10.8)	1.1% (0–9)	6.5% (3–9.8)	
Poor ABCG2 and normal SLCO1B1 functions	17.2% (9.7–24.8)	6% (0–13.6)	11.1% (1.1–21.8)	1.3% (0–9.3)	2.6% (0–11.7)	10.9% (3.8–18.9)	8.5% (5.1–12)	Starting dose adjustment (≤20 mg/day)
Poor ABCG2 and decreased SLCO1B1 functions	2.9% (0–10.4)	2.2% (0–9.8)	1.1% (0–11.8)	0% (0–7.9)	0.9% (0–10)	0% (0–8)	1.2% (0–4.8)	Starting dose adjustment (≤10 mg/day)

[†]Subgroups with other combined phenotypes such as decreased ABCG2 and poor SLCO1B1, and poor ABCG2 and poor SLCO1B1, were not detected in our sample subgroups.
[‡]CPIC genotype-based guidelines for statins [3].
[§]Caution: possible increased risks for SAMS with higher rosuvastatin doses (>20 mg).
[¶]The sample size represents the number of participants with genotype data for both ABCG2 and SLCO1B1 (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotype data for either of the two or any other single-nucleotide polymorphisms were excluded from the final analysis (n = 169).
CPIC: Clinical Pharmacogenetics Implementation Consortium; SAMS: Statin-associated musculoskeletal symptoms.

Table 8. Distribution of statin-associated musculoskeletal symptoms risk classifications based on risk alleles within fluvastatin pharmacogenes (*CYP2C9* and *SLCO1B1*) among different ethnicities.

SAMS risk score for fluvastatin[†]	Sample population subgroups, % (95% CI)						Overall prevalence (n = 895)[‡]
	Filipino (n = 174)	Japanese (n = 184)	Korean (n = 90)	Native Hawaiian (n = 147)	Marshallese (n = 117)	Samoan (n = 183)	
Normal (0)	76.5% (70.6–83.9)	70.7% (64–77.2)	64.4% (55.5–75)	77.6% (71.4–84.4)	93.2% (89.7–97.8)	97.8% (96–99.6)	80.8% (78.3–83.4)
Low (1)	21.8% (16–28.3)	28.8% (22.2–35.3)	30% (21–40.6)	21% (15–28)	6.8% (3.4–11.5)	2.2% (0.5–4)	18% (15.5–20.6)
Intermediate (2)	1.7% (0–8.2)	0.5% (0–7.1)	5.6% (0–16.7)	1.4% (0–8.3)	0% (0–4.7)	0% (0–1.9)	1.2% (0–3.9)

[†]Based on the total number of variant alleles in the two statin pharmacogenes (*SLCO1B1* and *CYP2C9*), the maximum possible number is two. The higher the number, the more SAMS risk alleles and the higher the risk of exposure to statins and development of statin-associated myopathy symptoms, where no variants indicates normal, one variant indicates low risk, two variants indicates intermediate risk and three variants indicates high risk.
[‡]The sample size represents the number of participants who have genotype data for both *CYP2C9* and *SLCO1B1* (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotype data for either of the two or any other single-nucleotide polymorphisms were excluded from the final analysis (n = 169).
SAMS: Statin-associated muscle symptoms.

and Samoans (0.5, 0.7 and 0.5%, respectively) and undetected in the remaining subgroups, compared with a 2.6% rate in Europeans (Table 5).

Combinatorial pharmacogenetic assessment of SAMS risk

Combinatorial pharmacogenetic recommendations by the CPIC for rosuvastatin and fluvastatin dosing could provide comprehensive SAMS risk evaluation before starting statin-based therapies [2]. Participants with a missing genotype in any of the genes were excluded (n = 169), with 895 participants included in calculating the proportions shown in Figures 1 & 2 & Tables 6–9. The prevalence of SAMS risk classifications/scores among each ethnic subgroup, shown in Tables 6–9, demonstrates the possible permutations of phenotypes within our studied clinically actionable rosuvastatin and fluvastatin pharmacogenes. Figures 1 & 2 show the implications of various combined pharmacogenes in the starting dose recommendations for rosuvastatin and fluvastatin based on the 2022 CPIC guidelines.

Table 9. Distribution of combined ABCG2 and SLCO1B1 phenotypes among different ethnicities and implications for fluvastatin dosing.

Possible combined CYP2C9 and SLCO1B1 phenotypes[†]	Sample population subgroups, % (95% CI)						Overall prevalence (n = 895)[¶]	Recommended fluvastatin starting dose[‡]
	Filipino (n = 174)	Japanese (n = 184)	Korean (n = 90)	Native Hawaiian (n = 147)	Marshallese (n = 117)	Samoan (n = 183)		
Normal function	76.4% (70.6–82.8)	70.6% (64.7–77.6)	64.5% (55.5–76.6)	77.5% (71.4–84)	93.3% (89.7–97.9)	97.8% (96.2–99.5)	80.6% (78–83)	Standard starting dose
NM CYP2C9 and decreased SLCO1B1 function[§]	20.1% (14.3–26.5)	25.6% (19.5–32.5)	21.2% (12.2–31.3)	10.8% (4.7–17.4)	5.9% (2.6–10.5)	1.1% (0–2.8)	14.3% (11.8–16.8)	
NM CYP2C9 and poor SLCO1B1 function[§]	0.6% (0–7)	0.5% (0–7.5)	2.2% (0–12.4)	0% (0–6.4)	0% (0–4.6)	0% (0–1.8)	0.4% (0–3)	Starting dose adjustment (≤40 mg/day)
IM CYP2C9 and normal SLCO1B1 function	1.7% (0–8)	3.3% (0–10.3)	8.8% (0–19)	10.3% (4.1–16.6)	0.8% (0–5.4)	1.1% (0–2.8)	3.9% (1.4–6.5)	
IM CYP2C9 and decreased SLCO1B1 function	0.6% (0–7)	0% (0–6.9)	3.3% (0–13.5)	0.7% (0–7.1)	0% (0–4.6)	0% (0–1.8)	0.6% (0–3.1)	Starting dose adjustment (≤20 mg/day)
PM CYP2C9 and normal SLCO1B1 function	0.6% (0–7)	0% (0–6.9)	0% (0–10.2)	0.7% (0–7.1)	0% (0–4.6)	0% (0–1.8)	0.2% (0–2.7)	

[†]Subgroups with other combined phenotypes, such as PM CYP2C9 and poor SLCO1B1 function, were not detected in our sample subgroups.
[‡]CPIC genotype-based guidelines for statins [3].
[§]Caution: possible increased risks for SAMS with higher fluvastatin doses (>40 mg).
[¶]The sample size represents the number of participants who have genotype data for both CYP2C9 and SLCO1B1 (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotype data for either of the two or any other SNPs were excluded from the final analysis (n = 169).
CPIC: Clinical Pharmacogenetics Implementation Consortium; IM: Intermediate metabolizer; NM: Normal metabolizer; PM: Poor metabolizer; SAMS: Statin-associated musculoskeletal symptoms.

Combinatorial pharmacogenetic assessment of SAMS risk for rosuvastatin

The rosuvastatin SAMS risk score distribution among our population subgroups is shown in Table 6. Overall, the maximum cumulative score detected among our sample was three out of a possible four. The proportions of rosuvastatin SAMS risk scores among our studied subgroups were 46.6, 36.9, 15.3 and 1.2% for normal, low, intermediate and high risk, respectively. This also shows that more than one-half (~53%) of our sample population subgroups have at least one of the two clinically actionable alleles *SLCO1B1*5* and *ABCG2* Q141K. Noticeably, the proportion of normal SAMS risk scores in Filipinos was substantially lower (21.3%) compared with other Asian and NHPI subgroups (Table 6), including Japanese (43.5%), Korean (38.9%), Native Hawaiian (66.7%), Marshallese (65.8%) and Samoan (48.7%) individuals. Among our sample population subgroups and across all SAMS risk scores, Filipinos had the highest rates of abnormal SAMS risk scores (i.e., low, intermediate and high; 79%), followed by Korean (61%), Japanese (56%), Samoan (51%), Native Hawaiian (33%) and Marshallese (34%) subgroups (Table 6).

The proportions of individuals with low SAMS risk scores (i.e., individuals carrying one risk allele) were 50% in Filipino, 39% in Korean, 36% in Japanese, 29% in Native Hawaiian and Marshallese, and 39% in Samoan subgropus. Individuals with intermediate SAMS risk scores (i.e., those carrying two risk alleles) were more common in the Filipino group (30%), followed by Korean (21%), Japanese (18%), Samoan (12%), Marshallese (4.3%) and Native Hawaiian (4.1%) individuals. Similarly, the proportions of high SAMS risk scores (i.e., individuals carrying three risk alleles) were 3% of Filipino, 2% of Japanese, 1% of Korean and 0.8% of Samoan individuals; high SAMS risk scores were not detected in the Native Hawaiian and Marshallese subgroups. Seven possible phenotypes were identified in the study subgroups with the combined ABCG2 and SLCO1B1 phenotypes (Figure 1 & Table 7). Among our population subgroups, 53% had abnormal combined phenotypes (carriers of decreased or poor function phenotypes; Table 7). If all our sample population were to be prescribed rosuvastatin, 20.7% of Filipino, 14% of Korean, 11% of Samoan, 8.7% of Japanese, 3.5% of Marshallese and 1.3% of Native Hawaiian individuals would need a dose adjustment according to the 2022 CPIC guidelines for combined phenotypes of rosuvastatin pharmacogenes (Figure 1 & Table 7) [2]. Noticeably, Filipinos had the highest likelihood of having their rosuvastatin starting dose adjusted if rosuvastatin were to be prescribed compared with non-Filipino population subgroups.

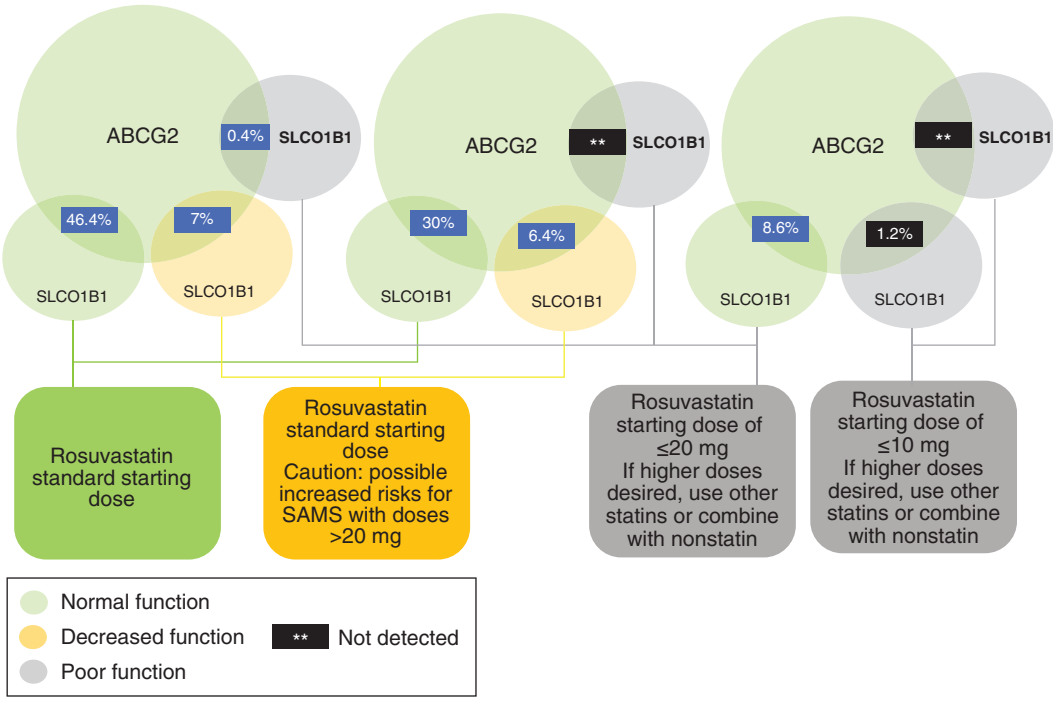

Figure 1. The overall proportions of combined ABCG2 and SLCO1B1 phenotypes and their implications for rosuvastatin starting dose among our population sample. Based on the combined SAMS risk genotypes in the two rosuvastatin pharmacogenes (*ABCG2* and *SLCO1B1*) and using the CPIC allele definition and diplotype-to-phenotype tables [2], different phenotype combinations were detected among our sample subgroups (blue boxes). The proportions (blue boxes) represent the overall proportions of combined ABCG2 and SLCO1B1 phenotypes in Asian, Native Hawaiian and Pacific Islander subgroups and their implications for rosuvastatin starting dose from the CPIC genotype-based statin guidelines [3]. Note: the sample size represents the number of participants who have genotype data for both *ABCG2* and *SLCO1B1* (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotype data for either of the two or any other single-nucleotide polymorphisms were excluded from the final analysis (n = 169).
CPIC: Clinical Pharmacogenetics Implementation Consortium; SAMS: Statin-associated musculoskeletal symptoms.

Combinatorial pharmacogenetic assessment of SAMS risk for fluvastatin

The fluvastatin SAMS risk score distribution among our population subgroups is shown in Table 8. The maximum score detected among our sample was two out of a possible four. The fluvastatin SAMS risk score proportions among our studied subgroups were 80.8, 18 and 1.2% for normal, low and intermediate, respectively. Abnormal fluvastatin SAMS risk scores were less prevalent than abnormal rosuvastatin SAMS risk scores (19.2 vs 53%, respectively). The proportion of abnormal SAMS risk scores was higher (35.6%) in Koreans compared with other Asian and NHPI subgroups (Table 8), including Japanese (29.3%), Filipino (23.5%), Native Hawaiian (22.4%), Marshallese (6.8%) and Samoan (2.2%) individuals.

The proportions of individuals with low SAMS risk scores (i.e., those carrying one risk allele) were 30% in Korean, 28.8% in Japanese, 21.8% in Filipino, 21% in Native Hawaiian, 6.8% in Marshallese and 2.2% in Samoan subgroups. Individuals with an intermediate SAMS risk score (i.e., those carrying two risk alleles) were more of Korean ethnicity (5.6%), followed by Filipino (1.7%), Native Hawaiian (1.4%) and Japanese (0.5%); such scores were undetected in Samoan and Marshallese subgroups (Table 8). Six possible phenotypes were identified in the subgroups with combined CYP2C9 and SLCO1B1 phenotypes (Figure 2 & Table 9). Among our population subgroups, 19.4% had abnormal combined phenotypes (carriers of intermediate or poor CYP2C9 metabolizer and decreased or poor SLCO1B1 function phenotypes; Table 9). If all our sample population were prescribed fluvastatin, 14.3% of Korean, 11.7% of Native Hawaiian, 3.5% of Filipino, 3.8% of Japanese, 1.1% of Samoan and 0.8% of Marshallese individuals would need a dose adjustment according to the CPIC guidelines for combined phenotypes of fluvastatin pharmacogenes (Figure 2 & Table 9) [2]. Specifically, Koreans would have the highest likelihood of having their fluvastatin starting dose adjusted compared with other population subgroups.

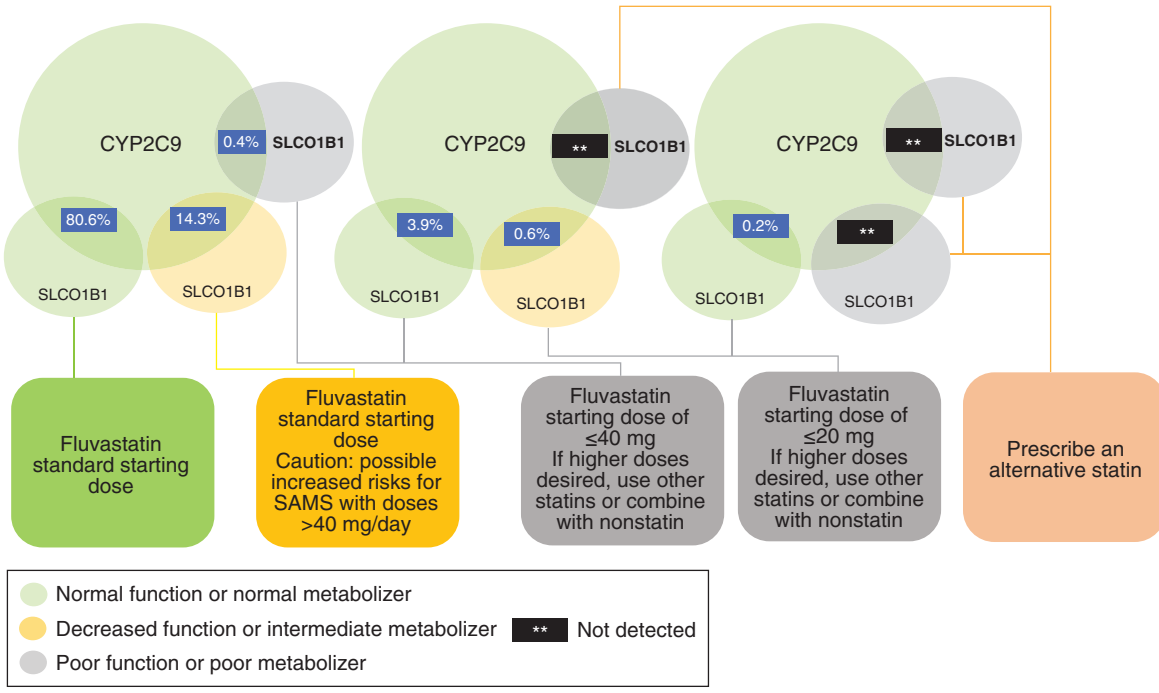

Figure 2. The overall proportions of combined CYP2C9 and SLCO1B1 phenotypes and their implications for fluvastatin starting dose among our population sample. Based on the combined SAMS risk genotypes in the two fluvastatin pharmacogenes (*CYP2C9* and *SLCO1B1*) and using the CPIC allele definition and diplotype-to-phenotype tables [2], different phenotype combinations were detected among our sample subgroups (blue boxes). The percentages (blue boxes) represent the overall proportions of combined CYP2C9 and SLCO1B1 phenotypes in Asian, Native Hawaiian and Pacific Islander subgroups and their implications for rosuvastatin starting dose from the CPIC genotype-based guidelines for statins [3]. Note: the sample size represents the number of participants who have genotype data for both *CYP2C9* and *SLCO1B1* (n = 895). Participants genotyped for one of the two genetic variants or who had missing genotype data for either of the two or any other single-nucleotide polymorphisms were excluded from the final analysis (n = 169).
CPIC: Clinical Pharmacogenetics Implementation Consortium; SAMS: Statin-associated musculoskeletal symptoms.
References [1,2,4].

Discussion

To the best of our knowledge, this is the first report on allele frequencies of statin-associated genetic variants (*SLCO1B1*5*, *ABCG2*, *CYP2C9*2* and *CYP2C9*3*) in women of Filipino, Native Hawaiian, Marshallese and Samoan descent. Also, our study is the first to estimate the proportion of individuals from different ethnic subgroups of ANHPI, with a combined genotype for statin pharmacogenes (Figures 1 & 2), which was highlighted in the most contemporary CPIC statin guidelines [2]. Our findings expand the knowledge of allele and genotype frequencies of *SLCO1B1* and *CYP2C9* among under-represented ethnic groups and should improve the clinical decision-making process to achieve more individualized patient care. Compared with Europeans, our results showed that Filipino, Japanese and Korean subgroups have comparable *SLCO1B1*5* diplotype frequencies, while Native Hawaiian, Marshallese and Samoan subgroups have significantly lower *SLCO1B1*5* diplotype frequencies. Additionally, ANHPI subgroups had significantly lower *CYP2C9*2* and **3* diplotype frequencies compared with Europeans. Prior reports found that the frequency of the Q141K polymorphism in *ABCG2* was significantly higher in ANHPI individuals than in Europeans, with Filipinos having the highest frequency [1,21,34,39]. The implication of such allele frequency differences in statin-related pharmacogenes between population subgroups emphasizes that Filipinos are the most likely to be impacted by the poor-functioning ABCG2 phenotype compared with non-Filipinos [21]. The latter observation underscores the importance of considering preemptive pharmacogenetic testing for the Q141K (*ABCG2*) genotype as a top priority in ANHPI patients, especially Filipinos, and to a lesser extent *SLCO1B1*5*, before commencing statin-based therapy, in order to optimize statin benefits to prevent cardiovascular disease and minimize the risks of SAMS. Although earlier studies indicated that the *SLCO1B1*5* and *CYP2C9*2* and **3* genetic variants were either less prevalent or undetected among East Asians and NHPI

individuals, they overlooked the differences within Asian ancestral subgroups [40,41]. In contrast to prior research, our data show that different allele frequencies within distinct Asian and Pacific Islander subgroups do exist. Our findings may provide new insights to inform future genetic research investigations to focus on high-risk ancestral subgroups.

The implications of different genetic variants on statin pharmacokinetics and pharmacodynamics are prominent. They can influence the treatment decisions for patients from under-represented ancestral subgroups with a high prevalence of dyslipidemia. Specifically, the three clinically actionable genetic variants within key transporters and drug-metabolizing enzymes (i.e., *SLCO1B1*, *ABCG2* and *CYP2C9*) involved in different statin dispositions may affect the risk of statin-related adverse events [4].Increased exposure to various statins, such as rosuvastatin, atorvastatin, simvastatin, lovastatin and fluvastatin, is broadly associated with *SLCO1B1*5* [4]. Compared with individuals with the normal phenotype, poor-function phenotype carriers (*SLCO1B1*5/*5*) were shown in one study to have 144 and 65% greater exposure (area under the plasma atorvastatin concentration–time curve from 0 to 48 h) to atorvastatin and rosuvastatin metabolites, respectively ($p < 0.01$) [42]. Differences in *SLCO1B1*5* allele frequency have been observed in prior studies [43–45]. Asian ancestral subgroups have a slightly lower prevalence of *SLCO1B1*5* than Europeans (~12 vs ~16%, respectively) [43–45]. The same variant allele frequency was markedly lower in African–Americans (~4%) than in Asians and Europeans [45]. Our results are consistent with those findings, with Asian subgroups having a *SLCO1B1*5* allele frequency comparable to that of Europeans (11–14 vs.15.5%, respectively; Table 2).

The *SLCO1B1*5* genotype distribution showed marked differences between ethnic groups, possibly contributing to the observed interindividual and interpopulation differences in statin exposure [4,45]. The frequencies of the decreased- and poor-function OATP1B1 phenotypes were previously reported to be 18 and 2.9% in Japanese (n = 104), 20.5 and 1.5% in Korean (n = 200), and 23 and 2% in Chinese individuals (n = 103), respectively [1,21,34,39]. African–Americans (n = 1054) exhibited much lower or undetectable frequencies of decreased- and poor-function OATP1B1 (2.4 and 0.2%, respectively) compared with Asians (~20 and ~2%, respectively), whose frequencies were equal to or slightly lower than those in Europeans (25.5 and 2.8%, respectively) [1,21,34,39]. Our estimates of the predicted decreased- and poor-function phenotypes in Japanese individuals (25 and 1.1%, respectively) and Koreans (24 and 2.2%, respectively) were comparable with the previous reports [1,21,34,39]. At the time of this publication, our study is the first to report on the prevalence of *SLCO1B1*5* in Filipinos, Native Hawaiians, Marshallese and Samoans (11, 6, 3 and 0.5%, respectively; Table 2). This highlights the importance of pharmacogenetic investigations in under-represented population subgroups to identify potential allele frequency differences and, eventually, to better characterize drug exposure.

Similar to *SLCO1B1*, genetic variations within *CYP2C9* can affect the pharmacokinetics of fluvastatin [4]. *CYP2C9* is highly polymorphic, with more than ~80 known variants [46]. *CYP2C9*2* and **3* are the most studied variants, but their allele frequencies are, respectively, low or rare in East Asians (0.03 and 1–3%) [47] and African–Americans (2.5 and 1%) compared with Europeans (13 and 7%) [3].

Sangkuh *et al.* suggested that individuals from ancestries like European (13%), Central/South Asian (11%) and Latino (8%) have greater allele frequencies of the decreased-function allele *CYP2C9*2* than African–Americans (<3%) [46]. Similarly, the no-function allele *CYP2C9*3* was more common in Europeans (7.6%) and Central/South Asians (11%) than in East Asians (4%) [46]. Our results of *CYP2C9*3* frequency in Asian population subgroups were lower than the frequency reported by Sangkuh *et al.* [46] (~1.7 vs 4%, respectively). The possible reason for the observed inconsistency is that the prevalence of *CYP2C9*3* in the East Asian major racial categorization was predominantly represented by only two ethnicities: Vietnamese and Malay. However, the prevalence of the same variant in our Asian subgroups aligns with published Pharmacogenomics Knowledge Base (PharmGKB) reports [3]. According to PharmGKB, the frequency of *CYP2C9*2* in East Asians (n = 1008) was 0.1%, similar to our rates of 0.2% in Asians (Table 4). Conversely, *CYP2C9*3* was detected at 3.3% in East Asians, which was relatively higher than the frequency reported in our Asian subgroups (0.5–2.7%) [3,34]. When we disaggregate the prevalence of both variants reported by PharmGKB under the broad racial categorization of East Asians, we see that *CYP2C9*2* was nearly undetectable (0.1%) in Japanese individuals (n = 208). Additionally, *CYP2C9*3* prevalence in Japanese individuals was detected at a rate of 1.9% [3,34]. Compared with the latter estimates of *CYP2C9*2* and **3* allele frequencies in the Japanese population [3,34], our sample of the Japanese subgroup had comparable estimates of *CYP2C9*2* (undetected) but lower *CYP2C9*3* allele frequency at 0.5% (Table 4).

Leland *et al.* [47] estimated the frequency of *CYP2C9* variants in Filipinos residing in the Philippines (n = 99) and reported the frequencies of *CYP2C9*2* and **3* to be 0 and 1%, respectively [47]. In our Filipino cohort, we observed

comparable allele frequencies of *CYP2C9*2* and *CYP2C9*3* at a rate of 0.5 and 1.9%, respectively [47]. Our findings indicate that Filipinos have significantly higher CYP2C9 normal metabolizer (95.8%) but lower intermediate (3.6%) and poor metabolizer (0.5%) predicted phenotypes than Europeans (63.3, 34.1 and 2.6%, respectively; Table 5). The rates of CYP2C9 phenotypes reported in our Filipino cohort were similar to those published by Leland *et al.* [47] at 98, 2 and 0% for CYP2C9 normal, intermediate and poor metabolizers, respectively. The Korean subgroup had similar frequencies of *CYP2C9*2* and **3* (0 and 2.7%, respectively) compared with Filipinos and Japanese individuals (Table 4). Yoon *et al.* also detected relatively similar frequencies in Koreans residing in Korea (0 and 1.1% for *CYP2C9*2* and **3*, respectively) [48]. Based on our findings and prior reports [46–48], it is very likely that *CYP2C9*2* is rare in East Asian populations.

Our study is the first to report on the prevalence of *CYP2C9* variants in NHPI subgroups. *CYP2C9*2* was rare in Marshallese and Samoan individuals (0.4 and 0.3%, respectively) and uncommon in Native Hawaiians (1.4%), while *CYP2C9*3* was rare in Native Hawaiian (0.7%) and Marshallese populations (0.8%) and uncommon in Samoans (1.7%; Table 4). These observations suggest that the NHPI population subgroups, besides Asians, are less impacted by both variants compared with Europeans. The rare allele frequencies of *CYP2C9*2* and **3* in the NHPI populations suggest that routine pharmacogenetic testing for these genetic variants has low priority before prescribing statins, compared with the more common allele within *ABCG2* (Q141K) [49]. This observation does not rule out whether these population subgroups may carry other *CYP2C9* variants. However, the 2022 CPIC statin dosing guidelines suggest a combinatorial phenotype recommendation for rosuvastatin and fluvastatin pharmacogenes (*SLCO1B1* and *ABCG2* or *CYP2C9*) for a more accurate dosing and informative clinical decision-making process if genotype data are available [4,50,51].

The Q141K (rs2231142 G>T) variant within the efflux transporter gene *ABCG2* has also been found to be a clinically relevant variant for rosuvastatin dosing [4]. Notably, the frequencies of decreased- and poor-function ABCG2 phenotypes were 51 and 21% in Filipino, 35 and 8% in Japanese, and 32 and 12% in Korean populations [8,37,52,53]. These frequencies were substantially higher than those in Europeans (20 and 1%) and African–Americans (6 and 0.1%) [8,37,52,53]. The allele frequency of Q141K is significantly more than double in all Asian subgroups (46, 26 and 28% in Filipino, Japanese and Korean populations, respectively) than in non-Asians (11 and 3% in Europeans and African–Americans, respectively; $p < 0.001$) [8,11,37,52,53]. According to earlier data, the pleiotropic genetic polymorphism Q141K in *ABCG2* is significantly more prevalent in Filipinos versus non-Filipinos [8,11,37]. The same variant was found to be associated with rosuvastatin exposure. In individuals homozygous for the variant allele (TT), the exposure (area under the plasma rosuvastatin concentration–time curve from 0 h to infinity) after a single 20 mg oral dose was 100% greater than that in heterozygous carriers (GT), and it was over 140% greater than that in individuals with the wild-type homozygous genotype (GG; $p \leq 0.01$) [54].

While single genetic variants could predict the response to selected statin drugs, a combinatorial pharmacogenetic approach to statin therapy, including *SLCO1B1*, *ABCG2* and *CYP2C9*, is more relevant for statin prescribing among the general population [4,50,51,55]. Importantly, the CPIC statin dosing guidelines consider the combinatorial effects of *SLCO1B1* and *ABCG2* for rosuvastatin and of *SLCO1B1* and *CYP2C9* for fluvastatin [4]. Our combinatorial pharmacogenetic results suggest that 8.3% of our studied population have biallelic or three variants within rosuvastatin (7.7%) and fluvastatin (0.6%) pharmacogenes (Figures 1 & 2) that would impact their exposure and starting doses. When commencing statin-based therapy, individuals with the above-mentioned combined phenotypes could be at higher risk for developing SAMS versus individuals carrying one genetic variant in one gene. If rosuvastatin were to be prescribed to the entire sample population, a dose adjustment would be needed for 20.7% of the Filipino, 14% of the Korean, 11% of the Samoan, 8.7% of the Japanese, 3.5% of the Marshallese and 1.3% of the Native Hawaiian patients (Figure 1 & Table 7). In contrast to non-Filipino subgroups, Filipinos have the highest chance of having their rosuvastatin starting dose changed if rosuvastatin were to be prescribed according to the CPIC guidelines. For fluvastatin, Koreans would have the highest chance of having their initial fluvastatin dose changed if this medication were to be prescribed (Figure 2 & Table 9). These gene–drug interactions highlight how crucial (and difficult) it is to fully comprehend how variations in drug transporters and drug-metabolizing genes might affect the therapeutic use of statins [4]. Patients with combined genetic information for *SLCO1B1* and *ABCG2* or *CYP2C9* could garner additional benefits by closely estimating the starting dose. However, the limited knowledge about the effect of combinatorial genetic variations within statin pharmacogenes limits the strength of the same recommendations. Studies estimating the prevalence of population subgroups with combined phenotypes, like the current study, ascertaining their association with statin pharmacokinetics and providing information on statin dosage adjustment are greatly needed.

Preemptive or point-of-care pharmacogenetic testing continues to be the most effective and appropriate way to implement pharmacogenetic knowledge for patient care [56–60]. Nonetheless, we acknowledge the need for genetic research studies investigating the prevalence of clinically actionable variants within pharmacogenes in under-represented population subgroups. When resources are limited, for instance, pinpointing populations with high frequencies of specific pharmacogenetic alleles can help guide targeted screening and inform areas of focus for future pharmacogenetic research. The allele frequencies of the above genetic variants represent those seen at the population subgroup level. However, they can be viewed as an approximation of the prevalence at the individual level. Hence the findings of this study can serve as a tool to inform future pharmacogenetic studies.

The clinically relevant *CYP2C9*2* and **3* variants are linked with decreased or poor enzyme function and higher fluvastatin exposure; however, they are rare or undetectable among ANHPI individuals (Table 4). While routine pharmacogenetic testing for *CYP2C9*2* and **3* variants in the context of fluvastatin dosing in individuals of ANHPI ancestry may not be necessary, it does not rule out the possibility that patients carry novel *CYP2C9* variants that are yet to be discovered [46]. People of African ancestry, for instance, are more likely to have different *CYP2C9* alleles affecting enzymatic activity, such as *CYP2C9*5* (~1.2%), **6* (~0.9%), **8* (~7.6%) and **11* (~2.6%) [46,61]. Future pharmacogenetic studies focused on well-characterized population subgroups could enhance the detection of population-specific variants besides **2* and **3*, to refine the haplotype block structure of *CYP2C9*. Ultimately, pharmacogenetic studies among diverse populations will optimize the genotype–phenotype prediction of *CYP2C9* and improve the overall prediction models for safe and effective drug use [61]. Conversely, routine testing for the statin transporter encoding gene *ABCG2* (Q141K) should be of top priority in individuals of Asian and NHPI ancestries (Supplementary Tables 1 & 2). Filipino and Samoan subgroups have the highest phenotype frequencies of decreased-/poor-function ABCG2 than other Asians [21] and NHPI [49] subgroups, indicating the need for lower rosuvastatin starting doses in the same population groups. Along with *SLCO1B1*5*, Q141K in *ABCG2* can synergistically predispose carriers to increased exposure and higher risk of SAMS (Table 6) [4]. Genetic testing of *SLCO1B1* could be considered; however, *SLCO1B1*5* allele frequency among Asians was not significantly different from that in Europeans. Statin exposures in Samoan, Marshallese and Native Hawaiian patients are less likely to be impacted by *SLCO1B1*5* as the allele frequency was substantially lower in NHPI individuals than in Asians and Europeans (~3% vs 13 and 16%, respectively; Table 2).

The 'one size fits all' drug prescription approach undermines the individual's unique genetic makeup and interpopulation subgroup differences, especially among Asian and NHPI populations. Asian and NHPI ancestries are major categorizations composed of distinct subgroups enriched with markedly variable genetic makeup and cultural and social constructs [7,62]. Particularly, the major categorization of Asian subgroups under the general Asian categorization can obscure genetic architecture differences and distinct ancestral patterns among Asian individuals [62]. On the one hand, patients from European ancestry have pharmacogenetic variant frequencies closest to the overall population mean [63]. This observation suggests that Europeans are more likely to receive the most appropriate treatment from this approach. On the other hand, Asian population subgroups have significantly variable pharmacogenetic variant frequencies, especially the decreased-function variant in *ABCG2* [7,8,11,21,37,52,53]. The broad categorization approach to statin prescription puts individuals of ANHPI ancestry at risk of receiving suboptimal statin treatment. Suboptimal treatment can hinder optimal therapy and potentially expose impacted groups to unnecessary ADRs [7,62]. To this end, the broad recommendation of a starting dose of 5 mg of rosuvastatin in all Asians by the US FDA without considering pharmacogenetic testing for *ABCG2* is an example of a race-based guideline that presents major challenges among markedly diverse population subgroups [64]. Based on the proportions of individuals with combined ABCG2 and SLCO1B1 phenotypes (Table 7), it is estimated that a significant proportion of Japanese (91%), Korean (85.6%) and Filipino (79%) individuals would be undertreated if started on the race-based recommended starting dose of 5 mg rosuvastatin. With the well-established benefits of statin therapy, rosuvastatin underdosing may further delay achieving the desired therapeutic outcomes among population groups such as Southeast Asians [21] and NHPI individuals [49] who are already at high risk for developing atherosclerotic diseases.

Furthermore, prior observational studies highlighted that Filipinos have the highest reported pharmacogenetic variant frequency within *ABCG2*, making them more likely to benefit from preemptive pharmacogenetic testing for *ABCG2* and lower doses of rosuvastatin compared with other Asian groups [7,8,11,21,37,49,52,53]. In our study, Filipinos were more likely to carry clinically actionable statin pharmacogenetic variants (higher SAMS risk score) than other Asian and NHPI subgroups (Table 6). Considering the latter observation, the allele frequency data of *ABCG2* (Q141K) and the high rates of dyslipidemia and mortality from coronary heart disease in this subgroup

indicate the remarkable uniqueness of individuals of Filipino ancestry [9]. These observations underscore the need for more inclusive studies to identify the risk factors contributing to the high prevalence of dyslipidemia and the interethnic differences in statin pharmacokinetics/pharmacodynamics among Asians [9].

Limitations

First, we have reported the frequencies of targeted and limited SNPs in *SLCO1B1, ABCG2* and *CYP2C9*. This could be a potential limitation because other or novel variants within those genes were not evaluated, and they may have important effects on statin exposure in ANHPI subgroups. With the limited tested SNPs, our estimates of the reference alleles (**1*) may be overestimated. Indeed, the reference allele in our analysis was inferred from the absence of the other variant alleles. Specifically, *SLCO1B1*1* and *CYP2C9*1* alleles were assigned based on the absence of *SLCO1B1*5* and *CYP2C9*2* and **3*, respectively. Second, our study only covered selected genes involved in the disposition of statins; other candidate genes could interfere with the pharmacokinetic pathways of individual statins. Third, we used CPIC guidelines to translate diplotypes into phenotypes. These prediction tools indicate the effect of genetic variants on the phenotypes without considering other variables such as concurrent medications, diet, gender and other comorbidities that may affect the transporters and the metabolizing enzymes. Fourth, participants' race was self-reported, which is subjective and may not reflect the truth of an individual's ancestral background. Lastly, all study participants were women. Although this may limit the true estimation of the population's allele frequencies, sex-linked allele frequencies are unlikely for our studied genes. Nevertheless, distinct sex differences in the levels of gene expressions in response to statin treatment have been previously reported in animal models [65].

Conclusion

This study is the first to report the frequencies of clinically actionable statin pharmacogenetic variants among ANHPI subgroups residing in the USA. Our Asian subgroups have comparable *SLCO1B1*5* frequencies to Europeans. However, *SLCO1B1*5* allele frequencies were significantly lower in NHPI individuals than in Europeans. On the other hand, the frequencies of the defective alleles *CYP2C9*2* and **3* were significantly lower in all ANHPI subgroups than in Europeans, except for Koreans. The Q141K (*ABCG2*) allele was significantly more common among ANHPI individuals than Europeans. The combined genotypes approach to statin prescribing could be a more precise tool to identify the risks of developing SAMS, which will play a pivotal role in achieving desired therapeutic outcomes. Our study concludes that Filipinos are a distinct Asian subgroup that needs to be more engaged in studies due to their disproportionate risk of dyslipidemia and propensity for higher statin exposure. Notably, Filipinos and Koreans had the highest proportions of abnormal SAMS risk alleles affecting both rosuvastatin and fluvastatin exposures. This could impact their ADR risk and hinder them from harnessing the benefits of statins. The knowledge of the combined genetic information of *SLCO1B1* plus *ABCG2* or *CYP2C9* may warrant substantive treatment modifications and ultimately reduce the racial health disparities associated with statin exposure, especially in individuals of Asian and NHPI descent.

Future perspective

Our findings underscore the limitations of the broader ethnic and racial classification of ANHPI population subgroups. Prior reports on *ABCG2* and the current study demonstrate subgroup differences in the frequencies of three clinically actionable variants in *SLCO1B1* and *CYP2C9*. Once replicated and validated, our results could prompt pharmacogenetic testing among selected ANHPI subgroups with a high frequency of decreased or poor ABCG2 function before initiating some statins. Patient genetic information could enhance treatment outcomes and ADR prediction models, allowing us to move toward more personalized patient care. Also, it is necessary to study and analyze well-characterized population subgroups to identify population-specific genetic polymorphisms and distinctive allele frequencies that could optimize risk stratification among population subgroups. Finally, integrating distinct ancestral subgroups in genetic and pharmacogenetic research can improve the clinical utility of polygenic risk scores to accurately predict the response and exposure to statins and dyslipidemia risks. Nevertheless, personalized efforts to increase the representation of minority groups are needed to increase the diversity in the genetic and pharmacogenetic research landscapes and reduce health disparities linked with accessing genetic testing.

Summary points

- Statins are keystone medications in dyslipidemia management and are used for the primary and secondary prevention of cardiovascular diseases.
- Statin-associated musculoskeletal symptoms (SAMS) are one of the most reported causes of low adherence to statin therapy, heightening the risk of poor disease management and worse treatment outcomes.
- The risk of developing SAMS is multifactorial and varies by age, sex, concurrent diseases, concomitant medications and specific gene variations in drug transporters and metabolizing enzymes.
- Recent Clinical Pharmacogenetics Implementation Consortium guidelines have highlighted the importance of assessing statin pharmacogenetic genotypes while prescribing statins.
- However, the allele frequencies of major variants within these genes are unknown for Filipinos and for Native Hawaiian and Pacific Islander individuals.
- The frequency of *SLCO1B1*5* was significantly lower in NHPI (0.5–6%) and insignificantly lower in Asian subgroups (11–14%) than in Europeans (16%). Prior reports showed that Q141K (*ABCG2*) allele frequencies in Asians, Native Hawaiians and Pacific Islanders were significantly higher than in Europeans, with Filipinos having the highest frequency.
- In all Asian, Native Hawaiian and Pacific Islander subgroups, the frequency of *CYP2C9*3* was significantly lower (0.5–3%) than in Europeans (8%), while *CYP2C9*2* was undetected or rare (0–1.4%) relative to Europeans (12.7%).
- The combined phenotype approach, which accounts for the clinically actionable statin pharmacogenetic variants, could play a crucial role in improving therapeutic outcomes while lessening the risk of developing SAMS. It is suggested as a risk assessment tool to be integrated before prescribing rosuvastatin and fluvastatin.
- Filipinos are a noteworthy Asian subgroup with risk factors for dyslipidemia and cardiovascular diseases with abnormal SAMS risk alleles, suggesting the need for genotype-based dosing, lower statin dosing, alternative medications, or closer monitoring for adverse drug reactions versus non-Filipinos.
- Incorporating pharmacogenetic testing and genotype-based dosing allows for personalized medicine and addresses the challenges of grouping diverse populations into a broad racial category.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pgs-2023-0043

Disclaimer

The views and opinions presented here represent those of the authors and should not be considered to represent advice or guidance on behalf of the US FDA.

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