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ARTICLE

Global distribution of *CYP2C19* risk phenotypes affecting safety and effectiveness of medications

Mohitosh Biswas[1]

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Abstract

Genetic variability of *CYP2C19* may affect safety or efficacy of many clinically important medications as outlined in the clinical pharmacogenetics implementation consortium (CPIC) dosing guidelines. To determine the predictive prevalence of high-risk phenotypes due to *CYP2C19* genetic variants collectively in the world population and to establish a correlation how the identified high-risk phenotypes may affect safety or effectiveness of drugs, this study was conducted. Frequency of *CYP2C19*2, *3 and *17* alleles were obtained from 1000 Genomes project Phase III in line with Fort Lauderdale principles. Phenotypes were assigned using international standardized consensus terms based on the carrier of characteristics alleles. Association of predicted high-risk phenotypes with the safety or effectiveness of medications was gained from CPIC dosing guidelines. Ultrarapid and poor metabolizers were considered as being as high-risk phenotypes for at least ten clinically important medications. Meta-analysis of the prevalence of high-risk phenotypes showed that it was statistically significant (p<0.0001) in different ethnic groups with pooled prevalence of 27.4% (95% CI 18–37%). The present study suggests that African (37.2; 95% CI 34–41%) and European (35.4; 95% CI 31–40%) population are being at particularly higher risk of either sub therapeutic drug responses or toxicities due to combined effects of *CYP2C19*2*, **3* and **17* variants. Large scale clinical studies are warranted to assess clinical outcomes of these medications considering *CYP2C19* pharmacogenomics effects.

Introduction

Precision medicine (PM) is an emerging novel approach to treat particular group of patients based on their genetic characteristics intended to optimize safety and effectiveness of medications [1, 2]. It can be achieved in many ways mostly including the consideration of genetic polymorphisms of cytochrome P450 (CYP) enzymes, which play pivotal role either in the activation of pro-drugs or detoxification of pharmacologically active drugs through phase-1 drug metabolism [3–5]. Although about a dozen CYP enzymes are accountable for the biotransformation of most drugs in clinical use but CYP family 2, subfamily C member 19 (CYP2C19) is substantially important since 10% of current clinically used drugs are metabolized by CYP2C19 [5]. The CYP2C19 enzyme encoded by *CYP2C19* gene is highly polymorphic since at least 35 single nucleotide polymorphisms have been identified to date. Among these *CYP2C19* variants, *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560) may affect safety or effectiveness of many clinically important medications as outlined in the Pharmacogenomics Knowledgebase (PharmGKB) website and Clinical Pharmacogenetics Implementation Consortium (CPIC) pharmacogenomics (PGx) based dosing guidelines [6–9]. For example, carriers of two copies of no function *CYP2C19*2* allele (i.e., *CYP2C19*2/*2*) treated with clopidogrel may increase 1.8 fold risk for secondary severe adverse cardiovascular events such as death, myocardial infarction and stroke whereas four fold increased risk for stent thrombosis [10–12].

This is because due to the presence of homozygous *CYP2C19*2* variant (i.e., *CYP2C19*2/*2;* poor metabolizers), functionally inactive CYP2C19 metabolic enzyme cannot convert the pro-drug clopidogrel to the active form and hence therapeutic failure leads to severe secondary adverse cardiovascular events. Similarly, carriers of

✉ Mohitosh Biswas
biswas_07pharm@ru.ac.bd

[1] Department of Pharmacy, University of Rajshahi, Rajshahi 6205, Bangladesh

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heterozygous *CYP2C19*2* variant (i.e., *CYP2C19*1/*2;* intermediate metabolizers) treated with clopidogrel may increase 1.5 fold for secondary severe adverse cardiovascular events such as death, myocardial infarction and stroke whereas 2.6 fold increased risk for stent thrombosis [10–12]. The *CYP2C19*3* variant has the similar effects like *CYP2C19**2 variant. In contrast, patients carrying one or two copies of 'gain-of function' *CYP2C19**17 alleles treated with clopidogrel may increase the risk of bleeding due to over activation of the prodrug, clopidogrel [13]. Therefore, the genetic polymorphisms of *CYP2C19**2, C*YP2C19**3, and *CYP2C19**17 are potential predictors to determine the safety or effectiveness of many clinically important medications and need to explore in the world population.

Although numerous studies reported *CYP2C19* genetic polymorphisms in different ethnic groups [14–16] but there is a definite paucity of studies providing collective information of *CYP2C19*2,*3 and *17* genetic polymorphisms and determine the predictive phenotypes consecutively carrying all these variants representing wide range of world population. Also, no study so far has actually boldly established the correlation of the *CYP2C19* risk phenotypes with the safety or effectiveness of a number of clinically prescribed drugs.

The objectives of this study were to determine the predictive prevalence of genetic polymorphisms of *CYP2C19*2, *3* and **17* variants collectively in the world population (26 population comprising 2504 participants) participated in 1000 Genomes project and determine predictive risk phenotypes consecutively. Predictive risk phenotypes were then linked up to a number of clinically important medications for which the safety or effectiveness may be affected.

Methods

Study participants

This study utilized all genetic data pertaining *CYP2C19*2, *3* and **17* obtained from five continental groups, the Americas (AMR), Europe (EUR), Africa (AFR), South Asia (SAS) and East Asia (EAS) [17, 18]. In the continent of America four ethnic groups (CLM = Colombian in Medellin, Colombia; MXL = Mexican Ancestry in Los Angeles, California; PEL = Peruvian in Lima, Peru; PUR = Puerto Rican in Puerto Rico) consisting of 347 healthy volunteers were participated in the 1000 Genomes project. Similarly, in the Europe five ethnic groups (CEU = Utah residents with Northern and Western European ancestry; FIN = Finnish in Finland; GBR = British in England and Scotland; IBS = Iberian populations in Spain; TSI = Toscani in Italy) consisting of 503 healthy volunteers were participated in the 1000 Genomes project. In the Africa seven ethnic groups (ACB = African Caribbean in Barbados; ASW = African Ancestry in Southwest US; ESN = Esan in Nigeria; GWD = Gambian in Western Division, The Gambia; LWK = Luhya in Webuye, Kenya; MSL = Mende in Sierra Leone; YRI = Yoruba in Ibadan, Nigeria) consisting of 661 healthy volunteers were participated in the 1000 Genomes project. In the South Asia five ethnic groups (BEB, Bengali in Bangladesh; GIH = Gujarati Indian in Houston, TX; ITU = Indian Telugu in the UK; PJL = Punjabi in Lahore, Pakistan; STU = Sri Lankan Tamil in the UK) consisting of 489 healthy volunteers were participated in the 1000 Genomes project. In the East Asia five ethnic groups (CDX = Chinese Dai in Xishuangbanna, China; CHB = Han Chinese in Bejing; CHS = China, Southern Han Chinese, China; JPT = Japanese in Tokyo, Japan; KHV = Kinh in Ho Chi Minh City, Vietnam) consisting of 504 healthy volunteers were participated in the 1000 Genomes project.

Genetic data

The allele and genotype frequency of 26 populations consisting of 2504 participants from five continental groups of the world that contained *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560) variants were obtained from 1000 Genomes project Phase III in line with Fort Lauderdale principles. Based on carrying *CYP2C19**2, *3 or *17 alleles, *CYP2C19* genotypes were assigned accordingly. For example, if any participant carrying two copies of *CYP2C19**2 alleles, then genotypes were assigned as *CYP2C19**2/*2. Similarly, other genotypes were assigned based on carrying characteristics alleles.

Determination of predicted phenotypes

Phenotypes were assigned using international standardized consensus terms based on the carrier of characteristics alleles [19]. Individual carrying two copies of normal function alleles (e.g., *CYP2C19*1/*1*) were considered to represent possible CYP2C19 extensive metabolizers (EM). Individuals carrying two copies of no or decreased function alleles (e.g., any combination of *2 and *3 allele i.e., *CYP2C19*2/*2*, *CYP2C19*2/*3*, *CYP2C19*3/*3*) were considered to represent possible CYP2C19 poor metabolizers (PM). Similarly, the individuals carrying one copy of normal function allele and one copy of either decreased or no function or increased function allele or carrying one copy of no/decreased function allele and one copy of increased function allele (e.g., *CYP2C19*1/*2*, *CYP2C19*1/*3*, *CYP2C19*2/*17*,

*CYP2C19*3/*17*) were considered to represent possible CYP2C19 intermediate metabolizers (IM). Finally, the individuals carrying one or two copies of increased function alleles (e.g., *CYP2C19*1/*17*, *CYP2C19*17/*17*) were considered to represent possible CYP2C19 ultrarapid metabolizers (UM).

Determination of medium-risk and high-risk phenotypes

Van Driest et al. specifically defined 'high-risk' genotypes for those carrying two copies of no function alleles in *CYP2C19* gene (i.e., *CYP2C19*2/*2*) as these variants are known to greatly increase the risk of severe adverse cardiovascular outcomes [20]. Similarly, Van Driest et al. suggested 'actionable' genotypes for those carrying one normal function and one no function allele in *CYP2C19* gene (i.e., *CYP2C19*1/*2*) as these variants warrant change in dose or medication. As the incidence of secondary adverse outcomes due to therapeutic failure or the risk for increased adverse effects has usually not been quantified for any given drug, this study has proposed the level of risk for any genotypes either 'high-risk' or 'medium-risk' or 'no-risk' in a comparative fashion and determine the risk phenotypes respectively.

For example, participants representing poor or UM were considered high-risk phenotypes. Similarly, IM correspond to medium-risk phenotypes and EM correspond to no-risk phenotypes.

Linking *CYP2C19* risk phenotypes with the safety and effectiveness of medications

The evidence of *CYP2C19* clinical annotations of different clinically important medications and PGx label information affected by *CYP2C19*2, *3* and **17* was obtained from internationally well recognized pharmacogenomics working group such as the PharmGKB, US Food and Drug Administration (FDA) approved drug label, European Medicines Agency (EMA) approved drug label, Health Canada Santé Canada (HCSC) approved drug label. All these information was taken from PharmGKB website [21, 22]. The correlation of predicted risk phenotypes with the safety or effectiveness of medications were established using the freely available CPIC PGx-based dosing guidelines information of different medications [6–9].

Human ethics approval

All the genetic data of human presented in this study were obtained from 1000 Genomes project Phase III in line with Fort Lauderdale principles. By this principle, no further human ethics approval is required to publish any results using 1000 Genomes project data as it has already published elsewhere [17, 18].

Statistical analysis

Data were analyzed as descriptive statistics. Meta-analysis for proportion was carried out using MedCalc statistical software. P value < 0.05 was considered statistically significant.

Validation of data analysis

All the genetic data presented in this paper were taken from 1000 Genomes project as a raw data. Data were then analyzed by the author using Macros formula. All the analysis was also carried out independently by two other researchers. Finally, the author double checks the analyzed data provided by these two researchers and amended it if found any anomalies.

Results

Prevalence of *CYP2C19*2, *3* and **17* allele and associated genotypes in 26 population

The *CYP2C19*2* allele was found highest in South Asian population (35.8%; 95% CI 33–39%) followed by East Asian (31.3%; 95% CI 29–34%), African (17%; 95% CI 15–19%), European (14.5%; 95% CI 12–17%) and Americans (10.5%; 95% CI 8–13%), respectively. However, *CYP2C19*17* was found highest in Africa (23.5%; 95% CI 21–26%) and lowest in East Asia (1.5%; 95% CI 1–2%). In contrast, *CYP2C19*3* was not found in American And European population but was found highest in Africa (22.7%; 95% CI 47–66%). The allele frequency of *CYP2C19*2, *3* and **17* of the 26 populations comprising 2504 participants are shown in Fig. 1.

The pooled prevalence was 21.1% (95% CI 13–31%) for *CYP2C19*2*; 0.8% (95% CI 0.6–1%) for *CYP2C19*3* and 13.2% (95% CI 5–24%) for *CYP2C19*17* as identified from meta-analysis using random effect model and the prevalence was statistically significant in different ethnic groups (p<0.0001) as shown in Fig. 2.

The predictive genotypes obtained from different combinations of *CYP2C19*2, *3* or **17* variants alleles are shown in Table 1. Participants carrying two copies of normal function alleles (e.g., *CYP2C19*1/*1*) were highly prevalent (37.9%; 95% CI 36–40%) in 26 populations. However, 26.3% (95% CI 25–28%) of the participants were carrying one copy of no function *CYP2C19*2* allele and one copy of functional allele comprising *CYP2C19*1/*2* genotype was prevalent second highest.

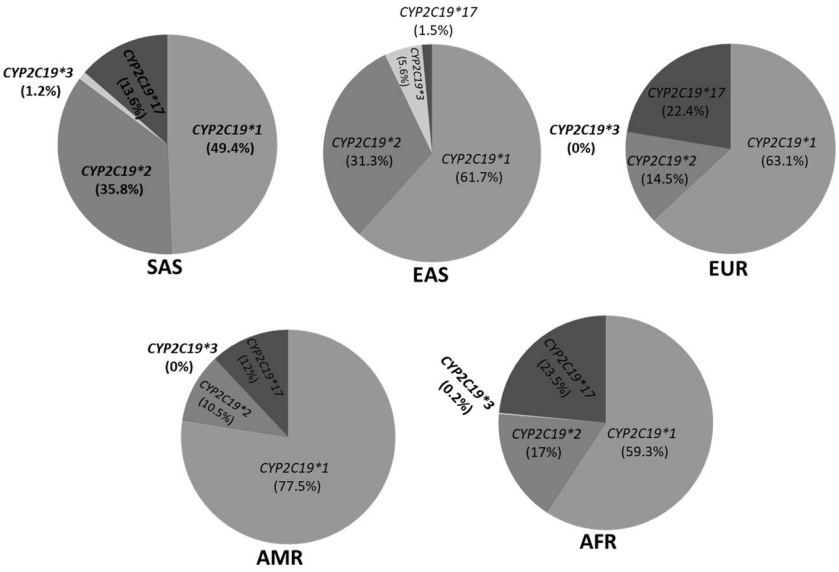

Fig. 1 Frequency of *CYP2C19*1, CYP2C19*2, CYP2C19*3* and *CYP2C19*17* alleles in 26 world population comprising 2504 participants participated in the 1000 Genomes Project. Here SAS: South Asia, EAS: East Asia, EUR: Europe, AMR: America, AFR: Africa.

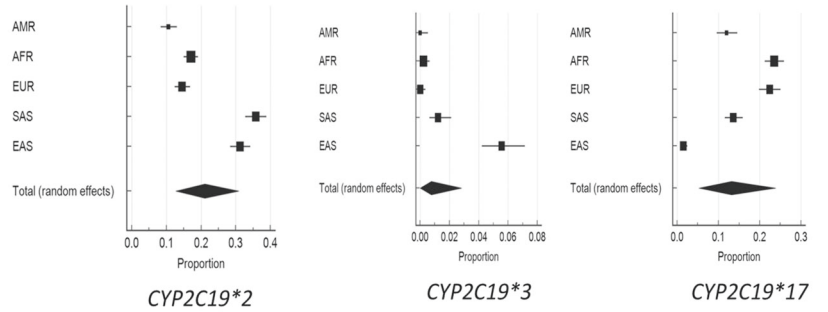

Fig. 2 Prevalence of *CYP2C19* genetic polymorphisms. Meta-analysis of the prevalence of *CYP2C19 *2, *3* and **17* variants in different ethnic groups of the 26 populations participated in the 1000 Genomes project.

Q	262.7841 for *2; 135.7298 for *3; 402.1142 for *17
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	98.48% for *2; 97.05% for *3; 99.01% for *17
95% CI for I^2	97.72 to 98.98 for *2; 95.14 to 98.21 for *3; 98.59 to 99.30 for *17

Table 1 Predicted prevalence of different genotypes associated with *CYP2C19*2, *3* or **17* variants for 26 populations participated in 1000 Genomes project.

Population	Genotypes									
	**1/*1*	**1/*2*	**1/*3*	**1/*17*	**2/*2*	**3/*3*	**2/*3*	**2/*17*	**3/*17*	**17/*17*
SAS	24.5	33.9	0.6	15.5	15.5	0.0	0.8	6.5	0.2	2.5
EAS	36.7	42.5	6.2	1.4	7.5	0.2	4.0	1.0	0.6	0.0
EUR	38.2	20.3	0.0	29.6	1.2	0.0	0.0	6.4	0.0	4.4
AMR	63.1	16.7	0.0	17.6	0.9	0.0	0.0	0.0	0.0	1.7
AFR	35.2	18.8	0.3	28.3	3.5	0.3	0.0	8.3	0.2	5.1
All population	**37.9**	**26.3**	**1.4**	**19.4**	**5.7**	**0.1**	**1.0**	**5.2**	**0.2**	**2.8**

Bold entries show the average prevalence in all population.

Prevalence of predicted phenotypes in 26 population

As described in method section, the prevalence of different phenotypes in different ethnic groups of 26 populations is shown in Fig. 3. The PM were prevalent highest in South Asia (16.4%; 95% CI 13–20%) followed by East Asia (11.7%; 95% CI 9–15%). The IM were prevalent highest in East Asia (49.6%; 95% CI 45–54%) followed by South Asia (41.1%; 95% CI 37–45%). In contrast, UM were prevalent highest in Africa (33.7%; 95% CI 30–37%) and lowest in East Asia (1.4%; 95% CI 0–2%). The prevalence

of predicted phenotypes in different ethnic groups was statistically significant (Chi-square test, $p<0.00001$).

Prevalence of risk phenotypes in 26 population

Following CPIC pharmacogenomics-based dosing guidelines, UM (*CYP2C19*1/*17*; *CYP2C19*17/*17*), IM (*CYP2C19*1/*2; CYP2C19*1/*3*; *CYP2C19*2/*17*; *CYP2C19*3/*17*) and PM (*CYP2C19*2/*2*; *CYP2C19*3/*3*, *CYP2C19*2/*3*) were considered risk phenotypes. Overall, 62.2% (95% CI 60–64%) of the total 2504 participants participated in the 1000 genomes project were identified as being at risk phenotypes that may need either dose adjustments or alternative drugs of standard therapy. Among these, UM and PM were considered as high-risk phenotypes and IM was considered as medium-risk phenotype as identified from the CPIC dosing guidelines. This is because out of the ten drugs having CPIC pharmacogenomics-based dosing guidelines, nine of these are recommended either increased dose, dose reduction or alternative drug of the current standard therapy for the UM and PM phenotypes. From the meta-analysis using random effect model, it was found that the prevalence of pooled high risk (27.4%; 95% CI 18–37%) and medium-risk (32.4% 95% CI 32–43%) phenotypes in different continents was statistically significant ($p<0.0001$) as shown in Fig. 4. The high-risk phenotypes were highly prevalent in Africa (37.2%; 95% CI 34–41%) followed by Europe (35.4%; 95% CI 31–40%) because of considering both ultrarapid and PM as high-risk phenotypes where UM were highly prevalent in Africa and Europe than Asian participants. In contrast, medium-risk phenotypes were highly prevalent in East Asia (51.2%; 95% CI 47–56%).

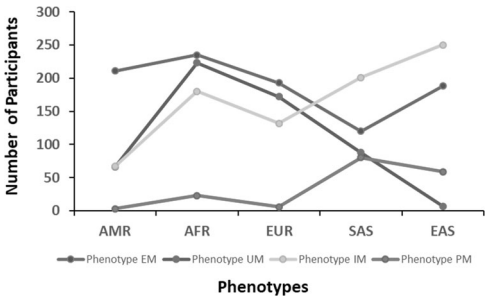

Fig. 3 Predicted prevalence of different phenotypes of different population participated in 1000 Genomes project. The phenotypes were assigned based on the carrier of *CYP2C19**1, *2, *3 or *17 alleles following international guidelines. Here SAS: South Asians, EAS: East Asians, EUR: Europeans, AMR: Ad.Mix Americans, AFR: Africans. EM-Extensive/normal metabolizers, UM-Ultra-rapid metabolizers, IM-Intermediate metabolizers, PM-Poor metabolizers.

Linking *CYP2C19* risk phenotypes with the safety and effectiveness of drugs

For at least 44 clinically important medications identified from PharmGKB clinical annotations having different level of evidence (Level 4; preliminary to Level 1A; strong), as shown in Fig. 5 are affected by the *CYP2C19*2, *3* or **17* genetic variabilities [23]. Altogether six drugs (i.e., clopidogrel, sertraline, citalopram, escitalopram, amitriptyline, and voriconazole) have strong evidence (Level 1A) replicated in numerous clinical studies affecting safety or effectiveness of these medications associated with *CYP2C19*2, *3* or **17* genetic variabilities.

For at least 25 drugs had PGx label information in line with *CYP2C19*2*, **3* or **17* variants identified from FDA, EMA, and HCSC as shown in Fig. 6. The majority of the drug PGx information was obtained from the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" although four drugs (clopidogrel, esomeprazole, voriconazole, brivaracetam) had PGx information that were identified from all resources. Seventeen drugs had PGx actionable information interfered by *CYP2C19*2, *3* or **17* genetic variabilities. Clinically actionable PGx means 'the label may

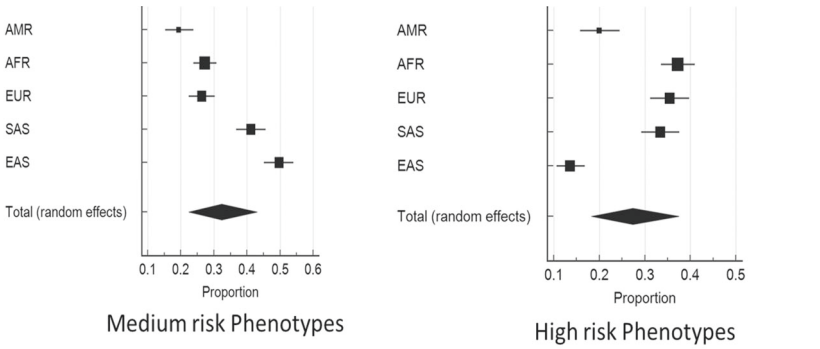

Fig. 4 Prevalence of risk phenotypes. Meta-analysis of the prevalence of risk phenotypes in different ethnic groups of the 26 populations participated in the 1000 Genomes project.

Q	132.2962 for Medium risk Phenotypes and 121.3097 for High risk Phenotypes
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	96.98% for Medium risk Phenotypes and 96.70% for High risk Phenotypes
95% CI for I^2	95.00 to 98.17 for Medium risk Phenotypes and 94.47 to 98.03for High risk Phenotypes

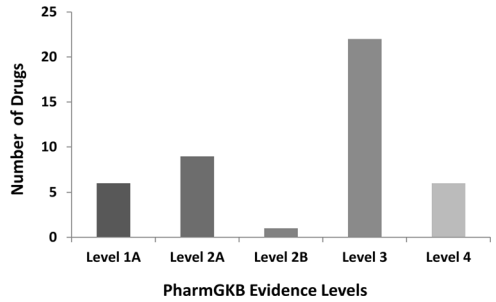

Fig. 5 PharmGKB evidence levels of drugs affected by *CYP2C192, *3 or *17 genetic variability.** Level 1A = Strong, Level 2A/2B = moderate, Level 3 = Weak, Level 4 = Preliminary.

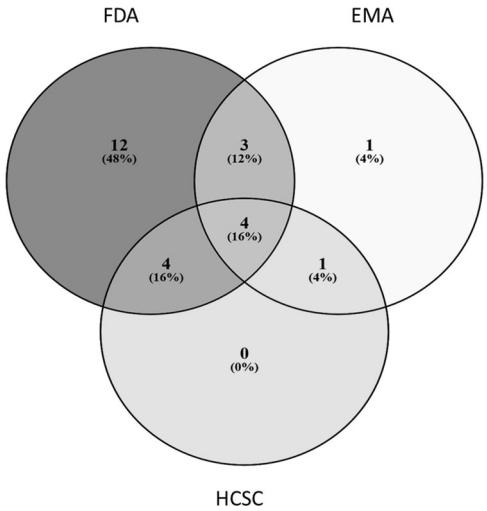

Fig. 6 Drug labels information. Number of drugs affected by *CYP2C19*2, *3* or **17* variants having different pharmacogenomics drug labels information provided by FDA, EMA, and HCSC.

contain information about changes in efficacy, dosage, metabolism or toxicity due to gene variants or phenotypes, or the label may mention contraindication of the drug in a particular subset of patients with particular gene variants/genotypes/phenotypes. However, the label does not require gene testing' [24]. Seven drugs have informative PGx information influenced by *CYP2C19*2, *3* or **17* genetic variabilities. Informative PGx means 'the label contains information stating that particular gene variants or metabolizer phenotypes do not affect a drug's efficacy, dosage, metabolism or toxicity. Or, the label states that particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, but this effect is not "clinically" significant' [24].

To date, ten drugs have prescribing recommendations based on *CYP2C19*2, *3* or **17* genetic variabilities provided by the CPIC, as shown in Table 2. For the achievement of PM, it is clearly evident from this table that PM and UM phenotypes require more clinical attention in order to ensure optimal safety and effectiveness of these medications. For example, tricyclic antidepressants e.g., amitriptyline and selective serotonin reuptake inhibitors e.g., citalopram/escitalopram should not be prescribed for patients who are considered to be ultrarapid or PM because of possibilities for developing either sub-therapeutic or toxicities of these drugs. Similarly, clopidogrel should not be prescribed for those patients who are considered to be either intermediate or PM because of exacerbating major adverse cardiovascular events, instead, prasugrel/ticagrelor may improve clinical outcomes in these patients since these drugs are not affected by *CYP2C19* genetic variants.

In summary, about a third of the world population constituting 2504 participants were identified as being as high-risk phenotypes that may affect safety or effectiveness for at least ten clinically important medications.

Discussion

The findings of the present study suggest that although certain percentage of all parts of global population participated in the 1000 Genomes project may be at risk of either sub therapeutic responses or toxicities for at least ten clinically important drugs due to the *CYP2C19* genetic variability, however African and European population are being at particularly higher risk.

The prevalence of *CYP2C19*2, *3* and **17* alleles in the 26 population of different ethnic groups is consistent with the published results. Also the prevalence of different combinations of genotypes carrying the characteristics alleles and associated phenotypes in different ethnic groups are also in consistent with the published results [6, 14]. However when the phenotypes were predictively classified as 'no-risk', 'medium-risk' and 'high-risk' based on CPIC dosing guidelines, the study found that high-risk phenotypes were highly prevalent in Africa (~37%) followed by Europe (~35%) which pave the new research dimension as the people of these regions are at particularly higher risk for developing either sub-therapeutic drug responses or increased toxicities for the drugs metabolized by CYP2C19.

Although many international PGx-working groups are facilitating translation of PGx into clinical practice in terms of providing different PGx evidence, however PharmGKB is pioneering in providing evidence for PGx interactions. As for example, PharmGKB provided different level of evidence for at least 44 drugs involving only *CYP2C19* genetic polymorphisms, based on the approved PGx information provided by different international bodies. These PGx information is categorized as 'PGx testing recommended, clinically actionable PGx and informative PGx. From the Venn diagram it is evident that FDA is pioneering in providing PGx information compared to other international bodies. Almost 90% of the PGx information of the

Table 2 List of drugs having *CYP2C19*2, *3 and *17* pharmacogenomics based prescribing recommendations provided by CPIC.

Drug	*CYP2C19* Phenotypes	CPIC therapeutic recommendations	Severity of phenotypes
Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	UM	Avoid use of these drugs due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19.	High-risk
	EM/IM	Initiate therapy with recommended starting dose	No-risk
	PM	Consider alternative drug not metabolized by CYP2C19. For using these drugs, consider a 50% reduction of the recommended starting dose.	High-risk
Citalopram Escitalopram	UM	Consider an alternative drug not predominantly metabolized by CYP2C19.	High-risk
	EM/IM	Initiate therapy with recommended starting dose	
	PM	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.	High-risk
Sertraline	UM	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19	High-risk
	EM/IM	Initiate therapy with recommended starting dose	No-risk
	PM	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19	High-risk
Voriconazole	UM	Choose an alternative agent e.g., isavuconazole, liposomal amphotericin B, posaconazole	High-risk
	EM/IM	Initiate therapy with recommended standard of care dosing	
	PM	Choose an alternative agent e.g., isavuconazole, liposomal amphotericin B, posaconazole.	High-risk
Clopidogrel	UM/EM	Label-recommended dosage and administration	No-risk
	IM[a]	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Medium-risk
	PM	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	High-risk

[a]Although CPIC guidelines recommend alternative antiplatelet for IM taking clopidogrel but it is evident from various meta-analysis that PM has more increased risk to major adverse cardiovascular events than IM. Therefore, this study has assigned IM as medium-risk phenotype in a comparative fashion to PM (high-risk phenotypes).

CYP2C19 was provided only by the FDA although it had different two-way and three-way combinations with other international pharmacogenomics bodies.

To date, CPIC has provided PGx-based dosing recommendations for at least 40 drugs having different genetic interference but ten of these are affected by only *CYP2C19* genetic variability mainly due to the presence of *CYP2C19*2, *3* and **17* genetic polymorphisms. This study was uniquely designed to identify the phenotypes based on the CPIC dosing recommendations following CPIC consensus standardization for determining phenotypes based on the carrier of these polymorphisms. To the authors' very best knowledge, no study found in the literature that combines all of these three variants of *CYP2C19* genetic polymorphisms to determine the ultimate phenotypes in a global scale and further categorize the phenotypes based on their risk for safety or effectiveness of medications. This is the novelty of this study and found that about a third (~28%) of the 26 populations comprising 2504 participants were as being at risk of very severe adverse clinical outcomes.

For example, acute coronary syndrome patients undergoing PCI carrying two copies of *CYP2C19*2* variants (*CYP2C19*2/*2*; PM) and treated with clopidogrel has increased risk of severe adverse cardiovascular events such as death, recurrent myocardial infarction, stroke, stent thrombosis as evidenced from multiple meta-analysis [11, 25–27]. For these patients as recommended by the CPIC pharmacogenomics based dosing guidelines, alternative antiplatelets such as prasugrel or ticagrelor may be an effective therapeutic target for improving clinical outcomes since these drugs are not affected by *CYP2C19* genetic variants. A recent meta-analysis found that the risk of major adverse cardiovascular events were significantly reduced in acute coronary syndrome patients undergoing PCI treated with prasugrel/ticagrelor compared with clopidogrel, both carrying *CYP2C19* LoF alleles (RR 0.58; 95% CI 0.45–0.76; $p<0.0001$) [28].

It is important to noted that besides *CYP2C19* genetic variability, many studies found associations between other genetic variants e.g., *ABCB1*, *P2Y12*, or *CES1* with clinical outcomes of clopidogrel. These genetic effects should also need to be taken into clinical considerations for optimizing efficacy or safety of clopidogrel [29–31]. However, generation of a pharmacogenomic polygenic response score (PgxRS) may be a good predictor of cardiovascular events when it is expecting that various co-existing genetic polymorphisms may affect efficacy or safety of clopidogrel or any other drugs. For instance, a recent study found that patients who carried a greater number of *CYP* mutant alleles were associated with increased cardiovascular events compared with patients who carried fewer *CYP* variants of these alleles. This is reflecting that polygenic pharmacogenomics response modeling for various genetic variants of medications may advance future PM initiatives [32].

Although different international pharmacogenomics working groups are facilitating translation of PGx into clinical practice in terms of providing prescription recommendations based on the pharmacogenomics information available. However, translation of PGx into clinical practice is still in infancy because of the lack of sufficient PGx evidence and appropriate correlation of PGx with the phenotypes. Hence, the findings of this study will fill the scientific gap in this area and will driving the policy makers of genomics and stakeholders to deeply consider why it is more essential to bring PGx into routine clinical practice especially for those drugs having high level of evidence for genetic interference. If it is appropriately adopted and implemented, millions of human beings will get rid of severe drug toxicities and severe adverse secondary outcomes due to drug ineffectiveness.

Limitations

This a predictive study therefore the prediction for the prevalence of risk phenotypes may vary accordingly as the current study didn't measure the CYP2C19 enzyme function particularly when different combinations of *CYP2C19* variants were considered for selecting the risk phenotypes. This study was unable to assess genetic data that cover the population from all parts of the world especially missing data from Oceania continents and MENA (Middle East and North Africa) region as 1000 Genomes project didn't include the population from this region.

Conclusions

Approximately one-third of the world population of five continents comprising 2504 participants were identified as being as high-risk phenotypes that may affect safety or effectiveness for at least ten very clinically important medications. For the achievement of PM of these medications, large scale randomized longitudinal studies collecting medication and genetic data from different ethnicities are warranted that could be able to assess clinical outcomes of these medications considering *CYP2C19* pharmacogenomics effects in the real-world treatment settings.

Future directions

As the association of risk phenotypes due to *CYP2C19* genetic polymorphisms with the safety or effectiveness of at least ten drugs has firmly established in this study, henceforth, large scale longitudinal *CYP2C19* genotype guided

therapy is warranted to observe the clinical outcomes of these medications.

Data availability

The datasets generated during and/or analysed during this current study are available in the 1000 Genomes data repository (https://www.internationalgenome.org/).

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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References

1. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–5.
2. Ashley EA. Towards precision medicine. Nat Rev Genet. 2016;17:507–22.
3. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS ONE. 2013;8. https://doi.org/10.1371/journal.pone.0082562.
4. Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. Genom Proteom Bioinforma. 2016;14:298–313.
5. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138:103–41.
6. Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94:317–23.
7. Hicks JK, Bishop JR, Sangkuhl K, Muller DJ, Ji Y, Leckband SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98:127–34.
8. Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102:37–44.
9. Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther. 2017;102:45–51.
10. Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol. 2012;60:9–20.
11. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA - J Am Med Assoc. 2010;304:1821–30.
12. Xi Z, Fang F, Wang J, AlHelal J, Zhou Y, Liu W. CYP2C19 genotype and adverse cardiovascular outcomes after stent implantation in clopidogrel-treated Asian populations: a systematic review and meta-analysis. Platelets. 2019;30:229–40.
13. Huang B, Cui DJ, Ren Y, Han B, Yang DP, Zhao X. Effect of cytochrome P450 2C19*17 allelic variant on cardiovascular and cerebrovascular outcomes in clopidogrel-treated patients: a systematic review and meta-analysis. J Res Med Sci. 2017;22. https://doi.org/10.4103/jrms.JRMS_590_16.
14. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide Distribution of Cytochrome P450 Alleles: a meta-analysis of population-scale sequencing projects. Clin Pharmacol Ther. 2017;102:688–700.
15. Mirzaev KB, Zelenskaya EM, Barbarash OL, Ganyukov VI, Apartsin KA, Saraeva NO, et al. CYP2C19 polymorphism frequency in Russian patients in central Russia and Siberia with acute coronary syndrome. Pharmgenom Pers Med. 2017;10:107–14.
16. Hashemizadeh Z, Malek-Hosseini SA, Badiee P. Prevalence of CYP2C19 genetic polymorphism among normal people and patients with hepatic diseases. Int J Organ Transplant Med. 2018;9:27–33.
17. Sudmant PH, Rausch T, Gardner EJ, Handsaker RE, Abyzov A, Huddleston J, et al. An integrated map of structural variation in 2,504 human genomes. Nature. 2015;526:75–81.
18. Auton A, Abecasis GR, Altshuler DM, Durbin RM, Bentley DR, Chakravarti A, et al. A global reference for human genetic variation. Nature. 2015;526:68–74.
19. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19:215–23.
20. Van Driest SL, Shi Y, Bowton E, Schildcrout J, Peterson J, Pulley J, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther. 2014;95:423–31.
21. Relling MV, Klein TE. CPIC: Clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin Pharmacol Ther. 2011;89:464–7.
22. Barbarino JM, Whirl-Carrillo M, Altman RB, Klein TE. PharmGKB: A worldwide resource for pharmacogenomic information. Wiley Interdiscip Rev Syst Biol Med. 2018;10:e1417.
23. PharmGKB. CYP2C19 clinical annotations. 2020. https://www.pharmgkb.org/gene/PA124/clinicalAnnotation (accessed 28 Feb 2020).
24. PharmGKB. Drug Label Information and Legend. 2020. https://www.pharmgkb.org/ (accessed 15 Jun 2019).
25. Zheng L, Yang C, Xiang L, Hao Z. Genotype-guided antiplatelet therapy compared with conventional therapy for patients with acute coronary syndromes: a systematic review and meta-analysis. Biomarkers. 2019;24:517–23.
26. Sorich MJ, Rowland A, McKinnon RA, Wiese MD. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. Circ Cardiovasc Genet. 2014;7:895–902.
27. Liu J, Qin L, Xi S, Tong W, Yuan M, Peng L, et al. Genotype-guided personalization of antiplatelet treatment: a meta-analysis of patients with ACS or undergoing PCI. Thromb Res. 2019;179:87–94.
28. Biswas M, Kali MSK, Biswas TK, Ibrahim B. Risk of major adverse cardiovascular events of CYP2C19 loss-of-function genotype guided prasugrel/ticagrelor vs clopidogrel therapy for acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. Platelets. 2020. https://doi.org/10.1080/09537104.2020.1792871.
29. Tang XF, Zhang JH, Wang J, Han YL, Xu B, Qiao S, Bin, et al. Effects of coexisting polymorphisms of CYP2C19 and P2Y12 on clopidogrel responsiveness and clinical outcome in patients with

acute coronary syndromes undergoing stent-based coronary intervention. Chin Med J (Engl). 2013;126:1069–75.
30. Winter MP, Grove EL, De Caterina R, Gorog DA, Ahrens I, Geisler T, et al. Advocating cardiovascular precision medicine with P2Y12 receptor inhibitors. Eur Hear J - Cardiovasc Pharmacother. 2017;3:221–34.
31. Xiao FY, Luo JQ, Liu M, Chen BL, Cao S, Liu ZQ et al. Effect of carboxylesterase 1 S75N on clopidogrel therapy among acute coronary syndrome patients. Sci Rep. 2017;7. https://doi.org/10.1038/s41598-017-07736-1.
32. Lewis JP, Backman JD, Reny J-L, Bergmeijer TO, Mitchell BD, Ritchie MD et al. Pharmacogenomic Polygenic Response Score Predicts Ischemic Events and Cardiovascular Mortality in Clopidogrel-Treated Patients. Eur Hear J - Cardiovasc Pharmacother. 2019. https://doi.org/10.1093/ehjcvp/pvz045.