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PHARMACOGENOMIC ANALYSIS OF CYP2C19 VARIANTS AND THEIR PREDICTED METABOLIZER PHENOTYPES ACROSS SOUTH ASIAN, EUROPEAN AND EAST ASIAN POPULATIONS – AN *IN-SILICO* DESCRIPTIVE STUDY

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ABSTRACT: Objectives: CYP2C19 is an important enzyme involved in the metabolism of drugs such as proton pump inhibitors, antiplatelets, and antiepileptics. Genetic variations in CYP2C19 can alter drug response and safety. This study aimed to analyze the distribution of three key CYP2C19 variants (*2, *3, *17) and predict metabolizer phenotypes across South Asian, European, and East Asian populations using *in-silico* methods. **Methodology:** Allele frequencies were obtained from gnomAD and the 1000 Genomes Project. Genotype frequencies were estimated using Hardy–Weinberg equilibrium, and metabolizer phenotypes poor, intermediate, normal, rapid, and ultrarapid were assigned. Data processing and visualization were performed using R (version 4.5.1). **Results:** The *2 loss-of-function allele was most frequent in South Asians (31.8%), followed by East Asians (28.0%) and Europeans (15.0%), leading to a higher proportion of poor metabolizers in South Asians. The *3 allele was rare but slightly higher in South Asians (5.7%). The *17 gain-of-function allele was most common in Europeans (22.0%), moderate in South Asians (14.0%), and rare in East Asians (2.0%). Normal metabolizers predominated in Europeans and East Asians, whereas South Asians had more intermediate and poor metabolizers. **Conclusion:** CYP2C19 variants show significant interethnic differences. South Asians carry more loss-of-function alleles, while Europeans have more gain-of-function variants. Population-specific pharmacogenomic insights can guide personalized drug therapy and minimize adverse effects.

INTRODUCTION: Cytochrome P450 2C19 (CYP2C19) is an important enzyme in the metabolism of numerous clinically significant drugs, including proton pump inhibitors (PPIs), antiepileptics, and antiplatelet agents. Variations in the CYP2C19 gene lead to distinct metabolizer phenotypes poor metabolizers (PMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs) which significantly influence drug efficacy and safety profiles [1].

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Genetic polymorphisms such as CYP2C19*2* and *CYP2C19*17 are well-documented, with the *2 allele being a common cause of PM status and the *17 allele associated with UM status. These polymorphisms exhibit considerable interethnic variability, affecting the distribution of metabolizer phenotypes across different populations [2].

In South Asian populations, the *2 allele frequency is notably high, leading to a higher prevalence of PMs. Conversely, East Asian populations, particularly those of Chinese descent, demonstrate a higher frequency of the *17 allele, correlating with an increased proportion of UMs. European populations exhibit a more balanced distribution of these alleles, resulting in a diverse range of metabolizer phenotypes [1]. Understanding these genetic variations is crucial for optimizing drug

dosing regimens and minimizing adverse drug reactions. In this study, we employed *in-silico* tools to analyze the distribution of CYP2C19 variants and predict the corresponding metabolizer phenotypes across South Asian, European, and East Asian populations. The findings aim to enhance the precision of pharmacogenomic applications and contribute to the advancement of personalized medicine strategies.

METHODOLOGY:

Study Design: This was a computational *in-silico* descriptive study conducted in 2025 at the Department of Pharmacology. The objective was to assess CYP2C19 allele frequencies and predict metabolizer phenotypes across South Asian, European, and East Asian populations. As the study relied solely on secondary data from public databases, no human participants were involved and no clinical interventions were performed. Hence, Institutional Ethics Committee (IEC) approval was not required.

Study Population: Population genomic data were retrieved from publicly available databases, including the Genome Aggregation Database (gnomAD) and the 1000 Genomes Project. The populations analyzed were South Asians (SAS, including Indians), Europeans (EUR), and East Asians (EAS).

Inclusion Criteria: All genomic datasets reporting CYP2C19 allele frequencies for rs4244285 (*2), rs4986893 (*3), and rs12248560 (*17) were included in the analysis.

Allele and Phenotype Analysis: Allele frequencies for CYP2C19 variants were extracted for each population. Predicted genotype frequencies were calculated using the Hardy–Weinberg equilibrium (HWE) principle, which assumes random mating, no selection, no mutation, and no migration. Expected genotype frequencies were as follows: Homozygous reference (*1/*1) = p^2, Heterozygous (*1/*2, *1/*3) = 2pq, Homozygous variant (*2/*2, *3/*3) = q^2. These frequencies were then extrapolated to a hypothetical population size to obtain genotype counts. Predicted metabolizer phenotypes were classified as: Poor metabolizers (PM): *2/*2, *2/*3, *3/*3, Intermediate metabolizers (IM): *1/*2, *1/*3, Extensive metabolizers (EM): *1/*1 (excluding *17), Rapid/Ultrarapid metabolizers (RM/UM): *1/*17, *17/*17

Data Analysis: All data extraction, calculations, and visualization were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with the tidyverse and ggplot2 packages. Statistical comparisons of allele and phenotype distributions across populations were carried out using built-in R functions.

RESULTS: **Table 1** summarizes the allele frequencies of the CYP2C19 variants (*2: rs4244285, *3: rs4986893, and *17: rs12248560) in South Asian (SAS), European (EUR), and East Asian (EAS) populations. The *2 allele (rs4244285), associated with loss-of-function, was most prevalent in South Asians (31.8%), followed by East Asians (28.0%) and Europeans (15.0%). The *3 allele (rs4986893), another loss-of-function variant, showed the highest frequency in South Asians (5.7%), with lower prevalence in Europeans (2.9%) and East Asians (1.6%).

In contrast, the *17 allele (rs12248560), a gain-of-function variant, was relatively rare in South Asians (14.0%) and East Asians (2.0%), but more frequent in Europeans (22.0%). Overall, South Asians exhibited a higher burden of loss-of-function alleles, Europeans had a greater prevalence of the gain-of-function *17 allele, and East Asians had comparatively lower frequencies of both loss- and gain-of-function variants.

TABLE 1: OBSERVED ALLELE FREQUENCIES

rsid	Population	Reference Allele (Normal)	Alternate Allele (Variant)	Frequency of Reference Allele	Frequency of Reference Allele
rs4244285	SAS	G	A	68.2%	31.8%
rs4244285	EUR	G	A	85.0%	15.0%
rs4244285	EAS	G	A	72.0%	28.0%
rs4986893	SAS	C	T	94.3%	5.7%
rs4986893	EUR	C	T	97.1%	2.9%
rs4986893	EAS	C	T	98.4%	1.6%

rs12248560	SAS	G	A	86.0%	14.0%
rs12248560	EUR	G	A	78.0%	22.0%
rs12248560	EAS	G	A	98.0%	2.0%

TABLE 2: SUMMARY OF SIMULATED STAR ALLELES

rs id	Population	Star Genotype	Count	Frequency	Phenotype
rs4244285	SAS	*1/*1	464	46.4%	Normal Metabolizer
rs4244285	SAS	*1/*2	433	43.3%	Intermediate Metabolizer
rs4244285	SAS	*2/*2	101	10.1%	Poor Metabolizer
rs4244285	EUR	*1/*1	722	72.2%	Normal Metabolizer
rs4244285	EUR	*1/*2	255	25.5%	Intermediate Metabolizer
rs4244285	EUR	*2/*2	23	2.3%	Poor Metabolizer
rs4244285	EAS	*1/*1	518	51.8%	Normal Metabolizer
rs4244285	EAS	*1/*2	403	40.3%	Intermediate Metabolizer
rs4244285	EAS	*2/*2	79	7.9%	Poor Metabolizer
rs4986893	SAS	*1/*1	943	94.3%	Normal Metabolizer
rs4986893	SAS	*1/*3	54	5.7%	Intermediate Metabolizer
rs4986893	SAS	*3/*3	3	0.3%	Poor Metabolizer
rs4986893	EUR	*1/*1	971	97.1%	Normal Metabolizer
rs4986893	EUR	*1/*3	28	2.9%	Intermediate Metabolizer
rs4986893	EUR	*3/*3	1	0.1%	Poor Metabolizer
rs4986893	EAS	*1/*1	984	98.4%	Normal Metabolizer
rs4986893	EAS	*1/*3	16	1.6%	Intermediate Metabolizer
rs4986893	EAS	*3/*3	0	0.0%	Poor Metabolizer
rs12248560	SAS	*1/*1	860	86.0%	Normal Metabolizer
rs12248560	SAS	*1/*17	140	14.0%	Rapid Metabolizer
rs12248560	SAS	*17/*17	0	0.0%	Ultrarapid Metabolizer
rs12248560	EUR	*1/*1	780	78.0%	Normal Metabolizer
rs12248560	EUR	*1/*17	220	22.0%	Rapid Metabolizer
rs12248560	EUR	*17/*17	0	0.0%	Normal Metabolizer
rs12248560	EAS	*1/*1	980	98.0%	Normal Metabolizer
rs12248560	EAS	*1/*17	20	2.0%	Rapid Metabolizer
rs12248560	EAS	*17/*17	0	0.0%	Ultrarapid Metabolizer

Table 2 summarizes the simulated CYP2C19 star allele genotypes and predicted metabolizer phenotypes across South Asian, European, and East Asian populations. For the *2 allele (rs4244285), South Asians had the highest proportion of Intermediate (*1/*2, 43.3%) and Poor Metabolizers (*2/*2, 10.1%), while Europeans had the highest proportion of Normal Metabolizers (*1/*1, 72.2%). The *3 allele (rs4986893) showed a predominance of Normal Metabolizers in all populations, with Intermediate Metabolizers more frequent in South Asians (5.7%) than in Europeans (2.9%) and East Asians (1.6%), and Poor Metabolizers being rare (<0.3%). The gain-of-function *17 allele (rs12248560) was most common in Europeans (Rapid Metabolizers *1/*17, 22.0%), less frequent in South Asians (14.0%), and rare in East Asians (2.0%), with Ultrarapid Metabolizers (*17/*17) absent or extremely rare. Overall, South Asians carried the highest burden of loss-of-function alleles, Europeans had the highest prevalence of the gain-of-function *17 allele, and East Asians exhibited comparatively low frequencies of both loss- and gain-of-function variants, highlighting population-specific differences in predicted CYP2C19 metabolizer phenotypes.

TABLE 3: COMPARISON OF ALLELE FREQUENCIES ACROSS POPULATIONS

rs id	Reference in SAS	Reference in EUR	Reference in EAS	Alternate in SAS	Alternate in EUR	Alternate in EAS
rs4244285	68.2%	85.0%	72.0%	31.8%	15.0%	28.0%
rs4986893	94.3%	97.1%	98.4%	5.7%	2.9%	1.6%
rs12248560	86.0%	78.0%	98.0%	14.0%	22.0%	2.0%

Table 3 compares the allele frequencies of CYP2C19 variants (*2: rs4244285, *3: rs4986893, and *17: rs12248560) across South Asian, European, and East Asian populations. The *2

allele was most frequent in South Asians (31.8%), followed by East Asians (28.0%) and Europeans (15.0%). The *3 allele was observed at low frequencies across all populations but was slightly higher in South Asians (5.7%) compared with Europeans (2.9%) and East Asians (1.6%). In contrast, the *17 gain-of-function allele was most prevalent in Europeans (22.0%), followed by South Asians (14.0%) and rare in East Asians (2.0%). Overall, South Asians exhibited higher frequencies of loss-of-function alleles, Europeans had the highest prevalence of the gain-of-function allele, and East Asians generally showed lower frequencies of both loss- and gain-of-function variants.

TABLE 4: CYP2C19 STAR ALLELE MAP

rs id	Star	Effect
rs4244285	*2	LOF
rs4986893	*3	LOF
rs12248560	*17	GOF

Table 4 summarized the functional classification of CYP2C19 alleles. The *2 (rs4244285) and *3 (rs4986893) alleles were categorized as loss-of-function, whereas *17 (rs12248560) was categorized as a gain-of-function allele. This classification provided the basis for defining the predicted metabolizer phenotypes in this study.

DISCUSSION: CYP2C19 is a critical enzyme involved in the metabolism of many commonly prescribed medications, including proton pump inhibitors, antiplatelets, and some antiepileptic drugs. Variations in this gene significantly influence individual drug metabolism, which can affect both therapeutic efficacy and the risk of adverse reactions. In this study, we examined the distribution of CYP2C19 variants (*2: rs4244285, *3: rs4986893, *17: rs12248560) and predicted metabolizer phenotypes across South Asian, European, and East Asian populations using *in-silico* methods.

Our findings demonstrated that the *2 loss-of-function allele was most frequent in South Asians (31.8%), followed by East Asians (28.0%) and Europeans (15.0%). Consequently, South Asians exhibited the highest proportion of poor metabolizers, while Europeans had the lowest. This aligns with previous observations by Ionova Y *et al.,* who reported that poor metabolizer phenotypes are more common in South Asian populations, primarily driven by higher *2 allele frequencies [3]. Magavern EF *et al.* also noted that *2 is a major contributor to poor metabolizer status in South and East Asian cohorts, though less prevalent in Europeans [4].

The *17 gain-of-function allele, associated with ultrarapid metabolism, was most frequent in Europeans (22.0%), moderately present in South Asians (14.0%), and rare in East Asians (2.0%). This pattern suggests that ultrarapid metabolism may be more clinically relevant in European populations, while toxicity due to accelerated drug clearance is likely uncommon in East Asians. Nieh HV et al. similarly reported low *17 frequencies in East Asian cohorts, reinforcing interethnic differences in metabolic capacity [5].

The *3 allele was infrequent across all populations, with slightly higher occurrence in South Asians (5.7%) compared with Europeans (2.9%) and East Asians (1.6%). This confirms prior reports by Ionova Y *et al.,* who described *3 as a rare allele globally but a modest contributor to poor metabolizer phenotypes in South Asians [3]. Eken E *et al.* further emphasized that while *3 is a minor determinant overall, it should be considered when assessing drug response in populations where it occurs [6]. Additionally, Li XP *et al.* (2025) observed that the *3 allele is uncommon in individuals of Caucasian and African origin (0.04% and 0.037%, respectively) but is more common in Asians (2–9%) [7].

Normal metabolizers predominated in European and East Asian populations, indicating that standard dosing regimens are likely appropriate for these groups. In contrast, the higher prevalence of intermediate and poor metabolizers among South Asians suggests that genotype-guided dosing may improve therapeutic outcomes, particularly for medications such as PPIs and antiplatelets. The extremely low prevalence of ultrarapid metabolizers (*17/*17) across all populations indicates that adverse effects due to excessive metabolism are rare, yet still clinically relevant for carriers [3, 8]. This study highlights the utility of *in-silico* approaches for predicting population-level metabolizer phenotypes without involving human participants.

The allele frequency and phenotype distributions derived from publicly available genomic databases closely mirrored trends reported in clinical pharmacogenomic studies, supporting the use of computational analyses as a cost-effective tool for informing precision medicine and guiding future clinical investigations.

However, there are several limitations to *in-silico* analyses. First, they rely entirely on the accuracy and completeness of publicly available genomic datasets, which may not fully represent local or underrepresented populations [9]. Second, *in-silico* predictions do not account for environmental factors, epigenetic modifications, or drug–drug interactions that can affect enzyme activity in real-world scenarios [10]. Third, computational predictions cannot capture rare or novel variants not included in existing databases, potentially underestimating metabolizer diversity [11]. Finally, *in-silico* studies provide genotype-to-phenotype estimates but cannot directly measure actual drug metabolism or clinical outcomes, limiting their immediate applicability in patient care [12].

CONCLUSION: The distribution of CYP2C19 alleles varied notably among South Asian, European, and East Asian populations. South Asians carried the highest frequency of the *2 loss-of-function allele (31.8%), leading to a greater proportion of poor metabolizers, while Europeans had the lowest frequency (15.0%).

The *3 allele was uncommon across all groups, slightly more frequent in South Asians (5.7%) than in Europeans (2.9%) or East Asians (1.6%). In contrast, the *17 gain-of-function allele, associated with ultrarapid metabolism, was most prevalent in Europeans (22.0%), moderately present in South Asians (14.0%), and rare in East Asians (2.0%). These patterns highlight how population-specific genetic differences can influence drug metabolism, underscoring the potential benefits of tailoring drug dosing to genetic profiles. At the same time, it is important to recognize that computational predictions, while informative, cannot fully account for environmental factors, epigenetic changes, or rare variants that also affect drug response.

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REFERENCES:

1. de Andrés F, Altamirano-Tinoco C, Ramírez-Roa R, Montes-Mondragón CF, Dorado P, Peñas-Lledó EM and L-Lerena A: Relationships between CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 metabolic phenotypes and genotypes in a Nicaraguan Mestizo population. Pharmacogenomics J 2021; 21(2): 140–51. doi:10.1038/s41397-020-00190-9.
2. Bakar NS: Pharmacogenetics of common SNP affecting drug metabolizing enzymes: comparison of allele frequencies between European and Malaysian/Singaporean. Drug Metab Pers Ther 2021; 36(3): 173–81. doi:10.1515/dmpt-2020-0153.
3. Ionova Y, Ashenhurst J, Zhan J, Nhan H, Kosinski C, Tamraz B and Chubb A: CYP2C19 allele frequencies in over 2.2 million direct-to-consumer genetics research participants and the potential implication for prescriptions in a large health system. Clin Transl Sci 2020; 13(6): 1298–306. doi:10.1111/cts.12830.
4. Magavern EF, Jacobs B, Warren H, Finocchiaro G, Finer S and van Heel DA: CYP2C19 genotype prevalence and association with recurrent myocardial infarction in British–South Asians treated with clopidogrel. JACC Adv 2023; 2(7): 100573. doi:10.1016/j.jacadv.2023.100573.
5. Nieh HV and Roman YM: Major allele frequencies in CYP2C9 and CYP2C19 in Asian and European populations: a case study to disaggregate data among large racial categories. J Pers Med 2025; 15(7): 274. doi:10.3390/jpm15070274.
6. Eken E, Estores D, Cicali EJ, Wiisanen K and Johnson JA: A pharmacogenetics-based approach to managing gastroesophageal reflux disease: current perspectives and future steps. Pharmacogenomics Pers Med 2023; 16: 645–64.
7. Li XP, Wang JL, Lei SX, Chen BY, Ma X and He F: Prevalence of CYP2C19 variants in patients with cardiovascular disease from the Yunnan–Guizhou Plateau in Southwestern China. Pharmgenomics Pers Med 2025; 18: 105–13. doi:10.2147/PGPM.S509794.
8. Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L and Ingelman-Sundberg M: A common novel CYP2C19 genetic variant causes ultrarapid drug metabolism relevant for treatment with proton pump inhibitors and antidepressants. Pharmacogenetics 2021; 31(2): 56–65. doi:10.1097/FPC.0000000000000432.
9. Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin AR and Kuchenbaecker K: A roadmap to increase diversity in genomic studies. Nat Med 2022; 28(2): 243–50. doi:10.1038/s41591-021-01672-4.
10. Qahwaji R, Ashankyty I, Sannan NS, Hazzazi MS, Basabrain AA and Mobashir M: Pharmacogenomics: a genetic approach to drug development and therapy. Pharmaceuticals (Basel) 2024; 17(7): 940. Available from: https://www.mdpi.com/1424-8247/17/7/940
11. McInnes G, Sharo AG, Koleske ML, Brown JEH, Norstad M and Adhikari AN: Opportunities and challenges for the computational interpretation of rare variation in clinically important genes. Am J Hum Genet 2021; 108(4): 535–48. doi:10.1016/j.ajhg.2021.03.003.
12. Arbitrio M, Milano M, Lucibello M, Altomare E, Staropoli N and Tassone P: Bioinformatic challenges for pharmacogenomic study: tools for genomic data analysis. Front Pharmacol 2025; 16: 1548991. doi:10.3389/fphar.2025.1548991.

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