

## The Prevalence of Allele Frequencies of CYP2C19 Polymorphisms of Clinically Important Drug-Metabolizing Enzymes CYP2C19 in Moldova Healthy Population

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## Abstract

Genetic polymorphisms of drug-metabolizing enzymes, such as cytochrome P450 oxidases, can alter the pharmacokinetic properties of administered drugs, leading to variability in drug responses. Prior knowledge of allele frequencies of cytochrome P450 polymorphisms in a population is crucial. In the current study, the frequency of the CYP2C19\*2, CYP2C19\*3, CYP2C19\*17 alleles, genotypes and phenotype in healthy population of Republic of Moldova was examined. Tests for polymorphisms of CYP2C19 was performed using method TaqMan® SNP Genotyping Assays in 430 healthy subjects, assessing the phenotypes, which included normal metabolizer (NM), intermediate metabolizer (IM), poor metabolizer (PM), rapid metabolizers (RM) and ultrarapid metabolizer (UM). 112 individuals (26.2%) were CYP2C19\*1/\*2 heterozygotes, 7 (1.6%) were CYP2C19\*2/\*2 homozygotes, 119 subjects (28.4%) were CYP2C19\*1/\*17 heterozygotes and 31 subjects (7.4%) were CYP2C19\*17/\*17 homozygotes, while 1 individual (0.2%) was a CYP2C19\*1/\*3 compound heterozygote. Therefore, 7 individuals CYP2C19\*2/\*2 homozygotes (1.6%) are predicted to be CYP2C19 PM. The allele frequencies for CYP2C19\*2, \*3 and \*17 was 14.7%, 0.1% and 21.6%, respectively. The results of this study provide important information about the distribution of CYP2C19 genetic variants in the healthy population of the Republic of Moldova. These findings may have implications for understanding population differences in drug responses, and they



support the potential application of genetic testing in medical practice to guide personalized treatment approaches.

*Keywords:* polymorphisms, genotyping, moldova population, drug-metabolizing enzymes

## References

1. Bank, P.C., Caudle, K.E., Swen, J.J.: Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the dutch pharmacogenetics working group. Clin. Pharmacol. Ther. **103**, 599–618 (2018)

2. Ahmed, S.: Pharmacogenomics of drug metabolizing enzymes and transporters: Relevance to precision medicine. Genomics Proteomics Bioinform. **14**(5), 298–313 (2016)

3. Preissner, S.C.: Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS ONE **8**(12), e82562 (2013)

4. Ibeanu, G.C., Goldstein, J.A.: Identification of new human CYP2C19 alleles (CYP2C19\*6 and CYP2C19\*2B) in a Caucasian poor metabolizer of mephenytoin. J. Pharma. Experim. Therap. **286**(3), 1490–1495 (1998). PMID 9732415

Fukushima-Uesaka, H.: Genetic variations and haplotypes of CYP2C19 in a Japanese population.
Drug Metab. Pharmacokinet. 20(4), 300–307 (2005). <u>https://doi.org/10.2133/dmpk.20.300</u>.
PMID16141610

6. Sim, S.C., Risinger, C.: A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin. Pharmacol. Ther. **79**(1), 103–113 (2006). https://doi.org/10.1016/j.clpt.2005.10.002.PMID16413245.S2CID20989576

7. Dorji, P.W., Tshering, G.: CYP2C9, CYP2C19, CYP2D6 and CYP3A5 polymorphisms in South-East and East Asian populations: a systematic review. J. Clin. Pharm. Ter. **44**(4), 508–524 (2019)

8. Wedlund, P.J.: The CYP2C19 enzyme polymorphism. Pharmacology **61**(3), 174–183 (2000). https://doi.org/10.1159/000028398. PMID10971203.S2CID24471776

9. Bertilsson, L.: Geographical/interracial differences in polymorphic drug oxidation. Current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. Clin. Pharmacokinet. **29**(3), 192–209 (1995). https://doi.org/10.2165/00003088-199529030-00005. PMID8521680.S2CID111743



Desta, Z., Zhao, X.: Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin.
Pharmacokinet. 41(12), 913–958 (2002). <u>https://doi.org/10.2165/00003088-200241120-00002</u>.
PMID12222994.S2CID27616494

11. Ionova, Y., Ashenhurst, J.: CYP2C19 Allele frequencies in Over 2.2 million direct-toconsumer genetics research participants and the potential implication for prescriptions in a large health system. Clin. Transl. Sci. **13**, 1298–1306 (2020). <u>https://doi.org/10.1111/cts.12830</u>

12. Zhou, Y., Ingelman-Sundberg, M.: Worldwide distribution of cytochrome P450 alleles: a metaanalysis of population-scale sequencing projects. Clin. Pharmacol. Ther. **102**, 688–700 (2017). https://doi.org/10.1002/cpt.690

13. Buzoianu, A.: Screening for CYP2C19\*2, \*3 and \*4 gene variants in a Romanian population study group. Farmacia **58**(6), 806–817 (2010)

14. Gaikovitch, E.A., Cascorbi, I.: Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population. Eur. J. Clin. Pharmacol. **59**, 303–312 (2003)

15. Petrovi'c, J., Peši'c, V.: Frequencies of clinically important CYP2C19 and CYP2D6 alleles are graded across Europe. Eur. J. Hum. Genet. **28**, 88–94 (2020). <u>https://doi.org/10.1038/s41431-019-0480-8</u>

16. Aynacioglu, A.S., Sachse, C.:Lowfrequency of defective alleles of cytochrome P450 enzymes 2C19 and 2D6 in the Turkish population. Clin. Pharmacol. Ther. **66**(2), 185–192 (1999)

17. Allabi, A.C., Gala, J.L.: Genetic polymorphisms of CYP2C9 and CYP2C19 in the Beninese and Belgian populations. Br. J. Clin. Pharmacol. **56**(6), 653–657 (2003)

18. Zhong, Z., Hou, J.: Analysis of CYP2C19 genetic polymorphism in a large ethnic Hakka population in Southern China. Med. Sci. Monit. **23**, 6186–6192 (2017). <u>https://doi.org/10.12659/msm.905337</u>

19. Ota, T., Kamada, Y.: Combination analysis in genetic polymorphisms of drug-metabolizing enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 in the Japanese population. Int. J. Med Sci. **12**(1), 78–82 (2015). <u>https://doi.org/10.7150/ijms.10263</u>

20. Sabırlı, R.: CYP2C19\*1 and CYP2C19\*2 polymorphism in Turkish patients being diagnosed with stable coronary artery disease and using clopidogrel. BagcilarMed. Bull. (2020).

https://doi.org/10.4274/BMB.galenos.2020.08.040



21. Dehbozorgi, M.: Prevalence of the CYP2C19\*2 (681 G>A), \*3 (636 G>A) and \*17 (-806 C>T) alleles among an Iranian population of different ethnicities. Mol. Med. Rep. **17**,4195–4202 (2018). https://doi.org/10.3892/mmr.2018.8377

22. Sukprasong, R.:Allele frequencies of single nucleotide polymorphisms of clinically important drugmetabolizing enzymes CYP2C9, CYP2C19, and CYP3A4 in a Thai population. Sci. Rep. **11**, 12343 (2021). <u>https://doi.org/10.1038/s41598-021-90969-y</u>

23. Hamdy, S.I., Hiratsuka, M.: Allele and genotype frequencies of polymorphic cytochromes P450 (CYP2C9, CYP2C19, CYP2E1) and dihydropyrimidine dehydrogenase (DPYD) in the Egyptian population. Br. J. Clin. Pharmacol. **53**(6), 596–603 (2002)

24. Pratt, V.M.: Recommendations for clinical CYP2C9 genotyping allele selection: A joint recommendation of the association for molecular pathology and college of American pathologists. J. Mol. Diagn. **21**(5), 746–755 (2019)

25. Martis, S., Peter, I.: Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. Pharmacogenomics J. **13**(4), 369–377 (2013)

26. Sukasem, C., Tunthong, R.: CYP2C19 polymorphisms in the Thai population and the clinical response to clopidogrel in patients with atherothrombotic-risk factors. Pharmgenomics Pers. Med. **6**, 85–91 (2013)

27. Klein, M.: Clinical utility of CYP2C19 genotyping to guide antiplatelet therapy in patients with an acute coronary syndrome or undergoing percutaneous coronary intervention. Arterioscler. Thromb. Vasc. Biol. **39**, 647–652 (2019). <u>https://doi.org/10.1161/ATVBAHA.118.311963</u>

**28.** Bank, P.C., Caudle, K.E.: Comparison of the guidelines of the Clinical Pharmacogenetics Implementation consortium and the Dutch pharmacogenetics working group. Clin. Pharmacol. Ther. **103**, 599–618 (2018)