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Structural Insights into Afrocentric CYP3A4 Alleles: A Post-Molecular Dynamics Characterization

Cytochrome P450 3A4 (CYP3A4) is regarded as the most important CYP enzyme due to its high hepatic and gastrointestinal abundance and its involvement in the metabolism of over 50% of the clinically administered drugs. Genetic variants of this enzyme, which influence drug bioavailability and systemic clearance, are poorly characterized with no definitive clinical phenotypes due to substrate selectivity in metabolic profiles. These subsequently result in unguided personalized treatment with drugs metabolized by CYP3A4. Furthermore, the African population harbors one of the highest polymorphic diversity and frequencies compared to other populations. To advance the personalized treatment, it is important to decipher how the variants specific to this population affect the enzyme's metabolic activity. This study leverages high-performance computing and the GROMACS all-atom molecular dynamics simulations to characterize the effects of missense mutations on the structure and dynamics of 13 Afrocentric CYP3A4 alleles. From post-MD simulation analysis, we identified variation-induced alterations at the global structural level. We further observed changes in the active site vicinity, as well as in the size and dynamics of the key substrate-binding channel, which may be linked to observed cases of drug efficacy and toxicity. The findings underscore the importance of computational approaches in understanding the molecular mechanisms of altered drug metabolism and pave the way for strategic personalized medicine.

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