

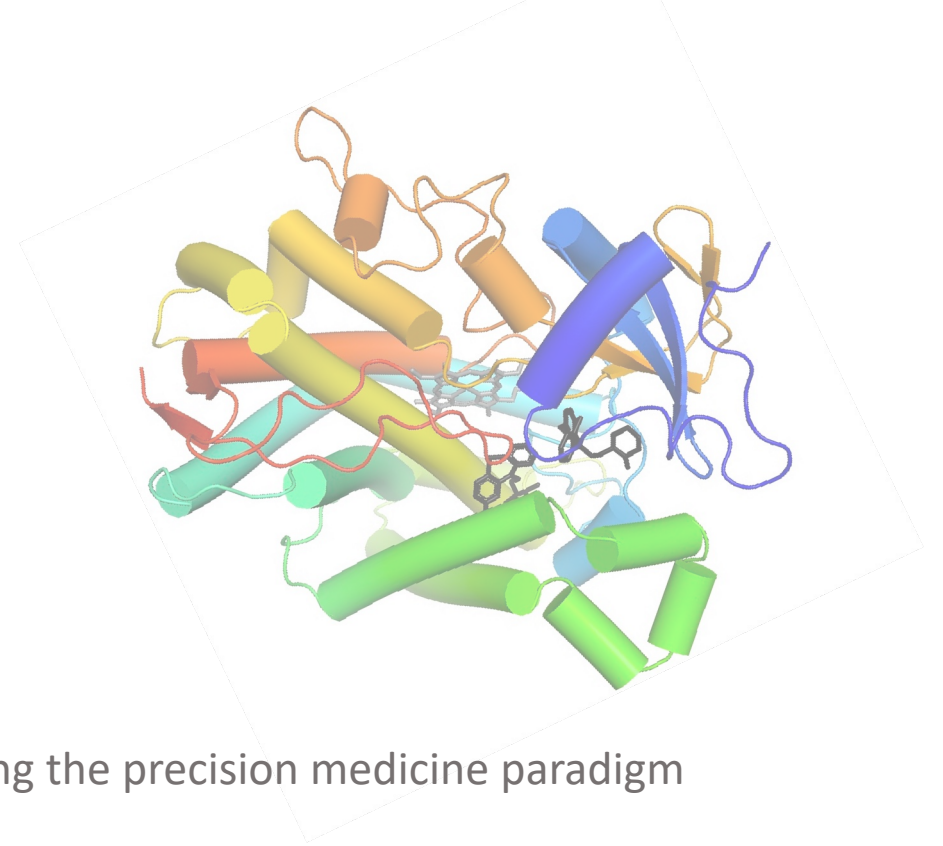
Characterising the the combined effect of cytochrome P450 missense variation within the star allele definitions

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Rationale

- CYP (Cytochrome P450) proteins process 75-90% of drugs.
- CYP variation described as star alleles
- CYP prescription guidelines issued by CPIC
 - Limited guidelines for African populations
- Studying the functional impact of star allele is crucial in elucidating the precision medicine paradigm

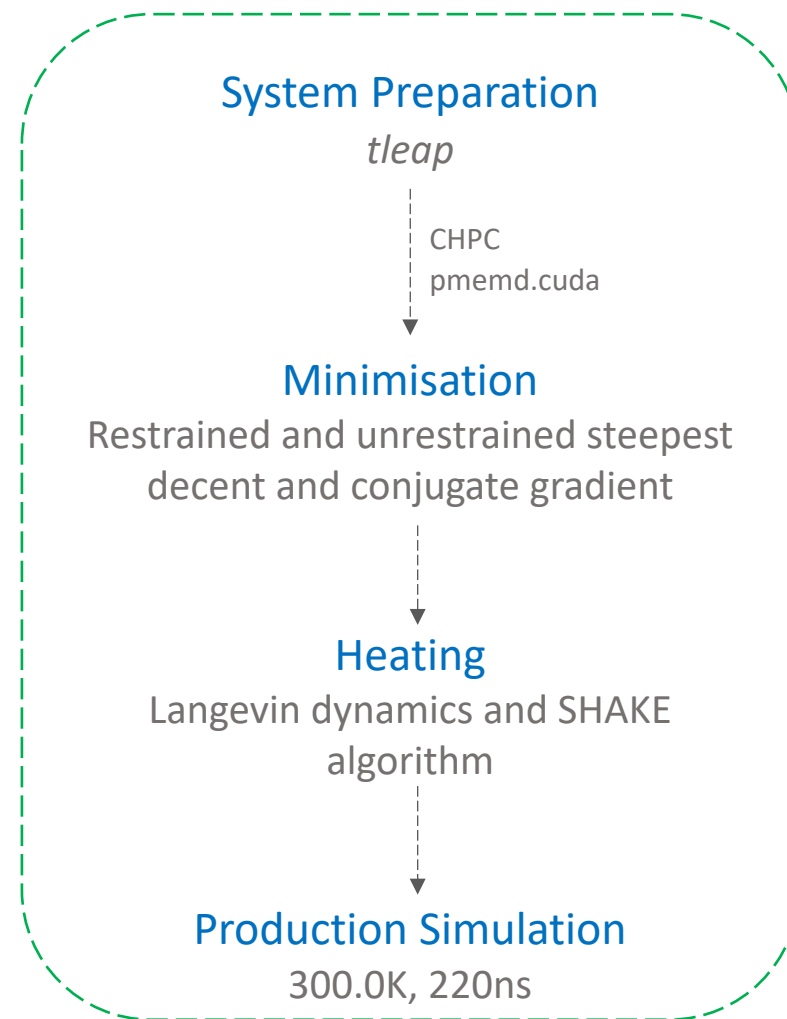
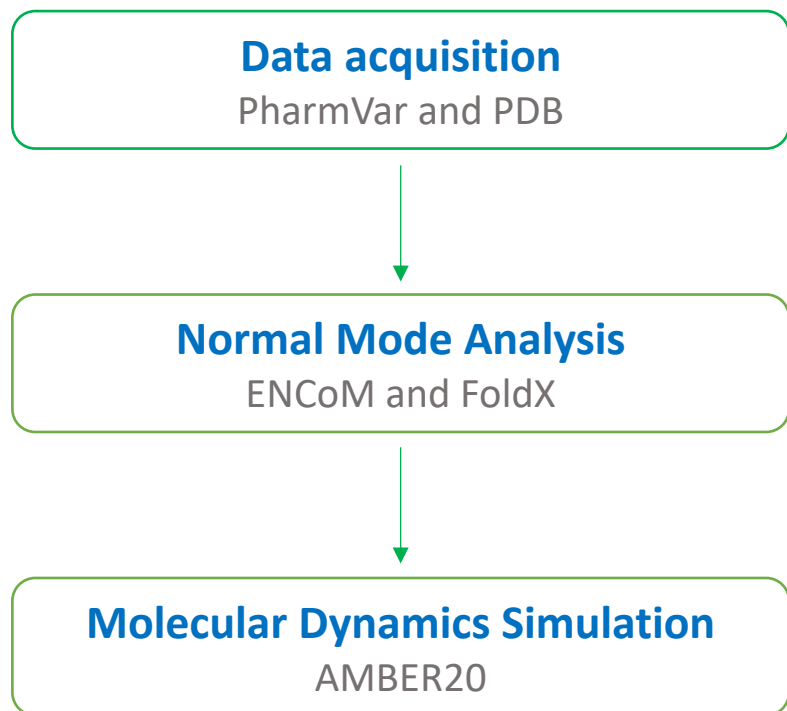


Aim

Assess the potential impact of a combination of missense variants, within CYP star allele definitions, on protein stability and conformational dynamics.



Methods



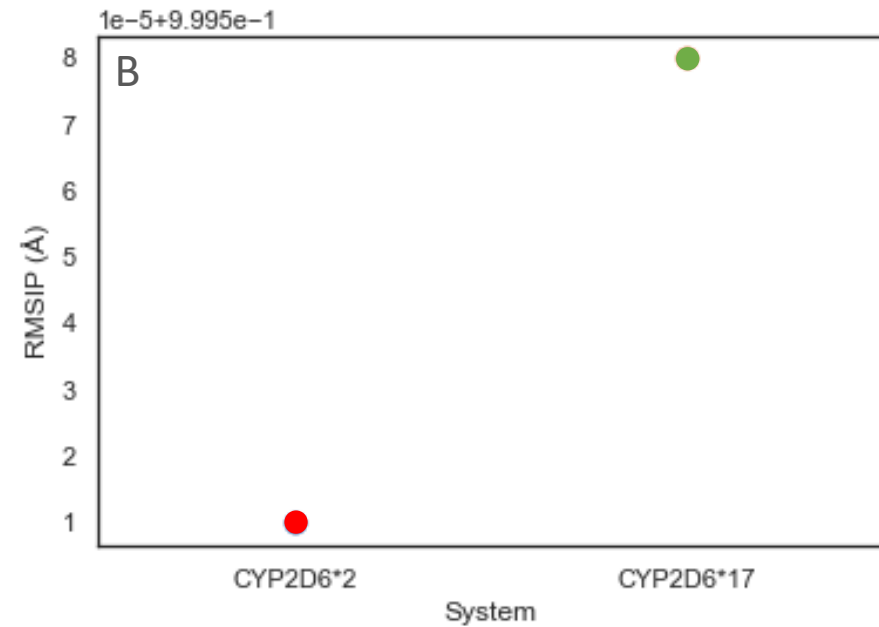
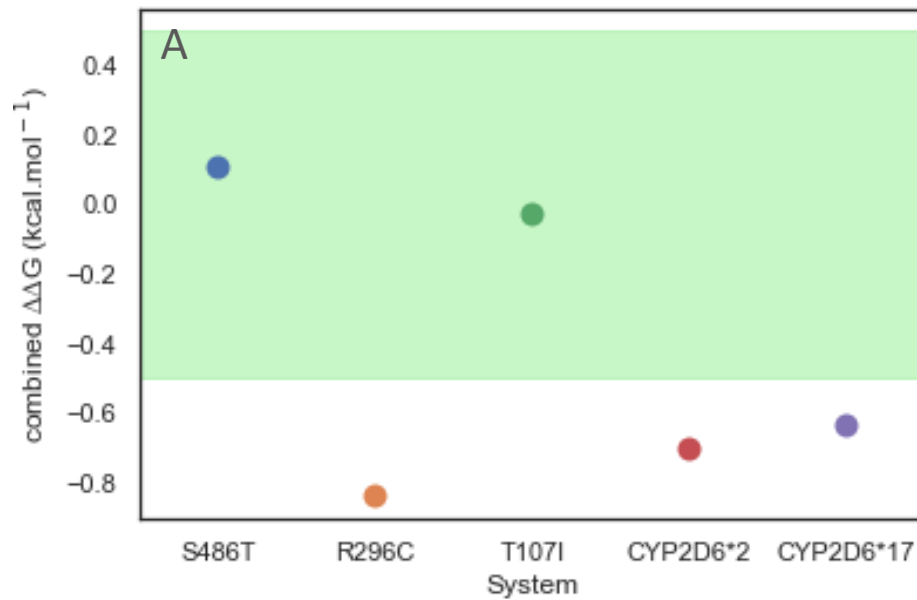
Results and Discussion

- CYP2D6*2 → S486T and R296C
- CYP2D6*17 → S486T, R296C and **T107I**

CPIC → Benign

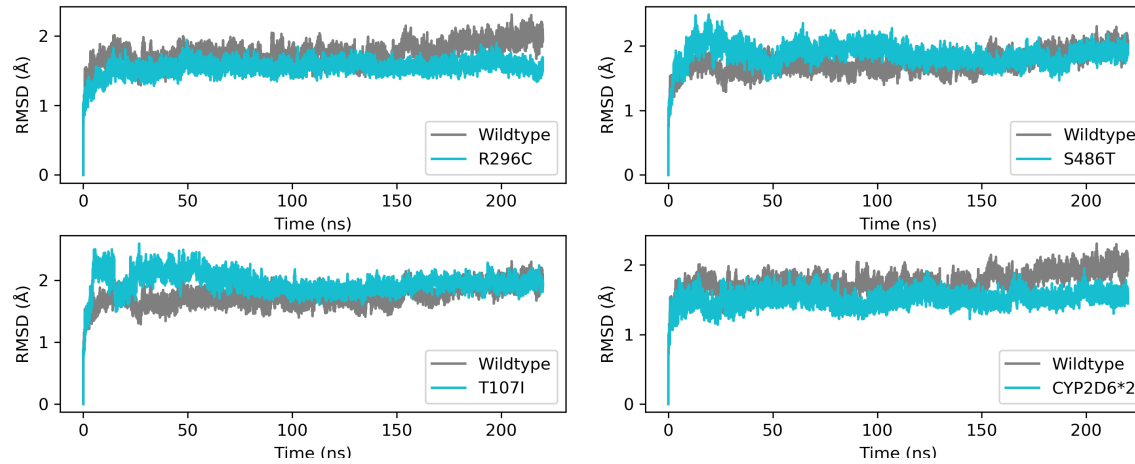
CPIC → Decreased function

Normal Mode Analysis (NMA)



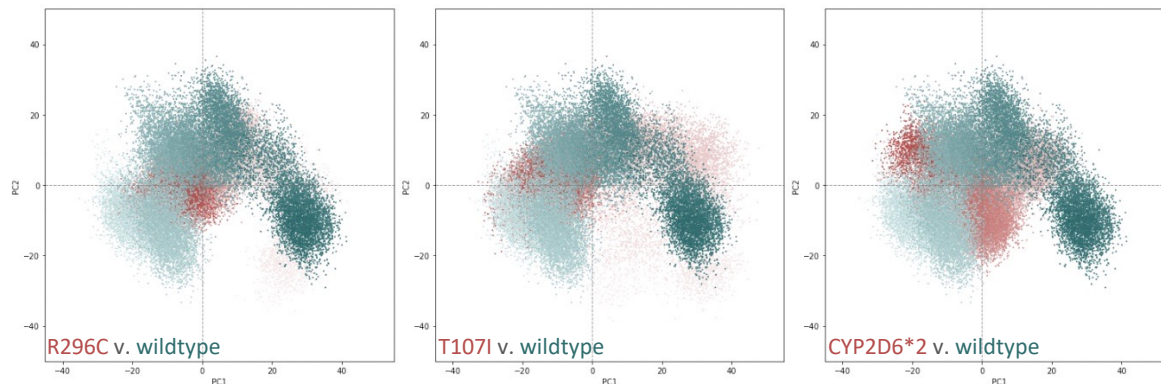
Molecular Dynamics (MD) Simulation

RMSD



- R296C and CYP2D6*2 → relatively greater deviations from wildtype

PCA



- T107I dynamics overlap less with wildtype compared to R296C



Discussion and Conclusion

T107I

- Located in functionally crucial BC loop
- Reduce flexibility of protein
- Little effect on protein function

R296C

- Located within the substrate-binding pocket in the functionally crucial I-helix
- Substrate-dependent effects on protein flexibility

The effects of the CYP2D6*17 may be described by changes in protein conformation and flexibility, driven by T107I, with apparent modulations by R296C.





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