

PP 19 - Design and implementation of novel pharmacogenomic assays for clinically important *CYP2C19* variants to predict the response to clopidogrel in a cohort of Sri Lankan population

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Introduction: Cytochrome *P450 2C19* (*CYP2C19*) catalyses the metabolism of a range of clinically important drug classes. It plays a major role in the clopidogrel drug metabolism, which determines its varied therapeutic level and its effectiveness. *CYP2C19*2*, *CYP2C19*3* and *CYP2C19*17*(with a double SNP; -806C>T, -3402C>T) are three clinically important variants of the *CYP2C19* gene leading to a poor metabolizer and ultra-rapid metabolizer phenotypes respectively. This study was undertaken to design and implement novel pharmacogenetic assays for selected *CYP2C19* gene variants: *CYP2C19*3*, *CYP2C19*17*(-806C>T) and *CYP2C19*17*(-3402C>T) to predict response to clopidogrel.

Methods: Novel single variant tetra-primer amplification refractory mutation system (T-ARMS) polymerase chain reaction (PCR) and Restriction Fragment Length Polymorphism polymerase chain reaction (RFLP-PCR) assays were designed and validated by Sanger Sequencing. T-ARMS PCR assay was used to genotype the selected *CYP2C19* variants in a cohort of Sri Lankan population (n=100). Prior informed written consent was obtained for such studies. The metabolizer phenotypes of the study individuals were determined collectively by analysing the presence of the *CYP2C19*3* and *CYP2C19*17*(-806C>T, -3402C>T) variants.

Results: The variant allele frequency of *CYP2C19*17* and *CYP2C19*3* in the study population were 0.20 and 0.01, respectively. All *CYP2C19* genotype frequencies were consistent with Hardy-Weinberg equilibrium. The frequency of extensive metabolizer (EM) (*1*1), rapid metabolizer (RM) (*1*17), ultra-rapid metabolizer (UM) (*17*17) and Intermediate metabolizer (IM) (*3*17) phenotypes of the selected variants were 64%, 33%, 5% and 1% respectively.

Conclusions: We successfully designed and implemented novel genotyping assays for *CYP2C19*3* and (-806 C>T), (-3402 C>T) SNP's of the *CYP2C19*17* variant. The most prevalent allele in the Sri Lankan population was *CYP2C19*17* (C/C, C/T for both SNPs) and the most prevalent phenotype predicted was EM followed by RM. The designed pharmacogenomic assays could be offered to patients to predict their response to clopidogrel enabling physicians to tailor the dosages accordingly.

Keywords: *CYP2C19*, Pharmacogenomic, T-ARMS-PCR, Clopidogrel

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