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High frequency of PM phenotype in warfarin, clopidogrel, SSRIs and homocysteine/methotrexate pathway genes: Results support the need for pre-emptive genotyping across global populations to improve clinical decision-making

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Adverse drug reactions are the fourth leading cause of death that leads to over 130 million deaths each year in United States alone. Earlier studies have reported variation in potentially important actionable genes to be influencing variation in drug response. However, there is paucity of genetic information across ethnically and genetically diverse populations. In this study, we have analyzed 25 SNPs from 15 pharmacogenomics actionable genes in a population of Punjabi Sikhs (N=1616), as part of the Sikh diabetes study (SDS) to compare the distribution of allele frequencies associated with poor metabolism (PM) phenotype across 11 HapMap populations. The frequencies of PM phenotype in four of the 15 genes (*CYP2A1, CYP2C9, CYP2C19* and *MTHFR*) were significantly higher in Punjabis (SDS) and Gujarati Indians (GIH) compared to other HAPMAP populations. The PM phenotype associated with *CYP1A2*1F* allele was significantly higher in Indians (SDS 43%, GIH 51%) compared to Caucasians (CEU 29%) (p=0.01). Similarly, Indians had significantly higher frequency of *CYP2C9*3* (11% SDS, 13% GIH) vs. 5% in CEU (p=0.008). While the frequency of 'T' risk allele *MTHFR* (*C677T*) was lower in Indians compared to Caucasians (0.19 SDS, 0.16 GIH vs. 0.31 CEU), the 'C' risk allele of *A1298C* of *MTHFR* was strikingly higher in SDS (44%) compared to GIH (39%) and CEU (34%) ($p=4.9\times10^{-3}$). In summary, this is the first study reporting a significant ethnic difference in the frequency of PM phenotype in Sikhs. These findings underscore the need for establishing global benchmark for preemptive genotyping before starting therapeutic intervention.

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