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CYP2D6 gene polymorphism in pakistani population

Abstract

CYP2D6 is an important enzyme mediating phase I metabolic reactions and is involved in metabolism of 20-25% of the clinically useful drugs. High frequency of polymorphism in CYP2D6 gene has resulted in the categorization of individuals as poor, intermediate, extensive and ultra-rapid metabolisers of CYP2D6 substrate drugs. The CYP2D6 polymorphism significantly affects the pharmacokinetic profile of about 30-40% of CYP2D6 drug substrates which are about 10% of the clinically used drugs thus leading to altered therapeutic efficacy of the substrate drugs and adverse drug reactions. It has been estimated that predictive CYP2D6 genotyping can be beneficial for optimum therapy with CYP2D6 drug substrates. Because of wide geographic and ethnic variability in CYP2D6 genotypes, pharmacogenomics studies to find interethnic and geographic differences in CYP2D6 genotypes are however mandatory to get benefit from predictive genotyping. This review was therefore conducted to enlist pharmacogenomics studies conducted on Pakistani population to find frequency of CYP2D6 genotypes in this region.

Keywords: cyp2d6, gene polymorphism, frequency, Pakistan

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Introduction

CYP2D6 belongs to CYP450 super family, the major phase I enzymes, and is one of the key enzymes involved in the metabolism of a number of endogenous and exogenous substances including 20-25% of the drugs.[1] Antipsychotics, antidepressants, beta blockers and Tamoxifen are among notable substrates of this enzyme.[2] CYP2D6 gene, located on chromosome 22, is known as highly polymorphic with significant ethnic difference in frequency of the alleles.[3] More than 46 major polymorphic alleles of CYP2D6 are known today. Of which, CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17 and CYP2D6*41 variant forms of the gene are the most important. These allelic variants are classified into categories with abolished, decreased, normal, increased or qualitatively altered catalytic activity. The most common allelic variant of CYP2D6 world over is CYP2D6*10 which is also most common (allele frequency of 45%) among Asians. The enzyme product of CYP2D6*10 is highly unstable and exhibits reduced substrate affinity.[1] CYP2D6*4 isoform is poor metabolizing enzyme and is more common among Caucasians with 12-23% frequency whereas CYP2D6*17 and CYP2D6*10 are more prevalent among Africans and Asians, respectively.[1] Metabolic status of individuals may vary depending upon activity of the CYP2D6 enzyme product or allelic frequency, which has led to the categorization of individuals as poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs) and ultra-rapid metabolizers (UMs). Deficient alleles can result from gene deletion, gene conversions into pseudogenes or single base mutations resulting in frame shift, missense, nonsense or splice-site mutations.[4] PMs are either homozygous for one deficient allele or heterozygous for two variant deficient alleles. IMs are individuals heterozygous for one type of deficient allele or carriers of two alleles with reduced enzyme activity. Reduced enzyme activity is the result of impaired folding capacity of the enzyme and therefore severely diminished expression of the enzyme leading to diminished or altered drug metabolism.[5,6] EMs has two wild-type alleles; and UMs are those who carry multiple copies of the wild-type gene.

The CYP2D6 polymorphism has high clinical importance. The altered metabolic status of the individuals has resulted in inter-individual differences in drug response and incidence of untoward drug effects. It has been estimated that predictive genotyping of CYP2D6 can be beneficial in the case of 30-40% drugs metabolized by this enzyme which are up to 10% of the clinically used drugs.[7] In view of the significance of CYP2D6 enzyme in drug metabolism and impact of CYP2D6 gene polymorphism on the enzyme activity and resultant effect on drug efficacy, safety and cost of the treatment, this review was conducted to enlist studies conducted on Pakistani population to find presence of various allelic variants of CYP2D6 in this population and their frequencies to underscore the importance and cost-effectiveness of predictive genotyping in Pakistani population. This review was also aimed to compare CYP2D6 allele frequency in Pakistani population with other populations of the world.

Method

Research articles published over last 20years and available in Pubmed and Medline databases were searched using "CYP2D6 genotypes", "frequency" and "Pakistan" as keywords. Because of scarcity of pharmacogenomics data available on Pakistani population, all studies, prospective as well as retrospective, relevant to the frequency of CYP2D6 genotypes have been included in this review.

Results and discussion

We could find only a few research articles and one dissertation pertaining to investigation on frequency of various CYP2D6 polymorphic forms among Pakistani population. In a study conducted by Nazir et al.,[8] women pre-diagnosed with breast cancer were studied for the presence and frequency of CYP2D6*4 genotype and the findings were related to the incidence and severity of Tamoxifen induced hot flushes. Both pre and post-menopausal women were included to the study. Patient genotype was investigated using polymerase chain reaction-restriction fragment length chain polymorphism. Among 223 women investigated for the presence of various CYP2D6 genotypes, 3.1% of the patients were CYP2D6 homozygous for CYP2D6*4 genotype variant, 22% were CYP2D6*1/*4 heterozygous, and 74.9% were homozygous for CYP2D6 wild type genotype (CYP2D6*1). The allele frequency of CYP2D6*1 was 86% and CYP2D6*4 was 14%. The enzyme product of CYP2D6*4 genotype is an inactive enzyme as a result of defective splicing. The CYP2D6*4 homozygous individuals are therefore categorized as poor metabolizers.[9] When women carrying wild type allele were compared with those having

heterozygous and homozygous variant genotypes, there was a significant association between incidence of host flushes and the genotypes. Women homozygous for the variant allele (CYP2D6*4) experienced no hot flushes, which is due to the presence of inactive CYP2D6 enzyme. Active form of CYP2D6 enzyme is required to convert Tamoxifen into its active metabolite endoxifen which possess anti-estrogenic activity leading to the hot flushes as untoward effect of Tamoxifen and failure of therapy. Compare to the reported 1% frequency of CYP2D6*4 genotype in Asians.[1] CYP2D6*4 frequency, as reported in this study, is a little higher in the Pakistani population. This difference in allelic frequency can be ascribed to insufficient number of subjects selected from a limited clinical setting.

Another study was conducted to investigate the frequency of CYP2D6*10 in Pakistani population using breast cancer patients as study subjects.[10] Allelic frequency of CYP2D6*10 was ascertained using 232 participants. Among studied subjects: the allele frequency of cytochrome CYP2D6*1 was 93% and that of CYP2D6*10 was found 7 %. The frequency of CYP2D6*10 in Pakistanis was thus found significantly less (7% vs 51%) compare to the Asian populations and other ethnic groups but was comparable to the reported frequency in South Indians. None of the patients under study was homozygous for CYP2D6 variant genotype CYP2D6*10, around 14% patients were CYP2D6 heterozygous with CYP2D6*1/*10 genotype and 85.8% were homozygous for the wild type allele CYP2D6*1. The respective allelic frequencies of CYP2D6*1 and CYP2D6*10 were 93% and 7%. Allelic frequency of CYP2D6*10 in Pakistani breast cancer patients was comparable to South Indians but was found significantly less than general population from other Asian countries. This study has reported the frequency of CYP2D6*10 in Pakistani population for the first time. The CYP2D6*10 enzyme is lacking sequence necessary for proper protein folding and is therefore very unstable besides having reduced affinity for the substrates.[1]

To determine differences in CYP2D6 allele frequencies between various ethnic groups of Pakistan, four hundred and sixty three individuals of Pathan, Kalash, Sindi, Parsi and Hazara ethnic groups were enrolled in a study to find CYP2D6 genotype (CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6). The genotype was determined by using allele-specific PCR primers for CYP2D6 alleles.[11] The only variant found to be present in the studied group was CYP2D6*4. Whereas rest of the alleles were absent in the ethnic groups studied. The frequency of CYP2D6*4 allele was ranging from 7.46 % in Kalash population to 20 % in Pathans. The average allele frequency of CYP2D6*4 for all the studied groups was 13.17 %, which is far higher than reported previously.[1] Compiled results of the above studies along with a comparison for CYP2D6 genotype frequencies with other populations of the world are given in Table 1.

Table 1 Frequency of various mutant forms of CYP2D6 in Pakistani population in comparison with other populations of the world[1,8,10,11]

Genotype	Effect of Mutation On Enzyme	% Frequency in Various Populations					
		Pakistani breast cancer patients	Pakistani ethnic groups	Caucasian	Asian	Black Africans	Ethiopians and Saudi Arabians
CYP2D6*4	Inactive	3.1	13.17	12-21	1	2	1-4
CYP2D6*10	Unstable	7	-	1-2	51	6	3-9

Conclusion

Allelic frequency of CYP2D*4 and CYP2D*10 in Pakistani breast cancer patients is 3.1 and 7% respectively, whereas average frequency of CYP2D*4 among various ethnic groups of Pakistan is reported as 13.17%, which also exists with interethnic differences in the frequency of this allele.

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Conflicts of interest

Author declares there are no conflicts of interest.

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