

In This Issue**Editor's Summaries of the Articles Published in This Issue of Molecular Medicine Communications****Editorial Staff**

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In this issue, Khokhar and colleagues describe their analysis of the HBV small S gene partial sequences and its implications for detection, prevention, and treatment in Pakistani patients, Chaudhary et al., reviewed studies on CYP2D6, its genetic polymorphism, and the brain, Usman and Ghaffar compiled studies on Alzheimer's disease therapy, and discussed the effects of genetic polymorphisms on its efficacy and safety, Ximenes and her colleagues described their study to determine the certain polymorphisms in CYP2C8 gene in Pakistani population and their frequencies in various ethnic groups, Zulfiqar et al shared their study where they reported a lack of association of CYP2C9 genetic polymorphism with oral squamous cell carcinoma, and Ullah and his colleagues compiled important studies discussing venlafaxine pharmacogenetics and their implications for therapeutic efficacy and adverse effects in major depressive disease patients.

Genetic Analysis of Hepatitis B Virus from Pakistani Patients

Hepatitis B virus (HBV) causes significant morbidity and mortality throughout the world, especially in developing countries. In Pakistan, the HBV infection rate is one of the highest in the world and about one-third of the infected population is co-infected with hepatitis C virus

(HCV) and hepatitis D virus (HDV). Khokhar and colleagues isolated HBV from 49 HBV mono-infected and 25 HBV/HCV co-infected Pakistani patients and classified them based on the partial sequences of S gene. They further investigated mutations in these sequences that might result in the failure of hepatitis B surface antigen (HBsAg) detection, as well as vaccination and treatment failure. The D and D1 were identified as the most prevalent HBV genotype and sub-genotype respectively in Pakistani samples. The same genotype/sub-genotype pattern was observed for the HBV/HCV co-infected patients. They also identified several mutations in the small S gene, which are previously reported to have roles in HBV diagnosis and treatment. Especially, the sT127P mutant, previously known to be implicated in vaccine escape, was prevalent with 98 and 96% frequencies in HBV mono-infected and HBV/HCV co-infected patients respectively. These findings have implications with respect to the prevention, diagnosis, and treatment of HBV infections in the Pakistani population.

CYP2D6, Its Genetic Polymorphism, and the Brain

The Cytochrome P450 system comprises several families of non-specific monooxygenases that catalyze Phase-I biotransformation reactions of an extensive list of drugs. The genes encoding

for these Cytochrome P450 (CYP) enzymes are highly polymorphic. Further, these enzymes are susceptible to inhibition or induction by various drugs. So far, these enzymes have been extensively studied in the context of drug-drug interactions and drug-gene interactions. However, their role in different organs other than the liver and intestines during health and disease remains largely unknown. Among these CYP enzymes, CYP2D6 represents a highly polymorphic isozyme that has a low content in the liver compared to other isozymes, yet metabolizes a significant proportion of the clinically used drugs. Chaudhary and Colleagues explore the role of CYP2D6 in the brain during health and disease in a mini-review. They discuss that CYP2D6 is expressed in different regions of the brain and also, its expression varies among different brain cells. CYP2D6 and its genetic polymorphism have an important impact on normal brain functions ranging from brain metabolism, and cerebral perfusion to cognition and behavior. CYP2D6 and its genotypes are also associated with the risk of Parkinson's disease, Schizophrenia, and depression. Since CYP2D6 activity is modifiable, they argue, it represents a potential therapeutic target that can be used to treat various neuropsychiatric, neurodegenerative, and cerebrovascular diseases

Pharmacogenetics of Alzheimer's Disease Therapy

In this review, Usman & Ghaffar discuss the current understanding of Alzheimer's disease (AD) pathophysiology, treatment, and genetic influence on the efficacy and adverse effects of the current state-of-the-art treatment. AD continues to be a significant health burden worldwide as the global population is getting older and health care costs are escalating. AD is a heterogeneous condition having diverse phenotypes and genotypes, which is a major

challenge in understanding disease etiopathogenesis. The difficulty in understanding the intricacies of the disease has led to the recurrent failure of therapeutic agents in clinical trials resulting in an extremely slow and low success in the new drug discovery process for AD. Currently approved agents for AD therapy are acetylcholinesterase inhibitors (AChEIs) (donepezil, galantamine, and rivastigmine) and n-methyl d-aspartate (NMDA) antagonist (memantine) that provide symptomatic relief only. However, extensive inter-individual variability in drug responsiveness is observed. 'Pharmacogenomics' which refers to how the genome of a patient might affect the treatment response to a drug, appears to play an important role in this inter-individual variability. By bringing the pharmacogenomics profile of patients on AD therapy into consideration, it might be possible to gain maximum benefits from available treatments in terms of safety, therapeutic optimization, and minimizing adverse effects. The review provides a better understanding of AD pathogenesis, challenges of current AD therapy, and insight into the role of genetic polymorphism in drug response with a focus on available therapeutic options in AD.

Prevalence of CYP2C8 Gene Polymorphisms in the Pakistani Population

Cytochrome P450C8 represents 7% of the hepatic cytochrome system and metabolizes around 5% of drugs in phase I processes. It also plays a significant role in the metabolism of endogenous compounds. More than 20 single nucleotide polymorphisms (SNPs) have been reported, mainly in exons 3, 5, and 8. Some of the SNP lead to decreased enzyme activity and may have an impact on drug metabolism. Ximenes and colleagues conducted a study to determine the frequencies of the most common SNPs of the CYP2C8 gene (CYP2C8*2, *3, *4) in the Pakistani

population. A cross-sectional study consisting of 391 healthy humans was conducted. The rate of minor allele was found to be 11.64% for *CYP2C8*2*, 14.71% for *CYP2C8*3*, and 1.53% for *CYP2C8*4*. Comparison with the 1000 Genome project reveals that the allelic frequencies of *CYP2C8*4* in the Pakistani population were similar to other South Asian populations while the frequencies of *CYP2C8*2* and *CYP2C8*3* as significantly different from other South Asian populations. A significant interethnic variation was also observed among Pakistani ethnicities. The *CYP2C8*2* allele was highest in the Sindhi population, *CYP2C8*3* in the Pashtoon population, and *CYP2C8*4* in the Balochi population. Their data suggest that the frequency of poor metabolizers of *CYP2C8* is high enough in the Pakistani population to warrant further genotype-phenotype correlations studies on individual drugs metabolized by the *CYP2C8* enzyme.

***CYP2C9* Genetic Polymorphism with Oral Squamous Cell Carcinoma**

There is increasing evidence for the role of polycyclic aromatic hydrocarbons and heterocyclic aromatic amines in carcinogenesis, including oral squamous cell carcinoma (OSCC). Several of these mutagenic substances are cytochrome (*CYP*)*2C9* enzyme substrates. In this study, Zulfiqar and colleagues examined the association of *CYP2C9*2* and **3* genetic polymorphisms in 58 OSCC patients and 174 healthy, age and sex-matched controls. Their results show that wild-type genotype (*CYP2C9*1*1*) was observed at 83%, **1*3* at 8%, **1*2* at 5%, **2*2* at 2%, and **2*3* at 2% in combined case and control groups. On further analysis, however, their results did not reveal an association of these variants with OSCC samples (Odds ratio: 0.608, 95% Confidence Interval: 0.289 - 1.281, p-value: 0.190). The authors recommend larger studies to confirm or refute

these results. However, in their study cohort, they argue, that a lack of association of *CYP2C9*2* and **3* polymorphisms with OSCC is observed.

Pharmacogenetics of Venlafaxine in Depression

Response to antidepressant drugs varies considerably and a significant portion of this variation stems from genetics. Venlafaxine (VEN) is one of the most prescribed antidepressant drugs in the world. There is substantial interindividual variation in therapeutic response and adverse effects of VEN. Several studies suggest the importance of single nucleotide polymorphisms (SNPs) in determining the therapeutic outcome of VEN. In this review article paper, Ullah and colleagues reviewed several studies showing significant associations with VEN therapeutic efficacy and/or adverse effects. They propose that pharmacogenetic knowledge should be incorporated in decisions regarding VEN treatment outcomes and adverse effect management. They, however, also recommend additional, larger pharmacogenetic studies with VEN to reproduce already produced data and to incorporate additional variables. They further discuss that the issue of personalized medicine could be a key driver for providing the highest possible quality of treatment to patients. They argue that bringing the pharmacogenomics profile of patients on depression therapy with VEN into consideration will help patients gain maximum benefits from available treatments in terms of safety, therapeutic optimization, and minimizing adverse effects.

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