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Editorial

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Defining the Role of Single Nucleotide Polymorphic (SNP) in Drug Development and Toxicity

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The sequencing of human genome has lead to define the variations among humans, which is quite astonishing. Before sequencing of human genome, variant among genes were observed as mutations. It was known that mutations in key regulatory and functional genes cause diseases. With the advent of single nucleotide polymorphism (SNP) among genes, which is believed to be present in every 1.0 kb in human genome ($3X10^6$ SNP in $3X10^9$ bps genome), has changed the very paradigm of disease progression, drug action and toxicity. Before sequencing of the human genome, such variations were thought far less to exist. Although SNPs are found every 1.0 kb sequence but they are not uniformly distributed. In addition to be present in regulatory sequences, SNPs are found in introns and intergenic sequences. Determining the effects of these variants on biological process is a daunting task. Utilizing the modern molecular biological techniques, the role(s) of the regulatory SNPs has been defined for many genes. However, the structural SNPs, which are part of the coding sequences of genes, have been difficult to define. Models to describe the messenger RNA stability (Mfold analysis) due to such SNPs are welcome. However, such a correlation in terms of end product as protein is still confusing. Attempts have been made to decipher the gene function of individual SNP variant what is referred as "allelic expression variant" of haplotype as compared to wild type. In this context it is noteworthy that allelic variants have been found to possess varying activities.

In addition to SNPs, multinucleotide polymorphism in terms of double nucleotide polymorphism (DNPs) and triple nucleotide polymorphism (TNPs) have also been observed in human genome. Frequency of DNPs and TNPs are far less as compared to SNPs. Comparison of DNPs and TNPs from Chinese and Venter data demonstrate that a total of 164 in Chinese and 127 in Venter as DNPs were found. A far less TNPs (3 with Chinese and 6 with Venter genome) were found. It is predicted that SNPs leads to nonsynonimous substitution with 50-50 occurrence while DNPs cause higher nonsynonimous substitutions. DNPs are predicted to convert stop codon into read through codon but both Chinese and Venture genome did not possess any read through DNPs [1].

Responses to drug action and therapies, and interactions with environmental factors and its outcome have been linked to SNPs. For example, one of the most common agents for human use is ethanol. Both binge and chronic ethanol usage is responsible for hepatosteatosis, steatohepatitis (alcohol liver disease), followed by fibrosis and cirrhosis. Not all alcoholics manifest alcohol toxicity, only 20-30% drinkers develop steatohepatitis while less than 10% progress to cirrhosis [2]. It is thought that variations among various genes ultimately determine the fate of liver towards steatohepatitis, fibrosis and cirrhosis (alcohol liver disease (ALD)) after ethanol. Variation among wide variety of genes from alcohol metabolizing enzymes, genes related to resolve oxidative stress, genes of cytokines and receptors, growth factor TGF-β1, matrix metalloproteinase 3 and genes associated with steatosis have been implicated in the ALD. A variant of patatin-like phospholipase 3 (PNPLA3, rs 738409) has been found to affect steatosis, increased inflammation in liver and fibrosis in nonalcoholic fatty liver disease. Identification of these genes involved genetic-case controlled studies while comparing allelic or genotype frequencies (SNPs) in between individuals with ALD and healthy controls with alcohol usage [3]. The molecular mechanism of these gene variants towards pathophysiology and progression of ALD after chronic ethanol intake is not defined [4]. In order to define the regulatory SNP, often, transgenic models are employed. With greater understanding of susceptibility of individuals towards diseases and treatment outcome due to SNPs, special emphasis should be placed on defining the role of SNPs of genes involved in disease process and drug therapy outcome.

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