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LETTER TO THE EDITOR

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Functional Genetic Polymorphisms from Phase-II Drug Metabolizing Enzymes

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We read the article by Murali et al. in the original articles section with great interest. The authors observed significant association of genetic variants from phase-II drug metabolizing enzyme (DME) with phenytoin(PHT)-induced adverse drug reactions [ADRs; Ref. 1].

There are known to be substantial inter-individual variations in predisposition to these ADRs specifically with first-generation antiepileptic drugs (AEDs) including PHT in patients receiving similar dose regimen. In the absence of any other extrinsic causal factor, such variability may be attributed to differential genetic variability in expression and activity of DMEs. Working in the field of epilepsy pharmacogenomics, understanding the distribution of genetic variants from DMEs in predicting response to first-generation AEDs is central to our interests. Although, present article has put forward interesting findings, we wish to point out some shortcomings in the Discussion section which should be clarified with respect to the existence of genotypic data of phase-II DMEs from a similar ethnic background. In the Discussion section, author wrote, *"The allele and genotypic frequency of genes encoding phase II enzymes have been reported for a number of populations and revealed a wide ethnical variation. However, there are no data available about the polymorphisms of phase II drug metabolizing enzymes in the North Indian population."*

However, we have already reported distribution of phase-II DMEs variants namely *UGT2B7*2* (rs7439366; c.801C>T) and *UGT1A1*6* (rs4148323; c.211G>A) in 492 north Indian individuals. [2]. Although UGT2B7 variant may result in its decreased activity, UGT1A1 variant on other hand is expected to increase the rate of metabolism of its substrates. However, of both the variants, only *UGT2B7*2* was observed to be highly polymorphic with a minor allele frequency (MAF) greater than 0.35 in both healthy individuals as well as epilepsy patients. Further, nonpolymorphic distribution (MAF < 0.05) of *UGT1A1*6* lays the need for exploring other functional variants of clinical significance including those from other phase-II DMEs of PHT.

The number of studies reporting role of functional genetic variants in drug response is rapidly rising and may lead to better accountability for variability observed in efficacy as well as toxicity of PHT. In this regard, Murali et al. in the present article has uncovered role of genetic variants from gene encoding Human N-acetyltransferase 2 (NAT2) for their role in influencing phase-II metabolism of PHT. NAT2 is known to catalyze biotransformation of aryl and heterocyclic amines with a role in metabolism of several drugs [3]. It is highly polymorphic and several genetic variants have been demonstrated for their role in reducing the rate of acetylation of its substrates. Compared to wild type allele *NAT2*4*, individuals harboring mutant alleles *NAT2*5A* (*rs1799929; 481C>T; Leu161Leu)*, *NAT2*5C* (rs1208; *803A>G;* Lys268Arg), *NAT2*6* (*rs1799930, 590G>A, Arg197Glu,)* and *NAT2*7* (*rs1799931; 857G>A; Gly286Glu)* are known to exhibit slow metabolizer or acetylator phenotype. Distribution of functional variants from several other genes encoding phase-II DMEs including *NAT2* have been reported in Indian population by several groups including Indian Genome Variation (IGVDB) consortium [4,5]. IGVDB reported distribution data of several *NAT2* SNPs mainly *NAT2 *5C* and *NAT2*6* in 1871 individuals from diverse 55 endogamous Indian populations including several north Indian subpopulations. Each variant was observed to be highly polymorphic with MAF ranging from 0.24 to 0.52 across 17 diverse north Indian subpopulations [4]. The highly

polymorphic distribution of *NAT2* alleles in north Indian population were in conformance with a reported publishing frequencies of 0.37 and 0.25 of *NAT2*5* and *NAT2*6*, respectively, in addition to *NAT2*7* observed in a small proportion (freq. = 0.07) of 147 healthy controls from north India [5]. In addition, there is also a considerable heterogeneity in genetic profile of individuals both ethnically as well as geographically. Although interethnic variability in frequency of several genetic variants is now well-established, however, little is known about influence of phase II DMEs including *NAT2* on pharmacokinetics of AEDs. An understanding of ethnically determined altered activity of *NAT2* variants may help us to lower the risk of serious side-effects attributed to increased serum level of AEDs by changing regimen of AEDs prescribed to individuals across different geographical locations.

The *NAT2*5A* (freq = 0.33) was observed to be the most common variant in the present study by Murali et al. from North India which was also reflected in its most significant association with PHT induced toxicity ($P = 0.006$; OR = 2.29 [1.20–4.41]). Although role of NATs in phase-II metabolism of PHT needs to be demonstrated by in vitro studies. Nevertheless, if validated, *NAT2*5* genotyping may help in safe optimization of PHT therapy. Additional studies exploring gene–gene interactions with other DMEs, drug transporters and drug targets should be conducted to estimate the overall involvement of *NAT2* genetic variants in influencing serum PHT levels [6]. In summary, although data on several functional variants is now available for different ethnic groups, however, realization of its clinical significance would also require considerably large sample size, clearly defined endophenotypes, accurate statistical interpretations and characterization of respective drug substrates [7].

In conclusion, the article appears to be well-written providing a novel hypothesis implicating role of acetylation in clearance of PHT. However, some phrases need to be re-examined for veracity, acknowledging the achievements accomplished by other groups working with a common goal. In the interests of avoidance of misinterpretation of facts introduced into the literature by article published in such a prestigious journal, we are herein publishing our Letter, based on the original version communicated to the editor.

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