RESPONSE TO COMMENTS ON HOSKINS ET AL. [(2005) DRUG METAB DISPOS 33:1564–1565]

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We had described the presence of a CYP2D7 splice variant in human brain that contained the partial inclusion of 57 bp of intron 6 (Pai et al., 2004). The presence of a 138delT frameshift mutation generates an open reading frame that encodes the protein with alternate functionality with respect to the metabolism of codeine. We identified this variant but did not attempt to quantitate the relative amount of this variant vis-à-vis CYP2D6 to determine whether it was a major splice variant. In the recent paper, Gaedigk et al. (2005) amplified the complete ORF of CYP2D6 and 2D7 using brain and liver cDNA from a 12-year-old Caucasian female. The major goal was to determine whether the functional CYP2D7 protein with partial inclusion of intron 6 was present in these samples, as described earlier (Pai et al., 2004). Although the authors were able to detect several alternate spliced variants (some of which were present exclusively in brain), they were unable to detect a functional CYP2D7 in their samples. It was then concluded that the functional CYP2D7 protein is likely to be a low frequency event and thus have limited clinical importance. We screened a human brain cortex cDNA library using a fragment of cDNA of CYP2D6 (exons 6–9) and isolated a clone containing a complete ORF, which we identified as a functional CYP2D7 having a frameshift mutation 138delT (that converted the pseudogene to a functional gene) and the partial inclusion of 57 bp of intron 6. We further validated this observation by demonstrating the expression of the functional protein, in vitro, in cell lines and the presence of the protein in human brain autopsy tissue. This has been contested by Gaedigk et al. (2005), since they were unable to detect the 138delT mutation in the samples genotyped by them.

As mentioned by us (Pai and Ravindranath, 2005) and Hoskins et al. (2005), genotyping of CYP2D alleles is fraught with problems due to the high degree of homology among the three members of this family (CYP2D6, 2D7, and 2D8). Careful genotyping to separate CYP2D6 and CYP2D7 and CYP2D8 alleles (138delT and 1130 G>C) is currently being carried out in our laboratory.

We would like to reiterate that unique P450 enzymes generated by alternate splicing may represent a source of novel biotransformation pathways, and we have recently reported the presence of an alternate spliced variant of CYP1A1 that has deletion of 87 bp of exon-6 (Chinta et al., 2005). The presence of such an alternate spliced P450 enzyme adds a new dimension to metabolism of drugs at the site of action, and their functional significance cannot be overlooked. There is a need to examine the functional significance and genotypic segregation of these alternate spliced enzymes across different ethnic groups in greater detail.

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ABBREVIATIONS: ORF, open reading frame; bp, base pair(s); P450, cytochrome P450.