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Characterization of CYP2A13*2, a variant cytochrome P450 allele associated with decreased incidences of lung adenocarcinoma in smokers

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CYP2A13.1 has high efficiencies in metabolically activating tobacco-specific nitrosamines. CYP2A13.2 has two sequence variations, Arg25Gln and Arg257Cys. We had previously found that the Arg257Cys change leads to decreases in CYP2A13 activity. In this study, we compared the activities of heterologously expressed CYP2A13.1 and CYP2A13.2 proteins using a number of known CYP2A13.1 substrates, including the tobacco-specific procarcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Our results indicate that CYP2A13.2 is only slightly less active than CYP2A13.1 with all substrates tested. We also found that the *2 allele is associated with a slightly lower allelic expression than that of the *1 allele, and that this decrease in expression may be due to a deletion in the 5'-flanking region of CYP2A13*2. Consistent with the differing allelic expression of the *1 and *2 alleles, total CYP2A13 mRNA levels in *1/*2 lung samples appeared to be lower than those in *1/*1 samples, although large inter-sample variations made it difficult to demonstrate statistical significance of the difference. These findings suggest that the reported association of the *2 allele with decreased incidences of lung adenocarcinoma in smokers may not be solely due to a decrease in CYP2A13 function; other genetic variations in linkage disequilibrium with the *2 allele might also be involved. (Supported in part by NIH grant CA092596)