

#

EHT

Judging Dept.

Hong Wu

Student

EHT

2

Xinxin Ding

Dept or Program Years in program

Mentor

Mechanisms For The Decreased Expression Of The Cyp2a13 7520c>g Variant Allele

Author (s)

Hong Wu, Xiuling Zhang, Guoyu Ling, Jaime D'Agostino, and Xinxin Ding

Our aim was to identify genetic polymorphisms and epigenetic factors that influence CYP2A13 expression. CYP2A13, expressed mainly in the respiratory tract, is highly efficient in the metabolic activation of tobacco-specific nitrosamines. Large interindividual differences exist in the expression of CYP2A13, which likely contribute to the differing susceptibility to lung cancer among smokers. A common 7520C>G variation in CYP2A13 was recently found to be associated with decreased allelic expression in human adult and fetal lung. In vitro data indicated that this SNP, located in the 3'-untranslated region, does not cause changes in the stability of the CYP2A13 transcript. In contrast, the decreased CYP2A13 expression appeared to be manifested at the transcriptional level. Thus, the 7520C>G change is probably a marker, rather than the cause, of the decreased CYP2A13 allelic expression. The 7520C>G variation is associated with other SNPs in the 5'-flanking region. Further sequence analysis of 5'-intergenic region of 7520C/G heterozygotes identified additional SNPs, some of which are expected to affect CYP2A13 transcription. In addition, we determined the possible roles of DNA methylation in the decreased expression of the 7520G allele. A CpG site, at -1479, was identified to be associated with 7520G. This allele-specific CpG site was for the most part methylated in human adult and fetal lung samples, suggesting that DNA methylation might be involved in the differential expression of the 7520C/G alleles. Our findings provide the basis for further studies of the mechanisms of regulation of CYP2A13 expression, and for identification of genetic markers for lung adenocarcinoma susceptibility. (Supported in part by NIH grant CA092596)