Effect of GSTM2-5 polymorphisms in relation to tobacco smoke exposures on lung function growth: a birth cohort study.

BMC Pulm Med. 2013 Sep 3;13(1):56. [Epub ahead of print]

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Abstract

BACKGROUND:
Genetic variation within GSTM2-5 genes may interfere with detoxification of environmental compounds, thereby having a detrimental effect on lung function following exposures such as tobacco smoke. We aim to investigate the influence of variants and associated methylation in the GSTM gene cluster with changes in lung function growth during adolescence.

METHODS:
Growth in forced expiratory volume (FEV1), forced vital capacity (FVC), and change in FEV1/FVC ratio measures were obtained from children in the Isle of Wight birth cohort at ages 10 and 18. Illumina GoldenGate assays were used to genotype 10 tagging polymorphisms from GSTM2 (rs574344 and rs12024479), GSTM3 (rs1537236, rs7483, and rs10735234), GSTM4 (rs668413, rs560018, and rs506008), and GSTM5 (rs929166 and rs11807) genes. Diplotypes were generated in the software Phase 3.0.2. DNA methylation was measured in over 450,000 CpG sites using the Infinium HumanMethylation450 BeadChip (Illumina 450K) in a subsample of 245 18-year olds from the Isle of Wight birth cohort. Gender, age, in utero smoke exposure, secondhand smoke exposure (SHS), and current smoking status were assessed via questionnaire; smoke exposures were validated with urine cotinine. We used linear mixed models to estimate the effect of GSTM diplotypes on lung function across time and examine interactions with tobacco smoke.

RESULTS:
1,121 (77%) out of 1,456 children had information on lung function at ages 10 or 18. After adjustment for false discovery rate, one diplotype in GSTM3 had a detrimental effect on changes in FEV1 (p=0.03), and another diplotype in GSTM3 reduced FVC (p=0.02) over time. No significant interactions with smoking were identified. SHS significantly modified the relationship between diplotypes and methylation levels in one GSTM2 CpG site; however, this site did not predict lung function outcomes at age 18. Joint effects of GSTM loci and CpG sites located within these loci on adolescent lung growth were detected.

CONCLUSIONS:
Diplotypes within GSTM2-5 genes are associated with lung function growth across adolescence, but do not appear to modify the effect of tobacco smoke exposures on adolescent lung growth. Interactions between DNA methylation and diplotypes should be taken into account to gain further understanding on lung function in adolescence.

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