

Genomic interactions with exposure to inhaled pollutants

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Exposure to inhaled pollutants occurs in various forms. Smokers intentionally inhale tobacco smoke, and others are exposed secondhand. Ambient air is a complex mix of particles and gases, few of which are routinely monitored. Workers in many occupations inhale toxicants at greater concentrations than the general population. These exposures pose potential risks for human health.

There has long been interest in how our genomes influence the respiratory and allergic health effects of inhaled pollutants (ie, gene-environment interactions). Most studies of gene-environment interaction have examined how variations in DNA sequences (typically single nucleotide polymorphisms) interact with exposure to influence disease risk. Many studies have examined candidate genes, primarily selected based on involvement in inflammation or oxidative stress pathways, and results have been mixed. Individual studies have generally been underpowered to investigate these interactions. Efforts to combine studies to increase sample size to investigate candidate genes have increased power, but few variants have been examined in this coordinated manner. A consortium of 6 European and North American birth cohorts (>15,000 children) found no interaction between traffic-related air pollution exposure and variants in genes *GSTP1*, *TNF*, *TLR2*, or *TLR4* for allergic rhinitis or sensitization.¹ However, other analyses suggested that children carrying specific *GSTP1* variants might constitute a susceptible population at increased risk of asthma associated with air pollution.² Evidence exists for interactions with air pollution exposure with

respect to asthma and allergic outcomes for genetic variation in *GSTM1*, but results are inconsistent.^{E1}

With the advent of genome-wide association approaches, a few studies have examined interactions with sequence variation in an agnostic manner, which can identify novel genes and pathways. However, very large sample sizes are needed to reliably identify interactions in genome-wide analyses. Incorporating environmental interactions in genome-wide analyses has been shown to facilitate discovery of novel loci that would otherwise be missed with comparable sample sizes when these interactions are ignored. The first genome-wide study of respiratory or allergic outcomes to consider environmental interactions examined exposure to cigarette smoking in relation to pulmonary function. By incorporating interaction with smoking, 3 novel loci were identified that were missed in traditional main-effect genome-wide association studies of comparable size.³ Among the identified genes, *DNER* and *SOX9* showed evidence of differential expression in human airway epithelium in smokers compared with nonsmokers, strengthening the findings.

This study was followed by a few that have examined genome-wide interaction with air pollution in relation to respiratory and allergic outcomes. By using coordinated land-use regression models to estimate individual air pollution exposure across birth cohort studies, evidence for interaction in relation to childhood asthma was identified and replicated for *ADCY2*, *B4GALT5*, and *DLG2*.⁴ Identified single nucleotide polymorphisms in *ADCY2* and *B4GALT5* influenced gene expression in blood and lung tissue, respectively, and air pollution was also associated with differential *DLG2* methylation and expression. There are few studies of modest size of genome-wide interaction with occupational exposures, but a small number of replicable interactions with respiratory or allergic phenotypes have been identified.^{E2}

Gene-environment interactions are not limited to those involving DNA sequence variation. Environmental exposures also interact with the genome through epigenetic modifications, changes to DNA that do not alter the sequence. The best studied epigenetic modification in human subjects is methylation, the addition of a methyl group, generally to cytosines adjacent to guanines. The availability of stable platforms to measure methylation with reasonable genome-wide coverage has facilitated studies of environmental epigenetic effects (as noted for *DLG2* above⁴). Epigenome-wide association studies (EWASs) have shown that cigarette smoking is associated with widespread and highly reproducible changes in methylation across the genome, both for newborns whose mothers smoked during pregnancy⁵ and for adults from personal smoking.⁶ Although methylation signals in the much smaller literature on ambient air pollution are less widespread and reproducible than those for smoking, in EWASs pollution exposure has also been associated with differences in methylation across the lifecourse.^{7,8} There are even fewer EWASs of occupational exposure, but some associations have been found. Much larger studies with coordinated

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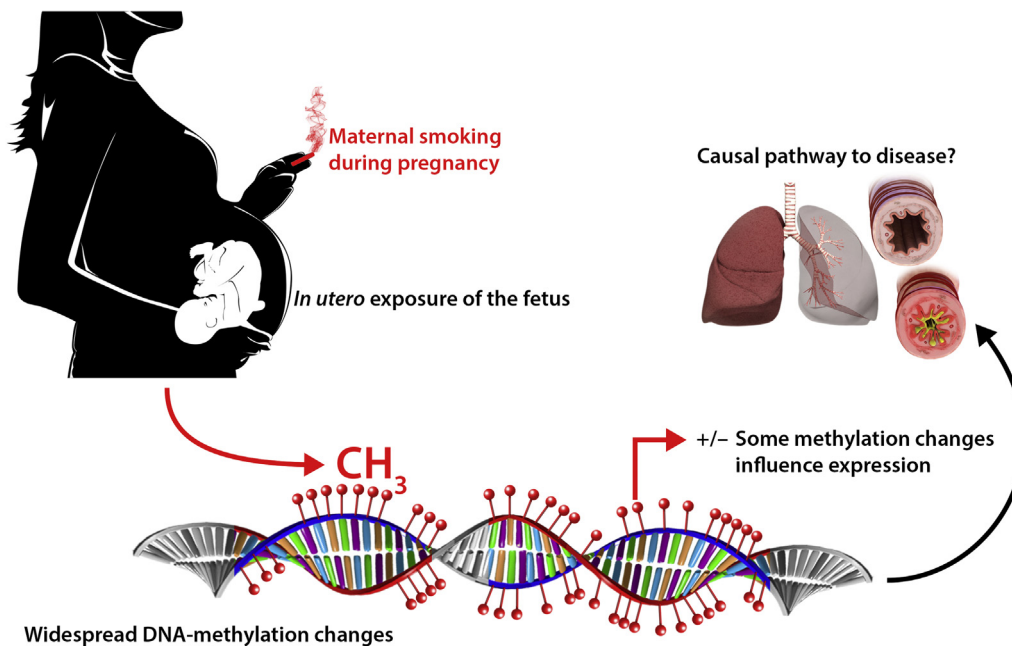


FIG 1. Maternal cigarette smoking during pregnancy exposes the fetus. This exposure is associated with widespread and highly reproducible DNA methylation changes in the blood of offspring at birth, and many of these changes persist into childhood. These have been shown to be excellent biomarkers of this *in utero* exposure. Some of these methylation changes in blood can also occur in other target tissues, such as the lung. DNA methylation changes can directly influence gene expression levels. However, it is not yet known whether some of the methylation changes are on the causal pathway from exposure to disease, here exemplified by asthma. Functional studies will be needed to firmly establish such causal relationships.

exposure assessment will be needed to characterize robust methylation signatures of ambient and occupational inhaled pollutants.

Recently, reproducible methylation differences at birth and in childhood have been identified for asthma.⁹ Exposure-related methylation changes are potential biologic mediators of respiratory health effects, including asthma. However, caution is required in interpretation of mediation analyses because these methylation changes can be excellent biomarkers of exposure, as has been shown for smoking.¹⁰ Furthermore, for ambient and occupational inhaled pollutants, exposure-related differential methylation might better reflect individual exposure, including the internal dose, than usual area-level exposure estimates. In these settings, and when the exposure is misclassified, as often occurs, analyses examining whether exposure-related methylation changes mediate health effects can provide false-positive evidence for mediation.¹⁰ Functional studies will likely be needed to establish whether methylation changes are indeed on the causal pathway between exposure and disease (Fig 1).

Negative health effects from environmental exposures, such as tobacco smoke or air pollutants, vary among subjects. Our genetic makeup might explain some of this heterogeneity. Although there are many suggestive gene-environment interactions in the literature from both candidate gene and genome-wide efforts, there are few, if any, robust findings across studies and populations. Although larger studies are needed to detect reproducible gene-environment interactions, some of the heterogeneity might reflect differences in exposure profiles or contextual factors, including coexposures, that vary across populations. Hence larger studies that also better characterize air pollution

exposures and the complex correlated coexposures in different populations will be needed to identify reproducible interactions. Furthermore, studies to date have looked at variants and exposures one by one. More sophisticated models that incorporate the complexity of exposure mixtures, multiple variants, and multiple types of genomic data (eg, epigenetic, genetic, and transcriptomic) will likely shed new light on this issue. Using genetic risk-score approaches might also increase power to discover environmental interactions, including enabling examination of multiple exposures.^{E3} Fortunately, ongoing initiatives around the world are attempting to understand the complex interplay between genes and the environment and should generate exciting new insights.

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