

A STATISTICAL FRAMEWORK FOR ENVIRONMENTAL EPIGENETICS

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Background and Aims: Several lines of evidence—experimental and environmental—suggest that epigenetic mechanisms such as DNA methylation may play a role in mediating exposure-response relationships, including possible transgenerational effects. For example, in the Southern California Children's Health Study (CHS), we have previously reported an effect of grandmaternal smoking during pregnancy on asthma risk in the second generation, which could be mediated epigenetically.

Methods: We propose a latent variable modeling framework for investigating such phenomena, fitted using Markov chain Monte Carlo methods. The model is specified in terms of components for (1) the risk of disease given exposure, genotype, and methylation, (2) the level of acquired methylation given exposure and inherited methylation, (3) the inherited methylation given parental methylation, and (4) the error structure of methylation measurements.

Results: In simulation studies, we have shown that all parameters of the model are estimable, provided the model is correctly specified. In a sample size of 1000 3-generation pedigrees, a RR of 3.2 for the mediating effect of methylation on exposure-response relationships is detectable with 90% power (comparing 0 vs. 100% methylation; estimated mean differences in methylation were 24% by subjects' own exposure, 12% per exposed parent, and 7% per exposed grandparent). Coefficients of variation for other parameter estimates were 1.8% for the exposure effect and 3.2% for the methylation effect in submodel (2), and 6.7% for the transmission effect in submodel (3).

Conclusions: We have previously shown associations of PM and ozone with DNA methylation of inducible nitric oxide synthase (iNOS), modified by a common promoter haplotype in the gene *NOS2A*, and a 3-way interaction between PM exposure, *NOS2A*, and iNOS methylation on exhaled NO measurements. This presentation will provide a unifying framework for synthesizing such observations.