Gene variants may determine lung function and susceptibility to maternal smoking

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A tiny variation within a single gene can determine not only how quickly and well lungs grow and function in children and adolescents, but how susceptible those children will be to exposure to second-hand tobacco smoke, even in utero, according to researchers from the University of Southern California.

"Many factors can affect lung function and growth, including genetic variation and environmental exposures such as tobacco smoke and air pollutants," said Carrie Breton, Sc.D., lead author of the study conducted at the University of Southern California. "We wanted to determine whether specific gene variations would have measurable and predictable effects on lung function growth and susceptibility to environmental insults. We looked at a class of genes known to be involved in antioxidant defense, the glutathione-s transferase (GST) genes. Overall, we found that variation in several of the GST genes was important. This was particularly true for children of mothers who had smoked during pregnancy."

The researchers analyzed eight years' worth of lung function metrics and genotyping data from more than 2,100 children from two cohorts of fourth-graders. The lung function measurements used were maximal mid expiratory flow rate (MMEF), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1).

"FEV1 is a measure of large airways, FVC of total lung volume and MMEF of smaller airways, so they measure slightly different things and

we wouldn't necessarily expect to see all outcomes behaving the same," said Dr. Breton.

They found that for three of the specific haplotypes (patterns of genetic variation within genes) they investigated, each had a significant effect on lung function.

For one gene, GSTM2, two variant patterns were analyzed. These patterns occurred in 30-35 percent of the white population. One was found to promote stronger lung function, while the other variant was correlated with poorer lung function and greater susceptibility to damage caused by maternal cigarette smoking during pregnancy. Moreover, the reduction in lung function was greater in children who had two copies of the variant pattern that reduced lung function, compared to children with only one copy.

For a relatively rarer haplotype in GSTM3, occurring in only 6-8 percent of the white population, they found a strong negative effect on MMEF.

Finally, another haplotype in GSTM4, occurring in 16-22% of the population, showed significantly decreased rates of growth for FEV1, FVC and MMEF. Like GSTM2, the reduction in lung function was greatest in children who had two copies of the variant pattern that reduced lung function.

The researchers suggest that the gene variants may not alter the development of the lung, but its ability to defend itself against damage caused by free radicals. "The GST genes are important to the detoxification of reactive oxygen species, including carcinogens and environmental exposures, such as cigarette smoke. We speculate that the patterns of genetic variation we investigated may alter this process, thereby reducing the lung's ability to detoxify harmful agents and causing a cascade of other events that promote inflammation, bronchial

constriction, airway hyperresponsiveness and asthma-like symptoms," said Dr. Breton.

"The next step would be to investigate how these genes interact with one another to jointly effect lung development. Future studies should also investigate the timing and quantity of tobacco smoke exposure during pregnancy in combination with variation in these genes to further understand how they jointly affect fetal lung development," said Dr. Breton.

Source: American Thoracic Society (news : web)