Asthma is the most common chronic illness in childhood and it is widely recognized that there is a major genetic component to asthma susceptibility. Previous studies of the entire genome have identified common variants in more than 15 genes significantly associated with asthma or related problems. While the majority of these findings have been observed in multiple studies they account for only a small portion of the genetic contribution to asthma. Our aim is to now identify new genetic variants which may be substantially influencing the development of asthma.

Here, we suggest a model in which both rare and common genetic variants are contributing to asthma. This project will use modern DNA sequencing technology to identify rare variants traveling with asthma within families. We are taking advantage of the family-based nature of several studies conducted at the Yale School of Public Health’s (YSPH) Center for Perinatal, Pediatric and Environmental Epidemiology (CPPEE) by selecting families based on information collected in these previous studies. For this project, we are re-contacting families with asthmatic children to collect blood for DNA, update the asthma phenotype information in the parents and children, and conduct family-based sequencing analyses.

Our goal is to identify rare genetic mutations that correlate with asthma. We will then look for clusters of mutations in the same gene(s) across the families in the study. This will hopefully provide new clues into the genetic nature of asthma.

Dr. Andrew DeWan, an assistant professor in the Department of Chronic Disease Epidemiology at YSPH, is the principal investigator on this project. This research is supported by NIH/NHBLI Grant #: 1R01HL116742-01.
Infants of Asthmatic Mothers (PRAM) study, led by Michael B. Bracken, the Susan Dwight Bliss Professor of Epidemiology. The study assessed the extent to which the well-documented increased risk of asthma to children of asthmatic mothers is due to genetic factors and how much is due to factors occurring in the intrauterine and perinatal period, specifically related to the mother's own asthma status.

A second technique used a novel approach to rank genes for asthma. The researchers systematically reviewed the published literature and identified genes previously reported to be associated with asthma. The top 50 genes were further tested for mutations in the PRAM subjects. One of these genes—RAD50—contained a mutation that was associated with an increased risk of asthma. This gene has previously been implicated in the control of inflammatory responses, suggesting that mutations to this region result in altered immune system functioning that may lead to a predisposition toward asthma.

Finally, the group replicated an association between asthma and missing genetic material in the T-cell receptor γ gene. They were able to demonstrate that this deletion was present in only a small proportion of the cells collected for DNA extraction. This is potentially significant because it suggests that this type of mutation is not inherited and therefore may be caused by environmental factors.

Taken together, these three genes highlight the complex nature of asthma and support the hypothesis that numerous factors play a role in determining whether or not a child will develop asthma.

Examples of PRAM In The Literature


CHAS Study continued...

Initial findings suggest that both high nitrogen dioxide concentrations as well as high mold concentrations in the home are risk factors for increased asthma symptoms during the first year of life.

This study is still producing valuable data, as work is ongoing in this dataset to examine the relationship between traffic-related pollutants and respiratory health. Stay tuned for more findings in the near future.

Examples of CHAS In The Literature


From all of us at the CPPEE, we thank you for your previous participation in one of our research studies. For more information on the FAstGen study, please see our webpage at: www.yale.edu/cppee/FAstGen.html