Genome sequencing identifies variants possibly linked to childhood asthma

The first comprehensive sequencing study of the protein coding regions of the genome in a family with both asthmatic and non-asthmatic members has identified several variants that may contribute to the potentially debilitating condition.

Scientists at the School of Public Health's Center for Perinatal, Pediatric and Environmental Epidemiology used a technique that sequenced only the small fraction of the genome that codes for proteins and identified tens of thousands of variants in each subject's genome. To understand if there were genetic variants found only within this family that contributed to asthma, the investigators focused on novel variants not present in databases containing sequencing data compiled from more than 1000 subjects, leaving them with hundreds of family-specific variants.

These variants were then examined to see which ones tracked with asthma in this family and 10 of them tracked perfectly. The investigators were then able to narrow this list down to four based on how likely each specific variation would result in a change in the protein for which it coded. Of these, three genes- PDE4DIP, CBLB and KALRN-are of increased interest due to their potential relationship to asthma.

The research comes from the Perinatal Risk of Asthma in Infants of Asthmatic Mothers study, led by Michael B. Bracken, Susan Dwight Bliss Professor of Epidemiology. Andrew DeWan, assistant professor in the Department of Chronic Disease Epidemiology, led the sequencing effort.

The researchers are seeking to determine 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.

While the study does not provide definitive proof that any of these variants contribute to asthma, the work suggests that careful filtering of variants can provide genes for further investigation. Future work will focus on whether or not any of these genes contain family-specific variants tracking with asthma in additional families. If so, it would provide support for the hypothesis that extremely rare variants in a handful to genes may be contributing to asthma, in concert with common

variants in several genes.

Previous work from the group has identified common variants in two genes that may be contributing to asthma susceptibility, as well as a rare genetic deletion. Taken together, the research highlights the complex nature of asthma and supports the hypothesis that numerous genetic factors play a role in determining whether or not a child will develop asthma.

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Source: Yale University