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Discovers new asthma gene in African-Americans, replicates four others

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A new national collaboration of asthma genetics researchers has revealed a novel gene associated with the disease in African-Americans, according to a new scientific report.

By pooling data from nine independent research groups looking for genes associated with asthma, the newly-created EVE Consortium identified a novel gene association specific to populations of African descent. In addition, the new study confirmed the significance of four gene associations recently reported by a European asthma genetics study.

The findings, published in Nature Genetics, are a promising first step for a new national scientific effort to hunt for the genetic roots of asthma.

"We now have a really good handle on at least five genes that anyone would be comfortable saying are asthma risk loci," said Carole Ober, PhD, co-chair of the EVE Consortium, senior author of the study, and Blum-Riese Professor of human genetics and obstetrics/gynecology at the University of Chicago. "I think it's an exciting time in asthma genetics."

"Asthma rates have been on the rise in recent years, with the greatest rise among African Americans," said Susan B. Shurin, M.D., acting director of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, which co-funded the study. "Understanding these genetic links is an important first step towards our goal of relieving the increased burden of asthma in this population."

Genome-wide association studies, or GWAS, are a popular method used by geneticists to find genetic variants associated with elevated risk for a particular disease. Genetic data from a group of patients with the target disease are compared to data from a control group without the disease, and researchers look for variants that appear significantly more often in the disease group.

But the ability, or power, of GWAS to find disease-associated variants is dependent on the number of participants enrolled in a study. To find variants involved in complex diseases, thousands of participants may be necessary--a logistical and financial demand often beyond the capacity of an individual research team.

"It has become clear to geneticists studying nearly every common disease that GWAS are often under-powered, and unless you pull together many researchers doing the same thing you're just not going to have the power to find genes," said Dan Nicolae, PhD, associate professor of medicine, statistics, and human genetics at University of Chicago, co-chair of the consortium and another senior author of the study. "That was the motivation for nine groups of investigators coming together to form EVE."

Spurred by support from the NHLBI and the National Institutes of Health, research groups from the nine institutions discussed pooling their GWAS data to create a larger, shared dataset. But it wasn't until they received a $5.6 million grant from the American Recovery and Reinvestment Act of 2009 that the EVE Consortium could officially form and hire the necessary personnel to execute the collaboration.

"It would never have been possible without the grant, this was a huge amount of work," said Nicolae, "The key was the ARRA funding that allowed us to move it faster."

In addition to increased power to find variants associated with asthma risk, the EVE dataset comprised a more ethnically diverse population than similar efforts in other countries by including European Americans, African Americans/African Caribbeans, and Latinos.

"We believe that this heterogeneity is important," Ober said. "There are differences in asthma prevalence in these three groups, so it's important to understand whether these are caused by environmental exposures or by differences in genetic risk factors."

The diverse sample enabled the researchers to discover a novel genetic association with asthma observed exclusively in African-Americans and African-Caribbeans. The polymorphism, located in a gene called PYHIN1, was not present in European-Americans and may be the first asthma susceptibility gene variant specific to populations of African descent.

Four more gene variants were found significant for asthma risk by the meta-analysis: the 17q21 locus, and IL1RL1, TSLP, and IL33 genes. All four of these sites were concurrently identified in a separate dataset by the GABRIEL Study of more than 40,000 European asthma cases published last year in the New England Journal of Medicine. Confirming these associations in the more diverse EVE population offers additional evidence that the gene variants are significant across ethnicities, the researchers reported.

"We were able to show that almost all of the genes other than PYHIN1 are trans-ethnic and important in all of the groups," Ober said.

The Nature Genetics study is only the first fruit of the EVE Consortium mission to understand the genetics of asthma. A deeper meta-analysis looking at a longer list of gene variants is currently underway, and individual groups within the consortium are using the pooled dataset to

answer additional questions. Topics of interest include gene-environment interactions, genetic associations with asthma-associated phenotypes such as allergies and lung function, and the role of tissue-specific gene expression.

"What you see here in this paper is only the beginning," Nicolae said. "The foundation was to make people work together, share the data, and share research ideas, and that will generate a lot of research down the road."

More information: "Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations," *Nature Genetics* DOI: 10.1038/ng.888

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