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A novel gene found for childhood-onset asthma

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Pediatric researchers have identified a novel gene involved in childhood asthma, in one of the largest gene studies to date of the common respiratory disease. Because the gene, called DENND1B, affects cells and signaling molecules thought to be instrumental in the immune system overreaction that occurs in asthma, the discovery may have singled out an important target for new treatments.

A research team led by Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia, implicated a location on chromosome 1 associated with moderate-to-severe, childhood-onset asthma. The study appeared today on the Online First website of the New England Journal of Medicine. It will be published in the journal's print issue on January 7, 2010.

Asthma is a complex disease, in which a large number of genes, as yet mostly undiscovered, are thought to interact with each other and with environmental factors to produce asthma's characteristic wheezing, coughing and shortness of breath. It also is highly heterogeneous, manifesting differently in different patients, and appears to operate differently in childhood-onset asthma compared to adult-onset asthma.

Previously, researchers had identified only one other asthma-susceptibility gene using a genome-wide association study (GWAS), in which automated genotyping tools scan the entire human genome seeking gene variants that contribute to disease risk. That gene, ORMDL3, on chromosome 17, was discovered in 2007 by U.K.

researcher William O.C. Cookson, M.D., who collaborated with Hakonarson in the current study.

In this current study, Hakonarson's team performed GWAS on a sample of 793 white North American children with persistent asthma, compared to control group of 1,988 children. They replicated the study in a separate group of 2,400 European subjects and controls, then did further analyses on a third group of 3,700 African American children.

"By analyzing a large cohort of children with moderate to severe asthma, all of whom require controller medications on a regular basis, we managed to enrich our study for genetic signals and achieve sufficient statistical power to uncover and replicate a novel asthma gene," said Hakonarson. In addition to observing the previous results for chromosome 17, his group found a novel location on chromosome 1q31, with eight single nucleotide polymorphisms (SNPs) associating robustly with asthma. A SNP (pronounced "snip") is a change to a single chemical base along the DNA helix. Unlike other studies, here the researchers found the same gene for asthma susceptibility in children of both European and African-American ancestries.

Within this region on chromosome 1q31 the gene with an apparent role in asthma is DENND1B, already suspected as a player in the body's immune response. DENND1B expresses a protein of the same name, which is active in particular types of dendritic cells and specific T lymphocytes, including natural killer cells. Both of these immune cell subtypes form cross-talks between them (commonly referred to as the antigen presenting synapse) and regulate how the body responds to foreign material such as viruses, bacteria and allergens.

"We now know that the DENND1B gene and its protein are involved in the release of cytokines, which are signaling molecules that in this case tell the body how it should respond to foreign particles," said

Hakonarson, who is a pulmonologist. "Many of these particles are well-known triggers of asthma. In asthma, patients have an inappropriate immune response in which they develop airway inflammation and overreaction of the airway muscle cells, referred to as airway hyperresponsiveness. The gene mutations in DENND1B appear to lead to overproduction of cytokines that subsequently drive this oversensitive response in asthma patients. "

By identifying an asthma susceptibility gene with a compelling link to the pathobiology of asthma, says Hakonarson, his team may also have pinpointed a tempting therapeutic target, if researchers can develop drugs to contain this signaling pathway. "Because this gene seems to regulate many different cytokines, intervening in this pathway has great potential for treating asthma," he added. "Other asthma-related genes remain to be discovered, but finding a way to target this common gene variant could benefit large numbers of children."

Provided by Children's Hospital of Philadelphia

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