



## News Release

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### **Study proves genetic variations influence cystic fibrosis' severity**

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UNC News Services

**CHAPEL HILL**—Subtle differences in other genes—besides the defective gene known to cause the illness cystic fibrosis (CF)—can significantly modify the inherited disease's severity, a large new multi-center national study has concluded.

The study, led by University of North Carolina at Chapel Hill and Case Western Reserve University researchers, for the first time shows that particular versions of the transforming growth factor beta 1 (TGFB1) gene are largely responsible for how badly the illness affects patients' lungs. A report on the findings appears in the Oct. 6 issue of the *New England Journal of Medicine*.

“As this gene is one of about 30,000 genes in our bodies, its identification as a modifier of the CF lung disease allows us a specific target to focus on for improving CF therapy,” said Dr. Mitchell L. Drumm, associate professor of pediatrics and genetics at Case. “As we better understand its function in lung disease, we hope it will allow us to design better and more specific therapies. Because other researchers have found a similar effect of this gene in asthma, the implications likely extend to other disorders affecting the lungs as well.”

More than 50 hospitals and medical centers and scores of physicians across the United States and Canada participated in the investigation, which was actually two closely related studies with separate groups of patients. Findings were essentially the same for both, according to principal investigator Dr. Michael R. Knowles, professor of medicine at the UNC School of Medicine.

“This study is especially important in the field of genetic modifiers, because we had enough patients—more than 1,300—and a robust study design to assure that our observation is likely correct,” Knowles said. “That is in contrast to much of the previous work in this area where the number of subjects was usually too small to be conclusive.

“The observation has tremendous implications about the future for prognosis and potential new therapies in CF,” he said. “We are on the verge in the next two or three years of being able to test for other such genetic variants across the entire human genome. Our hope is to be able to identify most of the important gene modifiers in CF so that they can be used for prognosis, the identification of novel therapeutic targets and perhaps even directing therapy in an individual patients toward different types of adverse gene modifiers.”

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Initially, the study involved 808 CF patients who had inherited an altered form of a gene known as delta F508 from both parents. The second study involved 498 people with the condition. By measuring the volume of air when patients' exhaled strongly into a machine, researchers determined how severe each subject's lung disease was.

Scientists then correlated patients' level of illness against various genetic mutations and found that variants of a gene known as TGFb1 were associated with worse disease. The findings appear to exonerate certain other previously suspected mutations.

Besides Drumm and Knowles, authors of the report include Drs. Fred A. Wright and Fei Zou, associate professor and assistant professor of biostatistics, respectively, at the UNC School of Public Health, and, at Case, Drs. Mark D. Schluchter and Michael Konstan, professors of pediatrics; and Dr. Katrina Goddard, associate professor of epidemiology and biostatistics. Thirteen other scientists and clinicians also contributed to the work and were listed as co-authors.

In an accompanying editorial, Drs. Christina K. Haston and Thomas J. Hudson of McGill University in Montreal praised the new study.

"There are many lessons about modifier genes to be extrapolated from this study, starting with recognition of the tremendous importance of the study design," Haston and Hudson wrote.

Among its strengths, they said, were its large size—which is essential for such studies if they are to be useful—that it focused on a single class of gene variation and that it took into account numerous possible confounders such as sex, other illnesses like asthmas, enrollment sites, associated diseases and infections.

"There are likely a number of gene modifiers in CF and other diseases, and this current paper describes one of the first robust examples," Knowles said. "Some CF patients may do worse because of 'severe inflammation' genes, whereas others may do worse because of differences in mucus genes. Still others might because of their growth and metabolism genes, etc... Thus, therapy might need to be targeted to a particular area or areas in individual patients. This is important not only for CF, but for other lung diseases as well because gene modifiers we discover in CF will be seen in other diseases, and there are already examples of that."

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