

Researchers uncover genes at fault for cystic fibrosis-related intestinal obstruction

April 23 2012

Researchers at Johns Hopkins have identified a gene that modifies the risk of newborns with cystic fibrosis (CF) developing neonatal intestinal obstruction, a potentially lethal complication of CF. Their findings, which appeared online March 15 in *PLoS Genetics*, along with the findings of their Toronto-based colleagues, published April 1 in *Nature Genetics*, may lead to a better understanding of how the intestines work and pave the way for identifying genes involved in secondary complications of other disorders.

Soon after birth, most babies excrete their first stool, a tar-like substance called meconium. But not babies with neonatal intestinal obstruction, or meconium ileus (MI), which affects 15 percent of newborns with CF and, rarely, newborns without CF. Their stool is different.

"It is abnormally viscous due to high [protein content](#) and low levels of hydration, and the child can't move it through the [intestine](#)," says Garry Cutting, M.D., professor of [pediatrics](#) at the Johns Hopkins McKusick-Nathans Institute of [Genetic Medicine](#).

The condition results in death if not treated by surgery or enema. But why some newborns with CF get it and others don't is not well understood. To better understand why this is so and to develop models for finding so-called modifier genes—genes that modify the effects of other genes—Cutting and his colleagues aimed to figure out which modifier genes contribute to the development of MI. (From their previous work, they already knew that modifier genes contribute to its

development.)

Working with Toronto-based collaborators, members of Cutting's team looked for gene variants that occur in CF patients with MI. They knew that CF is caused by disruption of the CFTR gene, which encodes for a cell membrane protein, so they thought that maybe the genes that alter CFTR's activity and cause MI might also encode for cell membrane proteins; after all, a cell membrane protein is more likely to interact with a nearby cell membrane protein than with a protein that's deep inside the cell. They tested DNA samples from 3,763 CF patients—611 who had had MI and 3152 who hadn't—to compare genes that encode for cell membrane proteins to those that encode for unrelated proteins. Three of the 155 genes tested that encode for [cell membrane](#) proteins correlated with risk for MI, compared with none of the 231 genes tested that encode for unrelated proteins.

"These genes have common variants that all of us happen to be carrying around," says Cutting, "and just by chance, if you have a child with CF, these common variants play a role in modifying risk for meconium ileus." The researchers wanted to look for additional gene variants associated with an increased risk for MI, using a different approach.

In an earlier study, Cutting's team had found a region of human chromosome 8 to be linked to MI. To pinpoint which gene within that region leads to the condition, the researchers analyzed the DNA of 133 families with at least two CF children, at least one of whom previously had MI. The DNA was tested to determine which parts of chromosome 8 parents had passed down to their children who had MI.

Using this approach, the researchers found variants of the methionine sulfoxide reductase (MSRA) gene—in this case, a particular combination of DNA alterations close to and within the gene—that appeared significantly more often in children who had MI. In an

unrelated CF patient population from Canada, they found evidence of the same link between MSRA and MI, which helped confirm their results.

While the researchers now knew that CF patients with a certain MSRA gene variant tended to have had MI as [newborns](#), they didn't yet know whether MSRA actually plays a role in MI and hence whether it is truly a modifier gene. To address this question, they turned to mice engineered to have CF that tend to die from intestinal obstruction and developed three genetically modified versions of these mice: one with both MSRA genes intact, one with only one intact, and one with none intact. The fewer the copies of intact MSRA genes, the more likely the mice were to survive. In other words, the loss of MSRA protected the mice from fatal intestinal obstruction.

Cutting and his colleagues don't know how exactly the loss of MSRA reduces risk for fatal [intestinal obstruction](#), but they suspect that MSRA's ability to alter the activity of specific intestinal enzymes may be the key. They suspect that with reduced levels of MSRA, the enzymes are free to do their job breaking down proteins that make up meconium so that meconium can pass through the intestines and be evacuated normally at birth.

The researchers' work on MSRA could shed light on how meconium normally gets broken down in the intestines. Moreover, use of the techniques pioneered by Cutting and his colleagues may lead to identification of modifier [genes](#) that play roles in other complications of CF, like lung function, and in other diseases caused by a single gene, like Huntington's disease.

Provided by Johns Hopkins Medical Institutions

Citation: Researchers uncover genes at fault for cystic fibrosis-related intestinal obstruction (2012, April 23) retrieved 23 April 2024 from <https://medicalxpress.com/news/2012-04-uncover-genes-fault-cystic-fibrosis-related.html>

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