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Scientists Identify New Genetic Culprit for Intellectual Disability

Howard Hughes Medical Institute researchers and their colleagues in Israel have identified a genetic mutation that plays a role in intellectual disability. The mutation, which was identified in three Arab-Israeli sisters with severe mental retardation, is one of only a handful of genes outside the X chromosome that have been linked to intellectual disability.

The international research team linked the girls' intellectual disability to a change in a single "letter," or base pair, in the *TRAPPC9* gene. Both copies of the gene must be faulty to cause the disability, and the mutation's effects occur only in the brain, the researchers say. The findings are published in the December 11, 2009, issue of the *American Journal of Human Genetics*.

"A lot of children have intellectual disability, and about half of the time we cannot attribute it to a specific cause," says senior author Christopher A. Walsh, a Howard Hughes Medical Institute investigator at Beth Israel Deaconess Medical Center in Boston. "The child has intellectual problems but there's nothing else that tells us what might be going on. In an age of complete genome sequence, this is unacceptable and will hopefully change soon."

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- Christopher A. Walsh

Walsh is an expert on the development of the human cerebral cortex. His research team is interested in identifying genes that direct the development of the cerebral cortex, both because of their importance in human diseases and because studying those genes will help in learning about the normal development and evolution of the brain. Walsh says research on the genes that cause intellectual disability has focused overwhelmingly on mutations

traced to the X chromosome. These are easy to recognize because they affect males, who have just one X chromosome, more frequently than females, who would require both of their X chromosomes to be faulty for the impairment to appear.

“We know a lot about genes that cause intellectual disability on the X chromosome. But 90 percent of our genes are not on the X chromosome,” Walsh says, adding that genes located elsewhere that cause intellectual disability probably number in the hundreds, but are much more difficult to identify.

Much of Walsh’s search for genetic factors that influence brain development takes place in the Middle East, where large families in which parents are frequently related by blood make recessive disorders more common -- and their causes much easier to find -- than they are in the United States. “In studying genetic disorders of human cortical development, we are fortunate to have extremely talented collaborators, including pediatricians, neuroradiologists, geneticists, and other neurologists, since the conditions are individually rare but collectively common,” said Walsh. “In addition to our gene-mapping efforts, we try to provide diagnostic expertise for doctors and patients, since the surprising diversity of genetic disorders of human cortical development is only beginning to be appreciated.”

The sisters in the current study initially were evaluated by Walsh's colleagues in Israel for developmental delay. When they were examined, the eldest girl was 7 years, 10 months; the middle child was 4 years, 8 months; and the youngest was 2 years, 10 months. All of the girls had smaller-than-average heads for their ages, although their head sizes had been normal at birth. These measurements suggested that the girls had a normal number of brain cells – most of which are produced before birth – but they had abnormally slow growth of the brain cells, Walsh says.

“You might have the right number of cells, but the cells might not grow in size. That’s why we think that the problems these kids have are more in the connections their cells make than in actually getting the right number of cells in the first place,” he says.

MRI studies of the three girls showed improper development of nerve fibers in the brain, including in the corpus callosum, which connects the brain’s two hemispheres.

In their search for a culprit gene, the researchers localized the gene to a small region of the genome, and then sequenced six candidate genes, based on their roles in early brain development. A single disabling change—an alteration of one nucleotide—was found in the *TRAPPC9* gene in all three girls.

In individuals without the mutation, the TRAPPC9 protein is abundant in mature brain cells. But the mutation that Walsh’s team identified causes cells

to produce a TRAPPC9 protein that is less than half its usual length.

“If there are abnormal proteins like that, the body usually destroys them,” Walsh notes. “That’s what we found in our patients’ cells -- that we couldn’t even see the shorter protein.”

The TRAPPC9 protein helps regulate a molecule called NF-KappaB, the researchers noted. NF-KappaB affects many biological processes, but its role in signaling in the brain is not well understood.

Researchers have identified only about six non-X-chromosome genes implicated in intellectual disability. Surprisingly, *TRAPPC9* is the second of those genes that seems to be involved with NF-KappaB, Walsh says. The gene is also involved in protein trafficking – the routing of proteins to their proper destination within cells. NF-KappaB is probably one of the things that TRAPPC9 helps route, Walsh says.

Our study implicates NF-KappaB as potentially a very important pathway in human intellectual function,” Walsh says.