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Possible Gene for Form of Mental Retardation, Brain Development Identified

Researchers funded by the National Institute of Child Health and Human Development (NICHD) have come one step closer to identifying one of the causes of previously unexplained mental retardation. The researchers report finding a single gene on the X chromosome, called AGTR2 for short, that when abnormal, appears to result in mental retardation (MR). The study, by Dr. Anand K. Srivastava and colleagues of the J.C. Self Research Institute of Human Genetics at the Greenwood Genetic Center in South Carolina, is published in the June 28 issue of *Science*.

“The identification of a single gene mutation that may prove to be the cause of some cases of mental retardation is very encouraging,” said Duane Alexander, M.D., Director of the NICHD. “This advance not only may lead to insights into a variety of new therapies, but may also help us to better understand the processes involved in normal brain development.”

Like an instruction manual, a gene contains information that tells the body how to make one or more specific proteins. A protein, in turn, performs a specific activity or group of activities within the body’s cells. When a gene is mutated, or altered, however, it will produce an altered protein or will not produce a protein at all. Often, a gene mutation does not noticeably affect the body. Other gene mutations, however, can result in disease or disrupt normal development.

The researchers linked a mutation in the AGTR2 (Angiotensin II receptor 2) gene to mental retardation by studying a female patient with unexplained MR. The researchers knew that this patient had a chromosome translocation between one of the X chromosomes and one of the number 7 chromosomes, meaning that during development, two of her chromosomes broke, and then switched pieces. They suspected that this translocation resulted in a mutation in one of the genes on the broken X chromosome and that the mutation could have resulted in the patient’s developmental disabilities. To test this hypothesis, they identified genes near the break point in the broken chromosome (candidate genes) and analyzed them to see if any of them were damaged or altered. Dr. Srivastava’s team showed that the patient’s AGTR2 gene was affected by the break point and found that its expression was absent in this female patient.

The researchers then studied the AGTR2 gene in 590 other male patients with unexplained MR, and found mutations in this gene in eight of them. “Although an AGTR2 mutation only appears to be present in 1.5 percent of males with unexplained mental retardation, this percentage is significant,” said James Hanson, M.D., Chief of NICHD’s Mental Retardation & Developmental Disabilities Branch. “With a total of 30,000-35,000 genes in the human body, the discovery of even a single gene that may play a

pivotal role in brain development could be an extremely important discovery. This study also shows that the technique of identifying candidate genes in a single individual with MR and testing them for mutations is useful for identifying genes related to mental retardation.”

The AGTR2 gene, found on the X chromosome, is structurally similar to the AGTR1 (Angiotensin II receptor 1) gene, which plays an important role in blood vessel functioning, regulating blood pressure, water and electrolyte balance, and hormone secretion. The researchers suspect that AGTR2 is also involved in blood vessel function or development. Blood vessel development and function is likely to be important for the formation of structures and relationships or for maintenance of important functions in the brain.

Next, researchers will study individuals with both MR and the AGTR2 mutation to determine if there is a common area on the gene that is altered in some or all of them. They will then try to determine if the AGTR2 mutation is, in fact, related to a defect in blood vessel development or function in the brain.

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The NICHD is part of the National Institutes of Health, the biomedical research arm of the federal government. The Institute sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. NICHD publications, as well as information about the Institute, are available from the NICHD Web site, <http://www.nichd.nih.gov>, or from the NICHD Clearinghouse, 1-800-370-2943; e-mail NICHDClearinghouse@mail.nih.gov.