Aberrations in region of chromosome 1q21.1 associated with broad range of disorders in children

10 September 2008

Researchers have discovered a submicroscopic aberration in a particular region of human chromosome 1q21.1 that appears to be associated with a variety of developmental disorders in children. The aberration can manifest itself as unexplained mild or moderate mental retardation, growth retardation, learning disabilities, seizures, autism, heart defects, other congenital abnormalities, cataracts, small head size, unusual facial features, hand deformities, or skeletal problems. Some people who have the aberration are only slightly affected or apparently unaffected, others are more seriously impaired.

The multinational research was led by Dr. Heather C. Mefford, acting assistant professor of pediatrics at the University of Washington, and Dr. Andrew J. Sharp of the University of Geneva Medical School in Switzerland. Mefford practices medical genetics at Children's Hospital and Regional Medical Center in Seattle and the UW Medical Center Medical Genetics Clinic.

The results will be published in the Sept. 11 *New England Journal of Medicine* in an article titled, "Recurrent Rearrangements of Chromosome 1q21.1 and Variable Pediatric Phenotypes." The results are discussed in an accompanying editorial by David H. Ledbetter of Emory University in Atlanta.

Deletions and duplications of major sections of the human genome have long been known to cause disease or make a person susceptible to disease. Recent technological advances, called cytogenetic arrays, are enabling scientists to test large numbers of people to determine the presence or absence of submicroscopic imbalances in small sections of their chromosomes.

Using these new advances, the researchers checked for the presence of microdeletions and microduplications in a specific region of chromosome 1q21.1 in groups of patients with unexplained mental retardation, autism, or congenital abnormalities, and compared their findings with similar testing of a group from the general population. In these 4,737 controls from the general population, no microdeletions were found. Two controls had one small duplication at the far end of the region under study, and only one had duplication of the entire region.

The authors explained that the genomic structure of 1q21.1 is extremely complex. There are still 15 assembly gaps, or 700 kb of missing sequence in 1q21.1, in the most recent map of the human genome.

These gaps, the researchers noted, might contain as yet unknown genes that contribute to the differences in the types of developmental abnormalities that occur in children with the deletion. Supposedly unaffected deletion carriers might in fact have more subtle disorders that could be found during further clinical evaluations. For example, an examination of one apparently unaffected carrier revealed mild cataracts and a heart defect that were previously undetected.

Studies by other groups of researchers have also found a connection between 1q21.1 deletions and schizophrenia in some people, and parts missing in the reproductive tract in other people. These results, the authors of the Sept. 11 New England Journal of Medicine article noted, confirm the association of 1q21.1 rearrangements with a broad spectrum of disorders, and also further dispel the notion that such rearrangements will necessarily follow the one-gene, one-disease model.

The authors recognize that the diversity of

disorders and the lack of a distinct syndrome accompanying 1q21.1 rearrangements will complicate genetic diagnosing and counseling. They suggest that clinicians caring for patients who have unexplained developmental abnormalities consider the identification of a 1q21.1 rearrangement in a patient a significant clinical finding and probably an influential genetic factor contributing to the patient's disorder. Evaluating the patient's family members may reveal apparently unaffected or mildly affected relatives carrying the same rearrangement. Keeping in mind the many possible repercussions of having this rearrangement in the chromosome, the authors suggest that young carriers should be monitored over the long term for the emergence of learning disabilities, autism, schizophrenia, or other neuropsychiatric disorders.

This study, the authors said, adds 1q21.1 as a chromosomal locus to the growing list of structural variants that might eventually be included in genetic screening panels for people with developmental delays or neuropsychiatric diagnoses.

"Counseling in the prenatal setting," the researchers wrote, "will present the greatest challenge: although the likelihood of an abnormal outcome is high in a person with a 1q21.1 rearrangement, current knowledge does not allow us to predict which abnormality will occur in any given person."

Source: University of Washington