Genetic mutation linked to lethal disease

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Researchers have identified a genetic mutation found in the Ohio Amish population as the cause of a fatal developmental disease in fetuses and infants, according to research published in the April 8, 2011, issue of *Science*.

The genetic mutation is caused by a defect during the cellular protein-making process, causing microcephalic osteodysplastic primoridal dwarfism type 1 (MOPD1), a rare developmental disorder that greatly slows fetal growth in the uterus and causes severe brain and organ abnormalities, deformities of the arms and legs, and death in infancy or early childhood.

MOPD1 is seen throughout the world but this study found that the MOPD1-associated mutation is particularly prevalent in the Ohio Amish population, appearing in approximately 6 percent of the community.

Richard Padgett, Ph.D., Staff Researcher in the Department of Molecular Genetics in Cleveland Clinic's Lerner Research Institute, led the functional genetic portion of the study. The study was led by Albert de la Chapelle, M.D., Ph.D., Professor, Department of Molecular Virology, Immunology and Medical Genetics of The Ohio State University's Comprehensive Cancer Center.

The findings could lead to a test for people who unknowingly carry a copy of the mutation, a better understanding of RNA splicing, and information about whether these mutations that arise during an individual's lifetime contribute to the development of cancer or other

diseases.

This research represents the first report of a human disease caused by mutations in a small RNA required for "splicing," a molecular process that removes regions of genetic material that are not expressed as proteins.

According to Padgett, "This study provides a solid example of the profound effect that RNA processing can have on disease. As a result, other disorders that share similar clinical features with MOPD1 may be more reliably diagnosed."

In an accompanying Perspectives article in the journal, Finnish researchers wrote, "The findings provide important genetic tools for diagnosing the disease and for counseling mutation carriers in affected families."

An arduous search by Dr. de la Chapelle's group for the genetic cause of MOPD1 identified a single mutation in the RNU4ATAC gene of affected Amish patients, as well as three other mutations in the RNU4ATAC gene in different groups of affected patients. They found that the MOPD1-associated mutation was present in 6 percent of the Ohio Amish population, while very rare in other groups.

Upon identifying the involvement of RNU4ATAC, the OSU group sought out the molecular genetic expertise of Padgett, who has studied RNA splicing, including U4atac snRNA, for many years. U4atac snRNA is essential for the correct expression of approximately 1 percent of human genes. Padgett's laboratory determined that the mutations identified in the MOPD1 patients resulted in U4atac snRNA that had lost over 90 percent of its activity. They also showed decreased splicing activity in cultured cells derived from Amish MOPD1 patients. Notably, this effect allowed correct diagnosis of the primary genetic defect

causing this disease.

Provided by Lerner Research Institute