Discovery of the gene responsible for multiple intestinal atresia in newborns

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Physicians and researchers from Sherbrooke, Montreal and Quebec City have conducted a study that has led to the discovery of a gene that causes multiple intestinal atresia (MIA), a rare and life-threatening hereditary disorder that affects newborns. In addition to exploring novel therapeutic treatments for children with the disease, the discovery of the gene TTC7A will make it possible to develop a prenatal diagnostic test and a screening test for parents who are carriers. The Centre hospitalier universitaire de Sherbrooke (CHUS) should offer the tests.

MIA is a congenital disease characterized by multiple obstructions all along the digestive tract – from the stomach to the small intestine and colon – often associated with severe immune deficiency. By studying the DNA of children with MIA, the research team identified mutations in the TTC7A gene, including one that turns out to be relatively common in the French-speaking population of Quebec.

A devastating and life-threatening disease

While the disease is rare, about thirty cases have been recorded in Quebec over the last 30 years. Even today, it remains a devastating and fatal condition. "Multiple surgeries, intestinal transplants and bone marrow transplants have not led to any real solutions for the disease. Even after such interventions, the newborns' digestive tract does not always work the way it should. The life expectancy of these children is about two to three months. With the discovery of the gene responsible

for the disease, it will now be possible to confirm an MIA diagnosis in newborns using genetic tests," states Dr. Bruno Maranda, who is a physician-geneticist at the CHUS, an investigator at the CHUS' Centre de recherche clinique Étienne-Le Bel (CRCELB) as well as a professor in the Faculty of Medicine and Health Sciences at the Université de Sherbrooke (UdeS).

Heredity thought to be the cause

Although the disease is very rare, it nevertheless seems to occur at a higher frequency in the French-Canadian population of Quebec. According to the research, this population is affected more than any other population group in the world. The condition seemed to be most probably of genetic origin, since in some families more than one child is born with the condition. This suggests recessive heredity, which is carried by the parents. "We have discovered that a number of children born with MIA carry the same genetic mutation from both parents. This finding confirms the recessive disease hypothesis that the mutation is inherited from both the father and the mother. As they do not suffer from the disease and do not know that they can transmit the mutation. The identification of the defective gene (TTC7A) makes it possible for us to know the cause of the condition. This is excellent news both for Quebec families with the disease and families around the world where the mutation is present," confirms Vincent Raymond, co-author of the study and a researcher at the CHU de Québec Research Center.

Screening tests for pregnant women and family members who are potential carriers

Couples with an MIA child have a 25% risk of recurrence in subsequent pregnancies. "The concept of prenatal diagnosis allows couples to proceed with tests at the beginning of the pregnancy to determine

whether the child they are expecting will be affected. We can also, within the same family, determine whether, for example, siblings are carriers of this genetic condition, and eventually, whether their partner is at risk in order to predict the risk of recurrence in the following generations," stresses Dr. Maranda, the study's principal investigator and Head of the Department of Medical Genetics at the CHUS.

The CHUS will offer the prenatal diagnostic test and the screening test for MIA carriers in the summer of 2013. Further research will help to prevent MIA in children and support carriers of the gene. Prescription procedures, implementation dates and the conditions under which the tests will be carried out will be made known in the weeks to come by the CHUS. The test will fall within an overall research offer on genetic diseases.

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Novel therapeutic avenues

"The discovery of the gene opens the way to potential treatments for children with MIA, since it will help us understand the pathways of the disease, including the modulation of the immune system, in which the gene seems to be involved," explains the study's lead author Dr. Mark Samuels, a researcher in genetics at the Sainte-Justine University Hospital Research Center and a professor at the University of Montreal. "Why do certain patients also suffer from severe immune deficiency?" asks co-author Dr. Elie Haddad, a Sainte-Justine physician and

researcher in immunology and University of Montreal professor. "The discovery of the gene will allow us to better understand the link between abnormal development of the digestive tract and abnormal development of the immune system."

More information: The study published in May 2013 in the *Journal of Medical Genetics* under the title "Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia".

Provided by University of Montreal

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