Discovery of a novel heart and gut disease: The genetic mutation involved would date back to 12th century Vikings

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The disease, which has been named 'chronic atrial intestinal dysrhythmia syndrome', is a serious condition caused by a rare genetic mutation. This finding demonstrates that heart and guts rhythmic contractions are closely linked by a single gene in the human body.

Physicians and researchers at CHU Sainte-Justine, Université de Montréal, CHU de Québec, Université Laval, and Hubrecht Institute have discovered a rare disease affecting both heart rate and intestinal movements. The disease, which has been named "Chronic Atrial Intestinal Dysrhythmia syndrome" (CAID), is a serious condition caused by a rare genetic mutation. This finding demonstrates that heart and guts rhythmic contractions are closely linked by a single gene in the human body, as shown in a study published on October 5, 2014 in *Nature Genetics*.

The research teams in Canada have also developed a diagnostic test for the CAID syndrome. "This test will identify with certainty the syndrome, which is characterized by the combined presence of various cardiac and intestinal symptoms," said Dr. Gregor Andelfinger, a pediatric cardiologist and researcher at CHU Sainte-Justine "The symptoms are severe, and treatments are very aggressive and invasive, added Dr. Philippe Chetaille, a pediatric cardiologist and researcher at the university hospital CHU de Québec." At cardiac level, patients suffer primarily from a slow heart rate, a condition which will require the implantation of a pacemaker for half of them, often as early as in their childhood. At digestive level, a chronic intestinal pseudo-obstruction will often force patients to feed exclusively intravenously. Furthermore, many of them will also have to undergo bowel surgery.

Discovery of the CAID Syndrome

By analysing the DNA of patients of French-Canadian origin and a patient of Scandinavian origin showing both the cardiac and the gastrointestinal condition, the researchers were able to identify a mutation in the gene SGOL1 that is common to all of patients showing both profiles. "To lift any doubts concerning the role of the identified mutation, we also made sure it was ruled out in people showing only one of the profiles," said Dr. Andelfinger. Similarly, Dr. Jeroen Bakkers, at Hubrecht Institute, in The Netherlands, who also collaborated to the project, studied zebrafish with the same gene mutation "The mutated fish showed the same cardiac symptoms as humans, which confirms the causal role played by SGOL1", he continued.

A Transatlantic Founder effect The research team traced back the genealogy of eight patients of French-Canadian origin using the Quebec population BALSAC historical data base. They were able to identify a common ancestry dating back to the 17th century, more precisely a founder couple married in France in 1620. Molecular genetic tests also proved that the identified French-Canadian and the Swedish mutations share the same origin, suggesting the existence of a founder effect and the major role played by migration of populations. According to the investigators' calculations, the genetic legacy would date back to the 12th century, then following the migration route of the Vikings from Scandinavia to Normandy, then that of the settlers who migrated to New France in the 17th century.

An Unsuspected Role for SGOL1

The researchers believe that the mutation of SGOL1 acts mechanistically to reduce the

protection of specific nerve and muscle cells in the gut and the heart, causing them to age prematurely due to an accelerated replication cycle. Their findings suggest an unsuspected role for SGOL1 in the heart's ability to maintain its rhythm throughout life. The specific role played by the gene and the impact of its mutation will take center stage in future investigations of the research group. Along with physicians and patients, the group hopes their understanding of the disease will help them identify new avenues for treatments specifically targeting the underlying genetic and molecular causes.

More information: Mutations in SGOL1 cause a novel cohesinopathy affecting heart and gut rhythm , *Nature Genetics*, DOI: 10.1038/ng.3113

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