Genetic cause discovered for rare bleeding disorder

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For some Canadians, any cut such as from dental work or surgery can cause days or more of bleeding. Although they are not hemophiliacs, for some an ordinary bruise can balloon into the size of an orange. For others, knees, elbows and ankles are crippled when bleeding seeps into joints. In very serious cases, hundreds of blood transfusions are required for recovery.

Now a team led by McMaster University hematologist Dr. Catherine Hayward has discovered the genetic cause of Quebec Platelet Disorder (QPD). They have gone on to develop a genetic test for the condition - a major advance in diagnosing this serious and unusual bleeding problem.

The condition is called a platelet disorder because it transforms platelets (blood cells that control bleeding) from clot formers into clot busters.

It is called QPD because careful detective work has traced all individuals with this condition back to one Quebec family. In parts of Canada, about one out of 150,000 persons have QPD and the new genetic test is expected to uncover many more.

Hayward, a professor of both the departments of medicine and pathology and molecular medicine in the Michael G. DeGroote School of Medicine, calls the discovery of the genetic cause of QPD a "milestone" in her career.

Because the genetic cause of most bleeding disorders continues to be a

mystery, "it's satisfying to know that our team tackled the genetic cause of a really fascinating genetic disorder and have an answer," she said. "And, it's not the answer anybody expected, which makes it even more interesting."

QPD is an autosomal dominant bleeding disorder, which means a person only needs to receive the abnormal gene from one parent to inherit the disease. The research team discovered that QPD is caused by a mutation involving an extra copy of the gene PLAU, the urokinase plasminogen activator (uPA) gene that causes overproduction of an enzyme that accelerates blood clot breakdown and this turns platelets into clot busters.

This is "novel," Hayward said, "as QPD is the very first bleeding disorder attributed to having an extra copy of a gene, rather than a defective copy. QPD is also the first bleeding problem attributed to a mutation in the uPA gene."

"The types of mutation that causes some bleeding problems are mistakes that are likely to happen again, and typically, they cause a protein to become defective or deficient," said Hayward. "Now that we know the mutation, we can focus on solving why there is tremendous uPA overproduction in QPD platelets, which will give us fundamental, new insights on how the uPA gene is controlled."

The work is already having a positive impact on the lives of many people. A recent newborn of the family most impacted by the condition was able to have a test immediately to discover whether he had the condition.

"The family needed to know whether this child would need life-long monitoring, and treatments to counteract their clot busting platelets, as having a definite yes or no answer early is key to proper treatment," said

Hayward.

Hayward's group at McMaster worked with a Canadian team of investigators including Andrew Paterson at the Hospital for Sick Children in Toronto, and Georges Rivard at the University of Montreal.

Hayward and Rivard believe that the known cases they have studied over the last decade are "the tip of the iceberg" and that the true prevalence of QPD has been underestimated because, until the genetic test became available, there was no way to routinely test bleeders for this condition.

"Diagnosis is important as drugs for other platelet problems and transfusions just don't work for the QPD clot busting problem," said Hayward.

Provided by McMaster University