UW-Madison School of Medicine and Public Health: Researchers discover cause for rare genetic blood disorder

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MADISON, Wis. – An eight-year quest to find the cause of a disease has apparently ended now that scientists at UW-Madison have identified the mutations that produce a form of myelofibrosis, a rare genetic blood disorder.

Mutations in a protein that controls the production of blood platelets appear to be the source of a genetically inherited form of macrothrombocytopenia with focal myelofibrosis, according to Dr. Inga Hofmann, assistant professor of pediatrics, medical director for the UW Program for Advanced Cell Therapy, and lead author on the paper.

The results were recently featured as the September cover article in the journal *Blood*.

Hofmann and her team showed that the protein, G6b-B, which also regulates the production and function of megakaryocyte – a large bone marrow cell –can be manipulated to increase production of blood platelets, suggesting a potentially new treatment approach, Hofmann said.

“This is the first cause ever identified,” she said.

Hofmann had been looking for this cause since 2010, when she was introduced to three Middle Eastern families referred to her for a second opinion involving their children's cases of myelofibrosis.

Myelofibrosis is a serious bone-marrow disorder that disrupts the body's production of red blood cells, and in children it is typically caused by a type of blood cancer called megakaryoblastic leukemia. But, the cause of myelofibrosis when that condition isn't present, and the source is genetic, hasn't been discovered until now, Hofmann said.

Only about 50 cases of this disease have ever been reported.

The disease, regardless of origin, can lead to bone marrow scarring and severe anemia, weakness and an enlarged spleen. The only known treatment is a hematopoietic stem cell transplant.

At the time Hofmann met the first family, she was a pediatric hematology specialist at Boston Children's Hospital. At first, the cause was elusive because though she understood to target her research on the blood-producing aspects of the genetic puzzle, it was like looking for a needle in a haystack.

"It wasn't until the other two families came around that we found it," she said. "[G6b-B] was basically the only gene (protein) that came through all three."

Then, in 2017 her eventual collaborator on this research, Yotis Senis, professor of hemostasis at the University of Birmingham in England, and a well-known researcher in the platelet field and expert in G6b-B, presented a fourth family, also from the Middle East, to Hofmann with the same phenotype and same genetic mutation in G6b-B.

Once they understood the common thread, Hofmann and Senis set about trying to understand how G6b-B works in the marrow and ways to treat these children.

They discovered that loss of the G6b-B protein leads to abnormal megakaryocytes, marrow scarring and low platelet counts.

"If we could manipulate the pathway involving the G6b-B protein in myelofibrosis patients, we might be able to restore normal platelet producing cells in the bone marrow cells and stimulate the production of normal blood cells" Hofmann said.

Understanding the relationship between megakaryocyte and the G6b-B protein is a significant advancement in the entire field of myelofibrosis, which also impacts adults. “This is a real paradigm- shifting idea,” Hofmann said.

“These types of diseases give us a better understanding of the bigger picture, not just in children,” she said.