Inherited platelet disorders and cancer risk: a spotlight on *RUNX1* Familial Platelet Disorder (*RUNX1-FPD*)

Did you know that some platelet disorders are inherited, or passed down through families? In fact, there are many different types of inherited platelet disorders. Inherited platelet disorders are caused by coding errors (“variants”) in over 50 different genes, the units of cellular ‘instruction’ that determine specific characteristics in all of us and are passed on from generation to generation. Genetic testing is the only way to confirm a suspected inherited platelet disorder. Obtaining an accurate diagnosis can help avoid extra or inappropriate treatment, provide information about required follow up and monitoring, and about familial risk. Inherited variants in three genes that cause a platelet disorder also pose an increased risk of blood cancer.

**Background on *RUNX1-FPD*, an inherited platelet disorder**

One of these three genes is *RUNX1*. The gene provides the blueprint for a protein called *RUNX1* that is essential to our blood system. When a variant in the *RUNX1* gene occurs that lowers the levels of the *RUNX1* protein, it causes a disorder called *RUNX1* Familial Platelet Disorder (*RUNX1-FPD*) with predisposition to hematologic malignancy (blood cancer). This disorder is autosomal dominant, meaning that each child has a 50% chance of inheriting the variant from an affected parent. A survey of centers who report caring for *RUNX1-FPD* patients determined that there are over 200 families that have been diagnosed, but experts agree that the disorder is highly underdiagnosed, largely due to the lack of genetic testing required to diagnose patients. In addition, some patients with a germline *RUNX1* variant may only present to medical attention with a blood cancer without ever having been diagnosed with a platelet disorder. Although certain genetic testing is routine for such patients, specialized next generation sequencing that would identify *RUNX1* is not. Current estimates suggest as many as 18,000 people may be living with *RUNX1-FPD* in the United States.

Individuals with *RUNX1-FPD* have a close to 50% (median 44%; range 11-100%) risk of developing a blood cancer, and the average age of cancer onset is 33 years. The most common blood cancer *RUNX1-FPD* patients develop is acute myeloid leukemia (AML). The second most common bone marrow problem is generally considered a pre-leukemia state called myelodysplastic syndrome (MDS). However, there have also been reports of patients developing B- and T-cell acute lymphoblastic leukemia, chronic myelomonocytic leukemia, lymphomas and hairy-cell leukemia. The leukemia can occur in childhood, but is more commonly diagnosed in adults.

While the risk of blood cancer is worrisome, for more than half of individuals, cancer will not develop. What makes this disorder difficult to diagnose in some families is that *RUNX1-FPD* causes a variable decrease in platelet counts (from profoundly abnormal counts to those that are within the normal range) and variably disrupts platelet function, so the severity of bleeding varies across individuals, even within the same family. Common to many patients with thrombocytopenia, *RUNX1-FPD* patients can experience easy and large skin bruising, “petechiae” or pinpoint burst blood vessels, prolonged bleeding from even minor injury or surgery, gum oozing, and excessive nose bleeds. Women often experience heavy periods and sometimes hemorrhage at childbirth. Brain bleeds are exceedingly rare in this disorder, but may occur after little to no head trauma. More recently, the scientific community has begun to explore the association of additional symptoms, beyond platelet-related symptoms, that may be related to having a *RUNX1* variant, these include eczema or rosacea, respiratory problems such as reactive airway disease, allergies and gastrointestinal issues. Because many of these are also common in the general population, the true relationship of these with *RUNX1* has yet to be fully defined.

Currently there are no standard U.S. practice guidelines for the testing, monitoring or treatment of *RUNX1-FPD*, but several experts in the field have published recommendations. Because of the blood cancer risk, experts recommend a baseline bone marrow biopsy (although this may deferred if the patient is very young at diagnosis), and regular follow ups that include basic blood tests (CBCs) every 3-6 months. It is also recommended that patients avoid aspirin and non-steroidal analgesics (such as ibuprofen), maintain optimal dental and gum care, and know how to manage nosebleeds and the warning signs of an intracranial bleed. Management of heavy periods is usually done in combination with a gynecologist. It is critical that surgeons and hematologists are in contact for optimal surgical management. Additionally, because systems other than blood may be affected with *RUNX1-FPD*, patients may want to share the diagnosis with their full health care provider team.

When a blood cancer is diagnosed, the current standard treatment approaches for those specific blood cancers are followed. For patients who receive a stem cell transplant recommendation as part of their treatment plan it is very important that genetic testing is performed on potential stem cell donors, particularly siblings (who are often the best matched donors). Siblings have a 50% chance of carrying the inherited variant, and if positive for *RUNX1-FPD*, should not be selected as a donor.

**Questions to Ask Yourself and Your Doctor**

*RUNX1-FPD*, and other inherited platelet disorders, can be difficult to diagnose correctly given the range of symptoms that are shared across these disorders. Genetic testing might be considered if you answer “yes” to any of the following:
(a) Do you have a family history of thrombocytopenia, bone marrow failure or blood cancer?

(b) Do you have a family history of an undefined bleeding disorder?

(c) Do you have a diagnosis of “familial” ITP?

It is important to discuss the risks and benefits of testing with an experienced genetic counselor before agreeing to test. If you and your health care team decide to test for RUNX1-FPD, or other inherited platelet disorders, a qualified genetic testing lab can test saliva samples. In some cases, blood, bone marrow or skin samples are required for an accurate and complete diagnosis.

Advancing Research on RUNX1-FPD

There are a number of research studies ongoing with the goal of discovering effective treatments for RUNX1-FPD patients. One study that aims to help accelerate towards this goal is a longitudinal, natural history study at the National Institutes of Health in Bethesda, Maryland. The Study, formally titled “Longitudinal Studies of Patients with FPDMM”, NCT03854318, includes a number of specialists who gather clinical, genetic and patient-reported data from RUNX1-FPD patients across the US and internationally. This study will improve our understanding of how the disease evolves and will contribute to developing effective prevention, management and treatment strategies. The study team works closely with patients’ local hematologists to monitor patients’ over time.

More information on this study:
www.clinicaltrials.gov/ct2/show/NCT03854318
www.runx1-fpd.org/nih-study
Email the Research Nurse: Kathleen.Craft@NIH.gov

For More Information

The RUNX1 Research Program (RRP), is a patient-led non-profit organization that is focused on improving the quality of life and preventing cancer in RUNX1-FPD patients. Founded in 2016 by a patient-family, the organization brings together patients, families, health care workers and researchers to facilitate connections and accelerate the shared understanding of the disorder. RRP funds and facilitates research with the goal of discovering treatments and eventually a cure for RUNX1-FPD. Furthermore, RRP facilitates an online support community, and this November they will launch their first-ever Patient Meeting to provide patients the opportunity to forge in-person relationships with other RUNX1-FPD patients.

More information: www.runx1-fpd.org
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*Often also referred to as Familial Platelet Disorder with Associated Myeloid Malignancy (FPDMM) or Familial Platelet Disorder with Predisposition to Acute Myeloid Leukemia (FPD/AML), or RUNX1 Deficiency

Thank you to the RUNX1 Research Program for providing the information in this article.

Ohio Family Learns to Deal with RUNX1 Diagnosis of Three Family Members

By Jody Shy

Joy and Nathan Anderson were shocked to learn in 2018 that two of their four sons, along with Nathan, were diagnosed with a rare bleeding disorder caused by changes in the RUNX1 gene. The family, which includes Griffin, 10, Maxwell, 9, Nolan, 8, and Brennan, 5, along with their parents all underwent genetic testing at the suggestion of their doctor after Griffin had years of bruising and low platelets. Griffin was the first to be diagnosed, followed by Nathan and finally Brennan. Neither Maxwell nor Nolan share the mutation. While Nathan never showed many outward symptoms, he does acknowledge that routine blood work over the years did show low platelet counts. At his first bone marrow biopsy, doctors discovered he has myelodysplastic syndrome (MDS) or pre-leukemia. For now, he will continue to be monitored for the condition. For Griffin and Brennan, the mutation presents differently for each boy. Griffin experiences more pronounced bruising and Brennan deals with pulmonology issues – asthma, seven bouts with pneumonia. Researchers are just starting to explore the immune system in this disorder.

For the Anderson family, the most important thing is raising awareness for the disease, which has only been diagnosed in 200 or so families throughout the world. Joy is focused on being proactive with the disease and gaining as much information as she can for her family and others. The family, especially Joy, have become outspoken advocates for RUNX1, from speaking at the RUNX1 research annual meeting (the first patient to do so besides the organization founders), traveling to the NIH for biopsies and presenting their genetic counselor with an award. They are thankful for all they have learned about this diagnosis, and how strong it has shown them to be.