Evaluating the prevalence of primary immunodeficiency in immune thrombocytopenia
Investigator: Sioban Keel, MD
Institution: University of Washington (Seattle)

While immune thrombocytopenia (ITP) isn't considered to be a genetic disorder, in some cases it may be. Particularly, if the cause of a person's low platelet count is a secondary condition that presents just like ITP. One type of secondary ITP includes inborn errors in immunity, previously called primary immunodeficiency disorders.

This study was designed to investigate the role of genetic testing in identifying inborn errors in immunity among patients with a diagnosis of ITP to identify how common IEIs are in adults with ITP for better clinical care and a more informed prognosis and possibly more appropriate treatments. In addition, it would allow other family members to be counseled about possible risks for them and have appropriate surveillance.

Inborn errors of immunity (IEI) are a group of inherited disorders that impair normal functioning of the immune system and can result in autoimmune diseases, including ITP. IEI's are often thought about in individuals who have recurrent infections such as pneumonia, sinus and respiratory infections, chronic ear infections and generally a propensity for frequent infections. They also often present with other health concerns, particularly inflammatory bowel disorders, skin disorders such as eczema, cancer predispositions, lymphoproliferation (enlarged lymph nodes or spleen), and autoimmune disorders causing abnormal blood cell counts (affecting one or multiple blood cell types: platelets, red blood cells, and white blood cells).

In fact, almost one-third of patients with an IEI have an autoimmune cytopenia (abnormalities in one of the three blood cell types) with a 120-fold risk to develop an autoimmune cytopenia compared to the general population. Autoimmune cytopenia's can present at any age and may increase in likelihood as a person with an IEI ages. Thus, even if the IEI is inherited (meaning 'genetic') not all symptoms associated with the condition may present at an early age. In fact, many with an inherited IEI are diagnosed as adults.

IEIs can be thought of as a spectrum disorder leading more to an immune deficiency or immune dysregulation. The recognition of IEI's has grown with advancements in genetic testing options, such as sequencing (the ability to 'read' genes) and next-generation sequencing (NGS) which allows for many genes to be sequenced at once. This has allowed researchers to identify approximately 400-500 genes associated with IEIs enabling more patients to be diagnosed with these disorders.

Eligibility was restricted to ITP patients evaluated in Seattle who were over the age of 18 years, had ITP for at least three months, and did not have a lymphoid malignancy. There was a total of 32 participants recruited into the pilot study. Of these, ten participants reported having secondary ITP (six of whom disclosed they have Evans syndrome).

Analysis of data collected used a combination of collected medical history on the participant, their reported family history, and data generated through a specialized laboratory that is certified to perform and interpret NGS. When asked about a personal or family history of autoimmunity, approximately 40-55% reported having another autoimmune condition separate from ITP, or a relative with an autoimmune disorder of some kind.

Within the 32 participants, nobody had an IEI based on their genetic testing results; seven were found to 'carry' a variant (a change within a gene) for an IEI that only causes disease if a person has two of these pathogenic (disease-causing) variants; and over 200 variants of unknown significance were identified.

One participant was reclassified from having primary ITP to having an inherited thrombocytopenia, distinct from an IEI.

These results suggest that IEIs are rare, even among individuals with ITP or even Evans syndrome. Results may represent 'false negative' results, otherwise known as uninformative negative results, whereby an identifiable damaging variant was not found because it was not picked up using the available testing technology.

We will continue to sequence additional ITP patients and attempt to recruit family members to help in the reclassification of the many identified variants of unknown significance. Overall, diagnosing an underlying IEI in patients with ITP may prove directly relevant to patient care as it could inform prognosis, surveillance care, and even guide the choice of therapy.

PDSA has designed our research program to specifically focus on patient priorities and funds studies that will make a significant impact on ITP diagnosis, therapies, and quality of life. If you'd like to donate to our research fund, please visit https://www.pdsa.org/pdsa-donation.html.