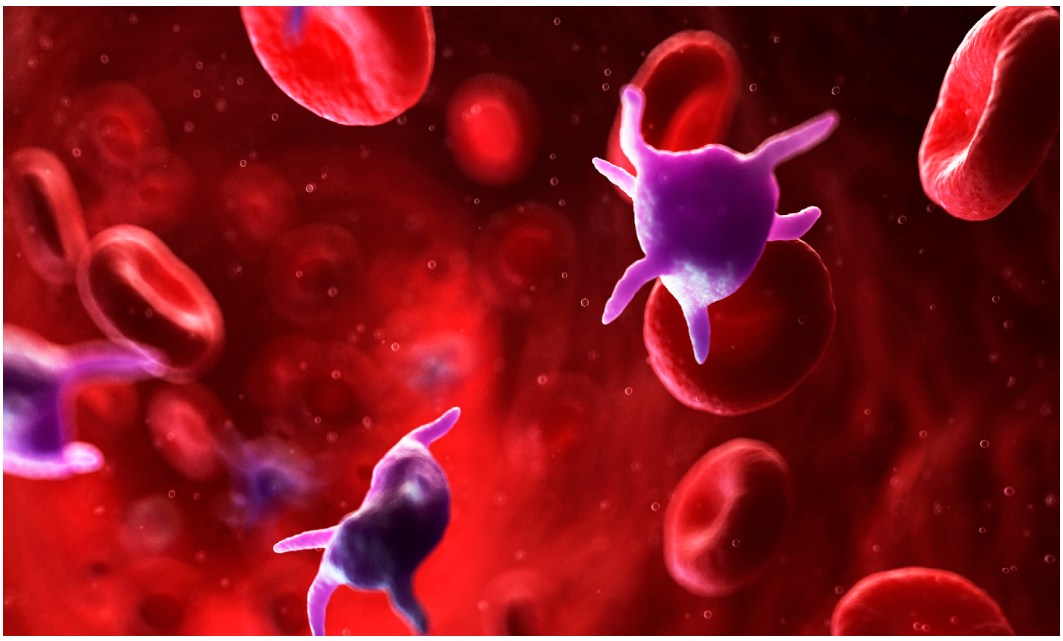
National Human Genome Research Institute



NIH RUNX1
Natural History Study

Newsletter

Dear RUNX1 Natural History Study Participant,

Time has been flying by, and it's hard to believe that it's been almost 2 years since we opened the doors to the RUNX1 Natural History Study! We've learned so much already but know that there is so much more to learn.

Our team has been working away to pull together the first of many publications that outline the results of the study so far. We are so profoundly grateful to each and every one of you for your contributions to our research. We cannot wait to share this paper with you and the scientific community. In the meantime, here are some updates on what else we've been up to.

Study statistics so far

- 101 participants with germline (heritable) RUNX1 variants enrolled from 26 different families
- 47 patients evaluated at the Clinical Center
- 67 unaffected family members
- Participants from all different ages (1-75 years old)
- More than 15,000 pages of medical records obtained
- 40 unique variants in the *RUNX1* gene
- Exome data on bone marrow from 37 patients

What are we learning?

If you've visited us at the National Institutes of Health (NIH), you probably know that our participants see a lot more people than just our RUNX1 team. We want to understand this disease from head to toe to make sure we have a complete picture of the disease and can take care of you in the best way possible.

We are fortunate to have experts from 7 of the 27 Institutes that make up the NIH who collaborate on the study. This month we met with representatives from several of the teams to think about the data that each group has collected.

Gastrointestinal Team (Sumona Bhattacharya, M.D., Monica Passi, M.D., and Theo Heller, M.D., NIDDK) – Our Gastrointestinal (GI) team has been taking detailed clinical histories, labs and, in some cases, endoscopy samples from our patients to screen for different digestive conditions. GI issues aren't something we've ever thought to be a part of RUNX1 deficiency syndrome, but it seems like there may be higher than expected number of patients with certain GI symptoms in our cohort than in the general population.

Allergy (Keith Sacco, M.D., and Pamela Guerrerio, M.D., Ph.D., NIAID) – So far, the allergy team has evaluated 42 patients. There seem to be much higher rates of allergic rhinitis, conjunctivitis, food allergies and breathing difficulties in patients with RUNX1 deficiency syndrome than in the general population. Now that we're seeing the symptoms in our patients, we will dive into the blood samples to see what is going on at cellular and biochemical level to understand if and how RUNX1 variants could be lead to these symptoms.

Dermatology (Ed Cowen, M.D., MHSc, NIAMS) – Eczema has long been a hallmark of RUNX1. While most patients do seem to have some form of skin disease at some point in time, it's not entirely clear that people with RUNX1 have higher rates of eczema than the general population. We'll continue to ask questions about the involvement of skin in RUNX1. We are starting to further analyze affected skin (i.e., patches of eczema) to better understand what is going on in those cells at the time of symptoms on a molecular level.

Neurology/Rheumatology (Sophie Cho, M.D., NINDS, and Kaitlin Quinn M.D., NIAMS) – While neurological symptoms are not thought to be a major feature of RUNX1, a handful of patients have joined our protocol with histories of neurological disease. These include hyporeflexia, compressive neuropathy, joint hypermobility and possible myopathy. Some studies suggest that *RUNX1* may play a role in nerve, muscle and bone development, so we hope to dig further into seeing if *RUNX1* (likely in combination with other risk factors) may have an impact on the symptoms we have seen in these patients. Several patients have also reported having migraine headaches, so we are working with Neurology to better understand if this finding may be related to RUNX1 deficiency.

Patient Reported Outcomes Measures (Lori Wiener, Ph.D., NCI) – We have results of our validated patient reported outcomes measure for 19 patients. These measures are a way to further evaluate our participant's symptoms in a way that can be compared to others in the study. These assessments help us identify what questions matter most to our RUNX1 study participants and how we can best support our families.

Hematology/Pathology (Alina Dulau-Florea, M.D., and Kathy Calvo, M.D., Ph.D., C.C.) – You may have heard that people with RUNX1 have both quantitative and qualitative platelet defects. We look for quantitative (too few) platelet defects every time participants get bloodwork done. Our hematology/pathology colleagues have been using a test called platelet aggregation to look at how platelets clump together to form blood clots to assess for qualitative defects. As expected, most RUNX1 study participants have had abnormal aggregation studies, which tells us that the platelets are not working so well. Next, we'll try to see if these results correlate with how severe each person's bleeding and bruising may be and if there are any clues in the genetics that can help us understand why different people have different levels of bleeding and bruising.

We also use a powerful microscope called electron microscopy to evaluate the platelet granules. Granules are tiny sacks in the platelet containing important immune factors. We have found that a significant proportion of patients with RUNX1 deficiency have defects in both their dense and alpha granules.
We are also looking deep at the blood and bone marrow of all the patients in our study to understand how the blood is working. So far, we've seen that about 25% of patients had increased eosinophils (a type of white blood cell commonly associated with inflammation, allergies and fighting certain types of infections). We saw that almost 50% of patients had hypocellular (fewer cells than expected) bone marrows for their age. We also learned that many patients have different sorts of anemias such as iron deficiency anemia. It may be that this anemia is caused by excess bleeding from the platelet defects. These are important clues for us to understand what RUNX1 does and how it affects all the cells in the blood.

Benign Hematology (Charles Bolan, M.D., and Shelley Kalsi, M.D., NHLBI) – Along with validated clinical bleeding phenotype determined by International Society on Thrombosis

and Haemostasis (ISTH) scoring guidelines, we use quantitative and qualitative platelet information to determine which patients will require therapies, such as amicar or tranexamic acid, with their procedures. We try to have a formal consultation with the benign hematology service for any participants who appear to have excessive bleeding to ensure that they get the care they need.

Pulmonary function testing – We are trying to unravel whether airway issues like asthma or obstructive sleep apnea are more frequent in the RUNX1 cohort. Each patient age 5 or older now has pulmonary function testing during their visit. We have been working closely with the pulmonary team to evaluate these results and determine the best steps forward. Patients can meet with the pulmonary team for individual consults as well on an as-needed basis.

Obstetrics and Gynecology – Many of our female RUNX1 patients have shared stories of heavy periods, which is not surprising given that excessive bleeding is a hallmark of the disease. A few participants have also experienced miscarriages or had trouble getting pregnant. While it is unclear if this is related to RUNX1, we are working with the Ob/Gyn service at NIH to provide consultation as needed moving forward.

What's in a name?

From time to time someone will ask us, "What's the difference between RUNX1, RUNX1 - Familial Platelet Disorder (FPD) and RUNX1 - Familial Platelet Disorder with Myeloid Malignancy (FPD-MM)?" The truth is that they all refer to the same phenomenon — when a person has a germline genetic change that makes it so that their copy of the *RUNX1* gene doesn't work correctly, eventually leading to disease.

This may seem like semantics, but it can be important. Saying familial platelet disorder may help doctors remember RUNX1 when they see a family with lots of platelet issues. Attaching the myeloid malignancy can remind doctors that blood cancers are something they should check for in these patients.

However, as we've learned from this study, germline variants in RUNX1 can lead to a lot more than platelets and risk of AML, and we want a name to reflect that. We worry that focusing on platelet disorder in the name may also lead doctors to miss patients who do not have platelet disorder as a major symptom. While myeloid malignancy is a concern, not all patients will develop malignancy, and some patients may develop types of blood cancers that are not myeloid (e.g., acute lymphoblastic leukemia (ALL), lymphoma or aplastic anemia). We also want to highlight the important difference between germline (a genetic change someone is born with that they can pass on in the family) and somatic (a change that is acquired — often in leukemia — and cannot be passed on) *RUNX1* variants, because they are very different things.

Because of this our team usually refers to it as "Germline RUNX1 Deficiency Syndrome." It's normal for doctors and scientists to change disease names as we learn more about the condition. In fact, if you go really far back you may have seen *RUNX1* called things like *AML1* or *CBFA2*. We hope to host a meeting soon with a group of patients, families, health care providers and scientists to come to a consensus on what name best fits this disease to help avoid confusion. With this effort we also need to continue to push for RUNX1 awareness so that families can get the care they need as soon as possible. Stay tuned for more!

Hot off the press!

Our team recently published a busy clinician's guide to RUNX1 in the GeneReviews series. This guide is clinician focused and provides an overview of the current guidelines for diagnosis, management and genetic counseling for patients with RUNX1 variants. We hope this will be a helpful resource for both our participants and their home team providers. Feel free to share this with your doctors who may ask you, "So what is RUNX1?"

Fun genetics naming fact:

You may notice that sometimes people italicize *RUNX1*, and sometimes it's just written RUNX1. This is because in genetics we italicize the names of human genes, but if we are referring to the protein that that gene ultimately produces it's written in standard text. So, a change in the *RUNX1* gene leads to abnormal RUNX1 protein. Things get even more complicated if you think about other organisms. For example, in a Zebrafish (one of the model organisms we use to study the disease) it's written *runx1* in all lowercase, and in mice it's written *Runx1* with just the first letter capitalized.

We will continue to update this guide as we learn more about RUNX1 through the study. The guide can be accessed here: https://www.ncbi.nlm.nih.gov/books/NBK568319/

What does *RUNX1* mean for getting the COVID-19 vaccine?

We have been getting questions about if those with RUNX1 should receive the COVID-19 vaccine. In general, we feel people with RUNX1 should get the vaccine as soon as it is available to them. However, some individuals may have additional risk factors (such as immunosuppressive medications, adverse reaction to vaccination or difficulty with intramuscular injections due to low platelets) that may warrant further discussion.

We have posted a letter on our website that outlines this information. We can also write a more tailored explanation with consideration to individual clinical features upon request.

Of note, we are interested in tracking how individuals with RUNX1 react to the COVID-19 vaccination. We will send out a survey in the coming weeks to track which vaccines our participants are getting and if there are any adverse reactions.

COVID-19 and the Natural History Study

Like the rest of the country, the NIH Clinical Center has been navigating the challenge of minimizing patient safety concerns and maximizing research and innovation in medicine. Right now, we can bring in most participants, but we may not be able to bring in everyone that would like to be seen as we would in other years. We are working with the administration to assess which RUNX1 participants will be able to come back and when. As you can imagine, this is an ever-changing process and becoming less restrictive as more people are vaccinated. We are not sure when we can begin to accept international patients.

In the meantime, the RUNX1 team is always available to answer any of your questions or concerns.

New options for participating in the RUNX1 Natural History Study

Understanding RUNX1 will take enrolling as many participants as possible; however, we also understand that everyone has busy lives outside of having RUNX1, so we want to offer as many options as possible for those who want to participate in our study. If you or other members of your family are interested in joining the study but are unsure if you have the time to commit to the full in-person work up, some of these options may be helpful:

1. **Annual NIH Clinical Center visit for 1.5 - 5 days**. The shorter visits are available to participants who can tolerate procedures performed with local anesthesia. Longer visits allow for participants to have additional subspecialty consultations to provide more detailed and consistent data for the study and provide more tailored results and care.

2. **Remote enrollment with a telehealth visits with our team**. We would ask for participants to work with their home care provider to get certain clinical labs drawn and to share data from any procedures they may have at home. We would also ask that participants send a few research samples to our team for analysis in our lab. We would then be able to meet via telehealth and go over clinical history and any recommendations just as we would if they came to NIH. In some cases, we may also ask for participants to meet with our consulting teams, such as allergy and immunology over telehealth.

3. **Remote enrollment with e-consent signing**. This is the most hands-off approach. Participants would be able to share medical records with us through a secure NIH Box account, and we will arrange for a remote blood draw for our research level tests approximately once a year. Consent is electronic. There is no planned interaction with the study team unless there are urgent clinically actionable results that must be disclosed from genetic studies.

We often say that this is a “chose your own adventure” clinic. We are happy to work with you to come up with the best plan for your participation in the study using any combination of the options above.

Preparing your child for their visit to the clinical center

With the help of Dr. Wiener and her team, we’ve recently developed Social Story to help kids prepare for their study visit to the NIH. We know that coming to the Clinical Center can be scary (for adults and kids alike), so this book will give them an opportunity to “walk through” pictures of their upcoming trip to

NIH to give them an idea of what to expect. Please reach out to Katie Craft, R.N., at kathleen.craft@nih.gov, and she would be happy to share the social story with you.

Save the date

We are tentatively planning to have an NIH participant meeting in June 2022 where we will be able to come together as a community to discuss our study findings and hear more from you all. We will plan to have both virtual and in-person options for attending this meeting. Stay tuned for more.

Accessing your NIH Medical Record

As a reminder, you can access clinical results from our study through the NIH FollowMyHealth Patient Portal.

Information about setting up your patient portal can be found here: https://clinicalcenter.nih.gov/followmyhealth/index.html

Changes to our team

Our team is always changing and growing. This quarter we are excited to welcome Kevin and Erica to the team.

Kevin J. O'Brien, R.N., MS-CRNP, is a senior nurse practitioner with a focus on internal medicine and a clinical investigator at NHGRI. He's been with NHGRI for 20 years and provides clinical care for patients with a variety of genetic disorders.

Erica Bresciani, Ph.D., is a staff scientist in Dr. Paul Liu laboratory at the National Human Genome Research Institute, who coordinates the bench research activities of the RUNX1- Research Study. Dr. Bresciani received her Ph.D. in cellular and molecular biology from The University of Milan, Italy. She has been studying the roles of RUNX1-CBFB in blood development and blood stem cells since 2011.

We are also ecstatic that Dr. Matt Merguerian has accepted a faculty pediatric hematology position at Johns Hopkins University. Lucky for us, Dr. Merguerian will stay on the research part of the study part time, so you will still see him around from time to time.

Our postbaccalaureate fellow Victoria Sanchez-Guzman, who has been helping to collect records for many of our participants, recently left us to begin medical school at Brown. We are incredibly proud of her and hope that she finds her way back to working with the RUNX1 community in the future.

Thank you for your participation in the NIH RUNX1 Study! Please contact us with any questions!

Sincerely,
The RUNX1 Study Team