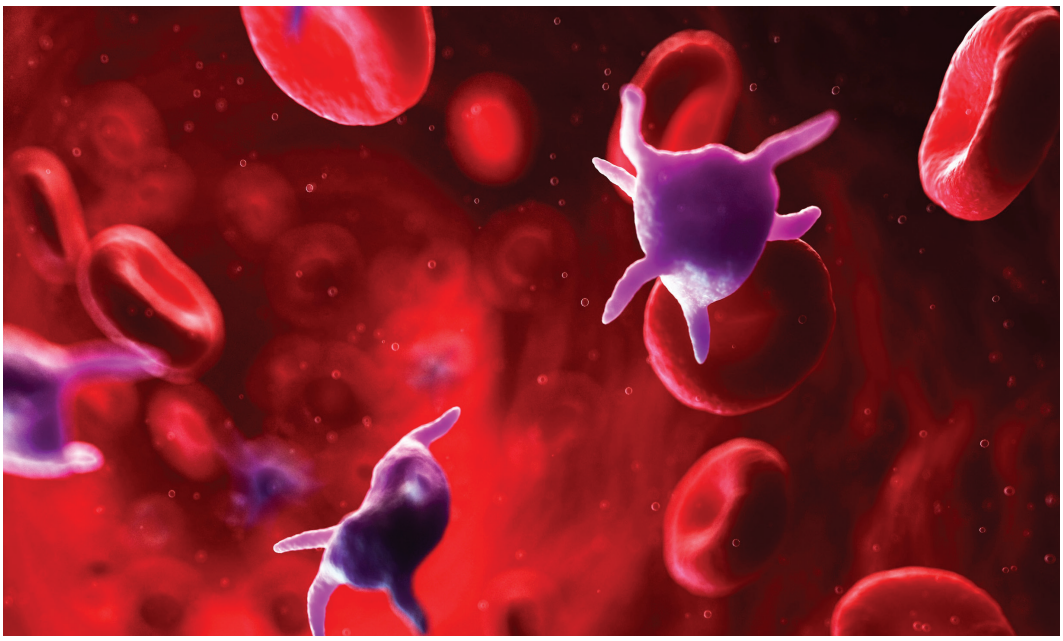
National Human Genome Research Institute



NIH RUNX1
Natural History Study

Newsletter

Dear RUNX1 Natural History Study Participant,

Welcome to the first of many newsletters from the *RUNX1* Natural History Study at the National Human Genome Research Institute (NHGRI)!

We've heard from a number of you that you'd like to find out what we are learning from your medical records and test results during your visit to the NIH Clinical Center. We hope to send out a newsletter every six months or so, to update you on how the study is going and how you are helping to support *RUNX1* research.

Study statistics so far

- 51 participants with germline *RUNX1* enrolled from 26 different families
- Participants from all different ages (1-73 years old)
- More than 10,000 pages of medical records obtained
- 20 unique variants in the *RUNX1* gene
- Whole Exome Sequencing (WES) results for 31 participants
- 6,893 unique genetic variants detected on WES so far

What's going on with the genetic studies?

One of the primary goals of our study is to understand the role that genetics plays in the *RUNX1*-related disease.

We all have thousands of changes (or variants) in our genes and the DNA that make us who we are. Most of these changes are completely harmless. They tell us things like the color of our eyes, or how tall we'll be, or are just part of what makes each of us unique. But if one of these variants makes a certain gene not work correctly, they can significantly impact a person's health.

We already know that people with disease-causing variants in the *RUNX1* gene are likely to have fewer platelets and platelets that don't work as well, eczema, and have a higher risk of developing blood cancers such as myelodysplastic syndrome or leukemia.

But what we don't know is whether there are other things that a person's genes could tell us about their disease. Are certain variants in *RUNX1* associated with more or less severe disease? Are there variants in other genes that might work with *RUNX1* to increase a person's risk of developing leukemia or make their disease more severe? Are there variants that decrease a person's risk and make their disease milder?

There are a couple of different ways we look at genes throughout participation in the study.

First, we look for germline variants. Germline just means that these are changes in the DNA that we are born with. These types of variants are found in the DNA of nearly every cell in the body. They may have been inherited from a parent (although sometimes they are de novo or new; they occur in an individual for the first time, but they can pass these variants on to their children). Participants in this study have germline variants in the *RUNX1* gene.

We're also looking at variants that are somatic. Somatic variants happen naturally as we age and occur in just some of our cells. We all have somatic variants, but people with different types of cancer tend to have more of these variants in specific genes and in specific cells. You may even read about people with somatic mutations in *RUNX1* that happened after they developed leukemia – this is a bit different than having germline *RUNX1* disease. Since people with germline *RUNX1* variants have a higher risk of developing leukemia and other cancers, it's important for us to check for changes in somatic variants annually, as they could be an indicator that we need to watch them more carefully or intervene if these variants cause cancer.

For each participant in this study we get information about germline and somatic variants from a couple of different tests. We do whole exome sequencing (WES) that looks for variants in all of the genes in the body, as well as some smaller tests that look at just genes that are known to be involved in hematologic disease. We do these tests on blood samples, bone marrow samples and skin biopsies. This means there is a lot of data. In addition, some of these tests are already clinically validated. Some of these tests are research grade and pathogenic variants must be clinically validated.

Now our job is to sort through all of the thousands of genetic variants we've found to see which are part of just being a human, and which could impact or even predict how germline *RUNX1* variants may influence a person's health. We'll be comparing data from all of the participants in the study to look for the variants they have in common and those that are different. We know very little about some of the variants we find. It'll take a lot more research in the lab to find out exactly how those variants interact with *RUNX1.*

Since all of this research takes a long time, you may not get answers back from us right away. But rest assured, we're still working away! We'll check in with each participant about their genetics results each year when you come back to the NIH. ***However, if we find anything that could significantly impact clinical care, we'll let you know sooner.*** We'll also send out any discoveries that could impact the broader *RUNX1* community through this newsletter.

New additions to our protocol

Our study protocol is very much a living document. As we learn from you, we adapt the protocol to make sure that we are doing everything possible to provide the best quality data. Great data is the best way to learn about this important disease!

So far, it seems that a lot of participants have features of allergies, rashes and even gastrointestinal issues, which may be caused by excess inflammation. We've always known that germline *RUNX1* variants increase a person's risk of developing eczema, but it seems that it may have an even bigger role in inflammation and the immune system. You might have learned about this if you tuned into the *RUNX1* Research Program's (RRP) webinar on Inflammation and *RUNX1* (RRP is a 501c non-profit organization based in California interested in providing education and advocacy for the *RUNX1* community). Understanding *RUNX1*'s role in the immune system could influence how we treat this disease.

Because of the new symptoms and signs we have observed, we've collaborated with experts in immunology and gastroenterology here at the NIH to help us characterize these features in our participants. You may be contacted by these teams to get a little bit more information that we may not have asked you yet. Don't worry -- we try to make these calls as short as possible to make sure you can get back to living your life.

We're also in the process of incorporating Patient Reported Outcomes Measures (PROMS) into our study. These PROMS are just surveys you'll be able to take at home, possibly from a smartphone app. They're being developed by Dr. Lori Weiner, our amazing psychologist at the National Cancer Institute (NCI); many of you will have met with her during your trip to NIH to evaluate the burden of all of the symptoms you may be experiencing. The surveys will help us see how all of the different symptoms of *RUNX1*, from mild to severe, add up to impact your overall quality of life. Think of it as your time to tell us what the most important things about this disease are to you. Stay tuned for more information about this.

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

How is COVID-19 impacting the study

Our number one priority is keeping all of our research participants safe. In late March, the NIH decided to reduce the number of people on campus to only the most essential so as to limit the spread of the novel corona virus sars-cov-2 which causes the COVID-19 constellation of symptoms. This meant restricting patients to those who are having acute interventions performed such as bone marrow transplant, or those who are directly participating in research on COVID-19. Accordingly, all visits for the *RUNX1* study scheduled through late June have been postponed.

The NIH is in the process of re-opening and is slowly bringing outpatients back – starting with those with the most urgent clinical needs such as folks requiring procedures. NIH Clinical Center senior leadership must approve all outpatient visits on a case by case basis. We are working with the administration to assess which *RUNX1* participants will be able to come back and when, but as you can imagine, this is an ever-changing process.

In the meantime, the *RUNX1* team continues to work hard in the hospital and remotely and we are always available for any questions or concerns.

Study on the Impact of COVID on patients with Rare Diseases

The Rare Diseases Clinical Research Network (RDCRN), which is supported by the NIH, is doing a study on the impacts of COVID-19 on patients and families with rare diseases like *RUNX1*. If you're interested you can learn more about that study here https://www.rarediseasesnetwork.org/COVIDsurvey.

Thank you very much for your participation in the NIH RUNX1 Study! Sincerely,

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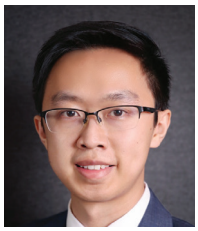

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