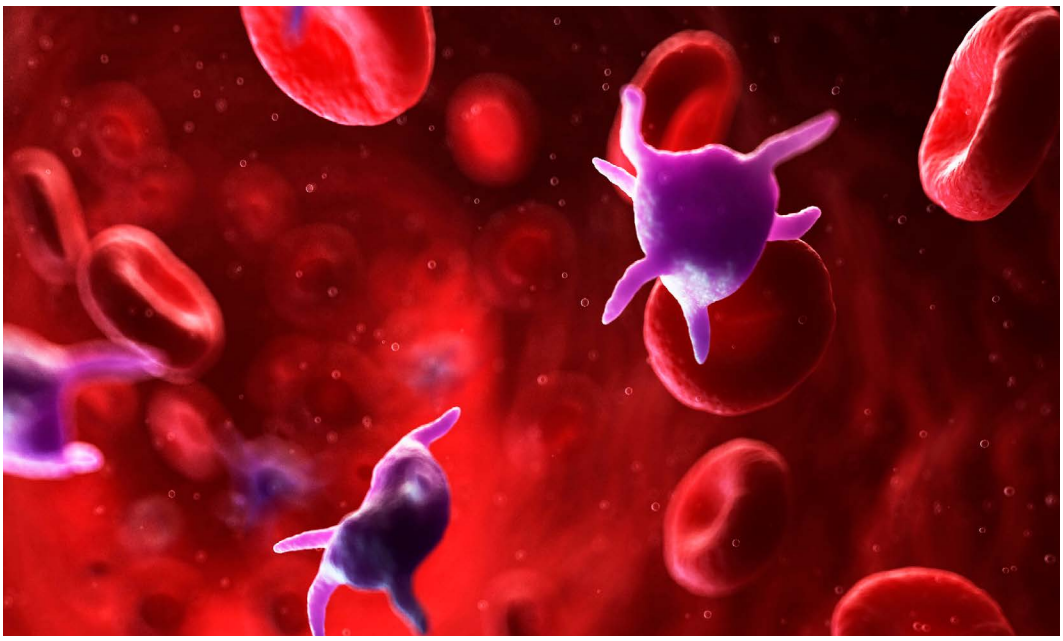
National Human Genome Research Institute



NIH RUNX1
Natural History Study

Newsletter

Dear RUNX1 Natural History Study Participant,

It's been a while, but we've been busy over here in Bethesda. We wanted to share some updates with you all!

Study statistics so far

- 211 individuals with *RUNX1* variants from 110 families enrolled.
- 45 unaffected family members enrolled.
- 113 affected participants have visited the NIH Clinical Center.
- Participants from all different ages (0-99 years old) included.
- More than 30,000 pages of medical records obtained.
- 86 unique variants in the *RUNX1* gene catalogued.

The First RUNX1 Natural History Study Publication

We are thrilled that our first paper documenting the findings of our Natural History Study is online in the journal *Blood!* As you'll see, this version looks like just a word document. A more official version of the paper will be available in December. We are so thankful to all of you for participating in the study — we could not have done it without you.

This first paper outlines clinical findings from the first 126 patients (from 45 families) enrolled in the Natural History Study between 2019 and 2021.

Here are some of the highlights:

- We reported 39 unique *RUNX1* genetic variants. This will help labs identify people with RUNX1-FPD and will set the stage for understanding how a person's specific *RUNX1* variant may impact their disease. Of these variants:
  - 18 families had frameshift or truncating variants (that either throw off the gene or cut it short in a way that leads it to be degraded in the body).
  - 10 families had deletions in part or all of the gene sequence and 1 family had a duplication.
  - 9 families had missense variants (that change just one letter of the gene).
  - 7 families had splicing variants (that lead *RUNX1* to be assembled the wrong way).

- We documented different clinical features of the disease so that doctors will better know what to look out for in their patients. For example:
  - 91% of participants with RUNX1 had thrombocytopenia (too few platelets).
  - 100% of participants had qualitative platelet defects (platelets that don't work correctly).
  - 51% of participants had abnormal bleeding scores.
  - We also found increased rates of allergies and gastrointestinal disease. By no means will everyone with RUNX1-FPD develop these symptoms, but it's helpful for us to be on the lookout for them.

- We detailed different marrow findings to help pathologists better understand what the marrow from a person with RUNX1-FPD looks like. Unfortunately, some RUNX1-FPD patients have been misdiagnosed with cancer due to bone marrow changes that are normal in RUNX1-FPD but abnormal in the general population. Spreading awareness about these findings will help our patients get accurate results wherever they are evaluated.
- We reported 19 patients who developed a blood cancer.
  - Of our adult patients, 4 had MDS, 6 had AML, 2 had CMML and 1 had smoldering myeloma. Of our pediatric patients, 4 had AML, 1 had B-ALL and 1 had T-ALL.
  - 62% of families had at least one case of blood cancer, and more than half of those had 3 or more individuals with a blood cancer.
  - On the flip side, this means that 38% of families had ***no*** history of blood cancer, which is reassuring that cancer is not inevitable with this disease.

It's important to note that in almost all diseases, the most severe cases present first. It is highly possible that as this study continues and as more people are diagnosed through screening, we will find milder cases of RUNX1-FPD and find that some of the numbers presented may actually go down.

Why is this paper important?

Blood is the top journal in hematology and reaches a broad audience of hematologists who may see patients with RUNX1-FPD. We know that RUNX1-FPD is greatly underdiagnosed. Hopefully, this paper will increase awareness of this condition so that more patients can get their diagnosis sooner and start proactive monitoring.

Understanding the natural history of this disease will also be critical for clinical trials. As we move towards new treatments for this condition, we need to know their impact on improving our participants' disease course. For example, if a drug is proposed to reduce the risk of a person with FPD developing leukemia, we really need to know how high their risk of developing leukemia is in the first place.

How does the peer review process work?

We've been saying that this paper was coming out "soon" for too long. Pulling together the data for manuscripts like this and distilling down the key points can take quite some time, but once a paper is submitted to a journal, it still has quite a way to go before it can be published.

When an article is submitted to a medical journal first, it typically goes to a journal editor who will review the paper and see if it seems like a good fit for the journal. Not all journals are the same and some have very different goals and audiences (e.g., hematologists, pediatricians, scientists).

If the editor decides that the paper could fit the journal, they will send it out to two to five experts in the field to review it. The reviewers critically read the paper to make sure that it is scientifically accurate and offer suggestions to improve the manuscript. This process is called **peer review**. Authors will then address any feedback and resubmit it. Sometimes the

editors will send the paper out again and the whole process can repeat several times until everyone agrees that the paper is ready for publication.

As you can imagine, this whole process can take quite some time — even more than a year in some cases. At any point in the process, the paper can be rejected by the journal and the authors will have to submit it to another journal. Needless to say, we are delighted that our papers are out!

The Genomics Paper

Our second paper outlines the findings from all of that genetic testing we've been doing. This paper was recently published, also as an online-first version, in the journal *Blood Advances*, which is a sister journal to *Blood*. You may have seen a version of this paper posted on a website called *BioRxiv. BioRxiv* allows scientists to get important data out to the scientific community, while acknowledging that the final published version may change based on feedback from the reviewers.

In this paper, we dove into all of the different types of *RUNX1* variants that were identified in the initial cohort of patients.

Beyond the *RUNX1* variants, we looked at the exome data for additional germline variants (those that are typically shared with family members and present in nearly every cell in the body) to try to understand if there may be other genetic factors that could increase or decrease a person's chance of developing leukemia.

We also report on the different somatic variants that were identified in our patients. Somatic variants are genetic changes that happen in just a few cells as we age and that are not shared with family members. When these genetic changes happen in a certain set of genes and in just a few cells in the blood and bone marrow, it's called clonal hematopoiesis of indeterminate potential (CHIP).

In the paper, we focused on changes in genes that are associated with clonal hematopoiesis of indeterminate potential (CHIP) or leukemia. We saw that 75% of patients with malignancy (cancerous cells) had at least one somatic genetic variant. We also saw that 44% of patients without malignancy had similar variants. These variants are common in the general population, but we see that these types of variants are more frequent in RUNX1-FPD, and they happen at a younger age.

When we find a somatic variant in one of our participants, it's something that we watch carefully, but that does not necessarily mean that the participant will go on to develop malignancy. For example, we see that somatic variants in the *BCOR* gene are very common in people with RUNX1-FPD. However, as we've followed more patients over time, it seems that most *BCOR* variants are quite stable and may not increase a person's risk of developing leukemia.

It will take more data over time to really understand what these changes mean and how we can use them to better predict who may develop leukemia.

Why is this paper important?

Much like the clinical paper, this paper will help clinicians and labs better recognize RUNX1 and will overall increase awareness of the condition, which is critical. This paper also gives other researchers an idea of what genetic changes are common in RUNX1-FPD so that they can start to understand how those changes may affect the disease.

One of the major goals of our study is to better predict who is at a higher or lower risk of developing leukemia and when that may happen. This paper is an important first step in realizing that goal. We will need far more data from more patients over time to make strong clinical conclusions, but these results give us some early patterns to investigate and set the stage for more research to come.

Understanding your RUNX1 Variant

Everyone with RUNX1-FPD has a typo or variant in the *RUNX1* gene — that's what defines this disease after all. However, not everyone has the same variant. What can be even more confusing is that not all variants are created equal, and not every variant in *RUNX1* leads to Familial Platelet Disorder.

If you look at your RUNX1 genetic report, you'll probably see the term **Pathogenic, Likely Pathogenic, Likely Benign, Benign or Variant of Uncertain Significance (VUS)**. These are terms that we use to say how likely each of the thousands of different variants in *RUNX1* will lead to disease.

Pathogenic means that the variant almost certainly causes disease and has a ~99% chance of never being reclassified as benign. **Benign** means that the variant almost certainly does ***not*** cause disease and similarly has a ~99% chance of

not being reclassified as being pathogenic. **Likely benign** and **likely pathogenic** just means that the chance of the variant being reclassified is ~90% rather than ~99%.

Most families with RUNX1-FPD have variants that have never been seen before, so we have to do some digging to figure out if a new variant is pathogenic. When we do this, it's sort of like putting the variant on trial — we collect lots of evidence to put together a case for pathogenicity. RUNX1-FPD is a rare disease, so if we look in a population database and see that a lot of healthy people have a variant, that is good evidence that it's benign. If we see a family in which all members with the variant have symptoms, and those without the variant don't have symptoms, then that's good evidence that it's pathogenic. We can also use computer modeling systems and studies in the lab to see if the particular variant stops *RUNX1* from doing its job or not.

Things can get murky when we don't have enough evidence to call a variant one way or another, and this is where the **variant of uncertain significance (VUS)** classification comes in. We have a number of participants in this study who have VUSs. We have to treat each of these variants differently and sometimes that means we may follow a person for a few years to collect more information about the variant.

Through the study, a number of people who were initially referred to us had variants that looked concerning at first but could actually be reclassified as benign. This is great news, as those individuals generally do not need the same monitoring that individuals with RUNX1-FPD need (but should, of course, continue to follow with their local doctors if they have any medical issues).

If you have any questions about your particular *RUNX1* variant reach out to Natalie (natalie.deuitch@nih.gov).

So, what's next?

Since our original paper was published, we have more than doubled the number of families enrolled on the protocol. We learn from every single participant who walks in our clinic (or talks to us on the phone). We will continue to document symptoms, lab results, marrow findings, and continue to do genetic testing to better understand how this disease works. But having these first two papers published gives us some space to start focusing on other questions and issues with *RUNX1*.

Here are just a few things that we are working on right now:

We are digging into specific *RUNX1* variants to try to see if certain misspellings of the *RUNX1* gene are associated with different presentations of the disease. We are also doing functional studies in the lab to look at how the different variants impact *RUNX1*'s ability to do its job. The most common variant we see in our cohort is at position Arg201 (meaning there is a typo at the 201st letter of the *RUNX1* gene). Since this change is so common, we want to know why and if there is anything unique about this group of patients compared to the rest of the group. Similarly, a lot of our patients have part or all of the *RUNX1* gene deleted so we're looking at this group in aggregate.

If you've been to the NIH recently, you may have been asked to give some additional tubes of blood for research. This for a study in which we are analyzing the DNA in the platelets to try to see if there are differences in how different genes get turned on and off. We're hoping that this will help us better understand some of the biology behind the platelet dysfunction in FPD, and why some patients have very different bleeding and bruising symptoms. As you can imagine, trying to collect platelets from people who have characteristically too few platelets can sometimes take several tubes of blood. Thank you to those who have donated!

Our team is also working on efforts to increase diversity in our cohort. Most patients diagnosed with RUNX1-FPD — and enrolled in the study — are White. People who are not White or of European ancestry are likely to be diagnosed with *RUNX1*-FPD when they have already developed leukemia and are less likely to have a match in the national marrow registry if they need a bone marrow transplant. Our study serves as a pilot study at the National Human Genome Research Institute to enhance diversity in clinical research. We are working with a larger team to develop tools to increase recruitment in underrepresented groups.

After a brief pause, we are also resuming our Patient Reported Outcomes Measures (PROMs). These are the surveys that many of you have taken with Dr. Lori Weiner. The scientifically validated metrics allow us to learn about things like stress, pain,

fatigue, and mental health in people with RUNX1-FPD and their caregivers and how RUNX1-FPD impacts lives.

Our study participants are certainly our biggest collaborators. If there are questions you think we should be addressing, let us know!

Resources for RUNX1 Patients

Our goal as a study is not just to drive research in the lab, but also to better support all patients with RUNX1-FPD. Over the last four years, we've developed several resources with Dr. Lori Weiner and her team to help our participants better navigate this condition. These resources are linked below and are available on our website. Feel free to share them!

GeneReviews for RUNX1 is geared towards healthcare providers who may be taking care of a person with RUNX1-FPD, but who may not be experts in the condition themselves. Many of our study participants have said that explaining their diagnosis to their providers is one of the most frustrating parts of the disease. We encourage participants to share this guide with their providers so that they can better understand how to take care of them and recognize other patients who should be tested.

Paving the Road: A RUNX1 Communication Guide for Parents is a document geared towards parents who are having conversations with their children about RUNX1-FPD. The guide is broken into sections for different age groups and has a glossary at the end with easy-to-understand definitions of medical terms. Many parents have commented that the guide has also helped them understand RUNX1-FPD better, so it's worth a read for all ages!

RUNX-101: An Adolescent's Guide to Understanding and Communicating about RUNX1-Familial Platelet Disorder (FPD) builds on the communication guide and offers a written explanation for older children and young adults who may prefer to read the information for themselves.

Child & Teen Wellness Tool Kit: A Caregiver's Guide outlines several different wellness activities for children who may be dealing with stress, fear and uncertainty in relation to their diagnosis (or a diagnosis within their family). These activities are great for finding calm during stressful times like doctor's appointments or trips to the NIH.

NIH Social Story is a children's book to help kids prepare for their visit to the NIH. The book walks kids through the NIH Clinical Center, the different clinic rooms and where they'll be staying so that they will know what to expect during their visit.

Let us know if there are other resources that would be helpful to you all! We are always happy to develop more.

Scheduling your NIH Visit

If you haven't heard from us in a while and are interested in coming to the NIH or checking in with us virtually, make sure to reach out to Natalie (natalie.deuitch@nih.gov) or Katie (kathleen.craft@nih.gov).

As always, thank you for your participation in the NIH RUNX1 Study! Please contact us with any questions!

Sincerely,

The NIH RUNX1 Clinical Team

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