NIH NATIONAL CANCER INSTITUTE

Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics

Family Research *Matters*

Inherited Bone Marrow Failure Syndromes (IBMFS) Study Newsletter

MESSAGE FROM THE NCI IBMFS STUDY TEAM

Welcome to the latest issue of the National Cancer Institute (NCI) Inherited Bone Marrow Failure Syndromes (IBMFS) Study newsletter. Some of you have recently enrolled while others have been with us since the study first opened in 2001. The clinical and scientific community continues to make progress in understanding IBMFS and cancer. We share some of our latest findings in this newsletter. As a reminder, regular updates can be found on our website

www.marrowfailure.cancer.gov

Cancer in People with IBMFS

We recently reported on the occurrence of cancer in 530 people with an IBMFS enrolled in our study from 2002 to 2015.[1] Now that we have over fifteen years of follow-up on some of these patients, we are better able assess cancer risk.

Certain types of cancer were observed at higher rates among individuals with IBMFS prior to bone marrow transplant, compared with the general population. The major syndromes are listed below with the associated malignancies:

- **Diamond Blackfan Anemia:** lung, colon
- **Dyskeratosis Congenita:** head and neck squamous cell cancer, leukemia, non-Hodgkin lymphoma, anal cancer
- **Fanconi Anemia:** head and neck squamous cell cancer, leukemia, cancers of the vulva, esophagus, brain, and anus
- **Shwachman Diamond Syndrome:** leukemia

Overall, individuals with IBMFS have more cancer than the general population. Those who have undergone bone marrow transplant may be at even higher risk of cancer. Thus, we recommend that all people with IBMFS undergo routine cancer screening. Cancers not listed above may also occur. It is important to follow the recommendations of your treating physician because your specific needs may be different.

Our study team will continue to enroll new participants and follow-up on those of you already enrolled in our study to gain more information about cancer risk, including whether different genetic causes within a specific IBMFS have different risks of cancer, and to better understand how bone marrow transplant affects cancer risk.

[1] Alter, BP, Giri N, Savage SA, et al. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. *Haematologica.* 2018. Jan;103(1):30-39. doi: 10.3324/haematol.2017.178111. Epub 2017 Oct 19

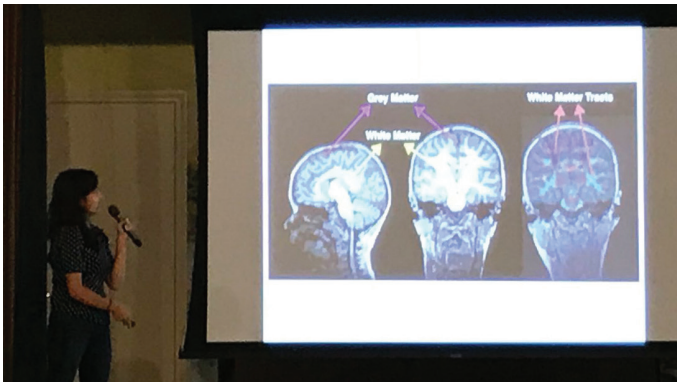
In this Issue

Workshop on Vascular Complications in Dyskeratosis Congenita

In October 2017, we collaborated with Team Telomere, Inc., to host a workshop on vascular complications, such as gastrointestinal bleeding, in patients with dyskeratosis congenita and related telomere biology disorders. This meeting brought together clinical and scientific experts, including six members of our study team, and patient advocates to share current knowledge on such complications, and to brainstorm future avenues for research. Our investigators contributed to a paper published in 2018 describing the workshop and the next steps for the scientific community.[2]

Engaging with Patients and Families

Camp Sunshine is an invaluable space for families with an IBMFS to come together to support one another, speak with experts, and learn more about their disease. Camp Sunshine offers disease-specific weeks for IBMFS disorders. In 2018, members of the NCI clinical study team attended camp for Dyskeratosis Congenita, Fanconi Anemia, Diamond Blackfan Anemia, and Shwachman Diamond Syndrome. Here, we presented our current work and held one-on-one sessions to talk to patients and their families. Learn more about at Camp Sunshine at www.campsunshine.org.



Sonia Bhala presents her study on the neurological complications associated with telomere biology disorders at Camp Sunshine.

Our Ongoing Commitment to Gene Discovery

There are many people in the NCI IBMFS Study with clinical features of a specific syndrome but for whom the genetic cause is unknown. These individuals and their family members may provide DNA that is used to discover new disease-causing gene variants.

Determining whether a specific change or variant in a person's DNA causes a disease is very challenging. Exome sequencing is a tool that we use to look at all the genes that can code proteins; these are the functional genes in our bodies. Eventually, a new gene variant may be classified as disease-causative (pathogenic) based on multiple sources of scientific evidence published in the peer-reviewed scientific literature, such as laboratory studies, reports of other patients with the same variant, and/or computational methods inferring the possible consequences of the variant on protein function.

We are committed to keeping our study participants informed about the most recent information related to their family-specific variant. Please do not hesitate to reach out to us if you have questions.

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[2] Higgs C, et al. "Understanding the evolving phenotype of vascular complications in telomere biology disorders." *Angiogenesis*. 2019 Feb;22(1):95-102. doi: 10.1007/s10456-018-9640-7. Epub 2018 Aug 25.

Engaging with the Scientific Community (2018)

Members of the NCI Study Team presented posters at the following meetings:

- *Esophageal Cancer in Fanconi Anemia.* 30th Annual Fanconi Anemia Scientific Symposium. Alter BP. Newport Beach, CA.
- *A Training Grant for Development of a Fanconi Anemia Cohort in Mexico.* 30th Annual Fanconi Anemia Scientific Symposium. Alter BP. Newport Beach, CA.
- *Central Nervous System, Neurologic, and Psychiatric Consequences of Very Short Telomeres.* Child Neurology Society Meeting. Bhala S, et al. Chicago, IL.
- *Genotype-Phenotype Associations in Fanconi Anemia: A Systematic Review.* Fanconi Anemia Research Fund Scientific Symposium. Fiesco-Roa M, et al. Atlanta, GA.
- *Phenotypes of Diamond-Blackfan Anemia Patients with RPL35A Mutations.* American Society of Hematology Meeting. Giri N, et al. San Diego, CA.
- *Fanconi Anemia and Mosaicism.* Fanconi Anemia Research Fund Symposium. Giri N, et al. Newport, CA.
- *Large Genomic Deletions in Shwachman-Diamond Syndrome.* American Society of Hematology. McReynolds L, et al. San Diego, CA.

Members of the NCI Study Team were invited to speak at the following conferences:

- *A Training Grant for Development of a Fanconi Anemia Cohort in Mexico.* 30th Annual Fanconi Anemia Scientific Symposium. Alter BP. Newport Beach, CA.
- *Hematologic complications of SDS.* 9th International Congress on Shwachman-Diamond syndrome. Alter BP. Houston, TX.
- *Cancer in heterozygote carriers of Fanconi anemia.* 30th Annual Fanconi Anemia Scientific Symposium. Alter BP. Newport Beach, CA.
- *Clonal alterations and survival after unrelated donor allogeneic hematopoietic stem cell transplant in individuals with Fanconi anemia.* BMT Tandem Meetings. Wang Y. Salt Lake City, UT.
- *Pregnancy outcomes in women with SDS.* Shwachman-Diamond Syndrome Congress. Giri N. Houston, TX.
- *Genetic and Epigenetic Changes Beyond Coding Mutations.* Aplastic Anemia & MDS International Foundation. Savage SA. Rockville, MD.
- *Dyskeratosis Congenita and Telomere Biology Disorders as Models for Understanding Cancer Risk: Perspectives in Skin Cancer Prevention.* EMBO Workshop. Savage SA. Les Diablerets, Switzerland.
- *The Genetics and Clinical Manifestations of Human Ribosome Biology Disorders.* 11th International Conference on Ribosome Synthesis. Savage SA. Orford, Quebec, Canada.
- *Advancing Understanding of Dyskeratosis Congenita and Related Telomere Biology Disorders: Challenges and Opportunities.* Fundacion Ramon Areces. Savage SA. Madrid, Spain.

Recent Publications from the NCI IBMFS Study

Studies of Pregnancy in Mothers With and Without IBMFS

We studied the outcomes of 575 pregnancies in 165 unaffected mothers carrying children with IBMFS.[3] Infants with Fanconi anemia (FA) and Dyskeratosis Congenita (DC) were more frequently born small for gestational age. Almost half of the fetuses with FA had complications that required a C-section and early delivery. Almost a third of fetuses with DC had fetal distress and almost 20% of fetuses with Diamond Blackfan Anemia (DBA) were not getting enough oxygen due to anemia. Overall, we found that pregnancies carrying a child with IBMFS were high-risk relative to the general population. Subsequent pregnancies by their mothers should also be considered high risk.

We also studied 102 pregnancies in 67 women with an IBMFS, including FA, DC, DBA, and SDS.[4] Almost half of these women were not able to have a pregnancy and almost a third (20 out of 67) had complications. Pregnancy requires a significant increase in blood cell production, an increase that may be difficult for someone with or at risk of bone marrow failure. About a third of women with an IBMFS in our study received red cell and/or platelet transfusions during pregnancy and/or delivery. Women with FA had decreased fertility and women with DC had normal fertility, but both had increased premature births and C-sections. Women with DC also had higher rates of miscarriage. We observed preeclampsia (dangerously high blood pressure during pregnancy) and placental problems in pregnant women with FA and DC.

Women with an IBMFS or who are carrying a child with an IBMFS would benefit from care provided by a multidisciplinary team of specialists with expertise in bone marrow failure disorders. We suggest pre-pregnancy counseling and high-risk monitoring of these pregnancies.

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[3] Giri N, Reed HD, Stratton P, Savage SA, Alter BP. Pregnancy outcomes in mothers of offspring with inherited bone marrow failure syndromes. *Pediatric Blood and Cancer*. 2018. Jan;65(1). doi: 10.1002/pbc.26757. Epub 2017 Aug 12.

[4] Giri N, Stratton P, Savage SA, Alter BP. Pregnancies in patients with inherited bone marrow failure syndromes in the NCI cohort. *Blood*. 2017. Oct 5;130(14):1674-1676. doi: 10.1182/blood-2017-08-802991. Epub 2017 Aug 24.

Androgens and Telomeres

Androgens are a potential treatment option for bone marrow failure in individuals with telomere biology disorders, such as Dyskeratosis Congenita (DC). Up to 70% of people with DC and severe bone marrow failure no longer require blood transfusions for anemia while taking androgens.[5]

We studied whether telomere length changes over time are different in people with DC who take androgens compared with those not taking androgens.[6] Ten people with DC were taking androgens (oxymetholone, danazol, or halotestin) and 16 were not. We followed these patients for between one and fifteen years and found that telomere length shortens with age at a similar rate whether or not the individual was treated with androgens.

Androgens are an effective treatment option for bone marrow failure caused by a telomere biology disorder such as DC, but they may have side effects, including liver toxicity, elevation of lipids and cholesterol, and masculinization. We do not know whether androgens change the progression of other DC-related side effects.

Recruiting for a Study of Cancer in Relatives of People with Fanconi Anemia

People with Fanconi Anemia (FA) have two pathogenic (disease-causing) variants in one of the genes in the FA/BRCA – DNA repair pathway; one variant is inherited from each parent. (Individuals are considered to be "FA carriers" if they inherited only one pathogenic variant). FA carriers usually include the parents of individuals with FA, half of the grandparents, and two-thirds of the siblings. We are studying these relatives to determine whether they are at increased risk of cancer. Our preliminary results suggest that the FA carriers do not have a substantially increased risk of cancer compared with the general population. However, we need to evaluate as many people as possible in order to thoroughly evaluate cancer risk in FA carriers.
If you are a relative of an individual with FA and would like to participate in our study, please contact us for information.

How Can I Join?

CONTACT US

Individuals with one of the inherited bone marrow failure syndromes and their family member are encouraged to participate.

Phone: 1-800-518-8474 to speak with referral nurse

Email: NCI.IBMFS@westat.com

Meet the NCI IBMFS Study Team

Back row from left: Matthew Gianferante, Lisa Leathwood, Sharon Savage, Gloria Chu, Payal Khincha, Moises Fiesco-Roa, Jessica Bayer;
Front row from left: Ann Carr, Lisa McReynolds, Maureen Risch, Stephanie Steinbart, Sonia Bhala, Neelam Giri, Blanche Alter;
Not pictured: Ashley Thompson, Lauren Vasta

Clinicians: Blanche P. Alter, MD, MPH, Sharon A. Savage, MD, Neelam Giri, MD, MBBS, Payal Khincha, MBBS, MSHS, Lisa McReynolds, MD, PhD, Matthew Gianferante, MD, MPH

Research Nurses: Lisa Leathwood, RN, BSN, Maureen Risch, RN, BSN

Research Assistant: Gloria Chu, BS

Program Manager: Jessica Bayer, BS

Genetic Counselor: Ann Carr, MS, CGC

Research Fellows: Moises Fiesco-Roa, MD, Sonia Bhala, BS, Ashley Thompson, BS, Lauren Vasta, MD

Please visit the NCI IBMFS website **www.marrowfailure.cancer.gov** to find out more about the key staff members and their roles on the study.

[5] Khincha PP, Wentzensen IM, Giri N, Alter BP, Savage SA. Response to androgen therapy in patients with dyskeratosis congenita. *Br J Haematol*. 2014 May;165(3):349-57. doi: 10.1111/bjh.12748. Epub 2014 Feb 12.

[6] Khincha PP, Bertuch AA, Gadalla SM, Giri N, Alter BP, Savage SA. Similar telomere attrition rates in androgen-treated and untreated dyskeratosis congenita patients. *Blood Advances*. 2018 Jun 12;2(11):1243-1249. doi: 10.1182/bloodadvances.2018016964.