NIH NATIONAL CANCER INSTITUTE

Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics

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Family Research *Matters*

Inherited Bone Marrow Failure Syndromes (IBMFS) Study Newsletter

In this Issue

We are collecting information on individuals in our IBMFS study who have had COVID-19 and who have received vaccination. Please fill out the attached short form to update our records.

Dr. Blanche Alter Retires

After more than 20 years at the NCI and over four decades of leadership in the inherited bone marrow failure disorders, Dr. Blanche Alter retired on June 30th, 2021. During her brilliant and extremely productive career in medicine, spanning more than five decades, Dr. Alter published over 350 peer-reviewed articles, books, and book chapters. Dr. Alter has devoted her career to the study of inherited bone failure syndromes (IBMFS). She joined the National Cancer Institute in 2000 to build the IBMFS program (https://marrowfailure.cancer.gov). Dr. Alter's vision in creating the world's only longitudinal cohort study of cancer in the IBMFS was the foundation that led to the quantification of cancer risks in these complex disorders, the discovery of more than a dozen causative genes, and characterization of previously unrecognized phenotypes. Her research helped to define novel diagnostic methods and elucidate numerous complications and manifestations of these disorders. Dr. Alter has received many awards for her ground-breaking research. Under Dr. Alter's leadership, the IBMFS program has come to serve as a model for the study of the mechanisms of cancer development in human populations. In addition to her in-depth scientific work, Dr. Alter has mentored many trainees over the years. More than twenty fellows and interns have benefited from the generous mentorship of Dr. Alter and have gone on to fulfilling careers in medicine, epidemiology, and other scientific disciplines. For the families with IBMFS, Dr. Alter continues to be deeply devoted to the care and well-being of patients and families with rare disorders, serving as a consistent resource and providing invaluable clinical expertise for them. While she will be greatly missed, Dr. Alter will continue to remain connected by serving as a special volunteer at NCI. Her unique and comprehensive IBMFS cohort will continue to advance the understanding of their underlying biology, connection with cancer etiology, and clinical manifestations. We wish Dr. Alter all the best in this new chapter of her life.

Team Members

Please see our website https://marrowfailure.cancer.gov/studyteam/ for full bios

The IBMFS Team
Back row from left: Matthew Gianferante, Burak Altintas, Sharon Savage, Marena Niewisch
Middle row from left: Maryam Rafati, Jessica Bayer, Lisa McReynolds, Ann Carr, Maureen Risch, Lisa Leathwood
Front row from left: Stephanie Steinbart, Blanche Alter, Neelam Giri

* Burak Altintas, MD is a post-doctoral fellow focusing on genotype-phenotype correlations in Fanconi anemia and gene discovery in IBMFS

Jessica Bayer was the project coordinator and protocol specialist for the IBMFS study

Ann Carr, MS, CGC is the genetic counselor for the IBMFS study

* Sarah Cole, MD is a pediatric hematology/oncology fellow at Walter Reed National Military Medical Center doing her research on Diamond Blackfan anemia

* Debbie Flamish, MA is a research assistant helping with many logistical aspects of the study

Matthew Gianferante, MD, MPH is a pediatric hematologist/oncologist working on the genetics of Diamond Blackfan anemia

Neelam Giri, MD is a pediatric hematologist/oncologist and is the principal investigator of the IBMFS study

* Rachel Hendricks is a post-baccalaureate fellow working on gene discovery in the IBMFS

Lisa Leathwood, RN is the lead research nurse and study manager for the IBMFS study

Lisa McReynolds, MD, PhD is a pediatric hematologist/oncologist working on the genomics of IBMFS

* Marena Niewisch, MD is a pediatric hematologist/oncologist characterizing the genotype-phenotype correlations in dyskeratosis congenita and related telomere biology disorders

* Valencia Owens is a post-baccalaureate fellow working on functional validation of novel telomere biology genes

Maureen Risch, RN is a clinical research nurse for the IBMFS study

* Maryam Rafati, MD is a medical geneticist working on novel IBMFS gene and variant discovery

* Camella Rising, PhD, MS, RDN- is a post-doctoral fellow co-leading the psychosocial study for dyskeratosis congenita and related telomere biology disorders

* Catherine Wilsnack, MSW, LMSW is a post-baccalaureate fellow co-leading the psychosocial study for dyskeratosis congenita and related telomere biology disorders

Sharon Savage, MD is the lead medical advisor for the IBMFS study and is in charge of the telomere biology disorders within the IBMFS study

* Mone't Thompson is a post-baccalaureate fellow working on the genetics of telomere biology disorders

* Ashley Thompson is a genetic counseling graduate student at Bay Path University working on the psychosocial study in dyskeratosis congenita and related telomere biology disorders

* Rebecca Trupp, RN, is a clinical research nurse for the IBMFS study

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* indicates new team members since our last newsletter

New Protocol in Development

Head and Neck Cancer in Fanconi Anemia (FA) and Dyskeratosis Congenita (DC) / Telomere Biology Disorders (TBD)

There has been a growing appreciation for the risk of head and neck cancer (squamous cell carcinoma) (HHSCC) in patients with FA or DC/TBD. The NCI investigators along with collaborators from NIH, other institutions, and input from the Fanconi Anemia Research Fund and Team Telomere are developing a protocol to enroll patients with FA and DC/TBD who are at risk of HNSCC. Stay tuned for details on how to enroll.

Update from the DC and Telomere Biology Group

The Clinical Care Consortium for Telomere-associated Ailments (CCCTAA) was officially formalized as a group of investigators across 18 institutions. The NCI IBMFS team will serve as the coordinating center for this important effort, working to create a database of telomere related research and serve as a resource to researchers.

NCI Launches a Study to Identify Unmet Needs of Families Living with Dyskeratosis Congenita (DC) and Related Telomere Biology Disorders (TBDs)

Project Background: During a 2019 conference of the organization Team Telomere, Catherine Wilsnack informally met a group of caregivers of children with DC and related TBDs. Ms. Wilsnack is a licensed social worker who, at the time, was completing a fellowship in the Clinical Genetics Branch (CGB) at the National Cancer Institute (NCI). Through shared conversation during breakfast, Catherine learned about many of the challenges experienced by families living with DC or a related TBD. This conversation, a small window into the lives of those affected, highlighted the need for families, clinicians, and the scientific community to better understand the potentially unmet needs of families living with DC or a related TBD.

Study Description: A collaboration formed between Team Telomere leaders and social science and medical researchers at the NCI (Ms. Wilsnack, Dr. Camella Rising, Dr. Sharon Savage, Dr. Sadie Hutson, and others) designed a needs assessment study for individuals and families living with DC or a related TBD. The aim of the study is to identify the informational, social, and emotional needs of families living with these rare diseases. To be eligible to participate in the study, you must be:

- Part of the Team Telomere community AND
- 18 years old or older AND:
  - An individual diagnosed with DC or a related TBD OR
  - A caregiver of an individual with DC or a related TBD OR
  - A bereaved parent of a family member who died due to complications of DC or a related TBD

How to Participate: The NCI researchers would be grateful for your participation. The study involves two components: a) completing an anonymous online survey that should take no more than 20 minutes and b) completing an approximately 1-hour confidential telephone interview. You may choose to complete only one component of the study (either the survey or the interview). If you complete BOTH the online survey and interview, you will have the option to choose either a $30 electronic gift card to Target or Amazon as acknowledgement of your time and effort.

If you are interested in participating in the study or have any questions, please contact Camella Rising, PhD, MS, RDN at 240-276-5262 or camella.rising@nih.gov.

COVID-19

COVID-19 has affected everyone across the globe, and patients with IBMFS and their families are no exception. Our team has had the opportunity to apply our expertise in collaboration with other NIH investigators studying the effects of COVID-19.

Many of you filled out the surveys tailored to rare disease communities for the study, COVID-19 in Communities- thank you! The data is incoming and will soon be analyzed.

If you or a family member has had COVID-19 please consider enrolling in COVIDcode (https://www.genome.gov/Current-NHGRI-Clinical-Studies/COVIDcode), a study to look at possible genetic susceptibility to severe COVID-19 disease. This can be done completely remotely.

A third study at the NIH is looking at the response to the COVID-19 vaccine in persons with immunodeficiencies. If you are interested, please see https://clinicaltrials.gov/ct2/show/NCT04852276 or email NIAIDCovidVaccineStudy@niaid.nih.gov

Recent Presentations and Papers from the Study

Presentations

Cancer Genotype-Phenotype Correlation in Patients with Fanconi Anemia and FANCD1/BRCA2 or FANCN/PALB2 Mediated Disease
McReynolds LJ, Biswas K, Giri N, Sharan SK, Alter BP.
Fanconi Anemia Research Fund Scientific Symposium, September 2020

Genetic Characterization of Schwachman Diamond Syndrome
Thompson AS, McReynolds LJ, Leathwood L, Carr AG, Giri N, Alter BP, Savage SA.
National Society of Genetic Counselors Annual Conference, November 2020

Genotype-phenotype Associations in Patients with Fanconi anemia: National Cancer Institute Cohort
Altintas B, Giri N, McReynolds LJ, Alter BP.
Fanconi Anemia Research Fund Scientific Symposium, September 2020
American Society of Hematology 62nd Annual Meeting, December 2020

Disease Progression and Outcomes in Patients with Telomere Biology Disorders
Niewisch MR, Giri N, McReynolds LJ, Bhala S, Alsaggaf R, Alter BP, Savage SA.
American Society of Hematology 62nd Annual Meeting, December 2020

Risk of Cancer in Individuals with a Single Pathogenic Variant of a Fanconi Anemia Gene: a Study of Relatives
McReynolds LJ, Leathwood L, Carr AG, Giri N, Alter BP.
American Society of Hematology 62nd Annual Meeting, December 2020

***FANCA* variants in exons 27-30 are associated with solid tumors**
Altintas B, Giri N, McReynolds LJ, Alter BP.
Fanconi Anemia Research Fund Scientific Symposium, July 2021

Fanconi Anemia: A Story of Multiple Syndromes
Alter BP, Giri N, McReynolds LJ, Altintas B.
Fanconi Anemia Research Fund Scientific Symposium, July 2021

Publications

Bhala, S., A. F. Best, N. Giri, B. P. Alter, M. Pao, A. Gropman, E. H. Baker, and S. A. Savage. "**Central Nervous System Manifestations in Patients with Telomere Biology Disorders.**" *Neurol Genet* 5, no. 6 (Dec 2019): 370.

Toufektchan, E., V. Lejour, R. Durand, N. Giri, I. Draskovic, B. Bardot, P. Laplante, S. Jaber, B. P. Alter, J. A. Londono-Vallejo, S. A. Savage, and F. Toledo. "**Germline Mutation of MDM4, a Major P53 Regulator, in a Familial Syndrome of Defective Telomere Maintenance.**" *Science Advances* 6, no. 15 (Apr 2020): eaay3511.

Alter, B. P., and A. F. Best. "**Frequency of Heterozygous Germline Pathogenic Variants in Genes for Fanconi Anemia in Patients with Non-BRCA1/BRCA2 Breast Cancer: A Meta-Analysis.**" *Breast Cancer Research and Treatment* 182, no. 2 (Jul 2020): 465-76.

Bhar, S., F. Zhou, L. C. Reineke, D. K. Morris, P. P. Khincha, N. Giri, L. Mirabello, K. Bergstrom, L. D. Lemon, C. L. Williams, Y. Toh, M. T. Elghetany, R. E. Lloyd, B. P. Alter, S. A. Savage, and A. A. Bertuch. "**Expansion of Germline RPS20 Mutation Phenotype to Include Diamond-Blackfan Anemia.**" *Hum Mutation* 41, no. 11 (Nov 2020): 1918-30.

Himes, R. W., E. H. Chiou, K. Queliza, D. S. Shouval, R. Somech, S. Agarwal, K. Jajoo, D. S. Ziegler, C. P. Kratz, J. Huang, T. L. Lucas, K. C. Myers, A. S. Nelson, C. D. DiNardo, B. P. Alter, N. Giri, P. P. Khincha, L. J. McReynolds, C. Dufour, F. Pierri, F. D. Goldman, Y. Sherif, S. A. Savage, T. Miloh, and A. A. Bertuch. "**Gastrointestinal Hemorrhage: A Manifestation of the Telomere Biology Disorders.**" *Journal of Pediatrics* 230 (Mar 2021): 55-61.e4.

Gianferante, M. D., M. W. Wlodarski, E. Atsidaftos, L. Da Costa, P. Delaporta, J. E. Farrar, F. D. Goldman, M. Hussain, A. Kattamis, T. Leblanc, J. M. Lipton, C. M. Niemeyer, D. Pospisilova, P. Quarello, U. Ramenghi, V. G. Sankaran, A. Vlachos, J. Volejnikova, B. P. Alter, S. A. Savage, and N. Giri. "**Genotype-Phenotype Association and Variant Characterization in Diamond-Blackfan Anemia Caused by Pathogenic Variants in RPL35A.**" *Haematologica* 106, no. 5 (May 1 2021): 1303-10.

Giri, N., B. P. Alter, S. A. Savage, and P. Stratton. "**Gynaecological and Reproductive Health of Women with Telomere Biology Disorders.**" *British Journal of Haematology* 193, no. 6 (Jun 2021): 1238-46.

Brodie, S. A., P. Khincha, N. Giri, A. J. Bouk, M. Steinberg, J. Dai, L. Jessop, F. X. Donovan, S. C. Chandrasekharappa, K. de Andrade, I. Maric, S. R. Ellis, L. Mirabello, B. Alter, and S. A. Savage. "**Pathogenic Germline IKZF1 Variant Alters Hematopoietic Gene Expression Profiles.**" *Cold Spring Harb Molecular Case Studies* (Jun 23 2021).

Thank you for participating in our IBMFS study!
The strength of our study is in our participants.