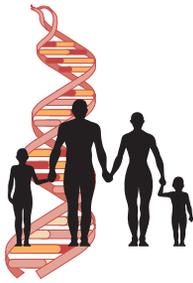


NATIONAL CANCER INSTITUTE



Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics

Family Research *Matters*

Inherited Bone Marrow Failure Syndromes (IBMFS) Study Newsletter

Thank You for Taking Part in the Inherited Bone Marrow Failure Syndromes Study

Our research team is truly grateful to you and your family members for taking part in this study. We appreciate the time and energy you spent completing the questionnaires, giving us access to your medical records, and providing various tissue samples for our research. We want to update you on the progress of the IBMFS Study (NCI 02-C-0052). An earlier newsletter, available on our website, www.marowfailure.cancer.gov, has details about each of the syndromes. The current newsletter contains summary information.

More than 700 families have begun enrollment, which starts with a telephone interview and then a set of questionnaires on your medical history. More than 450 families have completed this process. We saw more than 170 families at the National Institutes of Health (NIH) Clinical Center by the end of 2015, and we are continuing to enroll new families.

Those who traveled to the NIH Clinical Center received a detailed evaluation of clinical and genetic features, as well as results from laboratory tests. Those not seen at NIH supplied similar information.

Our research simply could not be done without your willingness to take part in this study. We thank you for your vital contributions.

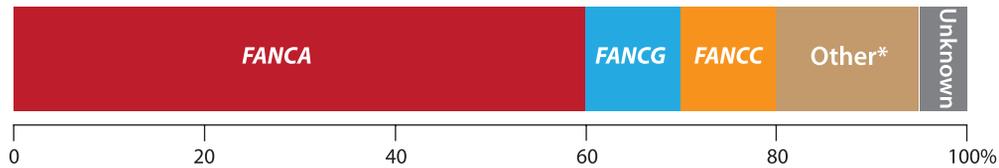
Blanche P. Alter, MD, MPH
Principal Investigator

Sharon A. Savage, MD
Co-Investigator

Neelam Giri, MD
Associate Investigator

FANCONI ANEMIA (FA)

Proportion of patients with mutations in specific genes



* Other: Between 1-3% carry a mutation in one of the following genes: *FANCB*, *FANCD1/BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG/XRCC9*, *FANCI*, *FANCL/BRIP1*, *FANCL*, *FANCM*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, *FANCO*, *FANCR/RAD51*, *FANCS/BRCA1*, *FANCT/UBE2*

FA can be diagnosed from birth to adulthood, but usually by age 10. It is inherited primarily as an autosomal recessive disorder. Patients frequently have physical characteristics such as short stature, café au lait spots, areas of increased or decreased pigmentation, absent or underdeveloped bones in the arms and/or thumbs, small eyes, small heads, abnormal kidney development, hearing problems, and more. They have very high rates of bone marrow failure (also called aplastic anemia), leukemia, and solid tumors.

In the past, FA was identified in young children with bone marrow failure and multiple birth defects; today, we diagnose patients at all ages. We look for specific medical complications, and test for increased chromosome breakage and mutated FA genes. Nineteen genes have been found so far; 17 are autosomal recessive.

FANCB is X-linked recessive; *FANCR (RAD51)* is autosomal dominant.

More than 85% of the families in our study have information about either their FA gene mutation(s) or specific complementation group.

What have we learned so far?

- About 1 in 180 individuals (called carriers) carry at least one copy of a mutated FA gene. This is higher than the rate of 1 in 300 suggested many years ago.
- About 10-15% of patients have changes in their blood that make the typical diagnostic test (chromosome breakage) unclear. This is called “mosaicism.” Skin cells may need to be examined for those individuals.

Definitions of Common Terms

Modes of inheritance

Autosomal dominant (AD): only one mutated gene is required to result in illness

Autosomal recessive (AR): affected individuals have mutations in both copies of a gene, one from each parent

X-linked (XLR): transmitted from a mother to a son with only one copy of the abnormal version of the X chromosome

For other definitions, please search the cancer.gov dictionary: <http://www.cancer.gov/publications/dictionaries/cancer-terms>

- One-third of the patients in our study also have other physical findings, including an association called “VACTERL-H,” which stands for Vertebral anomalies, Anal atresia, Congenital heart disease, Tracheo-esophageal fistula, Esophageal atresia, Renal anomalies, Limb anomalies (primarily radii and/or thumbs), and Hydrocephalus. Patients with this classification have a minimum of three of these eight features.
- Women with FA often have premature ovarian failure; clinicians can screen for this by testing serum levels of a hormone called anti-Müllerian hormone.

Current Research

- Detailed evaluation of endocrine functions.
- Pregnancy complications in mothers of patients with FA and in women who have FA.
- Hearing and ear abnormalities.
- Continued search for new genes using next generation sequencing.

Future Directions

- Is there a long-term benefit from hematopoietic stem cell transplant before obvious bone marrow failure or leukemia?
- What are the modifiers of cancer risk (type of mutated FA gene, other mutated genes which may interact, modifiers of genes, environmental factors)?
- Are there better screening tests for people who are at risk of cancer?
- Are there cancer prevention strategies unique to FA?

Cancer among patients in the NCI FA Study:

28 cases among 156 patients

Main types:

Leukemia, head and neck, gynecologic, and brain tumors

Risk of any cancer (including leukemia):

Much higher than in the general population

Risks of specific types of cancer are even higher:

Head and neck cancer, including cancer of the tongue, acute myeloid leukemia

Head and neck tumors did not show evidence of human papillomavirus (HPV) in patients with FA in our study. Routine HPV vaccine is as effective as in the general population, and should be given according to standard guidelines.

DYSKERATOSIS CONGENITA (DC)

Proportion of patients with mutations in specific genes



* Other: Between 1-3% carry a mutation in one of the following genes: *NOP10/NOLA3*, *NHP2/NOLA2*, *WRAP53/TCAB1*, *CTC1*, *RTEL1*, *ACD/TPP1*, *PARN*

DC has all modes of inheritance. Affected patients may be identified because they have features of the “diagnostic triad” of dysplastic fingernails, lacey pigmentation, and oral leukoplakia (white spots in the mouth). They may have other physical findings such as short stature, constant tearing, infected eyelids, loss of eyelashes, early gray hair, narrow esophagus, liver fibrosis or cirrhosis, abnormal teeth, hip necrosis, pulmonary fibrosis, excessive sweating, and developmental delay. The most frequent complication is bone marrow failure (aplastic anemia). Some patients may have few or none of these features but are identified because they have an affected family member, and/or have short telomeres (see below), and/or mutations in DC genes.

There are now 11 known genetic causes of DC. They include *DKC1*, *NOP10*, *NHP2*, *WRAP53*, *CTC1*, *ACD*, *PARN*, *TERC*, *TERT*, *TINF2*, and *RTEL1*. Our prior work led to the discovery of *TINF2* and *WRAP53*. We were also the first to describe *RTEL1* and *ACD* as DC genes.

About 70% of families with DC in our study have information about their genes, and more are under investigation.

What have we learned so far?

- The only clinically certified diagnostic test for DC is measurement of telomere length by flow cytometry and fluorescent *in situ* hybridization (flow-FISH), which we introduced in 2007. Patients with other syndromes do not have telomeres as short as patients with DC.
- Patients with DC require lower doses of androgens for their aplastic anemia than patients with FA. One side effect we observed is an increase in blood cholesterol.

- Hematopoietic stem cell transplant (HSCT) can be used to cure aplastic anemia in DC; lungs must be protected from side effects of preparative regimens such as radiation or chemotherapy because of the increased risk of pulmonary fibrosis.
- A rare recessive mutation in *RTEL1* was identified in individuals with Ashkenazi Jewish ancestry. The carrier frequency is between 0.5% and 1%—common enough to be included in prenatal screening tests for this population.
- DC is part of a spectrum of telomere biology disorders that also include Hoyeraal-Hreidarsson, Revesz syndrome, and Coats plus, and some individuals with illnesses such as aplastic anemia and pulmonary fibrosis.

Current Research

- Discovery of new DC-associated genes using the latest methods (next generation sequencing).
- Working with scientists to understand the way in which mutations in DC genes lead to the clinical findings.
- Collaborating with investigators from institutions around the world to create the Clinical Care Consortium of Telomere-Associated Ailments.
- Investigating how the physical features of DC relate to specific genetic mutations.

Future Directions

- What are the modifiers of cancer risk?
- Are there better screening tests for those at risk of cancer?
- Are there cancer prevention strategies unique to DC?
- Improved management of clinical complications in DC.

Cancer among patients in the NCI DC Study:

22 cases among 168 patients

Most common:

Oral cavity and leukemia, similar to those in FA

Risk of any cancer:

~4-times that of the general population

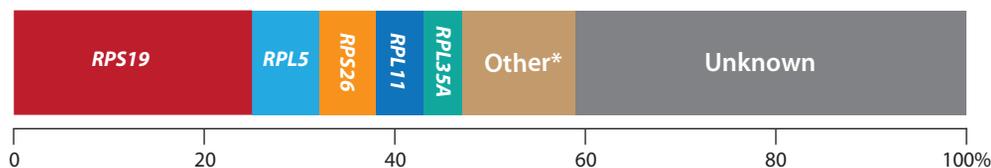
Risks of specific types of cancer are even higher:

Head and neck cancer, including cancer of the tongue, acute myeloid leukemia

Head and neck tumors did not show evidence of human papillomavirus (HPV) in patients with DC in our study. Routine HPV vaccine is as effective as in the general population, and should be given according to standard guidelines.

DIAMOND-BLACKFAN ANEMIA (DBA)

Proportion of patients with mutations in specific genes



* Other: Between 1-3% carry a mutation in one of the following genes: *RPS7*, *RPS10*, *RPS17*, *RPS24*, *RPS29*; *RPL15*, *RPL26*; *GATA-1*

The inheritance of DBA is primarily autosomal dominant (AD); half appear to be new mutations in the affected person that are not seen in parents (*de novo*). Mutations have been identified in 12 genes responsible for ribosome function—the microscopic “machines” in every cell that help build proteins responsible for maintaining cell function and human life. All of the ribosomal genes are AD; *GATA-1* is an X-linked recessive gene. Patients are often identified because of anemia during the first year of life; they have large red blood cells (macrocytic anemia), which distinguish them from patients with iron deficiency anemia. Physical findings may include short stature, abnormal thumbs, short neck, occasionally cleft

palate, and various other less common features. The diagnostic test is elevated levels of red cell adenosine deaminase.

More than half of the families with DBA in our study have information about their genes and more are under investigation.

Current Research

- Investigating additional genes using the latest methods of next generation sequencing.
- Collaborating with basic scientists to understand the way in which mutations in DBA genes lead to the clinical findings.

Future Directions

- What are the modifiers of cancer risk?
- Are there better screening tests for those at risk of cancer?
- Are there cancer prevention strategies unique to DBA?
- Are there specific treatments for the anemia of DBA?

Cancer among patients in the NCI DBA Study:

17 cases among 608 patients (analyzed from the Diamond-Blackfan Anemia Registry, in collaboration with Drs. Adrianna Vlachos and Jeffrey Lipton)

Risk of any cancer many times higher than the general population:

~5-fold higher than the general population

Risk of specific types of cancer are substantially higher:

Acute myeloid leukemia, colon carcinoma, osteosarcoma, female gynecologic cancers

DBA-related tumors are not in HPV-associated body sites so have not been tested for HPV. Routine HPV vaccine is as effective as in the general population, and should be given according to standard guidelines.

SHWACHMAN-DIAMOND SYNDROME (SDS)

Proportion of patients with mutations in the *SBDS* gene



The inheritance of SDS is autosomal recessive. Ninety-five percent of patients have two mutated *SBDS* genes reported, one from each parent. Patients with SDS are often diagnosed in infancy, due to neutropenia and abnormalities in the patients' ability to absorb nutrients from food. Physical findings include mostly short stature, and a bony abnormality called "metaphyseal dysostosis." Individuals with SDS are at risk of developing acute myeloid leukemia.

The SDS registry (<http://sdsregistry.org/>) enrolls patients with SDS. Our NCI study has enrolled 31 patients; 2 have developed acute myeloid leukemia, which is more than expected. Patients with SDS are examined in the same manner as those with the three syndromes described above. Their levels of red cell ADA, chromosome breakage, and telomere length are within the normal range. Eighty-four percent of SDS families in our study have two mutated copies of *SBDS*, 12% have one, and 4% have normal *SBDS* genes. Those patients are being studied further.

OTHER SYNDROMES

Thrombocytopenia Absent Radii (TAR): These patients are diagnosed in infancy because they are missing the radial bone in each arm (with thumbs present) and thrombocytopenia (low platelets). The usual pattern is that one parent has a chromosome 1 in which there is a small deletion of DNA at chromosome 1q21.1, and the other parent has a single change in the *RBM8A* gene also in the same region of chromosome 1. We are evaluating new genomic technologies to help understand this disorder. We have seen a limited number of families with TAR at the NIH.

Severe Congenital Neutropenia: We refer these families to the Severe Chronic Neutropenia International Registry (<http://depts.washington.edu/registry/>) which focuses on their disorder.

We have included families with findings that are “like” one of the syndromes, but do not have sufficient evidence for us to be clear on their label. We call them “X-like”, where X may be FA, DC, DBA, etc. We manage and advise them according to the recommendations for “X”, and are searching their DNA for variations in genes that may cause their syndrome.

The search for missing genes using comprehensive genomic approaches

We are very interested in identifying the disease-causing gene in all study participants and in matching this genetic information with the medical and laboratory features in each disorder. Families in the study who have not had the disease-causing gene identified at the time of enrollment in the study may have samples collected for our comprehensive genomic analyses. These methods include whole exome sequencing to evaluate the DNA “spelling” of each gene and analyses that look for insertions or deletions in genes. Detailed laboratory experiments are performed to prove that the genetic variant in the gene of interest affects the function of the RNA or protein it encodes.

For further details and explanations, please consult our website
www.marrowsfailure.cancer.gov

Selected *Recent Publications* are listed on the website.

If you are moving or changing your telephone or other contact information, please call 1-800-518-8474 and let the IBMFS Study Team know.



IBMFS Study Team (from left to right): Blanche Alter, MD; Sharon Savage, MD; Neelam Giri, MD; Lisa Leathwood, RN, BSN; Ann Carr, MS, CGC; Kristen Davis, BA; Maureen Risch, RN, BSN; Gloria Chu, BS.



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HHS/HIN/CI
Division of Cancer Epidemiology and Genetics
Clinical Genetics Branch
9609 Medical Center Drive
Room 6E526, MSC 9772
Bethesda, MD 20892-9772
Official Business
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