



Fanconi Anemia

RESEARCH FUND, INC.

Fanconi anemia and its diagnosis:

Fanconi anemia (FA), named for Swiss pediatrician, Guido Fanconi, is one of the inherited anemias that leads to bone marrow failure (aplastic anemia). FA is primarily a recessive disorder: if both parents carry a defect (mutation) in the same FA gene, each of their children has a 25% chance of inheriting the defective gene from both parents. When this happens, the child will have FA.

While the total number of FA patients is not documented worldwide, scientists estimate that the carrier frequency (carriers are people carrying a defect in an FA gene, whose matching FA gene is normal) for FA in the U.S. is 1 in 181. The incidence rate, or the likelihood of a child being born with FA, is about 1 in 131,000 in the U.S., with approximately 31 babies born with FA each year in this country.

Scientists have now discovered 15 FA genes [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, N, P and RAD51C]. These genes account for more than 95% of the cases of Fanconi anemia. Mutations in FA-A, FA-C and FA-G are the most common and account for approximately 85% of the FA patients worldwide. FA-D1, FA-D2, FA-E, FA-F and FA-L account for 10%. FA-B, FA-I, FA-J, FA-M, FA-N, FA-P and RAD51C represent less than 5% of FA patients. Some patients do not appear to have mutations in these 15 genes, so we anticipate that additional FA genes will be discovered in the future.

FA occurs equally in males and females. It is found in all ethnic groups. Though considered primarily a blood disease, it may affect all systems of the body. Most patients develop bone marrow failure, necessitating a stem cell transplant. Many patients develop acute myelogenous leukemia (AML). Patients who live into adulthood are extremely likely to develop head and neck, gynecologic, and/or gastrointestinal cancer and at a much earlier age (20s, 30s, and 40s) than the general population. Patients who have had a successful stem cell transplant and, thus, are cured of the blood problems associated with FA still must have regular examinations to watch for signs of cancer. Some patients do not reach adulthood; 80% reach age 18 or more. The current median lifespan is 29 years, with some patients living into their 30s, 40s, and 50s.

Fanconi anemia patients are usually smaller than average. FA usually reveals itself before children are 12 years old, but in rare cases no symptoms are present until adulthood. Patients may feel extreme fatigue and have frequent infections. Nosebleeds or easy bruising may be a first sign. Blood tests may reveal a low white, red cell or platelet count or other abnormalities. Sometimes myelodysplasia (MDS) or AML is the first sign of FA. On occasion, FA isn't diagnosed until squamous cell carcinoma has been identified.

At least 60% of FA patients are born with at least one physical anomaly. This may include any of the following:

- Short stature
- Thumb and arm anomalies: an extra or misshapen or missing thumbs and fingers or an incompletely developed or missing radius (one of the forearm bones)
- Skeletal anomalies of the hips, spine or ribs
- Kidney problems
- Skin discoloration (*café-au-lait* spots); portions of the body may have a suntanned look
- Small head or eyes
- Mental retardation or learning disabilities
- Low birth weight
- Gastrointestinal difficulties
- Small reproductive organs in males
- Defects in tissues separating chambers of the heart

The definitive test for FA at the present time is a chromosome breakage test: some of the patient's blood cells are treated, in a test tube, with a chemical that crosslinks DNA. Normal cells are able to correct most of the damage and are not severely affected whereas FA cells show marked chromosome breakage. There are two chemicals commonly used for this test: DEB (diepoxybutane) and MMC (mitomycin C). These tests can be performed prenatally on cells from chorionic villi or from the amniotic fluid.

Many cases of FA are not diagnosed at all or are not diagnosed in a timely manner. FA should be suspected and tested for in any infant born with the thumb and arm abnormalities described previously. Anyone developing aplastic anemia at any age should be tested for FA, even if no other defects are present. Any patient who develops squamous cell carcinoma of the head and neck, gastrointestinal or gynecologic system at an early age and without a history of tobacco or alcohol use, should be tested for FA. Many FA patients show no other abnormalities. It is absolutely essential to test for FA before contemplating stem cell transplantation for aplastic anemia or treatment for cancer, as standard chemotherapy and radiation protocols may prove toxic to FA patients.

The Fanconi Anemia Research Fund, Inc:

Lynn and Dave Frohnmayer started the Fanconi Anemia Research Fund, Inc. in 1989, to fund research into this disease and to provide support to affected families worldwide by medical referral, education, publications, and annual family meetings. To this end, more than \$28 million has been raised since the Fund's inception.

In the area of research, donors to the Fund have seen their gifts multiply many fold. Fifty-four universities and institutions have received support from the Fund for 183 research projects to study FA. Many of these researchers have gone on to receive major grants for FA research from the National Institutes of Health and other governmental and nationwide agencies. Grants from private foundations have helped us move FA science forward more quickly than was ever thought possible.

In addition, the Fanconi Anemia Research Fund, Inc. publishes *Fanconi Anemia: Guidelines for Diagnosis and Management*; the *FA Family Newsletter*; the *Fanconi Anemia International Treatment and Testing Resource Guide* and the *FA Courier*, a publication to encourage families to contribute research materials, such as tumor samples, for FA research. These publications are sent worldwide to thousands of researchers, physicians, and families.

The Fund convenes an annual International Fanconi Anemia Scientific Symposium at which researchers from around the world present the results of their research. In addition, the Fund sponsors a variety of smaller, highly specialized scientific meetings, gathering researchers together to focus on such topics as: bone marrow transplants, cytogenetics, squamous cell carcinoma, small molecules, and acute myelogenous leukemia. In April 2008, the Fund held a Clinical Care Conference which resulted in the publication of *Fanconi Anemia: Guidelines for Diagnosis and Management (2008)*.

For families, the Fund holds an annual Family Meeting, which is also a recreational camp for parents and children. Besides the networking and recreation aspects of the family meeting, physicians and researchers present updates to parents during a six day conference. This meeting is invaluable to youngsters who can meet with other FA youngsters in a fun- and activity-filled environment, for parents who can relax with other FA parents and have an opportunity to talk directly with FA experts, and for those experts to have an opportunity to talk with FA families. In addition, the Fund holds meetings for adults with FA, featuring presentations from physicians and researchers, as well as opportunities for patients to network with one another.

The Fund also provides ongoing telephone, letter and e-mail support to families affected by FA worldwide.

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