



Fanconi anemia and its diagnosis:

Fanconi anemia (FA), named for the Swiss pediatrician Guido Fanconi, is an inherited disorder that can lead to bone marrow failure (aplastic anemia), leukemia and/or solid tumors, with oral and gynecologic tumors being the most common. FA is almost exclusively 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 one copy of a particular FA gene, whose other copy of that same 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.

Scientists have now discovered 21 FA genes [*FANCA*, *B*, *C*, *D1* (also known as *BRCA2*), *D2*, *E*, *F*, *G*, *I*, *J*, *L*, *M*, *N*, *O*, *P*, *Q*, *RAD51*, *BRCA1*, *T*, *U* and *V*]. Mutations in these genes account for more than 95% of reported Fanconi anemia cases. Mutations in *FANCA*, *FANCC* and *FANCG* are the most common and account for approximately 85% of FA patients worldwide. *FANCD1*, *FANCD2*, *FANCE*, *FANCF* and *FANCL* account for 10%, while the remaining FA genes, *FANCB*, *FANCI*, *FANCI*, *FANCM*, *FANCN*, *FANCO*, *FANCP*, and *FANCQ* represent less than 5%. Some individuals with FA do not appear to have mutations in these 21 genes, so we anticipate that additional FA genes will be discovered in the future.

FA occurs equally in males and females, except for *FANCB* patients who are exclusively male. It is found in all ethnic groups. Though originally considered primarily a blood disease, it may affect all systems of the body. The majority of individuals affected by FA develop bone marrow failure, necessitating a stem cell transplant. Many patients develop Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS). Patients who live into adulthood are extremely likely to develop head and neck, gynecologic, and/or gastrointestinal cancer which occur 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. The current median lifespan varies depending on the complementation group, but the overall median lifespan for FA individuals is 33 years. Some adults live into their 30s, 40s, and 50s and 80% reach 18 or more.

Fanconi anemia individuals are usually smaller than average and some have developmental defects, including thumb and arm anomalies. FA usually reveals itself before children are 12 years old, but in rare cases no symptoms are present until adulthood. First signs of FA may be extreme fatigue, frequent infections, nosebleeds or easy bruising. Blood tests may reveal a low white, red cell or platelet count or other abnormalities, defined medically as anemia. Sometimes MDS or AML is the first sign of FA. On occasion, FA isn't diagnosed until cancer (usually the type called squamous cell carcinoma) has been identified.

At least 60% of individuals affected by FA are born with at least one physical anomaly. This may include:

- 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
- Intellectual developmental delay 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. Chromosomes are structures in the body that are made up of DNA. For the test, some of the patient's blood cells are treated, in a test tube, with a chemical that fuses different strands of DNA together (called crosslinkers). Normal cells are able to correct most of this type of DNA damage by unfusing the DNA strands and are not severely affected. However, FA cells are unable to break apart the strands of DNA and their chromosomes snap or break. 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 anyone born with thumb/arm abnormalities and anyone developing aplastic anemia at any age, even if no other defects are present. Any patient who develops cancers of the head and neck, gynecologic system or gastrointestinal system (squamous cell carcinoma or adenocarcinoma) 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 and therefore all siblings of FA patients (even those apparently unaffected) should be tested. 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:

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 \$32 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-six universities and institutions have received support from the Fund for more than 215 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 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 AML. In April 2013, the Fund held a Clinical Care Conference which led to publication of *Fanconi Anemia: Guidelines for Diagnosis and Management* in 2014.

For families, the Fund holds an annual Family Meeting which is also a recreational camp for parents and children. Besides the networking and recreational aspects of the meeting, physicians and researchers present updates to parents during a six day conference. This meeting is invaluable for youngsters to meet others with FA and is a fun- and activity-filled environment for parents who can relax with other FA parents and talk directly with FA medical experts. In addition, the Fund holds an FA Adult Meeting every year that features both presentations from physicians and researchers and opportunities for networking.

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

To contact the Fanconi Anemia Research Fund:

Fanconi Anemia Research Fund

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