



About Fanconi Anaemia

Fanconi Anaemia (FA) is a rare, life-limiting genetic disorder causing bone marrow failure in children and a predisposition to gynaecological and head & neck cancers, together with other complications both in childhood and in later life. Whilst the bone marrow failure element can be corrected through bone marrow transplantation from a well-matched donor, there is still no cure for the cancer-predisposing condition.

Fanconi Anaemia and its Diagnosis:

Fanconi anaemia (FA), named after Swiss paediatrician Guido Fanconi, is one of the inherited anaemias that leads to bone marrow failure (aplastic anaemia) and a predisposition to head, neck and gynaecological cancers. It is a recessive disorder, i.e. 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. Where 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 UK is 1 in 350. The incidence rate, or the likelihood of a child being born with FA, is 2-3 per million in the UK, with an estimated 100 to 150 families affected.

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 anaemia. 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 and 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 bone marrow transplant. Many patients eventually develop acute myelogenous leukaemia (AML). Patients who live into adulthood are extremely likely to develop head and neck, gynaecological, and/or gastrointestinal cancer and at a much earlier age (20s, 30s, and 40s) than the general population. Patients who have had a successful bone marrow transplant and, thus, are cured of the blood problem associated with FA still must have regular examinations to watch for signs of cancer. Many patients do not reach adulthood.

Fanconi anaemia 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 or AML is the first sign of FA.

FA sometimes is evident at birth through a variety of physical defects. These may include any of the following:

- 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 discolouration (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 anaemia 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 gynaecological 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 bone marrow transplantation for aplastic anaemia or treatment for cancer. FA patients respond extremely poorly to standard chemotherapy and radiation protocols.

The Wider Significance of Fanconi Anaemia

Although FA only affects a small number of people in the UK, the genes concerned, i.e. the 'Fanconi pathway', are of great potential importance for all, as they keep our DNA healthy and preventing cancers. The Fanconi pathway is often responsible for a cancer's resistance to chemotherapy drugs. Knowing how to manipulate the Fanconi pathway is likely to lead to better and more successful treatments for *all* cancers.

Information Sheet prepared by R Dagleish in 2015 with material sourced from the UK Fanconi Anaemia Standards of Care Document 2008 and from the Fanconi Anaemia Research Fund.