Fanconi Anemia

Subjects: Genetics & Heredity
Contributor: Nicole Yin

Fanconi anemia is a condition that affects many parts of the body. People with this condition may have bone marrow failure, physical abnormalities, organ defects, and an increased risk of certain cancers.

Keywords: genetic conditions

1. Introduction

In people with familial restrictive cardiomyopathy, the heart muscle is stiff and cannot fully relax after each contraction. Impaired muscle relaxation causes blood to back up in the atria and lungs, which reduces the amount of blood in the ventricles.

Familial restrictive cardiomyopathy can appear anytime from childhood to adulthood. The first signs and symptoms of this condition in children are failure to gain weight and grow at the expected rate (failure to thrive), extreme tiredness (fatigue), and fainting. Children who are severely affected may also have abnormal swelling or puffiness (edema), increased blood pressure, an enlarged liver, an abnormal buildup of fluid in the abdominal cavity (ascites), and lung congestion. Some children with familial restrictive cardiomyopathy do not have any obvious signs or symptoms, but they may die suddenly due to heart failure. Without treatment, the majority of affected children survive only a few years after they are diagnosed.

Adults with familial restrictive cardiomyopathy typically first develop shortness of breath, fatigue, and a reduced ability to exercise. Some individuals have an irregular heart beat (arrhythmia) and may also experience a sensation of fluttering or pounding in the chest (palpitations) and dizziness. Abnormal blood clots are commonly seen in adults with this condition. Without treatment, approximately one-third of adults with familial restrictive cardiomyopathy do not survive more than five years after diagnosis.

2. Frequency

Fanconi anemia occurs in 1 in 160,000 individuals worldwide. This condition is more common among people of Ashkenazi Jewish descent, the Roma population of Spain, and Black South Africans.

3. Causes

Mutations in at least 15 genes can cause Fanconi anemia. Proteins produced from these genes are involved in a cell process known as the FA pathway. The FA pathway is turned on (activated) when the process of making new copies of DNA, called DNA replication, is blocked due to DNA damage. The FA pathway sends certain proteins to the area of damage, which trigger DNA repair so DNA replication can continue.

The FA pathway is particularly responsive to a certain type of DNA damage known as interstrand cross-links (ICLs). ICLs occur when two DNA building blocks (nucleotides) on opposite strands of DNA are abnormally attached or linked together, which stops the process of DNA replication. ICLs can be caused by a buildup of toxic substances produced in the body or by treatment with certain cancer therapy drugs.

Eight proteins associated with Fanconi anemia group together to form a complex known as the FA core complex. The FA core complex activates two proteins, called FANCD2 and FANCI. The activation of these two proteins brings DNA repair proteins to the area of the ICL so the cross-link can be removed and DNA replication can continue.

Eighty to 90 percent of cases of Fanconi anemia are due to mutations in one of three genes, *FANCA*, *FANCC*, and *FANCG*. These genes provide instructions for producing components of the FA core complex. Mutations in any of the many genes associated with the FA core complex will cause the complex to be nonfunctional and disrupt the entire FA pathway. As a result, DNA damage is not repaired efficiently and ICLs build up over time. The ICLs stall DNA replication,

ultimately resulting in either abnormal cell death due to an inability make new DNA molecules or uncontrolled cell growth due to a lack of DNA repair processes. Cells that divide quickly, such as bone marrow cells and cells of the developing fetus, are particularly affected. The death of these cells results in the decrease in blood cells and the physical abnormalities characteristic of Fanconi anemia. When the buildup of errors in DNA leads to uncontrolled cell growth, affected individuals can develop acute myeloid leukemia or other cancers.

3.1. The Genes Associated with Fanconi Anemia

- BRCA2
- FANCA
- FANCC
- FANCG

4. Inheritance

Fanconi anemia is most often inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Very rarely, this condition is inherited in an X-linked recessive pattern. The gene associated with X-linked recessive Fanconi anemia is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- FA
- Fanconi hypoplastic anemia
- Fanconi pancytopenia
- Fanconi panmyelopathy

References

1. Auerbach AD. Fanconi anemia and its diagnosis. Mutat Res. 2009 Jul31;668(1-2):4-10. doi: 10.1016/j.mrfmmm.2009.01.013.
2. de Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia.Mutat Res. 2009 Jul 31;668(1-2):11-9. doi: 10.1016/j.mrfmmm.2008.11.004.
3. Deakyne JS, Mazin AV. Fanconi anemia: at the crossroads of DNA repair.Biochemistry (Mosc). 2011 Jan;76(1):36-48. Review.
4. Green AM, Kupfer GM. Fanconi anemia. Hematol Oncol Clin North Am. 2009Apr;23(2):193-214. doi: 10.1016/j.hoc.2009.01.008. Review.
5. Kee Y, D'Andrea AD. Expanded roles of the Fanconi anemia pathway in preservinggenomic stability. Genes Dev. 2010 Aug 15;24(16):1680-94. doi:10.1101/gad.1955310. Review.
6. Kitao H, Takata M. Fanconi anemia: a disorder defective in the DNA damageresponse. Int J Hematol. 2011 Apr;93(4):417-424. doi: 10.1007/s12185-011-0777-z.
7. Mathew CG. Fanconi anaemia genes and susceptibility to cancer. Oncogene. 2006 Sep 25;25(43):5875-84. Review.
8. Neveling K, Endt D, Hoehn H, Schindler D. Genotype-phenotype correlations inFanconi anemia. Mutat Res. 2009 Jul 31;668(1-2):73-91. doi:10.1016/j.mrfmmm.2009.05.006.
9. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recentprogress. Blood. 2006 Jun 1;107(11):4223-33.