Fanconi anemia

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.

The major function of bone marrow is to produce new blood cells. These include red blood cells, which carry oxygen to the body's tissues; white blood cells, which fight infections; and platelets, which are necessary for normal blood clotting. Approximately 90 percent of people with Fanconi anemia have impaired bone marrow function that leads to a decrease in the production of all blood cells (aplastic anemia). Affected individuals experience extreme tiredness (fatigue) due to low numbers of red blood cells (anemia), frequent infections due to low numbers of white blood cells (neutropenia), and clotting problems due to low numbers of platelets (thrombocytopenia). People with Fanconi anemia may also develop myelodysplastic syndrome, a condition in which immature blood cells fail to develop normally.

More than half of people with Fanconi anemia have physical abnormalities. These abnormalities can involve irregular skin coloring such as unusually light-colored skin (hypopigmentation) or café-au-lait spots, which are flat patches on the skin that are darker than the surrounding area. Other possible symptoms of Fanconi anemia include malformed thumbs or forearms and other skeletal problems including short stature; malformed or absent kidneys and other defects of the urinary tract; gastrointestinal abnormalities; heart defects; eye abnormalities such as small or abnormally shaped eyes; and malformed ears and hearing loss. People with this condition may have abnormal genitalia or malformations of the reproductive system. As a result, most affected males and about half of affected females cannot have biological children (are infertile). Additional signs and symptoms can include abnormalities of the brain and spinal cord (central nervous system), including increased fluid in the center of the brain (hydrocephalus) or an unusually small head size (microcephaly).

Individuals with Fanconi anemia have an increased risk of developing a cancer of blood-forming cells in the bone marrow called acute myeloid leukemia (AML) or tumors of the head, neck, skin, gastrointestinal system, or genital tract. The likelihood of developing one of these cancers in people with Fanconi anemia is between 10 and 30 percent.

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.
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. 

Inheritance Pattern
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.
Other Names for This Condition

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

Diagnosis & Management

Genetic Testing Information

- What is genetic testing? /primer/testing/genetictesting
• Genetic Testing Registry: Fanconi anemia, complementation group N

• Genetic Testing Registry: Fanconi anemia, complementation group O

• Genetic Testing Registry: Fanconi anemia, complementation group P

Research Studies from ClinicalTrials.gov
• ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Fanconi+anemia%22

Other Diagnosis and Management Resources
• Cincinnati Children’s Hospital: Fanconi Anemia Comprehensive Care Center
  https://www.cincinnatichildrens.org/service/f/fanconi-anemia

• Fanconi Anemia Research Fund: Fanconi Anemia Guidelines for Diagnosis and Management

• GeneReview: Fanconi Anemia
  https://www.ncbi.nlm.nih.gov/books/NBK1401

• MedlinePlus Encyclopedia: Fanconi’s Anemia
  https://medlineplus.gov/ency/article/000334.htm

• National Cancer Institute: Adult Acute Myeloid Leukemia Treatment PDQ

• National Cancer Institute: Myelodysplastic Syndromes Treatment PDQ

• National Heart Lung and Blood Institute: Fanconi Anemia Treatment
  https://www.nhlbi.nih.gov/health-topics/fanconi-anemia#Treatment

• The Rockefeller University: International Fanconi Anemia Registry
  http://lab.rockefeller.edu/smogorzewska/ifar/

Additional Information & Resources

    Health Information from MedlinePlus

• Encyclopedia: Fanconi’s Anemia
  https://medlineplus.gov/ency/article/000334.htm

• Health Topic: Acute Myeloid Leukemia
  https://medlineplus.gov/acutemyeloidleukemia.html
• Health Topic: Aplastic Anemia
  https://medlineplus.gov/aplasticanemia.html
• Health Topic: Bone Marrow Diseases
  https://medlineplus.gov/bonemarrowdiseases.html
• Health Topic: Myelodysplastic Syndromes
  https://medlineplus.gov/myelodysplasticsyndromes.html

Genetic and Rare Diseases Information Center
• Fanconi anemia
  https://rarediseases.info.nih.gov/diseases/6425/fanconi-anemia

Additional NIH Resources
• National Cancer Institute: Adult Acute Myeloid Leukemia Treatment PDQ
• National Cancer Institute: Inherited Bone Marrow Failure Syndromes
  https://dceg.cancer.gov/research/what-we-study/bone-marrow-failure-syndromes
• National Cancer Institute: Myelodysplastic Syndromes Treatment PDQ
• National Heart Lung and Blood Institute: Fanconi Anemia
  https://www.nhlbi.nih.gov/health-topics/fanconi-anemia
• National Heart Lung and Blood Institute: Fanconi Anemia Treatment
  https://www.nhlbi.nih.gov/health-topics/fanconi-anemia#Treatment

Educational Resources
• Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/f/fanconi-anemia
• MalaCards: fanconi anemia, complementation group a
  https://www.malacards.org/card/fanconi_anemia_complementation_group_a
• Merck Manual for Health Care Professionals: Aplastic Anemia
• Orphanet: Fanconi anemia
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=84
Patient Support and Advocacy Resources

- American Cancer Society: What is Acute Myeloid Leukemia?
- Fanconi Anemia Research Fund
  https://www.fanconi.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/fanconi-anemia/
- University of Kansas Medical Center Resource List
  http://www.kumc.edu/gec/support/fanconi.html

Clinical Information from GeneReviews

- Fanconi Anemia
  https://www.ncbi.nlm.nih.gov/books/NBK1401

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Fanconi+Anemia%5BMAJR%5D%29+AND+%28Fanconi+anemia%5BTI%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%5D+AND+%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- FANCM GENE
  http://omim.org/entry/609644
- FANCONI ANEMIA, COMPLEMENTATION GROUP A
  http://omim.org/entry/227650
- FANCONI ANEMIA, COMPLEMENTATION GROUP B
  http://omim.org/entry/300514
- FANCONI ANEMIA, COMPLEMENTATION GROUP C
  http://omim.org/entry/227645
- FANCONI ANEMIA, COMPLEMENTATION GROUP D1
  http://omim.org/entry/605724
- FANCONI ANEMIA, COMPLEMENTATION GROUP D2
  http://omim.org/entry/227646
- FANCONI ANEMIA, COMPLEMENTATION GROUP E
  http://omim.org/entry/600901
- FANCONI ANEMIA, COMPLEMENTATION GROUP F
  http://omim.org/entry/603467
• FANCONI ANEMIA, COMPLEMENTATION GROUP G
http://omim.org/entry/614082

• FANCONI ANEMIA, COMPLEMENTATION GROUP I
http://omim.org/entry/609053

• FANCONI ANEMIA, COMPLEMENTATION GROUP J
http://omim.org/entry/609054

• FANCONI ANEMIA, COMPLEMENTATION GROUP L
http://omim.org/entry/614083

• FANCONI ANEMIA, COMPLEMENTATION GROUP N
http://omim.org/entry/610832

• FANCONI ANEMIA, COMPLEMENTATION GROUP O
http://omim.org/entry/613390

• FANCONI ANEMIA, COMPLEMENTATION GROUP P
http://omim.org/entry/613951

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19622403
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2742943/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21568838

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19327579

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20713514
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2922498/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21331524

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  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16998502

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19464302