Fanconi Anemia

Synonym: Fanconi Pancytopenia

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Summary

Clinical characteristics

Fanconi anemia (FA) is characterized by physical abnormalities, bone marrow failure, and increased risk for malignancy. Physical abnormalities, present in approximately 75% of affected individuals, include one or more of the following: short stature, abnormal skin pigmentation, skeletal malformations of the upper and lower limbs, microcephaly, and ophthalmic and genitourinary tract anomalies. Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia. The incidence of acute myeloid leukemia is 13% by age 50 years. Solid tumors – particularly of the head and neck, skin, gastrointestinal tract, and genitourinary tract – are more common in individuals with FA.

Diagnosis/testing

The diagnosis of FA is established in a proband with increased chromosome breakage and radial forms on cytogenetic testing of lymphocytes with diepoxybutane (DEB) and mitomycin C (MMC). The diagnosis is confirmed by identification of one of the following:

- Biallelic pathogenic variants in one of the 19 genes known to cause autosomal recessive FA
- A heterozygous pathogenic variant in RAD51, known to cause autosomal dominant FA
- A hemizygous pathogenic variant in FANCB, known to cause X-linked FA

Management

Treatment of manifestations: Administration of oral androgens (e.g., oxymetholone) improves blood counts (red cell and platelets) in approximately 50% of individuals with FA; administration of G-CSF improves the neutrophil count in some; hematopoietic stem cell transplantation (HSCT) is the only curative therapy for the hematologic manifestations of FA, but the high risk for solid tumors remains and may even be increased in those undergoing HSCT. All these treatments have potential significant toxicity. Early detection and surgical removal remains the mainstay of therapy for solid tumors.
Prevention of primary manifestations: Human papilloma virus (HPV) vaccination to reduce the risk of gynecologic cancer in females, and possibly reduce the risk of oral cancer in all individuals.

Prevention of secondary complications: T-cell depletion of the donor graft to minimize the risk of graft vs host disease; conditioning regimen without radiation prior to HSCT to reduce the risk of subsequent solid tumors.

Surveillance: Annual evaluation with a multidisciplinary team including an endocrinologist; monitoring for evidence of bone marrow failure (regular blood counts; at least annual bone marrow aspirate/biopsy to evaluate morphology, cellularity, and cytogenetics); for those receiving androgen therapy, monitoring liver function tests and regular ultrasound examination of the liver; monitoring for solid tumors (oropharyngeal and gynecologic examinations).

Agents/circumstances to avoid: Transfusions of red cells or platelets for persons who are candidates for HSCT; family members as blood donors if HSCT is being considered; blood products that are not filtered (leukodepleted) or irradiated; toxic agents that have been implicated in tumorigenesis; unsafe sex practices, which increase the risk of HPV-associated malignancy; radiographic studies solely for the purpose of surveillance (i.e., in the absence of clinical indications).

Evaluation of relatives at risk: DEB/MMC testing or molecular genetic testing (if the family-specific pathogenic variants are known) of all sibs of a proband for early diagnosis, treatment, and monitoring for physical abnormalities, bone marrow failure, and related cancers.

Genetic counseling
Fanconi anemia (FA) can be inherited in an autosomal recessive manner, an autosomal dominant manner (RAD51-related FA), or an X-linked manner (FANCB-related FA).

Autosomal recessive FA: Each sib of an affected individual has a 25% chance of inheriting both pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being a carrier, and a 25% chance of inheriting both normal alleles and not being a carrier. Carriers (heterozygotes) for autosomal recessive FA are asymptomatic.

Autosomal dominant FA: Given that all affected individuals with RAD51-related FA reported to date have the disorder as a result of a de novo RAD51 pathogenic variant, the risk to other family members is presumed to be low.

X-linked FA: For carrier females the chance of transmitting the pathogenic variant in each pregnancy is 50%; males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will usually not be affected.

Carrier testing for at-risk relatives (for autosomal recessive and X-linked FA) and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant(s) in the family are known.

Diagnosis
Recommendations for diagnosis were agreed upon at a 2013 consensus conference (see Fanconi Anemia: Guidelines for Diagnosis and Management).

Suggestive Findings
Fanconi anemia (FA) should be suspected in individuals with the following clinical and laboratory features.

Physical features (in ~75% of affected persons)
- Prenatal and/or postnatal short stature
• Abnormal skin pigmentation (e.g., café au lait macules, hypopigmentation)
• Skeletal malformations (e.g., hypoplastic thumb, hypoplastic radius)
• Microcephaly
• Ophthalmic anomalies
• Genitourinary tract anomalies

**Laboratory findings**

• Macrocytosis
• Increased fetal hemoglobin (often precedes anemia)
• Cytopenia (especially thrombocytopenia, leukopenia and neutropenia)

**Pathology findings**

• Progressive bone marrow failure
• Adult-onset aplastic anemia
• Myelodysplastic syndrome (MDS)
• Acute myelogenous leukemia (AML)
• Early-onset solid tumors (e.g., squamous cell carcinomas of the head and neck, esophagus, and vulva; cervical cancer; and liver tumors)
• Inordinate toxicities from chemotherapy or radiation

**Establishing the Diagnosis**

The diagnosis of FA is established in a proband with the following findings:

• Increased chromosome breakage and radial forms on cytogenetic testing of lymphocytes with diepoxybutane (DEB) and mitomycin C (MMC)

  Note: (1) The background rate of chromosome breakage in control chromosomes is more variable with MMC; thus, some centers use DEB while other centers use both DEB and MMC. (2) If results of lymphocyte testing are normal or inconclusive and mosaicism is suspected, testing can be performed on an alternative cell type, such as skin fibroblasts. See Fanconi Anemia: Guidelines for Diagnosis and Management.

• Identification of biallelic pathogenic variants in one of the 18 genes known to cause autosomal recessive FA, or a heterozygous pathogenic variant in RAD51 known to cause autosomal dominant FA, or a hemizygous pathogenic variant in FANCB, known to cause X-linked FA (see Table 1)

Molecular testing approaches can include single-gene testing, use of a multigene panel, and more comprehensive genomic testing:

• **Single-gene testing.** Sequence analysis of FANCA can be performed first, followed by gene-targeted FANCA deletion/duplication analysis if only one or no pathogenic variant is found.

• **A multigene panel** that includes the genes in Table 1a and Table 1b and other genes of interest (see Differential Diagnosis) may be considered next if single-gene testing does not identify a FANCA pathogenic variant. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multigene panel provides the best opportunity to identify the genetic cause of the condition at the most reasonable cost while limiting identification of pathogenic variants in genes that do
not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of Fanconi anemia. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1a. Molecular Genetics of Fanconi Anemia: Most Common Genetic Causes

<table>
<thead>
<tr>
<th>Gene 1, 2</th>
<th>Complementation Group 3</th>
<th>% of FA Attributed to Pathogenic Variants in This Gene 4</th>
<th>Proportion of Pathogenic Variants Detected by Method 5</th>
<th>Gene-targeted deletion/duplication analysis 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequence analysis 6</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>FA-D1</td>
<td>~3%</td>
<td>&gt;90%</td>
<td>None reported</td>
</tr>
<tr>
<td>BRIP1</td>
<td>FA-J</td>
<td>~2%</td>
<td>&gt;90%</td>
<td>None reported</td>
</tr>
<tr>
<td>FANCA</td>
<td>FA-A</td>
<td>60%-70%</td>
<td>~60%</td>
<td>&gt;20 deletion/duplication variants reported; see HGMD</td>
</tr>
<tr>
<td>FANCB</td>
<td>FA-B</td>
<td>~2%</td>
<td>Unknown</td>
<td>Deletion/duplication variants reported; see HGMD</td>
</tr>
<tr>
<td>FANCC</td>
<td>FA-C</td>
<td>~14%</td>
<td>Unknown</td>
<td>Several deletion/ duplication variants reported; see HGMD</td>
</tr>
<tr>
<td>FANCD2</td>
<td>FA-D2</td>
<td>~3%</td>
<td>Unknown</td>
<td>Multiple deletion/ duplication variants reported; see HGMD</td>
</tr>
<tr>
<td>FANCE</td>
<td>FA-E</td>
<td>~3%</td>
<td>&gt;90%</td>
<td>None reported</td>
</tr>
<tr>
<td>FANCF</td>
<td>FA-F</td>
<td>~2%</td>
<td>Unknown</td>
<td>Deletion/duplication variants reported; see HGMD</td>
</tr>
<tr>
<td>FANCG</td>
<td>FA-G</td>
<td>~10%</td>
<td>&gt;90%</td>
<td>None reported</td>
</tr>
</tbody>
</table>
Table 1a. continued from previous page.

<table>
<thead>
<tr>
<th>Gene 1, 2</th>
<th>Complementation Group 3</th>
<th>% of FA Attributed to Pathogenic Variants in This Gene 4</th>
<th>Proportion of Pathogenic Variants 5 Detected by Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequence analysis 6</td>
</tr>
<tr>
<td>FANCI</td>
<td>FA-I</td>
<td>~1%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Pathogenic variants of any one of the genes included in this table account for >1% of FA
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Prior to identification of the genes, complementation groups were defined based on somatic cell-based methods. While complementation analysis testing has been supplanted by multigene panels; this terminology continues to be used in some contexts.
4. Shimamura & Alter [2010]
5. See Molecular Genetics for information on pathogenic variants detected.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Table 1b. Molecular Genetics of Fanconi Anemia: Less Common Genetic Causes

<table>
<thead>
<tr>
<th>Gene 1, 2, 3</th>
<th>Complementation Group 4</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC4</td>
<td>FA-Q</td>
<td>2 individuals w/FA &amp; biallelic ERCC4 pathogenic variants reported [Bogliolo et al 2013]; functional studies of ERCC4 missense variants reported by Osorio et al [2013]</td>
</tr>
<tr>
<td>FANCL</td>
<td>FA-L</td>
<td>13 FANCL pathogenic variants reported [Chandrasekharappa et al 2013, Nicchia et al 2015, Vetro et al 2015]</td>
</tr>
<tr>
<td>FANCM</td>
<td>FA-M</td>
<td>Assignment of a formal complementation group for persons w/FANCM pathogenic variants still controversial as only 1 reference family/cell line has been identified &amp; that cell line has been determined to have biallelic pathogenic variants in both FANCA &amp; FANCM. Of note, under experimental conditions specific knockdown of FANCM alone results in an FA phenotype [Singh et al 2009].</td>
</tr>
<tr>
<td>MAD2L2</td>
<td>FA-V</td>
<td>1 individual w/homozygous pathogenic variants reported [Bluteau et al 2016]</td>
</tr>
<tr>
<td>PALB2</td>
<td>FA-N</td>
<td>14 PALB2 pathogenic variants reported incl a deletion of exons 1-10 [Reid et al 2007, Xia et al 2007, Byrd et al 2016]</td>
</tr>
<tr>
<td>RAD51</td>
<td>FA-R</td>
<td>2 individuals w/features of FA &amp; a de novo RAD51 pathogenic variant reported [Ameziane et al 2015, Wang et al 2015]</td>
</tr>
<tr>
<td>RAD51C</td>
<td>FA-O</td>
<td>Assignment of a formal complementation group for persons w/RAD51C pathogenic variants still controversial as only 1 reference consanguineous family identified [Vaz et al 2010]</td>
</tr>
<tr>
<td>RFWD3</td>
<td>FA-W</td>
<td>1 individual w/features of FA &amp; compound heterozygous pathogenic variants in RFWD3 reported [Knies et al 2017]</td>
</tr>
<tr>
<td>SLX4</td>
<td>FA-P</td>
<td>Assignment of a formal complementation group for persons w/SLX4 pathogenic variants still controversial as only a handful of reference families have been identified &amp; SLX4 biology falls outside previously characterized FA proteins [Kim et al 2011, Stoepker et al 2011]</td>
</tr>
<tr>
<td>UBE2T</td>
<td>FA-T</td>
<td>1 individual w/biallelic UBE2T pathogenic variants incl a large paternal deletion &amp; a maternal duplication reported [Rickman et al 2015, Virts et al 2015]</td>
</tr>
</tbody>
</table>
Clinical Characteristics

Clinical Description

The primary clinical features of Fanconi anemia (FA) include physical features, progressive bone marrow failure manifest as pancytopenia, and cancer susceptibility; however, some individuals with FA have neither physical abnormalities nor bone marrow failure.

Physical features occur in approximately 75% of individuals with FA.

- Growth deficiency: prenatal and/or postnatal short stature, low birth weight
- Abnormal skin pigmentation (40%): generalized hyperpigmentation; café au lait macules, hypopigmentation
- Skeletal malformations of upper limbs, unilateral or bilateral (35%):
  - Thumbs (35%): absent, hypoplastic, bifid, duplicated, triphalangeal, long, proximally placed
  - Radii (7%): absent or hypoplastic (only with abnormal thumbs), absent or weak pulse
  - Hands (5%): flat thenar eminence, absent first metacarpal, clinodactyly, polydactyly
  - Ulnae (1%): dysplastic, short
- Skeletal malformations of lower limbs (5%)
  - Syndactyly, abnormal toes, club feet
  - Congenital hip dislocation
- Microcephaly (20%)
- Ophthalmic (20%): microphthalmia, cataracts, astigmatism, strabismus, epicanthal folds, hypotelorism, hypertelorism, ptosis
- Genitourinary tract anomalies:
  - Renal (20%): horseshoe, ectopic, pelvic, hypoplastic, dysplastic, or absent kidney; hydronephrosis or hydroureter
  - Males (25%). Hypospadias, micropenis, cryptorchidism, anorchia, hypo- or azoospermia, reduced fertility
  - Females (2%). Bicornuate or uterus malposition, small ovaries
    Note: Pregnancy is possible in females, whether or not they have undergone hematopoietic stem cell transplantation.
- Endocrine: hypothyroidism, glucose/insulin abnormalities
• Hearing loss, usually conductive secondary to middle ear bony anomalies; abnormal ear shape: dysplastic, narrow ear canal, abnormal pinna (10%)

• Congenital heart defect (6%): patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of the aorta, truncus arteriosus, situs inversus

• Gastrointestinal (5%): esophageal, duodenal, or jejunal atresia, imperforate anus, tracheoesophageal fistula, annular pancreas, malrotation

• Central nervous system (3%): small pituitary, pituitary stalk interruption syndrome, absent corpus callosum, cerebellar hypoplasia, hydrocephalus, dilated ventricles

• Other
  ◦ Facial features (2%): triangular, micrognathia, mid-face hypoplasia
  ◦ Spine anomalies (2%): spina bifida, scoliosis, hemivertebrae, rib anomalies, coccygeal aplasia
  ◦ Neck anomalies (1%): Sprengel deformity, Klippel-Feil anomaly, short or webbed neck, low hairline

Note: Percentages are calculated from 2,000 individuals reported in the literature from 1927 to 2009. Frequencies are approximate, since many reports did not mention physical descriptions.

**Developmental delay** and/or intellectual disability (10%)

**Bone marrow failure.** The age of onset is highly variable, even among sibs. An analysis of 754 individuals with pathogenic variants in *FANCA*, *FANCC*, and *FANCG* identified an average age of onset of 7.6 years. Rarely, bone marrow failure can present in infants and small children [Shimamura & Alter 2010]. The risk of developing any hematologic abnormality is 90% by age 40 years [Kutler et al 2003].

- Thrombocytopenia or leukopenia usually precede anemia. These are commonly associated with macrocytosis and elevated fetal hemoglobin.
- Pancytopenia generally worsens over time.
- Sweet syndrome (neutrophilic skin infiltration) was associated with progression of hematologic disease in six out of seven individuals with FA [Giulino et al 2011].
- The severity of bone marrow failure can be classified by the degree of cytopenia(s) (Table 3). Importantly, to meet these criteria for marrow failure, the cytopenias must be persistent and unexplained by other causes.

**Table 2. Severity of Bone Marrow Failure in Fanconi Anemia**

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>$&lt;1,500/mm^3$</td>
<td>$&lt;1,000/mm^3$</td>
<td>$&lt;500/mm^3$</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000–50,000/mm$^3$</td>
<td>$&lt;50,000/mm^3$</td>
<td>$&lt;30,000/mm^3$</td>
</tr>
<tr>
<td>Hemoglobin (Hb) level</td>
<td>$\geq 8$ g/dL</td>
<td>$&lt;8$ g/dL</td>
<td>$&lt;8$ g/dL</td>
</tr>
</tbody>
</table>

**Cancer susceptibility.** The relative risk for acute myelogenous leukemia (AML) is increased approximately 500-fold [Rosenberg et al 2008, Alter et al 2010, Tamary et al 2010]. In a competing risk analysis of the combined cohorts, the cumulative incidence of AML was 13% by age 50 years, with most individuals diagnosed between ages 15 and 35 years.

An increased risk of developing myelodysplastic syndrome (MDS)/AML is associated with monosomy 7 and most 7q deletions. Clonal amplifications of chromosome 3q26-q29 were reported in association with an increased risk of progression to MDS/AML [Neitzel et al 2007, Mehta et al 2010].

**Solid tumors** may be the first manifestation of FA in individuals who have no birth defects and have not experienced bone marrow failure.
• Head and neck squamous cell carcinomas (HNSCCs) are the most common solid tumor in individuals with FA. The incidence is 500- to 700-fold higher than in the general population. The HNSCCs in FA show distinct differences compared to HNSCCs seen in the general population. HNSCCs:
  ○ Occur at an earlier age (20-40 years) than in the general population;
  ○ Are most commonly in the oral cavity (e.g., tongue);
  ○ Present at an advanced stage;
  ○ Respond poorly to therapy.
• Individuals with FA are at increased risk for second primary cancers in the skin and genitourinary tract. The pattern of second primaries resembles that observed in HPV-associated HNSCC in the general population [Morris et al 2011].
• Individuals with FA receiving androgen treatment for bone marrow failure are also at increased risk for liver tumors.

**Phenotype Correlations by Gene**

**BRCA2.** Biallelic pathogenic variants in BRCA2 are associated with early-onset acute leukemia and solid tumors [Hirsch et al 2004, Wagner et al 2004, Myers et al 2012]. The cumulative probability of any malignancy was 97% by age six years, including AML, medulloblastoma, and Wilms tumor [Alter et al 2007].

**FANCG.** Pathogenic variants in FANCG may be associated with severe marrow failure and a higher incidence of leukemia compared to FANCC [Faivre et al 2000].

**PALB2.** Solid tumors (e.g., medulloblastoma, Wilms tumor) are associated with PALB2 pathogenic variants [Reid et al 2007].

**Genotype-Phenotype Correlations**

The clinical spectrum of FA remains heterogenous. There are no clearcut genotype-phenotype correlations [Neveling et al 2009]. In general, null variants lead to a more severe phenotype (e.g., congenital anomalies, early-onset bone marrow failure, and MDS/AML) than hypomorphic variants.

**BRCA2.** All persons with an IVS7 pathogenic variant in BRCA2 developed AML by age three years; those with other BRCA2 pathogenic variants who developed AML did so by age six years [Alter 2006].

**FANCA.** Individuals who are homozygous for null pathogenic variants in FANCA may have earlier onset of anemia and higher incidence of leukemia than individuals with pathogenic variants that permit production of an abnormal FANCA protein [Faivre et al 2000].

**FANCC**

- c.456+4A>T, p.Arg548Ter, and p.Leu554Pro are associated with earlier onset of hematologic abnormalities and more severe congenital anomalies than other pathogenic variants, such as del22G [Faivre et al 2005].
- c.456+4A>T results in a milder phenotype in Japanese individuals than in Ashkenazi Jewish individuals [Futaki et al 2000].

**Prevalence**

Fanconi anemia (FA) is the most common genetic cause of aplastic anemia and one of the most common genetic causes of hematologic malignancy.

The ratio of males to females is 1.2:1 (p<0.001 vs expected 1.00).
Rosenberg et al [2011] showed higher carrier rates for FA than previously reported. Carrier frequency was 1:181 in North Americans and 1:93 in Israel. Specific populations have founder variants with increased carrier frequencies (<1:100), including Ashkenazi Jews (FANCC, BRCA2), northern Europeans (FANCC), Afrikaners (FANCA), sub-Saharan Blacks (FANCG), Spanish Gypsies (FANCA), and others.

**Genetically Related (Allelic) Disorders**

Hereditary breast and ovarian cancer is associated with heterozygous pathogenic variants in BRCA2.

Heterozygous pathogenic variants in BRIP1 and PALB2 have been implicated in breast cancer and ovarian cancer predisposition [Seal et al 2006, Rahman et al 2007, Rafnar et al 2011].

Heterozygous pathogenic variants in PALB2 have been implicated in pancreatic cancer predisposition [Jones et al 2009].

Biallelic pathogenic variants in ERCC4 are associated with xeroderma pigmentosum, Cockayne syndrome, and XFE progeroid syndrome.

**Differential Diagnosis**

Cells derived from individuals with other chromosome breakage syndromes, such as Bloom syndrome or ataxia-telangiectasia, may also exhibit high rates of spontaneous chromosome breakage; however, only FA cells exhibit increased chromosome breakage in response to diepoxybutane (DEB).

Nijmegen breakage syndrome (NBS), characterized by short stature, progressive microcephaly with loss of cognitive skills, premature ovarian failure in females, recurrent sinopulmonary infections, and an increased risk for cancer (particularly lymphoma), may also manifest increased chromosome breakage with mitomycin C (MMC) [Chrzanowska et al 2012]. Inheritance is autosomal recessive. NBS may be distinguished from FA by NBN molecular genetic testing, which identifies pathogenic variants in almost 100% of individuals with NBS.

Seckel syndrome (OMIM PS210600), characterized by growth retardation, microcephaly with intellectual disability, and a characteristic "bird-headed" facial appearance, may also show increased chromosome breakage with DNA cross-linking agents (MMC, DEB) [Andreassen et al 2004]. Some individuals with Seckel syndrome also develop pancytopenia and/or AML. Inheritance is autosomal recessive. Biallelic pathogenic variants in ATR, NIN, ATRIP, RBBP8, CEP152, CENPJ, and CEP63 are causative.

Other disorders including neurofibromatosis 1 (which could be considered because of café au lait macules), TAR syndrome (thrombocytopenia with absent radii), and VACTERL association (radial ray defects) (OMIM 192350) can be distinguished from FA by testing for chromosome breakage with DEB and MMC.

**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease and management requirements in an individual diagnosed with Fanconi anemia (FA), the following evaluations are recommended:

- Evaluation by a hematologist, to include complete blood count, fetal hemoglobin, full blood typing, blood chemistries (assessing liver, kidney, and iron status), and bone marrow aspirate for cell morphology, FISH and cytogenetics, as well as biopsy for cellularity.

  Note: The bone marrow of individuals with FA can exhibit signs of dysplasia, such as nuclear/cytoplasmic dys-synchrony, hypo-lobulated megakaryocytes, and bi-nucleated erythroid cells. These features must be
distinguished from true forms of MDS by a hematopathologist experienced in the evaluation of MDS in individuals with FA.

- HLA typing of the affected individual, sibs, and parents for consideration of hematopoietic stem cell transplantation
- Examination by an ophthalmologist
- Ultrasound examination of the kidneys and urinary tract
- Formal hearing evaluation
- Echocardiogram
- Referral to an endocrinologist
- Developmental assessment (particularly important for toddlers and school-age children)
- Referrals as indicated to an otolaryngologist, hand surgeon, gastroenterologist, gynecologist, and urologist
- Evaluation by a clinical geneticist and genetic counseling

**Treatment of Manifestations**

Recommendations for treatment were agreed upon at a 2014 consensus conference ([full text]).

**Androgens** improve (at least transiently) the red cell and platelet counts in approximately 50% of individuals. Androgen therapy can be considered when the hemoglobin drops below 8 g/dL or the platelet count falls below 30,000/mm$^3$ ("severe" – see Table 2). Although only 10%-20% of individuals receiving continuous low-dose androgen therapy are long-term responders, this option can be particularly useful for individuals who do not have access to or are not ready for hematopoietic stem cell transplant (HSCT), or to individuals for whom a suitable donor is not available.

- Oxymetholone, given orally at a starting dose of 2 mg/kg/day, may be increased up to 5 mg/kg/day.
- Doses may be slowly tapered to the minimal effective dose with careful monitoring of the blood counts.
- Other synthetic androgens used in FA include stanazolol in Asia, and oxandrolone and danazol in North America.

Side effects of androgen administration include virilization and liver toxicity such as elevated liver enzymes, cholestasis, peliosis hepatitis (vascular lesion with multiple blood-filled cysts), and hepatic tumors. Individuals taking androgens should be monitored for liver tumors and undergo regular liver function tests (LFT) for abnormalities. Blood tests for LFTs should be performed every three to six months; liver ultrasound should be performed every six to 12 months. If no response is seen after three to four months, androgens should be discontinued [Scheckenbach et al 2012, Rose et al 2014].

**Granulocyte colony-stimulating factor** (G-CSF) improves the neutrophil count in some individuals. G-CSF dose should be titrated to the lowest possible dose and frequency to keep ANC above 1,000/mm$^3$. Note: (1) A bone marrow aspirate and biopsy should be performed prior to the initiation of G-CSF and monitored every six months throughout treatment, given the theoretic risk of stimulating the growth of a leukemic clone. (2) G-CSF should be administered in consultation with an FA expert.

**Hematopoietic stem cell transplantation** (HSCT) is the only curative therapy for the hematologic manifestations, including aplastic anemia, myelodysplastic syndrome, and acute leukemia. Ideally, HSCT is performed prior to onset of MDS/AML and before multiple transfusions [MacMillan & Wagner 2010, Mehta et
Individuals with FA are sensitive to chemotherapy and radiation, need special transplant regimens, and should be cared for and transplanted at centers with the most experience in HSCT in FA.

A multi-institutional study reported a one-year probability of overall survival of 80% in 45 individuals with FA transplanted for marrow failure and/or MDS, using alternative donors (including mismatched related and unrelated donors) and chemotherapy-only preparative regimen. Survival for individuals younger than age ten years transplanted for marrow failure was even better, at 91.3% (±5.9%) [Mehta et al 2017].

**Fludarabine** reduced the incidence of graft failure and allowed for removal of radiation from the preparative regimens in a matched sib donor setting [MacMillan et al 2015].

MDS/AML treatment remains challenging. Options include chemotherapy, HSCT with or without prior induction chemotherapy, and investigational trials. Chemotherapy should be undertaken in coordination with centers experienced with FA, as it can cause severe, prolonged, or irreversible myelosuppression. Plans for HSCT should be in place prior to starting chemotherapy. Published reports of chemotherapy regimens for AML in individuals with FA are sparse and limited by the unclear benefit to the overall outcome due to the lack of longitudinal follow up [Mehta et al 2007, Talbot et al 2014, Beier et al 2015].

**Solid tumors.** Prompt, aggressive workup for any symptoms suggestive of a malignancy is indicated. Early detection and surgical removal remains the mainstay of therapy. Treatment is challenging secondary to the increased toxicity associated with chemotherapy and radiation in FA. Data is limited on use of chemotherapy at standard doses or reduced doses and schedules in individuals with FA, and there are reports of severe or fatal toxicities and poor treatment outcomes [Masserot et al 2008, Hosoya et al 2010, Tan et al 2011, Spanier et al 2012]. Individuals diagnosed with a genital tract cancer should be referred to a gynecologic oncologist immediately, and care should be coordinated with FA experts.

**Prevention of Primary Manifestations**

Human papilloma virus (HPV) vaccination should be initiated at age nine years in order to reduce the risk of gynecologic cancer in females, and possibly reduce the risk of oral cancer in all individuals.

**Prevention of Secondary Complications**

Individuals with FA treated with HSCT who developed graft vs host disease (GVHD) had a 28% incidence of head and neck cancers in the ten years following treatment (vs 0% in those without GVHD); this finding points to the importance of minimizing the risk of GVHD [Guardiola et al 2004]. Increased risk for GVHD observed in earlier studies was reduced significantly by T-cell depletion of the donor graft [Chaudhury et al 2008, MacMillan et al 2015].

Individuals successfully treated with HSCT are at increased risk for solid tumors, in addition to the baseline increased risk [Rosenberg et al 2005]. Due to the known contribution of radiation to the long-term complication of secondary solid tumors most recent efforts have focused on using a conditioning regimen without radiation even in an unrelated donor setting. German, Brazilian, and US groups now report excellent outcomes with alternative donors with a "chemotherapy-only" preparative regimen in single-center studies. The study from Germany showed 88% survival and normal hematopoiesis at a median follow up of 30 months [Bonfim et al 2015, Chao et al 2015]. A prospective multi-institutional US study also showed similar excellent outcomes. One-year probabilities of overall and disease-free survival for the entire cohort, including patients with myeloid malignancy and those receiving mismatched related/haploidentical grafts, were 80% and 77.7% respectively at a median follow-up of 41 months. All young children (age <10 years) undergoing HSCT for marrow failure using low-dose busulfan-containing regimen survived [Mehta et al 2017].
Surveillance


- Annual evaluation with a multidisciplinary team including an endocrinologist
- Regular blood counts, every three to four months while stable and more often as needed
- Bone marrow aspirate/biopsy at least annually to evaluate morphology, cellularity (from the biopsy), FISH, and cytogenetics (the latter two for emergence of a malignant clone). Individuals on GCSF need to have a bone marrow aspirate/biopsy every six months, if possible.
- In individuals who develop Sweet syndrome (neutrophilic skin infiltration), prompt investigation for hematologic disease progression including bone marrow evaluation

Notes: (1) Progressively changing blood counts without a potential cause (e.g., acute infection or suppression from medication) require immediate evaluation with a complete blood count and bone marrow examination with FISH and cytogenetics. (2) It is important to recognize that rising blood counts can be due to either the development of MDS/AML or, rarely, reversion of a germline mutation in a stem cell, which repopulates the marrow with normal cells (somatic stem cell mosaicism). These individuals may require immediate HSCT (for MDS/AML) or continued close monitoring with complete blood counts at least every one to two months and a bone marrow examination with cytogenetics every six months.

Individuals receiving androgen therapy

- Liver function tests every three to six months
- Liver ultrasound examination every six to 12 months for androgen-related changes, including tumors

Cancer surveillance

- Annual gynecologic assessment for genital lesions beginning at age 13. Thorough vulvo-vaginal examinations and Pap smear can begin when women become sexually active or by age 18 years, whichever is earlier. Suspicious genital tract lesions should be biopsied.
- Examination every six months for oral, head, and neck cancers beginning by age nine to ten years. Screening should be performed by a dentist, oral surgeon, or ENT familiar with FA. Nasolaryngoscopy starting at age ten years, or within the first year after HSCT. Individuals with difficulty or pain with swallowing should be evaluated for esophageal cancer.
- For individuals with a history of premalignant or malignant lesions: surveillance examinations every two to three months
- For individuals with biallelic pathogenic variants in BRCA2: screening for neuroblastomas, brain tumors, and kidney tumors every six months (see also Autosomal Recessive FA, Risk to Family Members)

Agents/Circumstances to Avoid

Blood transfusions. Blood products should be cytomegalovirus (CMV)-safe and irradiated. To reduce the chances of sensitization, family members must not act as blood donors. Once an individual requires transfusions, he/she should be referred for transplantation.

Toxic agents to avoid include smoking, second-hand smoke, and alcohol, which have been implicated in tumorigenesis.

Unsafe sex practices increase the risk for HPV-associated malignancy.

Radiographic studies for the purpose of surveillance should be minimized in the absence of clinical indications. However, baseline skeletal surveys may be considered, in order to document bony anomalies that may lead to problems with age, such as anomalies of the wrist, hip, and vertebrae.
Evaluation of Relatives at Risk

It is appropriate to evaluate all sibs of an affected individual in order to identify as early as possible those who would benefit from appropriate monitoring for physical abnormalities, bone marrow failure, and related cancers.

- DEB/MMC testing can be used to clarify the disease status of at-risk sibs.
- If the pathogenic variant(s) in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy is possible in females with FA, whether or not they have undergone hematopoietic stem cell transplantation [Dalle et al 2004, Nabhan et al 2010].

Pregnancy needs to be managed by a high-risk maternal fetal obstetrician along with a hematologist.

Therapies Under Investigation

Previous clinical trials failed to accomplish permanent gene correction of stem cells; current work is focusing on development of novel vector and delivery strategies [Tolar et al 2011]. The first FA lentiviral gene therapy trial led by the University of Washington/Fred Hutchinson Cancer Research Center is now open [Becker et al 2010]. Dr Juan Bueren has an open trial of a hematopoietic stem cell mobilization in Madrid, Spain and plans to have their FANCA gene therapy trial opened soon.

A Phase I study of the antioxidant quercetin in children with Fanconi anemia is currently underway at Cincinnati Children’s Hospital Medical Center.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Fanconi anemia (FA) is inherited in an autosomal recessive manner, an autosomal dominant manner (RAD51-related FA), or an X-linked manner (FANCB-related FA).

Autosomal Recessive FA

Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive FA are obligate heterozygotes (i.e., carriers of one FA-related pathogenic variant).
- Heterozygotes (carriers) are not at risk for FA. However, heterozygous mutation of a subset of FA-related genes (e.g., BRCA2, PALB2, and BRIP1) is associated with an increased risk for breast and other cancers [Seal et al 2006, Berwick et al 2007, Rahman et al 2007] (see Hereditary Breast and Ovarian Cancer).

**Sibs of a proband**
- At conception, each sib of an individual with autosomal recessive FA has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are not at risk for FA. However, heterozygous mutation of a subset of FA-related genes (e.g., BRCA2, PALB2, and BRIP1) is associated with an increased risk for breast and other cancers [Seal et al 2006, Berwick et al 2007, Rahman et al 2007] (see Hereditary Breast and Ovarian Cancer).

**Offspring of a proband.** The offspring of an individual with autosomal recessive FA are obligate heterozygotes (carriers) for a pathogenic variant in an FA-related gene.

**Other family members of a proband.** Each sib of the proband's parents is at a 50% risk of being a carrier for a pathogenic variant in an FA-related gene.

**Carrier (Heterozygote) Detection**
Carrier testing for at-risk relatives requires prior identification of the FA-related pathogenic variants in the family.

Carriers of FA cannot be detected by the DEB/MMC test.

**Autosomal Dominant FA – Risk to Family Members**

**Parents of a proband**
- To date, reported probands with RAD51-related FA have the disorder as a result of a de novo RAD51 pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variant include molecular genetic testing.

**Sibs of a proband.** All affected individuals reported to date have had a de novo RAD51-related FA pathogenic variant, suggesting a low risk to sibs. However, because of the theoretic possibility of germline mosaicism in a parent, the risk is presumed to be greater than in the general population.

**Offspring of a proband.** Each child of an individual with RAD51-related FA is presumed to have a 50% chance of inheriting the pathogenic variant. However, only one individual with RAD51-related FA has reached adulthood and no offspring have been reported.

**Other family members.** Given that all probands with RAD51-related FA reported to date have the disorder as a result of a de novo RAD51 pathogenic variant, the risk to other family members is presumed to be low.

**X-Linked FA**

**Risk to Family Members**

**Parents of a male proband**
- The father of a male with X-linked FA will not have the disorder nor will he be hemizygous for the FANCB pathogenic variant; therefore, he does not require further evaluation/testing.
In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier).

Note: If a woman has more than one affected son and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.

If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a \textit{de novo} \textit{FANCB} pathogenic variant, in which case the mother is not a carrier.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a \textit{FANCB} pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be carriers and will usually not be affected.

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the \textit{FANCB} pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

**Offspring of a male proband**

- Affected males transmit the \textit{FANCB} pathogenic variant to all of their daughters (who will be carriers and will usually not be affected) and none of their sons.

- To date, no male with FA-B has been old enough to have children; they may also be infertile, as are many males with FA.

**Other family members of a proband.** The proband’s maternal aunts may be at risk of being heterozygotes (carriers) for the \textit{FANCB} pathogenic variant and the aunt's offspring, depending on their gender, may be at risk of being carriers or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a \textit{de novo} pathogenic variant arose – information that could help determine genetic risk status of the extended family.

**Heterozygote (Carrier) Detection**

Carrier testing for at-risk female relatives requires prior identification of the \textit{FANCB} pathogenic variant in the family.

Carriers of FA cannot be detected by the DEB/MMC test.

**Related Genetic Counseling Issues**

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.
Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the FA-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for FA are possible. Preimplantation genetic diagnosis has successfully identified at-risk embryos as unaffected with FA and HLA-matched to affected sibs [Kahraman et al 2014].

Chromosome breakage. Prenatal testing is also possible for pregnancies at increased risk for FA by performing cytogenetic testing in the presence of DEB/MMC to evaluate for increased chromosome breakage in fetal cells obtained by chorionic villus sampling (CVS) or amniocentesis; however, if the pathogenic variants are known in the family, molecular genetic testing is the method of choice for prenatal diagnosis.

Fetal ultrasound evaluation. Ultrasound examination can be used to evaluate for fetal anomalies consistent with FA. However, ultrasound examination is not a diagnostic test for FA. Many congenital anomalies characteristic of FA may not be detectable by ultrasound examination, and those that can be seen may be associated with diagnoses other than FA.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- Fanconi Anemia Cell Repository
  Department of Medical and Molecular Genetics
  3181 Southwest Sam Jackson Park Road L103
  Oregon Health & Science University
  Portland OR 97201
  **Phone:** 503-494-6888

- Fanconi Anemia Research Fund, Inc. (FARF)
  1801 Willamette Street
  Suite 200
  Eugene OR 97401
  **Phone:** 888-326-2664 (Toll-free Family Support Line); 541-687-4658
  **Fax:** 541-687-0548
  **Email:** info@fanconi.org
  [www.fanconi.org](http://www.fanconi.org)

- International Fanconi Anemia Registry (IFAR)
  The Rockefeller University
  1230 York Avenue
  New York NY 10065
  **Phone:** 212-327-8862
  **Fax:** 212-327-8262
  **Email:** auerbac@rockefeller.edu
International Fanconi Anemia Registry (IFAR)

- **National Cancer Institute Inherited Bone Marrow Failure Syndromes (IBMFS) Cohort Registry**
  
  **Phone:** 800-518-8474
  
  **Email:** NCI.IBMFS@westat.com
  
  www.marrowfailure.cancer.gov

- **Prospective Registry of MultiPlex Testing (PROMPT)**

  *PROMPT is an online research registry for patients and their families that helps researchers answer the question: “How do genetic variants affect your cancer risk?”*

**Molecular Genetics**

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A. Fanconi Anemia: Genes and Databases**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus-Specific Databases</th>
<th>HGMD</th>
<th>ClinVar</th>
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<td>BRCA2</td>
<td>13q13.1</td>
<td>Breast cancer type 2 susceptibility protein</td>
<td>BRCA2 homepage - LOVD Database of BRCA1 and BRCA2 sequence variants that have been clinically reclassified using a quantitative integrated evaluation Breast Cancer Information Core (BRCA2) Fanconi Anaemia Mutation Database (FANCD1 - BRCA2) BRCA2 @ ZAC-GGM</td>
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<td>BRIP1</td>
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<td>Fanconi anemia group J protein</td>
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<td>ERCC4 database</td>
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Table A. continued from previous page.

<table>
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<tr>
<th>Gene</th>
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<td>MAD2L2</td>
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<td>PALB2</td>
<td>16p12.2</td>
<td>Partner and localizer of BRCA2</td>
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<td>RAD51</td>
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Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Fanconi Anemia (View All in OMIM)

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<td>133520</td>
<td>EXCISION REPAIR, COMPLEMENTING DEFECTIVE, IN CHINESE HAMSTER, 4; ERCC4</td>
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<td>179617</td>
<td>RAD51 RECOMBINASE; RAD51</td>
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<td>FANCONI ANEMIA, COMPLEMENTATION GROUP D2; FANCD2</td>
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<td>300514</td>
<td>FANCONI ANEMIA, COMPLEMENTATION GROUP B; FANCB</td>
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<td>600185</td>
<td>BRCA2 GENE; BRCA2</td>
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</table>
Molecular Pathogenesis

At least twenty genes that are involved in Fanconi anemia (FA) and also account for each of the phenotypic complementation groups have been identified. The proteins encoded by the FA-related genes are considered to work together in a common pathway/network called "the FA pathway" or "the FA-BRCA pathway/network," which regulates cellular resistance to DNA cross-linking agents [Taniguchi & D'Andrea 2006, D'Andrea 2010, Deans & West 2011, Kee & D'Andrea 2012]. Disruption of this pathway leads to the common cellular and clinical abnormalities observed in FA [D'Andrea 2010, Nakanishi et al 2011, Williams et al 2011b, Crossan & Patel 2012, Kim & D'Andrea 2012].

Eight of the FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM), along with proteins FAAP24 [Ciccia et al 2007] and FAAP100 [Ling et al 2007] are assembled in a nuclear complex (FA core complex). This complex is a multisubunit ubiquitin ligase complex; monoubiquitination of two FA proteins (FANCD2 and FANCI) depends on the FA core complex [Garcia-Higuera et al 2001, Smogorzewska et al 2007]. In response to DNA damage or in S phase of the cell cycle, this FA core complex activates the
monoubiquitination of the FANCD2 and FANCI proteins. Monoubiquitinated FANCD2 and monoubiquitinated FANCI are translocated to nuclear foci containing the proteins BRCA1, BRCA2, PALB2, and RAD51. FANCI shares sequence similarity with FANCD2; together they form a protein complex (ID complex) [Smogorzewska et al 2007]. Monoubiquitination of FANCD2 and FANCI is interdependent [Smogorzewska et al 2007]. A nuclease, FAN1, has been shown to bind to monoubiquitinated FANCD2, which directs its enzymatic activity [Huang & D’Andrea 2010]. A cell-free system has been used to recapitulate cross-link repair in vitro [Knipscheer et al 2009].

One of the components of the FA core complex, FANCL, has a PHD (plant homeodomain) finger (a variant RING finger) domain with ubiquitin ligase activity [Meetei et al 2003a]. FANCL associates through its PHD/RING finger domain with UBE2T, a ubiquitin conjugating enzyme (E2), which is also required for FANCD2 monoubiquitination [Machida et al 2006]. Recombinant FANCL, the E2 UBE2T, FANCD2, FANCI, and FANCE recapitulate the monoubiquitination reaction in vitro [Alpi et al 2008].

Another component of the FA core complex, FANCM, is homologous to the archaeal DNA helicase/nuclease known as HEF. FANCM has DNA helicase motifs and a degenerate nuclease motif and exhibits DNA-stimulated ATPase activity and DNA translocate activity [Meetei et al 2005]. A FANCM-interacting protein, FAAP24, preferentially binds to single-stranded DNA and branched DNA structures [Ciccia et al 2007]. Therefore, it has been speculated that FANCM DNA translocate activity could play an important role in displacing the FA core complex along the DNA, allowing DNA damage recognition, or that FAAP24 may play a role in targeting the FA core complex to abnormal, branched DNA structures. This complex is thought to be responsible for a replication-associated checkpoint response involving RPA [Huang et al 2010] and the BLM helicase [Deans & West 2009]. As is true for multiple FA proteins, the complex appears to be regulated through ATR [Collis et al 2008].

Furthermore, the FA core complex forms a larger complex with BLM, RPA, and topoisomerase IIIα, called BRAFT (BLM, RPA, FA, and topoisomerase IIIα) [Meetei et al 2003b] in a further link to Bloom syndrome. FANCM is found in both separable complexes: the FA core complex as well as the BLM complex [Deans & West 2009].

A DNA damage-activated signaling kinase, ATR, a single-strand DNA-binding protein complex, RPA, and an ATR-associated protein, HCLK2, are required for DNA damage-inducible monoubiquitination and foci formation of FANCD2 [Andreassen et al 2004, Collis et al 2007]. BRCA1 [Garcia-Higuera et al 2001, Vandenberg et al 2003] and histone H2AX [Bogliolo et al 2007] are required for DNA damage-inducible foci formation of FANCD2, but not for monoubiquitination of FANCD2. These factors are considered to be upstream positive regulators of the FA pathway. ATR has been shown to directly phosphorylate FANCA and indirectly phosphorylate FANCD2 through CHK1 [Zhi et al 2009]. As described, ATR is also necessary for assembly of FANCM and recruitment of RPA at the ICL-induced checkpoint [Collis et al 2008].

BRCA2 (previously FANCD1) is a tumor suppressor that confers breast cancer susceptibility [Howlett et al 2002] and has a distinct clinical phenotype [Wagner et al 2004, Alter et al 2007, Myers et al 2012]. BRCA2 protein stability and localization is regulated by PALB2 (partner and localizer of BRCA2) [Xia et al 2006] encoded by PALB2 (previously FANCN), another breast cancer susceptibility gene [Rahman et al 2007]. Another breast cancer susceptibility gene [Seal et al 2006], BRIP1 (previously BACH1 or FANCJ) [Cantor et al 2001], is also associated with FA [Levitus et al 2005, Levran et al 2005, Litman et al 2005]. BRCA2, PALB2, and BRIP1 are not required for FANCD2 protein monoubiquitination or FANCD2 nuclear foci formation, but are still required for cellular resistance to MMC or DEB. BRCA2 has been found to act in multiple subcomplexes of FA proteins, including FANCG and FANCD2 [Wilson et al 2010], suggesting that the notion of acting downstream of FANCD2 monoubiquitination may be too simplistic. Phosphorylation of FANCD2 by CHK1 has been shown to be necessary for interaction with BRCA2 [Zhi et al 2009]. BRIP1 and FANCD2 have also been shown to be functionally linked in foci formation [Zhang et al 2010].
USP1 is a deubiquitinating enzyme that removes ubiquitin from monoubiquitinated FANCD2, and negatively regulates the FA pathway along with its coactivator UAF1 [Nijman et al 2005, Cohn et al 2007]. USP1 also removes ubiquitin from monoubiquitinated PCNA (proliferating cell nuclear antigen) [Huang et al 2006]. This may not be coincidental, since FANCD2 and PCNA have been shown to be bound [Howlett et al 2009]. The deubiquitination event has been shown to be vital for FA function [Oestergaard et al 2007]. Hematopoietic defects have been noted in knockout mice [Parmar et al 2010].

In nuclear foci, FANCD2 colocalizes with FANCI, BRCA1, BRCA2, PALB2, RAD51, BLM, RPA, ATR, FANCC, and FANCE [Garcia-Higuera et al 2001, Pace et al 2002, Taniguchi et al 2002a, Andreassen et al 2004, Wang et al 2004, Matsushita et al 2005, Xia et al 2006, Smogorzewska et al 2007]. FANCD2 also colocalizes partially with BRIP1 [Litman et al 2005] and NBS1 [Nakanishi et al 2002]. All of these factors are required for cellular resistance to DNA cross-linking agents and are considered to work together to repair interstrand DNA cross-links, although the precise mechanism is not understood. Recently, pathogenic variants in RAD51C have been detected in several FA-like cases in a consanguineous family, also associated with breast and ovarian cancer susceptibility [Meindl et al 2010, Vaz et al 2010].

Among FA proteins, BRCA2 has a clear role in regulating homologous recombination by controlling the activity of RAD51, the eukaryotic homolog of bacterial RecA [Davies et al 2001, Moynahan et al 2001]. PALB2 regulates BRCA2 stability and localization in nuclear structures (chromatin and nuclear matrix) and, thus, is required for homologous recombination [Xia et al 2006]. The FA core complex, FANCD2, FANCI [Smogorzewska et al 2007], and BRIP1 [Litman et al 2005] are also reported to be required for efficient homologous recombination, although conflicting reports exist [Taniguchi & D’Andrea 2006].

FANCD2 protein is also phosphorylated by the ataxia-telangiectasia kinase, ATM, in a process that regulates a radiation-induced S phase checkpoint [Taniguchi et al 2002b, Ho et al 2006]. While required for resistance to ionizing radiation, this phosphorylation event is dispensable for cross-linker resistance, implying a separation of or dual function for FANCD2. FANCD2 appears to be phosphorylated by CHK1, which is downstream of ATR, at serine 331 in a manner that results in activation by cross-links [Zhi et al 2009].

Importantly, a number of studies have shown defects in the FA-BRCA pathway to be implicated in cancer:

- Individuals with FA are susceptible to both leukemia and solid tumors [Alter 2003].
- Inherited and somatic variants of *FANCC* and *FANCG* are present in a subset of young-onset pancreatic cancers [van der Heijden et al 2003].
- *BRCA1* and *BRCA2* are well-known tumor suppressor genes responsible for familial breast/ovarian cancer [Turner et al 2004].
- Pathogenic truncating variants in the FA-related genes *BRIP1* and *PALB2* are breast cancer susceptibility alleles [Seal et al 2006, Erkko et al 2007, Rahman et al 2007, Tischkowitz et al 2007].

Amelioration of FA pathology has been implicated in reports of downregulation of elements of the non-homologous end-joining pathway [Adamo et al 2010]. These data propose that much of FA pathophysiology results from the unfettered work of NHEJ promoting inaccurate repair. On the other hand, FA involvement in homologous recombinatorial repair has been well established in interactions with BRCA1, BRCA2, and RAD51C. FANCD2 has also been shown to interact with PCNA and pol K, suggesting that translesion synthesis,
a variant of homologous recombinantion, may be the most direct function of FA proteins in bypass of the lesion [Ho & Schärer 2010, Song et al 2010].

For reviews of the molecular biology of FA, see Nakanishi et al [2011], Williams et al [2011b], Crossan & Patel [2012], Kim & D’Andrea [2012], and Huang et al [2014].

**BRCA2 (previously FANCD1)**

**Gene structure.** BRCA2 has 27 exons (NM_000059.3).

**Pathogenic variants.** See Table A.

**Normal gene product.** The breast cancer type 2 susceptibility protein (BRCA2) has 3418 amino acids. BRCA2 regulates homologous recombination repair through control of RAD51 recombinase [Davies et al 2001, Moynahan et al 2001]. Other functions of BRCA2 include stabilizing stalled replication forks and regulating cytokinesis [Daniels et al 2004]. BRCA2 works in concert with RAD51 to orchestrate the repair of double-strand break ends, prompting the nucleation of each end by RAD51. BRCA2 has been found in various subcomplexes with other FA proteins, including FANCG, FANCD2, and PALB2 [Xia et al 2007, Wilson et al 2010].

**Abnormal gene product.** See Molecular Pathogenesis.

**BRIP1 (previously FANCJ or BACH1)**

**Gene structure.** BRIP1 (NM_032043.2) has 20 exons.

**Pathogenic variants.** See Table A.

**Normal gene product.** The Fanconi anemia group J protein (BRIP1 or FANCJ) has 1249 amino acids and is a DNA-dependent ATPase and a 5'-to-3' DNA helicase (DEAH helicase) that binds directly to the BRCT domain of BRCA1 [Cantor et al 2001, Chen et al 2014, Zou et al 2014]. FANCJ acetylation regulates DNA damage response [Xie et al 2012], and it contains the seven helicase-specific motifs and C-terminal extension, which has 39% homology with synaptonemal complex protein 1, a major component of the transverse filaments of developing meiotic chromosomes [Cantor et al 2001, Wu et al 2012, Brosh & Cantor 2014, Sommers et al 2014]. FANCJ engages stable G4/G-quadruplex structures [Sarkies et al 2012, Castillo Bosch et al 2014], promotes stability of FAND2/FANCI [Zhang et al 2010, Clark et al 2015], and its helicase domain clearly is important for FA pathway function [Wu & Brosh 2009, Guo et al 2014]. FANCJ also appears to interdigitate with the mismatch repair pathway in binding to MLH1 [Cantor & Xie 2010] and centrosome amplification [Zou et al 2013].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCA**

**Gene structure.** The longest transcript variant NM_000135.2 has 43 exons.

**Pathogenic variants.** The pathogenic variants of FANCA are numerous and highly variable among families [Levran et al 1997, Morgan et al 1999, Wijkter et al 1999]. A small percentage of families share the pathogenic variants p.Phe1263del and p.Val372AlafsTer42; the latter is found in affected individuals of northern European ancestry. See Table A.
Table 3. Selected FANCA Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1115_1118del</td>
<td>p.Val372AlafsTer42</td>
<td>NM_000135.2</td>
</tr>
<tr>
<td>c.3788_3790del</td>
<td>p.Phe1263del</td>
<td>NP_000126.2</td>
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</table>

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.


**Abnormal gene product.** See Molecular Pathogenesis.

**FANCB**

**Gene structure.** FANCB has ten exons with the translation start in exon 3 (NM_001018113.1).

**Pathogenic variants.** See Table A.

**Normal gene product.** FANCB comprises 853 amino acids; some sequences have 859 residues, depending on the initiating methionine. FANCB is a component of the FA core complex and contains a putative bipartite NLS [Meetei et al 2004]. FANCB is relevant to normal development – as is evidenced by its dysfunction being linked to VACTERL association [McCaulley et al 2011, Umaña et al 2011].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCC**

**Gene structure.** FANCC has 15 exons.

**Pathogenic variants.** Three common pathogenic variants in FANCC have been identified (c.456+4A>T, c.1642C>T, and c.67delG) [Whitney et al 1993]. See Table A.
Table 4. Selected FANCC Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias)</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.456+4A&gt;T (IVS4+4A&gt;T)</td>
<td>--</td>
<td>NM_000136.2</td>
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<tr>
<td></td>
<td></td>
<td>NP_000127.2</td>
</tr>
<tr>
<td>c.37C&gt;T</td>
<td>p.Gln13Ter</td>
<td></td>
</tr>
<tr>
<td>c.67delG (322delG)</td>
<td>p.Asp23IlefsTer23</td>
<td></td>
</tr>
<tr>
<td>c.1642C&gt;T (IVS24+4A&gt;T)</td>
<td>p.Arg548Ter</td>
<td></td>
</tr>
<tr>
<td>c.1661T&gt;C</td>
<td>p.Leu554Pro</td>
<td></td>
</tr>
</tbody>
</table>

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions
2. Found primarily in the Ashkenazi Jewish population; but also reported in a Japanese cohort.
3. See Genotype-Phenotype Correlations.
4. Prevalent in individuals of northern European ancestry
5. Found in individuals from southern Italy

Normal gene product. FANCC has 558 amino acids. It is a component of the FA core complex, but localizes to both the nucleus and the cytoplasm [Yamashita et al 1994]. Some functions of FANCC outside of the FA core complex have also been proposed [Fagerlie et al 2004]. Reports suggest that STAT1 binds to FANCC to modulate JAK-STAT signaling and to protect cells from interferon gamma toxic effects [Pang et al 2000, Fagerlie et al 2004]. Further, FANCC binds to microtubule-associated protein stathmin-1 to regulate cytokinesis [Magron et al 2015].

Abnormal gene product. See Molecular Pathogenesis.

FANCD2

Gene structure. FANCD2 has two transcript variants. Variant 1 (NM_033084.3) has 43 exons; variant 2 (NM_001018115.1) has 44 exons and an alternate 3’ coding sequence resulting in a shorter and distinct C-terminus. FANCD2 protein encoded by variant 2 (exon 44 form) is the functional FANCD2 protein, while the other transcript variant encodes a non-functional protein [Montes de Oca et al 2005].

Pathogenic variants. See Table A.

Normal gene product. The functional FANCD2 (NP_001018125.1) has 1451 amino acids (isoform b) and shares sequence similarity with FANCI. FANCD2 and FANCI form a protein complex (ID complex). FANCD2 can be monoubiquitinated on lysine 561 in an FA core complex-, UBE2T- (also known as FANCT [Hira et al 2015, Rickman et al 2015, Virts et al 2015]), and FANCI-dependent manner [Sato et al 2012, Rajendra et al 2014]. Reports illuminated the structure of FANCI-FAND2 complex [Joo et al 2011], its coordinate nuclear targeting [Boisvert et al 2013], and its RAD18-mediated chromatin loading [Song et al 2010, Williams et al 2011a]. Monoubiquitinated FANCD2 is translocated to chromatin fraction – recruited by UHRF1 [Liang et al 2015] – to form nuclear foci with FANCI, BRCA1 (FANCS [Sawyer et al 2015]), BRCA2, RAD51, and other partners. FANCD2 can be phosphorylated by ATM [Taniguchi et al 2002b, Ho et al 2006] and by ATR [Andreassen et al 2004, Pichierri & Rosselli 2004] in response to DNA damage. FANCD2 is phosphorylated at serine 331 by CHK1 in a manner that is required for binding to BRCA2 [Zhi et al 2009]. Important studies have shown FANCD2 to have a function in resection of ends surrounding a cross-link in the repair process [Knipscheer et al 2009], in replication fork processes [Zhu et al 2015b], binding to mini-chromosome maintenance proteins in control of
replisome [Lossaint et al 2013]. A nuclease, FAN1, has been demonstrated to bind to FANCD2 [Huang & D’Andrea 2010, Kratz et al 2010, MacKay et al 2010], and to promote DNA interstrand cross-link repair [Smogorzewska et al 2010, Yoshikiyo et al 2010].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCE**

**Gene structure.** FANCE has 14 exons (NM_021922.2).

**Pathogenic variants.** See Table A.

**Normal gene product.** FANCE has 536 amino acids and is a component of the FA core complex. FANCE directly binds to FANCD2 and recruits it to the FA E3 ligase complex [Polito et al 2014]. FANCE contains two nuclear localization signals (NLS) and its nuclear accumulation depends on FANCC [Léveillé et al 2006]. FANCE has five tandem repeats of a short helical motif (FANC repeats) [Nookala et al 2007]. It functions as a shuttle protein between the FA core complex and FANCD2 in a fashion dependent on phosphorylation [Wang et al 2007], with functionality dependent on alternative splicing [Bouffard et al 2015].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCF**

**Gene structure.** FANC has a single exon (NM_022725.2).

**Pathogenic variants.** See Table A.

**Normal gene product.** FANCF has 374 amino acids and is a component of the FA core complex. FANCF acts as a flexible adaptor protein required for the assembly of the FA core complex [Léveillé et al 2004]. Crystallographic studies of the C-terminal domain revealed a helical repeat structure similar to the Cand1 regulator of the Cul1-Rbx1-Skp1-Fbox(Skp2) ubiquitin ligase complex [Kowal et al 2007], and recently next-generation sequencing refined genotype-phenotype correlations [Nicchia et al 2015].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCG**

**Gene structure.** FANCG has 14 exons (reference sequence NM_004629.1).

**Pathogenic variants.** Pathogenic variants in FANCG are highly variable, but more common variant alleles have been described in specific populations: c.307+1G>C (Korean/Japanese), c.925-2A>G (Brazilian), c.1480+1G>C (French Canadian), and p.Gly395TrpfsTer5 [Demuth et al 2000] and p.Trp599ProfsTer49 [Auerbach et al 2003] (northern European). See Table A.
Table 5. Selected FANCG Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias)</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.307+1G&gt;C (IVS3+1G&gt;C)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>c.925-2A&gt;G (IVS8-2A&gt;G)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>c.1183-1192del (1184-1194del)</td>
<td>p.Glu395TrpfsTer5</td>
<td>NM_004629.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_004620.1</td>
</tr>
<tr>
<td>c.1480+1G&gt;C (IVS11+1G&gt;C)</td>
<td>p.Trp599ProfsTer49</td>
<td></td>
</tr>
<tr>
<td>c.1794_1803del</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** FANCG has 622 amino acids. It is a component of the FA core complex. FANCG has seven tetratricopeptide repeat motifs [Blom et al 2004, Wilson et al 2010]. FANCG is a phosphoprotein; serines 383 and 387 on FANCG are phosphorylated in M phase, presumably by cdc2 [Mi et al 2004]. These two sites are important for exclusion of FANCG from chromatin in mitosis. Phosphorylation of serine 7 of FANCG is upregulated after MMC treatment [Qiao et al 2004]. FANCA and FANCG stabilize each other, and FANCG, BRCA2, FANCD2, and XRCC3 participate in the same protein complex. This implies multifunctionality of FANCG by its presence in the core complex as well as in homologous recombinatorial repair [Wang et al 2007]. FANCG further associates with Rap80-BRCA1 complex in DNA repair mediated by homologous recombination [Zhu et al 2015a], and it is operational in homing of hematopoietic stem cells [Barroca et al 2012].

**Abnormal gene product.** See Molecular Pathogenesis.

**FANCI**

**Gene structure.** FANCI has 37 exons (NM_018193.2).

**Pathogenic variants.** See Table A.

**Normal gene product.** FANCI has 1268 amino acids and shares sequence similarity with FANCD2. FANCD2 and FANCI form a protein complex (ID complex). FANCI can be monoubiquitinated on lysine 523 in an FA core complex-, UBE2T-, and FANCD2-dependent manner. Monoubiquitinated FANCI is translocated to nuclear foci and colocalizes with BRCA1, BRCA2, RAD51, FANCD2 [Boisvert & Howlett 2014, Rajendra et al 2014]. FANCI is a phosphoprotein. DNA damage-induced phosphorylation of p.Ser730, p.Thr952, and p.Ser1121 of human FANCI can be detected [Smogorzewska et al 2007]. FANCI functions in an analogous manner as FANCD2 and can be analyzed in the same fashion in assays including DNA repair foci, cell survival, and monoubiquitination [Ishiai et al 2008]. Reports illuminated the structure of FANCI-FAND2 complex [Joo et al 2011], its coordinate nuclear targeting [Boisvert et al 2013], and – remarkably – its FANCD2-independent function upstream of FA core complex recruitment [Castella et al 2015].

**Abnormal gene product.** See Molecular Pathogenesis.

Click here (pdf) for information on the genes less commonly involved in Fanconi Anemia (from Table 1b).

**References**
Literature Cited


Chapter Notes

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Revision History
- 8 March 2018 (aa, pm) Revision: addition of one gene: RFWD3
- 23 February 2017 (aa, pm) Revision: addition of two genes: MAD2L2 and XRCC2; edits to Prevention of Secondary Complications
- 22 September 2016 (sw) Comprehensive update posted live
- 7 February 2013 (cd) Revision: deletion/duplication analysis available clinically for FANCC
- 6 September 2012 (cd) Revision: sequence analysis for mutations in RAD51C and SLX4 available clinically
- 3 November 2011 (cd) Revision: deletion/duplication analysis available clinically for PALB2 deletions
- 10 February 2011 (me) Comprehensive update posted live
- 27 March 2008 (cd) Revision: sequence analysis and prenatal testing available clinically for FANCB-, FANCE-, FANCF- and FANCI-related Fanconi anemia
- 29 January 2008 (cd) Revision: sequence analysis of entire coding region of FANCG and prenatal testing available
- 7 November 2007 (cd) Revision: molecular genetic testing and prenatal diagnosis no longer available on a clinical basis for FANCF and FANCG
- 22 June 2007 (me) Comprehensive update posted live
- 1 March 2006 (cd) Revision: FANCB mutations: X-linked inheritance
- 3 January 2006 (as) Revision: deletion/duplication testing clinically available
- 13 September 2004 (me) Comprehensive update posted live
- 14 February 2002 (me) Review posted live
- 31 May 2001 (as) Original submission
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