U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Mehta PA, Ebens C. Fanconi Anemia. 2002 Feb 14 [Updated 2021 Jun 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Fanconi Anemia

Synonym: Fanconi Pancytopenia

Parinda A Mehta, MD[1] and Christen Ebens, MD, MPH[2]

Created: February 14, 2002; Updated: June 3, 2021.

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/or 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, 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) and/or one of the following identified on molecular genetic testing: biallelic pathogenic variants in one of the 21 genes known to cause autosomal recessive FA; 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.

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; granulocyte colony-stimulating factor improves the neutrophil count in some individuals; 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. Treatment of growth deficiency, limb anomalies, ocular anomalies, renal malformations, genital anomalies, hypothyroidism, cardiac anomalies, and

Author Affiliations: 1 Professor, Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Email: parinda.mehta@cchmc.org. 2 Assistant Professor, Division of Blood and Marrow Transplant & Cellular Therapy University of Minnesota, Minneapolis, Minnesota; Email: ebens012@umn.edu.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

dermatologic manifestations as recommended by the subspecialty care provider. Hearing aids may be helpful for hearing loss as per otolaryngologist; supplemental feeding as needed by nasogastric tube or gastrostomy; vitamin D supplementation; early intervention for developmental delays; individualized education plan for school-age children; speech, occupational, and physical therapy as needed; liberal use of sunscreen and rash guards; social work and care coordination as needed.

Prevention of primary manifestations: Human papilloma virus (HPV) vaccination to reduce the risk for 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 subsequent risk of developing solid tumors.

Surveillance: Clinical assessment of growth, feeding, nutrition, spine, and ocular issues at each visit throughout childhood. Annual ophthalmology examination; annual evaluation with endocrinologist including TSH, free T4, 25-hydroxy vitamin D, two-hour glucose tolerance testing, and insulin levels; assessment of pubertal stage and hormone levels at puberty and every two years until puberty is complete; follow up hearing evaluation if exposed to ototoxic drugs; annual developmental assessment; blood counts every three to four months or as needed; bone marrow aspirate and biopsy to evaluate morphology and cellularity, FISH and cytogenetics to evaluate for emergence of a malignant clone at least annually after age two years; liver function tests every three to six months and liver ultrasound examination every six to twelve months in those receiving androgen therapy; gynecologic assessment for genital lesions annually beginning at age 13 years; vulvo-vaginal examinations and Pap smear annually beginning at age 18 years; oral examinations for tumors every six months beginning at age nine to ten years; annual nasolaryngoscopy beginning at age ten years; dermatology evaluation every six to 12 months; annual abdominal ultrasound and brain MRI in those with *BRCA2*-related FA. Additional cancer surveillance for individuals with *BRCA1*-, *BRCA2*-, *PALB2*-, *BRIP1*-, and *RAD51C*-related FA.

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; excessive sun exposure. Radiographic studies solely for the purpose of surveillance (i.e., in the absence of clinical indications) should be minimized.

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 heterozygote, and a 25% chance of inheriting neither of the familial FA-related pathogenic variants. Heterozygotes are not at risk for autosomal recessive FA. However, heterozygous mutation of a subset of FA-related genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *BRIP1,* and *RAD51C*) is associated with an increased risk for breast and other cancers.

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 and preimplantation genetic testing 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 Clinical Care Guidelines, 2020 edition).

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; liver tumors)
- Inordinate toxicities from chemotherapy or radiation

Establishing the Diagnosis

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

- 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 Clinical Care Guidelines.

- Identification of biallelic pathogenic (or likely pathogenic) variants in one of the 21 genes known to cause autosomal recessive FA, or a heterozygous pathogenic (or likely pathogenic) variant in *RAD51* known to cause autosomal dominant FA, or a hemizygous pathogenic (or likely pathogenic) variant in *FANCB* known to cause X-linked FA (see Table 1)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

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 to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes the genes in Table 1 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 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 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., pathogenic variant[s] in 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 1. Molecular Genetic Testing Used in Fanconi Anemia

Gene [1, 2]	Comple-mentation Group [3]	% of FA Attributed to Pathogenic Variants in Gene [4]	Proportion of Pathogenic Variants [5] Detected by Method	
			Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
BRCA1	FA-S	<1%	>99%	None reported
BRCA2	FA-D1	2%	>99%	None reported
BRIP1	FA-J	2%	>99%	None reported
ERCC4	FA-Q	<1%	>99%	None reported

Table 1. continued from previous page.

Gene [1, 2]	Comple-mentation Group [3]	% of FA Attributed to Pathogenic Variants in Gene [4]	Proportion of Pathogenic Variants [5] Detected by Method	
			Sequence analysis [6]	Gene-targeted deletion/ duplication analysis [7]
FAAP100	FA-Y	1 individual [8]	>99%	None reported
FANCA	FA-A	60%-70%	~60%	~40%
FANCB	FA-B	2%	~70%	~30%
FANCC	FA-C	14%	>90%	<10%
FANCD2	FA-D2	3%	<90%	>10%
FANCE	FA-E	3%	>99%	None reported
FANCF	FA-F	2%	~85%	~15%
FANCG (*XRCC9*)	FA-G	10%	>99%	None reported
FANCI	FA-I	1%	>95%	<5%
FANCL	FA-L	<1%	>90%	<10%
FANCM	FA-M	<1%	~75%	1 reported
PALB2	FA-N	<1%	>95%	1 reported
RAD51	FA-R	2 reported	>99%	None reported
RAD51C	FA-O	<1%	>99%	None reported
REV7 (MAD2L2)	FA-V	1 reported	>99%	None reported
RFWD3	FA-W	1 reported	>99%	None reported
SLX4	FA-P	<1%	>90%	1 reported
UBE2T	FA-T	<1%	<50%	>50%
XRCC2	FA-U	1 reported	>99%	None reported
Unknown	NA	<5%		

NA = not applicable

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. See Molecular Genetics for information on pathogenic variants detected in these genes.

6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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 used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

8. Author, personal communication

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 Findings

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 (HSCT).
- Endocrine disorders (50%-75%). Hypothyroidism (30%-60%), diabetes (8%-10%), hyperglycemia / impaired glucose tolerance (25%-70%), and insulin resistance [Petryk et al 2015]
- Hearing loss (10%). Usually conductive secondary to middle-ear bony anomalies with or without additional ear anomalies (e.g., dysplastic auricle, narrow ear canal, abnormal pinna)
- 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 face shape, 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 2014. Frequencies are approximate, since many reports did not mention physical descriptions.

Developmental Delay / Intellectual Disability

Developmental delay and/or intellectual disability is seen in 10%.

Bone Marrow Failure

The age of onset of bone marrow failure 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 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 2). 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

	Mild	Moderate	Severe
Absolute neutrophil count (ANC)	<1,500/mm^3	<1,000/mm^3	<500/mm^3
Platelet count	150,000-50,000/mm^3	<50,000/mm^3	<30,000/mm^3
Hemoglobin (Hb) level	≥8 g/dL	<8 g/dL	<8 g/dL

Cancer Susceptibility

Acute myelogenous leukemia (AML). The relative risk for 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 from HNSCCs seen in the general population. HNSCCs:
  - Occur at an earlier age (20-40 years) than in the general population;
  - Most commonly occur 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 of the skin and genitourinary tract. The pattern of second primaries resembles that observed in HPV-associated HNSCCs 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].

FANCB. More recently *FANCB* pathogenic variants are shown to predominantly cause early-onset bone marrow failure and severe congenital abnormalities. Biochemical and cell-based assays of causative variants reveal functional properties of *FANCB* that are associated with clinical severity [Jung et al 2020].

FANCG. Pathogenic variants in *FANCG* may be associated with severe marrow failure and a higher incidence of leukemia than *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 clear-cut genotype-phenotype correlations. 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. A literature review of genotype-phenotype associations in Fanconi anemia was recently published [Fiesco-Roa et al 2019].

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. Conflicting reports have associated [Faivre et al 2000] and refuted association [Castella et al 2011] of homozygous *FANCA* null pathogenic variants with earlier-onset anemia and higher incidence of leukemia than individuals with pathogenic variants that permit production of an abnormal FANCA protein. Other *FANCA* variants (p.His913Pro, p.Arg951Gln, p.Arg951Trp) have been associated with slower hematologic disease progression [Bottega et al 2018].

FANCB. Truncating variants often present with VACTERL-H [McCauley et al 2011].

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 c.67delG [Faivre et al 2005]. However modifiers play a role as the c.456+4A>T variant in Japanese individuals results in a milder phenotype [Futaki et al 2000]

- c.67delG and p.Gln13Ter are associated with a lower risk for congenital anomalies and later progression to bone marrow failure [Yamashita et al 1996, Gillio et al 1997].
- c.165+1G>T founder variant in a Saudi population has been associated with a milder phenotype [Hartmann et al 2010].

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

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FAAP100*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *REV7/MAD2L2*, *RFWD3*, *SLX4*, or *UBE2T*.

Other phenotypes associated with germline pathogenic variants in *BRCA1*, *BRCA2*, *BRIP1*, *ERCC4*, *FANCA*, *FANCM*, *PALB2*, *RAD51*, *RAD51C*, and *XRCC2* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	MOI	Disorder
BRCA1	AD	Hereditary breast & ovarian cancer (See *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer.) Pancreatic cancer (OMIM 613347 & 614320) Prostate cancer (OMIM 176807)
BRCA2	AD	
BRIP1	AD	Breast cancer & ovarian cancer predisposition (OMIM 605882 & OMIM 167000)
ERCC4	AR	Xeroderma pigmentosum
	AR	Individuals reported w/phenotypes of Fanconi anemia, xeroderma pigmentosum (XP)/Cockayne Syndrome (CS) complex or w/combined XP/CS/Fanconi anemia (OMIM 278760)
	AR	XFE progeroid syndrome (OMIM 610965)
FANCA	AD	Breast cancer & ovarian cancer predisposition [Del Valle et al 2020]
FANCM	AR	Spermatogenic failure; premature ovarian failure (OMIM 618086 & 618096)
PALB2	AD	Breast cancer & ovarian cancer predisposition (OMIM 114480)
	AD	Pancreatic cancer predisposition (OMIM 613348)
RAD51	AD	Congenital mirror movements
RAD51C	AD	Breast cancer & ovarian cancer susceptibility (OMIM 613399)
XRCC2	AR	Spermatogenic failure; premature ovarian failure (OMIM 619145 & 619146)

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Sporadic tumors (including multiple squamous cell carcinomas, other carcinomas, melanoma, malignant peripheral nerve sheath tumor, glioblastoma, diffuse large B-cell lymphoma, Ewing sarcoma, AML [Nalepa & Clapp 2018], and pancreatic neuroendocrine tumor [Zheng et al 2021]) occurring as single tumors in the absence of any other findings of Fanconi anemia frequently harbor somatic variants in FA-related genes that are

not present in the germline. In some instances the mutated FA gene appears to function as a tumor suppressor, in others as an oncogene (particularly *FANCD2*). In these circumstances predisposition to these tumors is not heritable. Somatic FA variants and sporadic tumors are reviewed in two recent publications [Nalepa & Clapp 2018, Niraj et al 2019].

Differential Diagnosis

Cells derived from individuals with other chromosome breakage syndromes may also exhibit high rates of spontaneous chromosome breakage; however, only cells derived from individuals with Fanconi anemia (FA) exhibit increased chromosome breakage in response to diepoxybutane (DEB). See Table 4 for selected examples of chromosome breakage syndromes and for other disorders to consider in the differential diagnosis of FA.

Table 4. Genes and Disorders of Interest in the Differential Diagnosis of Fanconi Anemia

Gene(s)	Disorder	MOI	Chromosome Breakage	Clinical Characteristics
ATM	Ataxia-telangiectasia (A-T)	AR	Cells derived from persons w/A-T may exhibit high rates of spontaneous chromosome breakage.	Progressive cerebellar ataxia, oculomotor apraxia, choreoathetosis, conjunctival telangiectasias, immunodeficiency, frequent infections, ↑ risk for malignancy, hypersensitivity to ionizing radiation
ATR *CENPJ* *CEP152* *CEP63* *DNA2* *NIN* *NSMCE2* *RBBP8* *TRAIP*	Seckel syndrome (OMIM PS210600)	AR	May show ↑ chromosome breakage w/DNA cross-linking agents [1] (MMC, DEB)	Growth deficiency, microcephaly w/ID, characteristic facial appearance; may be assoc w/pancytopenia &/or AML
BLM	Bloom syndrome (BSyn)	AR	Cells derived from persons w/BSyn may exhibit high rates of spontaneous chromosome breakage.	Severe pre- & postnatal growth deficiency, immune abnormalities, sensitivity to sunlight, insulin resistance, high risk for many cancers that occur at an early age
NBN	Nijmegen breakage syndrome	AR	May manifest ↑ chromosome breakage w/MMC	Short stature, progressive microcephaly w/loss of cognitive skills, premature ovarian failure in females, recurrent sinopulmonary infections, ↑ risk for cancer (esp lymphoma)
NF1	Neurofibromatosis 1	AD	Not assoc w/↑ chromosome breakage	Multiple café au lait spots, axillary & inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, choroidal freckling
RBM8A [2]	Thrombocytopenia absent radius syndrome	AR	Not assoc w/chromosome breakage	Bilateral absence of the radii w/presence of both thumbs & thrombocytopenia that is generally transient

AD = autosomal dominant; AR = autosomal recessive; DEB = diepoxybutane; FA = Fanconi anemia; ID = intellectual disability; MMC = mitomycin C; MOI = mode of inheritance

1. Andreassen et al [2004]

2. The diagnosis of thrombocytopenia absent radius syndrome is confirmed by identification of a null heterozygous allele (most often a minimally deleted 200-kb region at chromosome band 1q21.1, but in some cases a heterozygous *RBM8A* pathogenic variant detected by molecular genetic testing) *in trans* with a heterozygous *RBM8A* hypomorphic allele.

VACTERL association (*v*ertebral defects, *a*nal atresia, *t*racheoesophageal fistula with *e*sophageal atresia, and *r*adial or renal dysplasia; OMIM 192350) can also be considered in the differential diagnosis. VACTERL

association can be distinguished from FA by testing for chromosome breakage with DEB and MMC. The molecular cause of VACTERL association is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and management requirements in an individual diagnosed with Fanconi anemia (FA), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended (See also 2020 consensus guidelines [full text]).

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Fanconi Anemia

System/Concern	Evaluation	Comment
Growth	Growth assessment; exam by endocrinologist	Additional studies (growth hormone levels, bone age radiographs) as recommended by endocrinologist
Musculoskeletal	Clinical assessment for limb anomalies, hip dislocation, neck/spine anomalies & scoliosis	Referral to orthopedic surgeon as indicated
Eyes	Exam by ophthalmologist	
Genitourinary	Ultrasound exam of kidneys & urinary tract	Referral to nephrologist, gynecologist &/or urologist as indicated
Endocrine	Exam by endocrinologist; thyroid function tests; brain MRI for pituitary abnormalities	Additional studies (glucose tolerance testing, lipids, pituitary & gonadal function testing) as recommended by endocrinologist
Hearing	Formal hearing eval	Referral to otolaryngologist as indicated
Cardiac/ Vascular	Echocardiogram; brain MRI & angiography for moya moya syndrome	Referral to cardiologist as indicated
Gastrointestinal	• Urgent eval w/gastroenterologist & surgery for those w/ obstructive GI malformations (e.g., esophageal atresia, duodenal atresia, or imperforate or bifurcated anus) &/or tracheoesophageal fistula, intestinal malrotation, or annular pancreas • Nutrition/feeding eval as needed	Referral to gastroenterologist, dietician, & surgeon as indicated
Development	Developmental assessment (esp important for toddlers & school-age children)	Referral to neuropsychologist or developmental/ behavioral pediatrician as indicated
Hematology/ Oncology	Eval by hematologist incl complete blood count, fetal hemoglobin, full blood typing, blood chemistries (assessing liver, kidney, & iron status), & bone marrow aspirate for cell morphology, FISH & cytogenetics, & biopsy for cellularity	The bone marrow of those w/FA can exhibit signs of dysplasia, e.g., nuclear/cytoplasmic dys-synchrony, hypo-lobulated megakaryocytes, & bi-nucleated erythroid cells. These features must be distinguished from true forms of MDS by a hematopathologist experienced in eval of MDS in those w/FA.
	HLA typing of the affected person, sibs, & parents for consideration of hematopoietic stem cell transplantation	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of FA to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

FA = Fanconi anemia; GI = gastrointestinal; HLA = human leukocyte antigen; MOI = mode of inheritance; MDS = myelodysplastic syndrome
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Recommendations for treatment were agreed upon at a 2014 consensus conference and updated in 2020 (full text).

Table 6. Treatment of Manifestations in Individuals with Fanconi Anemia

Manifestation/Concern	Treatment	Considerations/Other
Growth deficiency	Treatment per endocrinologist	
Limb anomalies & other orthopedic manifestations	• Mgmt per orthopedic surgeon • PT, OT	
Ocular anomalies	Mgmt per ophthalmologist	
Renal malformations	Mgmt per nephrologist &/or urologist	
Genital anomalies	Mgmt per gynecologist or urologist	
Hypothyroidism	Treatment per endocrinologist	
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Cardiac anomalies	Treatment per cardiologist & surgery	
Nutrition	• Supplemental feeding as needed by nasogastric tube or gastrostomy • Vitamin D supplementation	Low threshold for clinical feeding eval if clinical signs or symptoms of dysphagia
Development	Early intervention for DDs; individualized education plan for school-age children; therapies (speech, OT, PT) as needed	
Dermatologic manifestations	• Liberal use of sunscreen & rash guards • Treatment per dermatologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

DD = developmental delay; OT = occupational therapy; PT = physical therapy

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). Oxymetholone therapy suppresses osteopontin transcription and induces hematopoietic stem cell cycling in Fanconi mice suggesting downregulation of osteopontin as an important

potential mechanism for the drug's action [Zhang et al 2015]. 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 of 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 stanozolol in Asia, and oxandrolone and danazol in North America.

Side effects of androgen administration include virilization and liver toxicity (e.g., elevated liver enzymes, cholestasis, peliosis hepatis [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 (LFTs) for abnormalities. Blood tests for LFTs should be performed every three to six months; liver ultrasound should be performed every six to twelve months. If no response is seen after three to four months, androgens should be discontinued [Scheckenbach et al 2012, Rose et al 2014, Paustian et al 2016].

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.

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 [Mehta et al 2010, Ebens et al 2017]. 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]. Transplant outcomes for recipients of alternative stem cell donors have achieved those of matched sib donors [Mehta et al 2017, Ebens et al 2018]. Newer approaches to graft manipulation, either in vivo or ex vivo, permit use of haploidentical donors without prohibitive rates of graft-vs-host disease (GVHD) [Bonfim et al 2017, Strocchio et al 2021, Zubicaray et al 2021].

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, Mitchell et al 2014]. Recently published EBMT (European Society for Blood and Marrow Transplantation) experience suggests a survival benefit to achieving a complete remission prior to HSCT [Giardino et al 2020].

Solid tumors. Prompt, aggressive workup for any symptoms suggestive of a malignancy is indicated. Early detection and surgical removal remain the mainstay of therapy. Treatment is challenging due to the increased toxicity associated with chemotherapy and radiation in individuals with 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, Tan et al 2011, Spanier et al 2012, Kutler et al 2016]. 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 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, Turkish, and US groups now report excellent outcomes with alternative donors with a "chemotherapy-only" preparative regimen in single- and multi-center studies. The study from Germany showed 88% survival and normal hematopoiesis at a median follow up of 30 months. 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 individuals 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 [Bonfim et al 2015, Chao et al 2015, Mehta et al 2017].

Surveillance

See 2020 consensus guidelines (full text).

Table 7. Recommended Surveillance for Individuals with Fanconi Anemia

System/Concern	Evaluation	Frequency
Growth	Growth/feeding/nutrition assessment	At each visit throughout childhood
Scoliosis	Spine exam	
Strabismus/ Cataracts	Exam by ophthalmologist	At each visit throughout childhood, then annually
Endocrine manifestations [1]	Endocrine eval incl: • TSH & free T4 • 25-hydroxy vitamin D • 2-hr oral glucose tolerance test, insulin levels	Annually
	Pubertal stage & hormone levels	At puberty, then every 2 yrs until puberty complete
Hearing loss	Formal hearing eval	At diagnosis & serially if exposed to ototoxic medications (e.g., chemotherapy agents)
Development	Developmental assessment	Annually throughout childhood

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Pancytopenia	Blood counts	Every 3-4 mos while stable & more often as needed [2, 3]
Myelodysplasia	• Bone marrow aspirate/biopsy to evaluate morphology & cellularity • FISH; & cytogenetics to evaluate for emergence of a malignant clone	• At least annually (after age 2 yrs) • In persons on GCSF, bone marrow aspirate/biopsy every 6 mos, if possible • Prompt investigation for hematologic disease progression incl in those who develop Sweet syndrome
Liver dysfunction due to androgen therapy	Liver function tests	Every 3-6 mos in those receiving androgen therapy
	Liver ultrasound exam for androgen-related changes, incl tumors	Every 6-12 mos in those receiving androgen therapy
Genital tract cancers	Gynecologic assessment for genital lesions	Annually beginning at age 13
	Thorough vulvo-vaginal exam & Pap smear	Annually beginning at age 18 or w/onset of sexual activity
	Suspicious genital tract lesions should be biopsied	Every 3-6 mos in those w/history of premalignant or malignant lesions
Oral, head, & neck cancers	Exam by dentist, oral surgeon, or ENT familiar w/FA	• Every 6 mos beginning by age 9-10 yrs • Every 2-3 mos in those w/history of premalignant or malignant lesions
	Nasolaryngoscopy	Annually beginning at age 10 yrs, or w/in first year after HSCT
	Eval for esophageal cancer in those w/ difficulty or pain w/swallowing	
Skin cancers	Eval by dermatologist	Every 6-12 mos
***BRCA2*-related FA [4, 5]**	Abdominal ultrasound, brain MRI	Annually starting at diagnosis (incl newborns)

1. For example, hypothyroidism, vitamin D deficiency
2. 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.
3. 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 pathogenic variant 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.
4. Neuroblastomas, brain tumors, kidney tumors
5. These cancer surveillance recommendations may be considered for persons with *PALB2*-related Fanconi anemia in the absence of consensus guidelines.

Additional cancer surveillance for individuals with Fanconi anemia. Some of the genes associated with FA are known breast cancer susceptibility genes: *BRCA1*, *BRCA2*, *BRIP1*, *PALB2*, and *RAD51C*. Individuals who have FA due to pathogenic variants in one of these genes should follow the National Comprehensive Cancer Network (NCCN) screening guidelines that have been developed for individuals with a heterozygous pathogenic variant in one of these genes. This should be done under the care of a genetic health care professional. To date, the risk of breast cancer has not been established in individuals with FA due to biallelic pathogenic variants in these genes, and no additional recommendations have been determined for breast cancer screening.

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, the individual should be referred for transplantation.

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

Excessive sun exposure. Sunscreen and sun protective clothing should be used to limit UV exposure.

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 FA-related physical abnormalities, bone marrow failure, and related cancers. Evaluations include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Cytogenetic testing of lymphocytes with diepoxybutane (DEB) and mitomycin C (MMC) for detection of increased chromosome breakage and radial forms.

Breast cancer susceptibility. Some of the genes associated with FA are known breast cancer susceptibility genes (see Genetically Related Disorders). Family members found to have a pathogenic variant in a known breast cancer susceptibility gene should undergo cancer screening as recommended in the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (no-fee registration and login required) and under the care of a genetic health care professional.

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 HSCT [Nabhan et al 2010, Tsui & Crismani 2019].

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

Therapies Under Investigation

Gene therapy. Several early phase clinical trials of gene therapy targeting *FANCA* are under way using lentiviral vectors at sites across the world, including the University of Washington/Fred Hutchinson Cancer Research Center and Stanford University in the United States, as well as Hospital Universitari Vall d'Hebron Research Institute in Spain and Shenzhen Geno-Immune Medical Institute in China.

Separately, the United States National Heart, Lung, and Blood Institute completed a Phase I trial of retroviral vector transduction of autologous CD34+ stem cells in individuals with *FANCC*-FA (results pending).

While some trials aim to correct CD34+ stem cells obtained from bone marrow harvest, others are exploring peripheral blood mobilization with combination of G-CSF and plerixafor, shown advantageous in pre-clinical models [Río et al 2017].

HSCT. A multi-center study (Cincinnati Children's Hospital Medical Center, Memorial Sloan Kettering Cancer Center, and Fred Hutchinson Cancer Research Center) is investigating risk-adjusted busulfan dosing in a chemotherapy-only conditioning regimen for HSCT in Fanconi anemia (including individuals with MDS and leukemia in addition to those with bone marrow failure as HSCT indication).

Ex vivo T cell receptor alpha/beta depletion of the stem cell product in HSCT is additionally under investigation at the University of Minnesota to reduce the risk of GVHD and allow avoidance of post-HSCT immune suppression.

A Phase I/II trial will incorporate an anti-cKIT antibody into HSCT conditioning to aid in myeloablation and reduce chemotherapy/radiation toxicity. This will be given in combination with T-cell receptor alpha/beta depletion of the stem cell product to individuals older than age two years with bone marrow failure as the HSCT indication (Jasper Therapeutics sponsored at Stanford University in California).

Hematopoiesis support. Phase I/II studies of the antioxidant quercetin, anti-hyperglycemic metformin and thrombopoietin mimetic eltrombopag are currently under way in the United States for marrow failure in children and adults with FA.

Squamous cell carcinoma (SCC). A Phase II study of the antioxidant quercetin for prevention of SCC in individuals with FA is also currently under way 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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 Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive FA are obligate heterozygotes (i.e., presumed to be carriers of one FA-related pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an FA-related pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent of a child with autosomal recessive FA, the following possibilities should be considered:
  - **A *de novo* pathogenic variant.** One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - **Uniparental isodisomy** for the parental chromosome with the pathogenic variant resulting in homozygosity for the pathogenic variant in the proband.

- Heterozygotes are not at risk for autosomal recessive FA. However, heterozygous mutation of a subset of FA-related genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *BRIP1,* and *RAD51C*) is associated with an increased risk for breast and other cancers (see Genetically Related Disorders and *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer).

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive FA-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a heterozygote, and a 25% chance of inheriting neither of the familial FA-related pathogenic variants.
- Heterozygotes are not at risk for FA. However, heterozygous mutation of a subset of FA-related genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *BRIP1,* and *RAD51C*) is associated with an increased risk for breast and other cancers [Seal et al 2006, Berwick et al 2007, Reid et al 2007] (see Genetically Related Disorders and *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer).

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

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

Heterozygote detection. Heterozygote testing for at-risk relatives requires prior identification of the FA-related pathogenic variants in the family.

Individuals who are heterozygous for an autosomal recessive FA-related pathogenic variant cannot be detected by the DEB/MMC test.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All probands with *RAD51*-related FA reported to date have the disorder as a result of a *de novo RAD51* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *RAD51* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. (Parental germline mosaicism has not been described to date in *RAD51*-related FA.)

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 Inheritance – 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 child and no other affected relatives and if the *FANCB* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo FANCB* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

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 *FANCB* pathogenic variant, the chance of the mother 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 heterozygotes and will usually not be affected [McCauley et al 2011].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *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 *FANCB* pathogenic variant to all of their daughters (who will be heterozygotes and will usually not be affected) and none of their sons.
- To date, no male with *FANCB*-related FA has been old enough to have children; they may also be infertile, as are many males with FA. Further, *FANCB* has been demonstrated essential to regulation of spermatogenesis and affected mice are infertile [Kato et al 2015].

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

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

Heterozygote detection. Carrier testing for at-risk female relatives requires prior identification of the *FANCB* pathogenic variant in the family.

Individuals who are heterozygous for a *FANCB* pathogenic variant 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 and discussion of the availability of prenatal/preimplantation genetic 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 or are heterozygotes (carriers) or who are at increased risk of being heterozygotes.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

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 testing (PGT) for FA are possible. PGT has successfully identified at-risk embryos as unaffected with FA and HLA-matched to affected sibs [Kahraman et al 2014, Rechitsky et al 2020].

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 [Auerbach et al 2003]; 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 [Gandhi et al 2019].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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 Williamette 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

- **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

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

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BRCA1	17q21.31	Breast cancer type 1 susceptibility protein	BRCA1 homepage - LOVD Database of BRCA1 and BRCA2 sequence variants that have been clinically reclassified by a quantitative integrated evaluation Breast Cancer Information Core (BRCA1) BRCA1 @ ZAC-GGM	BRCA1	BRCA1
BRCA2	13q13.1	Breast cancer type 2 susceptibility protein	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	BRCA2	BRCA2
BRIP1	17q23.2	Fanconi anemia group J protein	BRIP1 @ LOVD Fanconi Anaemia Mutation Database (FANCJ - BRIP1)	BRIP1	BRIP1
ERCC4	16p13.12	DNA repair endonuclease XPF	ERCC4 database	ERCC4	ERCC4

Table A. continued from previous page.

FAAP100	17q25.3	Fanconi anemia core complex-associated protein 100		FAAP100	FAAP100
FANCA	16q24.3	Fanconi anemia group A protein	Fanconi Anemia Mutation Database (FANCA)	FANCA	FANCA
FANCB	Xp22.2	Fanconi anemia group B protein	FANCB @ LOVD Fanconi Anaemia Mutation Database (FANCB)	FANCB	FANCB
FANCC	9q22.32	Fanconi anemia group C protein	Fanconi Anemia Mutation Database (FANCC)	FANCC	FANCC
FANCD2	3p25.3	Fanconi anemia group D2 protein	Fanconi Anaemia Mutation Database (FANCD2)	FANCD2	FANCD2
FANCE	6p21.31	Fanconi anemia group E protein	Fanconi Anaemia Mutation Database (FANCE)	FANCE	FANCE
FANCF	11p14.3	Fanconi anemia group F protein	Fanconi Anaemia Mutation Database (FANCF)	FANCF	FANCF
FANCG	9p13.3	Fanconi anemia group G protein	Fanconi Anaemia Mutation Database (FANCG)	FANCG	FANCG
FANCI	15q26.1	Fanconi anemia group I protein	Fanconi Anemia Mutation Database (FANCI)	FANCI	FANCI
FANCL	2p16.1	E3 ubiquitin-protein ligase FANCL	Fanconi Anaemia Mutation Database (FANCL)	FANCL	FANCL
FANCM	14q21.2	Fanconi anemia group M protein	Fanconi Anaemia Mutation Database (FANCM)	FANCM	FANCM
MAD2L2	1p36.22	Mitotic spindle assembly checkpoint protein MAD2B		MAD2L2	MAD2L2
PALB2	16p12.2	Partner and localizer of BRCA2	PALB2 database	PALB2	PALB2
RAD51	15q15.1	DNA repair protein RAD51 homolog 1	RAD51 database	RAD51	RAD51
RAD51C	17q22	DNA repair protein RAD51 homolog 3	RAD51C @ LOVD	RAD51C	RAD51C
RFWD3	16q23.1	E3 ubiquitin-protein ligase RFWD3		RFWD3	RFWD3
SLX4	16p13.3	Structure-specific endonuclease subunit SLX4	SLX4 @ LOVD	SLX4	SLX4
UBE2T	1q32.1	Ubiquitin-conjugating enzyme E2 T		UBE2T	UBE2T
XRCC2	7q36.1	DNA repair protein XRCC2	XRCC2 @ LOVD	XRCC2	XRCC2

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)

113705	BRCA1 DNA REPAIR-ASSOCIATED PROTEIN; BRCA1
133520	ERCC EXCISION REPAIR 4, ENDONUCLEASE CATALYTIC SUBUNIT; ERCC4
179617	RAD51 RECOMBINASE; RAD51
227645	FANCONI ANEMIA, COMPLEMENTATION GROUP C; FANCC
227646	FANCONI ANEMIA, COMPLEMENTATION GROUP D2; FANCD2

Table B. continued from previous page.

227650	FANCONI ANEMIA, COMPLEMENTATION GROUP A; FANCA
300514	FANCONI ANEMIA, COMPLEMENTATION GROUP B; FANCB
300515	FANCB GENE; FANCB
600185	BRCA2 DNA REPAIR-ASSOCIATED PROTEIN; BRCA2
600375	X-RAY REPAIR CROSS COMPLEMENTING 2; XRCC2
600901	FANCONI ANEMIA, COMPLEMENTATION GROUP E; FANCE
602774	RAD51 PARALOG C; RAD51C
602956	FANCG GENE; FANCG
603467	FANCONI ANEMIA, COMPLEMENTATION GROUP F; FANCF
604094	MITOTIC ARREST-DEFICIENT 2 LIKE 2; MAD2L2
605724	FANCONI ANEMIA, COMPLEMENTATION GROUP D1; FANCD1
605882	BRCA1-INTERACTING PROTEIN 1; BRIP1
607139	FANCA GENE; FANCA
608111	FANCL GENE; FANCL
609053	FANCONI ANEMIA, COMPLEMENTATION GROUP I; FANCI
609054	FANCONI ANEMIA, COMPLEMENTATION GROUP J; FANCJ
609644	FANCM GENE; FANCM
610355	PARTNER AND LOCALIZER OF BRCA2; PALB2
610538	UBIQUITIN-CONJUGATING ENZYME E2 T; UBE2T
610832	FANCONI ANEMIA, COMPLEMENTATION GROUP N; FANCN
611301	FANCONI ANEMIA-ASSOCIATED PROTEIN, 100-KD SUBUNIT; FAAP100
611360	FANCI GENE; FANCI
613278	SLX4 STRUCTURE-SPECIFIC ENDONUCLEASE SUBUNIT; SLX4
613390	FANCONI ANEMIA, COMPLEMENTATION GROUP O; FANCO
613897	FANCF GENE; FANCF
613899	FANCC GENE; FANCC
613951	FANCONI ANEMIA, COMPLEMENTATION GROUP P; FANCP
613976	FANCE GENE; FANCE
613984	FANCD2 GENE; FANCD2
614082	FANCONI ANEMIA, COMPLEMENTATION GROUP G; FANCG
614083	FANCONI ANEMIA, COMPLEMENTATION GROUP L; FANCL
614087	FANCONI ANEMIA, COMPLEMENTATION GROUP M; FANCM
614151	RING FINGER AND WD REPEAT DOMAINS-CONTAINING PROTEIN 3; RFWD3
615272	FANCONI ANEMIA, COMPLEMENTATION GROUP Q; FANCQ
616435	FANCONI ANEMIA, COMPLEMENTATION GROUP T; FANCT
617243	FANCONI ANEMIA, COMPLEMENTATION GROUP V; FANCV
617244	FANCONI ANEMIA, COMPLEMENTATION GROUP R; FANCR
617247	FANCONI ANEMIA, COMPLEMENTATION GROUP U; FANCU

Table B. continued from previous page.

617784	FANCONI ANEMIA, COMPLEMENTATION GROUP W; FANCW
617883	FANCONI ANEMIA, COMPLEMENTATION GROUP S; FANCS

See Table A for gene and protein names.

Molecular Pathogenesis

At least 23 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 2011, 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].

Furthermore, the FA core complex forms a larger complex with BLM, RPA, and topoisomerase IIIα, called BRAFT (*B*LM, *R*P*A*, *F*A, and *t*opoisomerase IIIα) [Meetei et al 2003] 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].

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 [Reid 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].

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 non-homologous end joining 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 recombination, may be the most direct function of FA proteins in bypass of the lesion [Ho & Schärer 2010, Song et al 2010].

Mechanism of disease causation. Loss of function

Table 8. Fanconi Anemia: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change	Comment [Reference]
FANCA	NM_000135.4 NP_000126.2	c.1115_1118delTTGG	p.Val372AlafsTer42	Common in northern Europeans
		c.2738A>C	p.His913Pro	Assoc w/slower hematologic disease progression [Bottega et al 2018]
		c.2852G>A	p.Arg951Gln	
		c.2851C>T	p.Arg951Trp	
FANCC	NM_000136.3	c.456+4A>T (IVS4+4A>T)	--	Common in Ashkenazi Jewish; also reported in a Japanese cohort [3]
	NM_000136.3 NP_000127.2	c.37C>T	p.Gln13Ter	Common in northern Europeans [3]
		c.67delG (322delG)	p.Asp23IlefsTer23	Common in northern Europeans & southern Italy [3]
	NM_000136.3	c.165+1G>T	--	See Genotype-Phenotype Correlations.
	NM_000136.3 NP_000127.2	c.1642C>T	p.Arg548Ter	Common in northern Europeans & southern Italy [3]
		c.1661T>C	p.Leu554Pro	See Genotype-Phenotype Correlations.
FANCG	NM_004629.2	c.307+1G>C (IVS3+1G>C)	--	Common in Koreans & Japanese
		c.925-2A>G (IVS8-2A>G)	--	Common in Brazil & northern Europeans
	NM_004629.2 NP_004620.1	c.1183_1192del10 (1184-1194del)	p.Glu395TrpfsTer5	Demuth et al [2000]
		c.1480+1G>C (IVS11+1G>C)	p.Trp599ProfsTer49	Common in French Canadians & northern Europeans [Auerbach et al 2003]

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. Genes from Table 1 in alphabetic order
2. Variant designation that does not conform to current naming conventions
3. See Genotype-Phenotype Correlations.

Chapter Notes

Author Notes

Comprehensive Center for Fanconi Anemia
Dana Farber Cancer Institute
Mayer 676
44 Binney Street

Boston, MA 02115
Phone: 617-632-6302

Author History

Blanche P Alter, MD, MPH, FAAP; National Cancer Institute (2011-2016)
Alan D'Andrea, MD; Dana Farber Cancer Institute (2002-2007)
Christen Ebens, MD, MPH (2021-present)
Gary Kupfer, MD; Yale University School of Medicine (2011-2016)
Parinda A Mehta, MD (2016-present)
Lisa Moreau, MS; Dana Farber Cancer Institute (2002-2007)
Akiko Shimamura, MD, PhD; Dana Farber Cancer Institute (2002-2007)
Toshiyasu Taniguchi, MD, PhD; Fred Hutchinson Cancer Research Center (2007-2011)
Jakub Tolar, MD, PhD; University of Minnesota (2016-2021)

Revision History

- 3 June 2021 (sw) Comprehensive update posted live
- 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

References

Literature Cited

Adamo A, Collis SJ, Adelman CA, Silva N, Horejsi Z, Ward JD, Martinez-Perez E, Boulton SJ, La Volpe A. Preventing nonhomologous end joining suppresses DNA repair defects of Fanconi anemia. Mol Cell. 2010;39:25–35. PubMed PMID: 20598602.

Alter BP. The association between FANCD1/BRCA2 mutations and leukaemia. Br J Haematol. 2006;133:446–8.

Alter BP, Giri N, Savage SA, Peters JA, Loud JT, Leathwood L, Carr AG, Greene MH, Rosenberg PS. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol. 2010;150:179–88. PubMed PMID: 20507306.

Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. J Med Genet. 2007;44:1–9. PubMed PMID: 16825431.

Andreassen PR, D'Andrea AD, Taniguchi T. ATR couples FANCD2 monoubiquitination to the DNA-damage response. Genes Dev. 2004;18:1958–63. PubMed PMID: 15314022.

Auerbach AD, Greenbaum J, Pujara K, Batish SD, Bitencourt MA, Kokemohr I, Schneider H, Lobitzc S, Pasquini R, Giampietro PF, Hanenberg H, Levran O, et al. Spectrum of sequence variation in the FANCG gene: an International Fanconi Anemia Registry (IFAR) study. Hum Mutat. 2003;21:158–68. PubMed PMID: 12552564.

Berwick M, Satagopan JM, Ben-Porat L, Carlson A, Mah K, Henry R, Diotti R, Milton K, Pujara K, Landers T, Dev Batish S, Morales J, Schindler D, Hanenberg H, Hromas R, Levran O, Auerbach AD. Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. Cancer Res. 2007;67:9591–6. PubMed PMID: 17909071.

Bonfim C, Ribeiro L, Nichele S, Loth G, Bitencourt M, Koliski A, Kuwahara C, Fabro AL, Pereira NF, Pilonetto D, Thakar M, Kiem HP, Page K, Fuchs EJ, Eapen M, Pasquini R. Haploidentical bone marrow transplantation with post-transplant cyclophosphamide for children and adolescents with Fanconi anemia. Biol Blood Marrow Transplant. 2017;23:310–17. PubMed PMID: 27832981.

Bonfim C, Ribeiro L, Nichele S, Loth G, Kuwahara C, Koliski A, Bitencourt M, Scherer F, Rodrigues L, Pilonetto D, Pasquini R. Excellent outcomes for Fanconi anemia patients undergoing hematopoietic stem cell transplantation (HSCT) without radiation: a single center experience on 103 patients. Biol Blood Marrow Transplant. 2015;21:S94.

Bottega R, Nicchia E, Cappelli E, Ravera S, De Rocco D, Faleschini M, Corsolini F, Pierri F, Calvillo M, Russo G, Casazza G, Ramenghi U, Farruggia P, Dufour C, Savoia A. Hypomorphic FANCA mutations correlate with mild mitochondrial and clinical phenotype in Fanconi anemia. Haematologica. 2018;103:417–26. PubMed PMID: 29269525.

Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, Wahrer DC, Sgroi DC, Lane WS, Haber DA, Livingston DM. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. Cell. 2001;105:149–60. PubMed PMID: 11301010.

Castella M, Pujol R, Callén E, Trujillo JP, Casado JA, Gille H, Lach FP, Auerbach AD, Schindler D, Benítez J, Porto B, Ferro T, Muñoz A, Sevilla J, Madero L, Cela E, Beléndez C, de Heredia CD, Olivé T, de Toledo JS, Badell I, Torrent M, Estella J, Dasí A, Rodríguez-Villa A, Gómez P, Barbot J, Tapia M, Molinés A, Figuera A, Bueren JA, Surrallés J. Origin, functional role, and clinical impact of Fanconi anemia FANCA mutations. Blood. 2011;117:3759–69. PubMed PMID: 21273304.

Chao MM, Kuehl JS, Strauss G, Hanenberg H, Schindler D, Neitzel H, Niemeyer C, Baumann I, von Bernuth H, Rascon J, Nagy M, Zimmermann M, Kratz CP, Ebell W. Outcomes of mismatched and unrelated donor hematopoietic stem cell transplantation in Fanconi anemia conditioned with chemotherapy only. Ann Hematol. 2015;94:1311–8. PubMed PMID: 25862235.

Chaudhury S, Auerbach AD, Kernan NA, Small TN, Prockop SE, Scaradavou A, Heller G, Wolden S, O'Reilly RJ, Boulad F. Fludarabine-based cytoreductive regimen and T-cell-depleted grafts from alternative donors for the treatment of high-risk patients with Fanconi anaemia. Br J Haematol. 2008;140:644–55. PubMed PMID: 18302713.

Ciccia A, Ling C, Coulthard R, Yan Z, Xue Y, Meetei AR. Laghmani el H, Joenje H, McDonald N, de Winter JP, Wang W, West SC. Identification of FAAP24, a Fanconi anemia core complex protein that interacts with FANCM. Mol Cell. 2007;25:331–43. PubMed PMID: 17289582.

Crossan GP, Patel KJ. The Fanconi anaemia pathway orchestrates incisions at sites of crosslinked DNA. J Pathol. 2012;226:326–37. PubMed PMID: 21956823.

D'Andrea AD. Susceptibility pathways in Fanconi's anemia and breast cancer. N Engl J Med. 2010;362:1909–19. PubMed PMID: 20484397.

Deans AJ, West SC. FANCM connects the genome instability disorders Bloom's Syndrome and Fanconi Anemia. Mol Cell. 2009;36:943–53. PubMed PMID: 20064461.

Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer. 2011;11:467–80. PubMed PMID: 21701511.

Del Valle J, Rofes P, Moreno-Cabrera JM, Lopez-Doriga A, Belhadj S, Vargas-Parra G, Teulé À, Cuesta R, Muñoz X, Campos O, Salinas M, de Cid R, Brunet J, González S, Capellá G, Pineda M, Feliubadaló L, Lázaro C. Exploring the role of mutations in Fanconi anemia genes in hereditary cancer patients. Cancers (Basel). 2020;12:829. PubMed PMID: 32235514.

Demuth I, Wlodarski M, Tipping AJ, Morgan NV, de Winter JP, Thiel M, Gräsl S, Schindler D, D'Andrea AD, Altay C, Kayserili H, Zatterale A, Kunze J, Ebell W, Mathew CG, Joenje H, Sperling K, Digweed M. Spectrum of mutations in the Fanconi anaemia group G gene, FANCG/XRCC9. Eur J Hum Genet. 2000;8:861–8. PubMed PMID: 11093276.

Ebens CL, DeFor TE, Tryon R, Wagner JE, MacMillan ML. Comparable outcomes after HLA-matched sibling and alternative donor hematopoietic cell transplantation for children with Fanconi anemia and severe aplastic anemia. Biol Blood Marrow Transplant. 2018;24:765–71. PubMed PMID: 29203412.

Ebens CL, MacMillan ML, Wagner JE. Hematopoietic cell transplantation in Fanconi anemia: current evidence, challenges and recommendations. Expert Rev Hematol. 2017;10:81–97. PubMed PMID: 27929686.

Faivre L, Guardiola P, Lewis C, Dokal I, Ebell W, Zatterale A, Altay C, Poole J, Stones D, Kwee ML, van Weel-Sipman M, Havenga C, Morgan N, de Winter J, Digweed M, Savoia A, Pronk J, de Ravel T, Jansen S, Joenje H, Gluckman E, Mathew CG. Association of complementation group and mutation type with clinical outcome in Fanconi anemia. European Fanconi Anemia Research Group. Blood. 2000;96:4064–70. PubMed PMID: 11110674.

Faivre L, Portnoi MF, Pals G, Stoppa-Lyonnet D, Le Merrer M, Thauvin-Robinet C, Huet F, Mathew CG, Joenje H, Verloes A, Baumann C. Should chromosome breakage studies be performed in patients with VACTERL association? Am J Med Genet A. 2005;137:55–8. PubMed PMID: 16015582.

Fiesco-Roa MO, Giri N, McReynolds LJ, Fest AF, Alter BP. Genotype-phenotype associations in Fanconi anemia: A literature review. Blood Rev. 2019;37:100589. PubMed PMID: 31351673.

Futaki M, Yamashita T, Yagasaki H, Toda T, Yabe M, Kato S, Asano S, Nakahata T. The IVS4 + 4 A to T mutation of the Fanconi anemia gene FANCC is not associated with a severe phenotype in Japanese patients. Blood. 2000;95:1493–8. PubMed PMID: 10666230.

Gandhi M, Rac MWF, McKinney J, et al. Radial ray malformation. Am J Obstet Gynecol. 2019;221:B16–18.

Garcia-Higuera I, Taniguchi T, Ganesan S, Meyn MS, Timmers C, Hejna J, Grompe M, D'Andrea AD. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol Cell. 2001;7:249. PubMed PMID: 11239454.

Giardino S, de Latour RP, Aljurf M, Eikema DJ, Bosman P, Bertrand Y, Tbakhi A, Holter W, Bornhäuser M, Rössig C, Burkhardt B, Zecca M, Afanasyev B, Michel G, Ganser A, Alseraihy A, Ayas M, Uckan-Cetinkaya D, Bruno B, Patrick K, Bader P, Itälä-Remes M, Rocha V, Jubert C, Diaz MA, Shaw PJ, Junior LGD, Locatelli F, Kröger N, Faraci M, Pierri F, Lanino E, Miano M, Risitano A, Robin M, Dufour C, et al. Outcome of patients with Fanconi anemia developing myelodysplasia and acute leukemia who received allogeneic hematopoietic stem cell transplantation: A retrospective analysis on behalf of EBMT group. Am J Hematol. 2020;95:809–16. PubMed PMID: 32267023.

Gillio AP, Verlander PC, Batish SD, Giampietro PF, Auerbach AD. Phenotypic consequences of mutations in the Fanconi anemia FAC gene: an International Fanconi Anemia Registry study. Blood. 1997;90:105–10. PubMed PMID: 9207444.

Giulino L, Guinan EC, Gillio AP, Drachtman RA, Teruya-Feldstein J, Boulad F. Sweet syndrome in patients with Fanconi anaemia: association with extracutaneous manifestations and progression of haematological disease. Br J Haematol. 2011;154:278–81. PubMed PMID: 21501135.

Guardiola P, Socié G, Li X, Ribaud P, Devergie A, Espérou H, Richard P, Traineau R, Janin A, Gluckman E. Acute graft-versus-host disease in patients with Fanconi anemia or acquired aplastic anemia undergoing bone marrow transplantation from HLA-identical sibling donors: risk factors and influence on outcome. Blood. 2004;103:73–7. PubMed PMID: 12946993.

Hartmann L, Neveling K, Borkens S, Schneider H, Freund M, Grassman E, Theiss S, Wawer A, Burdach S, Auerbach AD, Schindler D, Hanenberg H, Schaal H. Correct mRNA processing at a mutant TT splice donor in *FANCC* ameliorates the clinical phenotype in patients and is enhanced by delivery of suppressor U1 snRNAs. American Journal of Human Genetics. 2010;87:480–93. PubMed PMID: 20869034.

Hirsch B, Shimamura A, Moreau L, Baldinger S, Hag-alshiekh M, Bostrom B, Sencer S, D'Andrea AD. Association of biallelic BRCA2/FANCD1 mutations with spontaneous chromosomal instability and solid tumors of childhood. Blood. 2004;103:2554–9. PubMed PMID: 14670928.

Ho TV, Schärer OD. Translesion DNA synthesis polymerases in DNA interstrand crosslink repair. Environ Mol Mutagen. 2010;51:552–66. PubMed PMID: 20658647.

Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, De Die-Smulders C, Persky N, Grompe M, Joenje H, Pals G, Ikeda H, Fox EA, D'Andrea AD. Biallelic inactivation of BRCA2 in Fanconi anemia. Science. 2002;297:606–9. PubMed PMID: 12065746.

Huang M, D'Andrea AD. A new nuclease member of the FAN club. Nat Struct Mol Biol. 2010;17:926–8. PubMed PMID: 20683477.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Jung M, Ramanagoudr-Bhojappa R, van Twest S, Rosti RO, Murphy V, Tan W, Donovan FX, Lach FP, Kimble DC, Jiang CS, Vaughan R, Mehta PA, Pierri F, Dufour C, Auerbach AD, Deans AJ, Smogorzewska A, Chandrasekharappa SC. Association of clinical severity with FANCB variant type in Fanconi anemia. Blood. 2020;135:1588–1602. PubMed PMID: 32106311.

Kahraman S, Beyazyurek C, Yesilipek MA, Ozturk G, Ertem M, Anak S, Kansoy S, Aksoylar S, Kuşkonmaz B, Oniz H, Slavin S, Karakas Z, Tac HA, Gulum N, Ekmekci GC. Successful haematopoietic stem cell transplantation in 44 children from healthy siblings conceived after preimplantation HLA matching. Reprod Biomed Online. 2014;29:340–51. PubMed PMID: 25066893.

Kato Y, Alavattam KG, Sin H-S, Meetei AR, Pang Q, Andreassen PR, Namekawa SH. FANCB is essential in the male germline and regulates H3K9 methylation on the sex chromosomes during meiosis. Hum Mol Genet. 2015;24:5234–49. PubMed PMID: 26123487.

Kee Y, D'Andrea AD. Molecular pathogenesis and clinical management of Fanconi anemia. J Clin Invest. 2012;122:3799–806. PubMed PMID: 23114602.

Kim H, D'Andrea AD. Regulation of DNA cross-link repair by the Fanconi anemia/BRCA pathway. Genes Dev. 2012;26:1393–408. PubMed PMID: 22751496.

Knipscheer P, Räschle M, Smogorzewska A, Enoiu M, Ho TV, Schärer OD, Elledge SJ, Walter JC. The Fanconi anemia pathway promotes replication-dependent DNA interstrand cross-link repair. Science. 2009;326:1698–701. PubMed PMID: 19965384.

Kutler DI, Patel K, Auerbach A, Kennedy J, Lach F, Sanborn E, Cohen M, Kuhel W, Smogorzewska A. Natural history and management of Fanconi anemia patients with head and neck cancer: a 10-year follow-up. Laryngoscope. 2016;126:870–9. PubMed PMID: 26484938.

Kutler DI, Singh B, Satagopan J, Batish SD, Berwick M, Giampietro PF, Hanenberg H, Auerbach AD. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood. 2003;101:1249–56. PubMed PMID: 12393516.

Levitus M, Waisfisz Q, Godthelp BC, de Vries Y, Hussain S, Wiegant WW, Elghalbzouri-Maghrani E, Steltenpool J, Rooimans MA, Pals G, Arwert F, Mathew CG, Zdzienicka MZ, Hiom K, De Winter JP, Joenje H. The DNA helicase BRIP1 is defective in Fanconi anemia complementation group J. Nat Genet. 2005;37:934–5. PubMed PMID: 16116423.

Levran O, Attwooll C, Henry RT, Milton KL, Neveling K, Rio P, Batish SD, Kalb R, Velleuer E, Barral S, Ott J, Petrini J, Schindler D, Hanenberg H, Auerbach AD. The BRCA1-interacting helicase BRIP1 is deficient in Fanconi anemia. Nat Genet. 2005;37:931–3. PubMed PMID: 16116424.

Ling C, Ishiai M, Ali AM, Medhurst AL, Neveling K, Kalb R, Yan Z, Xue Y, Oostra AB, Auerbach AD, Hoatlin ME, Schindler D, Joenje H, de Winter JP, Takata M, Meetei AR, Wang W. FAAP100 is essential for activation of the Fanconi anemia-associated DNA damage response pathway. EMBO J. 2007;26:2104–14. PubMed PMID: 17396147.

Litman R, Peng M, Jin Z, Zhang F, Zhang J, Powell S, Andreassen PR, Cantor SB. BACH1 is critical for homologous recombination and appears to be the Fanconi anemia gene product FANCJ. Cancer Cell. 2005;8:255–65. PubMed PMID: 16153896.

MacMillan ML, DeFor TE, Young JA, Dusenbery KE, Blazar BR, Slungaard A, Zierhut H, Weisdorf DJ, Wagner JE. Alternative donor hematopoietic cell transplantation for Fanconi anemia. Blood. 2015;125:3798–804. PubMed PMID: 25824692.

Masserot C, Peffault de Latour R, Rocha V, Leblanc T, Rigolet A, Pascal F, Janin A, Soulier J, Gluckman E, Socié G. Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. Cancer. 2008;113:3315–22. PubMed PMID: 18831513.

McCauley J, Masand N, McGowan R, Rajagopalan S, Hunter A, Michaud JL, Gibson K, Robertson J, Vaz F, Abbs S, Holden ST. X-linked VACTERL with hydrocephalus syndrome: further delineation of the phenotype caused by FANCB mutations. Am J Med Genet A. 2011;155A:2370–80. PubMed PMID: 21910217.

Meetei AR, Sechi S, Wallisch M, Yang D, Young MK, Joenje H, Hoatlin ME, Wang W. A multiprotein nuclear complex connects Fanconi anemia and Bloom syndrome. Mol Cell Biol. 2003;23:3417–26. PubMed PMID: 12724401.

Mehta PA, Davies SM, Leemhuis T, Myers K, Kernan NA, Prockop SE, Scaradavou A, O'Reilly RJ, Williams DA, Lehmann L, Guinan E, Margolis D, Baker KS, Lane A, Boulad F. Radiation-free, alternative donor HCT for Fanconi anemia patients: results from a prospective multi-institutional study. Blood. 2017;129:2308–15. PubMed PMID: 28179273.

Mehta PA, Harris RE, Davies SM, Kim MO, Mueller R, Lampkin B, Mo J, Myers K, Smolarek TA. Numerical chromosomal changes and risk of development of myelodysplastic syndrome—acute myeloid leukemia in patients with Fanconi anemia. Cancer Genet Cytogenet. 2010;203:180–6. PubMed PMID: 21156231.

Mehta PA, Ileri T, Harris RE, Williams DA, Mo J, Smolarek T, Auerbach AD, Kelly P, Davies SM. Chemotherapy for myeloid malignancy in children with Fanconi anemia. Pediatr Blood Cancer. 2007;48:668–72. PubMed PMID: 16609946.

Mitchell R, Wagner JE, Hirsch B. Hematopoietic cell transplantation for acute leukaemia and advances myelodysplastic syndrome in Fanconi anemia. Br J Haematol. 2014;164:384–95. PubMed PMID: 24172081.

Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011;29:739–46. PubMed PMID: 21189382.

Myers K, Davies SM, Harris RE, Spunt SL, Smolarek T, Zimmerman S, McMasters R, Wagner L, Mueller R, Auerbach AD, Mehta PA. The clinical phenotype of children with Fanconi anemia caused by biallelic FANCD1/BRCA2 mutations. Pediatr Blood Cancer. 2012;58:462–5. PubMed PMID: 21548014.

Nabhan SK, Bitencourt MA, Duval M, Abecasis M, Dufour C, Boudjedir K, Rocha V, Socié G, Passweg J, Goi K, Sanders J, Snowden J, Yabe H, Pasquini R, Gluckman E; Aplastic Anaemia Working Party, EBMT. Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation in Fanconi anemia patients. Haematologica. 2010;95:1783–7. PubMed PMID: 20494929.

Nakanishi K, Cavallo F, Perrouault L, Giovannangeli C, Moynahan ME, Barchi M, Brunet E, Jasin M. Homology-directed Fanconi anemia pathway cross-link repair is dependent on DNA replication. Nat Struct Mol Biol. 2011;18:500–3. PubMed PMID: 21423196.

Nalepa G, Clapp DW. Fanconi anaemia and cancer: an intricate relationship. Nature Reviews Cancer. 2018;18:168–85. PubMed PMID: 29376519.

Neitzel H, Kühl JS, Gerlach A, Ebell W, Tönnies H. Clonal chromosomal aberrations in bone marrow cells of Fanconi anemia patients: results and implications. In: Schindler D, Hoehn H, eds. *Fanconi Anemia. a Paradigmatic Disease for the Understanding of Cancer and Aging*. Monographs in Human Genetics. Vol 15. Basel: Karger. 2007:79-94

Niraj J, Färkkilä A, D'Andrea AD. The Fanconi anemia pathway in cancer. Annu Rev Cancer Biol. 2019;3:457–78. PubMed PMID: 30882047.

Paustian L, Chao MM, Hanenberg H, Schindler D, Neitzel H, Kratz CP, Ebell W. Androgen therapy in Fanconi anemia: a retrospective analysis of 30 years in Germany. Pediatr Hematol Oncol. 2016;33:5–12. PubMed PMID: 26900943.

Petryk A, Shaker RK, Giri N, Hollenberg AN, Rutter MM, Nathan B, Lodish M, Alter BP, Stratakis CA, Rose SR. Endocrine disorders in Fanconi Anemia: Recommendations from Screening and Treatment. J Clin Endocrinol Metab. 2015;100:803–11. PubMed PMID: 25575015.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rechitsky S, Kuliev A, San Ramon G, Tur-Kaspa I, Wang Y, Wang W, Wu X, Wang L, Leigh D, Cram DS. Single-molecule sequencing: A new approach for preimplantation testing and noninvasive prenatal diagnosis confirmation of fetal genotype. J Mol Diagn. 2020;22:220–7. PubMed PMID: 31751677.

Reid S, Schindler D, Hanenberg H, Barker K, Hanks S, Kalb R, Neveling K, Kelly P, Seal S, Freund M, Wurm M, Batish SD, Lach FP, Yetgin S, Neitzel H, Ariffin H, Tischkowitz M, Mathew CG, Auerbach AD, Rahman N. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. Nat Genet. 2007;39:162–4. PubMed PMID: 17200671.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint

consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Río P, Navarro S, Guenechea G, Sánchez-Domínguez R, Lamana ML, Yañez R, Casado JA, Mehta PA, Pujol MR, Surrallés J, Charrier S, Galy A, Segovia JC, Díaz de Heredia C, Sevilla J, Bueren JA. Engraftment and in vivo proliferation advantage of gene-corrected mobilized CD34(+) cells from Fanconi anemia patients. Blood. 2017;130:1535–42. PubMed PMID: 28801449.

Rose SR, Kim MO, Korbee L, Wilson KA, Douglas Ris M, Eyal O, Sherafat-Kazemzadeh R, Bollepalli S, Harris R, Jeng MR, Williams DA, Smith FO. Oxandrolone for the treatment of bone marrow failure in Fanconi anemia. Pediatr Blood Cancer. 2014;61:11–9. PubMed PMID: 24019220.

Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. Haematologica. 2008;93:511–7. PubMed PMID: 18322251.

Rosenberg PS, Socié G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. Blood. 2005;105:67–73. PubMed PMID: 15331448.

Rosenberg PS, Tamary H, Alter BP. How high are carrier frequencies of rare recessive syndromes? Contemporary estimates for Fanconi Anemia in the United States and Israel. Am J Med Genet A. 2011;155A:1877–83. PubMed PMID: 21739583.

Scheckenbach K, Morgan M, Filger-Brillinger J, Sandmann M, Strimling B, Scheurlen W, Schindler D, Göbel U, Hanenberg H. Treatment of the bone marrow failure in Fanconi anemia patients with danazol. Blood Cells Mol Dis. 2012;48:128–31. PubMed PMID: 22178060.

Seal S, Thompson D, Renwick A, Elliott A, Kelly P, Barfoot R, Chagtai T, Jayatilake H, Ahmed M, Spanova K, North B, McGuffog L, Evans DG, Eccles D, Easton DF, Stratton MR, Rahman N, et al. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet. 2006;38:1239–41. PubMed PMID: 17033622.

Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev. 2010;24:101–22. PubMed PMID: 20417588.

Smogorzewska A, Matsuoka S, Vinciguerra P, McDonald ER 3rd, Hurov KE, Luo J, Ballif BA, Gygi SP, Hofmann K, D'Andrea AD, Elledge SJ. Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. Cell. 2007;129:289–301. PubMed PMID: 17412408.

Song IY, Palle K, Gurkar A, Tateishi S, Kupfer GM, Vaziri C. Rad18-mediated translesion synthesis of bulky DNA adducts is coupled to activation of the Fanconi anemia DNA repair pathway. J Biol Chem. 2010;285:31525–36. PubMed PMID: 20675655.

Spanier G, Pohl F, Giese T, Meier JK, Koelbl O, Reichert TE. Fatal course of tonsillar squamous cell carcinoma associated with Fanconi anaemia: a mini review. J Craniomaxillofac Surg. 2012;40:510–5. PubMed PMID: 21925890.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Strocchio L, Pagliara D, Algeri M, Li Pira G, Rossi F, Bertaina V, Leone G, Pinto RM, Andreani M, Agolini E, Girardi K, Gaspari S, Grapulin L, Del Bufalo F, Novelli A, Merli P, Locatelli F. HLA-haploidentical TCRalphabeta+/CD19+-depleted stem cell transplantation in children and young adults with Fanconi anemia. Blood Adv. 2021;5:1333–9. PubMed PMID: 33656536.

Talbot A, Peffault de Latour R, Raffoux E, Buchbinder N, Vigouroux S, Milpied N, Leblanc T, Soulier J, Michallet M, Socié G. Sequential treatment for allogeneic hematopoietic stem cell transplantation in Fanconi anemia with acute myeloid leukemia. Haematologica. 2014;99:e199–200. PubMed PMID: 25085358.

Tamary H, Nishri D, Yacobovich J, Zilber R, Dgany O, Krasnov T, Aviner S, Stepensky P, Ravel-Vilk S, Bitan M, Kaplinsky C, Ben Barak A, Elhasid R, Kapelusnik J, Koren A, Levin C, Attias D, Laor R, Yaniv I, Rosenberg PS, Alter BP. Frequency and natural history of inherited bone marrow failure syndromes: the Israeli Inherited Bone Marrow Failure Registry. Haematologica. 2010;95:1300–7. PubMed PMID: 20435624.

Tan IB, Cutcutache I, Zang ZJ, Iqbal J, Yap SF, Hwang W, Lim WT, Teh BT, Rozen S, Tan EH, Tan P. Fanconi's anemia in adulthood: chemoradiation-induced bone marrow failure and a novel FANCA mutation identified by targeted deep sequencing. J Clin Oncol. 2011;29:e591–4. PubMed PMID: 21519011.

Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006;107:4223–33. PubMed PMID: 16493006.

Tsui V, Crismani W. The Fanconi anemia pathway and fertility. Trends Genet. 2019;35:199–214. PubMed PMID: 30683429.

Wagner JE, Tolar J, Levran O, Scholl T, Deffenbaugh A, Satagopan J, Ben-Porat L, Mah K, Batish SD, Kutler DI, MacMillan ML, Hanenberg H, Auerbach AD. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. Blood. 2004;103:3226–9. PubMed PMID: 15070707.

Williams SA, Wilson JB, Clark AP, Mitson-Salazar A, Tomashevski A, Ananth S, Glazer PM, Semmes OJ, Bale AE, Jones NJ, Kupfer GM. Functional and physical interaction between the mismatch repair and FA-BRCA pathways. Hum Mol Genet. 2011;20:4395–410. PubMed PMID: 21865299.

Wilson JB, Blom E, Cunningham R, Xiao Y, Kupfer GM, Jones NJ. Several tetratricopeptide repeat (TPR) motifs of FANCG are required for assembly of the BRCA2/D1-D2-G-X3 complex, FANCD2 monoubiquitylation and phleomycin resistance. Mutat Res. 2010;689:12–20. PubMed PMID: 20450923.

Xia B, Sheng Q, Nakanishi K, Ohashi A, Wu J, Christ N, Liu X, Jasin M, Couch FJ, Livingston DM. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. 2006;22:719–29. PubMed PMID: 16793542.

Yamashita T, Wu N, Kupfer G, Corless C, Joenje H, Grompe M, D'Andrea AD. The Clinical variability of Fanconi Anemia (Type C) results from expression of an amino terminal truncated FAC polypeptide with partial activity. Blood. 1996;87:4424. PubMed PMID: 8639804.

Zhang F, Fan Q, Ren K, Auerbach AD, Andreassen PR. FANCJ/BRIP1 recruitment and regulation of FANCD2 in DNA damage responses. Chromosoma. 2010;119:637–49. PubMed PMID: 20676667.

Zhang QS, Benedetti E, Deater M, Schubert K, Major A, Pelz C, Impey S, Marquez-Loza L, Rathbun RK, Kato S, Bagby GC, Grompe M. Oxymetholone therapy of fanconi anemia suppresses osteopontin transcription and induces hematopoietic stem cell cycling. Stem Cell Reports. 2015;4:90–102. PubMed PMID: 25434823.

Zheng K, Liu T, Zhao J, Meng P, Bian Y, Ni C, Wang H, Pan Y, Wu S, Jiang H, Jin G. Mutational landscape and potential therapeutic targets for sporadic pancreatic neuroendocrine tumors based on target next-generation sequencing. Exp Ther Med. 2021;21:415. PubMed PMID: 33747156.

Zhi G, Wilson JB, Chen X, Krause DS, Xiao Y, Jones NJ, Kupfer GM. Fanconi anemia complementation group FANCD2 protein serine 331 phosphorylation is important for Fanconi anemia pathway function and BRCA2 interaction. Cancer Res. 2009;69:8775–83. PubMed PMID: 19861535.

Zubicaray J, Pagliara D, Sevilla J, Eikema DJ, Bosman P, Ayas M, Zecca M, Yesilipek A, Kansoy S, Renard C, Dalle JH, Campos A, Faraci M, Kupesiz A, Smiers FJW, Velardi A, Abecasis M, Corti P, Fagioli F, González Muñiz S, Kriván G, Dufour C, Risitano A, Corbacioglu S, Peffault de Latour R. Haplo-identical or mismatched unrelated donor hematopoietic cell transplantation for Fanconi anemia: Results from the Severe Aplastic Anemia Working Party of the EBMT. Am J Hematol. 2021;96:571–9. PubMed PMID: 33606297.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.