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Fanconi Anemia

[*Fanconi Pancytopenia*]

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Summary

Disease characteristics. Fanconi anemia (FA) is characterized by physical abnormalities, bone marrow failure, and increased risk of malignancy. Physical abnormalities, present in 60%-75% of affected individuals, include short stature; abnormal skin pigmentation; malformations of the thumbs, forearms, skeletal system, eyes, kidneys and urinary tract, ear, heart, gastrointestinal system, oral cavity, and central nervous system; hearing loss; hypogonadism; and developmental delay. Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia. By age 40 to 48 years, the estimated cumulative incidence of bone marrow failure is 90%; the incidence of hematologic malignancies (primarily acute myeloid leukemia) 10%-33%; and of nonhematologic malignancies (solid tumors, particularly of the head and neck, skin, GI tract, and genital tract) 28%-29%.

Diagnosis/testing. The diagnosis of FA rests upon the detection of chromosomal aberrations (breaks, rearrangements, radials, exchanges) in cells after culture with a DNA interstrand cross-linking agent such as diepoxybutane (DEB) or mitomycin C (MMC). Molecular genetic testing is complicated by the presence of 13 genes, which are responsible for the 13 FA complementation groups [A, B, C, D1 *(BRCA2*), D2, E, F, G, I, J, L, M, and N]. Clinically available molecular genetic testing includes mutation analysis for the common Ashkenazi Jewish *FANCC* mutation (IVS4+4A>T) and sequence analysis for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*. Molecular genetic testing is used primarily for carrier detection and prenatal diagnosis.

Management. *Treatment of manifestations:* Oral administration of androgens (oxymetholone) improves blood counts (red cell, white cell, and platelets) in approximately 50% of individuals with FA; subcutaneous administration of hematopoietic growth factors (G-CSF or GM-CSF) improves neutrophil count in some; hematopoietic stem cell transplantation (HSCT) is the only curative therapy for the hematologic manifestations of FA, but the high risk for solid tumors remains. All these treatments have potential significant toxicity. *Surveillance:* monitoring of growth and pubertal development; monitoring for evidence of bone marrow failure (regular blood counts; at least annual bone marrow aspirate/biopsy to evaluate morphology, cellularity, and cytogenetics); for those receiving androgen therapy, monitoring liver chemistry profile and regular ultrasound examination/CT of the liver; monitoring for solid tumors (gynecologic examination and Pap smears; annual rectal examination; frequent dental and oropharyngeal examinations). *Agents/circumstances to avoid:* transfusions of red cells or platelets for persons who are candidates for HSCT; family members as blood donors if HSCT is being considered; blood products that are not filtered (leukodepleted) or irradiated; toxic agents that have been implicated in tumorigenesis; radiographic studies solely for the purpose of surveillance (i.e., in the absence of clinical indications). *Testing of relatives at risk:* DEB/MMC testing of all

sibs of a proband for early diagnosis, treatment, and monitoring for physical abnormalities, bone marrow failure, and related cancers.

Genetic counseling. Mutations in the genes for all but one of the Fanconi anemia complementation groups are inherited in an autosomal recessive manner. *FANCB* mutations are inherited in an X-linked manner. Each sib of an individual with autosomal recessive FA has a 25% chance of inheriting both mutations and being affected, a 50% chance of inheriting one mutated gene and being a carrier, and a 25% chance of inheriting both normal genes and not being a carrier. Carriers (heterozygotes) for autosomal recessive FA are asymptomatic. Prenatal testing is available for pregnancies at 25% risk using the DEB/MMC test on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation. If the disease-causing mutations for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, or *FANCI* within a given family are known, molecular genetic testing can be used for carrier detection and prenatal testing.

Diagnosis

Clinical Diagnosis

Fanconi anemia (FA) is suspected in individuals with the following:

- **Physical abnormalities** including short stature; abnormal skin pigmentation (e.g., café au lait spots or hypopigmentation); malformations of the thumbs, forearms, skeletal system, eye, kidneys and urinary tract, ear, heart, gastrointestinal system, oral cavity, and central nervous system; hearing loss; hypogonadism; and developmental delay. These findings are variable; approximately 25%-40% of individuals with Fanconi anemia have no physical abnormalities. Thus, the absence of physical abnormalities does NOT rule out the diagnosis of Fanconi anemia.
- **Progressive bone marrow failure,** manifest as thrombocytopenia, leukopenia, and anemia, typically presenting by age seven to eight years, often initially with either thrombocytopenia or leukopenia. Bone marrow, initially normocellular, becomes progressively hypoplastic with time.
- **Adult-onset aplastic anemia,** in which red cell macrocytosis and elevated hemoglobin F levels may be seen
- **Myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).** On occasion, MDS or AML is the initial manifestation.
- **Solid tumors,** including tumors of the head and neck, esophagus, cervix, vulva, and liver, presenting at an atypically young age and in the absence of other risk factors. Solid tumors may be the first manifestation of Fanconi anemia in individuals who have not experienced bone marrow failure.
- **Inordinate toxicities from chemotherapy or radiation**

Testing

Chromosomal breakage studies. The diagnosis of FA rests upon cytogenetic testing for increased chromosomal breakage or rearrangement in the presence of diepoxybutane (DEB), a bifunctional DNA interstrand cross-linking agent [Auerbach 1993] or mitomycin C (MMC). The background rate of chromosomal breakage in control chromosomes is more variable with MMC; thus, some centers prefer to use DEB while other centers use both DEB and MMC.

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Peripheral blood is obtained from the affected individual and cultured in the presence and absence of the cross-linking agent. A total of 50 cells in metaphase are scored and analyzed for chromosomal breakage including the formation of radials — a characteristic finding in this disease. Results are compared to normal control cells and positive control cells that have been run in parallel.

- The cultures without the DNA clastogenic agent are used to measure the spontaneous breakage rate.
- Results are reported as either average number of breaks/cell or as *x* number of cells with 1,2,3...>8 breaks.
- The number of cells with radial forms is recorded.

In response to DEB/MMC, individuals with FA show:

- Increased rates of spontaneous chromosomal breakage (may be seen in FA as well as other chromosomal breakage syndromes; see Differential Diagnosis;
- Increased breakage and radial forms that distinguish FA from other chromosomal breakage syndromes.

The increased sensitivity to DEB/MMC is present regardless of phenotype, congenital anomalies, or severity of the disease.

Note: Interpretation of the results of the chromosomal breakage test may be complicated by the development of mosaicism, defined as the presence of two populations of lymphocytes: one showing increased sensitivity to DEB/MMC and the other showing normal levels of chromosomal breakage in response to DEB/MMC. This reversion to a normal cellular phenotype has been attributed to gene conversion events, back mutations, or compensatory deletions/insertions leading to selective advantage of the reverted lymphocytes [Lo Ten Foe et al 1997, Waisfisz et al 1999, Gross et al 2002]. Lymphocyte mosaicism can develop in individuals initially found to be sensitive to DEB/MMC. These individuals may have a falsely negative DEB/MMC test. In individuals with a negative DEB/MMC test in whom a high degree of clinical suspicion of FA remains, DEB/MMC testing to establish the diagnosis could be performed on an alternative cell type, such as skin fibroblasts. Tabulation of the number of cells with chromosomal breaks and radials can assist in diagnosis in the presence of lymphocyte mosaicism.

FA heterozygotes cannot be detected by the DEB/MMC test.

Other cytogenetic testing. Abnormal bone marrow cytogenetic findings may develop over time. Cytogenetic abnormalities can wax and wane or progress to myelodysplastic syndrome (MDS) and leukemia. Clonal amplifications of chromosome 3q26-q29 are associated with a significantly increased risk for progression to MDS or acute myelogenous leukemia (AML) [Tonnies et al 2003].

Immunoblot assay of FANCD2 protein monoubiquitination. The Fanconi anemia proteins A, B, C, E, F, G, I, L, and M are required for the monoubiquitination of the downstream FANCD2 protein. FANCD2 protein monoubiquitination is essential for the functional integrity of the FA pathway as measured by resistance to MMC or DEB. Because FANCD2 protein monoubiquitination is intact in other bone marrow failure syndromes and chromosomal breakage syndromes tested to date [Shimamura et al 2002], evaluation of FANCD2 protein monoubiquitination by immunoblotting provides a rapid diagnostic test for Fanconi anemia. Note that the rare FA subtypes FA-D1, FA-J, and FA-N would be missed by this approach, as could individuals with somatic mosaicism. This test is available on a research basis only.

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Cell cycle arrest. MMC also induces cell cycle arrest in the G2 phase. Flow cytometric assessment of G2 arrest has also been used diagnostically [Pulsipher et al 1998]. In this test, primary skin fibroblasts are exposed to MMC and analyzed by fluorescence-activated cell sorting (FACS) for the percentage of cells in the G2 phase of the cell cycle. FA is suspected when a large fraction of cells accumulate in G2.

Determination of complementation groups. Based on somatic cell fusion studies, at least 13 complementation FA groups have been identified [A, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, and N]. The FA complementation group can be identified by identifying the cDNA of which the 13 FA genes, when expressed in the cells of the affected individual, corrects the DEB/MMC sensitivity phenotype [Pulsipher et al 1998, Nakanishi et al 2001, Hanenberg et al 2002]. Such testing is available on a research basis only.

Laboratory findings that may be found in association with FA:

- Macrocytic red blood cells, often with increased erythrocyte i antigen and fetal hemoglobin. These changes, which have no prognostic significance, often precede the onset of anemia.
- Normal or increased serum erythropoietin concentration

Molecular Genetic Testing

Molecular Genetic Testing —Genes. Genes responsible for all of the 13 FA complementation groups have been identified:

- *FANCA* [Apostolou et al 1996, Fanconi Anemia/Breast Cancer Consortium 1996, Lo Ten Foe et al 1996]
- *FANCB* [Meetei et al 2004]
- *FANCC* (10%) [Strathdee et al 1992]
- *FANCD1(BRCA2*), which has been shown to be the *BRCA2* gene associated with hereditary breast and ovarian cancer [Howlett et al 2002]
- *FANCD2* [Timmers et al 2001]
- *FANCE* [de Winter 2000]
- *FANCF* [de Winter et al 2000]
- *FANCG(XRCC9*) [de Winter et al 2000]
- *FANCI* [Dorsman et al 2007, Sims et al 2007, Smogorzewska et al 2007]
- *FANCJ/BRIP1/BACH1* [Levitus et al 2005, Levran et al 2005, Litman et al 2005]
- *FANCL* [Meetei, de Winter et al 2003]
- *FANCM* [Meetei et al 2005]
- *FANCN(PALB2)* [Reid et al 2007, Xia et al 2007]

Clinical testing

- **Targeted mutation analysis.** Targeted mutation analysis is widely available for the common Ashkenazi Jewish *FANCC* mutation (IVS4+4A>T).
- **Sequence analysis and/or mutation scanning**
  - Sequence analysis and/or mutation scanning is available for the genes *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI*.

Sequence analysis is complicated by the number of possible associated genes, the large number of possible mutations in each gene, and the large size of many of the FA genes. If the complementation group has been established in a research laboratory, the responsible mutation can be determined by sequencing the corresponding gene.

- *BRCA2* targeted mutation analysis and sequence analysis is available on a clinical basis for hereditary breast/ovarian cancer; however, information is limited regarding its possible application in FA.

- **Deletion/duplication analysis.** MLPA and SNP analyses are used to detect deletions of one or more exons or of the entire *FANCA* gene.

Research testing. Molecular genetic testing for the other genes associated with FA is available on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

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Table 1. Molecular Genetic Testing Used in Fanconi Anemia

Complementation Group	Proportion of FA Attributable to Mutations in This Complementation Group	Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
FA-A	66%	Sequence analysis	*FANCA* sequence variants	95% [2]	Clinical Testing
		Deletion/ duplication analysis	*FANCA* deletions		
FA-B	0.8% [3]	Sequence analysis	*FANCB* sequence variants	Unknown	Clinical Testing
FA-C	9.6%	Targeted mutation analysis	IVS4+4A>T	Varies by ethnic group	Clinical Testing
		Sequence analysis	*FANCC* sequence variants	Unknown	
FA-D1	3.3%	Direct DNA [3]	*BRCA2* sequence variants	NA	Research only
FA-D2	3.3%		*FANCD2* sequence variants		
FA-E	2.5%	Sequence analysis	*FANCE* sequence variants	Unknown	Clinical Testing
FA-F	2.1% [2]		*FANCF* sequence variants		Clinical Testing
FA-G	8.8% [2]		*FANCG* sequence variants		Clinical Testing
FA-I	Unknown		*FANCI* sequence variants		Clinical Testing
FA-J	Unknown	Direct DNA [3]	*BRIP1* sequence variants	NA	Research only
FA-L	0.4%		*FANCL* sequence variants		
FA-M	Unknown		*FANCM* sequence variants		
FA-N	Unknown		*PALB2* sequence variants		

1. Proportion of affected individuals with a mutation(s) as classified by gene/complemenation group and test method
2. 95% of all alleles; in approximately 80% of individuals, both alleles can be identified [personal communication, A Auerbach].
3. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with Fanconi anemia.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband. Perform cytogenetic testing for increased chromosomal breakage or rearrangement in the presence of diepoxybutane (DEB) or mitomycin C (MMC).

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

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Note: Carriers are either heterozygous for an autosomal recessive disorder and not at risk of developing the disorder or they are heterozygous for an X-linked disorder and could develop clinical findings related to the disorder.

Prenatal diagnosis / preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

Hereditary breast and ovarian cancer is associated with mutations in *BRCA2(FANCD1*).

Inherited monoallelic mutations in *BRIP1* (also known as *FANCJ*) and *PALB2* (also known as *FANCN*) have been implicated in breast cancer predisposition [Seal et al 2006, Rahman et al 2007].

Clinical Description

Natural History

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

Physical abnormalities. Physical anomalies are not generally a cause of mortality in individuals with Fanconi anemia. The most commonly reported abnormalities and their frequency include the following [Alter 2003, Saxon 2004]:

- **Skin pigmentary changes (55%)**
  - Hyperpigmentation (generalized or café au lait spots); hypopigmentation
  - Gray or bronze skin tone
- **Short stature (51%)**
- **Upper limb malformations (43%)**
  - **Thumbs.** Absent or hypoplastic or supernumerary with hypoplastic thenar eminence; stiff or hyperextensible
  - **Hands.** Clinodactyly, polydactyly, absent first metacarpal, short fingers, transverse crease
  - **Ulnae and radii.** Absent or hypoplastic (associated with abnormal thumbs)
- **Eyes (23%).** Microphthalmia, strabismus, epicanthal folds, hypertelorism/hypotelorism, ptosis, slanting palpebral fissures, cataracts, epiphora, nystagmus
- **Renal (21%)**
  - **Kidney.** Pelvic, horseshoe, hypoplastic, dysplastic
  - **Collecting system.** Hydronephrosis, hydroureter, reflux
  - **Vasculature.** Abnormal artery
- **Genitalia (32% males, 3% females)**
  - **Males.** Hypogenitalia; undescended, absent or atrophic testes; azoospermia; phimosis, delayed puberty. A few males with FA have fathered children.
  - **Females.** Hypoplastic vulva, bicornuate uterus, absence of uterus or vagina; ovarian atresia. Although delayed menarche, irregular menses, and early

menopause can be seen, successful pregnancies with liveborn children have been reported.

- **GI/cardiopulmonary (11%)**
  - **GI.** Esophageal/duodenual/jejunal atresia, tracheoesophageal fistula, anteriorly placed anus, imperforate anus, persistent cloaca, Meckel's diverticulum, umbilical hernia, abnormal biliary ducts, megacolon, abdominal diastasis, Budd-Chiari syndrome, annular pancreas
  - **Heart.** Structural defects, cardiomyopathy
- **Ears (9%)**
  - **Hearing loss.** Usually conductive secondary to middle ear abnormalities
  - **Abnormal pinna.** Low-set, large, or small
  - Stenosis or atresia of the external auditory meatus
- **Lower limbs (8%).** Toe syndactyly, pes planus, abnormal toes, congenital hip dislocation
- **Other.** High-arched palate, arterial malformation, moyamoya syndrome, absent breast buds, absent pulmonary lobes, microcephaly, hydrocephalus, micrognathia, vertebral abnormalities
- **None (25%)**

Bone marrow failure. The hematologic complications of FA typically occur within the first decade of life but are highly variable. Pancytopenia can present as early as the newborn period [Landmann et al 2004].

- Thrombocytopenia or leukopenia typically precedes anemia.
- Pancytopenia generally worsens over time.
- Neutropenia is associated with an increased risk for infections.
- Sweet's syndrome (neutrophilic skin infiltration) has been reported in a few individuals with FA and myelodysplastic syndrome (MDS) [Gross et al 2002].

Cancer. The relative risk for AML is increased 785-fold [Rosenberg et al 2003]. In a review of individuals reported with Fanconi anemia, 9% developed leukemia (primarily acute myeloid leukemia), and 7% developed myelodysplastic syndrome [Alter 2003].

The risk of developing solid tumors, particularly of the head and neck, skin, GI tract, and genital tract is also increased [Kutler et al 2003, Rosenberg et al 2003]. The skin and GI tumors are typically squamous cell carcinomas. An increased incidence of human papillomavirus DNA was detected in squamous cell carcinoma samples from individuals with Fanconi anemia (84%, n=25) as compared with unaffected controls (26%, n=50) [Kutler et al 2003].

Individuals with FA receiving androgen treatment for bone marrow failure are at increased risk for liver tumors.

The majority of tumors associated with FA develop after age 13 years, with an average age of 23 years. By age 40 to 48 years the estimated cumulative risk for bone marrow failure is 90%, hematologic malignancies 10%-33%, and non-hematologic malignancies 28%-29% [Kutler et al 2003, Rosenberg et al 2003].

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Such malignancies are difficult to treat because individuals with FA are sensitive to DNA-damaging agents such as chemotherapy and radiation.

Genotype-Phenotype Correlations

FANCA. Among individuals with mutations in *FANCA*, those who are homozygous for null mutations (no abnormal protein production) may have earlier onset of anemia and higher incidence of leukemia than individuals with mutations that permit production of an abnormal FANCA protein [Faivre et al 2000].

FANCC. The *FANCC* IVS4+4A>T mutation (the most common *FANCC* mutation, prevalent in individuals of Ashkenazi Jewish background) and the p.Arg548X and p.Leu554Pro mutations are associated with earlier onset of hematologic abnormalities and multiple birth defects. The 322delG and p.Gln13X mutations are associated with a lower risk for congenital abnormalities and later progression to bone marrow failure [Yamashita et al 1996, Gillio et al 1997]. Additional factors appear to influence disease severity for a given FA genotype, as the *FANCC* IVS4+4A>T mutation results in a milder phenotype in Japanese individuals [Futaki et al 2000].

BRCA2. Mutations in the *BRCA2* gene (also known as *FANCD1*) are associated with early-onset leukemias [Wagner et al 2004] and solid tumors [Hirsch et al 2004]. In addition to MMC/DEB-induced chromosomal breakage, increased spontaneous chromosomal aberrations are associated with this FA subtype [Hirsch et al 2004].

FANCG. Mutations in the *FANCG* gene may be associated with more severe cytopenia and a higher incidence of leukemia [Faivre et al 2000].

Prevalence

The prevalence of FA is estimated at 1:100,000 live births.

The carrier frequency for the general population in the United States, Europe, and Japan has been estimated at 1:300.

In some populations (Ashkenazi Jew, Spanish Gypsy, and black South African) the prevalence of FA is estimated to be higher [Kutler & Auerbach 2004, Callen et al 2005, Morgan et al 2005].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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

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

Nijmegen breakage syndrome (NBS), characterized by short stature, progressive microcephaly with loss of cognitive skills, premature ovarian failure in females, recurrent sinopulmonary infections, and an increased risk for cancer, particularly lymphoma, may also manifest increased chromosomal breakage with MMC [Nakanishi et al 2002, Gennery et al 2004]. Inheritance is autosomal recessive. NBS may be distinguished from FA by DNA-based testing of *NBS1*, which detects mutations in almost 100% of individuals with NBS.

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Seckel syndrome, characterized by growth retardation, microcephaly with mental retardation, and a characteristic 'bird-headed' facial appearance, may also show increased chromosome breakage with DNA cross-linking agents (MMC, DEB) [Andreassen et al 2004]. Some individuals with Seckel syndrome also develop pancytopenia and/or AML. At least three genes are responsible for Seckel syndrome, only one of which *(ATR*) has been identified [O'Driscoll et al 2003].

Other disorders such as neurofibromatosis 1, which could be considered because of café au lait spots, TAR syndrome (thrombocytopenia with absent radii), and non-FA-related VACTERL association [Faivre et al 2005], which could be considered because of radial ray defects, can be distinguished from FA by the DEB or MMC test.

Management

Management focuses on surveillance of and treatment for physical abnormalities, bone marrow failure, and related cancers.

Evaluations Following Initial Diagnosis

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

Physical abnormalities

- Ultrasound examination of the kidneys and urinary tract
- Formal hearing test
- Developmental assessment (particularly important for toddlers and school-age children)
- Referral to an ophthalmologist and endocrinologist
- Evaluation by a medical geneticist and genetic counseling

Bone marrow failure

- Evaluation by a hematologist
- HLA typing of the affected individual, sibs, and parents for bone marrow transplantation
- Full blood typing
- Blood chemistries (assessing liver, kidney, and iron status)

Treatment of Manifestations

Androgen administration. Androgens can improve the blood counts in approximately 50% of individuals with FA. The earliest response is seen in red cells, with reticulocytosis and increase in hemoglobin generally occurring within the first month or two of treatment. Responses in the white cell count and platelet count are variable. Platelet responses are generally incomplete and may not be seen before six to 12 months of therapy. Such responses may be transient and improvement is generally greatest for the red cell count. Resistance to therapy often develops over time (generally years). The standard recommended androgen is oxymetholone at a starting dose of 2-5 mg/kg/day given orally. Androgen doses may be slowly tapered to the minimal effective dose with careful monitoring of the blood counts. Side effects of androgen administration include liver toxicity such as elevated liver enzymes, cholestasis, peliosis hepatis (vascular lesion with multiple blood-filled cysts), and hepatic tumors.

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Of note, prior androgen treatment has been associated with a poorer outcome in those individuals who undergo subsequent bone marrow transplantation (BMT). Whether androgens constitute a causal factor resulting in increased risk from BMT or merely a confounding variable remains to be determined.

Hematopoietic growth factors. G-CSF or GM-CSF improves the neutrophil count in some individuals. In a few individuals, platelet or red cell counts have also improved following treatment with G-CSF/GM-CSF. These factors are generally administered subcutaneously. Growth factor treatment should be administered cautiously in the setting of a clonal cytogenetic bone marrow abnormality; thus, a bone marrow aspirate and biopsy should be performed prior to the initiation of growth factor therapy and monitored regularly throughout therapy.

Bone marrow transplantation (BMT). Hematopoietic stem cell transplantation is the only curative therapy for the hematologic manifestations of FA. Because individuals with FA are exquisitely sensitive to the toxicity of the usual chemotherapy and radiation regimens used in preparation for BMT, reduced doses are typically used.

Even if bone marrow transplantation successfully treats the hematologic manifestations of FA, individuals remain at high risk for the development of solid tumors.

Cancer treatment. Treatment of malignancies is challenging secondary to the increased toxicity associated with chemotherapy and radiation in FA. Treatment with decreased doses or modified regimens at experienced medical centers may be possible.

Bone marrow transplantation has been performed for MDS and AML at centers experienced in the treatment of Fanconi anemia.

Surveillance

Physical abnormalities. Growth and pubertal development must be monitored carefully and early referral to an endocrinologist should be made as indicated.

Bone marrow failure. General recommendations vary.

- Regular blood counts
- Bone marrow aspirate/biopsy recommended at least annually to evaluate morphology, cellularity, and cytogenetics — the latter for emergence of a malignant clone

Recommendations for monitoring blood and bone marrow parameters were outlined at a 2003 consensus conference; see FA Standards for Clinical Care (pdf).

Androgen administration. For individuals receiving androgen therapy:

- Monitoring of liver chemistry profile
- Regular ultrasound examination/CT of the liver

Cancer surveillance. The majority of solid tumors develop after the first decade of life, with an average age at presentation of 23 years. Prompt and aggressive workup for any symptoms suggestive of a malignancy should be pursued. Detection and removal of early-stage cancers remains the mainstay of therapy.

Surveillance regimens should include the following:

- Gynecologic examination and Pap smears
- Yearly rectal examination

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- Frequent dental and oropharyngeal examinations

Annual esophageal endoscopy may be considered.

Agents/Circumstances to Avoid

Blood transfusions. Transfusions of red cells or platelets should be avoided or minimized for individuals who are candidates for bone marrow transplantation.

To minimize the chances of sensitization, family members must not act as blood donors if bone marrow transplantation is being considered.

All blood products should be filtered (leukodepleted) and irradiated.

Cancer prevention. Given the increased susceptibility of individuals with FA of developing leukemias and other malignancies, affected individuals are advised to avoid toxic agents that have been implicated in tumorigenesis.

Given the sensitivity of individuals with FA to radiation, radiographic studies for the purpose of surveillance should be minimized in the absence of clinical indications.

Testing of Relatives at Risk

It is appropriate to perform DEB/MMC testing on all sibs of a proband for early diagnosis and appropriate monitoring for physical abnormalities, bone marrow failure, and related cancers.

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

Therapies Under Investigation

Gene therapy, a theoretical possibility, is at a research stage only. Early phase trials of gene therapy for individuals with mutations in *FANCC* described transient retroviral *FANCC* gene transduction in hematopoietic cells [Liu et al 1999]. Additional trials are in progress. This therapy would potentially correct the hematopoietic defect in individuals with FA but would not reduce the risk of developing solid tumors in other tissues.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

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

face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Abnormalities of Fanconi anemia (FA) genes are inherited in an autosomal recessive manner except for mutations in *FANCB*, which are inherited in an X-linked manner.

Risk to Family Members — Autosomal Recessive FA

Parents of a proband

- The parents of a child with autosomal recessive FA are obligate carriers of an FA gene mutation.
- Carriers (heterozygotes) are asymptomatic.

Sibs of a proband

- Each sib of an individual with autosomal recessive FA has a 25% chance of inheriting both mutations and being affected, a 50% chance of inheriting one mutated gene and being a carrier, and a 25% chance of inheriting both normal genes and not being a carrier.
- Unaffected sibs who have had a normal DEB/MMC test have a 2/3 chance of being carriers.
- Heterozygotes (carriers) are asymptomatic. Whether FA heterozygotes have an increased risk of developing malignancies is unknown (with the exception of *FANCD1/ BRCA2)*.

Offspring of a proband. The offspring of an individual with autosomal recessive FA are obligate heterozygotes (carriers).

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Risk to Family Members — X-Linked FA

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The father of a male with X-linked FA will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation and, thus, the mother is not a carrier.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in DNA from leukocytes, she has germline mosaicism.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.

- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.
- If the disease-causing mutation cannot be detected in the DNA extracted from leukocytes of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Males will pass the disease-causing mutation to all of their daughters and none of their sons.

Other family members of a proband. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending upon their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carriers of FA cannot be detected by the DEB/MMC test. Carrier testing is available on a clinical basis for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, and *FANCI* once the mutations have been identified in the family.

Related Genetic Counseling Issues

Sibs of a proband. Because 25%-40% of individuals with FA may have no physical abnormalities, it is appropriate to perform DEB/MMC testing on all sibs of a proband for early diagnosis and appropriate monitoring for physical abnormalities, bone marrow failure, and related cancers.

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. For laboratories offering DNA banking, see DNA Banking.

Prenatal Testing

Chromosomal breakage. Prenatal testing is available for pregnancies at 25% risk by performing cytogenetic testing in the presence of DEB/MMC to evaluate for increased chromosomal breakage in fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation.

Mutation analysis for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, or *FANCI*. Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The family-specific disease-causing mutation(s) must be identified before mutation analysis can be performed for prenatal testing.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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Mutation analysis for other genes. Prenatal testing may be available for families in which the disease-causing mutations in other genes have been identified. For clinical laboratories offering custom prenatal testing, see Testing.

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. Furthermore, some congenital anomalies characteristic of FA may not be detectable by ultrasound examination.

Preimplantation genetic diagnosis. Preimplantation genetic diagnosis has successfully identified at-risk embryos to be unaffected with FA and HLA-matched to affected sibs [Verlinsky et al 2001, Grewal et al 2004, Bielorai et al 2004].

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Fanconi Anemia

Complementation Group	Gene Symbol	Chromosomal Locus	Protein Name
FA-A	*FANCA*	16q24.3	Fanconi anemia group A protein
FA-B	*FANCB*	Xp22.3	Fanconi anemia group B protein
FA-C	*FANCC*	9q22.3	Fanconi anemia group C protein
FA-D1	*BRCA2*	13q12.3	Breast cancer type 2 susceptibility protein
FA-D2	*FANCD2*	3p25.3	Fanconi anemia group D2 protein
FA-E	*FANCE*	6p22-p21	Fanconi anemia group E protein
FA-F	*FANCF*	11p15	Fanconi anemia group F protein
FA-G	*FANCG*	9p13	Fanconi anemia group G protein
FA-I	*FANCI*	15q25-q26	Fanconi anemia group I protein
FA-J	*BRIP1*	17q22	Fanconi anemia group J protein
FA-L	*FANCL*	2p16.1	E3 ubiquitin-protein ligase FANCL
FA-M	*FANCM*	14q21.3	Fanconi anemia group M protein
FA-N	*PALB2*	16p12	Partner and localizer of BRCA2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Fanconi Anemia

227645	FANCONI ANEMIA, COMPLEMENTATION GROUP C; FANCC
227646	FANCONI ANEMIA, COMPLEMENTATION GROUP D2; FANCD2
227650	FANCONI ANEMIA; FA
300514	FANCONI ANEMIA, COMPLEMENTATION GROUP B; FANCB
300515	FANCB GENE; FANCB
600185	BREAST CANCER 2 GENE; BRCA2
600901	FANCONI ANEMIA, COMPLEMENTATION GROUP E; FANCE
602956	X-RAY REPAIR, COMPLEMENTING DEFECTIVE, IN CHINESE HAMSTER, 9; XRCC9
603467	FANCONI ANEMIA, COMPLEMENTATION GROUP F; FANCFFANCF GENE
605724	FANCONI ANEMIA, COMPLEMENTATION GROUP D1; FANCD1
605882	BRCA1-INTERACTING PROTEIN 1; BRIP1
607139	FANCA GENE; FANCA
608111	PHD FINGER PROTEIN 9; PHF9
609053	FANCONI ANEMIA, COMPLEMENTATION GROUP I
609054	FANCONI ANEMIA, COMPLEMENTATION GROUP J
609644	FANCM GENE; FANCM
610355	PARTNER AND LOCALIZER OF BRCA2; PALB2
610832	FANCONI ANEMIA, COMPLEMENTATION GROUP N

Table C. Genomic Databases for Fanconi Anemia

Gene Symbol	Locus Specific	Entrez Gene	HGMD
FANCA	FANCA	2175 (MIM No. 227650)	FANCA
FANCB	FANCB	2187 (MIM No. 300515)	
FANCC	FANCC	2176 (MIM No. 227645)	FANCC
BRCA2	BRCA2	675 (MIM No. 600185)	BRCA2
FANCD2	FANCD2	2177 (MIM No. 227646)	FANCD2
FANCE	FANCE	2178 (MIM No. 600901)	FANCE
FANCF	FANCF	2188 (MIM No. 603467)	FANCF
FANCG	FANCG	2189 (MIM No. 602956)	FANCG
FANCI		55215 (MIM No. 611360)	FANCI
BRIP1		83990 (MIM No. 605882)	BRIP1
FANCL	FANCL	55120 (MIM No. 608111)	FANCL
FANCM		57697 (MIM No. 609644)	FANCM
PALB2		79728 (MIM No. 610355)	PALB2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Note: The detailed discussion of protein interactions and signaling described in this section and Figure 1 has been simplified by replacing the long names of the proteins with their non-

italized gene acronym (e.g., FANCA instead of Fanconi anemia group A protein; BRCA2 instead of breast cancer type 2 susceptibility protein). See Molecular Genetics Table for gene and protein names.

Molecular Genetic Pathogenesis

All 13 genes that cause Fanconi anemia (FA), which also account for each of the 13 phenotypic complementation groups, have been identified. The proteins encoded by these 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]. Disruption of this pathway leads to the common cellular and clinical abnormalities observed in FA [Garcia-Higuera et al 2001].

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 multi-subunit ubiquitin ligase complex, and 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 and they form a protein complex (ID complex) [Smogorzewska et al 2007]. Monoubiquitinations of FANCD2 and FANCI depend on each other [Smogorzewska et al 2007].

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

Another component of the FA core complex, FANCM, is homologous to the archaeal DNA helicase/nuclease known as HEF. FANCM has DNA helicase motifs and a degenerate nuclease motif and exhibits DNA-stimulated ATPase activity and DNA translocase activity [Meetei et al 2005]. A FANCM-interacting protein, FAAP24, preferentially binds to single-stranded DNA and branched DNA structures [Ciccia et al 2007]. Therefore, it has been speculated that FANCM DNA translocase activity could play an important role in displacing the FA core complex along the DNA, allowing DNA damage recognition, or that FAAP24 may play a role in targeting the FA core complex to abnormal, branched DNA structures.

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, Sechi et al 2003].

A DNA damage-activated signaling kinase, ATR, a single-strand DNA binding protein complex, RPA, and an ATR-associated protein, HCLK2, are required for DNA damage-inducible monoubiquitnation and foci formation of FANCD2 [Andreassen et al 2004, Collis et al 2007]. BRCA1 [Garcia-Higuera et al 2001, Vandenberg et al 2003] and histone H2AX [Bogliolo et al 2007] are required for DNA damage-inducible foci formation of FANCD2, but not for monoubiquitination of FANCD2. These factors are considered to be upstream positive regulators of the FA pathway.

BRCA2 (previously known as *FANCD1*) is a tumor suppressor that confers breast cancer susceptibility [Howlett et al 2002]. BRCA2 protein stability and localization is regulated by PALB2 (partner and localizer of BRCA2) [Xia et al 2006]. The *PALB2* gene, another breast

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cancer susceptibility gene [Rahman et al 2007], is responsible for FA complementation group FA-N and the gene sometimes called *FANCN* [Reid et al 2007, Xia et al 2007]. Another breast cancer susceptibility gene [Seal et al 2006], *BRIP1* (originally known as *BACH1* for **B**RCA1-**a**ssociated **C**-terminal **h**elicase **1**) [Cantor et al 2001], is also an FA gene and is the basis for complementation group FA-J [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. Therefore, these factors are considered to work downstream of FANCD2 or in parallel pathways.

USP1 is a deubiquitinating enzyme that removes ubiquitin from monoubiquitinated FANCD2, and negatively regulates the FA pathway [Nijman et al 2005]. USP1 also removes ubiquitin from monoubiquitylated PCNA (**p**roliferating **c**ell **n**uclear **a**ntigen) [Huang et al 2006].

In nuclear foci, FANCD2 colocalizes with FANCI, BRCA1, BRCA2, PALB2, RAD51, BLM, RPA, ATR, FANCC and FANCE [Garcia-Higuera et al 2001; Pace et al 2002; Taniguchi, Garcia-Higuera, Andreassen et al 2002; Andreassen et al 2004; Wang et al 2004; Matsushita et al 2005; Xia et al 2006; Smogorzewska et al 2007]. FANCD2 also colocalizes partially with BRIP1 [Litman et al 2005] and NBS1 [Nakanishi et al 2002]. All of these factors are required for cellular resistance to DNA cross-linking agents, and are considered to work together to repair interstrand DNA cross-links, although the precise mechanism is not understood.

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

FANCD2 protein is also phosphorylated by the ataxia-telangiectasia kinase, ATM, in a process that regulates a radiation-induced S phase checkpoint [Taniguchi, Garcia-Higuera, Xu et al 2002, Ho et al 2006].

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

- Individuals with FA are susceptible to both leukemia and solid tumors [Alter 2003].
- *Fancd2*, *Fanca*, or *Fancc* knockout mice develop tumors [Houghtaling et al 2003, Wong et al 2003, Carreau 2004].
- Inactivation of the FA pathway by methylation of the *FANCF* gene has been found in a wide variety of human cancers (ovarian, breast, non-small cell lung, cervical, testicular, and head and neck squamous cell cancers) in the general population (non-FA individuals) [Olopade & Wei 2003, Taniguchi et al 2003, Marsit et al 2004, Narayan et al 2004, Wang et al 2006].
- Inherited and somatic mutations of *FANCC* and *FANCG* are present in a subset of young-onset pancreatic cancers [van Der Heijden et al 2003].
- *BRCA1* and *BRCA2* are well-known tumor suppressor genes responsible for familial breast/ovarian cancer [Turner et al 2004].

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- Truncating mutations in the FA genes *BRIP1* and *PALB2* are breast cancer susceptibility alleles [Seal et al 2006, Erkko et al 2007, Rahman et al 2007, Tischkowitz et al 2007].

These findings underscore the importance of the FA-BRCA pathway in tumor suppression. Because the FA pathway is required for cellular resistance to interstrand DNA cross-linking agents (cisplatin, MMC, melphalan, etc.), tumors with defects in the FA pathway are expected to be hypersensitive to these widely-used anti-cancer agents. Therefore, the FA-BRCA pathway is an attractive target for developing small molecule inhibitors that may be useful as chemosensitizers [Chirnomas et al 2006].

For reviews of the molecular biology of FA, see D'Andrea & Grompe 2003, Venkitaraman 2004, Collins & Kupfer 2005, Kennedy & D'Andrea 2005, Niedernhofer et al 2005, Bagby & Alter 2006, Gurtan & D'Andrea 2006, Lyakhovich & Surralles 2006, Mathew 2006, Mirchandani & D'Andrea 2006, Taniguchi & D'Andrea 2006].

FANCA

Normal allelic variants: The *FANCA* gene has two isoforms. Reference sequence NM_000135.2 has 43 exons and encodes the longer isoform.

Pathologic allelic variants: The pathologic alleles of *FANCA* are numerous and highly variable among families [Levran et al 1997, Morgan et al 1999, Wijker et al 1999]. A small percentage of families share the mutations 3788-3790del and 1115-1118del, the latter of which is found in affected individuals of northern European ancestry. See Genomic Databases table above.

Normal gene product: The FANCA protein encoded by the longer isoform has 1455 amino acids (reference sequence NM_000126). FANCA is a component of the FA core complex. FANCA contains two overlapping bipartite nuclear localization signals (NLS), five functional leucine-rich nuclear export sequences (NESs) and a partial leucine zipper sequence [Fanconi Anemia/Breast Cancer Consortium 1996, Lo Ten Foe et al 1996, Ferrer et al 2005]. The nuclear export of FANCA is regulated in a CRM1-dependent manner [Ferrer et al 2005]. FANCA is a phosphoprotein. FANCA is a client of Hsp90 [Oda et al 2007].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCB

Normal allelic variants: The *FANCB* gene has ten exons with the translation start in exon 3 (reference sequence NM_001018113.1). *FAAP95* is an alias for *FANCB*.

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: FANCB comprises 853 amino acids; some sequences have 859 residues, depending upon the initiating methionine. FANCB is a component of the FA core complex and contains a putative bipartite NLS [Meetei et al 2004].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCC

Normal allelic variants: The *FANCC* gene has 15 exons (reference sequence NM_000136.2).

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Pathologic allelic variants: Three common mutations in the *FANCC* gene have been identified (IVS4+4A>T, p.Arg548X, and 322delG) [Whitney et al 1993], as well as several rare mutations (p.Gln13X, p.Arg185X, and p.Leu554Pro). The mutation IVS4+4A>T has been found primarily in the Ashkenazi Jewish population; recently, it has also been reported in a Japanese cohort. The mutations p.Arg548X, 322delG, p.Arg185X, and p.Leu554Pro are prevalent in individuals of northern European ancestry. The mutation p.Gln13X is found in individuals from southern Italy. See Genomic Databases table above.

Normal gene product: FANCC has 558 amino acids. It is a component of the FA core complex, but localizes both to both the nucleus and the cytoplasm [Yamashita et al 1994]. Some functions of FANCC outside of the FA core complex have been also proposed [Fagerlie et al 2004].

Abnormal gene product: See Molecular Genetic Pathogenesis.

BRCA2

Normal allelic variants: The *BRCA2* gene, also known as *FANCD1*, has 27 exons (reference sequence NM_000059.3).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: The breast cancer type 2 susceptibility protein (BRCA2) has 3418 amino acids. BRCA2 regulates homologous recombination repair through control of RAD51 recombinase (eukaryotic homologue of bacterial RecA) [Davies et al 2001, Moynahan et al 2001]. BRCA2 also has other functions including stabilization of stalled replication forks and regulation of cytokinesis [Daniels et al 2004].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCD2

Normal allelic variants: The *FANCD2* gene has two isoforms. Isoform a (reference sequence NM_033084.3) has 43 exons. Isoform b (reference sequence NM_001018115.1) has 44 exons and an alternate 3' coding sequence resulting in a shorter and distinct C-terminus. FANCD2 protein encoded by isoform b (exon 44 form) is the functional FANCD2, and the protein encoded by isoform a (exon 43 form) is not functional [Montes de Oca et al 2005].

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: FANCD2 has 1451 amino acids (isoform b) and shares sequence similarity with FANCI. FANCD2 and FANCI form a protein complex (ID complex). FANCD2 can be monoubiquitinated on lysine 561 in an FA core complex-, UBE2T-, and FANCI-dependent manner. Monoubiquitinated FANCD2 is translocated to chromatin fraction, and form nuclear foci with FANCI, BRCA1, BRCA2, RAD51, etc. FANCD2 can be phosphorylated by ATM [Taniguchi, Garcia-Higuera, Xu et al 2002; Ho et al 2006] and possibly by ATR [Andreassen et al 2004, Pichierri & Rossellil 2004] in response to DNA damage.

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCE

Normal allelic variants: The *FANCE* gene has 14 exons (reference sequence NM_021922.2).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: FANCE has 536 amino acids and is a component of the FA core complex. FANCE directly binds to FANCD2. FANCE contains two nuclear localization signals (NLS). FANCE has five tandem repeats of a short helical motif (FANC repeats) [Nookala et al 2007].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCF

Normal allelic variants: The *FANCF* gene has a single exon (reference sequence NM_022725.2).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: FANCF has 374 amino acids and is a component of the FA core complex. FANCF acts as a flexible adaptor protein required for the assembly of the FA core complex [Leveille et al 2004]. Crystallographic studies of the C-terminal domain revealed a helical repeat structure similar to the Cand1 regulator of the Cul1-Rbx1-Skp1-Fbox(Skp2) ubiquitin ligase complex [Kowal et al 2007].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCG

Normal allelic variants: The *FANCG* gene has 14 exons (reference sequence NM_004629.1).

Pathologic allelic variants: The mutations in *FANCG* are highly variable, but more common variant alleles have been described in specific populations: IVS3+1G>C (Korean/Japanese); IVS8-2A>G (Brazilian); IVS11+1G>C (French Canadian); 1184-1194del (northern European); and 1794-1803del (northern European) [Demuth et al 2000, Nakanishi et al 2001]. See Genomic Databases table above.

Normal gene product: FANCG has 622 amino acids. It is a component of the FA core complex. FANCG has seven tetratricopeptide repeat motifs (TPRs) [Blom et al 2004]. FANCG is a phosphoprotein; serines 383 and 387 on FANCG are phosphorylated in M phase, presumably by cdc2 [Mi et al 2004]. These two sites are important for exclusion of FANCG from chromatin in mitosis. Phosphorylation of serine 7 of FANCG is upregulated after MMC treatment [Qiao et al 2004]. FANCA and FANCG stabilize each other.

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCI

Normal allelic variants: The *FANCI* gene has 37 exons (reference sequence NM_018193.2).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: FANCI has 1268 amino acids and shares sequence similarity with FANCD2. FANCD2 and FANCI form a protein complex (ID complex). FANCI can be monoubiquitinated on lysine 523 in an FA core complex-, UBE2T-, and FANCD2-dependent manner. Monoubiquitinated FANCI is translocated to nuclear foci and colocalizes with

BRCA1, BRCA2, RAD51, FANCD2, etc. FANCI is a phosphoprotein. DNA damage-induced phosphorylation of Ser730, Thr952, and Ser1121 of human FANCI can be detected [Smogorzewska et al 2007].

Abnormal gene product: See Molecular Genetic Pathogenesis.

BRIP1

Normal allelic variants: The *BRIP1* gene (BRCA1 interacting protein C-terminal helicase 1) has 20 exons. This gene has also been called *FANCJ* or *BACH1*.

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: The Fanconi anemia group J protein (BRIP1 or FANCJ) has 1249 amino acids and is a DNA-dependent ATPase and a 5'-to-3' DNA helicase (DEAH helicase) that binds directly to the BRCT domain of BRCA1 [Cantor et al 2001]. FANCJ contains the seven helicase-specific motifs and C-terminal extension, which has 39% homology with synaptonemal complex protein 1, a major component of the transverse filaments of developing meiotic chromosomes [Cantor et al 2001].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCL

Normal allelic variants: The *FANCL* gene has 14 exons (reference sequence NM_018062.2).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: The E3 ubiquitin-protein ligase FANCL has 375 amino acids. It is a component of the FA core complex with three WD40 repeats and a PHD finger motif (a variant RING finger motif) [Meetei, de Winter et al 2003] and is presumed to be the catalytic subunit of the FA core complex as an ubiquitin ligase for FANCD2 and FANCI. FANCL directly interact with UBE2T (E2 ubiquitin conjugating enzyme) [Machida et al 2006].

Abnormal gene product: See Molecular Genetic Pathogenesis.

FANCM

Normal allelic variants: The *FANCM* gene has 23 exons (reference sequence NM_020937.1).

Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: The Fanconi anemia group M protein (FANCM) has 2048 animo acids. It is a component of the FA core complex, contains the seven helicase-specific motifs, one degenerate endonuclease domain, and ssDNA and dsDNA-stimulated ATPase activity and DNA translocase activity [Meetei et al 2005]. FANCM is phosphorylated in response to DNA damage.

Abnormal gene product: See Molecular Genetic Pathogenesis.

PALB2

Normal allelic variants: The *PALB2* gene (also known as FANCN) has 13 exons (reference sequence NM_024675.3).

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Pathologic allelic variants: See Genomic Databases table above.

Normal gene product: The partner and localizer of BRCA2 protein (PALB2) has 1186 amino acids. It regulates localization and stability of BRCA2 protein. Short sections of the PALB2 N-terminus share homologies with a segment of prefoldin and the light chain 3 (LC3) of microtubule-associated protein MAP1. PALB2 also has two WD40 repeat-like segments at the C terminus [Xia et al 2006].

Abnormal gene product: See Molecular Genetic Pathogenesis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Fanconi Anemia Cell Repository
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Portland OR 97201
Phone: 503-494-6888

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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 10021
Email: auerbac@rockefeller.edu
IFAR

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

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Revision History

- 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 to live Web site
- 1 March 2006 (cd) Revision: *FANCB* mutations: X-linked inheritance
- 3 January 2006 (as) Revision: deletion/duplication testing clinically available

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- 13 September 2004 (me) Comprehensive update posted to live Web site
- 14 February 2002 (me) Review posted to live Web site
- 31 May 2001 (as) Original submission

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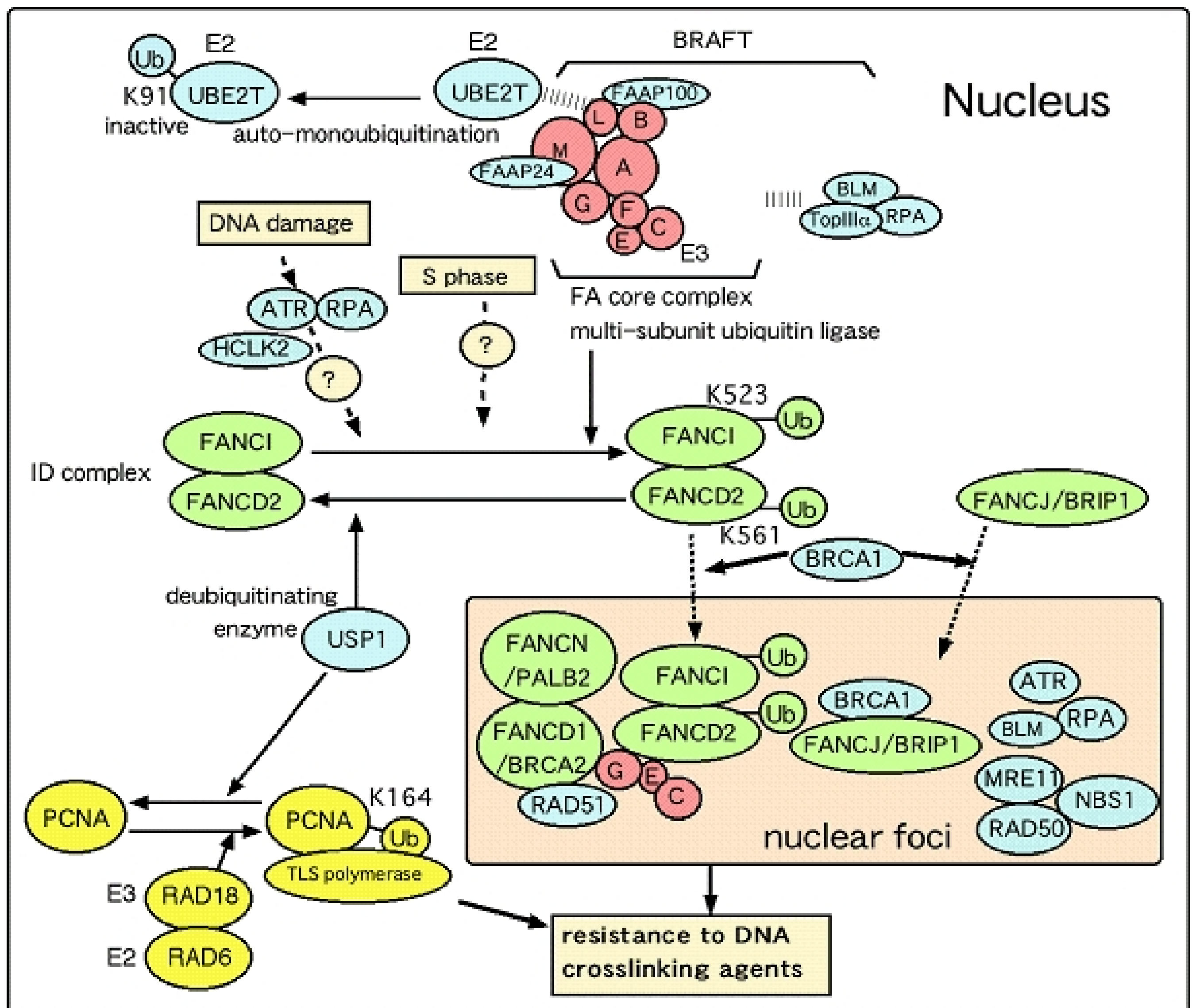

Figure 1. Current model of the Fanconi anemia pathway. Eight FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM), along with FAAP100 and FAAP24 form a nuclear protein complex (the FA core complex) with E3 ubiquitin ligase activity. FANCL is the catalytic subunit of the FA core complex and directly interacts with the E2 ubiquitin conjugating enzyme UBE2T through its PHD/RING domain. UBE2T can be inactivated by auto-monoubiquitination on lysine 91 (K91). The FA core complex, BLM, RPA, and topoisomerase IIIα form a super-complex called BRAFT. FANCI and FANCD2 form another complex called the ID complex. In response to DNA damage, or during S phase, FANCD2 and FANCI are monoubiquitinated on specific lysine residues (lysine 561 (K561) for FANCD2, lysine 523 (K523) for FANCI) in an FA core complex-, UBE2T-, and ID complex-dependent manner. DNA damage-induced monoubiquitination of FANCD2 also requires ATR, RPA and HCLK2. Monoubiquitinated FANCD2 and monoubiquitinated FANCI are translocated into nuclear foci and colocalizes with BRCA1, FANCD1/BRCA2, FANCN/PALB2, RAD51, FANCJ/BRIP1, and other proteins. BRCA1 is required for FANCD2 foci formation in response to DNA damage. FANCC, FANCE, and FANCG also

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form nuclear foci and colocalize with FANCD2. All of these factors are required for cellular resistance to DNA cross-linking agents. Monoubiquitination of PCNA on lysine 164 (K164) requires RAD6 as an E2 and RAD18 as an E3, but not the FA core complex. Monoubiquitination of PCNA causes recruitment of translesion synthesis (TLS) DNA polymerases at the site of stalled replication forks. USP1 deubiquitinates both PCNA and FANCD2, and possibly FANCI.

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