

Chapter 15

Genetic Counseling

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Introduction

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.¹ All individuals with FA and their families should receive genetic counseling from a genetic counselor familiar with FA at diagnosis and at various points throughout life. A genetic counseling consultation should include health, family, and pregnancy histories, should clarify the mode of inheritance of FA, and should explain the genetic testing process. Additionally, the consultation should include information about current research opportunities and support groups, future reproductive options and their familial implications.

Family History

The genetic counselor should obtain a detailed family history from the parents of children with FA or from young adults with FA. This history can be helpful in determining the inheritance pattern as well as the genetic basis of the disease. In obtaining the family history, the counselor should pay particular attention to FA-related clinical manifestations and associated cancers, as well as miscarriages and infertility.

Inheritance

Fanconi anemia is predominantly inherited in an autosomal recessive fashion. A small fraction of individuals,

less than 1%, has mutations in the *FANCB* gene which is inherited in an X-linked recessive manner.

Cancer Background

The counselor should obtain a detailed investigation of family cancer history, with a special emphasis on breast, ovarian, and prostate cancer. Each family history should be assessed using risk models to determine if the parents of an FA patient carry a *BRCA2*, *FANCF* or *FANCN* mutation. Features of hereditary cancer syndromes include multiple close family members with cancer, an autosomal dominant pattern of cancer inheritance, an early age of onset of cancer, bilateral breast cancer, more than one primary tumor, and male breast cancer. Cancer diagnoses should be verified with medical records whenever possible.²

Ethnic Background

Identification of an individual's ethnic background is important to determine the potential complementation group and/or specific gene mutations causing FA. Most mutations found in patients with FA have not arisen predominantly in one ethnic population, but in certain ethnic groups common mutations are found at an increased frequency. When an individual is of an ethnic background known to be associated with an FA founder mutation, targeted mutation analysis should be performed for that specific mutation. If a person's ethnic background is not indicative of a specific mutation, the complementation group should be determined before mutation analysis is attempted.

Consanguinity

In non-founder groups, the incidence of FA is rare and the carrier frequency is low. In the general population

of the United States, the chance of being a carrier for any of the FA gene mutations is ~1 in 300. Rare autosomal recessive diseases have an increased frequency of carriers who are consanguineous.

Table 1: Examples of FA Founder Mutations in Ethnic Populations³⁻¹⁰

Ethnicity	Gene	Mutation(s)	Carrier Frequency	Reference
Afrikaans-speaking South African (Transvaal Province)	<i>FANCA</i>	Deletion of Exons 12-31 (~60%) Deletion of Exons 11-17 (13%) 3398delA (6%)	~1/80	(Rosendorff et al., 1987) (Tipping et al., 2001)
Ashkenazi Jewish	<i>FANCC</i>	c.465+4A>T (IVS4+4A>T)	1/90	(Whitney et al., 1993) and (Verlander et al., 1995)
Black South African (Bantu-speaking populations of sub-Saharan Africa)	<i>FANCG</i>	Deletion (c.637_643delTACCGCC)	1/100	(Morgan et al., 2005)
French Acadian	<i>FANCG</i>	c.1480+1G>C (IVS11+1G>A)	Unknown	(Auerbach et al., 2003)
Japanese	<i>FANCG</i>	c.307+1G>A (IVS3+1>G)	Unknown	(Yagasaki et al., 2003)
Portuguese-Brazilian	<i>FANCG</i>	c.1077-2A>G (IVS8-2A>G)	Unknown	(Auerbach et al., 2003)

Genetic Testing

Genetic test results may determine medical management, prognosis, and mode of inheritance, and exclude diseases with similar manifestations. For these reasons, genetic testing should not be delayed and should be completed in a step-wise progression. Typically, experts first perform diagnostic chromosome breakage studies, then complementation group analysis and, finally, mutation analysis of the corresponding FA gene. Alternative

testing strategies include ethnicity-based genetic subtyping and comprehensive mutation screening.¹¹

Complementation Group Testing

Complementation group testing is used to classify individuals with FA according to the specific gene defect causing chromosomal instability. Retrovirus-mediated complementation group testing requires cells from patients that can be grown and are sensitive to cross-linking agents.¹² In some cases, multiple blood samples and/or other tissue samples may be needed to complete the testing. For some patients, complementation group testing will not be possible due to these sample limitations. Furthermore, complementation group testing can currently classify patients into 8 of the 13 known complementation groups. Groups that currently can be classified by complementation group testing include (A, B, C, G, E, F, J, and L). Genes not currently identifiable by complementation group testing include D1, D2, I, M, and N. Mutation analysis is necessary to classify individuals into one of these five groups. In approximately 2-3% of the cases, a complementation group will not be identified and a gene mutation will not be found in any of the known 13 genes (personal correspondence with Arleen Auerbach, PhD, The Rockefeller University).

Mutation Analysis

Mutation analysis identifies the specific gene changes that lead to FA. Mutation analysis is used to confirm the initial complementation group result, to perform other genetic tests such as carrier testing, prenatal testing, and preimplantation genetic diagnosis and, in some cases, to direct medical care and/or enroll in specific research studies. As of September 2008, mutation analyses of the *FANCA*, *FANCC*, *FANCD1*, *FANCE*, *FANCF*, and *FANCG* genes were available on a clinical basis in the

United States. Mutation analysis for other genes may be completed on a research basis.

Table 2: Examples of Benefits, Risks, and Limitations of Genetic Testing

Benefits	Risks	Limitations
Genetic testing results may give important information which would alter medical management (i.e., more frequent bone marrow biopsies).	Genetic testing information is a part of an individual's medical record and may be examined by health and life insurance providers.	Genetic testing results may not give additional information to guide medical management.
Genetic testing results can be used for carrier testing, prenatal testing, and preimplantation genetic diagnosis.	Genetic testing could show unknown family relationships (e.g., non-paternity).	Genetic testing results may be inconclusive or mutations may not be identified.
Genetic testing information can be helpful to family members (i.e., identify who may or may not be at increased risk of having a child with FA or developing cancer).	Family members may not want to know information obtained through genetic testing. Genetic information could alter family dynamics.	
Genetic testing results may relieve anxiety.	Genetic testing results may create anxiety, distress, and feelings of guilt.	
Genetic testing results may be used for inclusion in certain research projects or clinical trials.		

The decision to proceed with mutation analysis should be at the discretion of the parents of a child with FA or the adult patient with FA. Genetic testing can have many benefits, risks, and limitations and is a personal decision. For individuals with FA, the implications for the family can be even greater than in other genetic disorders due to the fact that carriers of mutations in certain FA genes have an increased risk of cancer.

Parents should be well informed of the possibility that their child's genetic testing results may affect their own health. A detailed conversation and informed consent of the patient and/or legal guardian must be completed prior to undertaking mutation analysis.

Genotype-Phenotype Correlations

In most cases it is not possible to predict the clinical course of this genetically and clinically heterogeneous disease. Lack of genotype-phenotype correlation is evidenced by siblings with the exact same gene mutations with radically different phenotypic manifestations. Medical management for most individuals with FA will be selected according to the presenting problems but, for complementation groups FA-D1 and FA-N, genotype is essential for proper cancer surveillance and medical management. For other groups, such as FA-A, FA-C, and FA-G, genotype information may be helpful for prognostic purposes.

FANCD1

Patients with FA in the FA-D1 complementation group have biallelic mutations in the *BRCA2* gene¹³ and have markedly increased spontaneous chromosomal aberration rates.¹⁴ These individuals commonly develop solid tumors such as medulloblastoma, astrocytoma, and Wilms tumor, which are rarely seen in individuals in other FA complementation groups. Leukemia is seen at a much earlier age than is expected for individuals of other FA subtypes. If *BRCA2*-related family history or clinical manifestations are suspected or if a patient is known to be in the D1 complementation group, additional tests such as a brain MRI and kidney ultrasound should be completed immediately to rule out any evidence of tumors. *BRCA2* testing should be considered in all patients with FA who have an unknown

complementation group and/or who develop leukemia at or before the age of five.¹⁵

FANCN

FANCN/PALB2 (partner and localizer of *BRC A2*) is another gene associated with a more severe clinical presentation. Individuals in the FA-N complementation group have a similar clinical presentation as FA-D1 individuals with development of early onset solid tumors and leukemia.¹⁶ Similar cancer surveillance recommendations as listed for patients with biallelic *FANCD1* mutations should be followed for individuals in the FA-N complementation group.

FANCA/FANCC/FANCG

An attempt to decipher distinct clinical manifestations between complementation groups and specific gene mutations was conducted by the European FA Research Group¹⁷ and the International Fanconi Anemia Registry (IFAR).¹⁸ The results of these studies showed several associations. Individuals with *FANCA* homozygous null mutations producing no protein had an earlier age of anemia and higher incidence of leukemia than those with an altered protein. In the European FA Research Group, it was reported that individuals in the FA-G complementation group had more severe cytopenia and a higher incidence of leukemia, but this was not found in the IFAR data set. Kutler et al. noted that individuals in complementation group C had an earlier age of onset of bone marrow failure when compared to complementation group A and G.¹⁸ Furthermore, it has been noted that *FANCC* *IVS4* and exon 14 mutations had an earlier age of hematological abnormalities and poorer survival compared to individuals who had exon 1 mutations.^{18,19} Since this publication, a study of Japanese patients with FA did not show an association with *FANCC* *IVS4+4A>T* mutation and a severe phenotype.²⁰

Hematologists may consider more frequent monitoring or early intervention for individuals with a specific mutation or a higher-risk group.

Cancer Risks for Fanconi Anemia Carriers

The current data collected through the International Fanconi Anemia Registry show that most carriers are not at increased risk of cancer, but several specific genes and particular mutations do confer cancer risks.²¹ Three FA genes, *FANCD1*, *FANCN* and *FANCI*, have been identified as identical to the breast cancer genes *BRCA2*, *PALB2* and *BRIP1* respectively. Case control studies have proven that *FANCI* and *FANCN* are low-risk breast cancer susceptibility alleles,^{22,23} whereas *FANCD1* is a higher-risk breast cancer susceptibility gene.

***FANCD1/BRCA2* Carriers**

Female and male family members of individuals with biallelic mutations in the *BRCA2* gene are at significantly increased risk of developing certain cancers. Most families with FA who have mutations in the *BRCA2* gene will present with the typical pattern of hereditary breast and ovarian cancer. However, in some families it has also been noted that a number of *BRCA2* alleles associated with a diagnosis of FA may not confer the same cancer risks seen in typical *BRCA2* families.²⁴ Female *BRCA2* carriers have a risk of breast cancer ranging from 40% at the age of 80 to a lifetime risk of ~80%. Ovarian cancer risks range from 10-20% at the age of 70. The risk of male breast cancer for *BRCA2* carriers is ~7%.²⁵ Prostate cancer risk is ~20% before the age of 80.²⁶ The estimated lifetime risk of pancreatic cancer in *BRCA2* carriers may be as high as 5%.²⁶ Melanoma may also be increased in *BRCA2* carriers. Due to the increase in these specific cancers,

recommendations for proper screening and surgical options have been created by the National Comprehensive Cancer Network as described below.²⁷ Individuals may wish to participate in research to help increase detection of cancers which currently do not have surveillance recommendations.

Female Screening	Recommendation
Breast	
Self Exam	Monthly, beginning at the age of 18 years of age
Clinical Breast Exam	Semi-annually, beginning at 25 years of age
Mammogram	Annually, beginning at 25 years of age or based on age of diagnosis
Breast MRI	Annually, beginning at 25 years of age or based on age of earliest onset in family
Ovarian	
Pelvic Exam	Every 6-12 months, beginning at age 25 years
Concurrent transvaginal ultrasound and CA-125 blood test	Every 6 months, starting at 35 years or 5-10 years earlier than earliest age of onset of ovarian cancer in the family
Prevention	Specifics
Breast	
Chemoprevention	Consider on a case-by-case basis
Prophylactic Surgery	Discussion of degree of protection, reconstructive options, and risk
Ovarian	
Prophylactic Surgery	Recommended between the ages of 35-40 years or when childbearing is complete. Discussion should include reproductive plans, menopausal symptoms, and degree of protection for breast and ovarian cancer.
Male Screening	Recommendation
Prostate	
Prostate specific antigen (PSA)	Annually, beginning at 40 years of age
Digital Rectal Exam	Annually, beginning at 40 years of age
Breast	
Self Exam	No standard screening recommendations have been created. Self exam may be advised.
Clinical Breast Exam	Seek medical advice for any breast mass, pain or change
Mammogram	Not typically advised in the absence of other risk factors such as gynecomastia

In addition to screening for cancer, ways to attempt to reduce the risks of cancer include chemoprevention and surgery. Chemoprevention for breast cancer is most commonly achieved using the drug tamoxifen. The use of tamoxifen for five years has been shown to reduce the incidence of breast cancer by 43% in women who have an increased risk.²⁸ The surgical interventions of salpingo-oophorectomy and mastectomy provide the greatest reduction in cancer incidence.²⁹ A physician or genetic counselor should discuss the risks and benefits of chemoprevention and surgery with possible *BRCA2* carriers.

***FANCN* Carriers**

Although FA-N and FA-D1 patients present with a similar phenotype, carriers of *FANCN* mutations may have a lower risk of cancer than *BRCA2* carriers. Monoallelic truncating mutations in *FANCN* (*PALB2*) are associated with an approximately two-fold increased risk of breast cancer.²³ Erkkö et al. analyzed cumulative breast cancer risk for the Finnish founder mutation c.1592delT and found a 40% cumulative risk at the age of 70.³⁰ Female *FANCN* carriers are encouraged to discuss this increased risk with their health care providers and design a breast cancer screening plan which may entail more frequent clinical breast exams, mammograms or breast MRI examinations. No specific recommendations have been published for screening of *FANCN* carriers.

***FANCI* Carriers**

Carrier risk in *FANCI* (*BRIP1*) individuals was first investigated in a group of patients with hereditary breast cancer who did not have mutations in the *BRCA1* or *BRCA2* genes. Investigators determined that truncating *FANCI* mutations confer a relative risk of 2.0.²² However, some missense variants confer a risk for

breast cancer while others do not. Carriers of mutations known to confer an increased risk of breast cancer should be aware of this increased risk and consider screening similar to *FANCN* carriers.

***FANCC* Carriers**

Mutations in the *FANCC* gene may confer an increased risk of breast cancer. Berwick et al. showed that grandmothers who carried a *FANCC* mutation were 2.5 times more likely to develop breast cancer than noncarriers.²¹ The molecular basis of this increased risk is not well understood and, thus, this finding must be further investigated. Carriers should be informed of this potential increased risk and be encouraged to discuss this finding with their health care providers.

Reproductive Issues

Reproductive counseling is part of the genetic counseling process. Individuals with FA may seek reproductive counseling for assistance with infertility and/or information of risks for their own children. Parents of individuals with FA should be aware of the chances of their children having FA to permit informed decision-making about future pregnancies. Reproductive choices include natural pregnancy, adoption, birth control, prenatal testing, and various reproductive technologies such as preimplantation genetic diagnosis (PGD).

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis is genetic testing used in combination with *in vitro* fertilization to allow parents the opportunity to choose embryos that do not have Fanconi anemia and/or are HLA matches for siblings. Selected embryos are transferred into the mother's uterus with the hope that the couple will have a pregnancy with the specific genetic make-up that they

choose. PGD reduces the likelihood that a family will have a child with Fanconi anemia and can increase the chances of an HLA-match, but it does not guarantee that the child will not have FA and/or be a match. There is always a chance that an error leading to misdiagnosis could occur in the testing or embryological process. Thus, it is recommended that prenatal testing in the form of chorionic villus sampling or amniocentesis be completed to validate the PGD results.

Individuals considering PGD should consider the following factors. The theoretical chances of an individual having a matched sibling with FA includes a 3 in 4 chance that the embryo will not have FA and a 1 in 4 chance that an embryo will be HLA identical; thus, the odds are 3 in 16 or 18.75% for each embryo to be non-affected and an HLA-match. In actuality, many couples will need multiple rounds of IVF and PGD to obtain a clinical pregnancy resulting in a live born baby. Each IVF and PGD center will have specific statistics on its experience, and couples considering this procedure should obtain that data. The major steps in the process from PGD to transplant are as follows:

- Consult with a transplantation physician and genetic counselor;
- Obtain complementation group and mutation analysis results;
- Obtain HLA typing of individual with FA as well as the mother and father;
- Consult with PGD center staff and affiliated IVF center staff;
- Complete PGD work-up, fertility work-up, and required medical procedures;

- Complete PGD and choose suitable embryos for implantation and, if applicable, embryo preservation;
- Obtain a pregnancy test and genetic testing with CVS/amniocentesis to confirm PGD results;
- Arrange umbilical cord collection and harvest;
- Obtain confirmatory testing of umbilical cord blood/newborn baby;
- Proceed to transplantation of HLA-matched umbilical cord for sibling.

PGD remains a controversial procedure. It can be a very stressful experience physically, emotionally, and financially for couples who undergo the procedure. PGD can require many doctor appointments, medical treatments, tough decisions, ethical/religious questions, and the addition of a new member to a family. It may be helpful for families to discuss PGD with other families who have gone through the process for a realistic description of their experiences.

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