Genetic Heterogeneity among Fanconi Anemia Heterozygotes and Risk of Cancer

Marianne Berwick,[1] Jaya M. Satagopan,[2] Leah Ben-Porat,[2] Ann Carlson,[3] Katherine Mah,[2] Rashida Henry,[3] Raffaella Diotti,[3] Kelly Milton,[3] Kanan Pujara,[3] Tom Landers,[3] Sat Dev Batish,[3] José Morales,[3] Detlev Schindler,[4] Helmut Hanenberg,[5] Robert Hromas,[1] Orna Levran,[3] and Arleen D. Auerbach[3]

[1]Cancer Research and Treatment Center/Internal Medicine, University of New Mexico, Albuquerque, New Mexico; [2]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center; [3]Laboratory for Human Genetics and Hematology, The Rockefeller University, New York, New York; [4]Department of Human Genetics, University of Wurzburg, Wurzburg, Germany; and [5]Department of Pediatric Oncology, Hematology and Immunology, University of Dusseldorf, Dusseldorf, Germany

Abstract

Fanconi anemia (FA) is a rare autosomal recessive disease characterized by a greatly increased risk of cancer among those diagnosed with the syndrome. The question as to whether FA heterozygotes are at increased risk for cancer is of great importance to those at risk for being a carrier. To address this question, we formed a cohort of grandparents of probands identified through the International Fanconi Anemia Registry. We obtained informed consent, a short questionnaire, and either blood or buccal swab DNA. After diagnosis of the proband was confirmed and complementation studies or DNA sequencing on the proband were completed, mutation analyses of the putative carriers and noncarriers was carried out. Standardized incidence ratios (SIR) were calculated to compare the observed cancer incidence of the grandparents and other relatives with the expected rates of cancer, using the Surveillance, Epidemiology, and End Results registries and the Connecticut Cancer registry. In the 944 study subjects who participated (784 grandparents and 160 other relatives), there was no suggestion of an increase in overall cancer incidence. On the other hand, a significantly higher rate of breast cancer than expected was observed among carrier grandmothers [SIR, 1.7; 95% confidence interval (95% CI), 1.1–2.7]. Among the grandmothers, those who were carriers of *FANCC* mutations were found to be at highest risk (SIR, 2.4; 95% CI, 1.1–5.2). Overall, there was no increased risk for cancer among FA heterozygotes in this study of Fanconi relatives, although there is some evidence that *FANCC* mutations are possibly breast cancer susceptibility alleles. [Cancer Res 2007;67(19):9591–6]

Introduction

A rare genetic disease, Fanconi anemia (FA) is characterized by congenital malformations, progressive bone marrow failure, cellular hypersensitivity toward DNA interstrand cross-linking agents, and a greatly increased risk of cancer among patients diagnosed with FA. The median age of survival of patients with FA ranges from 20 to 30 years, depending on the cohort examined (1). The cumulative incidence of solid tumors reaches 36% by age 50 years (2) and that of leukemia is ~10% by age 25 years (1).

The syndrome is genetically heterogeneous; there are at least 13 complementation groups and to date 13 genes have been identified. These genes encode components of the FA nuclear "core" complex (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM), key components of the FA pathway, FANCD2, FANCI, the familial breast cancer protein BRCA2/FANCD1, its partner and localizer, PALB2/FANCN, and the BRIP1/BACH1/FANCJ helicase. The role of FANC proteins in protecting the genome is clearly important (3). Although it has been proposed that the connections among the complementation groups represent a linear biological pathway (4), they may instead reflect a variety of protein networks affecting DNA stability during both S phase of the cell cycle and DNA damage recognition/repair (5). In addition, there is emerging evidence that some FA complexes function to suppress apoptosis and facilitate survival signaling pathways (6). Although associations of FA heterozygosity with breast and other cancers have been reported (7–15), the question as to whether heterozygotes with mutations in any of the Fanconi genes other than *FANCD1/BRCA2* and its interacting partners are at increased risk for developing cancer has been enigmatic. To date, "there has been little convincing evidence that FA heterozygotes are at increased risk for cancer, but larger studies are needed to address the possibility of modest risk effects" (16). Consistent with this suggestion, mutated alleles of *FANCJ* (12) and *FANCN* (15) have been identified recently as low-risk breast cancer susceptibility alleles in case-control studies.

There are two motives for assessing cancer risk among heterozygotes: to understand better the genetic basis of cancer and to provide prevention and screening information to families of FA patients. To address these issues, we designed a cohort study to characterize molecularly FA carriers and noncarriers and compare these groups in terms of risk for cancer.

Materials and Methods

Study Population

Family members of the 848 FA probands in the International Fanconi Anemia Registry (IFAR; ref. 2) as of March 31, 2005 were contacted by letter and followed up by telephone by an accredited genetic counselor. All participants signed informed consent and studies were approved by the Institutional Review Boards at The Rockefeller University, Memorial Sloan-Kettering Cancer Center, and The University of New Mexico Health Sciences Center. The main goal was to focus on the grandparents of the probands due to their age and likelihood of developing cancer. In families where three or all four of the grandparents of the probands participated, only the

Note: M. Berwick, J.M. Satagopan, and L. Ben-Porat contributed equally to this work.

Requests for reprints: Arleen D. Auerbach, Laboratory of Human Genetics and Hematology, The Rockefeller University, 1230 York Avenue, Box 77, New York, NY 10021-6399. Phone: 212-327-7533; Fax: 212-327-8262; E-mail: auerbac@mail.rockefeller.edu.

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Table 1. Characteristics of relatives of FA patients from questionnaire data

Variable		Grandparents (n = 784), n (%)	Other relatives (n = 160), n (%)
Relationship	Paternal grandfather	175 (22)	
	Paternal grandmother	183 (23)	
	Maternal grandfather	195 (25)	
	Maternal grandmother	231 (29)	
	Great grandfather		6 (4)
	Great grandmother		9 (6)
	Grand uncle		4 (3)
	Grand aunt		10 (6)
	Father		44 (28)
	Mother		44 (28)
	Uncle		7 (4)
	Aunt		29 (18)
	Cousin		4 (3)
	Sibling		3 (2)
Gender	Male	370 (47)	64 (40)
	Female	414 (53)	96 (60)
Race	White, non-Hispanic	713 (91)	147 (92)
	Hispanic or Latino	27 (3)	5 (3)
	Black, non-Hispanic	15 (2)	3 (2)

grandparents were eligible for inclusion in the study. However, in families of probands with none to two participating grandparents, two to four other relatives were also eligible.

Confirmation of Diagnosis

Diagnosis of FA for all probands was first confirmed by chromosomal breakage induced by diepoxybutane (17).

Complementation Studies

Once the diagnosis of FA was confirmed and appropriate cell lines were established, complementation studies with retroviral vectors containing normal *FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG*, and *FANCL* cDNAs were done as described (18). Immunoblotting for detection of monoubiquitinated FANCD2 was also done as described (19). Probands excluded from these complementation groups and with normal ubiquitination of FA-D2 were tested for group FA-D1 by genomic DNA sequencing of BRCA2 by Myriad Genetic Laboratories (Salt Lake City, UT). Patients in this group who were negative for FA-D1 were screened for groups FA-J and FA-N by direct sequencing for mutation detection and demonstration of abnormal protein by immunoblotting. A small percentage of FA patients could not be assigned to any complementation group, including FA-M as tested by immunoblotting. For these families, carrier status of grandparents was considered as unknown for the analysis.

Mutation Analysis

DNA extraction. Buccal swabs were stored frozen at −20°C until DNA was extracted, using Quick-Extract DNA extraction solution according to the manufacturer's instructions (Epicentre). Briefly, this consisted of several steps of 10 s of vortexing followed by incubations, first at 65°C for 30 min and then twice at 98°C for 8 min each. DNA was then stored at −20°C until analysis. PCR amplification was done using 1 μL in a 30 to 45 μL reaction.

Mutation screening. Probands identified by complementation testing as groups FA-A, FA-C, FA-F, or FA-G were screened for mutations in *FANCA, FANCC, FANCF,* and *FANCG* using the Transgenomic Wave dHPLC System. Under denaturing conditions at 50°C, small heterozygous insertions/deletions were detected as an additional peak on the chromatogram. PCR products were then denatured at 95°C for 5 min followed by cooling at 1°C/min to 25°C to allow heteroduplex formation in case of heterozygosity. They were then subjected to denaturing high-performance liquid chromatography analysis. In case of homozygosity, the samples are mixed with known normal controls, denatured as described above, and reanalyzed.

Sequencing. Direct genomic and cDNA sequencing was done for *FANCA/B/C/D2/E/F/G/J/N* according to standard protocols. PCR products were cleaned using ExoSAP-IT (USB) according to the manufacturer's protocol. Most of the sequencing was done by Genewiz, Inc. with Big Dye Terminator version 3.1 Cycle Sequencing Ready Reaction kits (Applied Biosystems) on a 3730xl DNA analyzer. Sequence data were generated by means of Sequencing Analysis version 5.1 (Applied Biosystems) and analyzed with Sequencher version 4.5 (Gene Codes Corp.).

Large deletions seem to be a frequent mutation subtype in *FANCA*, accounting for ~40% of mutated alleles in *FANCA*, the most common FA gene (20, 21). Multiplex ligation-dependent probe amplification allows quantitation of multiple sequences (22) and was done according to the MRC-Holland protocol for *FANCA* and consisted of DNA denaturation, probe hybridization, ligation, and PCR steps. The samples were then analyzed by capillary electrophoresis and analyzed with the Genotyper software.

As mutation assays for IFAR probands had been developed, family members were screened for the specific maternal or paternal mutations as applicable. In some FA-A families, assays based on segregation of informative single nucleotide polymorphisms (SNP) in three generations of the pedigree were used to determine carrier status of grandparents (23).

Statistical Methods

Standardized incidence ratios (SIR) were calculated to compare the cancer incidence observed in our study population with the expected rate of the U.S. population obtained from the Surveillance, Epidemiology, and End Results[6] registries, which provide cancer rates for years 1975 and beyond. Rates from the Connecticut Cancer Registry were used for years before 1975. The null hypothesis that the SIR is equal to 1 was tested, and 95% confidence intervals (95% CI) were calculated as described in Breslow and Day (24). Due to the descriptive nature of this work, we did not adjust the P values for multiple comparisons. The end point for SIR calculation was age at onset of the cancer of interest, age at death (without a cancer diagnosis for the cancer of interest), or age at last follow-up.

We report SIRs for cancers having >2% incidence in our study cohort: any cancer, breast cancer among female relatives, and prostate cancer among male relatives. First, SIRs were calculated using all the study subjects,

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regardless of their carrier status. Next, SIRs were estimated separately for heterozygous carriers of FANCA, FANCC, and FANCG mutations. Finally, we calculated SIRs separately for the grandparents and nongrandparent relatives.

Results

Questionnaires were obtained from the 944 study subjects, 784 grandparents and 160 other relatives (Table 1), from 312 families of probands in the IFAR. Three or all four grandparents participated in the study from 152 proband families. None or two grandparents participated from 160 proband families. Our study population consisted of 509 females and 435 males. This included 414 grandmothers, 370 grandfathers, and 160 nongrandparent relatives (Table 1).

A total of 184 cancers were observed among the study subjects, 151 among the grandparents (Table 2). Of the cancers diagnosed among grandparents, 126 (16%) grandparents reported diagnosis of a single cancer, 23 (3%) reported diagnosis of two cancer, and 2 (0.3%) grandparents reported diagnosis of three cancers. Similar cancer incidence was observed among other relatives (data not shown).

There were 404 heterozygous carriers (154 grandmothers, 144 grandfathers, and 106 other relatives), 329 noncarriers (161 grandmothers, 136 grandfathers, and 32 other relatives), and 211 relatives with unknown carrier status (99 grandmothers, 90 grandfathers, and 22 other relatives). The mutations in the 154 carrier grandmothers were composed of 86 *FANCA*, 33 *FANCC*, 14 *FANCG*, 8 *BRCA2*, 6 *FANCD2*, 5 *FANCF*, and 2 *FANCJ*. Mutations among the 144 carrier grandfathers were 99 *FANCA*, 21 *FANCC*, 11 *FANCG*, 1 *BRCA2*, 3 *FANCD2*, 6 *FANCF*, and 3 *FANCJ*. Of the 106 other relatives who were carriers, we observed 51 *FANCA*, 24 *FANCC*, 4 *FANCG*, 1 *BRCA2*, 4 *FANCD2*, 1 *FANCJ*, and 21 other, composed of 2 subjects for whom all known genes have been ruled out and 19 who could not be typed for complementation group (see Table 3).

Table 2. List of cancer diagnoses among the relatives

	Grandparent (n = 784), n (%)	Other relative (n = 160), n (%)
Any cancer	151 (19)	33 (20)
Bladder	7 (1)	1 (1)
Breast	38 (5)	13 (8)
Cervix	3 (0)	3 (2)
Colon or rectum	11 (1)	2 (1)
Kidney/Wilms' tumor	5 (1)	1 (1)
Leukemia	1 (0)	0 (0)
Liver	1 (0)	1 (1)
Lung	13 (2)	3 (2)
Lymphoma or Hodgkin's	9 (1)	1 (1)
Melanoma	15 (2)	1 (1)
Mouth or throat	7 (1)	2 (1)
Multiple myeloma	2 (0)	1 (1)
Ovary	4 (1)	2 (1)
Pancreas	6 (1)	0 (0)
Prostate	34 (4)	4 (3)
Sarcoma or bone	2 (0)	0 (0)
Stomach or esophagus	6 (1)	1 (1)
Testicle	3 (0)	0 (0)
Thyroid or parathyroid	1 (0)	0 (0)
Uterus or endometrium	10 (1)	2 (1)

There was no suggestion of an increase in overall cancer incidence among the carrier grandparents (SIR, 1.0; 95% CI, 0.8–1.3; P = 0.45; Table 4). SIR calculations for any cancer, breast cancer, and prostate cancer, overall and stratified by carrier status (carrier, noncarrier, unknown, and by complementation group of carriers), show that the only increased risk is among those carriers with breast cancer (Table 4).

The 38 breast cancers observed among all 414 grandmothers comprised a significantly higher rate than expected (SIR, 1.3; 95% CI, 1.0–1.8; P = 0.05; Table 4). Restricting the analysis to 154 carrier grandmothers showed that the 18 breast cancers observed were significantly higher than the 10.7 expected (SIR, 1.7; 95% CI, 1.1–2.7; P = 0.03). This increase was not observed among the 161 noncarriers (SIR, 1.1; 95% CI, 0.6–2.0; P = 0.38). There were 6 breast cancers observed among the 33 grandmothers heterozygous for *FANCC* mutations compared with 2.5 expected, representing a significantly increased rate (SIR, 2.4; 95% CI, 1.1–5.2; P = 0.04). The same trend was noted when all 47 female carriers of FA-C (33 grandmothers and 14 other female relatives) were analyzed (SIR, 2.4; 95% CI, 1.2–4.8; P = 0.02). No significant increase in risk was noted among *FANCA* carriers (P = 0.31), noncarriers (P = 0.38), or those of unknown carrier status (P = 0.43).

Discussion

The role of FA in breast cancer susceptibility has been recently the subject of intense study. Previous epidemiologic studies have been hampered by small sample sizes and lack of molecular characterization of FA carriers (16). We have overcome these limitations by providing the largest sample size to date of molecularly characterized heterozygotes of FA. Our study has two important results: (*a*) in general, there is not a striking or significant increase in cancer incidence among FA heterozygotes and (*b*) there is some evidence that *FANCC* mutations are possibly breast cancer susceptibility alleles. An unanswered question is how the 13 prostate cancers among the 90 males with unknown complementation status will distribute once their mutational status is known. It should be stressed that not all FA genes are likely to be cancer susceptibility alleles and that there are undoubtedly more pathways involved in breast cancer susceptibility related to FA (i.e., by FANCJ and FANCN).

In this study, three mutations were found among the eight *FANCC* carriers who developed breast cancer: p.L554P (n = 1), IVS4 (c.711+4A>T; n = 5), and c.322delG (n = 2). In the recently published Cancer Genetic Markers of Susceptibility,[7] three *FANCC* SNPs have a significantly increased risk, whereas one SNP has a significantly decreased risk for breast cancer among homozygotes (25). The question of how mutations in *FANCC* might act as susceptibility alleles should be further investigated. IFAR probands who carry the c.711+4A>T or the p.L554P mutation in *FANCC* have the most severe phenotype of all FA patients with mutations that effect the FA nuclear "core complex" proteins; their survival is poorer (52% at 10 years of age) and they have bone marrow failure sooner than other groups (26). Only probands in groups FA-D1 (BRCA2) and FA-N (PALB2), genes with known increased carrier risk for breast cancer, have a poorer survival, due to the unique predisposition of these patients to embryonal tumors.

[7] http://cgems.cancer.gov

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Table 3. Carrier status by FA family complementation group and cancer history of grandparent

Frequency		Carrier (n = 298)	Noncarrier (n = 297)	Unknown carrier status (n = 189)	Total
Group	A	185	192	34	411
	B	0	0	6	6
	BRCA2	9	7	10	26
	C	54	48	6	108
	D2	9	8	9	26
	E	0	0	3	3
	F	11	12	0	23
	G	25	24	0	49
	J	5	6	0	11
	Nx	0	0	32	32
	U	0	0	84	84
Cancer	No	232	247	154	633
History	Yes	66	50	35	151

Abbreviations: U, unknown group; Nx, unknown group for whom groups FA-A/B/C/D1/D2/E/F/G/J/L/M have been excluded by mutation or complementation studies.

The functions of FANCC are not yet totally clear. FANCC does not colocalize with BRCA1, BRCA2, and RAD51 in DNA repair foci to regulate DNA repair (27), and although it is part of the FA nuclear "core complex" necessary for FANCD2 and FANCDI monoubiquitination (28, 29), it seems to have additional functions independent of other FA proteins (30), in particular, regulation of apoptosis (31).

Several limitations to our study are important to note. Pathology was not available for all subjects who reported cancer and there could thus be misclassification present in the cancer outcomes.

Table 4. SIR calculations for all 784 grandparents of FA probands

Disease	Group	n	Observed cancer	Expected cancer	SIR (95% CI)	P
Any cancer	All grandparents	784	151	174.9	0.9 (0.7–1.0)	0.04
	Carrier	298	66	64.6	1.0 (0.8–1.3)	0.45
	A	185	38	41.3	0.9 (0.7–1.3)	0.34
	C	54	16	13.6	1.2 (0.7–1.9)	0.29
	G	25	3	4.4	0.7 (0.2–2.0)	0.36
	Other*	34	9	5.3	1.7 (0.9–3.2)	0.09
	Noncarrier	297	50	66.1	0.8 (0.6–1.0)	0.02
	Unknown status	189	35	44.2	0.8 (0.6–1.1)	0.09
Breast	All GM	414	38	28.6	1.3 (1.0–1.8)	0.05
	Carrier	154	18	10.7	1.7 (1.1–2.7)	0.03
	A	86	8	6.4	1.3 (0.6–2.5)	0.31
	C	33	6	2.5	2.4 (1.1–5.2)	0.04
	G	14	0			
	Other*	21	4	1.0	3.9 (1.5–10.1)	0.02
	Noncarrier	161	12	10.7	1.1 (0.6–2.0)	0.38
	Unknown status	99	8	7.2	1.1 (0.6–2.2)	0.43
Prostate	All GF	370	34	26.1	1.3 (0.9–1.8)	0.08
	Carrier	144	12	9.4	1.3 (0.7–2.2)	0.24
	A	99	7	6.4	1.1 (0.5–2.3)	0.45
	C	21	1	1.7	0.6 (0.1–3.3)	0.48
	G	11	1	0.6	1.8 (0.3–10.0)	0.43
	Other*	13	3	0.7	4.1 (1.4–12.2)	0.04
	Noncarrier	136	9	10.3	0.9 (0.5–1.7)	0.43
	Unknown status	90	13	6.4	2.0 (1.2–3.5)	0.02

Abbreviations: GM, grandmothers; GF, grandfathers.
*The "other" group includes BRCA2 carriers as well as those for who are obligate carriers (parents) but for whom we do not know the precise complementation status.

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However, this is negligible for breast and prostate cancers (32, 33). We found one gene with elevated risk out of the many comparisons made; thus, this finding could represent a false-positive result.

Another limitation is that we did not have carrier status for all grandparents because in some cases, the grandparents were dead (and therefore did not provide a DNA sample). Furthermore, families where all the grandparents were deceased at the time of study were less likely to participate in the study. Investigations are continuing to determine the complementation group of the Nx individuals, some of whom have been found to carry mutations in new complementation groups, such as PALB2 /FA-N (15) and FANCI (28, 29). Cancer incidence in the new complementation groups will be investigated in the future after genotyping efforts are completed to identify novel groups.

Finally, there is potential bias due to differences in participation by family history of cancer. Unfortunately, one cannot evaluate this potential bias because information on family history of cancer among nonparticipants is not available.

The 2.4-fold increased SIR was noted among all grandmothers as well as all female relatives heterozygous for *FANCC* mutations. This point estimate is similar to risk estimates found recently among heterozygotes in a case-control study of 1,212 individuals with breast cancer compared with 2,081 controls without breast cancer in the United Kingdom. Seal et al. (12) found that nine individuals with truncating mutations in the *FANCJ* gene have a relative risk for breast cancer of 2.0 (95% CI, 1.2–3.2) when compared with only two individuals in the control group with the same mutations. In another study of 923 individuals with familial breast cancer compared with 1084 controls, Rahman et al. (15) reported that carrying a PALB2 mutation (also known as FANCN) increased risk of breast cancer by 2.3-fold (95% CI, 1.3–3.9). They found 10 individuals with mutations from the case group and no individuals with mutations in the control group. Our cohort study found that 6 individuals out of 33 carriers of *FANCC* mutations had breast cancer.

These data suggest that carrier relatives of complementation group FA-C patients should carefully follow the recommendations for breast cancer screening to detect cancer at the earliest possible stage and may wish to test for *FANCC* mutations if they know that they are related to a patient with FA-C complementation group. The frequency of FA varies among ethnic groups and is particularly high among those of Ashkenazi Jewish heritage; the c.711+4A>T mutation occurs in approximately 1 out of 89 individuals in this population (34). With a carrier frequency of >1% and simple testing available, the c.711+4A>T mutation is now included in the battery of genetic tests routinely provided to the Ashkenazi Jewish population due to its severe consequences.

The question of whether *FANCC* mutations that cause FA are more common among individuals with breast cancer than in the general population needs further study. However, the major finding from this molecular study of FA carriers is that there does not seem to be an overall increase in risk for cancer. These results not only are of historical interest, being the first molecular characterization of heterozygotes among a large number of pedigrees of FA, but are also of importance to family members of individuals diagnosed with FA because they now have molecular evidence that they need to worry less about the heightened cancer risk found among probands, with the possible exception of breast cancer, for which screening is available.

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Marianne Berwick, Jaya M. Satagopan, Leah Ben-Porat, et al.

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