Short Communication

BRCA1 and *BRCA2* Mutations in a Study of African American Breast Cancer Patients

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Abstract

The spectrum of mutations in *BRCA1* and *BRCA2* among African Americans has not been well characterized because most studies to date have been done in Caucasian families. According to Myriad Genetic Laboratories, Inc., only ~3% of individuals undergoing *BRCA1*/*BRCA2* testing reported African American ancestry. Data from previous studies show that among African American women a greater proportion of breast cancer cases are diagnosed at age <45 years in comparison with Caucasians. Because breast cancer occurring at a young age is one of the hallmarks of high penetrance genes, the prevalence, spectrum, and effects of *BRCA1*/*BRCA2* mutations may differ substantially between African Americans and Caucasians, and further investigation is warranted. We conducted a hospital-based study of African American breast cancer patients with early age at diagnosis (≤45 years) or family history of breast or ovarian cancer. We identified four deleterious mutations in *BRCA1* or *BRCA2* among the 10 families tested, of which two were novel *BRCA2* mutations, one was the west African founder mutation (*BRCA1* 943ins10), and one was a recurrent mutation that may be a candidate for a second African American founder mutation (*BRCA1* IVS13+1G>A). Our results support previous data in demonstrating that (*a*) the spectrum of mutations among African Americans is unique, (*b*) family history of breast cancer is an important predictor of hereditary cancer susceptibility among African Americans, and (*c*) empirical data may be useful in estimating mutation risk among African Americans. (Cancer Epidemiol Biomarkers Prev 2004;13(11):1794–9)

Introduction

Although African American women have a lower overall incidence of breast cancer compared with Caucasian women, the incidence rate of early-onset breast cancer is actually higher (1-5). On average, African American women develop breast cancer a decade earlier than Caucasians (6). According to Surveillance, Epidemiology, and End Results data (3), 33.0% of African Americans were diagnosed with breast cancer at age <50 years compared with 21.9% of White women. Over 10% of African American women with breast cancer are diagnosed before age 40 years compared with 5% of Caucasian patients (5). Breast cancer occurring at a young age is one of the hallmarks of high penetrance genes such as *BRCA1* and *BRCA2*. Therefore, it is logical that these genes may account for a proportion of breast cancer cases occurring at a young age in African American women.

Overall, 5% to 10% of breast and ovarian cancer cases are due to mutations in *BRCA1* and *BRCA2* (7, 8). However, most studies of *BRCA1* and *BRCA2* have been done in Caucasian families with a strong history of breast cancer. The spectrum of mutations identified in the U.S. population thus far reflects mostly European migrations to North America. The spectrum of mutations in the African American population is slowly beginning to be characterized.

A few genetic studies have included African American women from breast cancer families unselected for ethnic background (9-12). As of November 2001, according to data from Myriad Genetic Laboratories, Inc., an estimated 308 African American individuals had undergone *BRCA1* and *BRCA2* testing (compared with ~9,500 Caucasians), of whom 52 had deleterious mutations (13). Twenty-six of the 52 mutations had been observed in only one family.

Newman et al. suggested that the incidence of *BRCA1* mutations might be lower among breast cancer patients of African American ancestry. They conducted a population-based study including 99 African American women with breast cancer and identified no disease-related *BRCA1* mutations in any of these women (12). However, no details regarding family history or age at diagnosis were specified. Recently, a study of 45 high-risk African American women identified only two deleterious *BRCA1* mutations (14).

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A few studies have exclusively investigated inherited breast cancer in African American women and most have evaluated only *BRCA1* (14-18). The results from these studies indicate that founder mutations are present in the African American population and additional studies are needed to determine their prevalence. Mefford et al. (14) reported three novel *BRCA1* mutations in African Americans, with one of these mutations (943ins10) identified in two unrelated families in the series. This mutation has now been reported in other families from Washington (DC), Florida, South Carolina, Bahamas, and the Ivory Coast, suggesting that it is an ancient African founder mutation (18, 19). More recently, in a hospital-based series from Nigeria, three novel mutations in *BRCA1* were reported in 70 young African women with breast cancer screened for *BRCA1* and *BRCA2* (15). A recent clinic-based sample of 28 African American families with breast cancer identified five deleterious *BRCA1* or *BRCA2* mutations, four of which were novel (17). Hence, data from several groups support the existence of a distinct spectrum of *BRCA1* and *BRCA2* mutations in African Americans. Further study is needed to examine the contribution of these mutations to the disproportionate number of cases occurring at a young age in this population.

To further characterize the role of *BRCA1* and *BRCA2* among African American breast cancer patients, we did a hospital-based study using full gene sequencing of *BRCA1* and *BRCA2*.

Materials and Methods

Eligible subjects were identified by query of the hospital-based cancer registry at the H. Lee Moffitt Cancer Center and Research Institute for living African American women seen between 1995 and 2000 with a personal history of breast cancer and (*a*) diagnosis at age ≤45 years or (*b*) reported family history of breast/ovarian cancer. There were 58 women identified, of whom 26 could be contacted. Patients were invited to participate in the study through their treating physician. Of 26 potential participants who could be contacted, 10 (38%) individuals enrolled in the study. Participants consisted of patients who were scheduled for follow-up appointments at the Moffitt Cancer Center. Patients no longer receiving follow-up care at the Moffitt Cancer Center indicated they were unwilling to travel to the center to participate.

All study participants obtained genetic counseling and gave informed consent prior to blood drawing in accordance with the protocol approved by the institutional review board of the University of South Florida. Funding for the study covered all costs including genetic counseling and testing. During the genetic counseling appointment, family history details were obtained including current age, age at diagnosis of cancer, and site (and where possible, histologic type) of cancer in three generations. Family history information was taken as that reported by the proband, as medical record verification of cancer in family members was not possible. Studies suggest that the diagnosis of cancer reported in relatives is likely to be accurate at least for first-degree relatives (20-22).

Risk assessment models used to estimate the likelihood of a mutation for all families included BRCAPRO (23) and the updated Myriad 2002 data (13). Mutation analysis in 9 of the 10 participants was done by Myriad Genetic Laboratories according to published protocol (13). Complete sequencing of the coding regions and flanking intron/exon boundaries was done. One analysis was done by OncorMed (Gaithersburg, MD) by alternate methodology. All participants chose to be informed of their genetic test results.

Results

Family Characteristics. Family history characteristics of all 10 families are summarized in Table 1. There were four deleterious mutations identified in either *BRCA1* or *BRCA2* in the 10 study participants. Pedigrees for the four mutation-positive families are shown in Fig. 1.

Of the participants from the three families with three or more breast cancer diagnoses (i.e., families 1, 7, and 8), two participants were found to be mutation carriers. The eighth family, in which a mutation was not found, had the oldest average age at breast cancer diagnosis (60.5 years) among all the 10 families studied. None of the families reported a history of ovarian cancer.

Our analysis would not have identified large deletions, noncoding region *BRCA1* and *BRCA2* mutations,

Table 1. Summary of family characteristics

Family	*BRCA1* results	*BRCA2* results	Age of breast cancer diagnosis proband	Mean age breast cancer diagnosis family	Total breast cancers	Total ovarian cancers	Other cancers in relatives
1	VUS	Del	40	41	3*	0	
2	Neg	Del	37	36†	2†	0	PGF prostate cancer
3	Neg	Neg	41	49.5	2	0	
4	Neg	Neg	45	40	2	0	
5	VUS	VUS	34	34	1	0	F lung cancer
6	VUS	Neg	39	39	1	0	MGF throat cancer
7	Del	Neg	30	34.3	4	0	
8	Neg	Neg	62	60.5	4	0	
9	Neg	Neg	40	40	1	0	
10	Del	Neg	29	29	1	0	F leukemia

NOTE: VUS, variants of uncertain significance; F, father; PGF, paternal grandfather; MGF, maternal grandfather.
*Includes bilateral breast cancer in the proband.
†Does not include the diagnosis of breast cancer in the proband's maternal grandmother, because the mutation was determined to be paternally inherited.

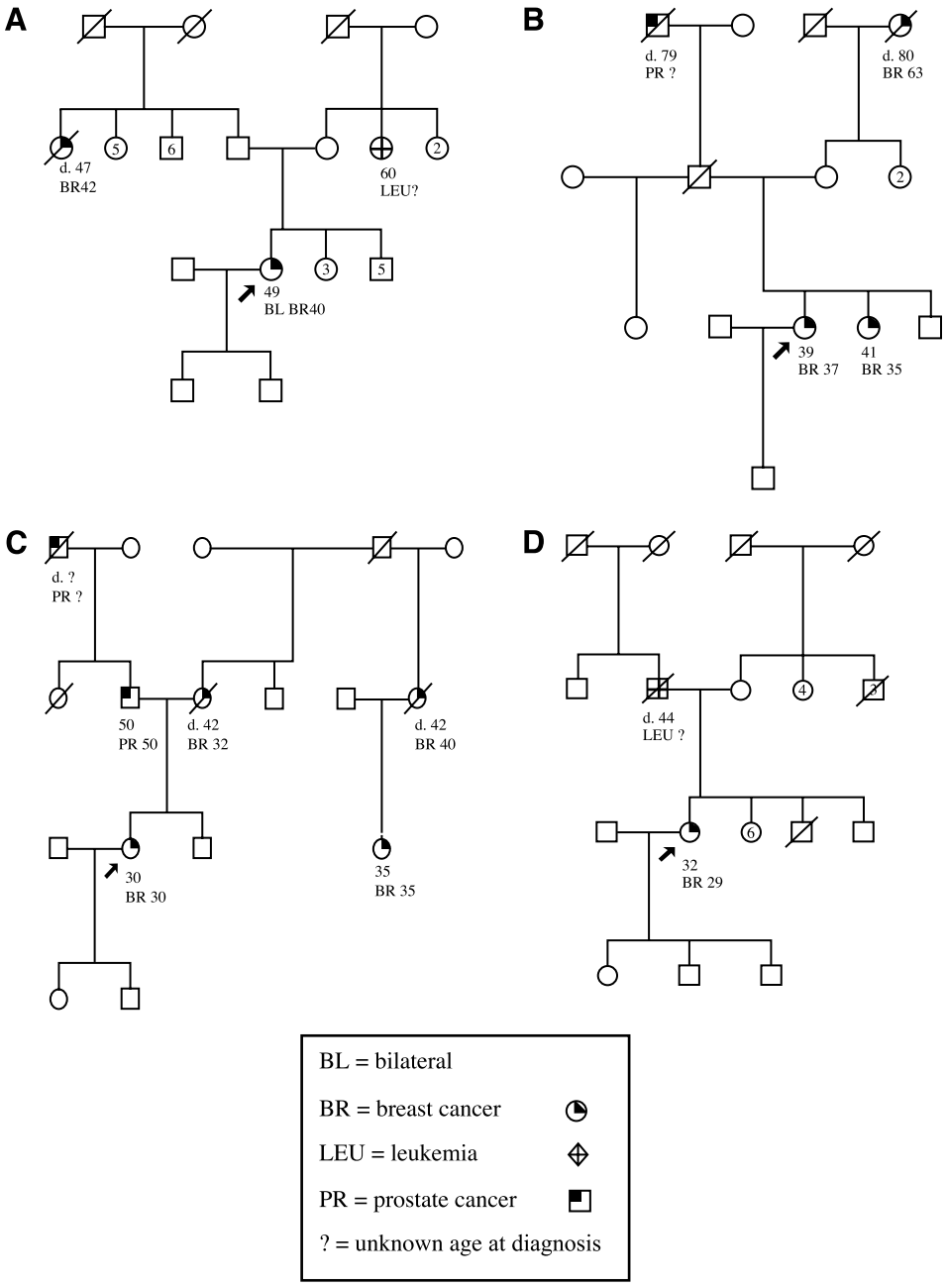

Figure 1. Pedigrees for *BRCA1/BRCA2* mutation-positive families: (**A**) family 1; (**B**) family 2; (**C**) family 7; and (**D**) family 10.

or other unidentified genes that may explain early age at diagnosis or familial clustering of breast cancer in the remaining families.

Risk Assessment. Risk assessment using BRCAPRO (23) and Myriad Genetic Laboratories empirical data (13) was done for each family (Table 2).

Estimates from the BRCAPRO model reflected mean mutation carrier risks in carriers and noncarriers of 32.5% and 3.6%, respectively. The Myriad 2002 model indicated mean mutation carrier risks in carriers and noncarriers of 18.75% and 7.03%, respectively.

DNA Testing Results. Results of the DNA analysis showed that 4 of the 10 participants were mutation carriers, of whom 2 carried *BRCA1* mutations and 2 carried *BRCA2* mutations (Table 3).

Two of the deleterious mutations that were identified in study participants were novel at that time and include two *BRCA2* frameshift mutations. The novel *BRCA2* mutation 5844del5 occurs within the ovarian cancer cluster region (24). Of mention, there is no known history of ovarian cancer in this family. The novel *BRCA2* mutation 9017delA is a frameshift mutation and

Table 2. Risk assessment models in prediction of mutation status

Family	Results		Mutation model/likelihood	
	BRCA1 deleterious mutation	*BRCA2* deleterious mutation	BRCAPRO (%)	Myriad 2002 (%)
1	—	9017delA	12.3	17.8
2	—	5844del5	22.80	17.8
3	—	—	1.53	7.8
4	—	—	15.50	7.8
5	—	—	0.90	7.8
6	—	—	1.10	7.8
7	IVS13-1G>A	—	92.60	31.6
8	—	—	0.80	3.2
9	—	—	1.70	7.8
10	943ins10	—	2.53	7.8

results in premature truncation of the *BRCA2* protein at amino acid position 2,936. The previously described *BRCA1* mutation 943ins10 (14, 18, 19, 25), the west African founder mutation, was seen in one family. The *BRCA1* IVS13+1G>A splice-site mutation was seen in one of the families. This mutation consists of a nucleotide substitution in a noncoding intervening sequence occurring adjacent to the end of exon 13. It has been seen previously in 10 families, 6 of whom indicated African American ancestry and 4 of whom indicated European ancestry.[4]

In addition, four variants of uncertain significance were identified (Table 3) in a total of three patients. The variants reported in our study have all been seen previously by Myriad Genetic Laboratories; however, their pathogenicity remains to be determined.

Tumor Histology. The histology reports for all mutation carriers were reviewed. The two *BRCA1* carriers had estrogen receptor– and progesterone receptor–negative tumors and the two *BRCA2* carriers had estrogen receptor– and progesterone receptor–positive tumors.

Discussion

The family characteristics of African American *BRCA1* and *BRCA2* mutation carriers seem to be similar to that seen in Caucasian mutation carriers (26-28), with the presence of breast cancer at age <40 years being a strong predictor of mutation-positive families. Conversely older age of breast cancer diagnosis is a strong predictor of mutation-negative families (26, 27, 29).

Studies in Caucasians show that *BRCA1* mutations contribute to more cases of early-onset breast cancer than do *BRCA2* mutations (30), with the average age of breast cancer in *BRCA1* and *BRCA2* carriers being 40 and 45 years, respectively (31). In our study, the average age of breast cancer diagnosis in *BRCA1* and *BRCA2* carriers was 33 and 39 years, respectively, suggesting a similar trend; however, our numbers are too small to draw firm conclusions.

Based on recent studies, the BRCAPRO risk assessment model has been verified as an adequate predictor of *BRCA1/BRCA2* mutation carrier status in Caucasians (32, 33). This model adequately predicted mutation carrier status of African American women in our study. Because the Myriad ''model'' is based on empirical data (primarily in Caucasians), it is likely to be an adequate predictor of mutation carrier status, which was also seen in this study. Hence, our data suggest that the same risk assessment models may be useful in prediction of carrier status of African Americans and Caucasians.

The spectrum of mutations seen in African Americans seems to be distinct from that seen in Caucasians (14-18, 34). Of the four deleterious mutations identified through our study, two mutations were novel. One mutation was the African American founder mutation, *BRCA1* 943ins10 (14, 18, 19). The fourth mutation (IVS13+1G>A) is a recurrent mutation and a candidate for being a second African American founder mutation.

Founder mutations, rather than mutation hotspots, are seen in certain ethnic subpopulations and are responsible for the increased frequencies of some mutations. Such founder mutations have been described in families from ethnic groups that were geographically or culturally isolated including Ashkenazi Jews (35), Icelandics (36), French Canadians (37), and Filipinos (38) as well as several other population groups. The benefits of identifying founder mutations in population groups include the ability to target testing to the founder mutations, allowing for a more rapid and inexpensive test. Among individuals of African ancestry, only one founder mutation (*BRCA1* 943ins10) has been identified previously and confirmed through haplotype analysis (14, 18, 19), which is necessary to establish founder mutations. The family in our study with this mutation reported west African ancestry, which is consistent with previously reported families with this mutation.

Table 3. Summary of BRCA1 and BRCA2 mutations and variants

	Family no.	Gene	Designation	Effect
Mutations	1	*BRCA2*	9017delA	Frameshift
	2	*BRCA2*	5844del5	Frameshift
	7	*BRCA1*	IVS13-1G>A	Splice site
	10	*BRCA1*	943ins10	Frameshift
Variants	1	*BRCA1*	I379M	Missense
	5	*BRCA1*	I379M	Missense
		BRCA2	I2944F	Missense
	6	*BRCA1*	R842W	Missense

[4] Myriad Genetic Laboratories, unpublished data.

One patient in our study had the *BRCA1* IVS13+1G>A splice-site mutation, a recurrent mutation seen 10 times previously, according to Myriad Genetic Laboratories[5] (although only six of these mutations have been reported in the Breast Cancer Information Core database; ref. 25); 6 of the 10 patients reported African Americans ethnicity. This mutation may represent a second African American founder mutation; however, haplotype analysis is required for confirmation.

The unclassified variants reported in our study have all been seen previously by Myriad Genetic Laboratories; however, their pathogenicity remains to be determined. The difficulties in interpreting unclassified variants, magnified in minority groups by the lack of clinical data, will likely continue until further study of these groups is accomplished. This highlights the need for development of functional assays for *BRCA1* and *BRCA2*.

Previous studies in Caucasians have indicated that breast cancer tends to be estrogen and progesterone receptor negative in *BRCA1* carriers and tends to be estrogen and progesterone receptor positive in *BRCA2* carriers (39, 40), which was consistent with that seen in our African American study population. We hypothesize that if tumor characteristics in African American and Caucasian *BRCA1/BRCA2* carriers are similar, this highlights the predominant role of *BRCA1/BRCA2* in hereditary tumorigenesis and suggests that other factors, which vary by race, may have a lesser role.

The limitations of this study included a small sample size, despite attempts to enhance recruitment. The patients were approached through an African American study coordinator and were offered genetic counseling and full *BRCA1/BRCA2* gene sequencing at no cost. Patients declined participation unless they were already planning a trip to the Moffitt Cancer Center for follow-up. Interest in study participation for African Americans has generally been reported as low (41), which was also seen in our study. Potential participants were identified through the Moffitt Cancer Registry, which records family history data reported by the proband. Another limitation of the study was that there was no verification of family history information, which was attempted through the cancer registry at the Moffitt Cancer Center.

Information about the role of the *BRCA1* and *BRCA2* genes in hereditary susceptibility to breast and ovarian cancer in African American families is limited. Data from this study add to the limited information available about (*a*) incidence and types of mutations, furthering the knowledge about founder mutations, and (*b*) family history factors and tumor characteristics among African Americans at risk for inherited breast and ovarian cancer susceptibility.

It is of interest that although the study was relatively small and only four mutations were identified, one of the mutations is a previously identified founder mutation and another one is a recurrent mutation and a candidate for a second founder mutation. Targeted efforts to define the spectrum and penetrance of *BRCA1* and *BRCA2* mutations in this ethnic group are warranted. We and others are continuing such efforts that will lead to more accurate risk assessment and more effective cancer control initiatives among African American women at high risk for breast and ovarian cancer.

[5] Unpublished data.

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