

Prevalence of *BRCA* Mutations and Founder Effect in High-Risk Hispanic Families

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Abstract

Approximately 12% of the U.S. population is Hispanic, with the majority residing in urban centers such as Los Angeles. The prevalence of *BRCA* mutations among high-risk Hispanic families is unknown.

Methods: One hundred and ten unrelated probands of Hispanic origin, with a personal or family history of breast and/or ovarian cancer, presented for genetic cancer risk assessment, were enrolled in an Institutional Review Board–approved registry and underwent *BRCA* testing. Haplotype analyses were done if *BRCA* mutations were observed in two or more unrelated probands.

Results: Mean age at diagnosis was 37 years (range = 23–59) for the 89 (81%) probands with invasive breast cancer. Overall, 34 (30.9%) had deleterious mutations (25 in *BRCA1*, 9 in *BRCA2*), 25 (22.7%) had one or more unclassified variants, and 51 (46.4%) had negative results. The mean pretest mutation probability using the Couch model, Myriad model, and BRCAPro was 19.6% (range = 4–77%). The combined average mutation probability was

32.8% for carriers, 15.5% for noncarriers, and 12.9% for variant carriers ($P < 0.0001$). The most common deleterious mutation was 185delAG (4 of 34, 11.8%). The Hispanic 185delAG carrier families share the same haplotype from D17s1320 through *BRCA1*, as do two reference Ashkenazi Jewish families. Haplotype analyses of additional recurrent *BRCA1* mutations [IVS5+1G>A ($n = 2$), S955X ($n = 3$), R1443X ($n = 3$), and 2552delC ($n = 2$)] also suggest founder effects, with four of six mutations seen almost exclusively in families with Latin American/Caribbean or Spanish ancestry.

Conclusion: This is the largest study to date of high-risk Hispanic families in the United States. Six recurrent mutations accounted for 47% (16 of 34) of the deleterious mutations in this cohort. The *BRCA1*185delAG mutation was prevalent (3.6%) in this clinic-based cohort of predominantly Mexican descent, and shared the Ashkenazi Jewish founder haplotype. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1666–71)

Introduction

Breast cancer is the most commonly diagnosed cancer in Hispanic women, and is the leading cancer cause of death, exceeding even lung cancer. Approximately 12% of the U.S. population is Hispanic,⁵ with rates expected to increase to 25% by 2050 (U.S. Census Data 2000). Whereas only 5% to 10% of breast and ovarian cancers are associated with mutations in *BRCA1* or *BRCA2*, there are thousands of prevalent cancer cases attributable to genetic predisposition. The magnitude of risk in hereditary cancer families is large. The lifetime risk of developing breast cancer associated with a *BRCA* mutation may be as high as 85% and the lifetime risk of ovarian cancer may be up to 44% (1). Genetic susceptibility to breast cancer has been observed in most races and ethnicities (2–8).

Genetic cancer risk assessment is an emerging interdisciplinary subspecialty and genetic testing for inherited breast cancer susceptibility has become a state-of-the-art standard of care option for appropriately selected patients (9–11). Features such as early-onset breast cancer (under the age of 40 years), bilateral disease, or family history of breast and/or ovarian cancer are suggestive of genetic predisposition (9).

The Hispanic population is not evenly distributed across the United States and consists of a range of individuals from different countries of origin (12). Whereas current trends in the movement of the Hispanic population include extension into more rural areas of the South and Midwest, the vast majority of the population is concentrated in traditional urban centers—almost 7 of every 10 Hispanics live in California, Texas, New York, New Jersey, or Florida (U.S. Census Bureau, 2000 Redistricting Data).

The prevalence of *BRCA* mutations among high-risk Hispanic families in major metropolitan areas is unknown. The purpose of this study was to determine the prevalence of *BRCA* mutations among Hispanic families attending a high-risk clinic in Southern California.

Materials and Methods

Subjects. The City of Hope's Cancer Screening & Prevention Program Network includes cancer center and community-based high-risk clinics that provide genetic cancer risk assessment to individuals with a personal or family history of cancer. All patients presenting for genetic cancer risk assessment were invited to participate in an Institutional Review Board–approved prospective Hereditary Cancer Registry at the time of their initial cancer risk assessment consultation. Ninety-eight percent of candidates chose to

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⁵Although we use "Hispanic," the most common census term for individuals of Spanish, Mexican, Central and South American, Cuban, or Puerto Rican descent, referring to "race," is "Latino." Latino is generally considered a more ethnically/culturally based term for individuals of the aforementioned groups.

participate in the registry. Between October 1998 and October 2004, 110 unrelated probands of Hispanic origin were seen through the Cancer Screening & Prevention Program Network, enrolled in the registry, and underwent *BRCA* testing. Participants with Hispanic ancestry only on one parental side were eligible if that side was significant for a history of breast or ovarian cancer.

Genetic cancer risk assessment was carried out in a uniform fashion in every case. In cases where the proband was Spanish speaking, a bilingual counselor fluent in Spanish conducted the counseling session. Demographic data and three- to five-generation pedigrees were obtained, focused on cancer history, and included family report of ethnicity and country of origin for each parental lineage. Probabilities of carrying a mutation in the *BRCA1* or *BRCA2* genes were estimated using the Couch model, the Myriad model, and BRCAPRO (13-15). These models rely on statistical analysis of testing experience, family patterns of cancer, and/or population mutation prevalence data to estimate an individual's probability of carrying a mutation and are used to select appropriate candidates for genetic testing. The Couch model estimate, which calculates the probability of a *BRCA1* mutation, was modified by factor of 1.3 to account for *BRCA2* (16).

Genetic testing was offered in cases with medical necessity and a calculated *BRCA* mutation probability $\geq 5\%$ by any model. All genetic testing was done at Myriad Genetic Laboratories, Inc. (MGL), according to their standard commercially available techniques, generally including full sequencing of exons and flanking intronic segments (14) and including five specific *BRCA1* rearrangements (exon 13 del 3.835 kb, exon 13 ins 6 kb, exon 22 del 510 bp, exon 8 to 9 del 7.1 kb, and exon 14-20 del 26 kb) for assays done after 2001. Results of genetic testing were disclosed and interpreted in person at a follow-up visit and risk management advice was provided.

Genotype Analysis. Genotype analyses were done if the same mutation in *BRCA1* was observed in two or more unrelated families. The approach generally followed that of Neuhausen et al. (17, 18). Genomic DNA was isolated from peripheral blood leukocytes using the FlexiGene kit (Qiagen, Valencia, CA). DNA samples from 11 individuals in 4 families with the *BRCA1* 185delAG mutation were genotyped. Two

families of Ashkenazi Jewish descent with the 185delAG mutation were genotyped for reference. Thirty-one individuals in 10 families with four recurrent *BRCA1* mutations IVS5+1G>A ($n = 2$), S955X ($n = 3$), R1443X ($n = 3$), 2552delC ($n = 2$) were genotyped at seven short tandem repeat markers in or adjacent to *BRCA1*. Standard PCR protocols were used. Primer sequences for *BRCA1* (D17S1320, D17S1321, D17S1322, D17S1323, D17S1327, and D17S1325) microsatellite markers were obtained from the genome database. For map pair D17S855 (*BRCA1*), novel primers were designed (F: 5'-TGC-CATTTCTTTTCTACTCTGG/R: 5'-GCAAATAAAGTGGGTAT-CACTTAAAA) to facilitate multiplex analysis of samples. All synthesis and labeling of primers with fluorescein derivatives (5'-6-FAM, 5'-TET, or 5'-HEX) were provided by Integrated DNA Technologies (Coralville, IA). PCR amplification of 50 ng of genomic DNA in $1\times$ reaction buffer, with 200 $\mu\text{mol/L}$ deoxynucleotide triphosphates, 0.4 $\mu\text{mol/L}$ primers, 1.5 mmol/L MgCl_2 , and 0.625 units of Taq DNA Polymerase (Qiagen) was used to amplify microsatellite markers (D17S855, D17S1320, D17S1323, D17S1325, and D17S1327) according to standard cycling protocols. Efficient amplification of D17S1321 and D17S1322 was dependent on the use of the hot start polymerase AmpliTaq Gold (Applied Biosystems, Foster City, CA). Amplification was done using 50 ng of genomic DNA in $1\times$ reaction buffer, with 200 $\mu\text{mol/L}$ deoxynucleotide triphosphates, 0.3 $\mu\text{mol/L}$ primers, 1.5 to 3.5 mmol/L MgCl_2 , and 1.25 units of AmpliTaq Gold under a modified cycling program (95°C 10 minutes, 35 cycles of 94°C 30 seconds, 59°C or 62°C 45 seconds, 72°C 30 seconds, followed by 72°C 60 minutes). Following amplification, all PCR products were size separated on a 36 cm Long Ranger Gel (Cambrex Bio Sciences, Walkersville, MD) and ran on a 377XL ABI Prism automated DNA sequencer (Applied Biosystems). TAMRA-labeled GeneScan 500 (Applied Biosystems) was used as a size standard in each lane. Gel file and molecular weight standard calibration were done using GeneScan (version 3.1) software (Applied Biosystems). Product size determination was assessed with Genotyper (version 2.1) software (Applied Biosystems).

Data Analysis. Statistical analyses were conducted using the SAS System, version 8.02, developed by the SAS Institute,

Table 1. Proband demographic characteristics and cancer history by *BRCA* genetic mutation status

Variable	<i>BRCA</i> mutation status			P
	Carriers	Noncarriers		
	Positive	Negative	Variant	
<i>n</i> (%)	34 (30.9)	51 (46.4)	25 (22.7)	
Gender				
Female	33	51	25	
Male	1	0	0	
Cancer status				
Unaffected (%)	3 (8.8)	4 (7.8)	5 (20.0)	
Affected with BC and/or OC* (%)	31 (91.2)	47 (92.2)	20 (80.0)	0.29
BC (%)	24 (70.6)	45 (88.2)	20 (80.0)	
OC* (%)	5 (14.7)	2 (3.9)	0 (0.0)	
BC and OC* (%)	2 (0.6)	0 (0.0)	0 (0.0)	
Average age at first cancer diagnosis \pm SD	40.5 \pm 10.7	36.4 \pm 7.3	37.0 \pm 6.4	0.10
Combined average predictive model probability \pm SD [†]	32.8 \pm 20.7	15.5 \pm 12.6	12.9 \pm 9.0	<0.0001
Overall probability = 19.6% (4-77%)				
Parental country (or countries) of origin of probands [‡]				
No. Mexican (%)	18 (52.9)	33 (64.7)	15 (60.0)	
No. Central American/Caribbean (%)	7 (20.6)	6 (11.8)	4 (16.0)	
No. South American (%)	1 (2.7)	3 (5.9)	0 (0.0)	
No. Spanish (%)	1 (2.7)	1 (2.0)	0 (0.0)	
No. mixed (%)	7 (20.6)	8 (15.7)	6 (24.0)	

Abbreviations: BC, breast cancer; OC, ovarian cancer.

*Includes fallopian tube and primary peritoneal cancer.

[†]Includes Myriad, Couch, and BRCAPRO Predictive *BRCA* probability models.

[‡]Applies to both parental lineages, except those with mixed ancestry indicated in the last category.

Table 2. Cases with deleterious BRCA mutations

Gene	Variant	Current study		BIC database	
		No. observations	Apparent country of origin	No. observations*	No. with Hispanic ancestry
<i>BRCA1</i>	IVS5+1G>A	2	Guatemala	3	2
	185delAG	4	Mexico/Spain	>500	30
	K654X	1	Mexico	2	2
	943ins10	1	Mexico	10	2
	S955X	3	Mexico/Spain	4	4
	1135insA	1	Cuba	28	2
	Q1200X	1	Mexico	12	1
	1205del56	1	Mexico	3	3
	R1443X	3	Mexico/Peru	80	5
	A1708E	1	El Salvador	23	12
	C1787S & G1788D	1	Mexico	2	2
	2415delAG	1	Mexico	1	1
	2525del4	1	Mexico	1	1
	2552delC	2	Mexico	8	8
	2925del4	1	Mexico	2	2
	5382insC	1	Mexico/Eastern European	>500	5
	<i>BRCA2</i>	Q742X	1	Mexico	2
957del4		1	Mexico	1	1
W2586X		1	Mexico	4	1
3417del4		1	Columbia	1	1
3492insT		2	Mexico	13	13
5164del4		1	Guatemala	7	1
8550insT		1	El Salvador	1	1
9254del5		1	El Salvador	6	4

NOTE: Recurrent variants bolded.

*Only those with ancestry data were included; cases from the current series that were not present in the BIC database as of November 2, 2004, were added to the totals.

Inc. (copyright 1999–2001 by SAS Institute, Cary, NC). Data were summarized using descriptive statistics, including means and SDs for continuous data or proportions for categorical data. All *P* values are two-sided with $\chi^2 = 0.05$. Univariate methods were done using the Pearson’s χ^2 test statistic for categorical data and the Student’s *t* test statistic for continuous data. A Fisher’s exact test statistic was used when categorical data had an average cell count of <5.

Each proband’s *BRCA* test result was characterized as one of the following: carrier (having a deleterious mutation), noncarrier (having no detectable mutation), or variant carrier (having an unclassified variant). Individuals with unclassified variants reported by MGL as “suspected deleterious” were categorized as carriers.

The Breast Cancer Information Core (BIC) database was searched for additional observations of the *BRCA* mutations found in our cohort and complete entries with information on ethnicity entered as of November 2004 were included in our tabulation. MGL patient accession numbers were compared with those in the BIC database to account for our BIC entries. In addition, a literature search using PubMed and Ovid databases was conducted to determine if the mutations detected in our cohort were also identified in other published studies with a focus on Hispanic cohorts.

Analysis of haplotyping results was carried out according to published criteria (17, 18). Where possible, haplotypes associated with each mutation were inferred from multiple samples of related individuals within each kindred known to have the same mutation.

Results

Demographics and Cancer History. The ancestries of both parents were the same for most probands and were distributed as follows: Mexico (*n* = 66, 60.0%), Central America (*n* = 17, 15.5%), South America (*n* = 4, 3.6%), and Spain (*n* = 2, 1.8%). Twenty-one (19.0%) probands had parents from a combination of regions, including those of non-Latino ancestry (Table 1).

The majority of the probands were female (99.1%) and had a history of invasive cancer (89.0%); 89 (90.8%) had breast cancer only, 7 (7.1%) had ovarian cancer only (including fallopian and/or peritoneal cancer), and 2 (2.0%) were affected by both breast cancer and ovarian cancers (Table 1). The average age at cancer diagnosis was 37.8 (SD = 8.4). Six probands had a history of ductal carcinoma *in situ*, and six were unaffected.

BRCA Mutation Prior Probability. The overall mean pretest *BRCA* mutation probability for all three models combined was 19.6% (range 4-77%; Table 1). The mean pretest mutation probability using the Myriad model was 22.6% for carriers, 12.5% for noncarriers, and 11.4% for variant carriers (*P* < 0.0001; data not shown). The mean mutation probability using the BRCAPro model was 43.7% for carriers versus 14.3% and 9.7% for noncarriers or variant carriers, respectively (*P* < 0.0001). The mean Couch model mutation probability for the 106 relevant probands was 28.6% for carriers, 19.0% for noncarriers carriers, and 17.6% for variant carriers (*P* = 0.03). Because the Couch model only applies to those probands with a personal or family history of breast cancer, the four probands with only a history of ovarian cancer were not included in the analysis. The combined average mutation risk across all three models using the 106 probands for whom all three models applied was 32.8% for carriers, 15.5% for noncarriers, and 12.9% for variant carriers (*P* < 0.0001; Table 1).

BRCA Testing Outcomes. Overall, 34 (30.9%) had deleterious mutations (25 in *BRCA1*, 9 in *BRCA2*), 25 (22.7%) had one or more unclassified variants, and 51 (46.4%) had negative results (Table 1). A personal history of ovarian cancer was highly predictive of a *BRCA* mutation. Probands with a history of ovarian cancer, either alone or in addition to breast cancer, were significantly more likely to have a detectable *BRCA* mutation (77.8%; Fisher’s exact *P* = 0.004; data not shown). A total of 24 unique deleterious *BRCA* mutations were detected in this cohort, 16 in *BRCA1* and 8 in *BRCA2* (Table 2). Six recurrent *BRCA* mutations were observed, *BRCA1* 185delAG (*n* = 4), 2552delC (*n* = 2),

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IVS5+1G>A ($n = 2$), R1443X ($n = 3$), S955X ($n = 3$) and *BRCA2* 3492insT ($n = 2$). Seventeen unclassified variants were detected; 6 in *BRCA1* and 11 in *BRCA2* (Table 3). *BRCA1* IVS13-10C>T has been classified by MGL as a possible polymorphism, and the *BRCA2* I2490T variant, detected in 19 of the probands in our series, was recently reclassified by MGL as a polymorphism. The overall rate of unclassified variants was 23% (25 of 110), which is higher than the prevalence of variants in the Caucasian population (14), but similar to other ethnic populations where there is less accumulated data on *BRCA* genotypes.

Nineteen of the 24 mutations detected in this cohort had been reported at least once in the BIC database (Table 2). Five of the mutations were single unique observations and have not been reported previously in the BIC database. Of the 18 mutations that were observed only once in this cohort, 11 seem to be of Hispanic origin according to BIC observations (*BRCA1* K654X, 1205del56, C1787S & G1788D, 2415delAG, 2525del4, 2925del4; *BRCA2* Q742X, 957del4, 3417del4, 8550insT, 9254del5). Three of the six recurrent mutations, 2552delC and S955X (*BRCA1*), and 3492insT (*BRCA2*), have been seen exclusively in those of Hispanic ancestry. *BRCA1* IVS5+1G>A has been seen predominantly in individuals of Hispanic ancestry; there was one observation of the mutation in a family of Asian and Indian descent.

Six of the deleterious mutations found in this cohort (*BRCA1* IVS5+1G>A, 185delAG, 1135insA, A1708E; *BRCA2* 3492insT, 9254del5) have been reported in the literature in families of Hispanic ancestry (6, 19-25). We were unable to verify that those reported in the literature were also reported in the BIC database due to inaccessibility of BIC accession numbers for cases identified at other institutions.

Genotype Analysis. Haplotypes of two Ashkenazi Jewish families with the *BRCA1* 185delAG mutation were included to determine whether the mutation occurred on the same haplotype in the Hispanic families. All the families seem to share the same haplotype (genotype) at five markers from D17s1320 through *BRCA1* (data not shown). One individual genotyped in a Hispanic family does not share the same allele at D17s1327, suggesting a possible recombination event or mutation of the short tandem repeat allele size. The shared allele at D17s1327 (206 bp) is rare (frequency 0.03), was shared by all the Hispanic 185delAG carriers, and seemed to be specific to Ashkenazi Jews in an earlier study (17).

Haplotype analyses of four recurrent *BRCA1* mutations, IVS5+1G>A ($n = 2$), S955X ($n = 3$), R1443X ($n = 3$), and 2552delC ($n = 2$), also suggest founder effects (data not shown). The two families found to carry *BRCA1* IVS5+1G>A share the same haplotype at six of seven markers. Marker D17s1327 could not be definitively assigned to the founder *BRCA1* IVS5+1G>A haplotype for one of the two families; however, the founder bp allele is present. One of the three families with the *BRCA1* S955X mutation allowed for the assignment of the deleterious haplotype associated with the mutation. All three families with this mutation seem to share the same haplotype. Two of the three families that carry the *BRCA1* R1443X mutation share the same haplotype, whereas the third family shares only two of the seven markers. Both families in which *BRCA1* 2552delC was detected share the same haplotype at all markers.

Genotype analysis of *BRCA2* 3492insT, detected in two unrelated families in this cohort, was done. However, a definitive haplotype for this deleterious mutation could not be assigned for one of the families due to too few individuals for assigning haplotypes (data not shown). Additional families with this mutation are needed to obtain sufficient information to compare across families.

Table 3. Unclassified variants detected and reported ancestry

Gene	Variant	n^*	No. observations	Predominant ancestry
<i>BRCA1</i>	IVS6+8T>C	1	3	African
	IVS13-10C>T	2	2-10	Western European
	S186Y	1	11-25	African
	Q284R	1	1	Latin American/ Caribbean
	L1564P	1	13	African
<i>BRCA2</i>	D1578G	1	1	Latin American/ Caribbean
	P168T	1	11	Latin American/ Caribbean
	S384F	1	127	Western European
	W395G	1	1	Latin American/ Caribbean
	S976I	1	28	African
	G1529R	1	66	Western European
	N1880K	1	40	African
	H2116R	1	>50	African
	I2490T [†]	19	>300	Latin American/ Caribbean
	G2793R	1	2	Latin American/ Caribbean
	D2611G	1	1	Latin American/ Caribbean
	K2950N	1	83	Western European

*Three individuals were found to have >1 unclassified variant.

[†]Reclassified as a polymorphism by MGL on November 2004.

Discussion

Although several *BRCA* mutations have been reported in small cohort studies of individuals of Spanish or Chilean descent, to our knowledge this is the largest published study of the prevalence of *BRCA* mutations in a largely immigrant Hispanic population residing in an urban center in the United States. The prevalence of detectable *BRCA* mutations among this high-risk immigrant Hispanic population was somewhat higher than the model-based predicted probabilities (observed 30.9% versus expected 19.6%). Due to the limited size of this cohort, a formal analysis of the performance of each predictive model was not possible. Our data suggests that caution should be used when applying predictive models absent validation in specific ethnic cohorts.

Interestingly, *BRCA1* 185delAG, a founder mutation seen in ~1% of individuals of Ashkenazi Jewish ancestry (26), was observed in 3.6% (4 of 110) of families and represented 11.7% (4 of 34) of *BRCA* mutations identified in this cohort. The 185delAG mutation in our cohort seems to arise on the same haplotype as a reference Ashkenazi Jewish population. Previous genotype analysis led to postulation that the 185delAG mutation may have arisen in the Ashkenazi (Eastern European) subpopulation of Jews in ~1200 C.E. (17). Identification of the 185delAG mutation among non-Ashkenazi Jewish families of Egyptian, Moroccan, Iraqi, and Turkish ancestry on the same allelic pattern suggested that this mutation may actually have arisen earlier in Jewish history—likely before the last major dispersion of the Jews from ancient Israel into the Diaspora after destruction of the second temple in ~70 C.E. (27-29).

None of the four unrelated Hispanic probands in our cohort who carry the 185delAG mutation have any knowledge of Jewish ancestry. This finding, along with identification of the 185delAG mutation among several apparently non-Jewish families in Spain (8, 20, 21, 30, 31), in a high-risk Mexican cohort (32) and in one Chilean family (5), as well as data from a founder cohort (established ~1598) in the rural San Luis Valley in Colorado (33), provide further biological evidence that the 185delAG mutation may have arisen before the

widespread geographic and cultural separation of the Jews in the early Common Era that gave rise to the development of distinct Ashkenazi, Asian, North African, and Sephardic (Iberian) Jewish subpopulations. Moreover, the unexpected finding of 185delAG among Hispanic non-Jews exquisitely correlates with the history of the Jews of Spain (Sephardim) in particular.

The first documented migration of Jews to Spain dates back to the 6th century B.C.E., where the Jewish population and culture grew until the first massive forced conversion of thousands of Spanish Jews to Christianity occurred under Christian Visigoth rule in the 7th century C.E. Spanish Judaism again flourished under Muslim rule during the 10th and 11th centuries. By the early 12th century, Spain had become the center of Jewish thought and culture and home of up to 90% of the world's Jewish population (34, 35). Beginning in the mid-12th century, progressive religious and cultural restrictions for Spanish Jews and Muslims occurred with the Christian *reconquista*, which culminated in the final expulsion of all nonconverted Jews from Spain in the spring of 1492 under Ferdinand and Isabella (36, 37). It is not known how many of the ~160,000 Jews expelled during the Spanish Inquisition emigrated to the Americas, because many *conversos* (New Christians—Jews converted to Christianity) and *crypto*-Jews (*conversos* who secretly practiced Judaism) had to obscure their identities to emigrate to the New World. The 185delAG families identified among the Spanish cohorts described above (8, 20, 21, 30, 31) are likely descendants of the estimated 150,000 *conversos* who remained in Spain through the Inquisition and assimilated into the non-Jewish population, whereas the carriers reported in our Hispanic-American cohort, as well as those identified in Mexico, Chile, and the San Luis Valley of Colorado, are likely descendants of *conversos* or *crypto*-Jews who emigrated to the Americas in the late 15th century and over generations assimilated into the larger Hispanic society.

Of note, one 185delAG proband from our cohort recalls partial Eastern European ancestry in a maternal grandfather, suggesting that this family may have descended from one of the thousands of Ashkenazi Jews who fled from Russia during the pogroms of the late 19th century, or from Europe to South and Central America in the 1930s to escape the Holocaust.

The *BRCA1* 5382insC Eastern European founder mutation, commonly seen among Ashkenazim, was detected in one proband (38). In this family, maternal lineage was of Mexican descent, paternal lineage was of Northern European descent, and both lineages were significant for early onset breast cancer. The maternal lineage was also significant for ovarian cancer. The patient had no knowledge of Ashkenazi Jewish ancestry before genetic testing and no informative family members have been tested yet to determine the lineage of origin of the mutation.

Four of the six recurrent *BRCA* mutations identified in this cohort seem to have Latin American/Caribbean origins. According to data from the BIC database, *BRCA1* 2552delC and S955X have been seen exclusively in individuals of Latin American/Caribbean descent (eight and four observations, respectively). Both 2552delC families in our cohort were of Mexican descent, whereas two of the three families with mutation S955X were of Mexican descent and one was of Mexican and Spanish ancestry. *BRCA2* 3492insT is also seen primarily among those of Latin American/Caribbean descent and not surprisingly, has also been seen in those of Spanish ancestry; both families in this study with this mutation were from Mexico. The *BRCA1* IVS5+1G>A mutation has been observed in three families in the BIC database, two of which were of Latin American ancestry. *BRCA1* IVS5+1G>A and *BRCA2* 3492insT have been previously reported in the literature in families of Spanish ancestry (6, 25).

BRCA1 R1443X, identified in three individuals in this cohort, has been previously reported in those of French Canadian ancestry and is speculated to be a founder mutation of European origin (39). Of the 80 observations in the BIC database, only five were of Latin American/Caribbean ancestry, whereas the majority was of French Canadian and Western European ancestry.

The six recurrent *BRCA* mutations (above) accounted for 47% (16 of 34) of the deleterious mutations identified in our Hispanic cohort. In addition, 5 of the 18 mutations seen only once in our cohort were reported in other Hispanic families in the BIC database. This suggests the possibility that a multiplex assay for these 11 *BRCA* mutations could be a cost-effective approach to initial screening of Hispanic populations, and would have detected 62% (21 of 34) of the mutations. Ultimately, this would have decreased the number of cases requiring complete sequencing by 19% in this Southern California Hispanic cohort.

In Los Angeles County, 45% of the population reports Hispanic ethnicity and, of those, 72% are of Mexican descent with the next largest of Central American descent (8.8%), primarily from El Salvador (4.4%) and Guatemala (2.3%). Consequently, our findings may not be generalizable to Hispanic population centers on the East Coast because only 10% of the Hispanic population in New York identify Mexico as their country of origin, whereas 33% identify Puerto Rico and 31% the Dominican Republic. New Jersey reflects a similar breakdown in their population, but with 21% of Latinos identifying a South American country as their country of origin. Whereas 41% of the Florida Latinos identify Cuba as their country of origin, 17% identify Mexico, 18% Puerto Rico, and 13% a South American country (40).

Nonetheless, the findings from this study add to the body of knowledge about *BRCA* mutation prevalence and nature in the rapidly growing U.S. Hispanic population, and may inform strategies for genetic cancer risk assessment.

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