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LETTER

BRCA mutations in Italian breast/ovarian cancer families

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Baudi *et al*.[1] described the first example of a founder *BRCA1* (MIM 113705) mutation specific to the Italian population. They studied 24 patients from unrelated breast/ovarian cancer families from the southern region of Calabria and found the 5083del19 mutation to be present four times. This single mutation accounted for four of the six *BRCA1* mutations detected in the study. Haplotype analysis confirms the 5083del19 mutation to be a founder mutation. Here we present data on Italian breast/ovarian cancer families in North America, and ask whether or not this mutation is observed in these families.

Founder mutations in *BRCA1* and *BRCA2* (MIM 600185) have been described in several Western European countries, but, to date, no population has demonstrated founder effects as striking as those observed for Icelandic and the Ashkenazi Jewish groups.[2–4] Table 1 summarises the different *BRCA1* or *BRCA2* mutations that have been reported in more than one family from various studies and regions of Italy. To date, only the *BRCA1* 5083del19 mutation is recurrent and specific to individuals of Italian descent; most mutations are also found in other European countries.

At the Sunnybrook & Women's College Health Sciences Centre in Toronto, Canada, we evaluated DNA samples for germline mutations in *BRCA1* and *BRCA2* from 116 women with primary cancers of the breast or ovary, and with at least one parent with Italian ancestry. The 116 women participated in genetic studies for either clinical (high-risk families) or research (unselected patients) purposes. A variety of methods were employed for mutation analysis. All samples were tested for deleterious mutations in exons 10 and 11 of *BRCA2* and exons 2, 5, 11, 16, 20 and exon 13 duplication of *BRCA1*. This testing covered the majority of mutations described previously for Italian patients (Table 1), revealing 29 of the 39 mutations (Table 2). Subsequent testing by direct sequencing (by Myriad Genetic Laboratories) revealed ten additional mutations in other exons.

Thirty-nine *BRCA1* or *BRCA2* mutations were identified among the 116 families (33.6%); 23 in *BRCA1* and 16 in *BRCA2* (Table 2). In total, 19 of the 39 mutations (48.7%) were present in more than one family. Of particular significance was the detection of the *BRCA1* exon 16 5083del19 in five families. Three of these five families, who

Table 1 BRCA1 and BRCA2 mutations reported in two or more Italian families

Mutation	*Exon*	*No. families*	*BIC entries*	*Reference*	*Region or center*	*Ethnic populations assciated with mutation*
BRCA1						
T300G (C61G)	5	4	67	[1,6,7]	Calabria, Modena, Central and South	European
1135insA	11	2	30	[8]; our study	Milan	Norwegian, Austrian, French
1479delAG	11	2	1	[5]; our study	—	—
1499insA	11	7	1	[8–10]	Tuscany, Pisa, Milan	—
C1806T (Q563X)	11	2	37	[8,11]	Aviano, Milan, North	Swedish, Danish, Dutch, German, Austrian
2846del4	11	3	3	[8,11,12]	Aviano, Padova, Milan, North	Dutch
3596del4	11	2	2	[7,12]	Modena	—
3875del4	11	3	36	[5,8]; our study	Milan	Dutch, Czech
G4236T (E1373X)	12	3	3	[5]; our study	—	—
5083del19	16	11	18	[1,6,11]; our study	Calabria, Aviano, Central and South	—
3.2kb deletion	17	2	1	[13]	Padova	—
5382insC	20	Numerous	267	[7,8,11]; our study	Worldwide	Ashkenazi Jewish, European
5438insC	21	2	2	Our study	—	—
BRCA2						
5950delCT	11	2	13	[8,14]; our study	Central and South	French, German
6431insA	11	2	1	[15]; our study	Aviano	—
6696delTC	11	5	2	[6,8]; our study	Milan, Central and South	—
6819delTG	11	2	3	[5]; our study	—	Belgian
8765delAG	20	7	17	[16]	Sardinia	Fr. Canadian, Czech, Yemenite Jewish

provided specific information about their ancestry, indicated that they originated from Calabria. The 5083del19 mutation accounted for 21.7% of all *BRCA1* mutations. Seven other mutations were identified in two families each, including the *BRCA1* 3875del4, 5382insC and the *BRCA2* 6696delTC previously described in Italian studies. We did not detect two *BRCA1* mutations reported in multiple families in Italy (T300G (C61G) and 1499insA).

In a recent study of 649 unselected ovarian cancer patients in Canada, Risch *et al*.[5] reported that the highest *BRCA* mutation frequency (24.1%) was among women of Italian ancestry (for non-Jewish subjects). In our study of 116 women of Italian ancestry diagnosed with breast or ovarian cancer, one-third were carriers of mutations in *BRCA1* or *BRCA2*; this mutation frequency is likely an underestimate, as we did not screen all patients for all possible mutations in these genes. In the past, research centres have focused on the exon 11 region of the *BRCA1* gene, and interestingly 16 of the 23 *BRCA1* mutations identified in Italian families were outside of exon 11. Our data confirms the *BRCA1* exon 16 5083del19 mutation to be a founder mutation in the Italian population (from Calabria), in North America as well as in Italy. It may be prudent to screen for recurrent mutations prior to undertaking a full genetic screen in families of Italian origin.

Electronic Database Information

Accession numbers and URLs for data in this article are as follows:

Table 2 Characteristics of 23 BRCA1 and 16 BRCA2 families of Italian ancestry

Families†	*Exon*	*Mutation*	*BIC entries*	*Breast total*	*Cancer* ⩽50	*Ovarian cancer** *total*
BRCA1						
9080	8	633delC	8	4	4	0
270	11	1135insA	30	2	1	1
1024	11	1479delAG	1	1	1	3
10566	11	1479delAG	1	1	1	1
99-021	11	G3519T (E1134X)	2	2	2	5
6880	11	C3726T	–	6	5	0
10411	11	3875delGTCT	36	0	0	1
10987	11	3875delGTCT	36	0	0	2
103	12	4280delTC	1	5	4	0
10665	12	G4236T (E1373X)	3	6	4	1
0132	12	G4236T (E1373X)	3	2	1	1
1231	14	G4603T (R1495M)	7	0	0	2
2770	16	C4808G (Y1563X)	18	14	12	3
6716	16	5083del19	18	3	3	2
444	16	5083del19	18	2	2	1
9098	16	5083del19	18	6	6	1
9305	16	5083del19	18	6	5	8
1525	16	5083del19	18	1	1	2
9327	18	5225delA	–	3	3	1
3574	20	5382insC	267	3	3	1
166	20	5382insC	267	6	2	4
2973	21	5438insC	2	6	4	5
202	21	5438insC	2	15	6	7
BRCA2						
3694	9	924delT	–	7	6	0
11761	10	1538del4	1	1	0	1
9711	10	2024del5	5	4	4	1
9052	10	2034delA	5	4	2	0
9822	11	2331delTATT	1	1	2	0
002	11	3036delACAA	24	4	4	2
10051	11	4510insT	–	1	1	1
1703	11	5302insA	1	0	0	1
9098	11	5950delCT	13	2	2	1
0510	11	C6137A (S1970X)	1	5	3	1
1885	11	6431insA	1	4	2	0
7001	11	6696delTC	2	2	2	1
1777	11	6696delTC	2	6	3	0
071	11	6819delTG	3	2	2	0
11493	11	6819delTG	3	0	0	1
9207	26	G9800A (W3191X)	–	7	7	0

*Includes fallopian tube cancers; †Five-digit family numbers indicate unselected patients with ovarian cancer, as described by Risch *et al*. [5]

Online Mendelian Inheritance in Man (OMIM), http://www3.ncbi.nlm.nih.gov/Omim/, for inherited breast cancer type 1 and ovarian cancer [MIM 113705] and for inherited breast cancer type 2 [MIM 600185].

Breast Cancer Information Core Database (BIC), http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/ Bic/, for information on sequence alterations in *BRCA1* and *BRCA2*.

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