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Absence of the *BRCA1* del (exons 9–12) mutation in breast/ovarian cancer families outside of Mexican Hispanics

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To the editor

The frequency and spectrum of germ line mutations in the high-penetrance breast cancer susceptibility genes *BRCA1* and *BRCA2* shows considerable variation by ethnic group. Most genetic epidemiological studies of the *BRCA* genes have been performed among Caucasian populations [1],

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with the exception of a few studies involving other ethnic groups, such as Hispanics [2–4], Asians [5, 6], and African Americans [7–9]. In most of these studies only the frequencies of sequence detectable *BRCA* mutations were reported and large genomic rearrangements including deletions and insertions of one or more exons, which account for 6–15% of all deleterious mutations in these genes have infrequently been considered [10–12].

Most *BRCA* mutations are unique; however, few recurrent mutations with founder effects have been found in European, Hispanic, American and Asian populations [13]. In a recent study on Hispanic high-risk breast/ovarian cancer families of mainly Mexican descent from South California, Weitzel and colleagues reported the identification of a novel deletion of *BRCA1* exons 9 through 12 using multiplex quantitative differential polymerase chain reaction (PCR) analysis. The deletion was detected in 3.8% of families negative for sequence detectable *BRCA* mutations [14]. The large genomic rearrangement mutation is considered deleterious as it results in loss of critical functional domains as well as premature truncation of the *BRCA1* protein. Given the relatively high prevalence of the deletion in this cohort, the authors suggest to include the screening for this mutation in the genetic testing strategy in Hispanic women without sequence detectable *BRCA* mutations.

The spectra of recurrent sequence detectable *BRCA* mutations, including some with founder effects in a cohort of Hispanic breast/ovarian cancer families of predominantly Mexican descent from the United States and in a cohort from Colombia have previously been shown to differ completely, with different common mutations being identified in the two populations [2, 4]. In order to investigate, whether the novel *BRCA1* founder deletion is also specific for Hispanic families of Mexican descent or whether it also occurs in other Hispanic cohorts, we screened 229 cancer

families from Colombia for its presence. Moreover, we assessed whether this mutation is present in families belonging to two other ethnic groups, including 255 Asian families from Pakistan and 54 Caucasian families from Germany. A description of the families under investigation is shown in Table 1. Among the Colombian, Pakistani and German families, 40, 146 and 54 families without sequence detectable *BRCA*-mutations, respectively, have been previously described [4, 5, 15–17]. The remaining families were newly recruited within an ongoing breast cancer case-control study in Colombia and a hereditary breast cancer study in Pakistan. All newly recruited families were

screened for the presence of the common *BRCA* mutations specific for each of these ethnic groups (three founder mutations in Colombia; three founder and one recurrent mutation in Pakistan) and none were detected (unpublished data). The research study was approved by the local Ethics committees. *BRCA1* del (exons 9–12) mutation analysis was performed using a 3-primer PCR assay as previously described [14]. PCR products, including both positive and negative control samples, were separated by size on 1.5% agarose gels and visualized by ethidium bromide staining. The fragment sizes were 1,145 bp for the wild type and 742 bp for the deletion mutation.

Table 1 Breast/ovarian cancer families from Colombia, Pakistan and Germany under investigation

Phenotype of families	No. of families	No. of <i>BRCA1</i> del (exons 9-12) carriers
<i>Hispanic breast/ovarian cancer families from Colombia</i>		
All families	229	0/229
Female breast cancer families (bilateral)		
1 case (1) diagnosed ≤ 35 years	4	
2 cases (9)	99	
3 cases (4)	68	
≥ 4 cases	28	
Male breast cancer families		
≥ 1 case (1)	1	
Breast-ovarian cancer families		
≥ 1 breast cancer and ≥ 1 ovarian cancer	27	
Ovarian cancer families		
≥ 2 cases	2	
<i>Asian breast/ovarian cancer families from Pakistan</i>		
All families	255	0/255
Female breast cancer families (bilateral)		
1 case (2) diagnosed ≤ 30 years	135	
1 case (10) diagnosed ≤ 50 years	10	
2 cases (1) with ≥ 1 diagnosed ≤ 50 years	31	
3 cases (2) with ≥ 1 diagnosed ≤ 50 years	18	
≥ 4 cases with ≥ 1 diagnosed ≤ 50 years	9	
Male breast cancer families		
≥ 1 case of male breast cancer	11	
Breast-ovarian cancer families		
≥ 1 breast cancer and ≥ 1 ovarian cancer	18	
Ovarian cancer families		
1 case diagnosed ≤ 45 years	21	
2 cases with ≤ 1 case diagnosed before 45 years	2	
<i>Caucasian breast/ovarian cancer families</i>		
All families	54	0/54
Female breast cancer families (bilateral)		
3 cases (3) with ≥ 1 diagnosed ≤ 50 years	19 ^a	
≥ 4 cases (6) with ≥ 1 diagnosed ≤ 50 years	24 ^b	
Breast-ovarian cancer families		
≥ 1 breast cancer and ≥ 1 ovarian cancer	11	

^a Including one family with a male breast cancer

^b Including two families with a male breast cancer

The present study included 538 affected individuals from breast and/or ovarian cancer families. The mean ages of female breast cancer onset in Colombian, Pakistani and German patients were 50 years (range 23–83, $n = 224$), 30 years (range 19–70, $n = 218$) and 44 years (range 24–70, $n = 54$), respectively. The mean age of ovarian cancer onset was 54 years (range 34–71, $n = 4$) for Colombian patients and 33 years (range 22–48, $n = 26$) for Pakistani patients.

None of the 538 analyzed samples carried the *BRCA1* del (exons 9–12) mutation (Table 1). This finding suggests that this mutation is not present or is present at an extremely low frequency in Hispanic families from Colombia as well as in Pakistani and German populations.

The absence of the *BRCA1* del (exons 9–12) mutation in Hispanic families from Colombia shows that this mutation does not contribute to hereditary breast/ovarian cancer in this population, nor in Pakistani and German populations. Our data confirm our previous finding that the spectra of the *BRCA* founder mutations differ between Hispanic families of Mexican origin from the United States and families from Colombia. These findings provide further evidence that specific risk assessment strategies for the different Hispanic populations in South America and in the United States need to be developed.

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