Prevalence and impact of founder mutations in hereditary breast cancer in Latin America

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Abstract
Approximately 10% of all cancers are considered hereditary and are primarily caused by germline, high penetrance mutations in cancer predisposition genes. Although most cancer predisposition genes are considered molecularly heterogeneous, displaying hundreds of different disease-causing sequence alterations, founder mutations have been identified in certain populations. In some Latin American countries, founder mutations associated with increased risk of breast and other cancers have been described. This is particularly interesting considering that in most of these countries, populations are highly admixed with genetic contributions from native populations and from the influx of several distinct populations of immigrants. In this article, we present a review of the scientific literature on the subject and describe current data available on founder mutations described in the most common breast cancer predisposition genes: BRCA1, BRCA2 and TP53.

Keywords: breast cancer genes, BRCA1, BRCA2, TP53, cancer predisposition.

Introduction
Although most neoplasias are the result of complex interactions between genetic backgrounds and environmental factors, a proportion is due to inherited mutations that confer a high risk of developing cancer. It is currently estimated that 5-10% of many common adult life cancers are associated with highly penetrant germline mutations in tumor suppressor or DNA repair genes. Several genes associated with cancer predisposition syndromes have been identified (Lindor et al., 2008). Among the hereditary causes of breast cancer, hereditary breast and ovarian cancer (HBOC) syndrome, caused by mutations in the BRCA1 or BRCA2 genes, has been considered the most prevalent. Female carriers of germline loss-of-function mutations in either of these two genes are at high risk of developing breast cancer (cumulative lifetime risk up to 85%) and ovarian cancer (cumulative lifetime risk up to 45%). Male breast cancer and other neoplasias, such as melanoma and prostate cancers, as well as Fallopian tube, pancreatic and biliary tract tumors, have also been observed in these families. In young women, loss-of-function mutations in the TP53 gene, resulting in Li-Fraumeni syndrome (LFS) and its variants, are also an important cause of hereditary breast cancer. Identification of families that are at risk for hereditary breast cancer is fundamental for the implementation of vigilance and/or risk reduction strategies (Weitzel et al., 2012).

Although most cancer predisposition genes are considered heterogeneous, displaying hundreds of different disease-causing sequence alterations, founder mutations have been identified in certain populations (Ferla et al., 2007). Founder mutations are located within a genomic region that is in linkage disequilibrium and, therefore, segregates as a unit. For this reason, these mutations are inherited and often remain restricted to one or a few populations or specific geographic regions. When present in several different population groups and geographic regions, haplotype analysis of families with the same mutation can be used to distinguish whether high-frequency alleles derive from an older or more recent single mutational event or whether these mutations arose independently (for an excel-
lent definition of “founder mutations”, refer to Fackenthal and Olcape, 2007). The aim of the present study is to re-
view the founder mutations in the BRCA1, BRCA2 and
TP53 genes that have been associated with increased breast
cancer risk in Latin American countries.

Methods

A search for germline founder mutations in the
BRCA1, BRCA2 and TP53 genes was performed using the
PubMed and SciELO databases, considering publications
since the description of the first pathogenic germline muta-
tion in each of the genes. The search terms were “hereditary
breast cancer and Latin America”; “BRCA and Latin
America”; “hereditary breast cancer and Hispanics” and
“BRCA and Hispanics”. We also used these terms in asso-
ciation with the names of Latin American countries (e.g.,
“hereditary cancer and Colombia”; “BRCA and Colom-
bia”). The results of the searches were subsequently screened
for the presence of founder mutations associated with he-
reditary breast cancer. For each identified mutation, the
founder haplotype, as well as its prevalence and impact on
phenotype, are described, when available. The results are
presented by country.

Results

Brazil

BRCA1 c.5266dup

The BRCA1 5382insC mutation (more recently de-
scribed as c.5266dup) is the second most frequent mutation
described in this gene worldwide, according to the Breast
Cancer Information Core (BIC, http://www.re-
search.nhgri.nih.gov/bic/). The high prevalence of the
c.5266dup was described initially in Ashkenazi Jews, and
this mutation has subsequently been described in other pop-
ulations from Central and Eastern Europe. Haplotype stud-
ies have demonstrated a common origin of this mutation in
European populations, and several authors have described
its occurrence in Brazilian breast cancer patients (Lourenço
et al., 2004; Dufloth et al., 2005; Gomes et al., 2007). More
recent studies indicate that the mutation was introduced
into the Ashkenazi Jewish genetic pool approximately
400–500 years ago in Poland, but the mutation originated
from a single common European ancestor long before (Ha-
mel et al., 2011). According to Gomes et al. (2007), the
high prevalence of this mutation in Brazilian patients may
be associated with the immigration of converted Jews from
the Iberic Peninsula, which began in the 16th century. How-
ever, mutation studies in HBOC families from Portu-
gal and Spain identified only one Portuguese family carry-
ing c.5266dup (Infante et al., 2006; Salazar et al., 2006).
Haplotype characterization of Brazilian families from dif-
ferent ethnic backgrounds identified the same haplotype
described in Ashkenazi Jews in other countries (Costa et
al., 2008). An interesting phenotype, so far described only
in a Brazilian cohort of HBOC families, is an apparent asso-
ciation of the BRCA1 c.5266dup mutation with an in-
creased risk for bilateral breast cancer (Ewald et al., 2011).

TP53 p.R337H

The majority of TP53 germline mutations causing
LFS are missense substitutions that cluster in highly con-
served regions of the gene, corresponding to the DNA-
binding domain (DBD) of the protein (exons 5–8; codons
125–300) (Malkin et al., 1990; Chompret et al., 2000; Birch
et al., 2001; Olivier et al., 2010, Petitjean et al., 2007). In
Brazil, a particular mutation outside the DBD has been re-
ported in a significant proportion of families with LFS and
similar phenotypes (Li-Fraumeni-like syndrome, LFL). In-
Additionally, this mutation has been described at a fre-
cuency of approximately 1:300 individuals of the general
population in Southern Brazil (Custódio et al., 2013, Pal-
mero et al., 2008) which is exceedingly higher than the fre-
cuencies estimated for germline TP53 mutations
worldwide (1:2,000–1:5,000) (Lalloo et al., 2003; Lindor
et al., 2008). Within the spectrum of germline TP53 muta-

BRCA2 c.156_157insAlu

Machado et al. (2007) and Peixoto et al. (2009) iden-
tified an Alu insertion within BRCA2 exon 3
(c.156_157insAlu) in 34 Portuguese families with HBOC.
Haplotype characterization demonstrated a common hap-
lo-type in Portuguese carrier families. Two mutation preva-
ience studies included Brazilian patients. In the first study,
consisting of an international cohort of 5,453 cancer-
affected patients with clinical criteria for HBOC, the muta-
tion was not identified in 144 individuals from the Brazilian
states of São Paulo and Rio Grande do Sul, while it ac-
counted for 37.9% of the mutations identified in Portuguese
families (Peixoto et al., 2011). In the second study, per-
formed on 168 unrelated HBOC patients from the state of
Rio de Janeiro, the insertion was observed in three unre-
related probands. Two families shared the same haplotype
described in the Portuguese families, and the third family
had a different allele in one marker (D13S1246), suggest-
ing that a crossover event had occurred in this region. The
tumor phenotypes observed in the families of these carriers
seem to reinforce the high prevalence of breast cancer
among affected males. However, an apparent excess of gas-
trointestinal and tongue neoplasias were also identified. Al-
though these tumors are not part of the phenotypic
spectrum of the HBOC syndrome, they might result from
other risk alleles contained in the founder haplotype region.
(Moreira et al., 2012). The facts that this mutation is highly
prevalent in Central Portugal and that the Portuguese set-
ting in Southern Brazil was done mostly by families from
the Azores Islands may account for the low observed fre-
cuency of the BRCA2 c.156_157insAlu mutation in the
Brazilian samples studied.
Three independent studies have addressed the hypothesis of a founder effect associated with the high prevalence of TP53 p.R337H. In the first study, based on the analysis of four loci on chromosome 17p, a founder effect was rejected (Ribeiro et al., 2001). In 2004, Pinto et al. inferred that a founder effect was statistically probable based on two highly informative polymorphic intragenic markers (Pinto et al., 2004). Finally, an in-depth analysis of 29 TP53 tSNPs in 48 unrelated subjects (45 Brazilians, and 3 Portuguese), performed by Garritano and coworkers demonstrated a rare haplotype of Caucasian origin and suggested that the p.R337H mutation had most likely arisen in an individual of European ancestry (Garritano et al., 2010).

The p.R337H germline mutation was initially identified in Brazilian children with ACC and no documented familial history of other cancers (Ribeiro et al., 2001). Later, it was identified in families with LFL and even LFS criteria and in individuals with many other tumors, including all core tumors of the syndrome (Achatz et al., 2007, Assumpção et al., 2008, Seidinger et al., 2011.). However, when compared to other “classic” DNA-binding mutations, p.R337H has a reduced penetrance for cancer: 15-20% by age 30 years and 50-65% lifetime risk (Garritano et al., 2010). In their population-based series of infants tested for the mutation in a statewide newborn screening program in Paraná, Southern Brazil, Custódio et al. (2013) estimated the penetrance for ACC in mutation carriers at only 2.39% in the first five years of life. Preliminary results from Southern and Southeastern Brazil indicate that the mutation is present in the germline of a significant proportion of women with premenopausal breast cancer (Giacomazzi et al., 2011). In addition to the core tumors associated with Li-Fraumeni syndrome, p.R337H carriers also appear to be more prone to tumors not frequently reported in classic LFS patients, such as thyroid and gastric cancers and phyllodes tumors of the breast (Achatz et al., 2007; Giacomazzi et al., 2013).

### Chile

Mutation screening of a cohort of 64 HBOC families from Chile identified BRCA1 and BRCA2 mutations in seven (10.9%) and three (4.7%) families, respectively. Two mutations were observed in two unrelated probands each: BRCA1 c.187_188delAG (formerly known as 185delAG) and a novel mutation in BRCA1, c.4185_4188delCAAG (Jara et al., 2004, 2006). Previously, the prevalence of the supposed Ashkenazi founder mutations was found to be low in 382 Chilean breast cancer families; BRCA1 185delAG was present in 0.26%, whereas the BRCA1 5382insC and BRCA2 6174delT mutations were not identified (Jara et al., 2002a,b). In addition to sequencing analyses in Chilean population, Sanchez et al. (2011) employed multiple ligation primer amplification (MLPA) to search for gene rearrangements in BRCA1/2 in 74 BRCA HBOC families without identifiable mutations by sequencing. In two families, they identified a four-fold amplification of exons 3, 5, and 6 in a fragment lacking intronic sequences, suggesting the presence of a processed pseudogene (Sanchez et al., 2011).

### Colombia

Torres et al. (2007) searched for BRCA1/2 mutations in 53 HBOC families from Colombia. The authors observed that two recurrent BRCA1 mutations, 3450delCAAG and A1708E, accounted for 100% of the eight BRCA1 mutations identified in this cohort. Additionally, the BRCA2 3034delACAA mutation was found in two families, comprising 40% of all mutations identified in this gene. Haplotype analyses suggested that each of these mutations had arisen from a common ancestor (Torres et al., 2007). In a small series of 30 women from HBOC families in eastern Colombia (Bucaramanga), Sanabria et al. (2009) searched for the founder Ashkenazi BRCA1 185delAG and 5382insC mutations and did not encounter a carrier. Rodriguez et al. (2012) studied 96 women with ovarian cancer from Colombia (Bogotá region and northern and southern central regions of Colombia) and identified germline mutations in 15 (15.6%); 13 women had BRCA1 mutations, whereas 2 women had BRCA2 mutations. A striking finding was that a single founder mutation, 3450delCAAG, was diagnosed in 11 of the 13 BRCA1-

![Figure 1](image-url) - Distribution of germline mutations in TP53 by codon (%). Among 636 families reported in the TP53 database, 107 (16.8%) harbor mutations in codon 337; of these, 99 mutations (92%) are p.R337H (From: IARC TP53 database, 17th version).
itive patients. The authors concluded that approximately 11.5% of all ovarian cancer cases in the Bogotá region are attributable to a single BRCA1 founder mutation.

Venezuela

No founder mutations in the BRCA genes have been described in Venezuela to date. Lara et al. (2012) screened 58 familial breast cancer patients for mutations and found six pathogenic mutations in BRCA1 and four in BRCA2, but none of these mutations were recurrent.

Costa Rica

In a study of 111 breast cancer-affected women with a family history of the disease in the metropolitan area of San José, Gutierrez et al. (2012) identified five mutation carriers (4.5%). Two unrelated patients were found to carry the BRCA2 5531delTTT mutation, and two other patients carried the C5507G and 6174delT BRCA2 mutations. Only one BRCA1 mutation was encountered (C3522T). In a second independent cohort, the same group analyzed 116 HBOC families and identified BRCA mutations in 6 individuals (5.2%). Again, only one of these mutations was a BRCA1 mutation (García-Jiménez et al., 2012). Data from these two studies suggest that BRCA2 mutations may be more prevalent in Costa Rica than BRCA1 mutations.

Mexico

The contribution of BRCA1 and BRCA2 mutations to Mexican women with breast and/or ovarian cancer has been assessed in a few studies. When screening 40 breast cancer patients with a family history of breast and/or ovarian cancer or early onset breast cancer (< 40 years) Vidal-Millán et al. (2009) found deleterious mutations in 5% of the patients. Subsequently, Vaca-Paniagua et al. (2012) screened 39 HBOC patients for BRCA mutations using massive parallel pyrosequencing and identified four (10.2%) novel deleterious mutations (c.2805_2808delAGAT and c.3450delCAAG in BRCA1, as well as c.3124_3133delAGCAATATTA in BRCA2). None of these mutations was recurrent.

Discussion

Several distinct founder mutations have been reported in different Latin American countries. However, a few recurrent mutations, such as c.5266dup and c.3450delCAAG in BRCA1, have been observed in more than one country. In fact, the BRCA1 c.3450delCAAG mutation has been observed in Colombia (Torres et al., 2007), Chile (Jara et al., 2006), and Brazil (Lourenço et al., 2004). Importantly, the c.3450delCAAG mutation seems to be highly prevalent among ovarian cancer carriers in Colombia. The frequent reports of BRCA1 c.5266dup in different studies is in agreement with data from several mutation databases, which have suggested that this is one of the most common mutations ever described in BRCA1. Although a few studies have proposed that the haplotype identified in Latin America is identical to that described in Ashkenazi Jews, this has not been demonstrated in all of the mutation reports; therefore, a common founder origin for all BRCA1 c.5266dup mutations in Latin America remains to be determined.

Interestingly, as emphasized by Torres et al. (2007), the spectrum of mutations in the BRCA1/2 genes in Latin American countries is not the same as those described among Hispanics in the United States. Weitzel et al. (2005) screened 110 unrelated probands of Hispanic origin (predominantly of Mexican descent) in Southern California for mutations in BRCA1/2. All had personal and/or family histories of breast and/or ovarian cancer. The authors observed that six recurrent mutations accounted for 47% (16 of 34) of the deleterious mutations in this cohort. The most common deleterious mutation was 185delAG (4 of 34, 11.8% of the mutations and 3.6% of the entire cohort), and all Hispanic carriers shared the same haplotype described in Ashkenazi Jews (Weitzel al., 2005). Subsequently, Weitzel et al. (2007) identified and characterized a novel large BRCA1 deletion in five unrelated families (four of Mexican ancestry and one of African and Native American ancestry) among 106 Hispanic patients with the HBOC phenotype (Weitzel et al., 2007). Haplotype analysis confirmed a common ancestry among all carriers. More recently, Weitzel et al. (2013) performed mutational screening in 746 Hispanics from Southwestern USA with a personal or family history of breast and/or ovarian cancer and found that nine recurrent mutations were responsible for 53% all identified alterations. BRCA1 ex9-12del was observed in 13 unrelated families, rendering it the most common BRCA rearrangement observed in this USA/Hispanic/HBOC cohort. Again, a common haplotype is shared by all carriers, mainly of Mexican origin. In spite of that, we have not identified a specific study in women residing in Mexico that describes the founder mutations identified in Mexican women or women of Mexican descent women living in the USA.

From the review of the published literature we conclude that there is a lack of molecular epidemiology studies of hereditary breast cancer families in Latin America. Several countries are not represented; for instance, we could not find any reports of founder germline mutations associated with increased risk for breast cancer in countries such as Peru, Uruguay, Paraguay, and Bolivia, among others. Delgado et al. (2002) identified a BRCA2 6-bp insertion in a pair of Uruguayan monozygotic twins who developed breast cancer at the same age, but this mutation was described in only one family. Existing studies usually include relatively small numbers of patients recruited from selected reference centers, and it is impossible to assess how representative these series are of the populations of individuals at risk for hereditary breast cancer in each of these countries. Even for canonical genes associated with hereditary breast cancer, the true mutation prevalence remains largely
unknown in most countries. Furthermore, the existing studies are very heterogeneous regarding the mutation detection techniques used, coverage of the coding region of the genes tested (hot-spot or founder mutation testing vs. entire coding region) and criteria for referral to genetic counseling and testing, thus causing an even larger knowledge gap.

Despite all of these limitations, founder mutations in breast cancer predisposition genes appear to be common in several Latin American populations. This may be due to historical reasons, such as a drastic reduction of certain populations during colonization and/or selective advantage of mutation carriers. With few exceptions, however, most founder mutations appear to be selectively present in only one or a few countries or specific geographic regions. This “heterogeneity in founder mutations” among Latin American populations suggests that several other founders may exist and have not yet been identified due to the limited number of investigations performed to date. Recent reports from commercial North American laboratories claim that hereditary breast cancer testing of families with standard criteria and with multiple gene panels results in the identification of a mutation in approximately 50% of patients (25% in the BRCA1 and BRCA2 genes and 20-25% in several other genes, each at a low frequency) (Narod 2012). We currently lack reliable information on the molecular epidemiology of hereditary breast cancer in Latin America, with scarce data about the BRCA mutation prevalence and penetrance and even less about other genes. Further studies analyzing large series of families with the hereditary breast cancer phenotype in different geographic regions will be necessary to accurately estimate the prevalence of mutations and the relevance of founder mutations in these populations.

Acknowledgments

PA-P is a level 1D researcher of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and is funded by CNPq, Fundação de Amparo a Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Fundo de Incentivo a Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre, Brazil. FRV is a researcher of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and is funded by CNPq grant 476808/2010-3 and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) grant E26/110.535/2012.

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Internet Resources


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