*Genetics and Molecular Biology*, 37, 1 (suppl), 234-240 (2014)

www.sbg.org.br

Research Article

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

Patricia Ashton-Prolla[1,2] and Fernando Regla Vargas[3,4]

[1]*Departamento de Genética, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.*
[2]*Serviço de Genética Médica e Centro de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil*
[3]*Departamento de Genética e Biologia Molecular, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brasil*
[4]*Laboratório de Epidemiologia de Malformações Congênitas, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil.*

## 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-

Laboratório de Epidemiologia de Malformações Congênitas, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Pav. Leonidas Deane, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Av. Brasil 4365, 21045-900 Rio de Janeiro, RJ, Brazil. E-mail: fernando.vargas@ioc.fiocruz.br.

lent definition of "founder mutations", refer to Fackenthal and Olopade, 2007). The aim of the present study is to review 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 mutation 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 association with the names of Latin American countries (*e.g.*, "hereditary cancer and Colombia"; "BRCA and Colombia"). The results of the search were subsequently screened for the presence of founder mutations associated with hereditary 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 described as c.5266dup) is the second most frequent mutation described in this gene worldwide, according to the Breast Cancer Information Core (BIC, http://www.research.nhgri.nih.gov/bic/). The high prevalence of c.5266dup was described initially in Ashkenazi Jews, and this mutation has subsequently been described in other populations from Central and Eastern Europe. Haplotype studies 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 (Hamel *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. However, mutation studies in HBOC families from Portugal and Spain identified only one Portuguese family carrying c.5266dup (Infante *et al.*, 2006; Salazar *et al.*, 2006). Haplotype characterization of Brazilian families from different 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 association of the *BRCA1* c.5266dup mutation with an increased risk for bilateral breast cancer (Ewald *et al.*, 2011).

#### *BRCA2 c.156_157insAlu*

Machado *et al.* (2007) and Peixoto *et al.* (2009) identified an Alu insertion within *BRCA2* exon 3 (c.156_157insAlu) in 34 Portuguese families with HBOC. Haplotype characterization demonstrated a common haplotype in Portuguese carrier families. Two mutation prevalence 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 mutation was not identified in 144 individuals from the Brazilian states of São Paulo and Rio Grande do Sul, while it accounted for 37.9% of the mutations identified in Portuguese families (Peixoto *et al.*, 2011). In the second study, performed on 168 unrelated HBOC patients from the state of Rio de Janeiro, the insertion was observed in three unrelated probands. Two families shared the same haplotype described in the Portuguese families, and the third family had a different allele in one marker (D13S1246), suggesting 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 gastrointestinal and tongue neoplasias were also identified. Although 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 settling in Southern Brazil was done mostly by families from the Azores Islands may account for the low observed frequency of the *BRCA2* c.156_157insAlu mutation in the Brazilian samples studied.

#### *TP53 p.R337H*

The majority of *TP53* germline mutations causing LFS are missense substitutions that cluster in highly conserved 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 reported in a significant proportion of families with LFS and similar phenotypes (Li-Fraumeni-like syndrome, LFL). Additionally, this mutation has been described at a frequency of approximately 1:300 individuals of the general population in Southern Brazil (Custódio *et al.*, 2013, Palmero *et al.*, 2008) which is exceedingly higher than the frequencies 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-

tions, p.R337H is the most commonly described mutation; however, it is almost exclusively found in Brazilians. Among 636 families reported in the IARC *TP53* database, 107 (16.8%) harbor mutations in codon 337; of these, 99 mutations (92%) are p.R337H (Figure 1; IARC *TP53* database, 17th version). *TP53* p.R337H mutation was described in only two non-Brazilian individuals diagnosed with adrenocortical carcinoma (ACC): an eight-year-old girl with Portuguese ancestry living in France (Garritano *et al.*, 2010) and a German seventy one-year-old male (Herrmann *et al.*, 2012).

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

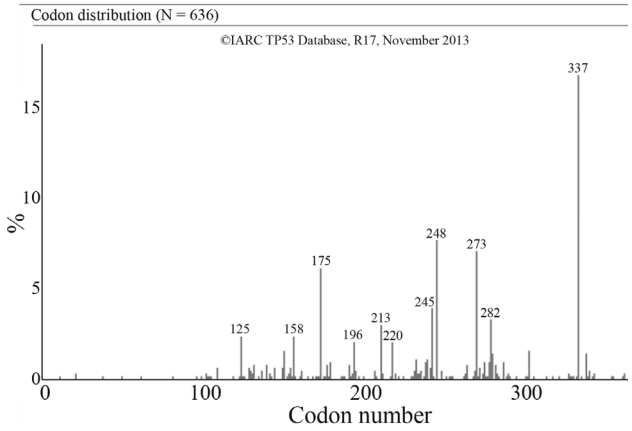


**Figure 1** - Distribution of germline mutations in *TP53* by codon (%). Among 636 families reported in the *TP53* database, 107 (16.8%) harbor mutations in codon 337; of these, 99 mutations (92%) are p.R337H (From: IARC *TP53* database, 17th version).

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. Rodríguez *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*-pos-

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 was 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* 5531delTT 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.3124_3133delAGCAATATTA in *BRCA1*; c.2639_2640delTG and c.5114_5117delTAAA in *BRCA2*).

## 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 a*l., 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 el 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 Clinicas 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.

## References

Achatz MIW, Olivier M, Calvez FL, Martel-Planche G, Lopes A, Rossi BM, Ashton-Prolla P, Giuliani R, Palmero EI, Vargas FR, *et al.* (2007) The *TP53* mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndrome in Brazilian families. Cancer Lett 245:96-102.

Assumpção JG, Seidinger AL, Mastellaro MJ, Ribeiro RC, Zambetti GP, Ganti R, Srivastava K, Shurtleff S, Pei D, Zeferino LC, *et al.* (2008) Association of the germline *TP53* R337H mutation with breast cancer in southern Brazil. BMC Cancer 8:e357.

Birch JM, Alston RD, McNally RJ, Evans DG, Kelsey AM, Harris M, Eden OB and Varley JM (2001) Relative frequency and morphology of cancers in carriers of germline *TP53* mutations. Oncogene 20:4621-4628.

Campos B, Díez O, Alvarez C, Palma L, Domènech M, Balmaña J, Sanz J, Ramírez A, Alonso C, Carvallo P, *et al.* (2004) Haplotype of the *BRCA2* 6857delAA mutation in 4 families with breast/ovarian cancer. Med Clin (Barc) 123:543-545.

Costa ECCB, Vargas FR, Moreira AS, Lourenço JJ, Caleffi M, Ashton-Prolla P and Martins Moreira MA (2008) Founder effect of the *BRCA1* 5382insC mutation in Brazilian patients with hereditary breast ovarian cancer syndrome. Cancer Genet Cytogenet 51:588-597.

Chompret A, Brugières L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A, Hua D, Ligot L, Dondon MG, *et al.* (2000) P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer 82:1932-1937.

Custódio G, Parise GA, Kiesel Filho N, Komechen H, Sabbaga CC, Rosati R, Grisa L, Parise IZ, Pianovski MA, Fiori CM, *et al.* (2013) Impact of neonatal screening and surveillance for the *TP53* R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol 31:2619-2626.

Delgado L, Fernández G, González A, Bressac-de Paillerets B, Gualco G, Bombled J, Cataldi S, Sabini G, Roca R and Musé IM (2002) Hereditary breast cancer associated with a germline BRCA2 mutation in identical female twins with similar disease expression. Cancer Genet Cytogenet 133:24-28.

Dufloth RM, Carvalho S, Heinrich JK, Shinzato JY, dos Santos CC, Zeferino LC and Schmitt F (2005) Analysis of *BRCA1* and BRCA2 mutations in Brazilian breast cancer patients with positive family history. Sao Paulo Med J 123:192-197.

Ewald IP, Izetti P, Vargas FR, Moreira MA, Moreira AS, Moreira-Filho CA, Cunha DR, Hamaguchi S, Camey AS, Schmidt A, *et al.* (2011) Prevalence of the *BRCA1* founder mutation c.5266dup in Brazilian individuals at-risk for the hereditary breast and ovarian cancer syndrome. Hered Cancer Clin Pract 9:12.

Fackenthal JD and Olopade OI (2007) Breast cancer risk associated with *BRCA1* and *BRCA2* in diverse populations. Nat Rev Cancer 7:937-948.

Ferla R, Calò V, Cascio S, Rinaldi G, Badalamenti G, Carreca I, Surmacz E, Clolucci G, Bazan V and Russo A (2007) Founder mutations in *BRCA1* and *BRCA2* genes. Ann Oncol 18(Suppl 6):93-98.

Gallardo M, Silva A, Rubio L, Alvarez C, Torrealba C, Salinas M, Tapia T, Faundez P, Palma L, Riccio ME, *et al.* (2006) Incidence of *BRCA1* and *BRCA2* mutations in 54 Chilean families with breast/ovarian cancer, genotype-phenotype correlations. Breast Cancer Res Treat 95:81-87.

García-Jiménez L, Gutiérrez-Espeleta G and Narod SA (2012) Descriptive epidemiology and molecular genetics of hereditary breast cancer in Costa Rica. Rev Biol Trop 60:1663-1668.

Garritano S, Gemignani F, Palmero EI, Olivier M, Martel-Plache G, LeCalvez - Kelm F, Brugières L, Vargas FR, Brentani RR, Ashton-Prolla P, *et al.* (2010) Detailed haplotype analysis at the *TP53* locus in p.R337H mutation carriers in the

population of Southern Brazil: Evidence for a founder effect. Hum Mutat 31:143-150.

Giacomazzi J, Toledo de Bueno Osorio CA, Koehler-Santos P, Graudenz MS, Martel-Planche G, Achatz MI, Soares FA, Goldim JR, Caleffi M, Hainaut P, *et al.* (2011) Contribution of TP53 p.R337H mutation to breast cancer incidence in Brazil. Cancer Res 15(Suppl 3):P1-09-07.

Giacomazzi J, Koehler-Santos P, Palmero EI, Graudenz MS, Rivero LF, Lima E, Putten AC, Hainaut P, Camey SA, *et al.* (2013) A *TP53* founder mutation, p.R337H, is associated with phyllodes breast tumors in Brazil. Virchows Arch 463:17-22.

Gomes MC, Costa MM, Borojevic R, Monteiro NA, Vieira R, Koiman S, Koifman RJ, Li S, Royer R, Zhang S, *et al.* (2007) Prevalence of *BRCA1* and *BRCA2* mutations in breast cancer patients from Brazil. Breast Cancer Res Treat 103:349-353.

Gutiérrez-Espeleta GA, Llacuachaqui M, García-Jiménez L, Aguilar Herrera M, Loaiciga Vega K, Ortiz A, Royer R, Li S and Narod SA (2012) *BRCA1* and *BRCA2* mutations among familial breast cancer patients from Costa Rica. Clin Genet 82:484-488.

Hamel N, Feng B-J, Foretova L, Stoppa-Lyonet D, Narod SA, Imyanitov E, Sininilkova A, Tihomirova L, Lubinski J, Gronwald J, *et al.* (2011) On the origin and diffusion of *BRCA1* c.5266dupC (5382insC) in European populations. Eur J Hum Genet 19:300-306.

Herrmann LJ, Heinze B, Fassnacht M, Willenberg HS, Quinkler M, Reisch N, Zink M, Allolio B, Hahner S, *et al.* (2012) *TP53* germline mutations in adult patients with adrenocortical carcinoma. J Clin Endocrinol Metab 97:E476-485.

Infante M, Durán M, Esteban-Cardeñosa E, Miner C and Velasco E (2006) High proportion of novel mutations of *BRCA1* and *BRCA2* in breast / ovarian cancer patients from Castilla-León (central Spain). J Hum Genet 51:611-617.

Jara L, Ampuero S, Seccia L, Bustamante M, Blanco R, Santibañez E, Reyes JM and Ojeda JM (2002a) Frequency of the 185delAG mutation in the *BRCA1* gene in Chilean healthy women with family history of breast cancer. Rev Med Chil 130:1113-1123.

Jara L, Ampuero S, Seccia L, Bustamante M, Blanco R and Ojeda JM (2002b) Analysis of 5382insC (*BRCA1*) and 6174delT (*BRCA2*) mutations in 382 healthy Chilean women with a family history of breast cancer. Biol Res 35:85-93.

Jara L, Ampuero S, Santibáñez E, Seccia L, Rodriguez J, Bustamante M, Lay-Son G, Ojeda JM, Reyes JM and Blanco R (2004) Molecular analysis of the eighteen most frequent mutations in the *BRCA1* gene in 63 Chilean breast cancer families. Biol Res 37:469-481.

Jara L, Ampuero S, Santibáñez E, Seccia L, Rodriguez J, Bustamante M, Martinez M, Catenaccio A, Lay-Son G, Blanco R, *et al.* (2006) *BRCA1* and *BRCA2* mutations in a South American population. Cancer Genet Cytogenet 166:36-45.

Lalloo F, Varley J, Ellis D, Moran A, O'Dair L, Pharoah P, Evans DG and Early Onset Breast Cancer Study Group (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361:1101-1102.

Lara K, Consigliere N, Pérez J, and Porco A (2012) *BRCA1* and *BRCA2* mutations in breast cancer patients from Venezuela. Biol Res 45:117-130.

Lindor NM, McMaster ML and Lindor CJ (2008) Concise Handbook of Familial Cancer Susceptibility Syndromes Second Edition. J Natl Cancer Inst Monogr 38:1-93

Lourenço JJ, Vargas FR, Bines J, Santos EM, Lasmar CAP, Costa CH, Teixeira EM, Maia MCM, Coura F, Silva CHD, *et al.* (2004) BRCA1 mutations in Brazilian patients. Genet Mol Biol 27:500-504.

Machado PM, Brandão RD, Cavaco BM, Eugenio J, Bento S, Nave M, Rodriguez P, Fernandez A and Vaz F (2007) Screening for a large *BRCA2* rearrangement in high-risk breast-ovarian cancer families: Evidence for a founder effect and analysis of the associated phenotypes. J Clin Oncol 25:2027-2034.

Malkin D, Li FP, Strong LC, Fraumeni Jr JF, Nelson CE, Kim DH, Hassel J, Gryka MA, Bischoff FZ, Tainsky MA, *et al.* (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233-1238.

Moreira MA, Bobrovnitchaia IG, Lima MA, Santos AC, Ramos JP, Souza KR, Peixoto A, Teixeira MR and Vargas FR (2012) Portuguese c.156_157insAlu *BRCA2* founder mutation: Gastrointestinal and tongue neoplasias may be part of the phenotype. Fam Cancer 11:657-660.

Narod S (2012) The tip of the iceberg. A countercurrent series. Curr Oncol 19:3.

Olivier M, Hollstein M and Hainaut P (2010) *TP53* mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2:a001008.

Palmero EI, Schüler-Faccini L, Caleffi M, Achatz MI, Olivier M, Martel-Planche G, Marcel V, Aguiar E, Giacomazzi J, Ewald IP, *et al.* (2008) Detection of R337H, a germline *TP53* mutation predisposing to multiple cancers, in asymptomatic women participating in a breast cancer screening program in Southern Brazil. Cancer Lett 261:21-25.

Peixoto A, Santos C, Rocha P, Pinto P, Bizarro S and Teixeira MR (2009) Molecular diagnosis of the Portuguese founder mutation *BRCA2* c.156_157insAlu. Breast Cancer Res Treat 117:215-217.

Peixoto A, Santos C, Pinheiro M, Pinto M, Soares MJ, Rocha P, Gusmão L, Amorim A, van der Hout A, Gerdes AM, *et al.* (2011) International distribution and age estimation of the Portuguese BRCA2 c.156_157insAlu founder mutation. Breast Cancer Res Treat 127:671-679.

Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P, and Olivier M (2007) Impact of mutant p53 functional properties on *TP53* mutation patterns and tumor phenotype: Lessons from recent developments in the IARC TP53 database. Hum Mutat 28:622-629.

Pinto EM, Billerbeck AE, Villares MC, Domenice S, Mendonça BB and Latronico AC (2004) Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol 48:647-650.

Ribeiro RC, Sandrini F, Figueiredo B, Zambetti GP, Michalkiewicz E, Lafferty AR, DeLacerda L, Rabin M, Cadwell C, Sampaio G, *et al.* (2001) An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci U S A 98:9330-9335.

Rodríguez AO, Llacuachaqui M, Pardo GG, Rover R, Larson G, Weitzel JN and Narod SA (2012) *BRCA1* and *BRCA2* muta-

tions among ovarian cancer patients from Colombia. Gynecol Oncol 124:236-243.

Sanabria MC, Muñioz G and Vargas CI (2009) Mutations in the *BRCA1* gene (185delAG and 5382insC) are not present in any of the 30 breast cancer patients analyzed from eastern Colombia. Biomedica 29:61-72.

Sanchez A, Faundez P and Carvallo P (2011) Genomic rearrangements of the *BRCA1* gene in Chilean breast cancer families: An MLPA analysis. Breast Cancer Res Treat 128:845-853.

Salazar R, Cruz-Hernandez JJ, Sanchez-Valdivieso E, Rodriguez CA, Gomez-Bernal A, Barco E, Fonseca E, Portugal T and Gonzalez-Sarmiento R (2006) *BRCA 1-2* mutations in breast cancer: Identification of nine new variants of BRCA 1-2 genes in a population from Western Spain. Cancer Lett 233:172-177.

Seidinger AL, Mastellaro MJ, Paschoal Fortes F, Godoy-Assumpção J, Aparecida Cardinalli I, Aparecida Ganazza M, Correia Ribeiro R, Brandalise SR, dos Santos Aguiar S and Yunes JA (2011) Association of the highly prevalent *TP53* R337H mutation with pediatric choroid plexus carcinoma and osteosarcoma in southeast Brazil. Cancer 117:2228-2235.

Torres D, Rashid MU, Gil F, Umana A, Ramelli G, Robledo JF, Tawil M, Torregrosa L, Briceno I and Hamann U (2007) High proportion of *BRCA1/2* founder mutations in Hispanic breast/ovarian cancer families from Colombia. Breast Cancer Res Treat 103:225-232.

Vaca-Paniagua F, Alvarez-Gomez RM, Fragoso-Ontiveros V, Vidal-Millan S, Herrera LA, Cantu D, Bargallo-Rocha E, Mohar A, Lopez-Camarillo C and Perez-Plasencia C (2012) Full-exon pyrosequencing screening of BRCA germline mutations in Mexican women with inherited breast and ovarian cancer. PLoS One 7:e37432.

Vidal-Millán S, Taja-Chayeb L, Gutiérrez-Hernández O, Ramirez Ugalde MT, Robles-Vidal C, Bargallo-Rocha E, Mohar-Betancourt A and Dueñas-Gonzalez A (2009) Mutational analysis of *BRCA1* and *BRCA2* genes in Mexican breast cancer patients. Eur J Gynaecol Oncol 30:527-530.

Weitzel JN, Lagos V, Blazer KR, Nelson R, Ricker C, Herzog J, Mcguire C and Neuhausen S (2005) Prevalence of *BRCA* mutations and founder effect in high-risk hispanic families. Cancer Epidemiol Biomarkers Prev 14:1666-1671.

Weitzel JN, Lagos VI, Herzog JS, Judkins T, Hendrickson B, Ho JS, Ricker CN, Lowstuter KJ, Blazer KR, Timlinson G, *et al.* (2007) Evidence for common ancestral origin of a recurring *BRCA1* genomic rearrangement identified in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev 16:1615-1620.

Weitzel JN, Blazer KR, Macdonald DJ, Culvert JO and Offit K (2013) Genetics, genomics, and cancer risk assessment: State of the art and future directions in the era of personalized medicine. CA Cancer J Clin [Epub ahead of print].

Weitzel JN, Clague J, Martir-Negron A, Ogaz R, Herzog J, Ricker C, Jungbluth C, Cina C, Duncan P, Unzeitig G, *et al.* (2013) Prevalence and type of *BRCA* mutations in Hispanics undergoing genetic cancer risk assessment in the southwestern United States: A report from the Clinical Cancer Genetics Community Research Network. J Clin Oncol 31:210-216.

## Internet Resources

International Agency for Research on Cancer (IARC) http://p53.iarc.fr/TP53GeneVariations.aspx