Common BRCA1 and BRCA2 Mutations among Latin American Breast Cancer Subjects: A Meta-Analysis

Leonardo M Porchia1, M Elba González Mejía1, Luis Calderilla-Barbosa1, Nirvana I Ordaz Díaz1, Fabiola Islas Lugo1, José Oldak1, Rossana C Zepeda1 and Gisela Aguirre*1

1Laboratorio de Geneticidad y Biología Molecular, D-SU Biotek S.A. de C.V, México
2Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, México
3Centro de Investigaciones Biomedicas, Universidad Veracruzana, México

Abstract

Background: Many BRCA1 and BRCA2 mutations have been characterized in breast cancer subjects; however, the overall prevalence in Latin American remains elusive. The aim of the study was to determine the prevalence of common BRCA1 and BRCA2 mutations in Latin American breast cancer subjects.

Methods: Pubmed, EBSCO, and OVID databases, and study bibliographies were systematically searched for observational studies that examined for mutations in BRCA1 and BRCA2 until March 2015. The pooled prevalence was obtained using the inverse double arcsine square root method. Publication bias was assessed by Beggs and Mazumdar’s test and the Egger’s test. The sensitivity was determined by reevaluation of the pooled estimate after removal of one study.

Results: Out of 294 retrieved studies, 32 studies met the inclusion criteria (n=9938 subjects). Twenty-nine BRCA1 and thirteen BRCA2 pathogenic mutations were described in two or more studies. For BRCA1, the most reported mutations were 185delAG and A1708E. The most prevalent BRCA1 mutations (>0.50%) were del exon 9–12 (1.45%, 95% CI: 0.61–2.63%), 185delAG (0.90%, 95% CI: 0.50–1.42%), R171G (0.64%, 95% CI: 0.43–0.87%), A1708E (0.58%, 95% CI: 0.40–0.79%), and del exon 16–17 (0.54%, 95% CI: 0.32–0.82%). For BRCA2, the most reported mutations were 6174delT and 3036del4t; however, the H372N (0.78%, 95% CI: 0.14–1.82%) was the most frequent (>0.50%). Comparing Mexican-based studies to the remaining Latin American reports, we provide evidence that certain mutations are specific only for Mexicans and their descendants (i.e. BRCA1 del exon 9–12 and BRCA2 3492insT, G273R, and W2586X).

Conclusion: Here we identify the most common BRCA1 and BRCA2 mutations among Latin Americans. This information will aid in selecting mutations for genetic testing and in epidemiological studies.

Keywords: BRCA1; BRCA2; Latin America; Meta-analysis; Breast cancer; Polymorphism; Mexico

Introduction

Breast cancer is the most common cancer among Latin American women and the leading cause of cancer-associated deaths [1,2]. It is estimated that 114,900 new cases and 37,000 deaths occur in Latin American populations annually [3]. Unfortunately, Latin American women have a poor 5 year survival rate than most other ethnic groups [4] and the incidence is increasing annually in these countries [5-7]. Genetic cancer risk assessment has become an integral part of disease prevention, especially in countries such as Spain and USA; however, the limited availability of clinical gene testing has prevented the implementation of prevention programs in Central and South American countries.

Five to ten percent of all breast cancers in Latin American women are attributed to germ-line mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 [8,9]. Conversely, in low-income countries with restricted financial resources for genetic testing, this percentage has been suggested to be underestimated. The lifetime risk of developing breast cancer increases up to 80% with certain BRCA1 and BRCA2 mutations [10]. BRCA mutations prevalence varies between country as well as ethnic groups [11]. With more than 300 documented BRCA1 and BRCA2 mutations found in Hispanic countries [12-22] and with limited reports describing the prevalence of BRCA1 and BRCA2 mutations, which can range from 0% to over 50%, we therefore conducted a meta-analysis to determine the prevalence of certain pathogenic mutations in Central and South American countries.

Methods and Materials

Publication search

Pubmed, OVID, and EBSCO databases were searched for all studies that investigated the prevalence of BRCA1 and BRCA2 mutations found among Latin American breast cancer individuals. The following keywords and index terms were used: “Latin, Hispanic, South and Central America” as well as other terms associated with all Latin American countries, “BRCA1 and BRCA2”, and “deletion, insertion, mutation, and polymorphism” for any publication published up to March 30, 2015. Only papers published in English, Spanish, and Portuguese were reviewed. Afterwards, the compiled publications’ references were hand searched. The titles and abstract were reviewed and reports that were not eligible for this study were eliminated. All

*Corresponding author: Gisela Aguirre, Laboratorio de Genética y Biología Molecular, D-SU Biotek S.A. de C.V. Paseo de los Heroes 1031 Int.301 Zona Urbana Río, 22010, Tijuana, Baja California, México, Tel: 01 (55) 1227 2200; E-mail: gisli@dsubiotek.com

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studies had to meet the following criteria: studies focused on examining the prevalence of BRCA1 or BRCA2 mutations in human subjects, with breast cancer, from Latin American countries or their descendants. Non-human studies, in vitro or in vivo studies, reviews, studies that failed to indicate the prevalence of mutations, or focused on other than breast cancer were excluded.

Data extraction

Two of the authors extracted all data independently. If there was a disagreement, another author assessed the publication in question. If a single sample was believed to be use in multiple publications, the publications were assessed to determine which one was the most representative and that data was used for that mutation, or the corresponding author was contacted to resolve the issue. The data collected were geographical location, criteria use to select sample, sample size, the mutation and the number of positive individuals, method used to detect the mutations, and exons and introns examined.

Statistical analysis

The term “Prevalence” corresponds to relative prevalence rate, which was defined as the total number of positive individuals with breast cancer for a specific mutation divided by the total number of breast cancer cases. The prevalence and the 95% confidence interval (95% CI) were calculated for each mutation. Next, the pooled prevalence estimate was calculated using the inverse double arcsine square root method (Stuart-Ord) [23]. It is worthy to note that only studies that examined the exon or the intron of the BRCA1 or BRCA2 gene or specifically indicated they examined for the mutation of interest were included in the meta-analysis, independent if the authors found the mutation or not. Heterogeneity was determined using the ψ^2-based Q test and its degree was assessed by the I^2 value (inconsistency index). The Fixed Effects Model was used when the sample was considered homogeneous (Mantel-Haenszel method) [24] and the random effects model was used when the sample was considered heterogeneous (DerSimonian and Laird Method) [25]. The stability and sensitivity of the results were assessed by removing one study and re-calculating the pooled prevalence. Publication bias was evaluated by Begg and Mazumdar adjusted rank correlation asymmetry test (Kendall’s tau) and the Egger regression asymmetry test [26,27]. The Fisher’s exact test was used to determined difference of frequencies between groups. Statistical analyses were performed using StatDirect Statistical Software version 3.0.147 (Cheshire, UK). P-values <0.05 (two-sided) were considered statistically significant.

Results

Characteristic of the studies

Using the search terms, we identified 294 possible studies from the multiple databases and from reviewing study’s bibliographies. We excluded 241 studies that focused on cancers other than Breast cancer (n=22), did not focus on Latin Americans (n=6), did not focus on human subjects (n=24), the BRCA genes were not the focus of the study (n=92), did not determine the frequency of BRCA mutations (n=74) or were not a research article (n=23). The remaining 53 studies were extensively evaluated. Thirteen studies were excluded because they lacked sufficient information and eight more studies were excluded due to shared samples. This led to 32 studies, consisting of 9938 subjects, which were included for the meta-analysis (Figure 1). Detailed characteristics of these studies are presented in Table 1. The most represented country

![Figure 1: Meta-analysis.](image-url)
<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>BRCA Coverage</th>
<th>Screening Method</th>
<th># of mutations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N</th>
<th>Study inclusion criteria</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuggattas, 2014 Peru</td>
<td>HISPANEL-114 mutations</td>
<td>Sequencing</td>
<td>4</td>
<td>1</td>
<td>266</td>
<td>[49]</td>
</tr>
<tr>
<td>Anton Culver, 2000 USA-Hispanics</td>
<td>BRCA1: 185delAG, 5382insC, R1443X, ind-11T-G, R841W, 4184delTCA, 2594delC</td>
<td>ASO</td>
<td>0</td>
<td>N/A</td>
<td>42</td>
<td>[51]</td>
</tr>
<tr>
<td>Carraro, 2011 Brazil</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>Sequencing</td>
<td>8</td>
<td>10</td>
<td>54</td>
<td>[33]</td>
</tr>
<tr>
<td>Delgado, 2011 Uruguay</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>HDA, PTT, Sequencing</td>
<td>7</td>
<td>14</td>
<td>42</td>
<td>[50]</td>
</tr>
<tr>
<td>Dufloth, 2005 Brazil</td>
<td>BRCA1: exon 2, 3, 5, 11, 20 BRCA2: exon 10, 11&lt;sup&gt;*&lt;/sup&gt;</td>
<td>SSCP, sequencing</td>
<td>1</td>
<td>2</td>
<td>31</td>
<td>[34]</td>
</tr>
<tr>
<td>Esteves, 2009 Brazil</td>
<td>BRCA1: exon 11 BRCA2: exon 10, 11</td>
<td>PTT, sequencing</td>
<td>7</td>
<td>3</td>
<td>612</td>
<td>[35]</td>
</tr>
<tr>
<td>Ewald, 2011 Brazil</td>
<td>BRCA1: 185delAG, 5382insC BRCA2: 6174delT</td>
<td>PCR</td>
<td>1</td>
<td>0</td>
<td>131</td>
<td>[36]</td>
</tr>
<tr>
<td>Gallardo, 2006 Chile</td>
<td>BRCA1 and BRCA2: covering coding sequences and intron-exon boundaries (exons 2 to 24)</td>
<td>PCR, SSCP, PTT, HDA, sequencing</td>
<td>15</td>
<td>11</td>
<td>54</td>
<td>[39]</td>
</tr>
<tr>
<td>Gomes, 2007 Brazil</td>
<td>BRCA1: exon 11 BRCA2: exon 10, 11</td>
<td>PTT, sequencing</td>
<td>2</td>
<td>2</td>
<td>402</td>
<td>[37]</td>
</tr>
<tr>
<td>Gonzalez-Hormazabal, 2011 Chile</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>CSGE, HDA, Sequencing</td>
<td>30</td>
<td>25</td>
<td>326</td>
<td>[40]</td>
</tr>
<tr>
<td>Hall, 2009 USA-Hispanics</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>Myraid&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>2</td>
<td>1936</td>
<td>[16]</td>
</tr>
<tr>
<td>Hernandez, 2014 Colombia</td>
<td>BRCA1: exon 11 BRCA2: exon 10, 11</td>
<td>PTT, sequencing</td>
<td>2</td>
<td>1</td>
<td>244</td>
<td>[43]</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>BRCA1/2 Genes</td>
<td>Methodology</td>
<td>N</td>
<td>Total N/A</td>
<td>Mutations/Characteristics</td>
</tr>
<tr>
<td>---------------</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>John, 2007 USA-Hispanics</td>
<td>All exons and adjacent intronic regions</td>
<td>CSGE, 2DGS, Myraid</td>
<td>11</td>
<td>N/A</td>
<td>393 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Judkins, 2012 USA-Hispanics</td>
<td>BRCA1 and BRCA2: All Large genomic rearrangements</td>
<td>multiplex PCR, Myraid</td>
<td>11</td>
<td>N/A</td>
<td>393 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Lara, 2012 Venezuela</td>
<td>BRCA1: All exons and adjacent intronic regions</td>
<td>CSGE, sequencing</td>
<td>24</td>
<td>30</td>
<td>58 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Nahleh, 2015 Mexico</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>Myraid</td>
<td>11</td>
<td>5</td>
<td>88 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Ruiz-Flores, 2002 Mexico</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>HDA, Sequencing</td>
<td>3</td>
<td>7</td>
<td>51 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Sanabria, 2009 Colombia</td>
<td>BRCA1: 185delAG, 5382insC</td>
<td>PCR</td>
<td>0</td>
<td>N/A</td>
<td>30 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Sanchez, 2011 Chile</td>
<td>BRCA1 and BRCA2: only Large Genomic rearrangements</td>
<td>MLPA</td>
<td>2</td>
<td>0</td>
<td>74 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Silva, 2014 Brazil</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>Sequencing, MLPA</td>
<td>18</td>
<td>6</td>
<td>120 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
<tr>
<td>Solano, 2012 Argentina</td>
<td>BRCA1 and BRCA2: All exons and adjacent intronic regions</td>
<td>Sequencing</td>
<td>36</td>
<td>23</td>
<td>134 A: patients whose cancers are likely to be hereditary 1) breast cancer diagnosis before age 35 years 2) bilateral breast cancer, with first diagnosis before age 50 years 3) prior ovarian or childhood cancer 4) at least 1 first-degree relative with breast or ovarian cancer. B: all other patients with cancers less likely to be hereditary</td>
<td></td>
</tr>
</tbody>
</table>
in this study was Mexico (n=7; [18,19,28-32]), followed by Brazil (n=6; [33-38]). Chile [39-42] and Colombia [43-46] both had four studies included in this meta-analysis and Argentina [47], Costa Rica [48], Peru [49], Uruguay [50], and Venezuela [17] each had one study. Six studies focused on Latin American subjects from multiple countries and their descendants [16,20,21,51,52]. The 32 studies used fourteen different methods to screen from BRCA mutations: sequencing (n=18), protein truncation test (PTT, n=8), PCR (n=6), heteroduplex analyses (HDA, n=4), multiplex ligation-dependent probe amplification (MLPA, n=3), and restriction fragment length polymorphism (RFLP, n=1). Six studies used Myriad Genetics, Inc. to screen for BRCA mutations and large genomic

Table 1: Characteristics of included studies.

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Latin Americans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Insertion</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Single Nucleotide variant</td>
<td>105</td>
<td>33</td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Mexicans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Insertion</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Single Nucleotide variant</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Mixed</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2: Distribution of BRCA1 and BRCA2 mutation among Latin Americans and Mexicans.
Table 2). However, when only pathogenic mutations were identified, the majority of mutations were single nucleotide variants (n = 105, 60.0%, in Latin American breast cancer patients (Supplemental Table 1). A total of 171 mutations were identified, of which 116 were substitutions, 36 were deletions (45.0%), 33 were single nucleotide variants (41.25%), and 11 were insertions (13.75%). Fifty pathogenic rearrangements.

Common BRCA1 mutations among Latin Americans

Using the 32 studies, we identified 175 BRCA1 mutations found in Latin American breast cancer patients (Supplemental Table 1). A majority of mutations were single nucleotide variants (n = 105, 60.0%, Table 2). However, when only pathogenic mutations were identified (n = 80, 45.7%), by using the CLINVAR database or the studies themselves, 36 were deletions (45.0%), 33 were single nucleotide variants (41.25%), and 11 were insertions (13.75%). Fifty pathogenic mutations (62.5%) were reported only once, whereas fifteen mutations (18.8%) were reported four times or more. The most identified mutation for BRCA1 was 185delAG and 1708E, found in eleven and ten studies, respectively.

The pathogenic mutations’ pooled prevalence was calculated for mutations presenting two or more studies using the inverse double
The four most prevalent BRCA1 mutations found in Latin American breast cancer subjects were del exon 9–12 (1.45%, 95% CI: 0.61–2.63%, Figure 2A), 185delAG (0.90%, 95% CI: 0.50–1.42%, Figure 2B), R71G (0.64%, 95% CI: 0.43–0.87%, Figure 2C), and A1708E (0.58%, 95% CI: 0.25–0.79%, Figure 2D). The remaining Forest Plots can be found in supplemental material (Supplemental Figure 1).

Next, to determine if these mutations occurred together, we examined the prevalence these mutations in a selected subgroup of subjects-Mexicans and Mexican descendents were selected because they had largest number of studies and compared them to the rest of the Latin American population. Anton Culver, 2000, Hall 2009, John 2007 (except for 185delAG analysis) and Vogel 2007 were excluded because Latin American origins could not be determined. The prevalence for the Mexican subjects for del exon 9–12 was 3.35% (95% CI: 1.18–6.57%, Figure 3A), for 185delAG was 0.94% (95% CI: 0.18–2.29%, Figure 3B), for R71G was 1.24% (95% CI: 0.67–1.98%, Figure 3C), and A1708E was 0.67% (95% CI: 0.35–1.08%, Figure 3D). The remaining Forest Plots can be found in supplemental material (Supplemental Figure 2). Comparison of these mutations indicated that the frequency between Mexicans and other Latin American countries was not similar. The frequency of the R71G mutation was higher in Mexicans than other Latin Americans (Fisher's exact test, p=0.0034), but there was no difference between the two groups for 185delAG (p=0.702) and A1708E (p=0.802). It is important to note that the deletion of BRCA1 exons 9–12 was only found in Mexican subjects.

Common BRCA2 mutation among Latin Americans

Twenty-five studies identified 162 mutations (Supplemental Table 2). The most common type of mutations were single nucleotide variants (n=103, 63.6%). Of the 162 mutations, only 69 (42.6%) of these were pathogenic. Of the pathogenic mutations, the most common type were deletions (n=34, 49.3%) followed by single nucleotide variants (n=24, 34.8%). Thirteen mutations (18.8%) were reported more than once. The most identified mutations were 6174delT and 3036del4, identified in six and five articles, respectively. The frequency of these mutations was determined by meta-analysis (Table 3). The most prevalent BRCA2 mutations found in Latin American Breast cancer subjects was H372N...
Next, we determined if the mutational frequencies were consistent between Mexican and other Latin American subjects. The prevalence of the pathogenic BRCA2 mutation among Mexicans was calculated (Table 3). The most prevalent BRCA2 mutations found in Mexican subjects were E49X (0.68%, 95% CI: 0.28–1.25%, Figure 5A), 3492insT (0.60%, 95% CI: 0.12–1.36%, Figure 5B), G273R (0.57%, 95% CI: 0.21–1.10%, Figure 5C), and W2586X mutations were only found in Mexican subjects. The E49X mutation prevalence was not different between Mexicans studies and other Latin American studies (p=0.159).

Test for sensitivity and publication bias

We assessed the publication bias for pathogenic mutation prevalence for BRCA1 and BRCA2 (Figure 6). For BRCA1, the Begg-Mazumdar’s test calculated Kendall’s tau to be 0.26 (p=0.036), and Egger’s test’s bias=2.12 (95% CI: 0.69–5.53, p=0.005). For BRCA2, the Begg-Mazumdar calculated Kendall’s tau to be 0.28 (p=0.037), and Egger’s test’s bias=2.35 (95% CI: 1.42–3.28, p<0.001). Examining the funnel plots, two studies (Lara 2012 and Solano 2012) could bias the results. To assess the sensitivity, one study was removed at a time and the effect on the pooled prevalence was reevaluated. For Latin American subjects, the pooled prevalence was resistance. These results suggest limited bias, which would minimally affect the results of the meta-analysis. The publication bias for each individual mutation was assessed for each meta-analysis and listed in Table 3.

Discussion

Breast cancer is the most common cancer among females in Latin American countries. While other risk factors, such as high estrogen exposure and age of menarche increases the risk of breast cancer development, mutations in the BRCA1 and BRCA2 genes have a more profound effect in certain population [53]. Genetic testing is an expensive procedure that can aid the development of specific treatment options. Unfortunately, with the large amount of possible mutations to test for, there is a need for a consensus on specific mutations.

In our study, we determined the prevalence of all BRCA1 and BRCA2 mutations among Latin American breast cancer subjects. This study is similar to Wang et al. and Forat-Yazdi et al., who determined the prevalence in breast cancer families and Iranians, respectively [54,55]; however, neither study examined the prevalence in nor contained Latin American subjects, specifically. Furthermore, Wang et al. and Forat-Yazdi et al. excluded studies from their meta-analysis that determine the absence of a mutation from their sample, which may have led them to overestimated the mutation’s prevalence. Here, we did incorporate any report that examined the region for these 80 BRCA1 and 69 BRCA2 pathogenic mutations. For example, Lara 2012 and Solano 2012, the two studies that found BRCA2 H372N, determined the frequency to be 55.2% and 25.5%, respectively, which would give a pooled prevalence of about 38.8%; however, including reports that determine the absence of this mutation, gives the pooled prevalence of 0.88%. Since many studies failed to determine this mutation in larger samples, this result would suggest that including the negative data would yield a more accurate value.
The most common BRCA1 mutation for Latin American breast cancer subjects was deletion exons 9-12. This mutation leads to an inactive form of BRCA1. However, this mutation was only found in Mexican studies and no other country. It is believed to have originated in the state of Puebla [31]; however, Weitzel et al., found this mutation present in subjects that originated from other distant regions of Mexico [21]. This would suggest emigration has led to the dispersion of this mutation. Interestingly, this mutation has not been reported in Southern Mexico or Guatemala, maybe due to a lack of studies. More research is required to determine the regions in Mexico where this mutation is prevalent.

The second most prevalent BRCA1 mutation was 185delAG. Unlike the deletion exon 9-12, the 185delAG mutation has been found in many different regions of Latin America (Argentina, Brazil, Chile, Mexico and Peru). Numerous reports have demonstrated that the BRCA1 185delAG increases the risk of developing breast cancer. This has led to the additional screening of subjects from certain ethnicities for the presence of this mutation, such as the Ashkenazi Jewish descendants. Nonetheless, within the Latin American populations, there is inconsistent evidence about the prevalence of this mutation in breast cancer subjects, which ranged from 0.0% (19 studies) to 5.22%. Here, we provide evidence that 185delAG frequency was significantly prevalent and was not different between Mexico and all other Latin American countries (0.90% vs. 0.94%, p=0.70); then again, not all countries in Central and South America were properly represented. A similar result was determined for BRCA1 A1708E and BRCA2 E49X. On the other hand, BRCA1 R71G was found in Mexicans as well as Argentinians but was more prevalent in Mexico. Moreover, BRCA2 6174delT and H372N were found in Argentina, Brazil, Chile, Costa Rica, and Venezuela and not Mexico. As well, the BRCA2 3492insT, G273R, and W2586X were found only in Mexico and not other Latin American country. These examples beg the question that should there be a select set of mutations examined for certain regions of Latin American countries.

Central and South America were settled by many different groups, with the Andes as a geographical barrier. It is believed that the ancestors of many Latin American countries were settled by many different groups, with the Andes as a geographical barrier. It is believed that the ancestors of many Latin American countries were settled by many different groups, with the Andes as a geographical barrier. It is believed that the ancestors of many Latin American countries were settled by many different groups, with the Andes as a geographical barrier.

The third most prevalent BRCA2 mutation was H372N. Unlike the deletion exon 9-12, the 185delAG mutation has been found in many different regions of Latin America (Argentina, Brazil, Chile, Mexico, and Peru). Numerous reports have demonstrated that the BRCA2 H372N increases the risk of developing breast cancer. This has led to the additional screening of subjects from certain ethnicities for the presence of this mutation. The question is that should there be a select set of mutations examined for certain regions of Latin American countries. Furthermore, it demonstrates that specific regions of Latin American are associated with certain BRCA2 mutations.
polymorphism has been identified in many regions of Spain: Asturias [56], Valencia [57-60], Aragon [60], Castilla-Leon [61], and Madrid [62], where the mutation frequency ranged between 0.22-2.08%. Interestingly, this mutation has not been reported in Barcelona or Galicia [63], suggesting that this mutation originated from a specific region of Spain. In Mexico, a majority of the population ancestry is from Spain, implying that the BRCA2 3492insT mutation could be found in Mexico. Indeed, this meta-analysis does provide evidence that BRCA2 3492insT was significantly present among Mexicans. A majority of the reports focused on Mexican subjects used in this meta-analysis failed to determine the presence of BRCA2 3492insT. These reports focused on highly-populated regions of Mexico City, the State of Mexico, Nuevo Leon and Veracruz and surrounding regions-most of the states located in the center of Mexico. However, Weitzel et al. did observe the mutation in subjects from Durango, Guerrero, Jalisco, Sinaloa, Sonora, and Zacatecas [21]. With the exception of Guerrero, these states are located in Western Mexico, which would posit the notion that these states present this mutation due to a more pronounced Spanish influence. This is supported by the work of Moreno-Estrada et al., which indicates that subjects from Western Mexico do have a greater Spanish genetic composition than states from Eastern or Southern Mexico [64]. Interestingly, the BRCA2 3492insT mutation has not been observed in other Central or South American countries [15,17,33,39,43,47-50]. As seen with the San Luis Valley studies, due to Spaniard expeditions, the BRCA1 185delAG mutation was introduced and spread among the region, leading to its extraordinary prevalence [65,66]. This would also support the notion that the BRCA2 3492insT mutation is specific for Mexico and Spain. Overall, the region-specific mutational patterns are likely caused by original differences of the native population and induced differences by emigration.

In this meta-analysis there are a few limitations. First, the included studies collected genomic DNA from either blood or a buccal sample, or both. Recent reports have suggest that a blood sample is the superior method, suggesting that studies that used a buccal sample could
underestimate or fail to determine the prevalence of BRCA mutations. Second, studies with smaller sample sizes does increase the prevalence of a single case found but also decrease the chance of discovering a positive case among the sample. Third, due to the emigration pattern that has led to the high diversity of Latin America, many regions of Central and South America are under-represented. For example, as mentioned above, the 3492insT mutation was mainly found on the Western part of Mexico and not in the Northern or the Eastern regions or any other Latin American country. This result demonstrates the need for more region-specific analyses.

In conclusion, this study identifies the most prevalent BRCA1 and BRCA2 mutations found in Latin American breast cancer subjects. Furthermore, we demonstrate that certain mutations are only specific for certain regions, whereas others are constant throughout Latin America. This information will aid in developing a more narrow genetic screening strategy based on the subject's background and lead to cheaper testing. However, with most Latin American countries have not been assessed for BRCA1 and BRCA2 mutations, further studies are required.

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