# Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations

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## Abstract

The prevalence and spectrum of germline mutations in *BRCA1* and *BRCA2* have been reported in single populations, with the majority of reports focused on White in Europe and North America. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has assembled data on 18,435 families with *BRCA1* mutations and 11,351 families with *BRCA2* mutations ascertained from 69 centers in 49 countries on six continents. This study comprehensively describes the characteristics of the 1,650 unique *BRCA1* and 1,731 unique *BRCA2* deleterious (disease-associated) mutations identified in the CIMBA database. We observed substantial variation in mutation type and frequency by geographical region and race/ethnicity. In addition to known founder mutations, mutations of relatively high frequency were identified in specific racial/ethnic or geographic groups that may reflect founder mutations and which could be used in targeted (panel) first pass genotyping for specific populations. Knowledge of the population-specific mutational spectrum in *BRCA1* and *BRCA2* could inform efficient strategies for genetic testing and may justify a more broad-based oncogenetic testing in some populations.

**KEYWORDS**
BRCA1, BRCA2, breast cancer, ethnicity, geography, mutation, ovarian cancer

## 1 | INTRODUCTION

Women who carry germline mutations in either *BRCA1* [MIM# 113705] or *BRCA2* [MIM# 600185] are at an increased risk of breast and ovarian cancers. Estimates of cancer risk associated with *BRCA1* and *BRCA2* mutations vary depending on the population studied. For mutations in *BRCA1*, the estimated average risk of breast and ovarian cancers ranges from 57 to 65% and 20 to 50%, respectively (Chen & Parmigiani, 2007; Kuchenbaecker et al., 2017). For *BRCA2*, average risk estimates range from 35 to 57% and 5 to 23%, respectively (Chen & Parmigiani, 2007; Kuchenbaecker et al., 2017). Mutation-specific cancer risks have been reported that suggest breast cancer cluster regions (BCCR) and ovarian cancer cluster regions (OCCR) exist in both *BRCA1* and *BRCA2* (Gayther et al., 1997; Kuchenbaecker et al., 2017; Rebbeck et al., 2015). The identification of mutations in *BRCA1* or *BRCA2* has important clinical implications, as knowledge of their presence is important for risk assessment and informs medical management for patients. Interventions, such as risk-reducing bilateral mastectomy and salpingo-oophorectomy or annual breast magnetic resonance imaging (MRI) screening, are available to women who carry deleterious *BRCA1* or *BRCA2* mutations to enable early detection of breast cancer and for active risk reduction by risk-reducing surgery (Domchek et al., 2010; Rebbeck et al., 2002; Saslow et al., 2007). The presence of *BRCA1* or *BRCA2* mutations can also influence cancer treatment decisions, principally around the use of platinum agents or poly(ADP-ribose) polymerase (PARP) inhibitors (Lord & Ashworth, 2017) or contralateral risk-reducing mastectomy. Increased numbers of women are having clinical genetic testing for *BRCA1* and *BRCA2* mutations, and recommendations continue to expand to whom testing should be offered (NCCN, 2017).

In Whites drawn from the general populations in North America and the United Kingdom, the prevalence of *BRCA1* and *BRCA2* mutations has been estimated around a broad range from 0.1 to 0.3% and 0.1 to 0.7%, respectively (Peto et al., 1999; Struewing et al., 1997; Whittemore et al., 2004). The Australian Lifepool study, studying a control population consisting of cancer-free women ascertained via population-based mammographic screening program, estimated the overall frequency of *BRCA1* and *BRCA2* mutations to be 0.65% (1:153), with *BRCA1* mutations at 0.20% (1:500) and *BRCA2* mutations at 0.45% (1:222) (Thompson et al., 2016). Estimates from the Exome Aggregation Consortium (ExAC) are similar, with frequencies of *BRCA1* and *BRCA2* mutations (excluding The Cancer Genome Atlas [TCGA] data) at 0.21% (1:480) and 0.31% (1:327), respectively; or combined at 0.51% (1:195) (Maxwell, Domchek, Nathanson, & Robson, 2016). As they do not include large genomic rearrangements, some newer population-based estimates may still underrepresent the total number of *BRCA1* and *BRCA2* mutations. Although the overall prevalence of *BRCA1* and *BRCA2* mutations in most general populations is low, many hundreds of thousands of yet-to-be-tested individuals worldwide carry these mutations.

The prevalence of founder mutations in some racial/ethnic groups is much higher. For example, the mutations *BRCA1* c.5266dup (5382insC), *BRCA1* c.68_69del (185delAG) and *BRCA2* c.5946del (6174delT) have a combined prevalence of 2–3% in U.S. Ashkenazi Jews (Roa, Boyd, Volcik, & Richards, 1996; Struewing et al., 1997; Whittemore et al., 2004). For these mutations, double heterozygotes in *BRCA1* and *BRCA2* also have been reported (Friedman et al., 1998; Moslehi et al., 2000; Ramus et al., 1997a; Rebbeck et al., 2016). Several other founder mutations have been identified, including the Icelandic founder mutation *BRCA2* c.771_775del (999del5) (Thorlacius et al., 1996), the French Canadian mutations *BRCA1* c.4327C > T (C4446T), the *BRCA2* c.8537_8538del (8765delAG) (Oros et al., 2006b; Tonin et al., 2001; Tonin, Mes-Masson, Narod, Ghadirian, & Provencher, 1999), the *BRCA1* mutations c.181T > G, and c.4034del in Central-Eastern Europe (Gorski et al., 2000), the *BRCA1* c.548-?–4185+?del in Mexico (Villarreal-Garza et al., 2015b; Weitzel et al., 2013),

the BRCA2 mutation c.9097dup in Hungary (Ramus et al., 1997b; Van Der Looij, et al., 2000), and others. These mutations represent the majority of mutations observed in these populations and have been confirmed as true founder mutations as they have common ancestral haplotypes (Neuhausen et al., 1996, 1998; Oros et al., 2006a). Recurrent mutations have been identified in other populations, but they represent a smaller proportion of all unique *BRCA1* and *BRCA2* mutations, and have not been characterized as true founder mutations. There are multiple recurrent mutations in Scandinavian, Dutch, French, and Italian populations (Ferla et al., 2007). Similarly, a number of recurrent mutations specific to non-European populations also have been reported in Hispanic/Mexican, African American, Middle Eastern, and Asian populations (Bu et al., 2016; Ferla et al., 2007; Kurian, 2010; Lang et al., 2017; Ossa & Torres, 2016; Villarreal-Garza et al., 2015b).

The mutational spectra in *BRCA1* and *BRCA2* are best delineated in Whites from Europe and North America. However, data on mutational spectra in non-White populations of Asian, African, Mediterranean, South American and Mexican Hispanic descent have also been reported (Abugattas et al., 2015; Ahn et al., 2007; Alemar et al., 2016; Bu et al., 2016; Eachkoti et al., 2007; Ferla et al., 2007; Gao et al., 2000; Gonzalez-Hormazabal et al., 2011; Ho et al., 2000; Jara et al., 2006; John et al., 2007; Kurian, 2010; Laitman et al., 2011; Lang et al., 2017; Lee et al., 2003; Li, et al., 2006; Nanda et al., 2005; Ossa & Torres, 2016; Pal, Permuth-Wey, Holtje, & Sutphen, 2004; Rodríguez et al., 2012; Seong et al., 2009; Sharifah et al., 2010; Solano et al., 2017; Song et al., 2005; Song et al., 2006; Toh et al., 2008; Torres et al., 2007; Troudi et al., 2007; Villarreal-Garza et al., 2015b; Vogel et al., 2007; Weitzel et al., 2005; Weitzel et al., 2007; Zhang et al., 2009). In the current study, we provide a global description of *BRCA1* and *BRCA2* mutations by geography and race/ethnicity from the investigators of the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).

## 2 | METHODS

Details of centers participating in CIMBA and data collection protocols have been reported previously (Antoniou et al., 2007). Details of the CIMBA initiative and information about the participating centers can be found at http://cimba.ccge.medschl.cam.ac.uk/ (Chenevix-Trench et al., 2007). All included mutation carriers participated in clinical or research studies at the host institutions after providing informed consent under IRB-approved protocols. Sixty-nine centers and multicenter consortia submitted data that met the CIMBA inclusion criteria (Antoniou et al., 2007). Only female carriers with pathogenic *BRCA1* and/or *BRCA2* mutations were included in the current analysis. One mutation carrier per family in the CIMBA database was included in this report. The actual family relationships (e.g., pedigrees) were not available, but a variable that defined family membership supplied by each center was used for this purpose. Less than 1% of families (86 of 29,700) had two family members with two different mutations. In these situations, each mutation observed in the family was included in the analysis. In the case of the 94 dual mutation carriers (i.e., individuals with both *BRCA1* and *BRCA2* mutations), one of the two mutations was chosen at random for inclusion in the analysis.

The CIMBA data set was used to describe the distribution of mutations by effect and function. For the remaining analyses, mutations were excluded if self-reported race/ethnicity data were missing. Pathogenicity of mutation was defined as follows: (1) generating a premature termination codon (PTC), except variants generating a PTC after codon 1854 in *BRCA1* and after codon 3309 of *BRCA2*, (2) large in-frame deletions that span one or more exons, and (3) deletion of transcription regulatory regions (promoter and/or first exon) expected to cause lack of expression of mutant allele. We also included missense variants considered pathogenic by using multifactorial likelihood approaches (Bernstein et al., 2006; Goldgar et al., 2004). Mutations that did not meet the above criteria but have been classified as pathogenic by Myriad Genetics, Inc. (Salt Lake City, UT) also were included. Classification of nonsense-mediated decay (NMD) was based on in-silico predictions and was not based on molecular classification (Anczukow et al., 2008).

Contingency table analysis using a chi-square test was used to test for differences in dichotomous variables, as was a *t*-test for continuous variables. Mutation counts are presented as the number of families with the mutation. Fisher's exact tests were used if sample sizes in any contingency table cell were less than five. Analyses were done in STATA, v. 14.2.

## 3 | RESULTS

### 3.1 | Mutations in *BRCA1* and *BRCA2*

From the 26,861 *BRCA1* and 16,954 *BRCA2* mutation carriers in the CIMBA data set as of June 2017, 18,435 families with *BRCA1* mutations and 11,351 families with *BRCA2* mutations were studied to count only one occurrence of a mutation per family. Figure 1 shows the countries that contributed mutations to this report. From among these families, 1,650 unique *BRCA1* and 1,731 unique *BRCA2* mutations were identified. The unique mutations and number of families in which each mutation was observed are listed in Supporting Information Table S1. In each gene, the five most common mutations (including founder mutations) accounted for 33% of all mutations in *BRCA1* (8,739 of 26,861 mutation carriers) and 19% of all mutations in *BRCA2* (3,244 of 16,954 mutation carriers). A website containing information about the most common mutations reported here can be found at: http://cimba.ccge.medschl.cam.ac.uk/. This information may be periodically updated as new data become available.

### 3.2 | Mutation type and effect

Table 1 presents a summary of the type of *BRCA1* or *BRCA2* mutations and their predicted effect on transcription and translation. The most common mutation type was frameshift followed by nonsense. The most common effect of *BRCA1* and *BRCA2* mutations was premature translation termination and most of the mutant mRNAs were predicted


**FIGURE 1** Countries (in red) that provided data on BRCA1 and/or BRCA2 mutation carriers in this report. Race/ethnic breakdown is reported for countries with more than 100 observations with multiple ethnicities totaling at least 10% of the country's sample (i.e., Australia, Brazil, Canada, USA)

to undergo nonsense-mediated mRNA decay (Anczukow et al., 2008). Despite having the same spectrum of mutations in *BRCA1* and *BRCA2*, the frequency distribution by mutation type, effect, or function differed significantly ($p < .05$) between *BRCA1* and *BRCA2* mutation carriers for many groups, as shown in Table 1. These observed differences are largely because genomic rearrangements and missense mutations account for a much higher proportion of mutations in *BRCA1* when compared with *BRCA2*, as previously described (Welcsh & King, 2001).

We and others have found that BCCR and OCCR exist that may confer differential cancer risks (Gayther et al., 1997; Gayther et al., 1995; Kuchenbaecker et al., 2017; Rebbeck et al., 2015). Figure 2 reports the relative frequency of mutations in the BCCR and OCCR by race/ethnicity. Compared with Whites, we observed differences in the relative frequency of mutations in the *BRCA1* BCCR and OCCR in Asians and Hispanics, and in the *BRCA2* OCCR in Hispanics. To the degree that the mutations within the BCCRs and OCCRs conferred differential cancer risks, these data suggest that *BRCA1* and *BRCA2* mutation-associated cancer risks may vary by race/ethnicity.

## 3.3 | Geography and race/ethnicity

The most common mutations by country are summarized in Table 2 (*BRCA1*) and Table 3 (*BRCA2*). The locations of the mutations that were observed in African American, Asian, and Hispanic populations are depicted in Figure 3 (*BRCA1*) and Figure 4 (*BRCA2*). Some countries (Albania, Bosnia, Costa Rica, Ireland, Honduras, Japan, Norway, Peru, Philippines, Qatar, Saudi Arabia, Romania, Venezuela and Turkey) contributed fewer than 10 mutation carriers to the CIMBA database. Many of these mutations were submitted to the central database by CIMBA centers that ascertained these patients, but these patients originated from a different country. Based on such small numbers, it was impossible to make inferences about the relative importance of mutations in these locations. A description of the major ethnicity by country is provided in Supporting Information Table S2.

The mutational distribution among the major racial/ethnic groups and by geography is summarized in Tables 4 and 5. Table 4 includes only those individuals for whom self-identified race/ethnicity was recorded. Note that in some countries it is prohibited to collect data on race and ethnicity, so this information is missing. Among the 10 most common *BRCA1* mutations in each racial/ethnic group, a few were seen in several populations, including the recurrent Jewish and Eastern European founder mutations c.5266dup (5382insC) and c.68_69del (185delAG), c.815_824dup in African Americans and Hispanics, c.3756_3759del in White and Jewish individuals, and c.5503C > T and c.3770_3771del in Asians and Jews. Similarly, recurrent mutations in *BRCA2* included c.5946del (6174delT) in Whites and Jews, c.2808_2811del in Whites, African Americans, Asians, Hispanics, and Jews, c.6275_6276del in Whites and Hispanics, c.3847_3848del in Whites and Jews, c.658_659del in African Americans and Hispanics, and c.3264dup in Hispanics and Jews. The majority of other recurrent *BRCA1* and *BRCA2* mutations were only observed within a single racial/ethnic group, particularly African Americans, Asians, and Hispanics. Of note, the vast majority of women who self-identified as Jewish carry the Ashkenazi Jewish founder mutations *BRCA1* c.5266dup and c.68_69del and *BRCA2* c.5946del. Only 72 (3.9%) of 1,852 *BRCA1* mutation carrier families and 55 (5.6%) of 990 *BRCA2* mutation carrier families who self-identified as being Jewish carried other (nonfounder) mutations. However, since many individuals of self-identified Jewish ancestry are

**TABLE 1** Characteristics of *BRCA1* and *BRCA2* mutations in the CIMBA database (by unique mutation)

| | | | *BRCA1* (*N* = 1,650) | | *BRCA2* (*N* = 1,731) | | |
|---|---|---|---|---|---|---|---|
| | **Designation** | **Definition** | ***N*** | **%** | **N** | **%** | ***p*-value** |
| Mutation Type | Large Deletion (DL) | Genomic DNA deletion (encompassing at least 1 exon) | 130 | 7.9 | 34 | 1.9 | <.0001 |
| | Large Duplication (DP) | Genomic DNA duplication (encompassing at least 1 exon) | 27 | 1.6 | 11 | 0.6 | .010 |
| | Frameshift (FS) | Deletion or insertion resulting in a disruption of the open reading frame | 948 | 57.5 | 1,141 | 65.9 | <.0001 |
| | In-Frame Deletion (IFD) | Small deletions, splice site mutations or large genomic rearrangements that result in a change in the mRNA but do not change the open reading frame | 1 | <0.1 | 2 | 0.1 | .518 |
| | Missense (MS) | Results in an altered amino acid | 46 | 2.8 | 13 | 0.8 | .0001 |
| | Nonsense (NS) | Point mutation resulting in a stop codon | 313 | 19.0 | 380 | 22.0 | .027 |
| | Splice (SP) | Results in aberrant RNA splicing | 166 | 10.1 | 131 | 7.6 | .013 |
| | Multiple Types (including those listed above) | | 20 | 1.1 | 19 | 1.1 | 1.00 |
| Mutation Effect | No RNA | Mutation is predicted to abrogate RNA production | 21 | 1.3 | 6 | 0.3 | .003 |
| | Premature Termination Codon (PTC) | Result of a nonsense substitution, frameshift due to small deletion or insertion, aberrant splicing, or large genomic rearrangement | 1,331 | 81.0 | 1,542 | 89.0 | <.0001 |
| | Unknown/Other | Unknown effect | 298 | 18.0 | 183 | 10.6 | <.0001 |
| Mutation Function | Nonsense-Mediated Decay (NMD)[a] (Anczukow et al., 2008) | Mutation is predicted to result in reduced transcript level due to decay of RNA and/or degradation/instability of truncated proteins | 1,213 | 73.9 | 1,523 | 88.0 | <.0001 |
| | No NMD | Mutations generating a premature stop codon in the first or last exon that is predicted not to result in NMD | 58 | 3.5 | 16 | 0.9 | <.0001 |
| | No RNA | Loss of expression due to deletion of promoter and/or transcription start site | 21 | 1.3 | 6 | 0.4 | .003 |
| | Re-Initiation | Mutations presumed to result in translation re-initiation but produce unstable protein | 4 | 0.2 | 0 | 0.0 | .294 |
| | NMD/Re-initiation | Mutations presumed to result in translation re-initiation but produce unstable protein | 60 | 3.7 | 0 | 0.0 | – |
| | Unknown/Other | Unknown function | 294 | 17.8 | 187 | 10.7 | <.0001 |
| Mutation Class | 1 | Mutations predicted to be associated with unstable or no protein | 1,298 | 78.6 | 1,529 | 88.3 | <.0001 |
| | 2 | Mutations predicted to be associated with stable mutant proteins | 112 | 6.8 | 36 | 2.1 | <.0001 |
| | 3 | Unknown function | 240 | 14.6 | 167 | 9.6 | <.0001 |

P-values reflect the comparison of frequencies between *BRCA1* and *BRCA2* mutation carriers.
[a]References (Anczukow et al., 2008; Buisson, et al., 2006; Mikaelsdottir, et al., 2004; Perrin-Vidoz, et al., 2002; Ware, et al., 2006)

only tested for the three founder mutations, this number is likely to be underestimated.

In African Americans, the majority of *BRCA1* mutations were not observed in any other racial/ethnic group, implying these mutations may be of African origin. In Hispanics, the most common *BRCA1* mutations also were observed among individuals from other regions who did not self-identify as Hispanic, including *BRCA1* c.3331_3334del (also observed in Australia, Europe, USA, and the UK), and *BRCA1* c.68_69del (the Jewish founder mutation) (Weitzel et al., 2005, 2013). The *BRCA1* c.815_824dup mutation has been reported as being of African origin, but has also been reported as a recurrent mutation in Mexican Americans, perhaps as a reflection of the complex continental admixture of this population (Villarreal-Garza et al., 2015b). *BRCA1* c.390C > A and c.5496_5506delinsA were most commonly found in the Asian population. In *BRCA2*, c.2808_2811del was found among the 10 most frequent mutations in all races/ethnicities.

## 3.4 | Recurrent mutations

As expected, the most common mutations in the entire data set were the founder mutations *BRCA1* c.5266dup (5382insC), *BRCA1* c.68_69del (185delAG), and *BRCA2* c.5946del (6174delT). In part, the


**FIGURE 2** Proportion of mutations in the breast cancer cluster regions (BCCR) and ovarian cancer cluster region (OCCR) in BRCA1 and BRCA2 by ethnicity as defined previously (Rebbeck et al., 2015). Asterisk indicates proportion is significantly different than Caucasian proportion (p-value < 0.05)

high frequency of these mutations is a consequence of panels that facilitate testing for these three mutations in women of Jewish descent. However, these two *BRCA1* mutations also are relatively common in regions with a low proportion of individuals who self-identify as Jewish (e.g., Hungary, Czech Republic, France, Germany, Italy, Poland Spain, Russia, and UK). *BRCA1* c.5266dup is a founder mutation thought to have originated 1800 years ago in Scandinavia/Northern Russia, entering the Ashkenazi-Jewish population 400–500 years ago, and thus has origins and a spread pattern independent of the Ashkenazim (Hamel et al., 2011). Haplotype studies have been used to determine the origin of *BRCA1* c.68_69del in populations not considered to have a high proportion of Jewish ancestry. In some populations, such as the Hispanics in the USA and Latin American, it is associated with the Ashkenazi Jewish haplotype, presumably due to unrecognized (Jewish) ancestry (Ah Mew, Hamel, Galvez, Al-Saffar, & Foulkes, 2002; Velez et al., 2012; Weitzel et al., 2005). In other populations, such as Pakistani and Malaysians, where *BRCA1* c.68_69del is a recurrent mutation, it appears to have arisen independently, as it is carried on a distinct haplotype (Kadalmani et al., 2007; Rashid et al., 2006). A different haplotype was also reported for several British families (the 'Yorkshire haplotype') that is distinct from both the Jewish and the Indian-Pakistani haplotypes (Laitman et al., 2013; Neuhausen et al., 1996).

The only locations in which these three founder mutations were not commonly observed were Belgium and Iceland. Iceland has another founder mutation (i.e., *BRCA2* c.771_775del). Yet other founder mutations included *BRCA1* c.4327C > T and *BRCA2* c.8537_8538del in Quebec. This latter mutation in *BRCA2* also is the most common mutation in high-risk families in Sardinia (Pisano et al., 2000) and was also reported in a few Jewish Yemenite families, with a distinct haplotype(Palomba et al., 2007). The *BRCA1* c.181T > G mutation was observed in Central Europe (Austria, Czech Republic, Germany, Hungary, Italy and Poland), but also observed in the US, Argentina, Latvia, Lithuania and Israel. This mutation has been found on a common haplotype in individuals of Polish and Ashkenazi Jewish ancestry, suggesting it is an Eastern European founder mutation (Kaufman, Laitman, Gronwald, Lubinski, & Friedman, 2009). The large rearrangement mutation in *BRCA1* c.548-?_4185+?del (ex9-12del) appears to be an important founder mutation in Mexico, with findings of a common haplotype and an estimated age at 74 generations (~1,500 years) (Weitzel et al., 2013).

We observed a number of other recurrent mutations. *BRCA1* c.3331_3334del comprised more than half of all mutations identified in Colombia, consistent with a previous report that this is a founder mutation in the Colombian population (Torres et al., 2007). However, this mutation has not been found at high rates in a second Colombian population (Cock-Rada, et al., 2017). *BRCA2* c.2808_2811del was frequently observed, not only as the most common mutation in France and Colombia, but also in other Western and Southern European countries, and destinations to which individuals from these countries have migrated. It estimated to have arisen approximately 80 (46–134)

**TABLE 2** Common *BRCA1* mutations by country of origin (by family)

| Conti-nent | Country | Families | Unique mutations | Five most common mutations (number observed) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 |
| Africa | Nigeria | 20 | 15 | c.303T > G(4) | c.191G > A(2) | c.3268C > T(2) | c.4240dup(1) | c.4122_4123del(1) |
| | South Africa | 49 | 16 | c.2641G >T(18) | c.5266dup(7) | c.1374del(4) | c.68_69del(4) | c.3228_3229del(4) |
| Asia | Hong Kong | 70 | 45 | c.470_471del(7) | c.4372C > T(5) | c.2635G > T(4) | c.5406+1_5406+3del(4) | c.3342_3345del(4) |
| | Israel | 679 | 7 | c.68_69del(510) | c.5266dup(151) | c.2934T > G(13) | c.181T > G(2) | c.981_982del(1) |
| | Korea | 158 | 61 | c.390C > A(19) | c.5496_5506delinsA(17) | c.922_924delinsT(11) | c.5030_5033del(9) | c.3627dup(8) |
| | Malaysia | 72 | 47 | c.2635G > T(5) | c.68_69del (4) | c.470_471del(3) | c.4148C > G(3) | c.3770_3771del(3) |
| | Pakistan | 93 | 45 | c.5503C > T(11) | c. 3770_3771del(8) | c.4508C > A(8) | c.66dup(6) | c.2269del(1) |
| | Singapore | 28 | 18 | c.2726dup(9) | c.2617dup(2) | c.2635G > T(2) | c.213-12A > G(1) | c.3214del(1) |
| | Turkey | 1 | 1 | c.3333del(1) | | | | |
| Australia | Australia | 581 | 173 | c.68_69del(56) | c.5266dup(45) | c.4065_4068del (23) | c.3756_3759del (22) | c.5503C > T(16) |
| Europe | Albania | 1 | 1 | c.4225C > T (1) | | | | |
| Europe | Austria | 391 | 115 | c.181T > G(51) | c.5266dup(46) | c.3018_3021del(35) | c.1687C > T(26) | c.962G > A(17) |
| | Belgium | 166 | 41 | c.2359dup(40) | c.212+3A > G(26) | c.3661G > T(12) | c.3607C > T(10) | c.3841C > T(9) |
| | Bosnia | 1 | 1 | c.4158_4162del(1) | | | | |
| | Czech Rep. | 208 | 42 | c.5266dup(87) | c.3700_3704del(25) | c.181T > G(20) | c.1687C > T(16) | c.3756_3759del(6) |
| | Denmark | 667 | 101 | c.2475del(91) | c.3319G > T(81) | c.5266dup(41) | c.3710del(39) | c.5213G > A(30) |
| | Finland | 57 | 31 | c.3485del(8) | c.4097-2A > G (5) | c 5266dup(4) | c.1687C > (T42) | c.4327C > T(3) |
| | France | 1,522 | 418 | c.5266dup(118) | c.3481_3491del(70) | c.68_69del(63) | c.4327C > T(49) | c.3839_3843delins AGGC (40) |
| | Germany | 2,287 | 381 | c.5266dup(411) | c.181T > G(196) | c.4689C > G(63) | c.1687C > T(62) | c.3481_3491del(55) |
| | Greece | 208 | 41 | c.5266dup(47) | c.5212G > A(29) | c.5406+644_*8273del(24) | c.5468-285_5592+ 4019del insCACAG(23) | c.5251C > T(13) |
| | Hungary | 235 | 47 | c.5266dup(78) | c.181T > G(60) | c.68_69del(22) | c.5278-?_5406+?del(5) | c.5251C > T(4) |
| | Iceland | 3 | 1 | c.5074G > A(3) | | | | |
| | Ireland | 2 | 2 | c.547+1G > T(1) | c.427G > T(1) | | | |
| | Italy | 1,120 | 254 | c.5266dup(124) | c.181T > G(44) | c.190T > C(43) | c.1687C > T(39) | c.1380dup(37) |
| | Latvia | 100 | 9 | c.5266dup(49) | c.4035del(40) | c.181T > G(5) | c.3756_3759del(1) | c.4675G > A(1) |
| | Lithuania | 223 | 21 | c.4035del(112) | c.5266dup(58) | c.181T > G221) | c.1687C > T(5) | c.5177_5180del(4) |
| | Netherlands | 782 | 126 | c.5333-36_5406+ 400del(87) | c.5277+1G > A(66) | c.2685_2686del(60) | c.2197_2201del(41) | c.5266dup(40) |

(Continues)

**TABLE 2** (Continued)

| Conti-nent | Country | Families | Unique mutations | Five most common mutations (number observed) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 |
| | Poland | 1,064 | 8 | c.5266dup(711) | c.181T > G(276) | c.4035del(69) | c.5333-36_5406+400del(3) | c.68_69del(2) |
| | Portugal | 49 | 23 | c.3331_3334del(15) | c.2037delinsCC(7) | c.3817C > T(3) | c.21A > G(2) | c.5266dup(2) |
| | Romania | 1 | 1 | c.5266dup(1) | | | | |
| | Russia | 160 | 10 | c.5266dup(135) | c.4035del(11) | c.68_69del(7) | c.5026_5027del(1) | c.4185+2T > C(1) |
| | Spain | 678 | 181 | c.211A > G(78) | c.68_69del(62) | c.5123C > A(61) | c.3770_3771del(23) | c.3331_3334del(23) |
| | Sweden | 438 | 108 | c.3048_3052dup(68) | c.1687C > T(31) | c.2475del(27) | c.1082_1092del(26) | c.5266dup(19) |
| | UK | 1,389 | 297 | c.68_69del(134) | c.4065_4068del(104) | c.4186-?_4357+?dup (78) | c.3756_3759del(62) | c.5266dup(60) |
| North America | Canada | 450 | 112 | c.68_69del(99) | c.4327C > T(66) | c.5266dup(50) | c.2834_2836delinsC(16) | c.3756_3759del(12) |
| | USA | 4,219 | 613 | c.68_69del(1130) | c.5266dup(554) | c.3756_3759del(113) | c.4065_4068del(58) | c.3756_3759(49) |
| | Argentina | 89 | 35 | c.68_69del(22) | c.5266dup(12) | c.211A > G(11) | c.181T > G(6) | c.427G > T(3) |
| South/ Central America | Brazil | 101 | 39 | c.5266dup(31) | c.3331_3334del(18) | c.135-?_441+?del(4) | c.1687C > T(4) | c.3916_3917del(3) |
| | Colombia | 55 | 2 | c.3331_3334del(36) | c.5123C > A(19) | | | |
| | Mexico | 25 | 15 | c.548-?_4185+?del(8) | c.68_69del(2) | c.824_825ins10(2) | c.211A > G(2) | c.5030_5033del(1) |
| | Peru | 1 | 1 | c.4986+6T > C(1) | | | | |
| | Venezuela | 1 | 1 | c.5123C > A(1) | | | | |

**TABLE 3** Frequently observed *BRCA2* mutations by country of origin (by family)

| Conti-nent | Country | Families | Unique mutations | Five most frequently observed mutations (number observed) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 |
| Africa | Nigeria | 12 | 9 | c.1310_1313del(3) | c.8817_8820delA(2) | c.5241_5242insTA(1) | c.2402_2412del(1) | c.994del(1) |
| | South Africa | 103 | 18 | c.7934del(80) | c.5946del(6) | c.6944_6947del(2) | c.5213_5216del(1) | c.6939del(1) |
| Asia | Hong Kong | 91 | 45 | c.3109C > T(22) | c.2808_2811del(5) | c.7878G > A(5) | c.7007G > T(4) | c.9294C > G(4) |
| | Israel | 339 | 5 | c.5946del(330) | c.8537_8538del(5) | c.4936_4939del(2) | c.3847_3848del(1) | c.6024dup(1) |
| | Japan | 1 | 1 | c.5645C > A(1) | | | | |
| | Korea | 220 | 93 | c.7480C > T(40) | c.3744_3747del(18) | c.1399A > T(16) | c.5576_5579del(14) | c.6724_6725del(6) |
| | Malaysia | 64 | 47 | c.262_263del(8) | c.2808_2811del(3) | c.3109C > T(3) | c.5073dup(3) | c.809C > G(2) |
| | Pakistan | 19 | 17 | c.5222_5225del(3) | c.8754+1G > T(1) | c.92G > A(1) | c.6468_6469del(1) | c.2990T > G(1) |
| | Philippines | 1 | 1 | c.2023del(1) | | | | |
| | Qatar | 1 | 1 | c.7977-1G > C(1) | | | | |
| | Saudi Arabia | 1 | 1 | c.473C > A(1) | | | | |
| | Singapore | 10 | 10 | c.200_1910-877dup(1) | c.2808_2811del(1) | c.8961_8964del(1) | c.8915del(1) | c.956dup(1) |
| Australia | Australia | 496 | 178 | c.5946del(53) | c.6275_6276del(25) | c.7977-1G > C(11) | c.5682C > G(10) | c.3487_3848del(10) |
| Europe | Austria | 185 | 87 | c.8364G > A(17) | c.8755-1G > A(15) | c.3860del(11) | c.1813dup(8) | c.7846del(6) |
| | Belgium | 116 | 39 | c.6275_6276del(17) | c.516+1G > T(16) | c.8904del(14) | c.1389_1390del(9) | c.3847_3848del(7) |
| | Czech Republic. | 81 | 42 | c.8537_8538del(12) | c.7913_7917del(5) | c.5645C > A(4) | c.2808_2811del(4) | c.9403del(4) |
| | Denmark | 442 | 101 | c.7617+1G > A(61) | c.6373del(44) | c.1310_1313del (25) | c.6486_6489del(25) | c.3847_3848del(16) |
| | Finland | 52 | 16 | c.9118-2A > G(18) | c.7480C > T(12) | c.771_775del(7) | c.8327T > G(2) | c.1286T > G(2) |
| | France | 997 | 375 | c.2808_2811del(34) | c.5946del(27) | c.9026_9030del(22) | c.8364G > A(22) | c.5909C > A(19) |
| | Germany | 1,109 | 367 | c.1813dup(51) | c.3847_3848del(34) | c.2808_2811del(29) | c.5946del(29) | c.5682C > G(23) |
| | Greece | 28 | 22 | c.7976G > A(3) | c.5722_5723del(2) | c.9097dup(2) | c.9501+1G > A(2) | c.5722_5723del(2) |
| | Hungary | 81 | 39 | c.9097dup(17) | c.5946del(11) | c. 7913_7917del(4) | c.6656C > G(3) | c.9403del(3) |
| | Iceland | 89 | 1 | c.771_775del(89) | | | | |
| | Ireland | 2 | 2 | c.8951C > G(1) | c.5576_5579del(1) | | | |
| | Italy | 706 | 242 | c.8878C > T(33) | c.6468_6469del(31) | c.7180A > T(29) | c.5682C > G(25) | c.8247_8248delGA(18) |
| | Lithuania | 26 | 11 | c.658_659del(13) | c.3847_3848del(4) | c.6580dup(1) | c.6410del(1) | c.7879A > T(1) |
| | Netherlands | 493 | 167 | c.6275_6276del(38) | c.8067T > A(26) | c.5946del(25) | c.9672dupA(23) | c. 5213_5216del (21) |

(Continues)

**TABLE 3** (Continued)

| Conti-nent | Country | Families | Unique mutations | Five most frequently observed mutations (number observed) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 |
| | Norway | 2 | 1 | c.771_775del(2) | | | | |
| | Poland | 23 | 20 | c.5946del(3) | c.8946del(2) | c. 7913_7917del(1) | c.9294C > A(1) | c.635_636del(1) |
| | Portugal | 71 | 22 | c.156_157insAlu(39) | c.9097dup(5) | c.9382C > T(3) | c.682-2A > C(2) | c.5645G > A(2) |
| | Romania | 1 | 1 | c.9097dup(1) | | | | |
| | Russia | 3 | 3 | c.3682_3685del(1) | c.5410_5411del(1) | c.5946del(1) | | |
| | Spain | 670 | 217 | c.3264dup(58) | c.2808_2811del(56) | c.9026_9030del(52) | c.6275_6276del(32) | c.9018C > A(16) |
| | Sweden | 123 | 68 | c.4258del(11) | c.2830A > T(7) | c.1796_1800del(6) | c.3847_3848del(6) | c.7558C > T(5) |
| | UK | 1,200 | 308 | c.6275_6276del(107) | c.5946del(66) | c.4478_4481del(37) | c.755_758del(36) | c.5682C > G(33) |
| North America | Canada | 311 | 108 | c.8537_8538del(48) | c.5946del(45) | c.2808_2811del(13) | c.6275_6276del(11) | c.5857G > T(10) |
| | USA | 3,064 | 626 | c.5946del(742) | c.2808_2811del(86) | c.1813dup(62) | c.658_659del(50) | c.6275_6276del(49) |
| | Argentina | 49 | 21 | c.5946del(18) | c.2808_2811del(5) | c.6037A > T(4) | c.9026_9030del(2) | c.5645C > G(2) |
| | Brazil | 47 | 33 | c.2T > G(5) | c.2808_2811del(4) | c.156_157insAlu(4) | c.6405_6409del(3) | c.1138del(2) |
| South/ Central America | Colombia | 19 | 4 | c.2808_2811del(15) | c.5851_5854del (2) | c.6275_6276del(1) | c.93G > A(1) | |
| | Costa Rica | 1 | 1 | c.9235del(1) | | | | |
| | Honduras | 1 | 1 | c.7558C > T(1) | | | | |
| | Mexico | 6 | 6 | c.3264dup (1) | c.6275_6276del (1) | c.2224C > T (1) | c.5542del (1) | c.6502G > T (1) |

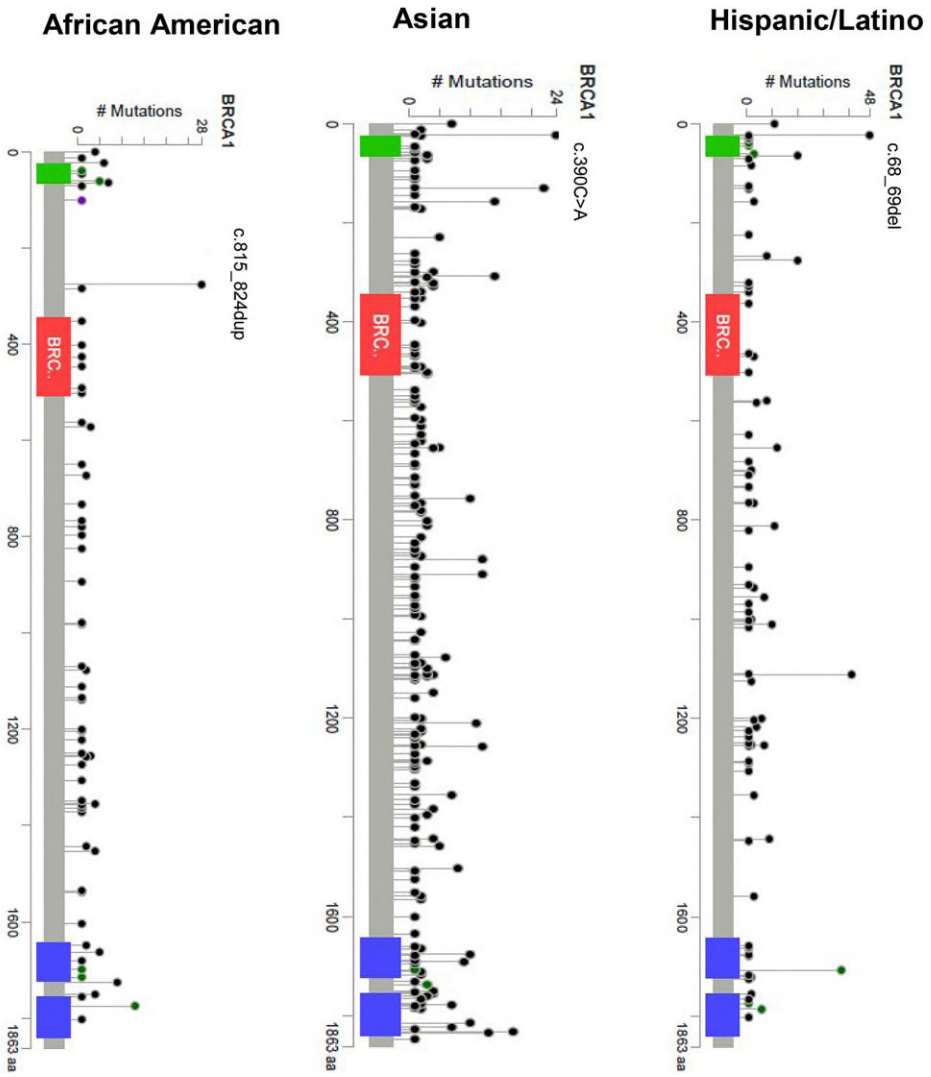


**FIGURE 3** *BRCA1* mutation distribution in African American, Asian, and Hispanic. Length of mutation indicator reflects the number of observed mutations. Domains are zinc/ring finger (green); BRCT domain (red); BRCT (C terminus) (blue). Mutation type is indicated for each mutation by color: green: missense mutations; black: truncating mutations (nonsense, nonstop, frameshift deletion, frameshift insertion, splice site, in-frame mutations); purple: all other types of mutations

generations ago. However, due to the diversity of the haplotypes, multiple independent origins could not be ruled out (Neuhausen et al., 1998). *BRCA2* c.6275_6276del was a recurrent *BRCA2* mutation in Australia, the UK, Belgium, Spain, the Netherlands, and North America. This mutation has been estimated to have originated 52 (24–98) generations ago from a single founder (Neuhausen et al., 1998). Recurrent or founder mutations were observed in diverse populations. For example, the c.115T > G (Cys39Gly) mutation has been described in Greenlanders (Hansen et al., 2009). The c.2641G>T and c.7934del mutations have both been reported as founder mutation in South African Afrikaners (Reeves et al., 2004).

## 4 | DISCUSSION

We have reported worldwide distribution of *BRCA1* and *BRCA2* mutations curated in the CIMBA dataset. These results may aid in the understanding of the mutation distribution in specific populations as well as imparting clinical and biological implications for our understanding of *BRCA1*- and *BRCA2*-associated carcinogenesis.

Clinical testing for *BRCA1* and *BRCA2* mutations has benefited substantially from knowledge about common mutations in specific populations. In many countries, the three Ashkenazi-Jewish founder mutations are offered as a mutation testing panel for self-reported Ashkenazim, based on their frequency. This approach is much less expensive than comprehensive gene sequencing. The identification of commonly-occurring mutations in other populations could lead to more efficient and cost-effective mutation testing for *BRCA1* and *BRCA2*. For example, Villareal-Garza et al. (2015a) have developed the HISPANEL of mutations that optimizes testing in Hispanic/Latino populations. In the present study, we have identified mutations that may exist at a sufficient prevalence to warrant consideration for population-specific mutation testing panels. Criteria for developing such panels for *BRCA1* and *BRCA2* mutation screening are not available. However, mutations that are in a specific population and that capture a sufficient

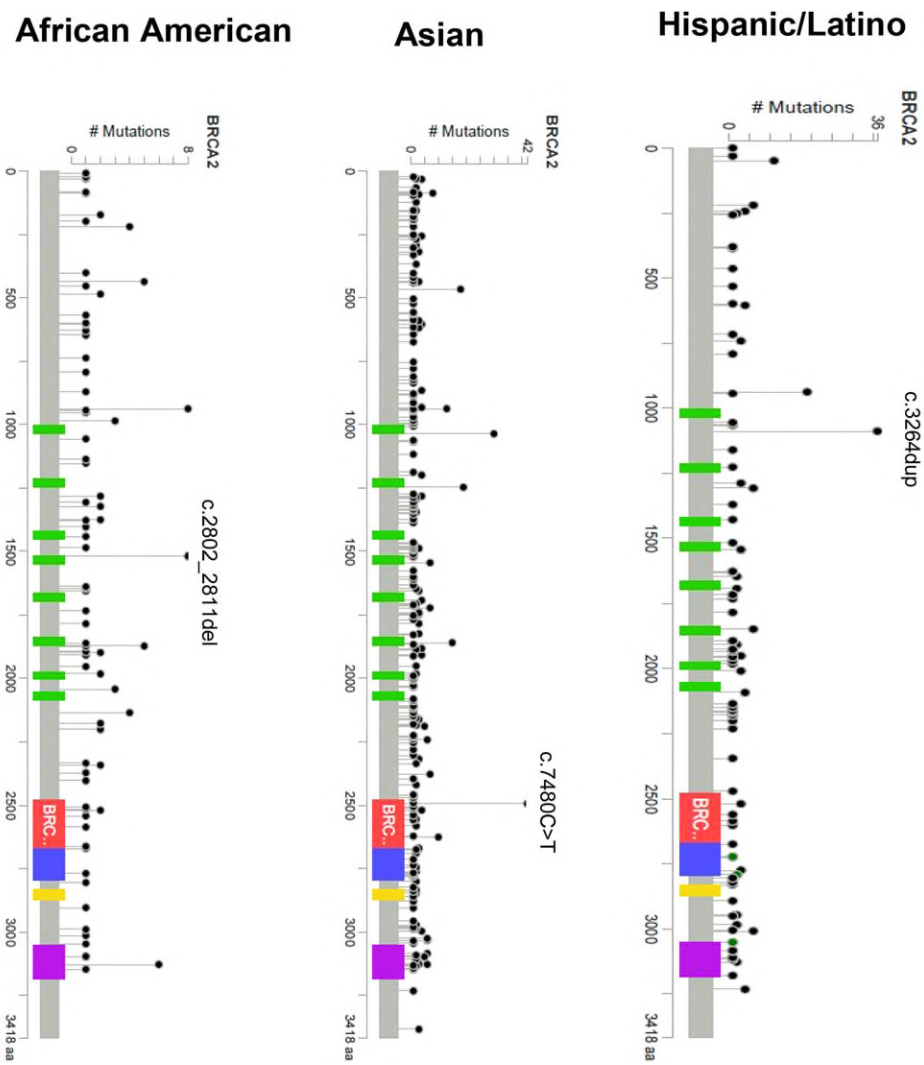


**FIGURE 4** *BRCA2* mutation distribution in African American, Asian, and Hispanic CIMBA sample (per family). Length of mutation indicator reflects the number of observed mutations. Domains are BRCA repeats (green); BRCA helica (red); OB binding domain (blue); tower (yellow) and OB3 binding domain (purple). Mutation type is indicated for each mutation by color: green: missense mutations; black: truncating mutations (nonsense, nonstop, frameshift deletion, frameshift insertion, splice site, in-frame mutations); purple: all other types of mutations

percentage of mutations in high risk individuals and families in that population may be appropriate for use in targeted genetic testing. Before such panels can be developed, population-based studies of mutation frequency in specific populations should be undertaken. The data reported herein provide a list of the recurrent mutations around which such panels could be developed, but the frequencies are not population based, particularly in settings where founder mutations are preferentially screened (e.g., the Jewish founder panels). Similarly, putative founder mutations identified by assessing common ancestral origins of specific mutations (rather than just high prevalence; Table 5) may form the basis of population-specific *BRCA1* and *BRCA2* mutation screening panels.

We report the distribution of *BRCA1* and *BRCA2* mutations in nearly 30,000 families of bona-fide disease-associated mutations. The strengths of this report include the large sample size that reflects a geographically and racially/ethnically diverse set of *BRCA1* and *BRCA2* mutation carriers. However, some limitations need to be considered. First, the sample set presented here does not reflect a systematic study of these populations or races/ethnicities; the data reflect patterns of recruitment (e.g., individuals with higher risk or prior diagnosis of cancer who consented to participate in research protocols) that contributed to the CIMBA consortium. Certain racial/ethnic or sociodemographic groups are under- or overrepresented or missing in our data set and, as a consequence, mutations may be over- or underrepresented. For example, the existence of a commercial panel of three Jewish founder mutations enhances genetic testing for those mutations. As a result, the most frequently observed mutations in some populations (e.g., the United States) reflect the widespread use of this testing panel in the US population. Similar arguments may also apply for other populations, where testing for certain founder mutations may be more frequent. Therefore, the relative frequencies of mutations by population in the present study may be subject to such testing biases. Comparing the relative frequencies is also complicated by the inclusion of related individuals.

Second, although the CIMBA data represent most regions around the world, there are limitations related to which groups of

**TABLE 4** Ten most frequently observed mutations by self-identified race/ethnicity (%) (by family)

| | Mutation rank | Caucasian | African American | Asian | Hispanic/Latino | Jewish | Other |
|---|---|---|---|---|---|---|---|
| *BRCA1* | 1 | c.5266dup(17%) | c.815_824dup(16%) | c.390C > A(4%) | c.68_69del(12%) | c.68_69del(72%) | c.5266dup(12%) |
| | 2 | c.181T > G (6%) | c.5324T > G (7%) | c.5496_5506delinsA (3%) | c.3331_3334del(10%) | c.5266dup(24%) | c.68_69del(17%) |
| | 3 | c.68_69del(6%) | c.5177_5180del(5%) | c.470_471del(3%) | c.5123C > A(9%) | c.3756_3759del (0.3%) | c.181T > G(5%) |
| | 4 | c.4035del(2%) | c.4357+1G > A(5%) | c.5503C > T(2%) | c.548-?_4185+?del(7%) | c.1757del(0.3%) | c.5333-36_5406+400del(3%) |
| | 5 | c.4065_4068del(2%) | c.190T > G(3%) | c.922_924delinsT(2%) | c.211A > G(5%) | c.2934T > G(0.2%) | c.3481_3491del(2%) |
| | 6 | c.3756_3759del(2%) | c.68_69del(3%) | c.68_69del(2%) | c.815_824del(3%) | c.5503C > T(0.1%) | c.1687C > T (2%) |
| | 7 | c.1687C > T(2%) | c.5467+1G > A(3%) | c.3770_3771del(2%) | c.2433del(3%) | c.4185+1G > T(0.1%) | c.4065_4068del(2%) |
| | 8 | c.4327C > T(2%) | c.182G > A(3%) | c.2635G > T(2%) | c.1960A > T(3%) | c.4689C > G(0.1%) | c.5277+1G > A (2%) |
| | 9 | c.2475del(2%) | c.5251C > T(2%) | c.2726dup(2%) | c.3029_3030del(3%) | c.3770_3771del (0.1%) | c.2685_2686del(68%) |
| | 10 | c.4186-?_4357+?dup(1%) | c.4484G > T(2%) | c.3627dup(2%) | c.4327C > T(2%) | c.4936del(0.1%) | c.4327C > T(1%) |
| Families | | 11,258 | 174 | 550 | 408 | 1,852 | 4,583 |
| Unique Mutations | | 1,206 | 77 | 240 | 104 | 56 | 765 |
| *BRCA2* | 1 | c.5946del(5%) | c.2808_2811del(6%) | c.7480C > T(8%) | c.3264dup(17%) | c.5946del(94%) | c.5946del(5%) |
| | 2 | c.6275_6276del(3%) | c.4552del(6%) | c.3109C > T(6%) | c.2808_2811del(9%) | c.3847_3848del (0.4%) | c.6275_6276del(4%) |
| | 3 | c.2808_2811del(3%) | c.9382C > T(5%) | c.3744_3747del(4%) | c.145G > T(5%) | c.1754del(0.4%) | c.2808_2811del(3%) |
| | 4 | c.771_775del(2%) | c.1310_1313del(4%) | c.1399A > T(3%) | c.9026_9030del(3%) | c.9382C > T(0.3%) | c.1813dup(3%) |
| | 5 | c.3847_3848del(2%) | c.5616_5620del(4%) | c.5576_5579del(3%) | c.658_659del(3%) | c.5621_5624del (0.2%) | c.5645C > A(2%) |
| | 6 | c.5682C > G(2%) | c.6405_6409del(3%) | c.2808_2811del(2%) | c.5542del(3%) | c.2808_2811del (0.2%) | c.1310_1313del(2%) |
| | 7 | c.1813dup(2%) | c.658_659del(3%) | c.7878G > A(2%) | c.3922G > T(3%) | c.4829_4830del (0.2%) | c.3847_3848del(2%) |
| | 8 | c.8537_8538del(1%) | c.2957_2958insG(2%) | c.262_263del(2%) | c.1813dup(2%) | c.5238del(0.2%) | c.5682C > G(1%) |
| | 9 | c.658_659del(1%) | c.7024C > T(2%) | c.7133C > G(1%) | c.9699_9702del(2%) | c.9207T > A(0.1%) | c.9672dup(1%) |
| | 10 | c.7934del(1%) | c.6531_6534del(2%) | c.5164_5165del(1%) | c.6275_6276del(2%) | c.3264dup(0.1%) | c.658_659del(1%) |
| Families | | 7,156 | 125 | 538 | 207 | 990 | 2,551 |
| Unique Mutations | | 1,242 | 77 | 248 | 91 | 44 | 753 |

**TABLE 5** Ten most frequently observed mutations by continent of ascertainment (%) (by family)

| | Mutation rank | North America | Africa | Asia | South/Central America | Europe | Australia |
|---|---|---|---|---|---|---|---|
| *BRCA1* | 1 | c.68_69del(26%) | c.2641G >T(26%) | c.68_69del(47%) | c.3331_3334del (20%) | c.5266dup(17%) | c.68_69del(10%) |
| | 2 | c.5266dup(13%) | c.5266dup(10%) | c.5266dup(14%) | c.5266dup(16%) | c.181T > G(7%) | c.5266dup(8%) |
| | 3 | c.181T > G(3%) | c.1374del(6%) | c.390C > A(2%) | c.68_69del(9%) | c.68_69del(4%) | c.4065_4068del(4%) |
| | 4 | c.4327C > T(2%) | c.68_69del(6%) | c.5496_5506delinsA (2%) | c.5123C > A(8%) | c.4035del(2%) | c.3756_3759del(4%) |
| | 5 | c.4065_4068del(1%) | c.3228_3229del(6%) | c.5503C > T(1%) | c.211A > G(5%) | c.1687C > T(2%) | c.5503C > T(3%) |
| | 6 | c.3756_3759del(1%) | c.303T > G(6%) | c.2934T > G(1%) | c.181T > G(3%) | c.4065_4068del(2%) | c.4186-?_4357+?dup(3%) |
| | 7 | c.213-11T > G(1%) | c.4838_4839insC (3%) | c.3770_3771del(1%) | c.548-?_4183+8?del(3%) | c.3481_3491del(1%) | c.4327C > T(2%) |
| | 8 | c.1687C > T(1%) | c.3268C > T(3%) | c.2726dup(1%) | c.1687C > T(2%) | c.2475del(1%) | c.5278-?_5592+?del (2%) |
| | 9 | c.4186-?_4357+?dup(1%) | c.1504_1508del(3%) | c.470_471del(1%) | c.135-?_441+?del(2%) | c.3756_3759del(1%) | c.70_80del(2%) |
| | 10 | c.1175_1214del(1%) | c.191G > A(3%) | c.922_924delinsT(1%) | c.5030_5033del (2%) | c.3770_3704del(1%) | c.1961del(2%) |
| Families | | 4,669 | 69 | 1,100 | 271 | 11,748 | 581 |
| Unique Mutations | | 654 | 30 | 187 | 75 | 1282 | 173 |
| *BRCA2* | 1 | c.5946del(23%) | c.7934del(47%) | c.5946del(34%) | c.2808_2811del (11%) | c.6275_6276del(2%) | c.5946del(5%) |
| | 2 | c.2808_2811del(3%) | c.5946del(4%) | c.7480C > T(4%) | c.5946del(9%) | c.5946del(2%) | c.6275_6276del(2%) |
| | 3 | c.8537_8538del(2%) | c.1310_1313del(2%) | c.3109C > T(3%) | c.2T > G(2%) | c.2808_2811del(2%) | c.7977-1G > C(1%) |
| | 4 | c.1813dup(2%) | c.6944_6947del(1%) | c.3744_3747del(2%) | c.156_157insAlu (2%) | c.771_775del(1%) | c.5682C > G(1%) |
| | 5 | c.6275_6276del(2%) | c.8817_8820del(1%) | c.1399A > T(2%) | c.6037A > T(2%) | c.3847_3848del(1%) | c.3847_3848del(1%) |
| | 6 | c.3847_3848del(3%) | c.5213_5216del(1%) | c.5576_5579del(2%) | c.6405_6409del(3%) | c.1813dup(1%) | c.2808_2811del(1%) |
| | 7 | c.658_659del(2%) | c.6535_6536insA (1%) | c.2808_2811del(1%) | c.5645C > G(1%) | c.5682C > G(1%) | c.755_758del(1%) |
| | 8 | c.9382C > T(1%) | c.774_775del(1%) | c.262_263del(1%) | c.658_659del(1%) | c.1310_1313del(1%) | c.4478_4481del(1%) |
| | 9 | c.3264dup(1%) | c.6393del(1%) | c.8537_8538del(1%) | c.7180A > T(1%) | c.5645C > A(1%) | c.8297del(1%) |
| | 10 | c.55073dup(1%) | c.5042_5043del(1%) | c.7878G > A(1%) | c.5851_5854del (1%) | c.9026_9030del(1%) | c.250C > T(1%) |
| Families | | 3,375 | 170 | 976 | 222 | 10,175 | 1,047 |
| Unique Mutations | 660 | 27 | 187 | 58 | 1,315 | 179 | |

individuals have been tested and which centers contributed data. In particular, non-White ancestry populations are still underrepresented in research reports of mutation spectrum and frequency. Genetic testing in the developing world remains limited.

Third, we presented the mutations in terms of type or effect (Table 1), but these designations are not always based on experimental evidence. For example, NMD mutation status is almost always defined by a prediction rule rather than in vitro experiments that confirm the presence of nonsense mediated decay.

Fourth, we presented the occurrence of putative founder mutations. Some of these founder mutations (e.g., *BRCA1* c.68_69del, *BRCA2* c.771_775del) have been demonstrated to be true founder mutations based on actual ancestry analyses. Others, however, have only been identified as occurring commonly in certain populations, but haplotype or similar analyses of founder status may not have been done.

Fifth, our analysis was based on self-reported race/ethnicity of study participants, but this information may misclassify some groups of individuals. For example, some Middle Eastern groups may have been classified as "Caucasian" based on the data available, but in fact may represent a distinct group that was not captured here. Moreover, in some large centers participating in CIMBA, collecting information on race/ethnicity is prohibited and these mutation carriers were excluded from the comparisons.

Finally, we evaluated mutations by racial/ethnic and geographic designations, but some of these may be misclassified. For example, while *BRCA1* c.68_69del has been shown to arise independently of the Jewish founder mutation in Pakistan (Rashid et al., 2006), we cannot determine if the identified group also contains some Ashkenazi Jewish individuals.

The data presented herein provide new insights into the worldwide distribution of *BRCA1* and *BRCA2* mutations. The identification of recurrent mutations in some racial/ethnic groups or geographical locations raises the possibility of defining more efficient strategies for genetic testing. Three Jewish founder mutations *BRCA1* c.5266dup (5382insC) and *BRCA1* c.68_69del (185delAG) and *BRCA2* c.5946del (6174delT) have long been used as a primary genetic screening test for women of Jewish descent. The identification here of other recurrent mutations in specific populations may similarly provide the basis for other mutation-specific panels. For example, *BRCA1* c.5266dup (5382insC) may be useful as a single mutation screening test in Central-Eastern European populations before undertaking full sequencing. However, this basic test may be supplemented with screening for *BRCA1* c.181T > G, as the second most common mutation of the region, and for some special cases, to include most common Hungarian *BRCA2* founder mutation c.9097dup (9326insA) for those with Hungarian ancestry (Ramus et al., 1997b; van der Looij et al., 2000). In Iceland, only two mutations were reported: the founder mutation *BRCA2* c.771_775del and the rarer *BRCA1* c.5074G > A (Bergthorsson et al., 1998). A number of other situations can be identified in which specific mutations explain a large proportion of the total mutations observed in a population. These and other such examples suggest that targeted mutation testing panels that include specific mutations could be developed for use in specific populations. Finally, we focused on female *BRCA1* and *BRCA2* mutation carriers in this report. However, the growing knowledge about *BRCA1* and *BRCA2*-associated cancers in men, particularly prostate cancer (Ostrander & Udler, 2008; Pritchard et al., 2016), suggests that the information presented herein will also have value in genetic testing of men.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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