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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 Caucasians 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 6 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; ovarian cancer; mutation; ethnicity; geography

BACKGROUND

Women who carry germline mutations in either *BRCA1* [OMIM 113705] or *BRCA2* [600185] are at a greatly 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 57–65% and 20–50%, respectively (Chen and Parmigiani, 2007; Kuchenbaecker, et al., 2017). For *BRCA2*, average risk estimates range from 35–57% and 5–23%, respectively (Chen and 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* (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 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 also can influence cancer treatment decisions, principally around the use of platinum agents or poly (ADP-ribose) polymerase (PARP) inhibitors (Lord and Ashworth, 2017) or contralateral risk-reducing mastectomy. Increasing 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 0.1–0.3%, and 0.1–0.7%, 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, et al., 2016). As they do not include large genomic rearrangements, some newer population-based estimates may still under-represent 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, et al., 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), and *BRCA2* c.8537_8538del (8765delAG) (Oros, et al., 2006b; Tonin, et al., 1999; Tonin, et al., 2001); the *BRCA1* mutations c.181T>G, and c.4034delA in Central-Eastern Europe (Gorski, et al., 2000); the *BRCA1* c.548-4185del in Mexico (Villarreal-Garza, et al., 2015b; Weitzel, et al., 2013)(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 and 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.; Ho, et al., 2000; Jara, et al., 2006; John, et al., 2007; Kurian, 2010; Laitman, et al.; Lang, et al., 2017; Lee, et al., 2003; Li, et al., 2006; Nanda, et al., 2005; Ossa and Torres, 2016; Pal, et al., 2004; Rodríguez, et al., 2012; Seong, et al., 2009; Sharifah, et al.; 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).

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/h> (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.

RESULTS

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 Supplementary Table 1. 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 web site containing information about the most common mutations reported here can be found at: <http://apps.ccge.medschl.cam.ac.uk/consortia/cimba/>. This information may be periodically updated as new data become available.

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 to undergo nonsense-mediated mRNA decay (NMD) (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 ($p < 0.05$) 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 (Welchsh and King, 2001).

We and others have found that breast (BCCR) and ovarian (OCCR) cancer cluster regions 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.

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 Supplementary Table 2.

The mutational distribution among the major racial/ethnic groups and by geography are 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 Caucasian and Jews; 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 (non-founder) mutations. However, since many individuals of self-identified Jewish ancestry are 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., 2013; Weitzel, et al., 2005). 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.

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 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_69delAG 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, et al., 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, et al., 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) 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).

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, Villarreal-Garza et al. (Villarreal-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 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 socio-demographic groups are under- or over-represented or missing in our data set and, as a consequence, mutations may be over- or under-represented. 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 USA) reflect the widespread use of this testing panel in the USA 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 individuals have been tested and which centers contributed data. In particular, non-white ancestry populations are still under-represented 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 a 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 (van der Looij, et al., 2000, Ramus, et al., 1997b). 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 which 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 and Udler, 2008; Pritchard, et al., 2016), suggests that the information presented herein will also have value in genetic testing of men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

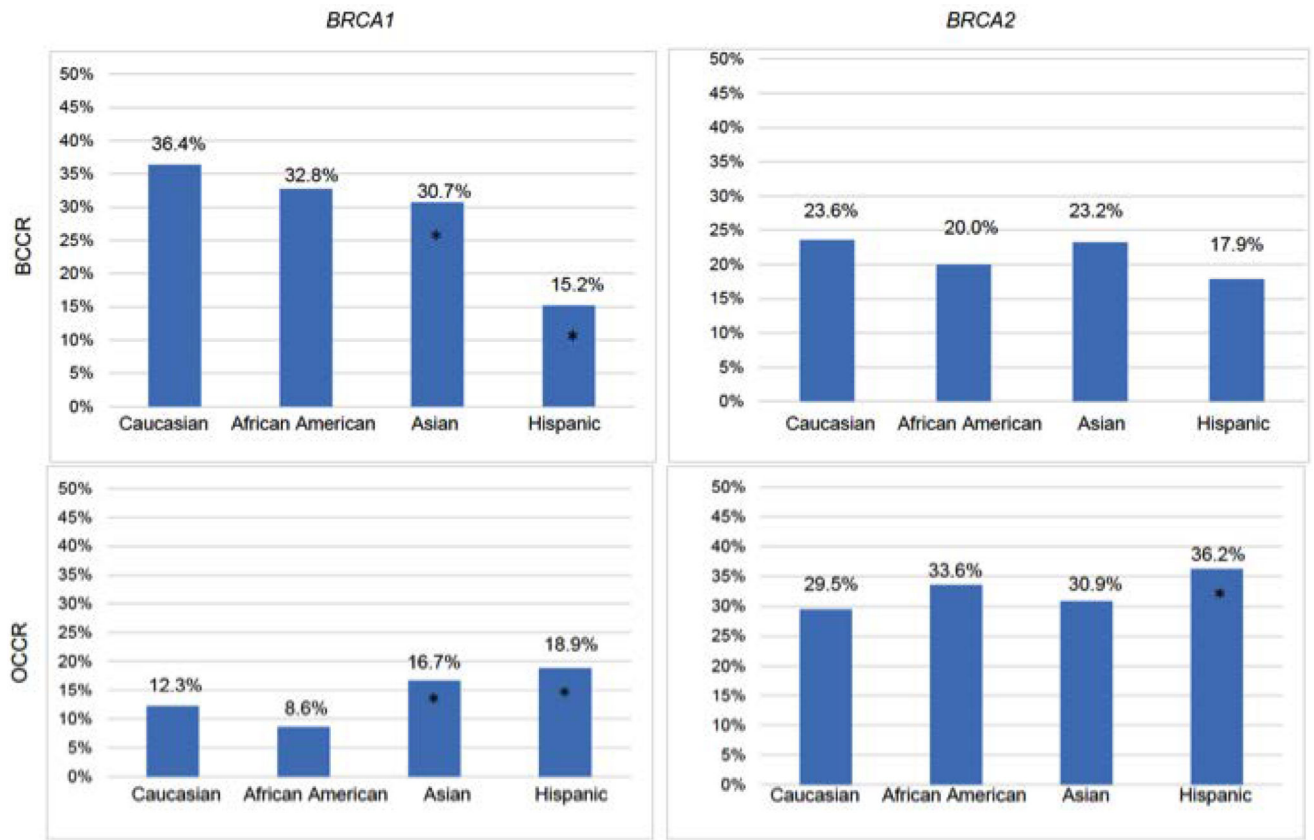


Figure 2.

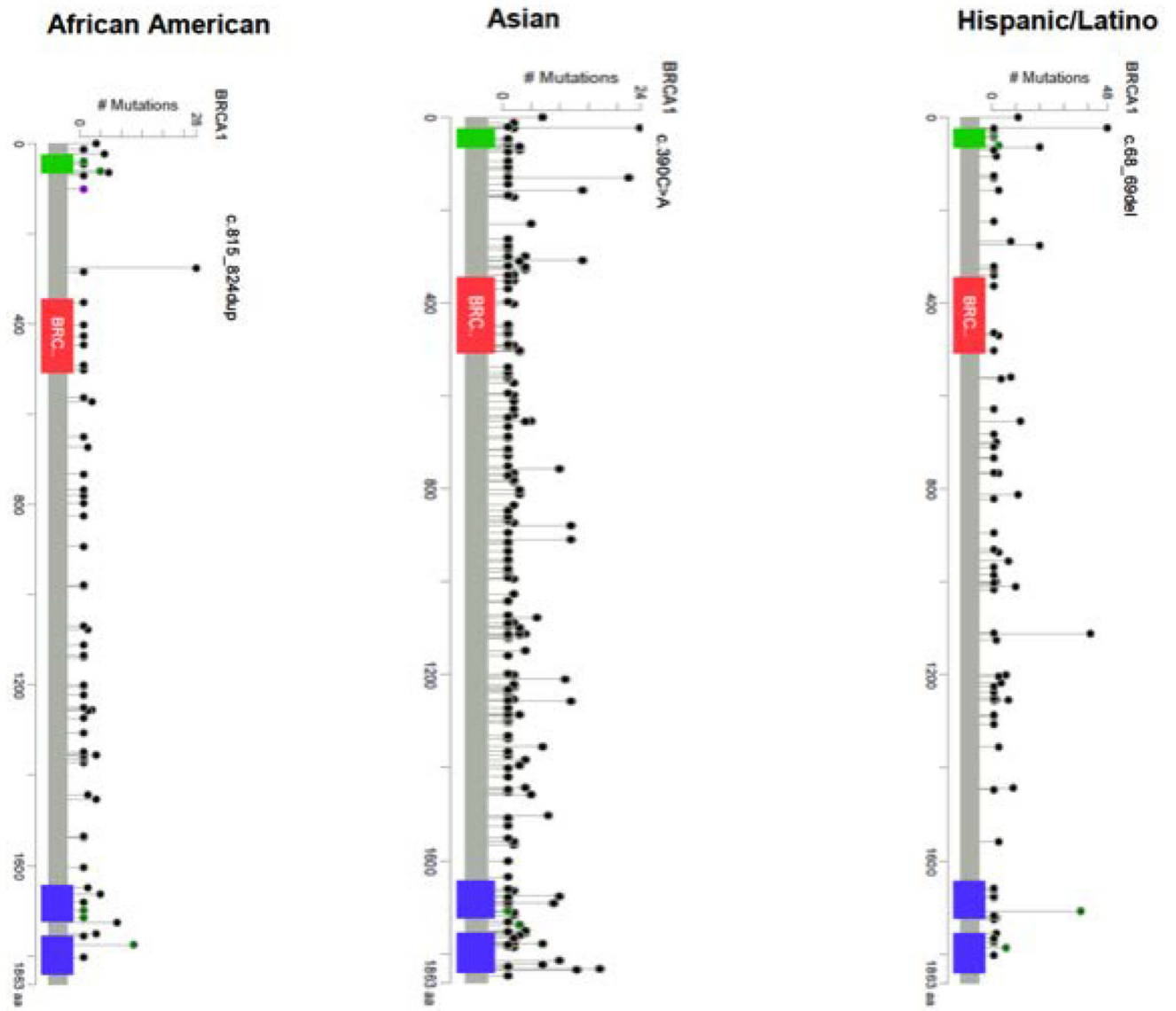


Figure 3.

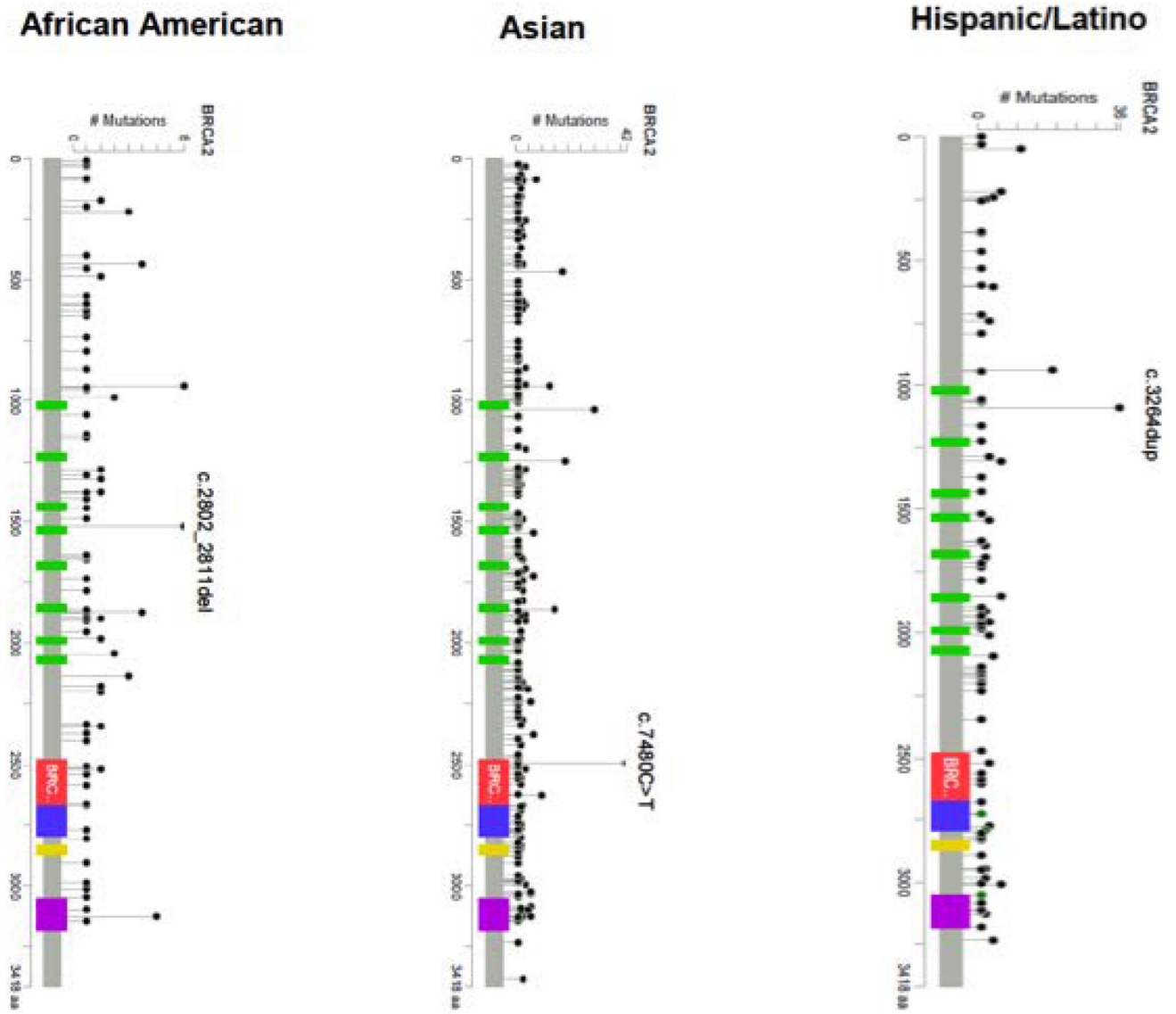


Figure 4.

Characteristics of *BRCA1* and *BRCA2* Mutations in the CIMBA Database (by unique mutation)

Table 1

	Designation	Definition	<i>BRCA1</i> (N=1,650)		<i>BRCA2</i> (N=1,731)		p-value	
			N	%	N	%		
Mutation Type	Large Deletion (DL)	Genomic DNA deletion (encompassing at least 1 exon)	130	7.9	34	1.9	<0.0001	
	Large Duplication (DP)	Genomic DNA duplication (encompassing at least 1 exon)	27	1.6	11	0.6	0.010	
	Frameshift (FS)	Deletion or insertion resulting in a disruption of the open reading frame	948	57.5	1,141	65.9	<0.0001	
	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	0.518	
	Missense (MS)	Results in an altered amino acid	46	2.8	13	0.8	0.0001	
	Nonsense (NS)	Point mutation resulting in a stop codon	313	19.0	380	22.0	0.027	
	Splice (SP)	Results in aberrant RNA splicing	166	10.1	131	7.6	0.013	
	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	0.003
		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	<0.0001
Unknown/Other		Unknown effect	298	18.0	183	10.6	<0.0001	
Nonsense-Mediated Decay (NMD)* (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	<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	<0.0001	
Mutation Function	No RNA	Loss of expression due to deletion of promoter and/or transcription start site	21	1.3	6	0.4	0.003	
	Re-Initiation	Mutations presumed to result in translation re-initiation but produce unstable protein	4	0.2	0	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	<0.0001	
	1	Mutations predicted to be associated with unstable or no protein	1,298	78.6	1,529	88.3	<0.0001	
Mutation Class	2	Mutations predicted to be associated with stable mutant proteins	112	6.8	36	2.1	<0.0001	
	3	Unknown function	240	14.6	167	9.6	<0.0001	

P-values reflect the comparison of frequencies between *BRCA1* and *BRCA2* mutation carriers.

* References (Anczukow, et al., 2008; Buisson, et al., 2006; Mikaelisdottir, et al., 2004; Perrin-Vidoz, et al., 2002; Ware, et al., 2006)

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Common *BRCA1* Mutations by Country of Origin (by family)

Table 2
Five Most Common Mutations (Number Observed)

Continent	Country	Families	Unique Mutations	1	2	3	4	5	
Africa	Nigeria	20	c.303T>G(4)	c.191G>A(2)	c.3268C>T(2)	c.4240dup(1)	c.4122_4123del(1)		
	South Africa	49	c.2641G>T(18)	c.5266dup(7)	c.1374del(4)	c.68_69del(4)	c.3228_3229del(4)		
Asia	Hong Kong	70	c.470_471del(7)	c.4372C>T(5)	c.2635G>T(4)	c.5406+_5406+3del(4)	c.3342_3345del(4)		
	Israel	679	c.68_69del(510)	c.5266dup(151)	c.2934T>G(13)	c.181T>G(2)	c.981_982del(1)		
	Korea	158	c.390C>A(19)	c.5496_5506delinsA(17)	c.922_924delinsT(11)	c.5030_5033del(9)	c.3627dup(8)		
	Malaysia	72	c.2635G>T(5)	c.68_69del(4)	c.470_471del(3)	c.4148C>G(3)	c.3770_3771del(3)		
	Pakistan	93	c.5503C>T(11)	c.3770_3771del(8)	c.4508C>A(8)	c.66dup(6)	c.2269del(1)		
	Singapore	28	c.2726dup(9)	c.2617dup(2)	c.2635G>T(2)	c.213-12A>G(1)	c.3214del(1)		
	Turkey	1	c.3333del(1)						
	Australia	581	c.68_69del(56)	c.5266dup(45)	c.4065_4068del(23)	c.3756_3759del(22)	c.5503C>T(16)		
	Europe	Albania	1	c.4225C>T(1)					
		Austria	391	c.181T>G(51)	c.5266dup(46)	c.3018_3021del(35)	c.1687C>T(26)	c.962G>A(17)	
Belgium		166	c.2359dup(40)	c.212+3A>G(26)	c.3661G>T(12)	c.3607C>T(10)	c.3841C>T(9)		
Bosnia		1	c.4158_4162del(1)						
Czech Rep.		208	c.5266dup(87)	c.3700_3704del(25)	c.181T>G(20)	c.1687C>T(16)	c.3756_3759del(6)		
Denmark		667	c.2475del(91)	c.3319G>T(81)	c.5266dup(41)	c.3710del(39)	c.5213G>A(30)		
Finland		57	c.3485del(8)	c.4097-2A>G(5)	c.5266dup(4)	c.1687C>T(42)	c.4327C>T(3)		
France		1,522	c.5266dup(118)	c.3481_3491del(70)	c.68_69del(63)	c.4327C>T(49)	c.3839_3843delinsAGGC(40)		
Germany		2,287	c.5266dup(411)	c.181T>G(196)	c.4689C>G(63)	c.1687C>T(62)	c.3481_3491del(55)		
Greece		208	c.5266dup(47)	c.5212G>A(29)	c.5406+644_#8273del(24)	c.5468-285_5592+4019delinsCACAG(23)	c.5251C>T(13)		
Hungary		235	c.5266dup(78)	c.181T>G(60)	c.68_69del(22)	c.5278-?_5406+?del(5)	c.5251C>T(4)		
Iceland		3	c.5074G>A(3)						
Ireland		2	c.547+1G>T(1)	c.427C>T(1)					
Italy		1,120	c.5266dup(124)	c.181T>G(44)	c.190T>C(43)	c.1687C>T(39)	c.1380dup(37)		
Latvia		100	c.5266dup(49)	c.4035del(40)	c.181T>G(5)	c.3756_3759del(1)	c.4675G>A(1)		

Five Most Common Mutations (Number Observed)

Continent	Country	Families	Unique Mutations	1	2	3	4	5
North America	Lithuania	223	21	c.4035del(112)	c.5266dup(58)	c.181T>G(221)	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)
	Poland	1,064	8	c.5266dup(711)	c.181T>G(276)	c.4035del(69)	c.5333-36_5406+400del(3)	.68_69del(2)
	Portugal	49	23	c.3331_3334del(15)	c.2037deinsCC(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)
	USA	4,219	613	c.68_69del(99)	c.4327C>T(66)	c.5266dup(50)	c.2834_2836deinsC(16)	c.3756_3759del(12)
South/Central America	Argentina	89	35	c.68_69del(22)	c.5266dup(12)	e.211A>G(11)	e.181T>G(6)	c.427G>T(3)
	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)	e.824_825ins10(2)	e.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)

Five Most Frequently Observed Mutations (Number Observed)								
Continent	Country	Families	Unique Mutations	1	2	3	4	5
Africa	Nigeria	12	9	c.1310_1313del(3)	c.8817_8820delA(2)	c.5241_5242msTA(1)	c.2402_2412del(1)	c.9944del(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)	

Five Most Frequently Observed Mutations (Number Observed)

Continent	Country	Families	Unique Mutations	1	2	3	4	5
North America	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)
	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)
South/Central America	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)
	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)

Table 4
Ten Most Frequently Observed Mutations by Self-Identified Race/Ethnicity (%) (by Family)

Mutation Rank	Caucasian	African American	Asian	Hispanic/Latino	Jewish	Other
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.1757de(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.4936de(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
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.1754de(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(@5)	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
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
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%)	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(92)	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