

DATA ARTICLE

Title: The spectrum of *BRCA1* and *BRCA2* Pathogenic Sequence Variants (PSVs) in Middle Eastern, North African, and South European countries

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Grant sponsor information:

[CIMBA: The CIMBA data management and data analysis were supported by Cancer Research – UK grants C12292/A20861, C12292/A11174. iCOGS: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer (CRN-87521), and the Ministry of Economic Development, Innovation and Export Trade (PSR-SIIRI-701), Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The work of Barbara Pasini has been supported by the program "Dipartimenti di Eccellenza 2018 – 2022". Project n°

D15D18000410001. This work was partially funded by the Associazione Italiana Ricerca Cancro (AIRC)"; IG2015 no.16732) to P. Peterlongo. Funds from Italian citizens who allocated the 5x1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects '5x1000') to S. Manoukian. DEMOKRITOS: European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program of the General Secretariat for Research & Technology: SYN11_10_19 NBCA. kConFab: The National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. MAYO: NIH grants CA116167, CA192393 and CA176785, an NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201) and a grant from the Breast Cancer Research Foundation. UCHICAGO: NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA125183), R01 CA142996, 1U01CA161032 and by the Ralph and Marion Falk Medical Research Trust, the Entertainment Industry Fund National Women's Cancer Research Alliance and the Breast Cancer research Foundation. OIO is an ACS Clinical Research Professor. UCLA: Jonsson Comprehensive Cancer Center Foundation; Breast Cancer Research Foundation]

Abstract (200 words max):

BRCA1 BRCA2 mutational spectrum in the Middle East, North Africa, and Southern Europe is not well characterized. The unique history and cultural practices characterizing these regions, often involving consanguinity and inbreeding, plausibly led to the accumulation of population-specific founder PSVs. To determine recurring *BRCA* PSVs in these locales, a search in PUBMED, EMBASE, BIC, and CIMBA) was carried out combined with outreach to researchers from the relevant countries for unpublished data. We identified 232 PSVs in *BRCA1* and 239 in *BRCA2* in 25 of 33 countries surveyed. Common PSVs that were detected in 4 or more countries were, c.5266dup (p.Gln1756Profs), c.181T>G (p.Cys61Gly), c.68_69del (p.Glu23Valfs), c.5030_5033del (p.Thr1677Ilefs), c.4327C>T (p.Arg1443Ter), c.5251C>T (p.Arg1751Ter), c.1016dup (p.Val340Glyfs), c.3700_3704del (p.Val1234Glnfs), c.4065_4068del (p.Asn1355Lysfs), c.1504_1508del (p.Leu502Alafs), c.843_846del (p.Ser282Tyrfs), c.798_799del (p.Ser267Lysfs) and c.3607C>T (p.Arg1203Ter) in *BRCA1* and c.2808_2811del (p.Ala938Profs), c.5722_5723del (p.Leu1908Argfs), c.9097dup (p.Thr3033Asnfs), c.1310_1313del (p. p.Lys437Ilefs) and c.5946del (p.Ser1982Argfs) for *BRCA2*. Notably, some mutations [e.g., p.Asn257Lysfs (c.771_775del)] were observed in unrelated populations. Thus, seemingly genotyping recurring *BRCA* PSVs in specific populations may provide first pass *BRCA* genotyping platform.

Data Repository Information:

[LOVD- Laitman 2019, submitted

([https://databases.lovd.nl/shared/variants/Laitman 2019](https://databases.lovd.nl/shared/variants/Laitman%2019),submitted)]

Or

[https://databases.lovd.nl/shared/individuals_reference query-](https://databases.lovd.nl/shared/individuals_reference_query-) Laitman 2019, submitted

Key Words (10 max):

BRCA1 BRCA2 mutational spectrum; underserved populations; Middle East; North Africa; Inherited breast cancer; first pass genotyping

Companion Article: None**Introduction (300 words max):**

Breast cancer (BC) is the most common female malignancy worldwide with a global age standardized rate (ASR) of 43.1/100,000 women (Cancer Incidence in five continents, n.d.). BC rates in developed countries are significantly higher than those in developing countries (Cancer Incidence in five continents, n.d.). Ethnicity impacts BC risk: in Israel, BC ASR in Jewish women is 89.4/100,000 and in non-Jews - 56.1/100000 (Cancer Incidence Table, n.d.). Moreover, the median age at diagnosis in Mediterranean countries is younger compared with Western European countries and is often diagnosed in premenopausal women (Al-Kuraya et al., 2005; Atoum & Al-Hourani, n.d.; Bener, Ayub, Kakil, & Ibrahim, n.d.; El Saghir et al., 2007). These

differences in BC phenotype between populations may be attributed to differences in BC risk factors, including genetic predisposition.

Germline pathogenic sequence variants (PSVs) in *BRCA1* and *BRCA2* are the predominant contributors to inherited BC. Since the mid 1990's, more than 3500 germline PSVs have been reported in both genes ("CIMBA - Consortium of Investigators of Modifiers of BRCA1/2 —," n.d.; "Online Research Resources Developed at NHGRI," n.d.). *BRCA* pathogenic PSVs in most world outbred populations – are unique (i.e., family specific) (Rebbeck et al., 2016). In some populations, the spectrum of *BRCA* PSVs is much more limited, with a few "founder PSVs". A relevant Mid-Eastern example are Ashkenazi Jews: three predominant PSVs (185delAG, 5382InsC**BRCA1* and 6174delT**BRCA2*, e.g, c.66_67del, c.5266dup in *BRCA1* and c.5946del in *BRCA2*) account for most of germline PSVs in high-risk women of Ashkenazi origin (Abeliovich et al., 1997). Given the traditions and cultural breeding habits in the Middle East, North Africa, and some South European countries, it seems plausible that in some populations of the region, founder and/or recurring *BRCA* PSVs may be detected. Indeed, some populations in these regions (e.g, Greek, North Africans, Jewish Ashkenazim) present recurring mutations (Bu et al., 2016; Mahfoudh et al., 2012).

Data Specifications:

Data type	Tables
Data acquisition method	Survey, NGS, Sanger sequencing.
Data format	Filtered and analyzed
Experimental factors	Irrelevant
Experimental features	Data collection from published manuscripts in the public domain, in and outreach and unpublished data from the PI's of leading laboratories in the relevant geographical regions
Data source location	Published manuscripts and unpublished data
Data accessibility	Data were deposited in the LOVD data base under Laitman 2019, submitted. LOVD- Laitman 2019, submitted (https://databases.lovd.nl/shared/variants/Laitman 2019 , submitted)] Or https://databases.lovd.nl/shared/individuals reference query- Laitman 2019, submitted

Impact of Data (200 words max):

The data presented herein provide the framework for a possible first pass genotyping platform in populations residing in the Middle East, North Africa, and South Europe. This platform should include the pathogenic sequence variants (PSVs) that were reported in more than 4 countries. As such, this genotyping platform may facilitate rapid, cheap, targeted BRCA genotyping for

unselected breast, ovarian cancer cases, asymptomatic individuals from high-risk families, and possibly enable population based screening.

Experimental Design, Materials and Methods:

Editorial Policies and Ethical Considerations-The data presented herein were obtained by protocols approved by the ethics committees of the contribution centers in their respective countries.

A search for “*BRCA1*” and “*BRCA2*” and “Middle East”, “North Africa”, “South East Europe”, “Arab”, “Muslim”, “Jewish”, specific country names (Morocco, Tunisia, Algeria, Libya, Egypt, Saudi Arabia, Jordan, Israel, Cyprus, Italy (the regions located in the South), Syria, Lebanon, Turkey, Greece, Malta, Macedonia, Albania, Serbia, Slovenia, Bulgaria, Yugoslavia, Montenegro, Bosnia, Romania, Armenia, Georgia, Iran, Iraq, Qatar, United Arab Emirates, Oman, Bahrain, and Yemen) was carried out using PUBMED, Google Scholar, and EMBASE. In addition, search by the specific country names in BIC database (Breast Cancer Information Core, n.d.) was also carried out.

All corresponding authors from the list of publications using the above listed scheme were contacted by mail and offered participation and contributing their unpublished data to the current study.

The CIMBA dataset (<http://cimba.ccge.medschl.cam.ac.uk>) was also searched for pathogenic PSVs deposited from the following countries represented in CIMBA (Greece, Cyprus, Israel, and Iran).

Sequencing data were derived from individuals that were genotyped for *BRCA* germline PSVs in the context of a variety of studies: population-based cohorts, consecutive breast and/or ovarian cancer, early onset BC (i.e., BC diagnosed under age 40 years) or based on high-risk criteria (National Comprehensive Cancer Network, 2018). No attempt was made in the context of this study to distinguish between the different types of ascertainment and eligibility in the original studies. Only studies that performed complete sequencing of the *BRCA1* and *BRCA2* genes were included. Reporting was limited to point PSVs and small indels and to *bona fide* PSVs. Large genomic rearrangements and unclassified or non-pathogenic missense PSVs or variants of unknown significance were excluded from the current study.

Data:

Table 1 displays the most common and recurring *BRCA1* and *BRCA2* pathogenic and likely PSVs that were reported in 4 or more countries. The PSVs that are enumerated in table 2 are those reported in more than one country. Table 3 summarizes all other PSVs, even those reported only once by any country.

Discussion (optional):

In the present study, an attempt to comprehensively collect and tabulate all documented PSVs in both the *BRCA1* and *BRCA2* genes in a defined geographical region was carried out. Of the total of 232 *BRCA1* and 239 *BRCA2* PSVs in the targeted populations, there are 38 (*BRCA1*) and 42 (*BRCA2*) PSVs that are recurring within the same population, or closely related populations (table 2). In these

populations, the next logical step should be genotyping of unselected BC and ovarian cancer cases, and, wherever feasible, the general population, to determine the rates of the top occurring founder PSVs in these cohorts. Given the increased capacity of genotyping platforms, at a minimum the top recurring 18 *BRCA* PSVs should be considered in all relevant populations. Indeed, in Israel “first pass *BRCA* genotyping” of a cluster of recurring PSVs (ranging from a minimum of the 3 recurring Ashkenazi PSVs to a maximum of 14 PSVs that have been described in more than 2 Israeli families of diverse ethnicity, depending on the policy of each medical center) is currently being offered to all BC and ovarian cancer cases, without preselection. The reasons for this inclusive approach are multiple: the ease and cost of genotyping, the fast turnaround time, and the rates of these recurring PSVs in unselected BC (up to 12% in Ashkenazi Jews) and ovarian cancer cases (~30% of all ovarian cancer cases with higher rates in Ashkenazim) (Abeliovich et al., 1997; Modan et al., 2009; Rubinstein, 2004), combined with the penetrance rates that are similar in high risk families and the PSV carriers identified through population screens (Manchanda et al., 2015). Moreover, these high rates in cancer cases and the rates in the general population, ~2.5% in Ashkenazim (Roa, Boyd, Volcik, & Richards, 1996), have led to a scientifically valid initiative to offer this limited genotyping platform to all Ashkenazi and Iraqi Jews, regardless of health status (Levy-Lahad, Lahad, & King, 2015, p.). Cost effectiveness analysis has shown that at least in the Ashkenazi population this approach is indeed cost effective (Manchanda et al., 2014). Moreover, a similar “first-pass” *BRCA* genotyping scheme is also applied in a cost-effective manner for the Greek population, as six recurrent *BRCA1* mutations account for

approximately 60% of the total mutation spectrum for both *BRCA* genes (Konstantopoulou et al., 2014). These include three PSVs in exon 20 [(c.5212G>A - p.Gly1738Arg); (c.5251C>T - p.Arg1751Ter); (c.5266dup - p.Gln1756Profs)] and three large genomic deletions (deletion of exon 20, exon 24, and exons 23 and 24). All three large deletions as well as the c.5212G>A - p.Gly1738Arg PSV have been characterized as population-specific founder mutations by haplotype analysis (Anagnostopoulos et al., 2008; Apostolou et al., 2017; Pertesi, Konstantopoulou, & Yannoukakos, 2011).

Applying this scheme to other countries in the region covered in the current study, may prove cost effective as well, and help in identifying high-risk, asymptomatic individuals who do not fulfil the currently practiced criteria for *BRCA* genotyping eligibility.

Recurring, identical PSVs in the *BRCA1* and *BRCA2* genes are either “founder PSVs” or represent a PSV hot-spot, reviewed by Ferla (Ferla et al., 2007). One indirect (and admittedly imprecise) way of distinguishing between these two possibilities, is assessing the rates of these PSVs in geographically and historically unrelated, distinct populations. Indeed, the 999del5 (c.771_775del) *BRCA2* PSV, clearly an Icelandic founder PSV (Thorlacius et al., 1997) was reported in Egyptian and Jordanian individuals. Similarly, the 1100delAT (herein referred to as c.981_982del) *BRCA1* PSV that was described in Jewish Libyan families (Gal et al., 2002) was also reported to recur in Chinese non-Jewish families (Li et al., 2008). Interestingly, the p.Cys61Gly and 5266dup *BRCA1* PSVs, seem to be the most prevalent PSVs in the present study, and were reported in 11 and 16 countries, respectively. These are the most common

PSVs in Poland (Górski et al., 2000) and other geographically related countries like Belarus (Uglanitsa et al., 2010). The prevalence and distribution of these PSVs in countries from the Middle East and North Africa, a region for which there is no recorded massive population exchange or North European influx is puzzling. Indeed, haplotype analysis of the 5266dup has shown that this PSV arose ~1800 years ago in Northern Europe (Hamel et al., 2011). The possibility of a common ancestor is still valid and can only be resolved using a haplotype analysis of these PSV carriers in a trio setting. Previous analysis of Jewish and non-Jewish individuals who carry the p.Cys61Gly PSV was suggestive of a common origin (Kaufman, Laitman, Gronwald, Lubinski, & Friedman, 2009). Several explanations should be considered in accounting for a seemingly common origin for a single PSV in distinct populations: a few individuals who migrated from one geographical region to another with no historical documentation of this migration, as the number of migrants was limited; an ancient, historically unrecognized common ancestor. In addition, the possibility of having a rare hot spot or a chance occurrence may also underlie identical PSVs in distinct populations, albeit having a different haplotype. From the historical perspective, the Middle East, South Europe and North Africa are regions where human culture has thrived and were prone to multiple conquests by regional forces (the ancient Iranians, Romans, Greek, Arabs, the crusaders, are notable examples), conquests that have reshaped and re-defined the borders of current countries. In addition, some conquerors applied an exile strategy as a means of asserting their rule over these territories. It is plausible that during such massive exiles (e.g., Jews from current day Israel to

Babylon, mass enslavement by the Roman Empire) a few PSV carriers may have been embedded in these new locales.

Much of the genetic trace of the more remote and recent demographic and migratory events has been fruitfully elucidated by examining the phylogenies of the uniparentally inherited mitochondrial DNA (Behar et al., 2006, 2008) and Y chromosome (Behar et al., 2017; Hammer et al., 2000; Karmin et al., 2015), and by investigating autosomal biparental variation (Behar et al., 2010; Haber et al., 2013). Overall, the emerging pattern is of a multilayered demographic history characterizing contemporary Middle Eastern populations. First, it is apparent that Middle Eastern populations share a distinctive background genetic layer that is readily separable from components dominating other continents (Behar et al., 2010; Haber et al., 2013). Accordingly, within a global context, Middle Eastern populations are found in close genetic proximity to each other pointing to a common ancient ancestral deme. However, within the Middle Eastern variation, various populations cluster separately from each other, suggesting more recent isolation and inbreeding. As the level of the uniploids, evidences from the Y-chromosome and mtDNA suggest local founding events (Badro et al., 2013), specific to a given population, and sometimes down to the village level (Shlush et al., 2008). For example, the Ashkenazi Jewish population was repeatedly demonstrated to derive its ancestral origins from the Levant and Europe (Atzmon et al., 2010; Behar et al., 2010), and strong isolation from its hosting population were suggestive for a strong parental founding event (Behar et al., 2006, 2017). This was suggested to be the reason for the high incidence of rare autosomal recessive disorders characterizing the population. Hence, it seems plausible to suggest

that the same mechanisms leading to the founding events proven for the mtDNA (Behar et al., 2006), Y-chromosome (Behar et al., 2004), and rare recessive disorders among Ashkenazi Jews (Baskovich et al., 2016), played also a major role in the accumulations of the three *BRCA1/2* PSVs in this population. Using haplotype analysis of individuals from diverse and unlikely related ethnicities may allow for distinguishing some of these possibilities. Indeed, haplotype analysis of the c.66_67del *BRCA1* PSV has shown that among Ashkenazi Jews, non-Ashkenazi Jews, and non-Jewish Hispanics the PSV has a common haplotype whereas the haplotype in Malaysians and English non-Jews is distinct (Laitman et al., 2013).

In conclusion, in a geographically defined region, a few *BRCA1* and *BRCA2* PSV have been reported with a handful of these PSV recurring within these populations or shared by some distinct ethnicities. Regardless of the mechanism that has led to such restricted PSVs reality, these PSVs may be considered as "first pass" *BRCA* genotyping for defined subsets of individuals (e.g., high risk families, consecutive breast/ovarian cancer cases, population screens) in these geographical regions and in these countries.

Acknowledgements:

The authors wish to thank Prof Johan T. den Dunnen and the LOVD team for their ongoing support and help in accurately curating the mutations and annotating according to the HGVS nomenclature.

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Tables:

Table 1: Top recurring mutations in BRCA1 and BRCA2 (in more than four countries)

Gene	BIC designation	HGVS designation	HGVS:protein level	dbSNP rs#	Countries (from literature)	No. in BIC	PMID
BRCA1	5382insC	c.5266dup	p.Gln1756Profs	rs80357906	Bulgaria, Croatia, Egypt, Greece, Iran, Israel, Italy , Lebanon, Macedonia, Romania, Serbia, Slovenia , Tunisia, Turkey, Uzbekistan, Yugoslavia	1088	29138730; 23958087; 10952777; 12461697; 23635950; 23697973; 25814778; 24052750; 29335924; 26183948; 10523726; 22713736; 17902052; 22366370
BRCA1	C61G	c.181T>G	p.Cys61Gly	rs28897672	Algier, Bulgaria, Croatia, Egypt, Greece, Israel, Italy , Macedonia, Morocco, Romania, Slovenia	239	12461697; 20683152; 22425665; 25814778; 24052750; 29335924; 26183948; 23958087; 22366370
BRCA1	185delAG	c.68_69del	p.Glu23Valfs	rs80357713	Egypt, Greece, Iran, Israel , Lebanon, Morocco, Slovenia, Turkey, Yugoslavia	2038	10952777; 28740454; 23697973; 25814778; 10523726; 257773438
BRCA1	5149del4	c.5030_5033del	p.Thr1677Ilefs	rs80357862	Bulgaria, Greece, Italy, Jordan, Kuwait, Lebanon, Saudi Arabia	18	26183948; 29409476; 257773438
BRCA1	R1443X	c.4327C>T	p.Arg1443Ter	rs41293455	Egypt, Greece, Italy, Kuwait , Lebanon, Saudi Arabia	136	29297111; 28202063; 25814778; 22366370
BRCA1	R1751X	c.5251C>T	p.Arg1751Ter	rs80357123	Croatia, Greece, Israel , Saudi Arabia, Slovenia	44	29297111; 12461697
BRCA1	1135insA	c.1016dup	p.Val340Glyfs	rs80357569	Greece, Iran, Israe, Italy , Morocco	48	23697973; 25352972
BRCA1	3819del5	c.3700_3704del	p.Val1234Glnfs	rs80357609	Albania , Greece, Italy , Macedonia, Turkey	61	10952777; 17902052; 29335924
BRCA1	4184del4	c.4065_4068del	p.Asn1355Lysfs	rs80357508	Algier, Greece, Israel , Saudi Arabia	141	27082205; 26997744
BRCA1	1623del5	c.1504_1508del	p.Leu502Alafs	rs80357888	Greece , Saudi Arabia, Tunisia, Turkey	29	29297111; 10952777; 25814778
BRCA1	962del4	c.843_846del	p.Ser282Tyfs	rs80357919	Croatia, Greece , Serbia, Slovenia	19	23635950; 12461697; 22366370
BRCA1	917delTT	c.798_799del	p.Ser267Lysfs	rs80357724	Algier, Italy, Morocco, Tunisia	26	23697973
BRCA1	3726C>T	c.3607C>T	p.Arg1203Ter	rs62625308	Greece, Israel, Italy, Turkey	36	12655560

BRCA2	3036del4	c.2808_2811del	p.Ala938Profs	rs80359352	Cyprus, Iran, Israel, Italy , Macedonia, Saudi Arabia, Turkey	23	27882536; 30199306; 24884828; 29335924
BRCA2	5950delCT	c.5722_5723del	p.Leu1908Argfs	rs80359531	Algier, Bulgaria, Greece, Iran, Italy , Macedonia, Turkey	45	24052750; 26183948; 10952777; 29335924
BRCA2	9326insA	c.9097dup	p.Thr3033Asnfs	rs397507419	Bulgaria, Greece, Romania, Turkey	27	
BRCA2	1538del4	c.1310_1313del	p.Lys437Ilefs	rs80359280	Algier, Morocco, Tunisia, Turkey, Lebanon	11	28577564; 20683152; 23697973; 21156238; 257773438
BRCA2	6174delT	c.5946del	p.Ser1982Argfs	rs80359550	Bulgaria, Greece, Iran, Israel	1093	26183948

Table 2: mutations in BRCA1 and BRC2 recurring in more than one country

Gene	BIC designation	HGVS designation	HGVS:protein level	dbSNP rs#	Countries (from literature)	No. in BIC	PMID
BRCA1	Q1811X	c.5431C>T	p.Gln1811Ter	rs397509283	Greece, Saudi Arabia	-	29297111; PC
BRCA1	P1812A	c.5434C>G	p.Pro1812Ala	rs1800751	Greece, Israel	2	PC
BRCA1	3480delAG	c.3599_3600del	p.Gln1200Argfs	rs398122674	Albania, Greece	-	PC
BRCA1	R1699W	c.5095C>T	p.Arg1699Trp	rs55770810	Morocco, Saudi Arabia	18	23697973
BRCA1	W1508X	c.4524G>A	p.Trp1508Ter	rs80356885	Israel, Saudi Arabia	23	27082205
BRCA1	W1815X	c.5444G>A	p.Trp1815Ter	rs80356962	Lebanon, Turkey	4	10952777
BRCA1	Y978X	c.2934T>G	p.Tyr978Ter	rs80357115	Iran, Israel	26	11248423
BRCA1	Q1182X	c.3544C>T	p.Gln1182Ter	rs80357296	Turkey, Bulgaria	1	PC
BRCA1	2388delG	c.2269del	p.Val757Phefs	rs80357583	Israel, Slovenia	10	21232165
BRCA1	5454delC	c.5335del	p.Gln1779Asnfs	rs80357590	Croatia, Egypt	5	20579331
BRCA1	2138delA	c.2019del	p.Glu673Aspfs	rs80357626	Serbia, Turkey	7	23635950
BRCA1	343del4	c.224_227del	p.Glu75Valfs	rs80357697	Greece, Israel	2	PC
BRCA1	5055delG	c.4936del	p.Val1646Serfs	rs80357705	Israel, Turkey	4	10952777
BRCA1	4160delAG	c.4041_4042del	p.Gly1348Asnfs	rs80357727	Israel, Tunisia	7	23697973
BRCA1	969ins7	c.844_850dup	p.Gln284Leufs	rs80357989	Serbia, Slovenia	2	12461697; 23635950
BRCA1	IVS21+1G>A	c.5332+1G>A		rs80358041	Algier, Israel	2	26997744
BRCA1	IVS11+1G>A	c.4096+1G>A		rs80358178	Cyprus, Greece, Turkey	5	21156238
BRCA1	5280C>T	c.5161C>T	p.Gln1721Ter	rs878854957	Israel, Saudi Arabia	-	PC; 30199306
BRCA1	C44F	c.131G>T	p.Cys44Phe	rs80357446	Lebanon, Kuwait	12	23289006; PC
BRCA1	R1835X	c.5503C>T	p.Arg1835Ter	rs41293465	Greece, Italy, Turkey	74	10952777
BRCA1	1140dupG	c.1140dup	p.Lys381Glufs	rs876659327	Kuwait, Saudi Arabia	-	29297111; PC
BRCA1	C64R	c.190T>C	p.Cys64Arg	rs80357064	Greece, Italy	12	PC
BRCA1	2072del4	c.1953_1956del	p.Lys653Serfs	rs80357526	Greece, Saudi Arabia	28	24010542; 30199306
BRCA1	3875del4	c.3756_3759del	p.Ser1253Argfs	rs80357868	Greece, Italy	130	17453335

BRCA1	5083del19	c.4964_4982del	p.Ser1655Tyrfs	rs80359876	Greece, Italy	48	PC
BRCA1	Q1537X	c.4609C>T	p.Gln1537Ter	rs80357229	Iran, Saudi Arabia	1	30199306
BRCA1	A1708E	c.5123C>A	p.Ala1708Glu	rs28897696	Israel, Italy	46	21063910
BRCA1	3228_3229delAG	c.3228_3229del	p.Gly1077Alafs	rs80357635	Israel, Italy	28	PC
BRCA1	1100delAT	c.981_982del	p.Cys328Terfs	rs80357772	Israel, Italy	13	PC
BRCA1	2530delAG	c.2411_2412del	p.Gln804Leu	rs80357664	Italy, Lebanon	15	257773438; PC
BRCA1	E368X	c.1102G>T	p.Glu368Ter	rs80357139	Italy, Macedonia	1	24052750; 29335924
BRCA1	2767ins4	c.2649_2650insGGCA	p.Thr884Glyfs	rs886038003	Greece, Iran	-	PC; 11248423
BRCA1	3450del4	c.3331_3334del	p.Gln1111Asnfs	rs80357903	Jordan, Lebanon, Tunisia	43	29409476; 23697973
BRCA1	448insA	c.329dup	p.Glu111Glyfs	rs80357604	Greece, Saudi Arabia, Tunisia	6	29297111; 17922257
BRCA1	G1738R	c.5212G>A	p.Gly1738Arg	rs80356937	Greece, Italy, Macedonia	15	17902052; 29335924
BRCA1	E720X	c.2158G>T	p.Glu720Ter	rs80356875	Iran, Israel, Lebanon	2	257773438; 26109977
BRCA1	1806C>T	c.1687C>T	p.Gln563Ter	rs80356898	Croatia, Macedonia, Slovenia	94	12461697; 29335924
BRCA1	1640_1650del10	c.1521_1531del	p.Thr509Serfs	-	Albania, Greece	-	PC
BRCA2	9158delA	c.8930del	p.Tyr2977Phefs	rs869320799	Greece, Italy	-	PC
BRCA2	9254del5	c.9026_9030del	p.Tyr3009Serfs	rs80359741	Israel, Turkey	16	PC; 29774317
BRCA2	5579insA	c.5351dup	p.Asn1784Lysfs	rs80359508	Macedonia, Slovenia	16	12461697; 29335924
BRCA2	5164del4	c.4936_4939del	p.Glu1646Glnfs	rs80359473	Israel, Slovenia	28	12461697
BRCA2	4075delGT	c.3847_3848del	p.Val1283Lysfs	rs80359405	Greece, Israel	64	PC
BRCA2	I2627F	c.7879A>T	p.Ile2627Phe	rs80359014	Greece, Macedonia	7	29335924
BRCA2	S1882X	c.5645C>A	p.Ser1882Ter	rs80358785	Greece, Iran, Italy	27	PC; 26109977
BRCA2	E510X	c.1528G>T	p.Glu510Ter	rs80358438	Algier, Slovenia	1	12461697; 26997744
BRCA2	9910delA	c.9682del	p.Ser3228Valfs	rs398122618	Greece, Bulgaria	-	26183948
BRCA2	R259X	c.775A>T	p.Arg259Ter	rs397507937	Macedonia, Slovenia	-	21232165; 29335924
BRCA2	6719delAGTT	c.6491_6494del	p.Gln2164Argfs	rs397507862	Croatia, Slovenia	-	21232165
BRCA2	3979insA	c.3751dup	p.Thr1251Asnfs	rs397507683	Iran, Israel	-	PC; 26109977
BRCA2	Q2893X	c.8677C>T	p.Gln2893Ter	rs397507409	Iran, Israel	-	PC; 26109977
BRCA2	4642del4	c.4415_4418del	p.Lys1472Thrfs	rs397507333	Iran, Greece	-	12100744
BRCA2	4391delCTinsA	c.4163_4164delinsA	p.Thr1388Asnfs	rs276174843	Serbia, Turkey	-	21954532
BRCA2	7463InsG	c.7235_7236insG	p.Lys2413Ter	rs397507906	Algier, Morocco	1	23697973; 20683152
BRCA2	2482del4	c.2254_2257del	p.Asp752Phefs	rs80359326	Jordan, Saudi Arabia (palestinian)	1	12070551; 29409476
BRCA2	999del5	c.771_775del	p.Asn257Lysfs	rs80359675	Egypt, Jordan	14	29409476; 20579331
BRCA2	Q1408X	c.4222C>T	p.Gln1408Ter	rs80358663	Albania, Italy	4	PC
BRCA2	K2013X	c.6037A>T	p.Lys2013Ter	rs80358840	Greece, Italy	16	PC

BRCA2	4512insT	c.4284dup	p.Gln1429Serfs	rs80359440	Greece, Italy	4	2085629; PC
BRCA2	6024delTA	c.5796_5797del	p.His1932Glnfs	rs80359537	Greece, Italy	9	11754111; PC
BRCA2	9474insA	c.9253dup	p.Thr3085Asnfs	rs80359752	Greece, Italy	19	PC
BRCA2	8765delAG	c.8537_8538del	p.Glu2846Gly	rs80359716	Israel, Italy	76	PC
BRCA2	IVS2+1G>A	c.67+1G>A		rs81002796	Israel, Italy	4	PC
BRCA2	5301insA	c.5073dup	p.Trp1692Metfs	rs80359480	Italy, Morocco	29	23697973
BRCA2	4366insTT	c.4139_4140dup	p.Lys1381Leufs	rs276174842	Croatia, Serbia	1	23635950
BRCA2	R2336H	c.7007G>A	p.Arg2336His	rs28897743	Iran, Italy, Saudi Arabia	20	PC; 11248423; 25923920
BRCA2	R2336P	c.7007G>C	p.Arg2336Pro	rs28897743	Greece, Israel, Saudi Arabia	26	29297111
BRCA2	2041insA	c.1813dup	p.Ile605Asnfs	rs80359308	Albania, Greece, Slovenia	75	12461697
BRCA2	3417del4	c.3189_3192del	p.Ser1064Leufs	rs80359374	Greece, Macedonia, Turkey	1	24884828; 29335924
BRCA2	886delGT	c.658_659del	p.Val220Ilefs	rs80359604	Greece, Kuwait, Lebanon	37	28202063; PC
BRCA2	Y1757X	c.5271T>A	p.Tyr1757Ter	-	Kuwait, Saudi Arabia	-	PC; 25923920
BRCA2	6678insA	c.6450dup	p.Val2151Serfs	rs80359595	Algier, Saudi Arabia	2	26997744; PC
BRCA2	4200delTACT	c.3972_3975del	p.Tyr1324Ter	rs886040507	Lebanon, Saudi Arabia		257773438; 25923920
BRCA2	6503delTT	c.6275_6276del	p.Leu2092Profs	rs11571658	Greece, Italy	95	PC
BRCA2	6714del4	c.6486_6489del	p.Lys2162Asnfs	rs80359598	Italy, Slovenia	1	PC; 27882536
BRCA2	IVS16-2A>G	c.7806-2A>G		rs81002836	Italy, Slovenia	5	PC; 12461697
BRCA2	IVS24-1G>C	c.9257-1G>C		rs81002889	Israel, Jordan	2	20960228; 29335924
BRCA2	6630del5	c.6405_6409del	p.Asn2135Lysfs	rs80359584	Italy, Turkey	30	10952777; PC
BRCA2	8138del5	c.7913_7917del	p.Phe2638Ter	rs80359686	Bulgaria, Greece	24	26183948; PC
BRCA2	6076del4	c.5851_5854del	p.Ser1951Trpfs	rs80359543	Bulgaria, Macedonia	14	29335924; 26183948

Table 3: uncommon mutations in BRCA1 and BRCA2

Gene	Country	no of fa mil ies	BIC designation	HGVS designation	HGVS:protein level	dbSNP rs#	N o i n B I C	PMID
BRCA1	Algier		138del29	c.19_47del	p.Arg7Cysfs	rs80359871	1	23697973
BRCA1	Algier		202delTG	c.83_84del	p.Leu28Argfs	rs80357728	1	20683152
BRCA1	Algier		2049delC	c.1817del	p.Pro606Leufs	rs397508910	-	23289006
BRCA1	Algier		3574delT	c.3715del	p.Ser1239Leufs	rs397509096	-	23289006
BRCA1	Algier		3834delTCTinsC	c.3715_3717delinsC	p.Ser1239Profs	rs273900714	1	18645608
BRCA1	Algier		2862delTC	c.2602_2603del	p.Ser868Terfs	rs80357540	1	23289006
BRCA1	Algier		IVS5+1G>A	c.212+1G>A		rs80358042	6	23697973
BRCA1	Bulgaria		583delA	c.465del	p.Gln155Hisfs	rs483353104	1	26183948
BRCA1	Bulgaria	1	E1535X	c.4603G>T	p.Glu1535Ter	rs80357366	4	26183948
BRCA1	Bulgaria	1	5515del7	c.5397_5403del	p.Leu1800Glnfs	-	-	26183948
BRCA1	Croatia		E1107X	c.3319G>T	p.Glu1107Ter	rs80357106	3	PC
BRCA1	Croatia		E418X	c.1252G>T	p.Glu418Ter	rs80357083	3	22366370
BRCA1	Cyprus	2	1819insA	c.1700dup	p.Asn567Lysfs	rs80357784	1	27882536
BRCA1	Cyprus	2	K614X	c.1840A>T	p.Lys614Ter	rs80357282	1	27882536
BRCA1	Cyprus	7	5429delG	c.5315del	p.Phe1772Serfs	rs397509261	-	15172753
BRCA1	Egypt		Q169X	c.505C>T	p.Gln169Ter	rs80357133	5	23877192
BRCA1	Greece	11	A1823T	c.5467G>A	p.Ala1823Thr	rs80357212	1 0	12142080
BRCA1	Greece	1	2004A>T	c.1885A>T	p.Arg629Ter	-		PC
BRCA1	Greece	1	2695delA	c.2576del	p.Asn859Ilefs	-		PC
BRCA1	Greece	1	1531insCAGT	c.1299_1302dup	p.Asp435Glnfs	-		PC
BRCA1	Greece	1	3555del4	c.3436_3439del	p.Cys1146Leufs	rs397509067	-	29310832
BRCA1	Greece	1	3099delT	c.2980del	p.Cys994Valfs	rs80357502	1	10980541
BRCA1	Greece	1	Q1409X	c.4225C>T	p.Gln1409Ter	rs886040218	-	PC
BRCA1	Greece	1	Q1848X	c.5542C>T	p.Gln1848Ter	rs886040303	-	PC
BRCA1	Greece	1	E1060X	c.3178G>T	p.Glu1060Ter	rs80357424	1 2	10980541
BRCA1	Greece	2	449delG	c.331del	p.Glu111Lysfs	rs886040114	-	24010542
BRCA1	Greece	1	E1526X	c.4576G>T	p.Glu1526Ter	rs878853294	-	PC
BRCA1	Greece	1	1329insCT	c.1210_1211insCT	p.Glu404Alafs	rs886039934	-	24010542
BRCA1	Greece	1	4324delA	c.4205del	p.His1402Leufs	rs886040214	-	PC
BRCA1	Greece	2	2623insA	c.2504dup	p.His835Glnfs	rs483353078	-	PC
BRCA1	Greece	1	3744insA	c.3624dup	p.Leu1209Ilefs	rs80357512	2	10980541
BRCA1	Greece	1	3896delT	c.3779del	p.Leu1260Tyrf	rs397509107	3	17453335
BRCA1	Greece	1	L502X	c.1505T>G	p.Leu502Ter	rs886039957	-	24010542
BRCA1	Greece	3	3741delA	c.3624del	p.Lys1208Asnfs	rs886038020	-	24010542
BRCA1	Greece	1	269delA	c.150del	p.Lys50Asnfs	rs273897662	1	PC

BRCA1	Greece	1	M1V	c.1A>G	p.Met1Val	rs80357287	8	10980541
BRCA1	Greece	1	3436delC	c.3317del	p.Pro1106Leufs	-		PC
BRCA1	Greece	4	3494delTC	c.3375_3376del	p.Pro1126Ilefs	rs80357828	1	24010542
BRCA1	Greece	4	4510delCTAinsTT	c.4391_4393delinsTT	p.Pro1464Leufs	rs273900730	5	24010542
BRCA1	Greece	5	5611delC	c.5492del	p.Pro1831Leufs	rs80357582	4	24010542; 29310832
BRCA1	Greece	1	4286delTG	c.4167_4168del	p.Ser1389Argfs	rs397509144	-	24010542
BRCA1	Greece	1	3082C>A	c.2963C>A	p.Ser988Ter	rs397507206	-	24010542
BRCA1	Greece	1	5447delC	c.5328del	p.Thr1777Glnfs	-	2	24010542
BRCA1	Greece	1	1789del4	c.1670_1673del	p.Thr557Lysfs	-		PC
BRCA1	Greece	4	W353X	c.1059G>A	p.Trp353Ter	rs80356935	4	29310832
BRCA1	Greece	1	5533dupT	c.5533dup	p.Tyr1845Leufs	rs397509294	-	PC
BRCA1	Greece	1	5789del13	c.5557_5569del	p.Tyr1853Argfs	-	1	PC
BRCA1	Greece	1	5675del5	c.5556_5560del	p.Tyr1853Aspfs	rs886040305	-	PC
BRCA1	Greece	1	3277insG	c.3158_3159insG	p.Val1054Serfs	rs80357769	1	10980541
BRCA1	Greece	1	IVS17-1G>A	c.5075-1G>A		rs1800747	1	24667779
BRCA1	Greece	1	IVS6-2A>G	c.302-2A>G		rs80358011	1	20406929
BRCA1	Greece	2	IVS22+5G>C	c.5406+5G>C		rs80358073	2	9354803
BRCA1	Greece	1	IVS20-1G>A	c.5278-1G>A		rs80358099	3	PC
BRCA1	Greece	1	IVS6-1G>C	c.302-1G>C		rs8035811	-	PC
BRCA1	Iran	1	3452delA	c.3333del	p.Glu1112Asnfs	rs80357966	1	PC
BRCA1	Iran		181insT	c.62dup	p.Glu23Argfs	rs397509303	-	PC
BRCA1	Iran		G1738E	c.5213G>A	p.Gly1738Glu	rs80357450	6	PC
BRCA1	Iran	1	1803insA	c.1684dup	p.Ile562Asnfs	-		27165220
BRCA1	Iran		L1418X	c.4253T>G	p.Leu1418Ter	rs397509157	-	PC
BRCA1	Iran	2	IVS2-1G>C	c.81-1G>C	p.Leu30Ter	-		PC
BRCA1	Iran		L3X	c.8T>G	p.Leu3Ter	-		PC
BRCA1	Iran	1	1411delT	c.1292del	p.Leu431Tyrfs	rs398122629	-	PC
BRCA1	Iran	2	1687delT	c.1568del	p.Leu523Trpfs	-		27165220
BRCA1	Iran	1	2374delTAAGT	c.2255_2259del	p.Leu752Trpfs	-		PC
BRCA1	Iran		1135delA	c.1016del	p.Lys339Argfs	rs80357618	2	25352972
BRCA1	Iran		K581X	c.1741A>T	p.Lys581Ter	rs397508905	-	PC
BRCA1	Iran	1	2080delA	c.1961del	p.Lys654Ser	rs80357522	3 9	PC
BRCA1	Iran	1	2335delAA	c.2216_2217del	p.Lys739Serfs	rs397508952	-	12100744
BRCA1	Iran		M1I	c.3G>T	p.Met1Ile	rs80357475	1 0	PC
BRCA1	Iran	1	Y856X	c.2568T>G	p.Tyr856Ter	rs80356832	3	PC
BRCA1	Iran	1	3477delGT	c.3358_3359del	p.Val1120Ter	rs80357945	4	PC
BRCA1	Iran	1	IVS12+1delG	c.4185+1delG		-	-	PC
BRCA1	Iran Kerman province	3	1088insC	c.669_670insC	p.Ala224Argfs	-		25352972
BRCA1	Israel		1269delC	c.1510del	p.Arg504Valfs	rs80357908	2	PC
BRCA1	Israel		3053delT	c.2934del	p.Arg979Valfs	rs80357741	2 6	PC

BRCA1	Israel		Q1273X	c.3817C>T	p.Gln1273Ter	rs80357208	8	PC
BRCA1	Israel		Q1721del	c.5161_5163del	p.Gln1721del	rs80358346	2	20960228
BRCA1	Israel		4154delA	c.4035del	p.Glu1346Lysfs	rs80357711	5 4	PC
BRCA1	Israel		1039-1040delCT	c.1039_1040del	p.Leu347Valfs	rs397508827	-	PC
BRCA1	Israel		2543del7	c.2311_2317del	p.Pro773Leufs	rs1060502354	-	PC
BRCA1	Israel		S864X	c.2591C>A	p.Ser864Ter	rs80357003	1	PC
BRCA1	Israel		Y1127X	c.3381T>G	p.Tyr1127Ter	rs781319410	-	PC
BRCA1	Israel			c.4359del	p.Val1454Tyrfs	-		PC
BRCA1	Italy	1		c.1297del	p.Ala433Profs	rs80357794	-	PC
BRCA1	Italy	1		c.407del	p.Arg136Asnfs	rs886040200	-	PC
BRCA1	Italy	6	R1495M	c.4484G>T	p.Arg1495Met	rs80357389	2 7	PC
BRCA1	Italy	1		c.882del	p.Asp295Thrfs	-	-	PC
BRCA1	Italy	1	236delTG	c.117_118del	p.Cys39Ter	rs80357972	3	PC
BRCA1	Italy	9	633delC	c.514del	p.Gln172Asnfs	rs80357872	2 3	PC
BRCA1	Italy	1		c.5476C>T	p.Gln1826Ter	-	-	29335924
BRCA1	Italy	1		c.784del	p.Gln262Argfs	rs886040318	-	29335924
BRCA1	Italy	1	E1134X	c.3400G>T	p.Glu1134Ter	rs80357018	1 5	PC
BRCA1	Italy	1		c.3514G>T	p.Glu1172Ter	rs397509079	-	PC
BRCA1	Italy	1		c.363_364del	p.Glu121Aspfs	rs886040155	-	PC
BRCA1	Italy	1	3888delGA	c.3770_3771del	p.Glu1257Glyfs	rs80357579	1	PC
BRCA1	Italy	2	E1302X	c.3904G>T	p.Glu1302Ter	rs80357461	3	PC
BRCA1	Italy	2	2508delGA	c.2389_2390del	p.Glu797Thrfs	rs80357695	4	PC
BRCA1	Italy	1		c.2637del	p.Glu880Argfs	rs886040056	-	PC
BRCA1	Italy	2	E908X	c.2722G>T	p.Glu908Ter	rs80356978	5 8	PC
BRCA1	Italy	1		c.4042G>T	p.Gly1348Ter	rs886040191	-	PC
BRCA1	Italy	1	IVS20-2delA	c.5278-2delA	p.Ile1760Serfs	-	-	PC
BRCA1	Italy	2	L1086X	c.3257T>G	p.Leu1086Ter	rs80357006	4	PC
BRCA1	Italy	1	4035delTT	c.3916_3917del	p.Leu1306Aspfs	rs80357678	1 1	PC
BRCA1	Italy	2	5154del5	c.5035_5039del	p.Leu1679Tyrfs	rs80357623	7	PC
BRCA1	Italy	1	L999X	c.2995_2996delinsTA	p.Leu999Ter	rs273899692	1	PC
BRCA1	Italy	1		c.1375A>T	p.Lys459Ter	rs886039947	-	PC
BRCA1	Italy	1		c.1513A>T	p.Lys505Ter	rs397508877	-	PC
BRCA1	Italy	1		c.2487dup	p.Lys830Ter	rs397508972	-	PC
BRCA1	Italy	1	1499insA	c.1380dup	p.Phe461Ilefs	rs80357714	1 2	PC
BRCA1	Italy	2		c.1887_1900dup	p.Pro634Glnfs	rs886039977	-	PC
BRCA1	Italy	1	4408insC	c.4289dup	p.Ser1431Phefs	rs80357556	1	PC
BRCA1	Italy	1		c.4456del	p.Ser1486Valfs	rs397509179	-	PC
BRCA1	Italy	1	4744delCT	c.4625_4626del	p.Ser1542Trpfs	rs80357542	4	PC
BRCA1	Italy	2	1479delAG	c.1360_1361del	p.Ser454Ter	rs80357969	1 9	PC
BRCA1	Italy	1		c.2350_2351del	p.Ser784Valfs	-	-	PC

BRCA1	Italy	1		c.3928dup	p.Thr1310Asnfs	rs886040176	-	PC
BRCA1	Italy	1		c.4453_4454delinsG	p.Thr1485Alafs	-	-	PC
BRCA1	Italy	1		c.815_824dup	p.Thr276Alafs	rs387906563	-	29335924
BRCA1	Italy	1	IVS7+2T>G	c.441+2T>G		rs397509173	-	PC
BRCA1	Italy	1	IVS3+2T>C	c.134+2T>C		rs80358131	2	PC
BRCA1	Italy	2	IVS18-1G>A	c.5153-1G>A		rs80358137	5	PC
BRCA1	Jordan	1	E1373X	c.4117G>T	p.Glu1373Ter	rs80357259	9	29335924
BRCA1	Lebanon		5210delTG	c.5091_5092del	p.Cys1697Ter	rs80357710	2	PC
BRCA1	Lebanon		Q12X	c.34C>T	p.Gln12Ter	rs80357134	1 3	257773438
BRCA1	Lebanon		Q804X	c.2410C>T	p.Gln804Ter	rs80356982	2	257773438
BRCA1	Lebanon		S955X	c.2864C>A	p.Ser955Ter	rs80357295	4	PC
BRCA1	Lebanon		604delTG	c.485_486del	p.Val162Glufs	rs80357708	1	257773438
BRCA1	Macedonia			c.4356del	p.Ala1453Glnfs	-		29335924
BRCA1	Macedonia		Q538X	c.1612C>T	p.Gln538Ter	rs80356893	3	29335924
BRCA1	Macedonia		2792dupA	c.2933dup	p.Tyr978Ter	rs878853292	-	29335924
BRCA1	Morocco		5061delA	c.4945del	p.Arg1649Glufs	rs80357761	1	23289006
BRCA1	Morocco		2924delA	c.2805del	p.Asp936Ilefs	rs397509012	1	22425665
BRCA1	Morocco		3398delC	c.3279del	p.Tyr1094Ilefs	rs397509050	1	22425665
BRCA1	Morocco		5181delGTT	c.5062_5064del	p.Val1688del	rs80358344	6	22425665
BRCA1	Morocco		1016dupA- 1137delG	c.1018del	p.Val340Terfs	rs80357774	8	23289006
BRCA1	Morocco		K1648X	c.4942A>T	p.Lys1648Ter	-		23289006
BRCA1	Romania		2360delC	c.2241del	p.Asp749Ilefs	rs80357650	2	23958087
BRCA1	Romania	1	2356insC	c.2241dup	p.Lys748Glnfs	rs397508953	-	20567915
BRCA1	Romania	1	461delTC	c.342_343del	p.Pro115Ter	rs80357881	1	20567915
BRCA1	Saudi Arabia	1	Q356X	c.1066C>T	p.Gln356Ter	rs80357215	2	30199306
BRCA1	Saudi Arabia	1	2274insA	c.2016dup	p.Glu673Argfs	rs80357715	-	30199306
BRCA1	Saudi Arabia			c.708_711dup	p.His238Ter	-		29297111
BRCA1	Saudi Arabia	1	243delA	c.124del	p.Ile42Tyrfs	rs80357943	3	30199306
BRCA1	Saudi Arabia	2	530insT	c.411dup	p.Leu138Serfs	-	-	30199306
BRCA1	Saudi Arabia	4		c.5530del	p.Leu1844Serfs	-		29297111
BRCA1	Saudi Arabia	8		c.4136_4137del	p.Ser1379Ter	rs397509141	-	29297111
BRCA1	Saudi Arabia		T1685I	c.5054C>T	p.Thr1685Ile	rs80357043	3	29297111
BRCA1	Saudi Arabia	1	2080insA	c.1961dup	p.Tyr655Valfs	rs80357853	1 4	30199306
BRCA1	Saudi Arabia	1		c.5512dup	p.Val1838Glyfs	-	-	30199306
BRCA1	Saudi Arabia	1	2524delTG	c.2405_2406del	p.Val802Glufs	rs80357706	5	30199306
BRCA1	Saudi Arabia	1	IVS18+2T>G	c.5152+2T>G		-	-	30199306
BRCA1	Saudi Arabia		5193+1G>A	c.5074+1G>A		rs80358053	3	29297111

BRCA1	Saudi Arabia		IVS18+1G>C	c.5152+1G>C		rs80358094	9	27082205
BRCA1	Saudi Arabia	1	IVS15-2A>G	c.4676-2A>G		rs80358096	1	30199306
BRCA1	Serbia	1	4765del20	c.4646_4665del	p.Glu1549Alafs	rs397509186	-	23635950
BRCA1	Slovenia	1	5296delGAAA	c.5177_5180del	p.Arg1726Lysfs	rs80357975	3 9	12461697
BRCA1	Slovenia	3	C39Y	c.116G>A	p.Cys39Tyr	rs80357498	5	12461697
BRCA1	Slovenia	4	300T>A	c.181T>A	p.Cys61Ser	-	-	12461697
BRCA1	Slovenia	4	C64Y	c.191G>A	p.Cys64Tyr	rs55851803	2 0	12461697
BRCA1	Slovenia		Q1240X	c.3718C>T	p.Gln1240Ter	rs80356903	6	28740454
BRCA1	Slovenia	1	3137delTTCA	c.3018_3021del	p.His1006Glnfs	rs80357749	2	28740454
BRCA1	Slovenia	2	K1793X	c.5377A>T	p.Lys1793Ter	rs397509274	-	12461697
BRCA1	Slovenia	1	576delAG	c.457_458del	p.Ser153Cysfs	rs397509185	-	21232165
BRCA1	Tunisia	2		c.211dup	p.Arg71Lysfs	rs397508938	2	23697973
BRCA1	Tunisia		3461del4	c.3342_3345del	p.Glu1115Ter	rs397509058	2	23697973
BRCA1	Tunisia		2789delG	c.2551del	p.Glu851Asnfs	rs397508977	-	23697973
BRCA1	Tunisia		IVS5+2insG	c.212+2T>C		rs80358026	1	23697973
BRCA1	Turkey	3	5366InsA	c.5249dup	p.Arg1751Alafs	-	-	24884828
BRCA1	Turkey		2190delA	c.2071del	p.Arg691Aspfs	rs80357688	2 5	24884828
BRCA1	Turkey	1	3664delA	c.3545del	p.Gln1182Argfs	-	-	24884828
BRCA1	Turkey		Q957X	c.2869C>T	p.Gln957Ter	rs80356973	3	12655560
BRCA1	Turkey		5378delA	c.5259del	p.Glu1754Asnfs	rs80357925	1	24884828
BRCA1	Turkey		185insA	c.66dup	p.Glu23Argfs	rs80357783	3 0	10952777
BRCA1	Turkey		5154delC	c.5035del	p.Leu1679Ter	rs80357896	2	21156238
BRCA1	Turkey		2990insA	c.2871_2872insA	p.Phe958Ilefs	rs80357693	1	24884828
BRCA1	Turkey	1	1642delC	c.1523del	p.Pro508Leufs	rs80357782	1	24884828
BRCA1	Turkey		5713X	c.2138C>G	p.Ser713Ter	rs80357233	1 8	24884828
BRCA1	Turkey		2595delA	c.2476del	p.Thr826Glnfs	rs80357631	8	10952777
BRCA1	Turkey		Y1463X	c.4389C>A	p.Tyr1463Ter	rs80356997	4	10952777
BRCA1	Turkey		IVS14+1G>A	c.4484+1G>A		rs80358063	2	10952777
BRCA1	Yugoslavia		3447del4	c.3331_3334del		rs80357777	2	10523726
BRCA2	Algiers		7882insA	c.7654dup	p.Ile2552Asnfs	rs879255463	-	26997744
BRCA2	Algiers		8560del301	c.8332_8632del	p.Ile2778Lysfs	-	-	26997744
BRCA2	Algiers		6678delA	c.6450del	p.Val2151Phefs	rs886038148	-	26997744
BRCA2	Bosnia	1	4162_4166delACTTT	c.4162_4166del	p.Thr1388Phefs	rs750704702	-	PC
BRCA2	Bulgaria	1	8760delAA		p.Glu2846Glyfs	rs397507990	-	26183948
BRCA2	Croatia		W2725X	c.8175G>A	p.Trp2725Ter	rs397507965	-	22366370
BRCA2	Croatia		6869insC	c.6641dup	p.Tyr2215Leufs	rs80359613	1	22366370
BRCA2	Cyprus	1	9007insA	c.8779dup	p.Arg2927Lysfs	-	-	27882536
BRCA2	Cyprus	1	5408delA	c.5180dup	p.Asn1727Lysfs	rs397507769	1	27882536
BRCA2	Cyprus	5	3758del4	c.3530_3533del	p.Asp1177Alafs	rs886040481	-	27882536
BRCA2	Cyprus	4	C1913X	c.5739T>A	p.Cys1913Ter	rs397507801	-	12552570

BRCA2	Cyprus	1	6308insA	c.6081dup	p.Glu2028Argfs	rs886040633	-	27882536
BRCA2	Cyprus	29	8984delG	c.8756del	p.Gly2919Valfs	rs80359728	2	15172753
BRCA2	Cyprus	1	9005insT	c.8777dup	p.Leu2926Phefs	-		27882536
BRCA2	Cyprus	3	2232delG	c.2004del	p.Lys669Asnfs	-		27882536
BRCA2	Cyprus	1	2876delTCTinsG	c.2648_2650delinsG	p.Phe883Cysfs	-		27882536
BRCA2	Cyprus	1	6319insA	c.6091dup	p.Thr2031Asnfs	rs587782717	-	27882536
BRCA2	Egypt		S2978X	c.8933C>A	p.Ser2978Ter	rs80359144	1	23877192
BRCA2	Greece	1	8821delC	c.8592del	p.Ala2864fs	-		PC
BRCA2	Greece	1	A3205L	c.9613_9614delinsCT	p.Ala3205Leu	rs276174926	6	PC
BRCA2	Greece	1	5338delAGAA	c.5110_5113del	p.Arg1704Ter	rs879254123	-	PC
BRCA2	Greece	2	R3128X	c.9382C>T	p.Arg3128Ter	rs80359212	5 0	PC
BRCA2	Greece	1	6295del10	c.6067_6076del	p.Asp2023Glnfs	rs886040632	-	PC
BRCA2	Greece	3	1633delGA	c.1405_1406del	p.Asp469Ter	rs397507586	-	PC
BRCA2	Greece	1	Q1931X	c.5791C>T	p.Gln1931Ter	rs80358807	1	PC
BRCA2	Greece	1	Q2164X	c.6490C>T	p.Gln2164Ter	rs397507860	-	24010542
BRCA2	Greece	1	9028delC	c.8800del	p.Gln2934Lysfs	rs886040793	-	PC
BRCA2	Greece	1	Q3126X	c.9376C>T	p.Gln3126Ter	rs80359210	3	24010542
BRCA2	Greece	1	Q373X	c.1117C>T	p.Gln373Ter	rs397507572	-	27165220
BRCA2	Greece	1	Q756X	c.2266C>T	p.Gln756Ter	-		PC
BRCA2	Greece	2	4147delG	c.3919del	p.Glu1307Lysfs	rs80359416	1	11754111
BRCA2	Greece	2	4883del4	c.4654_4657del	p.Gly1552Leufs	-		PC
BRCA2	Greece	1	G4X	c.10G>T	p.Gly4Ter	rs397507571	-	17902052
BRCA2	Greece	1	7591delC	c.7363del	p.His2455Ilefs	rs886040702	-	PC
BRCA2	Greece	1	4637delTA	c.4409_4410del	p.Ile1470Lysfs	rs80359446	1	17453335
BRCA2	Greece	2	766insT	c.537dup	p.Ile180Tyrfs	-		PC
BRCA2	Greece	1	4093del4	c.3865_3868del	p.Lys1289Alafs	rs80359412	3	PC
BRCA2	Greece	3	4998delA-ter1600	c.4769del	p.Lys1590Serfs	rs879255328		24010542
BRCA2	Greece	1	8774delA	c.8546del	p.Lys2849Argfs	rs397507991	-	PC
BRCA2	Greece	2	4743del11	c.4515_4525del	p.Phe1506Thrfs	rs863224827	-	PC
BRCA2	Greece	1	8989delTT	c.8761_8762del	p.Phe2921Glnfs	-		PC
BRCA2	Greece	2	2024del5	c.1796_1800del	p.Phe599Ter	rs276174813	1 2	12142080
BRCA2	Greece	4	4758delC	c.4530del	p.Pro1511Asnfs	-		PC
BRCA2	Greece	1	6828delTT	c.6600_6601del	p.Ser2201Ter	rs80359607	2	24010542
BRCA2	Greece	2	9218del32	c.8993_9024del	p.Ser2998Leufs	rs886040809	-	PC
BRCA2	Greece	1	9976insT	c.9748dup	p.Ser3250Phefs	rs886040850	-	24010542
BRCA2	Greece	1	S511X	c.1532C>A	p.Ser511Ter	-		PC
BRCA2	Greece	8	S780X	c.2339C>G	p.Ser780Ter	rs587781471	-	24010542
BRCA2	Greece	2	3783del10	c.3554_3563del	p.Thr1185Ilefs	rs397507675	-	29310832; 17902052
BRCA2	Greece	6	7169delC	c.6941del	p.Thr2314Lysfs	rs80359628	1	PC
BRCA2	Greece	2	W2788X	c.8364G>A	p.Trp2788Ter	rs80359080	1	PC
BRCA2	Greece	1	9243delAT	c.9016_9017del	p.Tyr3006Glnfs	rs80359739	1	PC
BRCA2	Greece	2	2718insT	c.2490_2491insT	p.Val831Cysfs	rs886040430	-	PC

BRCA2	Greece	4	IVS16-2A>T	c.7806-2A>T		-		PC
BRCA2	Greece	1	IVS21+1G>T	c.8754+1G>A		-		PC
BRCA2	Greece	4	IVS25+1G>A	c.9501+1G>A		-		PC
BRCA2	Greece	1	IVS8-1G>C	c.682-1G>C		rs81002831	2	PC
BRCA2	Greece	2	IVS22+1G>T	c.8953+1 G>T		rs81002882	2	25382762
BRCA2	Iran		6216insA	c.5984dup	p.Asn1995Lysfs	rs397507818	-	27165220
BRCA2	Iran	1	C3097X	c.9291T>A	p.Cys3097Ter	rs397508044	-	27165220
BRCA2	Iran	1	Q175X	c.523C>T	p.Gln175Ter	rs750385844	-	27165220
BRCA2	Iran	1	7901delAG	c.7673_7674del	p.Glu2558Valfs	rs80359672	4	27165220
BRCA2	Iran	1	E49X	c.145G>T	p.Glu49Ter	rs80358435	2 0	27165220
BRCA2	Iran	1	4446del4	c.4218_4221del	p.Lys1406Asnfs	rs80359435	1	12100744
BRCA2	Iran	1	459del22	c.231_252del	p.Pro78Glyfs	-		PC
BRCA2	Iran	1	S1341X	c.4022C>G	p.Ser1341Ter	-		PC
BRCA2	Iran	1	6261insGT	c.6033_6034insGT	p.Ser2012Valfs	rs397507824	-	12100744
BRCA2	Iran	1	6489insGT	c.6261_6262insGT	p.Thr2088Valfs	-		12100744
BRCA2	Iran	1	3003delT	c.2775del	p.Thr926Profs	rs1064793063	-	PC
BRCA2	Iran	1	W2830X	c.8490G>A	p.Trp2830Ter	rs587776351	-	27165220
BRCA2	Iran MBC	1	W3106X	c.9317G>A	p.Trp3106Ter	rs80359205	1	27478808
BRCA2	Israel		7887delC	c.7659del	p.Asn2553Lysfs	-		PC
BRCA2	Israel		3185insA	c.2957dup	p.Asn986Lysfs	rs80359365	2	PC
BRCA2	Israel		750delGACA	c.750_753del	p.Asp252Valfs	rs1455701926	-	PC
BRCA2	Israel		983del4	c.755_758del	p.Asp252Valfs	rs80359659	6 1	PC
BRCA2	Israel		8133insA	c.7905dup	p.Cys2636Metfs	-		PC
BRCA2	Israel		3339del46	c.3111_3157del	p.Gln1037Hisfs	-		PC
BRCA2	Israel		Q1595X	c.4783C>T	p.Gln1595Ter	rs886040549	-	PC
BRCA2	Israel		2082delCinsAA	c.1854delinsAA	p.Gln619Thrfs	rs276174815	1	PC
BRCA2	Israel		2589delT	c.2589del	p.Gln864Lysfs	rs397507632	-	PC
BRCA2	Israel	1	6854delTA	c.6626_6627del	p.Ile2209Argfs	rs80359610	1	20960228
BRCA2	Israel		1805insA	c.1813dup	p.Ile605Asnfs	rs1253401667	-	PC
BRCA2	Israel		5219dup	c.5219dup	p.Leu1740Phefs	rs886040583	-	PC
BRCA2	Israel		1155ins	c.925dup	p.Ser309Phefs	rs886038058	-	PC
BRCA2	Israel		3782delCA	c.3554_3555del	p.Thr1185Serfs	rs80359389	2	PC
BRCA2	Israel		6847insA	c.6619dup	p.Thr2207Asnfs	-		PC
BRCA2	Israel		2845delT	c.2845del	p.Tyr949Metfs	rs397507644	-	PC
BRCA2	Israel		5057delTG	c.4829_4830del	p.Val1610Glyfs	rs80359468	4	PC
BRCA2	Israel		IVS15+1G>T	c.7618+1G>T		rs397507922	1	PC
BRCA2	Israel		IVS13-2A>T	c.7008-2A>T		rs81002823	5	PC
BRCA2	Italy	1	3040del4	c.2812_2815del	p.Ala938Profs	rs80359354	1	PC
BRCA2	Italy	1		c.842_843del	p.Asp281Alafs	rs886040773	-	PC
BRCA2	Italy	6		c.6468_6469del	p.Gln2157Ilefs	rs80359596	1	PC
BRCA2	Italy	3		c.7681_7682insT	p.Gln2561Leufs	rs397507933	-	PC
BRCA2	Italy	1	Q2561X	c.7681C>T	p.Gln2561Ter	rs80358994	3	PC

BRCA2	Italy	2	2277delTC	c.2049_2050del	p.Gln684Glyfs	rs80359319	2	PC
BRCA2	Italy	2	E1308X	c.3922G>T	p.Glu1308Ter	rs80358638	1 5	PC
BRCA2	Italy	1	6310del5	c.6082_6086del	p.Glu2028Lysfs	rs80359558	1	PC
BRCA2	Italy	1	9683delAG	c.9455_9456del	p.Glu3152Glyfs	rs80359764	3	PC
BRCA2	Italy	1		c.9498del	p.Glu3167Argfs	rs397508055	-	PC
BRCA2	Italy	1	1636insG	c.1408dup	p.Glu470Glyfs	rs80359284	1	PC
BRCA2	Italy	1		c.7251_7252del	p.His2417Glnfs	rs397507907	-	PC
BRCA2	Italy	1	7218del5	c.6990_6994del	p.Ile2330Metfs	rs80359631	6	PC
BRCA2	Italy	1	2041delA	c.1813del	p.Ile605Tyrfs	rs80359309	1 6	PC
BRCA2	Italy	5	1466delT	c.1238del	p.Leu413Hisfs	rs80359271	6	PC
BRCA2	Italy	4	L557X	c.1670T>G	p.Leu557Ter	rs80358452	2	PC
BRCA2	Italy	1	9480del4insTT	c.9252_9255delinsTT	p.Lys3084Asnfs	rs276174918	2	PC
BRCA2	Italy	1	1676dupCAGT	c.1448_1451dup	p.Lys485Serfs	rs886040366	-	PC
BRCA2	Italy	2	K944X	c.2830A>T	p.Lys944Ter	rs80358533	6	PC
BRCA2	Italy	1		c.3723_3725delinsAT	p.Phe1241Leufs	rs397507682	-	PC
BRCA2	Italy	1		c.8283_8284dup	p.Pro2762Leufs	rs886040754	-	PC
BRCA2	Italy	1	9345G>A	c.9117G>A	p.Pro3039Pro	rs28897756	1 4	PC
BRCA2	Italy	1	928delT	c.700del	p.Ser234Profs	rs80359633	3	PC
BRCA2	Italy	1	1481C>A	c.1253C>A	p.Ser418Ter	rs397507266	-	PC
BRCA2	Italy	4		c.1796_1800del	p.Ser599Ter	-	-	PC
BRCA2	Italy	5	1377insXG	c.4131_4132insTGAG GA	p.Thr1378Ter	rs80359429	1 2	PC
BRCA2	Italy	1	W3127X	c.9380G>A	p.Trp3127Ter	rs80359211	5	PC
BRCA2	Italy	5	9904delT	c.9676del	p.Tyr3226Ilefs	rs80359774	2	PC
BRCA2	Italy	1		c.428dup	p.Val144Cysfs	rs886040519	-	PC
BRCA2	Italy	6	V211L	c.631G>C	p.Val211Leu	rs80358871	4	PC
BRCA2	Italy	1	IVS22-1del3insAA	c.8954- 1_8955delinsAA	p.Val2985(?)	rs276174916	2	PC
BRCA2	Italy	2	IVS18+2T>C	c.8331+2T>C		-	-	PC
BRCA2	Italy	1		c.8488-1G>T		-	-	PC
BRCA2	Italy	2	IVS19+1G>A	c.8487+1G>A		rs81002798	7	PC
BRCA2	Italy	5	IVS21-1G>A	c.8755-1G>A		rs81002812	6	PC
BRCA2	Italy	2	IVS5-2A>G	c.476-2A>G		rs81002853	7	PC
BRCA2	Italy	1	IVS26-2A>G	c.9649-2A>G		rs81002895	1	PC
BRCA2	Jordan	1	6862del4	c.6634_6637del	p.Cys2212Leufs	rs397507871		29335924
BRCA2	Jordan	2	E2229X	c.6685G>T	p.Glu2229Ter	rs730881548	-	29335924
BRCA2	Jordan	1	6855del8	c.6627_6634del	p.Ile2209Metfs	rs397507870	-	29335924
BRCA2	Jordan	1	L2039X	c.6116T>A	p.Leu2039Ter	-	-	29335924
BRCA2	Jordan	2	1461insA	c.1233_1234dup	p.Pro412Thrfs	rs80359270	1	29335924
BRCA2	Jordan	1	IVS23-1G>T	c.9118-1G>T		-	-	29335924
BRCA2	Kuwait	1	C138X	c.414T>A	p.Cys138Ter	-	-	PC
BRCA2	Kuwait	1	Q1507X	c.4519C>T	p.Gln1507Ter	-	-	PC
BRCA2	Lebanon		5804del4	c.5576_5579del	p.Ile1859Lysfs	rs80359521	2 9	257773438

BRCA2	Lebanon		902delC	c.674del	p.Thr225Ilefs	rs886038054	-	257773438
BRCA2	Lebanon		IVS24+1G>A	c.9256+1G>A		rs81002883	4	257773438
BRCA2	Macedonia			c.7895del	p.Ala2632Glufs	-	-	29335924
BRCA2	Macedonia			c.9304del	p.Ala3102Glnfs	-	-	29335924
BRCA2	Macedonia		D2723G	c.8168A>G	p.Asp2723Gly	rs41293513	6	24052750
BRCA2	Macedonia			c.7813_7816del	p.Cys2605Thrfs	-	-	29335924
BRCA2	Macedonia			c.9076C>T	p.Gln3026Ter	rs80359159	3	29335924
BRCA2	Macedonia		379G>T	c.151G>T	p.Glu51Ter	-	-	29335924
BRCA2	Macedonia		1827delTG	c.1599_1600del	p.Glu534Serfs	rs80359293	1	29335924
BRCA2	Macedonia		9580delAT	c.9352_9353del	p.Met3118Valfs	rs786203318	-	29335924
BRCA2	Macedonia		8545del14	c.8317_8330del	p.Ser2773Aspfs	rs397507976	-	29335924
BRCA2	Macedonia			c.4707_4708del	p.Tyr1569Ter	-	-	29335924
BRCA2	Morocco		7338delA	c.7110del	p.Lys2370Asnfs	rs397507897	-	22425665
BRCA2	Morocco		3609delT	c.3381del	p.Phe1127Leufs	rs397507666	1	22425665
BRCA2	Morocco		IVS6-1 G>A	c.517-1G>A		rs81002849	1	23697973
BRCA2	Qatar	1	IVS17-1G>C	c.7977-1G>C		rs81002874	1 6	PC
BRCA2	Romania		E2984X	c.8680C>T	p.Glu2894Ter	rs397508002	-	20567915
BRCA2	Romania		K2750del	c.8249_8251del	p.Lys2750del	rs80359703	2	20567915
BRCA2	Saudi Arabia	1		c.4177dup	p.Ala1393Glyfs	rs876659977	-	30199306
BRCA2	Saudi Arabia	1	R2494X	c.7480C>T	p.Arg2494Ter	rs80358972	1 1	25923920
BRCA2	Saudi Arabia	1	C2549X	c.7647C>A	p.Cys2549Ter	rs80358993	1	30199306
BRCA2	Saudi Arabia	1	Q2009X	c.6025C>T	p.Gln2009Ter	rs80358838	3	27082205
BRCA2	Saudi Arabia	1	6819delTG	c.6591_6592del	p.Glu2198Asnfs	rs80359605	1 8	30199306
BRCA2	Saudi Arabia			c.5762_5772del	p.Phe1921Serfs	-		29297111
BRCA2	Saudi Arabia			c.2670del	p.Phe890Leufs	-		29297111
BRCA2	Saudi Arabia	1	S158X	c.473C>A	p.Ser158Ter	rs80358701	-	30199306
BRCA2	Saudi Arabia	1	6054delTT	c.5826_5827delTT	p.Ser1943Ter	-	-	30199306
BRCA2	Saudi Arabia			c.8332-1G>A		rs397507979	-	29297111
BRCA2	Serbia	1	1991del4	c.1763_1766del	p.Asn588Serfs	rs80359303	5	23635950
BRCA2	Serbia	1	7511delT	c.7283del	p.Leu2428Trpfs	rs483353119	1	23635950
BRCA2	Serbia	1	5215delGTCA	c.4987_4990del	p.Val1663Leufs	rs397507753	-	23635950
BRCA2	Slovenia	3	4206 ins4 (TGCT) 4203_4206dup	c.3975_3978dup	p.Ala1327Cysfs	rs764689249	1 8	12461697
BRCA2	Slovenia	1	Q1089X	c.3265C>T	p.Gln1089Ter	rs80358573	1	12461697
BRCA2	Slovenia		5349C>T	c.5101C>T	p.Gln1701Ter	rs397507758	-	22923021
BRCA2	Slovenia	1	Q2435X	c.7303C>T	p.Gln2435Ter	rs397507910	-	12461697
BRCA2	Slovenia	1	1003delAG	c.778_779delG	p.Glu260Serfs	rs80359677	1	21232165
BRCA2	Slovenia	1	E3096X	c.9286G>T	p.Glu3096Ter	rs80359199	1	21232165
BRCA2	Slovenia	1	5836delTCinsAG	c.5609_5610delinsAG	p.Phe1870Ter	-	3	12461697

BRCA2	Slovenia		3972del4	c.3744_3747del	p.Ser1248Argfs	rs80359403	8	22923021
BRCA2	Slovenia	4	5518delTC	c.5290_5291del	p.Ser1764Lysfs	rs80359503	2	21232165
BRCA2	Slovenia	4	5519C>G	c.5291C>G	p.Ser1764Ter	rs397507778	-	21232165
BRCA2	Tunisia	1	1537del4	c.1311_1314del	p.Lys437Ilefs	rs886038065	7	17922257
BRCA2	Tunisia		5909InsA	c.5681dup	p.Tyr1894Ter	rs80359527	5	23697973
BRCA2	Turkey	1	6880InsG	c.6652dup	p.Asp2218Glyfs	rs397507874	-	11044644
BRCA2	Turkey		Q421X	c.1261C>T	p.Gln421Ter	rs80358419	2	24884828
BRCA2	Turkey		E1250X	c.3748G>T	p.Glu1250Ter	rs80358615	1	10952777
BRCA2	Turkey		9255delT	c.9027del	p.His3010Ilefs	rs80359742	1	12655560
BRCA2	Turkey		4693A>T	c.4465A>T	p.Lys1489Ter		-	21156238
BRCA2	Turkey		K467X	c.1399A>T	p.Lys467Ter	rs80358427	2	24884828
BRCA2	Turkey		S2219X	c.6656C>G	p.Ser2219Ter	rs80358893	2	10952777
BRCA2	Turkey		8643InsA	c.8415dup	p.Ser2806Ilefs	rs397507985	-	10952777
BRCA2	Turkey		S2835X	c.8504C>A	p.Ser2835Ter	rs80359102	1	21156238
BRCA2	Turkey		8733delA	c.8505del	p.Ser2836Leufs	rs80359713	1	24884828
BRCA2	Turkey		5295InsA	c.5073dup	p.Trp1692Metfs	rs80359480	-	10952777
BRCA2	Turkey		6910InsG	c.6682dup	p.Val2228Glyfs	rs80359621	1	24884828
BRCA2	Turkey		1620insT	c.1392_1393insT	p.Val465Cysfs	rs397507585	-	21156238

BIC – Breast cancer information core (<https://research.nhgri.nih.gov/bic/>)

HGVS – Human genome variation society (<https://www.hgvs.org/>)

dbSNP – database of Single nucleotide polymorphisms (<https://www.ncbi.nlm.nih.gov/snp/>)