ORIGINAL ARTICLE

No evidence that protein truncating variants in *BRIP1* are associated with breast cancer risk: implications for gene panel testing

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ABSTRACT

Background BRCA1 interacting protein C-terminal helicase 1 (BRIP1) is one of the Fanconi Anaemia Complementation (FANC) group family of DNA repair proteins. Biallelic mutations in *BRIP1* are responsible for FANC group J, and previous studies have also suggested that rare protein truncating variants in *BRIP1* are associated with an increased risk of breast cancer. These studies have led to inclusion of *BRIP1* on targeted sequencing panels for breast cancer risk prediction.

Methods We evaluated a truncating variant, p.Arg798Ter (rs137852986), and 10 missense variants of *BRIP1*, in 48 144 cases and 43 607 controls of European origin, drawn from 41 studies participating in the Breast Cancer Association Consortium (BCAC). Additionally, we sequenced the coding regions of *BRIP1* in 13 213 cases and 5242 controls from the UK, 1313 cases and 1123 controls from three population-based studies as part of the Breast Cancer Family Registry, and 1853 familial cases and 2001 controls from Australia.

Results The rare truncating allele of rs137852986 was observed in 23 cases and 18 controls in Europeans in BCAC (OR 1.09, 95% CI 0.58 to 2.03, p=0.79). Truncating variants were found in the sequencing studies in 34 cases (0.21%) and 19 controls (0.23%) (combined OR 0.90, 95% CI 0.48 to 1.70, p=0.75).

Conclusions These results suggest that truncating variants in *BRIP1*, and in particular p.Arg798Ter, are not associated with a substantial increase in breast cancer risk. Such observations have important implications for the reporting of results from breast cancer screening panels.

INTRODUCTION

Susceptibility to breast cancer is known to be mediated through a very large number of genetic variants conferring a wide range of disease risks relative to population incidence rates.[1] These variants include rare mutations in high-penetrance genes (fourfold or higher risk), notably *BRCA1* and *BRCA2*, mutations in genes conferring more moderate risks of breast cancer (twofold to fourfold higher risks), and approximately 100 common susceptibility variants (SNPs) conferring modest risks of the disease (typically 1.1–1.2-fold). Clinical genetic testing for breast cancer has largely focused on the high-risk genes. However, with the increasing use of high-throughput sequencing, genetic testing is being extended to larger panels of genes, including those in the 'moderate-risk' category.[2]

The known genes in the moderate-risk category encode proteins involved in DNA repair. One of the genes involved in DNA repair that has been proposed as a breast cancer susceptibility gene is *BRIP1*. *BRIP1* (BRCA1-interacting protein 1, also known as *BACH1*) encodes a helicase-like protein that was identified via its direct binding to the BRCA1 BRCT domains, and is known to contribute to DNA repair via homologous recombination.[3 4] *BRIP1* was shown to be the likely causative gene for Fanconi Anaemia Complementation group J through positional cloning and the identification of germline mutations in nine families from two studies.[4 5] The most common truncating mutation identified was c.2392C>T (p.Arg798Ter) in exon 17. Analysis of a cell line from a patient homozygous for this mutation showed complete absence of the full-length BRIP1 protein.[4] p.Arg798Ter has been found in patients from diverse populations, suggesting that it is either a relatively ancient founder mutation or is recurrent.

Given the role of *BRCA1* and other genes involved in DNA repair in susceptibility to breast and other cancers, it seems reasonable to speculate that germline mutations of *BRIP1* might also predispose to breast cancer. Seal *et al*[6] screened the coding sequence of 1212 women with breast cancer having a family history of disease and 2012 controls. They identified mutations predicted to lead to a truncated protein in nine cases versus two in controls and obtained an estimated relative risk of breast cancer, after adjustment for oversampling of cases with a family history, of 2.0 (95% CI 1.2 to 3.2, p=0.012). The most common mutation was p.Arg798Ter, accounting for five of the mutations in cases and one in controls.

Since the Seal *et al*[6] paper, several other studies have identified *BRIP1* variants through screening of breast cancer cases for specific mutations,[7–12] but no large-scale case–control mutation screening studies have been reported. To evaluate more definitively the evidence that *BRIP1* is a breast cancer susceptibility gene, we genotyped the p.Arg798Ter variant and 10 missense variants in >48 000 cases and 43 000 controls in studies participating in the Breast Cancer Association Consortium (BCAC). Additionally, we screened the entire coding sequence of *BRIP1* in three large case–control studies comprising >16 000 cases and 8000 controls.

METHODS

Breast Cancer Association Consortium

Breast cancer cases and controls were drawn from 52 studies participating in the BCAC. The analysis was restricted to 48 143 cases and 43 608 controls from 41 studies in populations of European origin (comprising ~87% of the data set) since the sample sizes for Asian and African-American women were too small for separate analysis. The truncating variant p.Arg798Ter and 10 missense variants in *BRIP1* (table 1) were genotyped using iCOGS, a custom array of ~200 000 variants.[13] Genotypes were subject to standard quality control procedures as described previously.[13]

For the purpose of this analysis, we manually recalled the genotypes for *BRIP1* p.Arg798Ter using the cluster plot of normalised intensities (figure 1). The experiment included a positive control previously identified as a carrier of the mutant allele through sequencing of a series of prostate cancer cases. This individual was genotyped correctly as a variant carrier. We further confirmed the genotypes through comparison with data from two re-sequencing experiments conducted in Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) and the Breast Cancer Family Registry (BCFR), for which individuals were also genotyped using iCOGS (see below). Thirteen individuals in the former study and two in the latter study were identified as carrying the variant allele at p.Arg798Ter; genotypes determined by the two methods were 100% concordant.

SEARCH study

Subjects

Cases were drawn from SEARCH, a population-based study of breast cancer in the region covered by the Eastern Cancer Registration and Information Centre, UK.[14] SEARCH recruited patients diagnosed with invasive breast cancer before the age of 55 years since 1991 and still alive at the start of the study in 1996 (prevalent cases; median age 48 years), together with all those diagnosed before 70 years of age between 1996 and 2014. The study was approved by the Cambridgeshire Research Ethics Committee. The present analysis is based on data from 13 824 case participants. Controls were drawn from the EPIC-Norfolk study, a population-based cohort study of diet and health women attending general practitioner (GP) practices, frequency matched to cases by age and geographic region (2003–present),[14] and women attending breast screening as part of the National Health Service Breast Screening Program participating in the Sisters in Breast Screening study.[15] The final analyses were

Table 1 Summary of missense variants tested for association with breast cancer risk in Breast Cancer Association Consortium

rs number	Position*	Substitution	Protein alteration	CADD[20]	PolyPhen	SIFT	MAF	OR (95% CI)	p Value
rs4988345	59924572	c.517C>T	p.Arg173Ser	20.8	Probably damaging	Deleterious	0.0043	1.05 (0.91 to 1.21)	0.49
rs4988346	59924512	c.577G>A	p.Val193Ile	0.342	Benign	Tolerated	0.0044	1.11 (0.97 to 1.28)	0.13
rs4988347	59924505	c.584T>C	p.Leu195Pro	0.578	Benign	Tolerated	0.0022	1.13 (0.93 to 1.37)	0.23
rs28997569	59885956	c.790C>T	p.Arg264Trp	16.72	Probably damaging	Deleterious	0.0011	1.01 (0.76 to 1.34)	0.96
rs28997570	59885856	c.890A>G	p.Lys297Arg	8.669	Benign	Tolerated	0.0016	1.06 (0.84 to 1.34)	0.60
rs4988350	59861668	c.1591T>G	p.Phe531Val	23.8	Probably damaging	Tolerated	0		
rs4988349	59861640	c.1619A>T	p.Gln540Leu	16.61	Possibly damaging	Tolerated	0		
rs137852986	59793412	c.2392C>T	p.Arg798Ter	39	–	–	0.00021	1.09 (0.58 to 2.03)	0.79
rs28904918	59770797	c.2569A>G	p.Ile857Val	18.50	Probably damaging	Tolerated	6×10^{-5}	0.87 (0.21 to 3.66)	0.85
rs4986764	59763347	c.2755T>C	p.Ser919Pro	4.321	Benign	Deleterious	0.42	1.00 (0.98 to 1.01)	0.66
rs4988356	59763298	c.2804T>G	p.Val935Gly	1.149	Benign	Deleterious	2×10^{-5}	0.44 (0.039 to 5.00)	0.51

*hg19 (build 37) position.
CADD, Combined Annotation-Dependent Depletion scores; MAF, minor allele frequency.

based on 13 213 cases and 5242 controls that passed QC filters (see below).

Mutation screening

Target enrichment was accomplished using the 48.48 Fluidigm Access Array system. This approach employed multiplexed microfluidic PCR reactions to first amplify targeted regions and then ligate one of 1536 unique barcodes and sequencing adapters. To cover the 19 protein-coding exons and associated splice junctions of *BRIP1*, we designed 45 PCR amplicons that were 133–199 bp in length, which together produced unique coverage of 3750 bp, as part of a larger multiplex panel involving ~500 amplicons. The amplicon designs covered 100% of the targeted regions. Fourteen 1536-sample sequencing libraries were produced according to the manufacturer's protocol (Fluidigm, San Francisco, California, USA) and assayed with the KAPA library quantification kit with specific probes for the ends of the adapters (KapaBiosystems, Boston, Massachusetts, USA). Libraries were sequenced in paired end mode on the Illumina HiSeq 2000 and CASAVA was used to construct demultiplexed sequence files, according to the manufacturer's protocols (Illumina, San Diego, California, USA). Cutadapt V.1.5 was used to remove primer sequences from both ends of each read, and untrimmed reads were discarded.[16] Reads were aligned to the hg19 human genome reference sequence using BWA-MEM V.0.7,[17] and GATK V.3.3-0-g37228af was used for base quality score recalibration and indel realignment, and for deriving quality and depth metrics.[18] *BRIP1* was segmented into intervals of 2–7 exons, and the GATK UnifiedGenotyper was used to perform SNP and indel discovery and genotyping across all samples simultaneously, according to GATK Best Practices recommendations.[19] The samples had a median coverage of 446.4, and a median of 97.47% of the targeted region (coding exons with 6 bp of flanking sequence) covered in each sample. In initial filtering, variants with >20% missing data were removed, and samples with no genotype at >20% of remaining positions were also excluded. Genotypes with depth <20 or genotype quality <13 were re-coded as no genotype. GATK was used to recalculate variant-level metrics without these failed samples and low-confidence genotypes, and positions genotyped in >95% of samples and with quality by depth between 3.0 and 25.0 were retained for further analysis. The remaining variants were annotated with Combined Annotation-Dependent Depletion (CADD) V.1.2,[20] and 40 truncating and predicted damaging missense variants were selected for Sanger sequencing. Of these, 39 (positive predictive value 97.5%) variants were successfully confirmed.

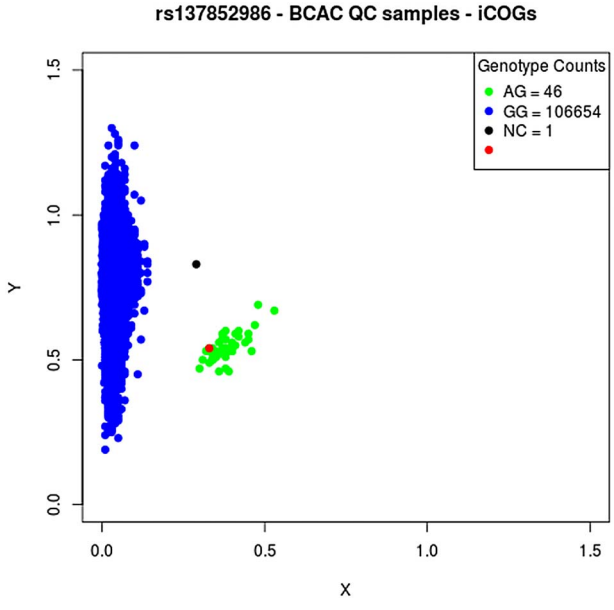

Figure 1 Cluster plot for genotype intensities for rs137852986 on the iCOGS array. Normalised intensities for the variant and wild-type allele for each individual are given by the X and Y coordinates, respectively. Individuals called as p.Arg798Ter carriers are indicated by green dots and non-carriers by blue dots. The red dot indicates a positive control individual known to carry the variant from prior sequencing. BCAC, Breast Cancer Association Consortium; NC, no call.

iCOGS data were available for 13 133 individuals that were also sequenced. Six rare coding variants (MAF<1%) were polymorphic in the iCOGS data. Of the 357 rare allele carriers identified by iCOGS, the sequencing identified 355 (99.4%), although for two of the variants (p.Val193Ile and p.Arg173Ser), 13/111 and 17/138 of individuals called heterozygotes by iCOGS genotyping were called rare allele homozygotes by sequencing, reflecting bias in PCR amplification. One common coding polymorphism (rs4986764, p.Ser919Pro) was concordant in 99.9% of samples.

BCFR study

Subjects

Eligible participants included women ascertained by population-based sampling by the Australian, Northern Californian and

Ontarian sites of the BCFR between 1995 and 2005.[21] For the present study, the selection criteria for cases (n=1313) were diagnosis of breast cancer at <45 years of age and self-reported race/ethnicity, plus grandparents' country of origin information consistent with Caucasian, East Asian, Hispanic/Latino, or African-American racial/ethnic heritage. The controls (n=1123) were frequency-matched to the cases within each centre by racial/ethnic group, with age at selection not more than 10 years older or younger than the age at diagnosis of the cases ascertained at the same centre. The design of this study has been described in detail previously.[22–27] Recruitment and genetic studies were approved by the Ethics Committee of the International Agency for Research on Cancer (Lyon, France), the University of Utah Institutional Review Boards (IRBs) and the local IRBs of the BCFR centres from which samples were received. Written informed consent was obtained from each participant.

Mutation screening

Mutation screening was carried out using 30 ng of whole-genome amplified (WGA) DNA and covered the 19 coding exons of *BRIP1* (NM_032043.2). The laboratory process has been described in detail for our recent studies of *ATM*,[22] *CHEK2*,[23] *XRCC2*,[24] *RAD51*,[25] *RINT1*[26] and *MRN* genes.[27] The semi-automated approach relies on mutation scanning by high-resolution melt curve (HRM) analysis followed by direct Sanger sequencing of the individual samples for which an aberrant melt curve profile is indicative of the presence of a sequence variant. In our previous work, we showed, by comparing the results with those obtained with Sanger sequencing,[28] that the HRM technique showed high sensitivity and specificity (1.0 and 0.8, respectively, for amplicons of <400 bp) for mutation screening. All rare exonic variants, plus intronic variants that fell within 20 bp of a splice acceptor site or 8 bp of a splice donor site, were independently re-amplified from the two WGA reaction products to confirm the presence of the variant using direct Sanger sequencing. Primer and HRM probe sequences are available from the authors upon request.

Peter MacCallum Cancer Centre study

Subjects

The familial cohort included 1853 index individuals with personal and family histories of breast cancer who were previously assessed at Familial Cancer Centres in Victoria and New South Wales. A total of 979 cases were obtained from the 'Variants in Practice' study, which recruited via the combined Familial Cancer Centers in Melbourne, Australia,[29] and 874 through the Hunter Area Pathology Service, Newcastle, Australia. All index cases were previously screened through their clinical genetics services and found to be negative for mutations in *BRCA1* and *BRCA2*. Large deletions and duplications in *BRCA1* and *BRCA2* were included in the mutational analysis as determined by multiplex ligation-dependent probe amplification analysis. The 2001 female controls were accessed through *Lifepool* (http://www.lifepool.org), which is a cohort of women attending population mammography screening programme in Victoria, Australia. Controls were aged 40 years and above (mean age 64) and were cancer-free at the time of blood collection. This study was approved by the Hunter New England Human Research Ethics Committee and the Peter MacCallum Cancer Centre Human Research Ethics Committee.

Mutation screening

Cases and controls were screened for germline mutations in all 19 exons of *BRIP1* on the HiSeq 2500 System (Illumina) using the Haloplex target enrichment system (Agilent) as described previously.[30] Paired-end sequence reads were aligned to the human genome (hg19 assembly) using the BWA-MEM software.[31] Base quality score recalibration and indel realignment was performed using the GATK software. Single-nucleotide variants and indels were identified using the GATK Unified Genotyper and Variant Quality Score Recalibration.[18 19] Variants were annotated with information from Ensembl release 62. The average percentage of bases covered at a depth of ≥10× was 94.8% for cases and 96.1% for controls with all samples having at least 85% of bases sequenced at a depth of ≥10×.

All truncating variants in *BRIP1* were validated by Sanger sequencing, as were any missense SNPs with a CADD score >10 that had not been previously reported in any databases. Previously reported SNPs were only validated in selected cases if the variant calling was unclear (quality score <150 or not identified in bidirectional reads).

Statistical analysis

Association between each of the variants in *BRIP1* and breast cancer risk was assessed in BCAC using logistic regression, with adjustment for study and seven principal components for women of European ancestry derived from genotypes of SNPs on the iCOGS array, as previously described.[13] For the three targeted sequencing studies, we carried out burden analyses, which evaluated the risk associated with carrying any one of a set of likely deleterious variants, since the variants were too rare to be analysed individually, and this is directly relevant to the potential clinical application of the findings of this study. We considered two sets of variants: those predicted to result in a truncated protein product and missense substitutions with a CADD score >20. ORs and 95% CIs were calculated for each of the three individual studies (SEARCH, BCFR and Peter MacCallum) and combined with those for BCAC/iCOGS using fixed effects meta-analysis. Heterogeneity in the OR among studies was assessed using a standard heterogeneity χ^2 test and I^2 statistic.

The BCAC data set partially overlapped with SEARCH and two of the BCFR studies (Australian Breast Cancer Family Study (ABCFS) and Ontario Familial Breast Cancer Registry (OFBCR)). Since p.Arg798Ter failed the minimum coverage threshold in SEARCH, for simplicity we excluded the p.Arg798Ter variant, and two other missense variants (rs4988345 and rs28997569) that were genotyped on the iCOGS from both the SEARCH and BCFR sequencing data (but retained them in the BCAC data set) when combining the results across all data sets. This resulted in an overlap in the (non-carrier) data sets between the BCAC, and the SEARCH and BCFR sequencing data sets, but the resulting bias in the combined odds ratio would be negligible since the variants are all extremely rare. The most probable haplotypes for markers across the *BRIP1* region were generated using SHAPEIT V.2.[32]

Nonsense-mediated mRNA decay analysis of BRIP1 p.ArgR798Ter

To investigate whether the protein truncating mutation p.Arg798Ter triggers nonsense mediated decay, we treated lymphoblastoid cell lines from a heterozygous carrier and wild-type controls with10 mg/mL cycloheximide for 5 h. We extracted

Table 2 Association between protein truncating variants in *BRIP1* and breast cancer risk

Study	Case carriers/ total (%)	Control carriers/ total (%)	OR (95% CI)	p Value
BCAC	23/47,654 (0.05%)	18/43,172 (0.04%)	1.09 (0.58 to 2.03)	0.79
SEARCH	24/13,213 (0.18%)	13/5242 (0.25%)	0.73 (0.36 to 1.57)	0.36
BCFR	4/1313 (0.30%)	2/1123 (0.27%)	1.71 (0.24 to 19.0)	0.69
PeterMac	6/1853 (0.38%)	4/2001 (0.20%)	1.62 (0.38 to 7.82)	0.45
Combined			0.98 (0.62 to 1.54)	0.93

BCAC, Breast Cancer Association Consortium; BCFR, Breast Cancer Family Registry.

total RNA and DNA from treated and untreated cells with the AllPrep DNA/RNA Micro kit (Qiagen), and then prepared cDNA with the QuantiTect Reverse Transcription Kit (Qiagen). PCR primers for DNA and cDNA analysis can be provided on request. The experiment was carried out in triplicate.

RESULTS

Truncating variants

In analyses restricted to women of European ancestry, the mutant allele was observed in 23 of 47 654 cases (0.050%) and 18 of 43 172 controls (0.04%) (OR 1.09, 95% CI 0.58 to 2.013, p=0.79) (table 2). Consistent results were obtained when analyses were restricted to women with known invasive breast cancer (OR 0.95, 95% CI 0.49 to 1.83). When the analysis was restricted to studies without oversampling of cases with a family history and/or bilaterality, the results were very similar to those for the whole data set (OR 1.09, 95% CI 0.56 to 2.09, p=0.81).

In the SEARCH, BCFR and Peter MacCallum Cancer Centre studies, we identified 34 truncating variants in cases (0.21%) and 19 in controls (0.23%) (combined OR 0.90, 95% CI 0.48 to 1.70, p=0.75) (table 2 and online supplementary tables S1–S3) The carrier frequency in controls was similar to that observed in exome sequencing data from 60 706 individuals in the Exome Aggregation Consortium (http://exac.broadinstitute.org/:0.21%). There was no evidence of heterogeneity in the OR among studies (p=0.49, I^2=0.0). After elimination of the overlaps between BCAC and the SEARCH and BCFR data sets, the combined OR across all four studies for identified *BRIP1* truncating variants was 0.98 (95% CI 0.62 to 1.54, p=0.93) (table 2).

There was weak evidence of an increased risk of oestrogen receptor (ER)-negative breast cancer for p.Arg798Ter carriers in BCAC (OR 2.25, 95% CI 0.93 to 5.46, p=0.07), but no evidence of an association with truncating variants in SEARCH (0.53, 95% CI 0.06 to 2.34, p=0.054; combined OR 1.71, 95% CI 0.77 to 3.80, p=0.19) (table 3). There was also weak evidence of an association with triple (ER/PR/HER2)-negative disease in BCAC (OR 3.62, 95% CI 0.99 to 13.2, p=0.05) but not in SEARCH (combined OR 2.71, 95% CI 0.84 to 8.74, p=0.10); however, these analyses were based on only four and one triple-negative cases carrying the variant in BCAC and SEARCH, respectively. There was no evidence for an association with ER-positive disease in either data set (combined OR 0.61, 95% CI 0.33 to 1.13, p=0.12).

Nonsense-mediated decay

We performed Sanger sequencing on both cDNA and DNA of cycloheximide-treated and untreated wild-type and p.Arg798Ter lymphoblastoid cell lines (figure 2). Sequencing chromatograms showed that the rare, truncating allele was much less abundant than the wild-type allele in cDNA from untreated cells, but not in the treated cells, consistent with the inhibition of nonsense-mediated decay with cycloheximide.

Missense variants

We considered missense variants with a CADD score >20 as the most likely deleterious variants. There was no evidence for association between carrying one of these missense variants, as a set, with breast cancer risk in the combined data set (OR 1.08, 95% CI 0.95 to 1.24, p=0.25; table 4), though there was some weak evidence of association in the Peter MacCallum Cancer Centre study. One variant, p.Arg173Ser, accounted for the majority of carriers of likely deleterious variants in the sequencing studies; it was also genotyped in BCAC and showed no evidence of association (combined OR 1.07, 95% CI 0.93 to 1.23, p=0.35). None of the other missense variants genotyped in BCAC showed evidence for association (table 1).

Distribution of p.Arg798Ter by population

Among European populations, there was substantial variation in the frequency of the p.Arg798Ter allele by country (p<0.0001); the carrier frequency was approximately 0.1% in the UK, Ireland and Australia, but virtually absent elsewhere in Europe. Also, 41 of the 42 carriers shared a common haplotype of 21 markers across 150 kb (see online supplementary figure s1 and supplementary table S4). In addition, we observed two occurrences among 12 893 women of Asian ancestry, both from a Malaysian study (MYBRCA) and both carrying the common haplotype in Europeans, and two occurrences among 2048 African-American women, one of which carried the founder European haplotype. These results suggest that the variant has arisen multiple times but that the majority of the carriers of p.Arg798Ter in Europeans have a common ancestral origin.

DISCUSSION

BRIP1 is included on many cancer gene sequencing panels and has been generally regarded as a 'moderate-risk' breast cancer susceptibility gene, together with other genes, including *ATM*, *CHEK2* and *PALB2*.[2] The evidence that deleterious mutations in these latter three genes confer an increased breast cancer

Table 3 Association between protein truncating variants in *BRIP1* and breast cancer risk by subtype

	ER-positive			ER-negative			Triple negative		
Study	Carrier/total (%)	OR (95% CI)	p Value	Carrier/total (%)	OR (95% CI)	p Value	Carrier/total (%)	OR (95% CI)	p Value
BCAC	4/27,680 (0.01%)	0.38 (0.13 to 1.15)	0.09	8/7707 (0.10%)	2.25 (0.93 to 5.46)	0.07	4/2983 (0.13%)	3.62 (0.99 to 13.2)	0.05
SEARCH	14/7391 (0.19%)	0.76 (0.36 to 1.63)	0.56	2/1521 (0.13%)	0.53 (0.06 to 2.34)	0.54	1/551 (0.18%)	0.73 (0.02 to 4.89)	1.0
Combined		0.61 (0.33 to 1.13)	0.12		1.71 (0.77 to 3.80)	0.19		2.71 (0.84 to 8.74)	0.10

BCAC, Breast Cancer Association Consortium; ER, oestrogen receptor.

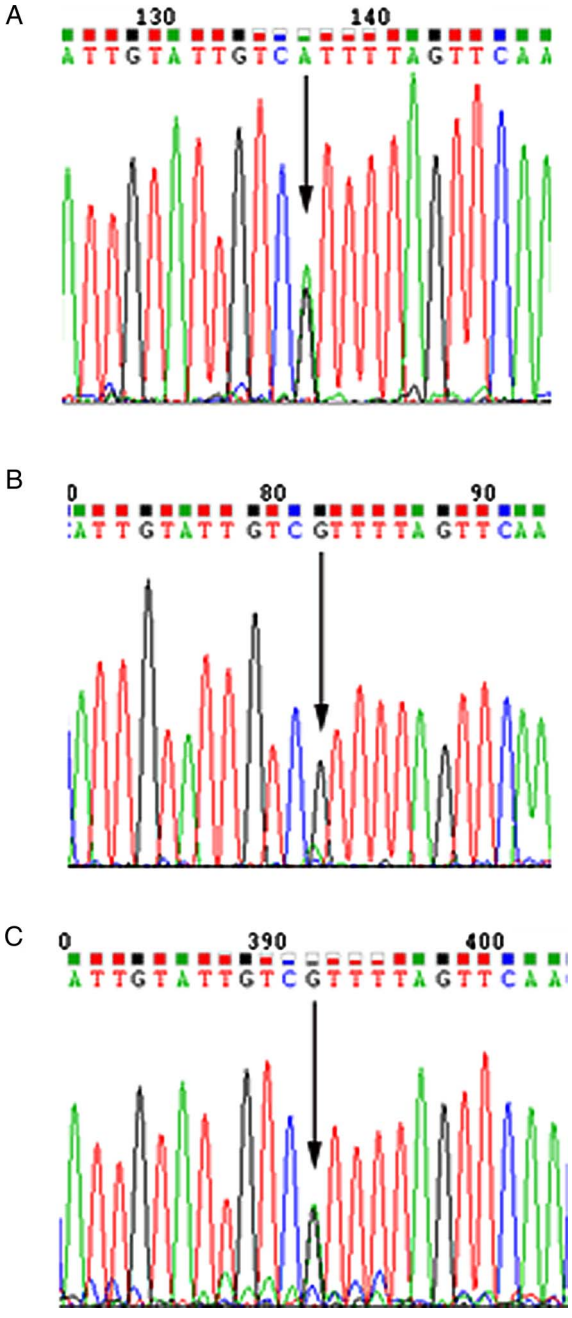

Figure 2 Sequencing of cDNA from a cycloheximide-treated and untreated lymphoblastoid cell line from a *BRIP1* p.Arg798Ter carrier. Forward sequence of (A) cDNA from cycloheximide-treated lymphoblastoid cell line, (B) cDNA from the untreated lymphoblastoid cell line and (C) DNA sequence from the same cell line.

risk is unequivocal, supported by large case–control, kin–cohort and segregation studies.[22 33–37] In the case of *BRIP1*, however, it is notable that no large systematic studies have been published since the original study by Seal *et al*[6] (see online supplementary table S1), although clear evidence of an association between truncating mutations and ovarian cancer risk has emerged.[38 39] We sought to evaluate the evidence that protein truncating mutations in *BRIP1* are associated with breast cancer, taking advantage of the large body of data generated as part of the iCOGS genotyping array. This allowed us to genotype one such variant, p.Arg798Ter, shown to be relatively frequent in previous studies, in >48 000 cases and 43 000 controls of European origin. In addition, we sequenced the coding region of *BRIP1* in >16 000 cases and 8000 controls, predominantly of European origin, from three studies. We found no evidence of an association with breast cancer risk either for p.Arg798Ter or for carrying any truncating variant in the gene. The upper 95% confidence limit (1.54) excludes a twofold risk of breast cancer, often taken as a lower threshold for a moderate-risk allele.[2]

We found weak evidence of an association between p.Arg798Ter and ER-negative disease and triple-negative disease in BCAC, but not for truncating variants in the combined analysis. A recent study found eight *BRIP1* truncating variants in 1853 triple-negative breast cancer cases, slightly higher than the frequency observed in our sequence analysis.[40] Assuming that there is association for triple-negative breast cancer, a sample size of ~1400 triple-negative cases, that is approximately threefold larger than the current data set, would be required to exclude an OR of 3 (upper 95% CI), assuming a large control set. Thus, while an association of this magnitude may exist for triple-negative disease, this should be resolvable by larger studies.

It remains possible that some subset variants in *BRIP1* do confer more substantial risks of breast cancer. p.Arg798Ter is a classic protein truncating mutation, which we showed undergoes nonsense-mediated decay. Rare homozygotes, with complete loss of the BRIP1 protein, are associated with Fanconi Anaemia.[4] Although the results from the sequence analyses found no other truncating variants of comparable frequency to pArg798Ter, additional founder mutations might exist at similar or greater frequency in other European or non-European populations. We also found no evidence of association for missense variants, defined as potentially deleterious by CADD score; again the upper 95% confidence limit in this analysis excludes a twofold risk, though it remains possible that individual missense variants might confer a more substantial risk, as occurs in *ATM*.[41–43]

It also remains possible that truncating (or missense) variants are associated with a smaller (less than twofold) risk of breast

Table 4 Association between missense variants in *BRIP1* with Combined Annotation-Dependent Depletion score >20 and breast cancer risk

Study	Case carriers/total (%)	Control carriers/total (%)	OR (95% CI)	p Value
BCAC	429/47,666 (0.90%)	370/43,176 (0.86%)	1.06 (0.92 to 1.22)	0.43
SEARCH	276/13,213 (2.1%)	107/5242 (2.0%)	1.06 (0.85 to 1.32)	0.66
BCFR	0/1313 (0%)	1/1123 (0.09%)	–	
PeterMac	40/1853 (2.2%)	28/2001 (1.4%)	1.68 (1.02 to 2.82)	0.03
Combined			1.08 (0.95 to 1.24)	0.25

BCAC, Breast Cancer Association Consortium; BCFR, Breast Cancer Family Registry.

cancer (perhaps with a higher relative risk for certain disease subtypes). However, in this case even larger studies would be required to establish the association and to provide reliable risk estimates. Moreover, this would place such variants in the same category as common risk SNPs and other modest risk variants, such as *CHEK2* p.Ile157Thr and *BRCA2* p.Lys3326Ter. If this were the case, the clinical implications would be quite different from those of established susceptibility genes since the risks conferred by the variant would only be substantial if combined with other risk factors.

These results highlight the importance of very large systematic studies to estimate disease risks associated with genetic variants. We conclude that there is no clear evidence for an association between protein truncating variants in *BRIP1* and breast cancer risk. While *BRIP1* screening might have utility for ovarian cancer risk prediction, in combination with other risk factors,[39] such variants should not be used for breast cancer risk prediction.

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