BRIEF REPORT

Human Mutation

OFFICIAL JOURNAL
HGVS
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Analysis of *RAD51C* Germline Mutations in High-Risk Breast and Ovarian Cancer Families and Ovarian Cancer Patients

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Communicated by David E. Goldgar

Received 6 July 2011; accepted revised manuscript 16 September 2011.
Published online 5 October 2011 in Wiley Online Library (www.wiley.com/humanmutation).DOI: 10.1002/humu.21625

ABSTRACT: **There is strong evidence that overtly inactivating mutations in *RAD51C* predispose to hereditary breast and ovarian cancer but the prevalence of such mutations, and whether they are associated with a particular clinical phenotype, remains unclear. Resolving these questions has important implications for the implementation of *RAD51C* into routine clinical genetic testing. Consequently, we have performed a large *RAD51C* mutation screen of hereditary breast and ovarian cancer families, and the first study of unselected patients diagnosed with ovarian cancer. Our data confirm a consistent but low frequency (2/335 families) of inactivating *RAD51C* mutations among families with a history of both breast and ovarian cancer and an absence of mutations among breast cancer only families (0/1,053 families). Our data also provide support for the designation of the missense variant p.Gly264Ser as a moderate penetrance allele.**
Hum Mutat 33:95–99, 2012. © 2011 Wiley Periodicals, Inc.

KEY WORDS: ***RAD51C*; cancer predisposition; ovarian cancer; breast cancer**

Monoallelic mutations within either the *BRCA1* or *BRCA2* gene locus account for 30–50% of families with a strong family history of both breast and ovarian cancer. The recognition that biallelic *BRCA2* mutations also gave rise to Fanconi Anemia (FA) highlighted the possibility that abrogation of other genes within this pathway may be associated with non-*BRCA1* or -*BRCA2* related familial breast and ovarian cancer. This proposal was confirmed when monoallelic mutations in both *FANCJ* (*BRIP1*) and *FANCN* (*PALB2*) were shown to confer susceptibility to breast and ovarian cancer [Howlett et al., 2002; Rahman et al., 2006; Seal et al., 2006]. FA is a rare, recessive chromosomal instability disorder, characterized by bone marrow failure, developmental defects, and cancer susceptibility that is caused by biallelic mutations in any one of 13 genes involved in the FA pathway. The FA pathway coordinates the repair of DNA interstrand crosslinks via nucleotide excision repair, translesion synthesis, and homologous recombination [Moldovan and D'Andrea, 2009].

Recently, the identification of a biallelic *RAD51C* (*FANCO*; MIM# 602774) mutation in a family with an FA-like disorder led to its examination in a large hereditary breast and ovarian cancer case–control candidate study [Meindl et al., 2010; Vaz et al., 2010]. Meindl et al. identified six independent pathogenic monoallelic mutations that included two frameshift insertions, two splice site mutations, and two missense mutations. Interestingly, these mutations were identified exclusively within the 480 families with breast and ovarian cancer (frequency 1.3%) but not among any of the 620 families with breast cancer only. In most subsequent studies, the mutation frequency has been found to be lower than 1.3%, with only three additional truncating mutations being identified in five families [by Romero et al. and Pelttari et al.] among more than 729 ovarian cancer families (with or without breast cancer) [Akbari et al., 2010; Pang et al., 2011; Pelttari et al., 2011; Romero et al., 2011; Silvestri et al., 2011; Wong et al., 2011; Zheng et al., 2010]. Despite the presence of breast cancer in 10 of the 15 *RAD51C* mutation positive families identified to date, analysis of more than 1,373 breast cancer only families (predominantly from high-risk families but also including a cohort of 97 unselected male breast cancers) by eight studies collectively has not identified any additional families with truncating *RAD51C* mutations. Therefore, while evidence of a causative role for *RAD51C* in breast and ovarian or ovarian only cancer families

Additional Supporting Information may be found in the online version of this article.

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Contract grant sponsors: NHMRC; National Breast Cancer Foundation and Cancer Australia (#628333); Queensland Cancer Fund; The Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia; The Cancer Foundation of Western Australia; Victorian Government via Victorian Cancer Agency; Cancer Australia and the National Breast Cancer Foundation (ID 628610).

(HBOC) is convincing, albeit with low prevalence, its role in breast cancer only (HBC) families remains unclear.

To provide more definitive data on the incidence of *RAD51C* mutations in hereditary breast and ovarian families, we utilized high-resolution melt (HRM) analysis to screen for germline mutations in all coding exons of *RAD51C* in index cases from 1,388 non-*BRCA1*, non-*BRCA2* high-risk Australian HBC and HBOC families, and 427 controls. In addition, the contribution of *RAD51C* in unselected ovarian cancer was examined through the analysis of germline DNA from an unselected cohort of 267 ovarian cancer patients.

The familial cohort included 909 individuals with verified personal and family histories of breast or ovarian cancer who were previously assessed at one of three Victorian Familial Cancer Centres (Peter MacCallum Cancer Centre, Victorian Clinical Genetics Services, or The Royal Melbourne Hospital). The remainder of the familial cohort was comprised of index cases from 479 multiple case breast cancer families obtained from the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab). kConFab families are recruited through Familial Cancer Centres throughout Australia and New Zealand. All individuals were consented for genetic testing of the genetic causes of hereditary breast and ovarian cancer and subsequently tested negative for mutations in *BRCA1* and *BRCA2*. This study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee. In total, index cases from 1,388 families, including 335 with ovarian cancer, were examined in this study.

The unselected ovarian cancer cohort included 267 individuals with various histological subtypes of ovarian cancer (139 serous, 75 endometrioid, six clear cell, 37 mucinous, six granulosa cell tumors, three adenocarcinomas, and one mixed mullerian tumor). These samples were obtained from patients presenting to hospitals in the south of England, UK. Matched tumor DNA extracted from frozen tissue for 89 of these cases was also examined for somatic mutations.

Noncancer control DNA samples were obtained from kConFab (190 age- and ethnicity-matched best friend controls) and from the Princess Anne Hospital, UK (237 Caucasian female volunteers, as described previously) [Baxter et al., 2002].

In most cases, DNA for mutation screening underwent whole-genome amplification (WGA) using the Repli-G Phi-mediated amplification system (Qiagen, Hilden, Germany) prior to mutation analysis. Primers were designed using the program Primer3 to screen the entire coding sequence and exon–intron boundaries and anneal at 60°C (http://frodo.wi.mit.edu/primer3/). Eleven primer pairs were used to amplify the nine coding exons of *RAD51C* with amplicons ranging in size from 199 to 303 bp for HRM analysis. Primer sequences and PCR conditions are available on request. HRM analysis and DNA resequencing were performed as described previously [Gorringe et al., 2008]. Variant positions were determined with reference to the following GenBank reference sequences, NG_023199.1 (DNA), NM_058216.1 (mRNA), and NP_478123.1 (protein). Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to HGVS guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1. All novel variants were verified by Sanger resequencing in non-WGA DNA. Where deleterious *RAD51C* mutations were identified in a family, available formalin-fixed, paraffin-embedded (FFPE) tumor tissues were assessed for loss of the wild-type allele and cosegregation of genetic variants was assessed by Sanger resequencing. Tumor cells were needle dissected from 10-μm FFPE sections to obtain high-purity (>80%) tumor DNA. DNA was extracted from FFPE tissue using a modified Qiagen protocol as described previously [Jacobs et al., 2007].

The following in silico prediction tools were used to assess the likely functional effect of the missense variants identified in this study: SIFT (http://sift.jcvi.org/), PANTHER (http://www.pantherdb.org/tools/csnpScoreForm.jsp), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SNPs&Go (http://snps-and-go.biocomp.unibo.it/snps-and-go/), MutPred (http://mutpred.mutdb.org/), nsSNP Analyzer (http://snpanalyzer.uthsc.edu/), and SNAP (http://rostlab.org/services/snap/). Human Splicing Finder (HSF) was used to assess the effect of all nontruncating variants on splice sites (http://www.umd.be/HSF/). *P*-values were calculated using two-tailed Fisher's exact tests.

Analysis of 1,053 HBC and 335 HBOC families and 267 unselected ovarian cancer cases identified 12 novel heterozygous variants in *RAD51C*, three of which were protein truncating, six nonsynonymous, one synonymous, and two noncoding. Numerous dbSNPs and variants from previous studies were also identified. Table 1 provides a summary of all detected variants.

Two truncating mutations, a 5-bp duplication (c.68_72dup) resulting in frameshift and premature protein termination (p.Val25CysfsX3) and a nonsense substitution (c.397C>T, p.Gln133X), were identified among the 1,388 familial cases. Consistent with the previously reported deleterious mutations, both variants were identified in families with at least one report of ovarian cancer. A third truncating variant, a single base pair deletion (c.230delG) also leading to frameshift and premature protein termination (p.Gly77ValfsX24), was identified in a high-grade serous tumor among the 267 unselected ovarian cancer cases.

The p.Gln133X variant was detected in a family with an extensive history of breast and ovarian cancer, including three women diagnosed with both breast and ovarian cancer and a fourth female with bilateral breast cancer (Fig. 1A). Three colorectal cancers were also reported; both of the cases for which germline DNA was available were carriers. Genotyping additional relatives for the variant revealed striking cosegregation with disease in the family, with all three breast and ovarian cancer affected individuals carrying the mutation. Attempts to determine whether there was loss of the wild-type allele by Sanger resequencing were unsuccessful due to the poor quality DNA obtained from the formalin-fixed tissue.

The p.Val25CysfsX3 variant was detected in a family with two reports of ovarian cancer but no breast cancer, although other cancer types are reported including cancers of unknown origin (Fig. 1B). No additional blood samples or tumor blocks could be accessed for segregation or loss of heterozygosity (LOH) analyses.

No family history information was available for the unselected ovarian cancer case carrying the p.Gly77ValfsX24 variant. However, this individual had metachronous breast cancer, suggesting that the variant may confer significant cancer risk. Moreover, analysis of the ovarian tumor DNA revealed loss of the wild-type allele indicating complete loss of *RAD51C* function within the tumor cells.

Among the 11 missense variants and one in-frame deletion identified, six have not previously been reported. Five of these variants were detected in cases (p.Phe103del, p.Gly114Val, p.Ala175Thr, p.Gln178Pro, p.Leu262Val) and one in a control (p.Ile52Leu). Seven in silico prediction tools were used to assess the functional relevance of the 11 missense variants. Three missense variants, p.Gly114Val, p.Gly162Glu (rs35151472), and p.Arg249Cys (rs28363311), were predicted to affect function by 6/6, 6/7, and 5/7 algorithms, respectively (Table 1 and Supp. Table S1). In-frame deletion p.Phe103del could not be assessed using these tools. In addition, analysis of all nontruncating variants using HSF indicated the possible introduction of a cryptic donor site caused by novel missense variant c.784T>G (p.Leu262Val). No other splice alterations were predicted.

Table 1. Summary of Germline *RAD51C* Variants

Variant type	Site[a]	Nucleotide change[b]	Protein change[b]	dbSNP (132)	Detected in previous *RAD51C* studies	HBC/HBOC families (n = 1,388)[c] BC (n = 1,053)	BC/OC (n = 314)	OC (n = 21)		Controls[d]	In silico prediction score[e]	HSF splice analysis[f]
Truncating	Ex1	c.68_72dup	p.Val25CysfsX3	No	No	-	-	1	-	0/427	-	-
	Ex2	c.230delG	p.Gly77ValfsX24	No	No	-	-	-	1	0/427	-	-
	Ex2	c.397C>T	p.Gln133X	No	No	-	1	-	-	0/427	-	-
Nonsynonymous	Ex2	c.154A>C	p.Ile52Leu	No	No	-	-	-	-	1/427	0/6	No
	Ex2	c.308_310delTCT	p.Phe103del	No	No	1	-	-	-	0/427	-	No
	Ex2	c.341G>T	p.Gly114Val	No	No	-	-	-	1	0/427	6/6	No
	Ex2	c.376G>A	p.Ala126Thr	rs61758784	Yes[h]	15	-	-	5	3/427	1/6	No
	Ex3	c.485G>A	p.Gly162Glu	rs35151472	No	3	1	-	-	0/190	6/7	No
	Ex3	c.506T>C	p.Val169Ala	No	Yes[i]	1	-	-	1	0/190	2/6	No
	Ex3	c.523G>A	p.Ala175Thr	No	No	1	-	-	-	0/190	2/6	No
	Ex3	c.533A>C	p.Gln178Pro	No	No	-	1	-	-	0/190	2/5	No
	Ex5	c.745C>T	p.Arg249Cys	rs28363311	No	1	-	-	-	0/427	5/7	No
	Ex5	c.784T>G	p.Leu262Val	No	No	1	-	-	1	0/427	2/6	Possible new donor site
	Ex5	c.790G>A	p.Gly264Ser	No	Yes[j]	8	2	-	8	1/427	1/6	No
	Ex6	c.859A>G	p.Thr287Ala	rs28363317	Yes[k]	14	5	-	3	0/190	3/6	No
Synonymous	Ex1	c.87T>C	p.(=)	No	No	-	-	-	-	1/190	-	No
	Ex2	c.195A>G	p.(=)	rs45511291	Yes[l]	2	1	-	-	0/427	-	No
Noncoding[g]	IVS3	c.571+64C>A	p.(=)	No	Yes[l]	-	-	-	2	0/190	-	No
	IVS3	c.572–17G>T	p.(=)	No	Yes[m]	2	-	-	-	1/190	-	No
	IVS8	c.1026+23G>A	p.(=)	No	No	-	-	-	-	2/190	-	No

[a]Ex, exon; IVS, intervening sequence.
[b]Variant positions are reported in reference to GenBank reference sequences NG_023199.1 (DNA) NM_058216.1 (mRNA) and NP_478123.1 (protein). Nucleotide numbering reflects cDNA position according HGVS recommendations.
[c]Breast cancer only family (BC), ovarian cancer only family (OC), breast and ovarian cancer family (BC/OC)
[d]The numbers of controls examined varied by exon, as indicated for each variant.
[e]Number of in silico tools that predicted the missense variant to be pathogenic/number of in silico tools used to assess the variant.
[f]Human Splicing Finder (HSF) was used to assess the affect of each variant on consensus splice motifs.
[g]In addition to the noncoding variants listed, dbSNPs rs12946397 (c.1–26C>T) and rs28363318 (c.904+34T>C) were detected at frequencies greater than 0.26 and 0.11, respectively.
[h]Meindl et al. [2010], Akbari et al. [2010], Wong et al. [2011], Romero et al. [2011].
[i]Meindl et al. [2010]
[j]Meindl et al. [2010], Pelttari et al. [2011].
[k]Meindl et al. [2010], Akbari et al. [2010], Zheng et al. [2010], Romero et al. [2011], Pelttari et al. [2011].
[l]Zheng et al. [2010].
[m]Romero et al. [2011].

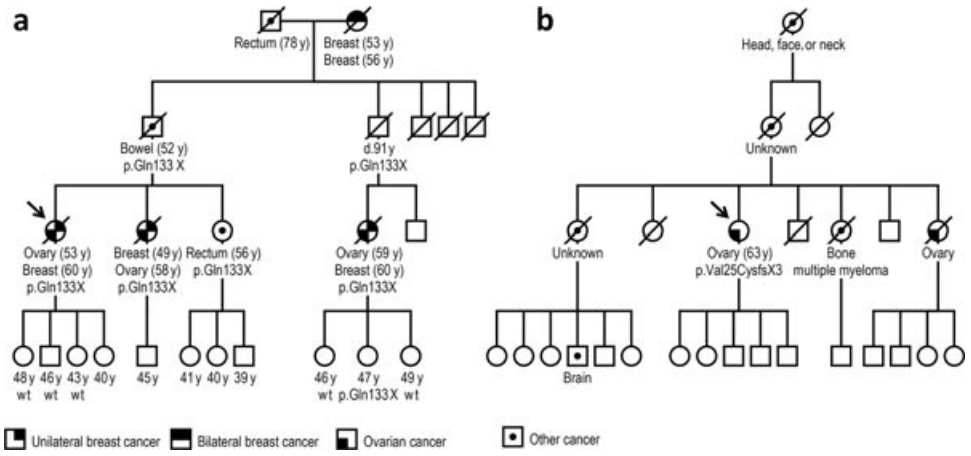

Figure 1. *RAD51C* mutations in HBOC cohort. Pedigrees for families carrying the (A) p.Gln133X nonsense and (B) p.Val25CysfsX3 frameshift mutations. Cancer type and age in years (y) at diagnosis (if known) are indicated underneath the symbol for each affected individual. Mutation status is indicated by the amino acid variation or wt (wild type). Current age (or age of death) is shown for cancer-unaffected mutation carriers and children of mutation carriers. The first tested individual (proband) is indicated with an arrow. In the p.Gln133X family (A), ovarian cancers were reported as a malignant cystadenoma (grade 3) and a malignant papillary serous adenocarcinoma (grade unknown) in the women diagnosed at 53 and 58 years, respectively. In the p.Val25CysfsX3 family (B), an undifferentiated adenocarcinoma was reported in the proband, and a serous cystadenocarcinoma in her sibling.

Four missense variants (p.Ala126Thr [rs61758784], p.Val169Ala, p.Gly264Ser, and p.Thr287Ala [rs28363317]) have been detected in other recent *RAD51C* mutation studies. Three of these variants, p.Ala126Thr (rs61758784), p.Gly264Ser, and p.Thr287Ala, are overrepresented among cases in this study. Missense variant p.Gly264Ser was reported by Meindl et al. to be significantly overrepresented among breast and ovarian cancer families (OR 3.44, 95% CI 1.51–7.80) and moreover, was shown experimentally to exhibit reduced function. This variant is not significantly overrepresented in our familial cohort ($P = 0.475$, OR 3.094, 95% CI 0.3947–24.25) but it is significantly overrepresented in the unselected ovarian cancer cohort compared to controls ($P = 0.0027$, OR = 13.16, CI 1.636–105.9), supporting the previously identified association.

The only novel synonymous variant (c.87T>C) was detected in a singleton control sample.

As is the case for most of chromosome 17, the *RAD51C* locus (17q25.1) is frequently affected by LOH in ovarian tumors [Gorringe et al., 2009]. We were therefore interested to find out whether *RAD51C* may be a target of inactivation in tumor cells via somatic mutation of the remaining allele. Analysis of 89 matched unselected ovarian tumors did not reveal any somatic mutations, suggesting this is not a frequent event in ovarian cancer.

The recent report by Meindl et al. demonstrated that germline mutations in *RAD51C* are associated with an increased risk of breast and ovarian cancer. However, the rarity of overtly deleterious mutations in *RAD51C* has made it difficult to predict the proportion of HBOC families that can be explained by this gene. In addition, Meindl et al. observed that deleterious mutations were found primarily in families with a history of breast and ovarian cancer but the subsequent smaller studies have not been sufficiently powered or configured to validate this association. Clarification of these issues has important implications as to whether and how *RAD51C* genetic testing should be implemented in familial cancer clinics as well as for understanding the molecular biology of *RAD51C*-mediated breast and ovarian cancer. Consequently, we have undertaken the largest single study to date of the frequency of germline *RAD51C* mutations in breast and ovarian cancer families as well as in unselected ovarian cancers.

We have identified two novel truncating mutations in our cohort of 1,388 HBC and HBOC families with both mutations being identified among the subset of 334 families affected by ovarian cancer. The frequency of truncating mutations identified in families with ovarian cancers in our study was 0.6%, which is less than the 1.3% reported by Meindl et al. but is consistent with some of the more recent studies. This disparity is likely due to chance but could also be influenced by differences in cohort acquisition or variant detection methods. Despite the rarity of deleterious mutations, our data are consistent with the conclusion that *RAD51C* protein truncating mutations predominate in families with a history of ovarian cancer (with or without breast cancer) and such mutations in breast cancer only families are likely to be extremely rare. Interestingly, the colorectal cancers reported in two *RAD51C* mutation carriers in the p.Gln133X family (Fig. 1A) suggest that there could be other cancers associated with *RAD51C* mutations, as has been reported for FA gene *PALB2* [Jones et al., 2009].

In contrast to the findings of Meindl et al., we did not observe a significant overrepresentation of missense variant p.Gly264Ser in our familial cohort compared to healthy controls but we did observe a significant association in our ovarian cancers. While the numbers are small and did not reach statistical significance, it is interesting to note that both we and Meindl et al. observed an overrepresentation of the p.Ala126Thr variant among breast cancer only families raising the possibility that this variant may confer a lower penetrance risk for ovarian cancer. In addition, in silico analyses identify four variants that may be pathogenic (p.Gly114Val, p.Gly162Glu, p.Arg249Cys, and p.Leu262Val). Interestingly, two of these variants are reported in dbSNP; however, we did not detect these in any of our controls nor have they been reported in 1000 genomes data (http://browser.1000genomes.org, 1000 Genomes release—May 8, 2011) or in previous *RAD51C* mutation studies suggesting that these are very rare alleles. We note that Pang et al. [2011] also identified two novel missense variants (p.Arg2Gly and p.Asp215Gly) that are predicted to be pathogenic. Since in silico predictions are inconclusive, functional studies in conjunction with segregation analyses will be required to determine whether any of these variants are pathogenic.

The proportion of unselected invasive ovarian cancers that are accounted for by pathogenic germline mutations in *BRCA1* and *BRCA2* is estimated to be 13.3% [Zhang et al., 2011]. Our study, which is the first to comprehensively investigate germline mutations in unselected ovarian cancers, suggests that a further small proportion of cases are due to truncating mutations in *RAD51C*. In addition, a much larger proportion may be attributable to *RAD51C* if the currently unclassified missense variants are established to be pathogenic.

Finally, we noted with interest that among six granulosa cell tumors screened, two harbored the p.Gly264Ser variants and another harbored the p.Ala126Thr variant. With such limited numbers, and considering the uncertain relevance of these variants, it is not possible to know whether this observation is significant but it warrants further investigation.

Overall, our findings are consistent with truncating *RAD51C* mutations being associated with an increased familial risk of ovarian cancer (especially in the context of breast cancer) but that the frequency of these mutations is low (<1%). It is noteworthy from a clinical testing perspective that two of three of the truncating mutations were identified in women with metachronous breast and ovarian cancer. In contrast to the exclusive association of overtly deleterious mutations with ovarian cancer predisposition, our data suggest that some *RAD51C* missense variants may also be associated with breast cancer only families. Larger studies are required to extend the phenotype–genotype correlation in regard to tumor spectrum and penetrance associated with *RAD51C* variants prior to introduction of this test into the clinical diagnostic arena.

Acknowledgments

We wish to thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, Kylie Shackleton and Rebecca Driessen from the Victorian Familial Cancer Clinical Trials Group, staff of the Family Cancer Clinics, staff of the Peter MacCallum Cancer Centre Pathology Department and the Clinical Follow Up Study (funded 2001–2009 by NHMRC and currently by the National Breast Cancer Foundation and Cancer Australia #628333) for their contributions to this resource, and the many families who contribute to kConFab. We also thank Sue Healey from the Queensland Institute of Medical Research for providing technical support.

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