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LETTER TO THE EDITOR

RAD51C germline mutations in Chinese women with familial breast cancer

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To the Editor,

Germline mutations in high penetrance breast cancer susceptibility genes, *BRCA1* and *BRCA2*, account for only approximately 10% of Chinese familial breast cancers [1], indicating other susceptibility genes related to Chinese familial breast cancer may exist. *RAD51C* gene (Ras-related associated with diabetes) is located on chromosome 17q23, a region that was found to be frequently amplified in breast tumors [2, 3]. *RAD51C* gene is a member of the *RAD51* family and plays an essential role in homologous recombination, DNA damage sensitivity, genomic integrity, embryonic development, activation of cell cycle checkpoint kinase 2 (*CHK2*), and cell cycle arrest in response to DNA damage [4–8].

Recently, a biallelic missense mutation in the *RAD51C* gene was found in a family from Pakistan with Fanconi anemia-like disorder [9]. In an accompanying article, six monoallelic deleterious mutations in the *RAD51C* gene were found in 480 *BRCA1/2*-negative breast/ovarian cancer families from Germany [10]. This study provides the first evidence to show that the *RAD51C* is a breast cancer susceptibility gene. Thus, the *RAD51C* gene may deserve to be comprehensively screened as a breast cancer susceptibility gene in other populations.

In this study, we screened the entire coding regions and exon–intron boundaries of the *RAD51C* gene in 273 Chinese women with familial breast cancer who do not carry mutations in *BRCA1* and *BRCA2* genes by polymerase chain reaction (PCR)-sequencing. Familial breast cancer cases were from the Breast Center, Peking University Cancer Hospital from July 2006 to May 2010. The criteria of familial breast cancer are (1) patients have at least one or more first- or second-degree relatives affected with breast cancer and/or ovarian cancer regardless of age and (2) bilateral breast cancer regardless of age. Four hundreds seventy-five healthy Chinese women serve as controls. Both of the cases and controls are Han Chinese women and reside in the north of China. The whole coding sequences of *RAD51C* were amplified using nine sets of primers described elsewhere with a minor modification [10]. All fragments were sequenced using BigDye Terminator Cycle Sequencing Kit and ABI 3730 automated sequencer (Applied Biosystems, Foster City, CA). Each mutation was confirmed by duplicate.

In total, we detected eight germline sequence variants in the *RAD51C* gene in the 273 *BRCA1/2*-negative familial breast cancer cases. Among them, three were non-coding variants and five were coding variants (Table 1). None of them were previously reported. Of the coding variants, one was synomenous and four were non-synomenous. Among the four amino-acid substitution variants, 4C>G (R2G) was located in exon 1, 635G>A (R212H) and 644A>G (D215G) in exon 4, and 882G>C (Q294H) in exon 6. The missense variants R2G, D215G, and Q294H were detected in one index case, whereas R212H was detected in two unrelated cases. We then screened the four missense variants in 475 healthy controls. The variant R212H was found in two healthy individuals, indicating this variant was unlikely to be pathogenic. In contrast, none of the

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Table 1 Sequence variants of the *RAD51C* gene in 273 *BRCA1/2*-negative familial breast cancer cases and 475 healthy controls

Site	Nucleotide change	Protein change	Cases	Controls	Predictive algorithms		
					SIFT	PolyPhen	PMut
Ex1	4C>G	R2G	1/273	0/475	Yes	Ps	No
Ex4	635G>A	R212H	2/273	2/475	No	Pb	Yes
Ex4	644A>G	D215G	1/273	0/475	Yes	Ps	Yes
Ex6	882G>C	Q294H	1/273	0/475	No	No	No
Ex2	348C>G	P116P	1/273	–			
IVS3	IVS3, 571 + 5G>A	Non-coding	1/273	–			
IVS5	IVS4, 706 − 18T>C	Non-coding	3/273	–			
IVS6	IVS6, 904 + 34T>C	Non-coding	2/273	–			

Ex exon, *IVS* intervening sequence

SIFT: *Yes* affects function, *No* tolerated. PolyPhen: *Ps* possibly damaging, *Pb* probably damaging, *No* benign. PMut: *Yes* pathological, *No* tolerated

remaining three variants R2G, D215G, and Q294H was found in the 475 healthy controls. Furthermore, alignment of the *RAD51C* ortholog and paralog sequences using data extracted from the National Center for Biotechnology Information (NCBI) database revealed that D215G is under strong functional constraint.

For further functional analysis of these missense variants, SIFT (http://sift.jcvi.org/), PolyPhen (http://genetics.bwh.harvard.edu/pph/), and PMut (http://mmb2.pcb.ub.es:8080/PMut/) were used for functional prediction. R2G and D215G are predicted to be pathogenic, whereas the Q294H is considered to be tolerated or benign (Table 1).

Taken together, in this study, we identified eight novel variants in the *RAD51C* gene in our cohort. Two missense variants R2G and D215G of the *RAD51C* gene are likely to be pathogenic in Chinese women. Therefore, *RAD51C* gene might be associated with breast cancer risk in Chinese women.

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