Null Results in Brief

Rad50 c.687delT Does Not Contribute Significantly to Familial Breast Cancer in a French Population

Nancy Uhrhammer, Laetitia Delort, and Yves-Jean Bignon
Laboratoire Diagnostic Génétique et Moléculaire, Centre Jean Perrin, Clermont-Ferrand, France

Abstract

Mutations in DNA repair genes are known for their association with hereditary breast cancer. BRCA1 and BRCA2 are the major genes for high-penetration familial breast and ovarian cancer, whereas mutations in ATM or Chek2 confer more modest cancer risk. Additional genes involved in DNA double-strand break repair have more recently been associated with breast cancer risk: heterozygosity for deleterious mutations in components of the Rad50-Mre11-Nbs1 complex seems to predispose to breast cancer. In particular, the c.687delT mutation in Rad50 conferred an odds ratio of 4.3 for the risk of breast cancer in a study of Finnish breast cancer families. To explore the contribution of this mutation to breast cancer in French families for which no BRCA mutation could be found, we analyzed the relevant exon in 618 familial breast cancer cases and 513 controls with no personal or familial history of breast cancer. Rad50 was analyzed in its entirety for 231 familial cases, with no clearly deleterious mutations detected. These data together suggest that although founder mutations may make Rad50 a significant breast cancer risk factor in certain populations, it is not a factor in others. (Cancer Epidemiol Biomarkers Prev 2009;18(2):684–5)

Introduction

Breast cancer is one of the most frequent cancers affecting women worldwide, with 5% to 10% of cases being attributed to mutations in major genes. As BRCA mutations cannot account for the majority of familial aggregations of breast cancer, more complex models involving rare mutations of other major genes and the cumulative effects of genes with modest penetrance are currently under study. Most of the genes known to contribute to breast cancer risk are involved in DNA repair, either directly or as part of a signaling/response network (1). A significant risk of breast cancer was recently associated with the c.687delT mutation in the Rad50 gene in the Finnish population (2). We therefore tested for the Rad50 c.687delT mutation in 618 BRCA-negative familial breast cancer cases and a control group of 513 women. No mutations were observed in either group, suggesting that this mutation does not contribute to hereditary breast and ovarian cancer (HBOC) families in central France.

Materials and Methods

All HBOC families were ascertained through the Oncogenetics consultation at the Centre Jean Perrin and met the minimum criteria of three breast or ovarian cancers in the same familial branch with at least two cases related in the first degree, two cases in the same branch with at least one diagnosed before age 40 years or with bilateral cancer, or two cases with at least one male breast cancer. Written informed consent was obtained from all subjects in accordance with institutional guidelines. Previous testing for BRCA mutations was done by direct sequencing of both genes and multiplex ligation-dependent probe amplification quantitative analysis for BRCA1. Six hundred eighteen cases representing 528 families with no detectable mutation in either gene were included for Rad50 exon 5 analysis. The average age at diagnosis of breast cancer was 48.8 ± 11.9 years. Three breast cancers occurred in men. Nine women had bilateral breast cancer. Eighteen women had ovarian cancer. The 231 cases representing 197 families randomly chosen for full Rad50 analysis included 5 bilateral breast cancers, 10 ovarian cancers, and no male breast cancer; the average age at breast cancer was 50.1 ± 12.4, with no notable difference in family size or structure.

A control population from the same region of France was established from 513 healthy local female volunteers with no personal history of any cancer or family history of breast or gynecologic cancer. Women aged 49 to 79 (average, 58.0 ± 9.0) years were enrolled at the time of routine mammography for which the result was normal. Written informed consent was obtained according to institutional guidelines.

DNA was extracted from 10 mL peripheral blood drawn on lithium heparin using the Talent kit and the manufacturer’s instructions (Euromedex) and resuspended in Tris-EDTA. Rad50 exon 5 was amplified by standard techniques (conditions and primer sequences available on request). Sequence reactions were done.
using BigDye.v3 reagents (Applied Biosystems) according to the manufacturer’s instructions, resolved on the 3130 capillary electrophoresis system (Applied Biosystems), and analyzed using Seqman software (Lasergene). For 231 cases, sequence analysis was continued for the entire coding sequence and all intron-exon boundaries. Reference sequences were NC_000005.8 for the genomic sequence and NM_005732.2 for the longer cDNA isoform.

Results and Discussion

The Rad50 c.687delT mutation was not observed in any case or control DNA. Full sequencing of 231 cases revealed no obviously deleterious mutations (i.e., stops, splice errors, or frameshifts).

The initial finding of mutations in the Rad50 gene associated with breast cancer risk is consistent with the involvement of DNA repair genes in oncogenesis. The BRCA1 and BRCA2 genes, responsible for high-penetrance hereditary breast cancer, both participate in double-strand break (DSB) repair: BRCA1 as a target of ATM and facilitator of repair in part through a direct interaction with Rad50, and BRCA2/FANCD1 through interactions with Rad51 and the FANC complex. Other risk genes include FANC complex members BRIP1/FANCJ and PALB2/FANCN (3, 4): mutations in these genes seem to be moderately penetrant (odds ratios for breast cancer in heterozygotes between 2.5 and 4) but infrequent.

The association of mutations in the DNA DSB detection/signaling kinase ATM with elevated breast cancer risk has been observed in many different populations worldwide (5). The functional interaction between ATM and the MRN complex involved directly in binding DSBs, treating the broken ends, and promoting homologous recombination repair strongly suggests that mutations perturbing the latter may also lead to increased cancer risk (6). This has been confirmed for the NBS1 gene in Slavic populations where the founder mutation responsible for the recessive Nijmegen breakage syndrome has been shown to confer breast cancer risk on heterozygotes (7).

Early reports of the contribution of mutations in different members of the MRN complex to hereditary breast cancer risk in specific populations, however, have been difficult to confirm elsewhere (8, 9). A study of 435 familial breast cancer cases from the United Kingdom also failed to observe Rad50 c.687delT; in this same study, a more extensive sample of Finnish familial cases also observed no additional instances of this mutation (10). Our results suggest that the c.687delT mutation and possibly deleterious mutations of Rad50 in general do not contribute significantly to hereditary breast cancer risk in France.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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