The AIB1 Polyglutamine Repeat Does Not Modify Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers

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Abstract

This is by far the largest study of its kind to date, and further suggests that AIB1 does not play a substantial role in modifying the phenotype of BRCA1 and BRCA2 carriers. The AIB1 gene encodes the AIB1/SRC-3 steroid hormone receptor coactivator, and amplification of this gene and/or protein occurs in breast and ovarian tumors. A CAG/CAA repeat length polymorphism encodes a stretch of 17 to 29 glutamines in the HR-interacting carboxyl-terminal region of the protein which is somatically unstable in tumor tissues and cell lines. There is conflicting evidence regarding the role of this polymorphism as a modifier of breast cancer risk in BRCA1 and BRCA2 carriers. To further evaluate the evidence for an association between AIB1 glutamine repeat length and breast cancer risk in BRCA1 and BRCA2 mutation carriers, we have genotyped this polymorphism in 1,090 BRCA1 and 661 BRCA2 mutation carriers from Australia, Europe, and North America. There was no evidence for an increased risk associated with AIB1 glutamine repeat length. Given the large sample size, with more than adequate power to detect previously reported effects, we conclude that the AIB1 glutamine repeat does not substantially modify risk of breast cancer in BRCA1 and BRCA2 mutation carriers. (Cancer Epidemiol Biomarkers Prev 2006;15(1):76–9)

Introduction

The AIB1 (NCOA3) gene encodes the AIB1/SRC-3 steroid hormone receptor coactivator, and amplification of the gene and/or protein occurs in breast and ovarian tumors (1-4), and is associated with tumor size (2), immunohistochemical profile (including estrogen receptor, progesterone receptor, p53, and HER2 status; ref. 5), and tamoxifen resistance (6). A CAG/CAA repeat length polymorphism encodes a stretch of 17 to 29 glutamines in the HR-interacting carboxy-terminal region of the protein, and although repeat number has not been directly assessed with respect to its effects on function, the repeat

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region has been shown to be somatically unstable in tumor tissues and cell lines. One study found that germ line DNA from BRCA1/2 carrier cases have a greater proportion of uncommon sequence patterns compared with normal controls, and a greater proportion of alleles ≥28 repeats compared with sporadic breast cancer cases (7).

Several studies have been undertaken to assess the role of the AIB1 glutamine repeat polymorphism as a modifier of breast cancer risk in BRCA1 and BRCA2 carriers, with the hypothesis-generating study of 448 female BRCA1 or BRCA2 mutation carriers reporting increased breast cancer risk associated with allele length ≥29 glutamines [odds ratio, 2.9; 95% confidence interval (CI), 1.7-5.0], an effect which appeared to be driven by the 370 BRCA1 mutation carriers in the sample (8). Longer repeat length was associated with modestly increased risk in a second study of 222 BRCA1 and 88 BRCA2 mutation carriers [rate ratio (RR) per repeat 1.25 (95% CI, 1.1-1.4) for BRCA1 carriers, and 0.9 (0.8-1.1) for BRCA2 carriers; ref. 9], but not in another much larger study of 851 BRCA1 and 324 BRCA2 mutation carriers [RR per repeat 1.1 (95% CI, 0.8-1.3) and 1.2 (0.9-1.6) for BRCA1 and BRCA2 carriers, respectively; ref. 10].

To further evaluate the evidence for an association between AIB1 glutamine repeat length and breast cancer risk in BRCA1 and BRCA2 mutation carriers, we have genotyped this polymorphism in a series of 1,754 BRCA1 and BRCA2 mutation carriers.

Materials and Methods

Subjects. The distribution of samples according to source, gene, and cancer status is shown in Table 1. Recruitment and genetic studies were approved by relevant ethics committees at all sites, and written informed consent was obtained from each participant. Mutation carriers were identified as part of clinic-, community-, multiple-case family-, and population-based research studies, as described elsewhere (11). Mutation classification was as described previously (11). A small subset of 17 individuals from the Australian Breast Cancer Family Study were also analyzed as part of a previous population-based case control study of AIB1 (16).

Molecular Methods. The AIB1 glutamine repeat length was measured by standard fluorescent PCR PAGE methodology, using the ABI Prism 373 Genescan and Genotyper systems.

<table>
<thead>
<tr>
<th>Sample sources</th>
<th>Mode of ascertainment</th>
<th>Grouping</th>
<th>BRCA1 n (% of total)</th>
<th>BRCA2 n (% of total)</th>
<th>BRCA1 and BRCA2 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBRACE</td>
<td>clinic-based</td>
<td>United Kingdom</td>
<td>386 (35.4)</td>
<td>175 (26.5)</td>
<td></td>
</tr>
<tr>
<td>kConFaB</td>
<td>clinic-based</td>
<td>Australia</td>
<td>237 (21.7)</td>
<td>217 (32.8)</td>
<td></td>
</tr>
<tr>
<td>BCFR-Australia-AJBCS</td>
<td>community-based</td>
<td>Australia</td>
<td>18 (1.7)</td>
<td>22 (3.3)</td>
<td></td>
</tr>
<tr>
<td>BCFR-Australia-ABCFS</td>
<td>population-based</td>
<td>Australia</td>
<td>20 (1.8)</td>
<td>23 (3.5)</td>
<td>1</td>
</tr>
<tr>
<td>BCFR-Philadelphia</td>
<td>clinic-based</td>
<td>North America</td>
<td>60 (5.5)</td>
<td>28 (4.2)</td>
<td>1</td>
</tr>
<tr>
<td>BCFR-Utah</td>
<td>clinic-based</td>
<td>North America</td>
<td>36 (3.3)</td>
<td>17 (2.6)</td>
<td></td>
</tr>
<tr>
<td>BCFR-New York</td>
<td>clinic-based</td>
<td>North America</td>
<td>104 (9.5)</td>
<td>32 (4.8)</td>
<td></td>
</tr>
<tr>
<td>BCFR-Ontario</td>
<td>population-based</td>
<td>North America</td>
<td>67 (6.1)</td>
<td>39 (5.9)</td>
<td></td>
</tr>
<tr>
<td>BCFR-Northern California</td>
<td>population-based</td>
<td>North America</td>
<td>31 (2.8)</td>
<td>29 (4.4)</td>
<td>1</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>clinic-based</td>
<td>North America</td>
<td>81 (7.4)</td>
<td>27 (4.1)</td>
<td></td>
</tr>
<tr>
<td>INHERIT BRCAAs-Quebec</td>
<td>multiple-case family-based</td>
<td>Quebec</td>
<td>50 (4.6)</td>
<td>52 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1,090 661</td>
<td>3</td>
<td></td>
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<tr>
<td>Affected with breast cancer</td>
<td></td>
<td></td>
<td>598 (54.9)</td>
<td>392 (59.3)</td>
<td>3</td>
</tr>
<tr>
<td>Affected with ovarian cancer</td>
<td></td>
<td></td>
<td>83 (7.6)</td>
<td>26 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Number of families</td>
<td></td>
<td></td>
<td>685 390</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Source abbreviations: EMBRACE, Epidemiological Study of Familial Breast Cancer; kConFaB, Kathleen Cunningham Consortium for Research into Familial Breast Cancer; BCFR, Breast Cancer Family Registry; AJBCS, Australian Jewish Breast Cancer study; ABCFS, Australian Breast Cancer Family Study; National Cancer Institute, Cancer Family Registry, Intramural program of the National Cancer Institute; INHERIT BRCAAs, Interdisciplinary Health Research International Team on Breast Cancer susceptibility.

†Cancer type refers to first primary cancer diagnosis. One BRCA2 carrier with breast cancer was censored as unaffected at age of prior mastectomy.

Results

Genotype distributions were similar to those in previous studies. The glutamine length ranged from 18 to 37 repeats, the most common alleles being 26 repeats (13%), 28 repeats (38%), and 29 repeats (47%). The estimated RRs associated by repeat length are given in Table 2. There was no evidence for an increased risk associated with AIB1 glutamine repeat length, for the ≥28 and ≥29 repeat cutpoints previously shown to be associated with risk (8), or for repeat length considered as a continuous variable. None of the estimated RRs were different from 1 at the 0.05 level of significance, for BRCA1 or BRCA2 mutation carriers. There was little difference between the estimates adjusted only for source group, ethnicity, and year of birth, and those...
adjusted also for reproductive factors. Risk estimates using the weighted Cox regression approach were similar to the unweighted estimates as expected when the null hypothesis is true (18).

Risk estimates did not differ materially when women with a first primary diagnosis of ovarian cancer were excluded [e.g., RR (95% CI) for the \( \geq 29 \) CAG cutoff of 0.96 (0.79-1.16) for BRCA1 mutation carriers (\( P = 0.7 \)), and 1.05 (0.83-1.33) for BRCA2 mutation carriers (\( P = 0.7 \))], or when carriers ascertained from population-based sites were excluded (data not shown), suggesting that the preferential ascertainment of cases versus controls from these sites did not bias results.

Our sample size was large enough to detect effects reported by Rebeck et al. (8). Assuming the age distribution of affected and unaffected carriers as shown in Table 1, simulations estimated the power of detecting risk ratios of 1.56 and 2.85 to be 91% and 100%, respectively, for BRCA1 mutation carriers and 58% and 100% for BRCA2 carriers. The upper 95% confidence limits on the RR in our analysis (1.21 for BRCA1, 1.70 for BRCA2 \( \geq 29 \) repeats based on the weighted analysis) exclude any substantial risk.

Conclusion

Our study found no evidence to support the previously reported associations of \( AIB1 \) glutamine repeat length with increased breast cancer risk in two relatively small studies of BRCA1 carriers (8, 9), supporting recently published negative findings from a much larger study of mutation carriers (10). Given the large sample size, with more than adequate power to detect previously reported effects, we conclude that the \( AIB1 \) glutamine repeat does not substantially modify risk of breast cancer in BRCA1 and BRCA2 mutation carriers.

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References


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