Polyglutamine Repeat Length in the NCOA3 Does Not Affect Risk in Familial Breast Cancer

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Null Results in Brief

The region of a trinucleotide repeat (CAG, CAA) in the NCOA3 gene was genotyped by fragment analysis using a case-control group of 1,127 women. This group composed of 591 women with familial breast cancer that were negative for BRCA1 and BRCA2 (BRCA1/2) mutation carriers, whereas shorter alleles seem to have a protective effect (2, 3). However, the NCOA3 polyglutamine repeat length alone has not been found to alter the breast cancer risk among unselected postmenopausal women (4). Unlike these studies, we used for the first time a large set of DNA samples from women with familial breast cancer, where the likelihood to detect possible risk factors is much higher than in unselected cases. To prove if the NCOA3 polymorphism has an impact on the breast cancer risk, we analyzed 591 breast cancer samples from German and Polish women together with 536 matched controls.

Materials and Methods

The region of a trinucleotide repeat (CAG, CAA) in the NCOA3 gene was genotyped by fragment analysis using a case-control group of 1,127 women. This group composed of 591 women with familial breast cancer that were negative for BRCA1/2 mutations and 536 ethnically and geographically matched controls from Poland and Germany (5). Seventy-five percent of the women with breast cancer were diagnosed under age 50 years. The cases were consecutive cases collected among unselected postmenopausal women (4). Unlike these studies, we used for the first time a large set of DNA samples from women with familial breast cancer, where the likelihood to detect possible risk factors is much higher than in unselected cases. To prove if the NCOA3 polymorphism has an impact on the breast cancer risk, we analyzed 591 breast cancer samples from German and Polish women together with 536 matched controls.

Results and Discussion

The most common alleles in the polymorphic region of NCOA3 contained 26 (12%), 28 (35%), and 29 (52%) CAG/CAA repeats, with 28/29 and 29/29 as most frequent genotypes (35% and 28%, respectively). No significant differences were found between populations or cases and controls. Allele distribution was similar to the ones reported previously for Caucasian women (3, 4). The genotype distribution among our familial breast cancer cases without BRCA1/2 mutations followed the same pattern as shown earlier among unselected postmenopausal women with breast cancer (4). No correlation was found between breast cancer risk and genotypes with longer or shorter NCOA3 alleles, respectively (Table 1). Women diagnosed for breast cancer at age ≥50 years tended to carry at least one allele shorter than 28 repeats. In German women, this effect was significant with an OR (95% confidence interval) of 2.17 (1.05-4.51; P = 0.023). However, in the joint population, this effect was not significant (OR, 1.45; 95% confidence interval, 0.9-2.31; P = 0.133).

In BRCA1/2 mutation carriers, an elevated breast cancer risk has been reported for women carrying longer NCOA3 alleles (2, 3). We found a comparable trend for 62 Polish samples from BRCA1/2 mutation carriers that were compared with the group of Polish controls. However, due to small sample size, woman carrying at least 29 repeats in both alleles had no statistically increased risk for breast cancer.
compared with women carrying shorter alleles.

The strength of our study was the use of DNA samples from women selected for familial breast cancer. With our sample size and a frequency of the rare genotype of $0.25$, we had a 90% power to detect an OR of $\geq 1.6$. Yet, according to Antoniou and Easton (6), the power of a study with familial breast cancer cases is at least twice higher than in a study using unselected cases. Therefore, we would even have a 90% power to detect an OR of $\geq 1.3$. Due to the lack of information about other factors than familial history, we cannot exclude the possibility that the NCOA3 polymorphism would have an effect on breast cancer risk in combination with hormonal or other risk factors. In conclusion, our moderately large, case-control study strongly suggests that the polyglutamine repeat length in NCOA3 alone is not influencing the breast cancer risk in women.

### Table 1. NCOA3 associated to the polyglutamine repeat lengths in NCOA3 in familial breast cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Gln repeats</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polish 646 samples</td>
<td>1 allele &lt;28</td>
<td>66 (18.7)</td>
<td>59 (20.1)</td>
<td>0.87 (0.56-1.34)</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>28/28, 28/29, 28/30</td>
<td>184 (52.1)</td>
<td>143 (48.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 alleles ≥29</td>
<td>103 (29.2)</td>
<td>91 (31.1)</td>
<td>0.88 (0.61-1.28)</td>
<td>0.481</td>
</tr>
<tr>
<td>German 481 samples</td>
<td>1 allele &lt;28</td>
<td>68 (28.6)</td>
<td>56 (23.0)</td>
<td>1.25 (0.79-1.98)</td>
<td>0.324</td>
</tr>
<tr>
<td></td>
<td>28/28, 28/29, 28/30</td>
<td>113 (47.5)</td>
<td>116 (47.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 alleles ≥29</td>
<td>57 (23.9)</td>
<td>71 (29.2)</td>
<td>0.82 (0.52-1.30)</td>
<td>0.383</td>
</tr>
<tr>
<td>Combined 1,127 samples</td>
<td>1 allele &lt;28</td>
<td>134 (22.7)</td>
<td>115 (21.5)</td>
<td>1.03 (0.75-1.41)</td>
<td>0.905</td>
</tr>
<tr>
<td></td>
<td>28/28, 28/29, 28/30</td>
<td>297 (49.8)</td>
<td>259 (48.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 alleles ≥29</td>
<td>160 (27.1)</td>
<td>162 (30.2)</td>
<td>0.86 (0.64-1.14)*</td>
<td>0.304</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel adjustment.

(OR, 1.31; 95% confidence interval, 0.71-2.40; $P = 0.355$)

### References

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