Null Results in Brief

Hyaluronan-Mediated Motility Receptor Gene Single Nucleotide Polymorphisms and Risk of Breast Cancer

Bolot Kalmyrzaev,1 Paul D.P. Pharoah,1 Douglas F. Easton,2 Bruce A.J. Ponder,3,4 and Alison M. Dunning,1 for the SEARCH Team

1Department of Oncology and Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Strangeways Research Laboratory, 2Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, and 3Department of Oncology, University of Cambridge, Cambridge, United Kingdom

Abstract

A recent study used a network modeling strategy to generate a set of genes linked by potential functional associations. The hyaluronan-mediated motility receptor (HMMR) gene was identified as being as functionally associated with BRCA1 and thus a candidate breast cancer gene. SNPs rs10515860, rs299290, and rs7712023 were reported to be significantly associated with breast cancer in a joint analysis of two small case-control studies. We have examined the association of these single nucleotide polymorphisms, together with others tagging the HMMR gene, in a larger, European case-control study and find no association of any of them with risk of breast cancer: rs10515860 [odds ratio (OR; AA/GG), 0.85; 95% confidence interval (CI), 0.65-1.12; \( P_{\text{trend}} = 0.9 \)], rs299290 [OR (CC/TT), 1.00; 95% CI, 0.87-1.15; \( P_{\text{trend}} = 0.7 \)], rs3756648 (rs7712023) [OR (TT/CC), 0.93; 95% CI, 0.84-1.02; \( P_{\text{trend}} = 0.1 \)], rs299284 [OR (TT/CC), 1.01; 95% CI, 0.76-1.35; \( P_{\text{trend}} = 0.5 \)], and rs13183712 [OR (TT/GG), 1.04; 95% CI, 0.88-1.23; \( P_{\text{trend}} = 0.6 \)].

Introduction

A recent publication reported significant associations between single nucleotide polymorphism SNPs in the HMMR gene, encoding the hyaluronan-mediated motility receptor, a centrosome unit, and risk of breast cancer (1). The study used a network modeling strategy, combining gene expression profiling with functional genomic and proteomic data from various species, to generate a set of genes linked by potential functional associations. The HMMR gene was identified as being functionally associated with BRCA1 and thus predicted to be a common, low-penetrance breast cancer candidate gene. SNPs rs10515860, rs299290, or rs7712023 were reported to be significantly associated with breast cancer in a joint analysis of two small case-control studies: a population-based case-control study of incident breast cancer in northern Israel and an independent case-control study in Ashkenazi Jewish cohort from New York (Table 1). We have attempted to confirm this finding in the >3-fold larger East Anglian SEARCH breast cancer study.

Materials and Methods

Cases and Controls. The SEARCH breast cancer case-control study has been described previously (2). This study has been approved by the Eastern Region Multi-centre Research Ethics Committee, and all patients gave written informed consent. The ethnic background of both cases and controls, as reported on the questionnaires, is similar with >98% being White Europeans. The total number of cases available for analysis was 6,762 and the total number of controls was 6,852.

Selection of Tagging SNPs. TagSNP selection was done using the Tagger feature within the Haploview program (3) on data from the CEU population from HapMap database.5 We aimed to define a set of tagSNPs that tagged all the known common SNPs (with minor allele frequencies of >0.05) in the gene, with a pairwise correlation \( r^2_p > 0.8 \).

Genotyping. Genotyping was carried out using Taqman (Applied Biosystems) according to manufacturer’s instructions. Primers and probes were supplied directly by Applied Biosystems as Assays-by-Design. All assays were carried out in 384-well plates. Each plate included negative controls (with no DNA) and positive controls

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Requests for reprints: Bolot Kalmyrzaev, University of Cambridge Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN United Kingdom.
Phone: 440-1223-741-166, Fax: 440-1223-740-147.
E-mail: bolot.kalmyrzaev@srli.cam.ac.uk
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http://www.hapmap.org
duplicated on a separate quality control plate. Plates were read on the ABI PRISM 7900 using the Sequence Detection Software (Applied Biosystems). Failed genotypes were not repeated.

Statistics. For each SNP, deviations of genotype frequencies in controls from Hardy-Weinberg equilibrium were assessed by a $\chi^2$ test with one degree of freedom. Genotype frequencies in cases and controls were compared by $\chi^2$ test for heterogeneity (2 degrees of freedom) and test for trend (1 degree of freedom). Genotype specific risks were estimated as odds ratios with associated confidence intervals using unconditional logistic regression.

Results and Discussion

The human HMMR gene spans ~31 kb and maps to chromosome regionSq.33.2.5qter (4). There are 32 SNPs listed on HapMap (HapMap Data Rel 22/phase III Apr07) within the HMMR gene footprint, of which 31 have minor allele frequency of >0.05. We selected 6 tagSNPs to represent all 31 known common SNPs in the gene (rs7712023, rs299284, rs299290, rs13183712, rs299316, and rs10515860) with $r^2 > 0.8$. The three SNPs examined in the original paper (rs7712023, rs299284, and rs10515860; ref.1) were forced into this tagging set. The TaqMan assays for two of the tagSNPs (rs7712023 and rs10515860; ref.1) were forced into this tagging set.

Table 1. Genotyped tagSNPs and breast cancer association analysis

<table>
<thead>
<tr>
<th>TagSNP genotypes</th>
<th>Our data</th>
<th>Pujana et al., 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls, n (%)</td>
<td>Cases, n (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>rs3756648</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>1760 (26.3)</td>
<td>1790 (27.7)</td>
</tr>
<tr>
<td>C/T</td>
<td>3325 (49.8)</td>
<td>3180 (49.1)</td>
</tr>
<tr>
<td>T/T</td>
<td>1598 (23.9)</td>
<td>1504 (23.2)</td>
</tr>
<tr>
<td>rs299284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>5350 (79.0)</td>
<td>5176 (78.5)</td>
</tr>
<tr>
<td>C/T</td>
<td>1327 (19.6)</td>
<td>1322 (20.1)</td>
</tr>
<tr>
<td>T/T</td>
<td>97 (1.4)</td>
<td>95 (1.4)</td>
</tr>
<tr>
<td>rs299290</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>3861 (56.9)</td>
<td>3708 (56.3)</td>
</tr>
<tr>
<td>T/C</td>
<td>2481 (36.5)</td>
<td>2450 (37.2)</td>
</tr>
<tr>
<td>C/C</td>
<td>445 (6.6)</td>
<td>426 (6.5)</td>
</tr>
<tr>
<td>rs13183712</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>4239 (62.5)</td>
<td>4076 (62.2)</td>
</tr>
<tr>
<td>G/T</td>
<td>2237 (33.0)</td>
<td>2180 (33.2)</td>
</tr>
<tr>
<td>T/T</td>
<td>303 (4.5)</td>
<td>303 (4.6)</td>
</tr>
<tr>
<td>rs10515860</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>5214 (76.6)</td>
<td>5039 (76.3)</td>
</tr>
<tr>
<td>G/A</td>
<td>1479 (21.7)</td>
<td>1472 (22.3)</td>
</tr>
<tr>
<td>A/A</td>
<td>114 (1.7)</td>
<td>94 (1.4)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval.

*SNPs rs3756648 and rs7712023 are perfectly correlated, $r^2 = 1.0$ in the HapMap CEU population sample.
good power to confirm the effect suggested for SNP rs10515860 (1).

It is possible that the causative variant is a founder mutation, present in the Jewish population, and not found in European populations. Ashkenazi founder mutations exist in the BRCA1 and BRCA2 genes but they do not have high frequencies (minor allele frequencies of <0.02; refs. 5, 6). A rare, founder variant would be very poorly tagged by the common SNPs used here and by Pujana et al. (1). We do not know of any examples of common, founder SNPs in the Ashkenazi population—common SNPs are, by definition, old and probably predate the formation of ethnic groups outside of Africa.

We conclude that the reported association between common SNPs in HMMR and breast cancer risk is likely to be a false positive association. This is not surprising, given that the results did not reach the level of statistical significance generally accepted as providing strong posterior evidence of association. In consequence, although the network modeling approach remains an interesting approach to explore disease biology, its ability to identify cancer susceptibility loci remains, as yet, unproven.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
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References
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