Non-random transmission of mutant alleles to female offspring of BRCA1 carriers in Poland

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Constitutional mutations in the BRCA1 gene predispose to an autosomal dominant syndrome of breast and ovarian cancer. The lifetime penetrance of BRCA1 gene mutations is high; approximately 50% of women with mutations will be affected by cancer by the age of 50 years, and over 80% of women with mutations will be affected with cancer by the age of 75 years.1 At birth, it is expected that 50% of the daughters of women who carry a mutation in BRCA1 should be carriers of this mutation based on principles of Mendelian transmission. The proportion of carriers among healthy daughters is expected to decline with increasing age as increasing numbers of these women become affected.

We measured the prevalence of founder BRCA1 mutations among 122 unaffected daughters of 91 carrier women. Seventy-five of the daughters were carriers (61.5%) and 47 of the daughters were non-carriers (38.5%) (p = 0.01).

Among women over the age of 20 we expected there to be more non-carriers than carriers. In contrast there were 63 carriers and 33 non-carriers (p = 0.002). The segregation of mutant and non-mutant alleles appears to be non-random in female offspring of BRCA1 carriers.

In total 387 carrier probands were identified, of whom 247 had one or more daughters. To avoid the possibility of selection bias we included only families in which the mothers received their genetic test result before any of the daughters were tested (218 of 247). Of these 218, 91 mothers had one or more daughters who were tested for the mutation and 127 had daughters who were not tested. The 91 carrier mothers had 141 daughters, of whom 126 were tested (range 1–4 daughters per mother). Fifty-nine of the 91 mothers had breast cancer, 21 had ovarian cancer and 11 were unaffected.

Four of the daughters had been affected by breast cancer and were excluded. None of the unaffected daughters had ovarian cancer or had a child affected with cancer. Thus, 122 unaffected daughters (61.5%) were carriers of the mutation; 61 would have been expected under a transmission ratio of 50% (p = 0.011).

Surprisingly, there was no evidence of declining prevalence of mutations with increasing age of the daughters. Among women aged 20 years or above, 63 carriers and 33 non-carriers were identified (p = 0.002).

Results were similar for each of the three groups of probands. Among the tested daughters of the unselected cases of breast cancer 18 mutations were observed (15 expected), among the daughters of the unselected cases of ovarian cancer 12 mutations were observed (nine expected), and among the daughters of the mothers referred to the genetics clinics 45 carriers were observed (37 expected).

Results were similar for the three mutations studied; among daughters of mothers with the 5382insC mutation 46 carriers were observed (36.5 expected); among daughters of mothers with the G61C mutation 16 mutations were observed (12 expected); and among daughters of mothers with the 4153delA mutation 13 mutations were observed (12 expected). For comparison purposes, we also tested 63 sons of the carrier mothers; 30 mutations were found (31.5 expected).

In summary, we observed a greater frequency than expected of carriers among daughters, but not among sons, of carriers of BRCA1 founder mutations in Poland. As a result, it was not possible to estimate the penetrance in these families by using the method of unaffected carriers. The reason for the surprisingly high observed frequency of carriers is not known, nor is it easy to explain the lack of decline in mutation prevalence with increasing age. If our results are due to a selective advantage for carriers then this
selection appears not to have been in operation for women born in the last 20 years. These data raise the possibility that the high frequency of founder \textit{BRCA1} mutations in Poland, and possibly in other populations may be due to a selective advantage to carriers. Future studies will extend these observations to other populations with founder effects.

Out data suggests that the selective advantage is restricted to females. If a female embryo carrying a \textit{BRCA1} mutation is more likely to survive to birth than a non-carrier female embryo, then carriers of \textit{BRCA1} mutations should have more daughters than sons. In support of this, among the children of the 57 probands unselected for family history, 73 were daughters and 53 were sons (p = 0.07). The lack of stillbirths and early deaths in this cohort suggests that any selective advantage must be operating very early \textit{in utero} or during gametogenesis, possibly during oocyte selection.

By studying only the unaffected offspring of carrier mothers we believe that we have limited possible biases in our study design. Fewer than 50% of unaffected first degree relatives are expected to carry the mutation. Results were similar for each of the \textit{BRCA} mutations and for each of the three groups of probands. Only women who were tested after the identification of the mutation in the mother were included.

In summary, we found that a greater number of daughters than expected inherited the deleterious \textit{BRCA1} allele. If confirmed, this finding has important implications both for genetic counselling and for the calculation of penetrance estimates using pedigree-based methods.

\textbf{Table 1} Mutation frequency by age among unaffected daughters of carrier mothers

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of carriers</th>
<th>Number of non-carriers</th>
<th>Proportion of carriers (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19</td>
<td>12</td>
<td>14</td>
<td>46</td>
<td>0.69</td>
</tr>
<tr>
<td>20–29</td>
<td>38</td>
<td>18</td>
<td>68</td>
<td>0.008</td>
</tr>
<tr>
<td>30–39</td>
<td>16</td>
<td>10</td>
<td>61.5</td>
<td>0.24</td>
</tr>
<tr>
<td>40–50</td>
<td>9</td>
<td>5</td>
<td>64</td>
<td>0.29</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>47</td>
<td>61.5</td>
<td>0.011</td>
</tr>
</tbody>
</table>

\textbf{REFERENCES}