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

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onstitutional 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 breast 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. At birth, it is expected that 50% of women with mutations will be affected by cancer by the age of 50 years, and over 80% of women with mutations is high; approximately 50% of women with mutations is expected to decline with age. Similarly, among unaffected women, the proportion of carriers is expected to decline with age. For example, if the gene is 50% penetrant by the age of 50 years, then one third of a sample of healthy 50 year old female offspring of carriers are expected to be carriers. Under the assumption that a mutant allele is transmitted to 50% of female offspring of carriers are expected to be carriers. Under the assumption that a mutant allele is transmitted to 50% of female offspring of carrier women, then the proportion of offspring expected to be carriers is transmitted to 50% of female offspring of 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 non-random in female offspring of BRCA1 carriers.

Key points

- 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 non-random in female offspring of BRCA1 carriers.

Three founder mutations in BRCA1 are common in Poland (5382insC, C61G, and 4153delA). In an attempt to estimate the age-specific penetrance of these three mutations, we systematically reviewed the genotypes of mothers and daughters in a selected group of 387 families from the Hereditary Cancer Center. The probands (mothers) were drawn from three sources: (a) 44 carrier probands were found in 490 consecutive cases of breast cancer diagnosed in women under 50 years of age; (b) 46 carrier probands were found in 347 consecutive ovarian cancer cases diagnosed at any age; and (c) 297 carrier probands were found among women with a family history of breast or ovarian cancer who were referred for genetic counseling. In these latter families, the proband refers to the individual who first received genetic testing in the family, and of the probands, 127 were affected with breast cancer, 35 were affected with ovarian cancer, 135 had neither form of cancer.

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 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 BRCA1 mutation is more likely to survive to birth than a non-carrier female embryo, then carriers of 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 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 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 BRCA1 allele. If confirmed, this finding has important implications both for genetic counselling and for the calculation of penetrance estimates using pedigree-based methods.

### 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>

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### REFERENCES
