Letter to the Editor

Assessment of the prevalence of de novo mutations in the BRCA1 and BRCA2 genes

To the Editor:

In the 16 years since the discovery of BRCA1 and BRCA2, only one de novo mutation in the BRCA1 gene and four de novo mutations in the BRCA2 gene have been reported in the literature (1–5). No systematic study of de novo mutation prevalence has been performed. This is surprising, given that the rates of de novo mutations can be as high as 30–50% for genes such as NF1, RET, and APC (6–8). We conducted the present study in an attempt to evaluate the prevalence of de novo mutations in BRCA1 and BRCA2 in a clinic-based cohort of women seeking risk assessment. To our knowledge, this study is the first to systematically approach this question.

Patients who would be most likely to carry de novo mutations in the BRCA1/2 genes were selected using the following criteria: (i) individuals with either a deleterious non-founder BRCA mutation or variant of uncertain clinical significance (VUCS) with either (a) both parents alive and not affected with breast, ovarian, pancreatic or prostate cancer or (b) one parent alive and the other deceased but with surgical tissue available, and (ii) no other family member shown to carry the mutation/VUCS. With appropriate consent, DNA from both parents was tested for the proband’s mutation. Paternity testing, if indicated, was performed using micro-satellite markers (Promega, Cat# DC6301and DC6071).

From 1996 to 2009, we identified 256 families at our institution carrying unique (non-founder) deleterious mutations or VUCS. Forty-five families met the selection criteria (Fig. 1). In the 18 eligible

Fig. 1. Summary of results for families studied to assess the prevalence of de novo mutations in the BRCA1 and BRCA2 genes.
families with deleterious mutations, we completed parental testing in 13 families and identified the proband’s mutation in one parent in 12 families. In the 13th family, the BRCA2 mutation was not found to be present in either mother or father (deceased). However, this mutation could not be confirmed as de novo because paternity could not be confirmed. Testing could not be completed in the remaining five families. In the 27 eligible families with VUCS, we were able to complete testing in 14 families. In 13 families, the VUCS was identified in one parent. The proband in the 14th family was found to be homozygous for the VUCS, which was subsequently identified in both parents. This family has reported consanguinity.

In conclusion, we found no confirmed de novo mutations in 27 families (0%, 95% CI: 0–13%). The major limitation of this study is the small sample size, further reduced by our inability to follow-up all families meeting our entry criteria despite extensive efforts to reach out to patients for participation in this study. This shows the inherent difficulty of determining the de novo mutation rate of a genetic syndrome that predisposes to only adult-onset disease. We also may have underestimated the de novo mutation rate in BRCA1 and BRCA2 by excluding families in which parents were affected with breast, ovarian, pancreatic or prostate cancer, relatively common cancers which may not denote the presence of a BRCA mutation. In addition, our clinic-based ascertainment generally excluded individuals without a family history, especially if they had later onset disease. This selection may have excluded cases more likely to carry a de novo mutation. However, we have tested over 1700 singleton breast or ovarian cancer cases at our institution, suggesting that our pool of possible de novo cases is quite deep. Nonetheless, our results suggest that de novo mutations in BRCA1 and BRCA2 are less common than in other hereditary cancer syndromes, although the apparent de novo prevalence in those syndromes may be artificially elevated if somatic mosaicism is not taken into account. Therefore, the prevalence of de novo mutations in these genes is unlikely to influence published estimates of penetrance.

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