

Electronic letter

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2157delG: a frequent mutation in *BRCA2* missed by PTT

Complete *BRCA1* and *BRCA2* mutation analysis is a time consuming and expensive process. Many laboratories have chosen to screen only those parts of the genes with a high yield of mutations: exons 2, 11, and 20 in *BRCA1* and exons 10 and 11 in *BRCA2*. While this may be a valid approach in optimising use of scarce resources, it is a somewhat self fulfilling prophesy on the location of most mutations. Furthermore, most institutions use the protein truncation test (PTT) to analyse the large exon 11 in both genes and exon 10 in *BRCA2*. PTT will not detect missense mutations (possibly a blessing given the difficulty in establishing their effect), but also mutations at the extreme of each exon will be missed, as they will not produce a recognisably different signal. Our initial strategy has been to screen all exons in both genes to offer a more complete gene screen, but also to ascertain whether any founder mutation exists in our local population. In *BRCA2*, we initially analysed 60 samples from affected subjects in families with four or more breast cancers diagnosed <60 years, and/or families containing male as well as female breast cancer, as well as a subset of 22 breast cancer cases aged <30 years with a family history of breast cancer. We undertook a combined approach of single strand conformation polymorphism (SSCP) for the smaller exons and each end of exons 10 and 11 and PTT of the two large exons. In these initial panels, we detected 15 truncating mutations (25%) of which three (5%) were in segment 11A on SSCP, but were not detected in segment 1 on PTT. On DNA sequencing, these were all found to be the result of a single base deletion (G) at position 2157. All three families contained early onset breast cancer cases with two containing a male breast cancer, one patient being diagnosed at <30 years. A further patient diagnosed aged 32 years with three affected relatives with breast cancer <40 years of age was sent to Myriad Genetic Laboratories Inc for full gene sequencing. She too was detected as having the 2157delG mutation. While samples from other families have been sent to Myriad, they did not meet the above criteria, although two families with breast and ovarian cancer have had different *BRCA2* mutations identified. This high detection rate of 2157delG prompted us to develop a PCR-ARMSTM test to screen a larger set of high risk families. We used this assay to test 46 families with four female breast cancers <60 years and 154 families with

three breast cancers <60 years. These families did not contain male breast cancer or ovarian cancer patients. The ARMSTM test detected three further 2157delG mutations which were confirmed on sequencing.

The overall detection rate was 1.5% for the sample set, but <8% (0-28%) of these families would be expected to harbour a *BRCA2* mutation.¹ Our data suggest that 10-20% of *BRCA2* mutations in the north west of England will be accounted for by a single mutation. 2157delG has been reported 10 times on the Breast Cancer Information Core database,² mainly by Myriad Genetics Inc (probably including one of our families), which undertakes whole gene sequencing. To our knowledge, the mutation has not been reported in a UK laboratory. This is probably because of the failure of most UK laboratories to undertake more than PTT for exon 11. We would strongly advise all UK laboratories (and those populations with migration from the UK, for example, North America) to screen for 2157delG, possibly as an initial screen for *BRCA2*. Our frequencies suggest that it will be more frequent than the exon 13 duplication in *BRCA1*,³ but not as frequent as the founder Jewish mutations in our own north west population⁴ or some other non-UK founder mutations in *BRCA2*.⁵ We are currently undertaking haplotype analysis to ascertain if 2157delG represents a significant founder mutation.

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- 1 Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BAJ, Gayther SA, Birch JM, Lindblom A, Stoppa-Lyonnet D, Bignon Y, Borg A, Hamann U, Haites N, Scott RJ, Maugard CM, Vasen H, Seitz S, Cannon-Albright LA, Schofield A, Zelada-Hedman M, the Breast Cancer Linkage Consortium. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. *Am J Hum Genet* 1998;62:676-89.
- 2 Breast Cancer Information Core. www.nhgri.nih.gov
- 3 The *BRCA1* Exon 13 Duplication Group. The exon 13 duplication in the *BRCA1* gene is a founder mutation present in geographically diverse populations. *Am J Hum Genet* 2000;67:207-12.
- 4 Laloo F, Cochrane S, Bulman B, Varley J, Elles R, Howell A, Evans DGR. An evaluation of common breast cancer mutations within a population of Ashkenazi Jews. *J Med Genet* 1998;35:10-12.
- 5 Arason A, Jonasdottir A, Barkardottir RB, Bergthorsson JT, Teare MD, Easton DF, Egilsson V. A population study of mutations and LOH at breast cancer gene loci in tumours from sister pairs: two recurrent mutations seem to account for all *BRCA1/BRCA2* linked breast cancer in Iceland. *J Med Genet* 1998;35:446-9.