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Short Communication

BRCA1 promoter deletions in young women with breast cancer and a strong family history: A population-based study

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ABSTRACT

Women diagnosed with breast cancer before the age of 40 years who have a strong family history of breast and/or ovarian cancer were selected from an Australian population-based case-control-family study for large deletion screening within the *BRCA1* promoter. Deletions within the *BRCA1* promoter region are usually not detected by the methods applied in routine clinical mutation detection strategies. Fifty-one of the 66 women (77%) who met our inclusion criteria were tested for promoter deletions using linkage disequilibrium analysis of two *BRCA1* polymorphic sites (C/G1802 and Pro871Leu) and multiplex ligation-dependent probe amplification. Two cases of *BRCA1* promoter deletion involving exons 1A-2 and exons 1A-23 were detected. The morphology of the breast cancers arising in these women with *BRCA1* promoter deletions was consistent with the morphology associated with other germline *BRCA1* mutations. Large genomic deletions that involve the promoter regions of *BRCA1* make up 20% (2/10) of all known *BRCA1* mutations in this group of young women with a strong family history of breast and ovarian cancer. Our data support the inclusion of testing for large genomic alterations in the *BRCA1* promoter region in routine clinical mutation detection within *BRCA1*.

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1. Introduction

Large genomic alterations within *BRCA1* are now known to represent a non-trivial proportion of deleterious, clinically relevant, *BRCA1* mutations. Early studies of genomic alterations reported several large deletions, many with evidence of founder effects (for example, Ref. [1]), but the molecular methods were laborious, technically challenging and usually required a large amount of genomic DNA. More recently, Hogervorst et al.[2] described a multiplex ligation-dependent probe amplification (MLPA) test to identify large genomic alterations in *BRCA1*. This methodology is easily applied to

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genomic DNA and larger scale screening for genomic alterations in *BRCA1*.

As it is the site of transcription initiation, a genetic mutation within the promoter could potentially disrupt normal expression of the *BRCA1* protein. The 5′ end of *BRCA1* lies head to head with the *NBR2* gene (Next to BRCA1 gene 2) and the two genes share a bi-directional promoter that is capable of transcription in both directions. Two promoter sites, α and β, exist for *BRCA1* resulting in the transcription of alternate mRNA transcripts with varying first exons (1A or 1B).[3,4] The relevance of mutation screening within the *BRCA1* promoter has also been demonstrated. In a family known to be *BRCA1*-linked and to lack the *BRCA1* transcript from the allele associated with disease susceptibility, Swensen et al.[5] identified a 14 kb deletion in *BRCA1* that removed exons 1A, 1B and 2. Brown et al.[6] using a method described by Catteau et al.[7] that utilised the strong linkage disequilibrium identified between the two *BRCA1* variants, C1802G and C2731T (Pro871Leu), reported a large genomic deletion in the 5′ region of *BRCA1* that included *NBR2*, ψ*BRCA1* and *NBR1* in an Australian multiple-case breast cancer family.[6,7]

The proportion of women with breast cancer, especially young women, whose cancers are attributable to deletions within the promoter region of *BRCA1* is currently unknown. Although methods vary between laboratories and services, deletions within the *BRCA1* promoter region are usually not detected by the methods applied in the majority of routine clinical mutation detection strategies. To quantitate this proportion, we identified 66 women from our Australian population-based case-control-family study of breast cancer who were diagnosed with breast cancer before the age of 40 years and had a strong family history of breast and/or ovarian cancer (two or more first- or second-degree relatives affected with breast and/or ovarian cancer). Previous mutation screening performed on the germline DNA of these 66 cases had included screening within *BRCA1*, *BRCA2* and *ATM* using a variety of mutation detection techniques.[8,9] This identified that 15 (23%) of these 66 cases have detectable *BRCA1* ($n = 8$), *BRCA2* ($n = 6$) or specific ATM ($n = 1$)[9] mutations. The study was approved by the ethics committees of The University of Melbourne and The Cancer Council Victoria.

2. Materials

2.1. The Australian breast cancer family registry

The Australian breast cancer family registry (ABCFR) includes a population-based, case-control-family study of breast cancer (in which cases, control subjects and their relatives were administered the same questionnaire) with an emphasis on early-onset disease that was carried out in Melbourne and Sydney, Australia.[10–12] Sixty-six women were identified within the ABCFR to be diagnosed with breast cancer before the age of 40 years and to have a strong family history of breast and/or ovarian cancer (two or more first- or second-degree relatives affected with breast and/or ovarian cancer). Previous mutation screening performed on the germline DNA of these 66 cases had included screening within *BRCA1*, *BRCA2* and *ATM* using a variety of mutation detection techniques.[8,9] This identified that 15 (23%) of these 66 cases have detectable *BRCA1* ($n = 8$), *BRCA2* ($n = 6$) or specific *ATM* ($n = 1$)[9] mutations, Table 1. The study was approved by the ethics committees of The University of Melbourne and The Cancer Council Victoria.

3. Methods

3.1. Promoter deletion screening

Genotyping for *BRCA1* variants, C1802G (β-promoter, GenBank Accession No. U37574), and C2731T (Pro871Leu, exon 11, U14680), was performed for 51/66 women who met our criteria (Table 1) using the method described by Catteau et al.[7]

Table 1 – Proband cancer family history

Families	Affecteds[a]	Cancers[b]	Breast cancers	Ovarian cancers	Mutation carriers[c]
6	3	3	3 (1 male)	0	
1	3	3	2	1	
2	3	3	2	1	
1	3	3	2	1	
29	3	3	3	0	3 BRCA1, 1 BRCA2, 1 ATM
1	3	4	3	1	1 BRCA1
1	3	4	4	0	1 BRCA2
15	4	4	4	0	3 BRCA1, 2 BRCA2
2	4	4	3	1	1 BRCA2, 1 CHEK2
1	4	4	2	2	
2	4	5	4	1	
2	4	5	5	0	1 BRCA1, 1 BRCA2
1	5	5	5	0	
1	6	7	7	0	
1	6	6	6	0	

a Total number of family members affected with breast or ovarian cancer (including proband and their first- and second-degree relatives).
b Total number of cancers in proband and first- and second-degree relatives.
c Number of *BRCA1*, *BRCA2*, *ATM* and *CHEK2* mutation carriers identified previously.[8,14,15]

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