Hidden Dangers: A Cryptic Exon Disrupts BRCA2 mRNA

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The first mutation that disrupts BRCA2 mRNA by including a novel, cryptic exon is reported in this issue. The mutation lies deep within an intron and would not have been detected by conventional screening methods. In the future, more mutations may be discovered by direct mRNA analysis. Clin Cancer Res; 18(18); 4865–7. ©2012 AACR.

In this issue of Clinical Cancer Research, Anczuków and colleagues report the first deep intronic BRCA2 mutation resulting in cryptic exon inclusion, the first such mutation to be found in either the BRCA1 or BRCA2 breast/ovarian tumor suppressor genes (1). Germline mutations in BRCA1 or BRCA2 (collectively BRCA1/2) predict generally high (but highly variable) lifetime risks of breast or ovarian cancer (2, 3). Given a positive BRCA1/2 mutation test result, presymptomatic interventions include intensive surveillance or prophylactic surgeries to remove healthy breasts and ovaries. Patients who already have breast or ovarian cancer, along with significant personal or family history of familial breast/ovarian cancer, may seek BRCA1/2 mutation testing, as positive results may inform treatment options and provide potentially life-saving information to family members (4). Thus, genetic testing for germline BRCA1/2 mutations is an important component of comprehensive breast/ovarian cancer care, and biologically informed mutation detection methods are critical to this effort. Conventional genetic testing involves germline sequence analysis of BRCA1/2 exons and flanking intron–exon boundaries, along with molecular assays for some large-scale BRCA1/2 genomic rearrangements. Anczuków and colleagues (1) provide an example of a functionally oriented mutation detection assay that revealed a mutation that would have been missed by more conventional methods. Specifically, they identified a BRCA2 splicing defect caused by inclusion of a cryptic exon, resulting from a deep intronic base change. This work illustrates a practical complement to older mutation detection methods, yet it is only used routinely by a handful of laboratories.

The authors further speculate on the interesting idea that the deleterious cryptic exon could be a target for antisense oligonucleotide therapy. Using their minigene system, they showed that an oligonucleotide spanning the 5′ promoter mutations, mutations in 5′ untranslated exons, and deletions in the first intron of BRCA2 are not recognized as deleterious even when they are detected. Thus, the authors further speculate on the interesting idea that the deleterious cryptic exon could be a target for antisense oligonucleotide therapy. Using their minigene system, they showed that an oligonucleotide spanning the 5′ promoter mutations, mutations in 5′ untranslated exons, and deletions in the first intron of BRCA2 are not recognized as deleterious even when they are detected.
In the current article, the authors make use of bioinformatics tools developed for splice site predictions (11) have successfully contributed to identification of novel cryptic exons in dystrophy research (12). Although bioinformatics may make increasingly powerful predictions about splicing defects in the future, such predictions will always require molecular testing. Also, as the number of rare mutant alleles of BRCA1 and BRCA2 and other cancer susceptibility genes grows, the need for creative methods for assessing the mutation status in individual families and their clinical significance becomes more pressing.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interests were disclosed.

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