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Editorial: BRCA1 and BRCA2 gene mutations screening in sporadic breast cancer patients in Kazakhstan

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Editorial

While the majority of breast cancer cases are sporadic, up to 30% have been described as familial. Hereditary breast cancer, accounting for approximately 10% of breast cancer cases, has classically been associated with highly penetrant gene mutations that are highly likely to cause cancer, vertical transmission, autosomal dominant inheritance pattern, association with other cancers, and early age of onset.[1-5] In contrast, these characteristics are often not exhibited in familial breast cancers. Therefore, although familial breast cancers occur more in an individual family than in the general population, they are thought to be due to a complex interaction between lower penetrance genes and environmental factors and/or random intra-familial sporadic cancer cases.[3-5]

In 1994, inherited mutations in BRCA1 and BRCA2 genes that encode for tumor suppressor proteins were linked to hereditary breast and ovarian cancer.[6,7] Since this groundbreaking scientific discovery, much has been learned about genetic risk of breast cancer (such as newer detection techniques with improved sensitivity to detect BRCA1 and BRCA2 large genomic rearrangements);[8] however, many BRCA-related questions remain unanswered. The prevalence of known deleterious BRCA1 and BRCA2 gene mutations is approximately 1 in 400 individuals.[9] Due to variable penetrance, the probability of cancer development varies amongst BRCA mutation carriers, (even amongst carriers in families with the same mutation),[10] but in general, BRCA deleterious mutations confer a 45-84% lifetime risk for breast cancer.[11] It is, therefore, not surprising that known deleterious BRCA mutations are variable across different ethnic and geographic populations. Moreover, founder mutations have been identified within Ashkenzi Jewish, Icelandic, and other populations.

When discussing BRCA1 and BRCA2 sequence variants, the terminology can be difficult to discern. Variations that confer increased cancer risk are termed "deleterious mutations," but a number of other changes in BRCA1 and BRCA2 are rapidly emerging, the significance of which are less clear. It is important, therefore, to use consistent language when discussing such findings. Mutations and polymorphisms are both sequence variants. The term "mutation" signifies any rare deviation in the DNA sequence of a gene from the normal wild type. Polymorphisms, on the other hand, are common variations in DNA that are generally considered to occur with a frequency greater than 1%.[12] If a polymorphism is known to be disease-causing, then it will typically be referred to as a deleterious mutation, although most, but not all, deleterious mutations are seen at a lower frequency in the population. Polymorphisms include, but are not limited to: single nucleotide polymorphisms (SNPs), insertions, deletions, or repeated sequences. SNPs are the most common type of polymorphism accounting for approximately 90% of all human genetic variation.[13] Most SNPs are benign or neutral polymorphisms with no known clinical impact;

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however, it is thought that some may provide useful clinical information, such as likelihood of developing disease, response to disease, and perhaps implications for treatment.[14]

Polymorphisms and mutations can be further classified as synonymous or non-synonymous based on their impact on the resulting amino acid. A synonymous substitution results in a codon that does not lead to a change in the coded amino acid, whereas non-synonymous substitutions, such as missense mutations, do result in an amino acid change. Lastly, variants of uncertain significance (VUS) are novel DNA changes with unknown effects on protein function and disease risk. Pending further investigation, an identified VUS could be reclassified as a deleterious mutation or a polymorphism of no clinical significance in the future.[15]

In the current publication, Akilzhanova and colleagues examine the role of BRCA1 and 2 mutations in Kazakhstan women with sporadic breast cancer. They studied genomic DNA from 156 sporadic breast cancer cases (defined as women without family history of affected first- or second- degree relatives with breast and/or ovarian cancer) and 112 controls (matched on age and ethnicity) from two different areas in Kazakhstan. Ultimately, mutational screening of BRCA1 and BRCA2 coding regions for these patients and controls identified 22 distinct variants (16 missense mutations of unknown clinical significance and 6 polymorphisms). No deleterious BRCA1 or 2 mutations were identified. There were significantly more variants in the Caucasians versus the Asian breast cancer cases and more variants in the Asian versus the Caucasian controls. They also found a number of women (79 of 156, 71%) who carried 4-6 alterations. This makes these alterations in the BRCA sequence much less likely to be deleterious, particularly if they were the same sequence variants that they termed "likely neutral polymorphisms," (those that were expressed at a high frequency in both cases and controls).

Models incorporating variables from cancer history of patients as well as multiple other factors into logistic regression analyses potentially have the ability to segregate uncertain BRCA1 and BRCA2 variants into deleterious and non-deleterious categories.[16-22] These models work best when there are enough occurrences of a single variant amongst unrelated families to help aid in its classification. We are still limited in finding ways to classify variants that occur rarely in a specific region.[23]

Several resources exist for obtaining information regarding previously identified VUS and SNPs including: the SNP Consortium,[24] the dbSNP database from the National Center for Biotechnology Information (NCBI), the Breast Cancer Information Core (BIC) (http://research.nhgri.nih.gov/bic/), and HGVbase (Human Genome Variation Database), which is a human gene-based polymorphism database. Due to the difficulty in screening the literature in order to determine whether a specific variant of uncertain significance has been classified, reporting variants to such large comprehensive databases of BRCA1 and 2 genes is critically important. Additionally, there is an ENIGMA consortium that has been established to evaluate the significance of uncertain variants in high-risk breast cancer genes. The success of this group can only be achieved by collecting genetic and clinical information, functional assays, and mRNA expression and splicing assays.[23]

Via computational approaches, functional assay data has been shown to correlate well with pathogenicity of BRCA1 variants of uncertain significance.[25] A guide for functional analysis of BRCA1 variants of uncertain significance has recently been published.[26] Additionally, a five-tiered classification scheme for DNA sequence variants and correlation of clinical recommendation with probability that any given alteration is deleterious has been developed based on the posterior probability model,

with Class 1 and 2 being not likely pathogenic, class 3 remaining a true VUS, and Class 4 and 5 considered pathogenic/deleterious for clinical purposes.[27,28] As an example, the authors of the current publication found a BRCA1 amino acid variant of Pro871Leu, which is listed as Class 1, likely not pathogenic,[28] which is consistent with the fact that it was found in about half of their total population, both in cases and controls.

In conclusion, despite major advances in our BRCA testing, in many instances we are still in a very elementary stage in applying such information clinically toward the care of patients. It is only through collaboration that the rapidly developing field of molecular genetics will lead to advances in patient care.

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