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Editorial

Clinical significance of variants of unknown significances in *BRCA* genes

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Previous studies have shown that up to 15% of *BRCA* gene testing in index cases of high-risk families identifies one or more variants of uncertain significance (VUSs) in the absence of any pathogenic variants [1]. The reported prevalence of VUSs in *BRCA* is 21.6% to 24.6% in patients with ovarian cancer in Korea [2-4]. The more genetic tests performed for a wide spectrum of genes beyond the *BRCA* gene, the more VUSs will be detected as genetic testing is covered by public insurance in Korea.

VUSs include predominantly 1) missense variations, or small in-frame deletions, whose effect on the protein structure cannot be inferred; 2) variants, both exonic and intronic, that may affect pre-mRNA splicing, even though no direct evidence is available; and 3) variants in regulatory sequences [1]. Pathogenic or likely pathogenic variants (i.e., mutations) increase individual predisposition to a certain disease or cancer, which comprise frameshift or nonsense mutations that lead to premature termination (i.e., protein truncation). Meanwhile change in an amino acid residue caused by a VUS is conserved in the corresponding protein. Therefore, a VUS may not lead to premature termination of a protein. Hence, classification of a VUS as pathogenic or benign has proven problematic. It is not clear whether such subtle changes are likely to alter the function of the protein sufficiently to predispose to cancer.

Recent several researches are used in the analysis of VUSs with the aim of providing evidence for their pathogenicity; 1) multifactorial prediction models (based on case-control studies, family history of cancer, co-segregation, co-occurrence, and loss of heterozygosity), 2) in vitro assays, and 3) in silico tools [1,5]. Several VUSs, including c.5339T>C in *BRCA1* [4,6,7], c.5096G>A in *BRCA1* [8], and several missense variants [9] have been reported to change its meaning to likely pathogenic. However, these changes in pathogenecity are very limited and considerable data should be accumulated and reported.

Therefore, VUSs represent a clinical burden in carriers and their families, as the pathogenic role is not easy to determine. Counseling of families is also problematic, since the result of genetic testing cannot provide tailored strategies for prevention and surveillance. In this sense, carriers and their families should be managed under the following basic principle; 'VUSs should be treated as a negative test result, and risk assessment should be based purely on family history' as described in the recently published article by Chern et al. [10] 'The

influence of *BRCA* variants of unknown significance on cancer risk management decision-making' in the *Journal of Gynecologic Oncology*. The study notably reported that risk-reducing salpingo-oophorectomy (RRSO), which should not be recommended for women with average risk of breast and ovarian cancer, was performed in 25% (25/99) of those with a VUS, despite above mentioned basic principle. It is caused by several bias that most patients with VUSs are Ashkenazi-Jewish descent (76%), have a personal history of breast cancer (79%), have a family history of breast cancer or ovarian cancer, and also patients' 'cancerphobia'.

Efforts are needed to clearly determine and understand the pathogenicity of VUSs at present using; 1) multifactorial prediction models that include co-segregation test for family members with known cancers, 2) periodic re-classification of VUSs, and 3) other genetic test beyond *BRCA* gene. In addition, physicians will have to do careful management with the principal based on that 'VUSs should be treated as a negative test result, and risk assessment should be based on family history' while waiting for more evidence to accumulate.

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