# ABC system used as an add-on to clarify germline variants previously classified as VUS according to ACMG guidelines

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The increasing number of patients screened by NGS to identify germline variants associated with hereditary breast/ovarian cancer (HBOC) syndromes, is leading to a growing number of variants classified as Variants of Uncertain Significance (VUS) according to ACMG guidelines[1]. Since the ACMG system merges functional and clinical data into a one-dimensional system, it is not always clear how the classification was obtained. The ABC system (ABCs) of variant classification[2] splits functional and clinical grading and aims to give a better guide to variant significance. The main goals of this work were i) to apply the ABCs to a group of previously classified ACMG-VUS and ii) to evaluate the potential clinical impact of this review/classification.
Germline variants (36 - 29 missense, 1 synonymous and 6 intronic) detected in 5 genes (*BRCA1*, *BRCA2, ATM*, *CHEK2*, *PALB2*) previously classified as ACMG-VUS, were selected from our database of patients with HBOC, to be reclassified with the ABCs. Variant assessment included: query of clinical and population databases, literature and in silico tools (VEP, HSF, Alamut, Varsome).
Eleven variants were classified as Class 0 (functional - fVUS); 17 as class E (functional - HFE (Hypothetical Function Effect), and 8 as Class D (functional - LFE (Likely Functional Effect). fVUS are not clinically graded.
Considering that ACMG-VUS are not actionable, it is still an ongoing debate if they should be reported or not. Since the ACMG merges functional and clinical data, it might be difficult for clinicians to understand how VUS classification is achieved. The ABCs allowed us to distinguish between VUS classified due to lack of data from those that might have a functional impact. Class 0 variants (11) should not be reported and class E (17) reporting is optional. The use of ABCs highlighted 8 variants (class D) which might be a susceptibility factor with functional impact and should be reported. Functional and segregation studies are of major importance to clarify the clinical significance of these variants.
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