Letter to the Editor

CHEK2 1157T - Pluto Among Numerous Low-Risk Genetic Factors Requiring Discharge From a Range of Pathogenic Variants?

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic1 provide substantial groundwork for specialist practice in diverse fields: medical oncology, genetic counseling, and even laboratory genetics. With respect to CHEK2 variant carriers, NCCN Guidelines state that “The risks for most missense variants are unclear but for some pathogenic/likely pathogenic (P/LP) variants, such as Ile157Thr, the risk for breast cancer (BC) appears to be lower [than for frameshift pathogenic/likely pathogenic variants]. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.” This implies that CHEK2 p.Ile157Thr variant is considered by the NCCN Guidelines panel members to be classified as P/LP, and should be reported for risk management (contrary to variants classified as benign/likely benign [B/LB]).

Without speculations on variant classification in accordance with American College of Medical Genetics and Genomics/Sherloc guidelines,2,3 we may state that, first, this variant may be considered as a rare polymorphism (minor allele frequency [MAF] based on ExAC project 0.40%; in comparison: highest MAF across BRCA1/2 P/LP variants at 0.026% [ExAC] for BRCA2 p.Ser1982fs and the second highest MAF at 0.0067% [ExAC] for BRCA2 p.Cys61Gly, which are 16 times and 60 times higher than MAF for the CHEK2 p.Ile157Thr variant, respectively). Second, risk for BC associated with this variant appears to be low (as noted by current NCCN Guidelines, odds ratio [OR] for BC, 1.58; 95% CI, 1.42–1.79).4,5 These put this variant in line with other rare polymorphisms, which, despite B/LB classification (as of majority of CLINVAR submissions), may convey increased risk for BC (though significantly lower, compared with P/LP variants of the same gene). For example, BRCA2 p.Lys3326Ter - ExAC MAF, 0.70%; OR for BC, 1.53; 95% CI, 1.00–2.34)6 in another study OR for estrogen receptor-negative BC, 1.46; 95% CI, 1.2–1.70%; BRCA2 p.Lys2729Asn - ExAC MAF, 0.082%; OR for BC, 1.41; 95% CI, 1.12–1.78; and BRCA2 p.Gly2508Ser - ExAC MAF, 0.01%; OR for BC, 2.6; 95% CI, 1.44–4.78, contrary to known P/LP BRCA2 variants: OR for BC, 5.23; 95% CI, 4.09–6.77.7 Even with a similar risk for BC caused by CHEK2 p.Ile157Thr, these BRCA2 variants may be missed in genetic test reports due to B/LB classification. Furthermore, it should be noted that according to the latest research, the risk for BC associated with CHEK2 p.Ile157Thr appears to be lower than mentioned in current NCCN Guidelines (OR, 1.28; 95% CI, 1.17–1.39).10

Despite further research being required for fine-tuning associated risks in diverse populations, current NCCN Guidelines seem to support discrepancy in incorporating such low-risk variants in risk management. The CHEK2 p.Ile157Thr variant appears to be a cornerstone of such discrepancy, although its importance in genetic counseling is overestimated in comparison with other CHEK2 (p.Arg180Gly)11 and non-CHEK2 hypomorphic variants, and presumably biased by legacy practice. Despite statistical significance, low clinical significance calls into question its classification as P/LP. It would be reasonable to consider it as a risk factor among other low-risk genetic factors (eg, other hypomorphic variants, protective variants, polygenic risk scores), although this would require more complex models for risk assessment. For now it seems doubtful to consider this variant as P/LP and incorporate it in risk management disregarding other low-risk genetic factors. We hope this growing evidence will engage consensus guidelines to solve discrepancy in classification, reporting and management of such lower risk variants.

1Maxim Ivanov, PhD1,2,7;
Margarita Sharova, MD1,4;
Andrea Olsen1;
Alexandra Lebedeva, MSC3;
Ekaterina Ignatova, MD, PhD1,4,5;
Gerald Mouse1; and
Vladislav Mileiko1

1Atlas Oncodiagnostics, LLC, Moscow, Russia;
2Department of Oncogenetics, Ministry of Health of the Russian Federation, Moscow, Russia; and
3Department of Oncogenetics, Institute of Higher and Additional Professional Education, Research Centre for Medical Genetics, Moscow, Russia
4Email: maksim.v.ivanov@phystech.edu

References