Letter to the Editor

CHEK2 I157T - 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, 1.42–1.75).⁴ These put this variant in line with other rare polymorphisms, which, despite B/LB classification (as of majority of CLINVAR submissions), may confer 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, 1.00–2.34⁵ (in another study OR for estrogen receptor-negative BC, 1.46; 95% CI, 1.2–1.70⁶); *BRCA2* p.Lys2729Asn - ExAC MAF, 0.082%; OR for BC, 1.41; 95% CI, 1.12–1.78⁷; and *BRCA2* p.Gly2508Ser - ExAC MAF, 0.01%; OR for BC, 2.6; 95% CI, 1.44–4.78,⁸ contrary to known P/LP *BRCA2* variants: OR for BC, 5.23; 95% CI, 4.09–6.77.⁹ 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.Arg180Cys¹¹) 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.

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References

- Daly MB, Pal T, Berry MP, et al. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021. Accessed August 27, 2021. To view the most recent version, visit NCCN.org
- Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–424.
- Nykamp K, Anderson M, Powers M, et al. Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. *Genet Med* 2017;19:1105–1117.
- Han FF, Guo CL, Liu LH. The effect of *CHEK2* variant I157T on cancer susceptibility: evidence from a meta-analysis. *DNA Cell Biol* 2013;32:329–335.
- Thompson ER, Goringe KL, Rowley SM, et al. Reevaluation of the *BRCA2* truncating allele c.9976A>T (p.Lys3326Ter) in a familial breast cancer context. *Sci Rep* 2015;5:14800.
- Meeks HD, Song H, Michailidou K, et al. *BRCA2* polymorphic stop codon K3326X and the risk of breast, prostate, and ovarian cancers. *J Natl Cancer Inst* 2015;108:djv315.
- Shimelis H, Mesman RLS, Von Nicolai C, et al. *BRCA2* hypomorphic missense variants confer moderate risks of breast cancer. *Cancer Res* 2017;77:2789–2799.
- Han MR, Zheng W, Cai Q, et al. Evaluating genetic variants associated with breast cancer risk in high and moderate-penetrance genes in Asians. *Carcinogenesis* 2017;38:511–518.
- Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med* 2021;384:440–451.
- Yang Y, Shu X, Shu XO, et al. Re-evaluating genetic variants identified in candidate gene studies of breast cancer risk using data from nearly 280,000 women of Asian and European ancestry. *EBioMedicine* 2019;48:203–211.
- Southey MC, Goldgar DE, Winquist R, et al. PALB2, *CHEK2* and ATM rare variants and cancer risk: data from COGS. *J Med Genet* 2016;53:800–811.