Guidance on clinical management of CHEK2 pathogenic variants and cancer risks

July 25 2023

Cases illustrating CHEK2 testing in practice. CHEK2 case #2 is a 35-year-old female who was originally diagnosed at age 33 years with stage 2 breast cancer,
at which time testing ordered by her oncologist included only BRCA1/2, with no P/LP variants identified. She was subsequently diagnosed with metastases to bone at age 35, at which time tumor testing was undertaken and identified a CHEK2 c.1100del pathogenic variant. BRCA1/2 testing was already covered through insurance, but additional germline testing for CHEK2 was declined for coverage by her insurer. The individual's father subsequently proceeded with germline testing and was identified to have the same CHEK2 c.1100del pathogenic variant. Discussion points are as follows. (1) the patient is young for a CHEK2-related breast cancer. (2) tumor sequencing may help clarify whether a CHEK2 variant is implicated in tumorigenesis in specific cancers. (3) a known common variant, such as CHEK2 c.1100del, uncovered in tumor sequencing can be presumed to be germline but still merits confirmation. Credit: Genetics in Medicine (2023). DOI: 10.1016/j.gim.2023.100870

An international workgroup of genetics and cancer experts convened by the American College of Medical Genetics and Genomics (ACMG) has published a highly anticipated and detailed clinical practice resource on CHEK2 pathogenic variants: "Management of Individuals with Germline Pathogenic/Likely Pathogenic Variants in CHEK2: a Clinical Practice Resource of the American College of Medical Genetics and Genomics."

A person with a pathogenic variant in the CHEK2 gene may be at an increased risk for developing breast and other cancers. This ACMG Clinical Practice Resource, published in ACMG's flagship journal, Genetics in Medicine, provides valuable information for health care professionals caring for individuals with pathogenic variants in the CHEK2 gene.

ACMG President Susan Klugman, MD, FACMG, FACOG, said, "This is an important resource for this moderate risk cancer predisposition gene and discusses risk influencers including family history, specific variant and genetic and nongenetic factors. This resource will clearly
have a worldwide impact for those taking care of cancer patients and patients who are predisposed to cancer because of their CHEK2 variant status."

The new ACMG practice resource points out that while CHEK2 has largely been considered a "moderate risk" breast cancer gene, the distinction is blurred with risk being on a continuum, ranging from low to moderate to high risk. It states that the association of cancer risk with CHEK2 variants is also complex and is influenced by a number of factors including the specific variant, family history, non-CHEK2 genetic background and other factors.

Therefore, personalized (rather than generalized) risk must be assessed by a specialist in cancer genetics and take into account family and personal history, the specific variant(s) and other risk factors. Early cancer detection, surveillance, prevention and clinical decisions should then be guided by these personalized risk estimates and shared decision making. Seeking consultation with a health care professional with expertise in cancer genetics and genetic counseling is recommended.

Lead author Helen Hanson, MD, said, "The association of CHEK2 with breast cancer predisposition has been recognized for many years, and a potential role for CHEK2 in predisposition of many other cancers has been described, but more difficult to establish."

"Coupled with the complexity of differing risk estimates depending on the population studied, genotype and the impact of modifying factors, it has proved challenging for clinicians to know how best to treat individuals with CHEK2 pathogenic or likely pathogenic variants in clinical practice. In developing this resource, we sought to make practical guidance based on current high-quality peer-reviewed evidence and input from an international team of specialists in cancer genetics to help guide clinical practice in this complex area."
Senior author Douglas Stewart, MD, FACMG, described the difficulty of developing this comprehensive resource, "Clinically, pathogenic germline variants in CHEK2 are a major challenge for three main reasons: 1) the gene is featured on many cancer panels, so there is a large volume of testing done; 2) CHEK2 pathogenic variants are common in many populations; and 3) for many cancers, the degree of CHEK2-associated risk is uncertain or unknown."

"For this paper, we gathered an international team of experts and, informed by the latest literature, developed, we hope, a practical way forward to best help patients with pathogenic CHEK2."

The international work group convened by the ACMG performed a comprehensive review of the evidence in peer-reviewed journals in order to guide clinicians in the surveillance, treatment and management of CHEK2 heterozygotes. The new ACMG Clinical Practice Resource also addresses knowledge gaps and needed future work.


Provided by American College of Medical Genetics and Genomics


This document is subject to copyright. Apart from any fair dealing for the purpose of private