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COMMENT

Index case identification and outcomes of cascade testing in high-risk breast and colorectal cancer predisposition genes

Malak Abedalthagafi [1]✉

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Approximately 10% of cancers are attributed to inherited genetic alterations. Genes in which germline mutations result in an increased risk of cancer are classified as cancer predisposition genes (CPGs). The contribution of CPGs varies according to gender, age of onset, cancer types, and ethnicity. Despite extensive research on this complex subject, there remain knowledge gaps in our understanding of genetic predisposition to cancer. The true value of the knowledge gained from the discovery of CPGs lies in its application in genetic testing of families and individuals with a history of CPGs. There remains an unmet need for larger, well-designed population- and family-based studies in diverse populations, to enable quantification of reliable risk estimates for the purpose of counseling. Currently, more than 100 CPGs have been discovered and advancements in gene sequencing technologies are expected to unravel more CPG discoveries in future. In addition, the rapid and cost-effective analysis of DNA sequencing will enable early diagnosis and substantially increase the clinical testing of CPGs. In this issue, Woodward et al. [1] present the 30-year outcomes of cascade testing in high-risk breast and colorectal CPGs conducted at the Manchester Centre for Genomic Medicine (MCGM), covering a diverse population of around 5 million in the North West of England.

It is known that approximately 5–10% of breast cancer cases involve single-gene mutations, which can be passed down in the family. These include the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes [1]. Germline *BRCA* mutations are associated with most hereditary breast cancer cases and women with *BRCA* mutations have a 55–70% risk of breast cancer by the age 70, with a corresponding lifetime risk of 12% [2]. On the other hand, pathogenic germline variants in genes associated with high cancer risk have been implicated in 2–8% of all colorectal cancers [3]. The authors describe the evolution of CPG testing since its initiation in the early 1990s. The methodology involves screening of genetic registers for the numbers of diagnostic and subsequent family cascade tests (positive and negative), and year of testing. The authors have limited their investigations to 15 high-risk CPGs associated with breast and gastro-intestinal tract cancers and included: *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *TP53*, *APC*, *BMPR1a*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *SMAD4*, *STK11*, and *MUTYH*. The research describes the variants of the BRCA1, BRCA2, and mismatch repair CPGs as the most common of all CPG variants, likely reflecting the higher rates of breast cancer in the UK, when compared to the colorectal or endometrial cancers. The study acknowledges that their data showed overall more BRCA1 than BRCA2 index cases and attribute this to the increased penetrance of BRCA1 as compared with BRCA2 despite BRCA2 alterations being more common in the population. It must be noted that the differences in population sampling methodology (i.e., between clinic-based and population-based) may yield disparate estimates of penetrance (e.g., for major cancer susceptibility genes) and therefore requires a stratified analysis.

The genetic testing for CPGs started in with the *TP53* in 1990 after it was identified as the causative of Li-Fraumeni Syndrome. This was followed by *APC* in 1993, *BRCA1* in 1994, and *BRCA2*, *MLH1*, and *MSH2* in 1996. The authors describe that the latest CPG to be included in clinical diagnostic testing in the MCGM was *PALB2* in 2016, only after later studies confirmed its role as a high-risk breast cancer CPG, despite being identified as causative of hereditary breast cancer in 2007. Across the 15 CPGs and 30 years of testing data, the authors have shown that each index-case diagnosis attained leads to an average of three cascade tests within a family, with approximately 1.5 family members testing positive for the index-case CPG variant. The authors acknowledge that it may be difficult to ascertain the exact index-case detection rate as their data are primarily extracted from the registry, where they did not have complete access to all diagnostic testing. Furthermore, index-case detection rates may not provide a true picture for each gene, as some genes, for example PALB2, have been included in the panel only since 2016.

Identification of a CPG variant in an index-case facilitates management strategies such as decisions around the extent of surgical management or targeted therapeutic strategies. It also defines the cancer prevention and early detection strategies in at-risk family members. Cascade screening also reassures non-carrier relatives, excluding them from intensive surveillance and at the same time, contributing to the cost-effectiveness of genetic testing for a wider population.

The primary limitation of this study is the quality and quantity of the clinical history information collected through the registry. It is understood that as the costs of DNA sequencing decline, gene-panel testing, and whole-exome and whole-genome sequencing, will become widespread. While rating the utility of a combination of variants can be accommodated by the index, attributing utility to one variant over another will be challenging. Population-based studies may strengthen our understanding of the precise prevalence of rearrangements in minority ethnic populations.

[1]Department of Genomics Research, Saudi Genome Program, King Fahad Medical City and King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia.
✉email: malthagafi@kacst.edu.sa

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The data presented in the manuscript include intragenic variants and (multi) exon copy number variations. With on-going advances in genetic technologies, it is likely that further families will be identified with alternate means of CPG disruption, for example, those affecting regulatory regions or large structural variants. More recent research has confirmed the role of de novo mutations in CPGs as a cause of cancer, especially in relatively young individuals without a family history. As an example, ~7% of germline mutations in the TP53 gene in individuals with Li-Fraumeni syndrome are known to occur de novo [4]. Furthermore, in case of breast cancers, recent study has shown mosaicism for a *BRCA2* mutation as an underlying cause of early-onset breast cancer [5]. Identification of de novo mutations as the cause of disease may be used to provide a prognosis based on data from other patients with similar mutations and information on the treatment options for the development and application of personalized therapeutic interventions.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Malak Abedalthagafi.