COMMENTARY

CDH1 on Multigene Panel Testing: Look Before You Leap

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Abstract

Multigene panel testing (MGPT) has become a critical component of cancer risk assessment in clinical practice. As technology and access improve and costs decrease, more individuals than ever are undergoing MGPT for genetic evaluation. One gene that deserves special consideration when included on MGPT is CDH1, which codes for the cell-cell adhesion protein E-cadherin. Pathogenic and likely pathogenic germline variants in CDH1 have been associated with hereditary diffuse gastric cancer syndrome, and in highly penetrant families, testing for these variants is critical for proper risk management. However, recent data demonstrated that gastric cancer penetrance in unselected CDH1 carriers may be lower than expected. Further complicating matters are the lack of effective screening strategies for gastric cancer and recommendation for risk-reducing total gastrectomy in CDH1 carriers. Therefore, the discovery of an unexpected pathogenic or likely pathogenic CDH1 variant on multigene panel testing, when testing for CDH1 would not normally be considered based on personal or family history alone, creates dilemmas for both patients and providers. In this commentary, we highlight the potential for unexpected CDH1 variants on MGPT, outline the uncertainties associated with these variants, and emphasize the importance of pretest counseling regarding the potential for an unexpected CDH1 variant. Although CDH1 testing is often important for clinical decision-making, individuals and providers need to be aware of the potential for an unexpected CDH1 variant when CDH1 is included on MGPT for cancer risk assessment.

With the advent of next-generation sequencing technologies, multigene panel testing (MGPT) is used increasingly for cancer risk assessment. MGPT allows for timely sequencing of multiple cancer susceptibility genes, is cost effective (1,2), and leads to incremental genetic findings (3–5). However, challenges remain to using MGPT for cancer risk assessment, including the incidental discovery of pathogenic or likely pathogenic germline variants in unexpected cancer risk genes, especially when testing for these genes would not otherwise be considered based on personal or family history. Given the increasing size of multigene panels, finding variants in these unexpected genes is inevitable and will continue to increase in frequency as MGPT is broadly used clinically and through direct-to-consumer marketing and testing. Managing cancer risk in individuals with unexpected genetic variants can prove extremely challenging for both clinicians and patients, especially when there is no personal or family history consistent with the cancer risk gene’s expected phenotype. These difficulties are compounded when patients do not receive appropriate genetic counseling about the potential for unexpected genetic findings before testing is performed. In our experience, this situation can lead to surprise and dissatisfaction on the patient’s part about the risks, uncertainties, recommended risk-reduction strategies, and familial implications of the newly identified unexpected gene variant.

Illustrating these challenges is the CDH1 gene, which codes for the protein E-cadherin. Pathogenic and likely pathogenic germline variants in CDH1 have been classically associated with hereditary diffuse gastric cancer (HDGC) syndrome, which carries a gastric cancer risk of up to approximately 70% in men and approximately 56% in women by age 80 years (6). Guidelines published by the International Gastric Cancer Linkage Consortium provide criteria to identify individuals who are candidates for CDH1 testing (7). However, given the association of CDH1 with lobular breast cancer (8) (but not invasive ductal cancer) as well as potentially with colon cancer (9), CDH1 is now included on many commonly ordered, cancer-focused multigene panels. Of note though, lobular breast cancer accounts for only 10% of breast cancer cases, and CDH1 mutations are uncommon.
in individuals with lobular breast cancer without a family history of gastric cancer (10). Unfortunately, there is currently no proven effective gastric cancer screening strategy for CDH1 carriers; thus, all individuals found to have pathogenic or likely pathogenic variants in CDH1 are counseled regarding and usually recommended to undergo risk-reducing total gastrectomy. Therefore, the discovery of an unexpected CDH1 variant on MGP7 in the absence of a family history of gastric cancer can create a conundrum for both clinicians and patients alike, and these challenging situations are being increasingly encountered in practice (11).

Case of an Unexpected CDH1 Variant

As an example, consider the case of a 43-year-old woman who was referred to our program to discuss her MGP7 results. Genetic testing was performed outside our institution given concern for Lynch syndrome based on the patient’s family history of cancer (Figure 1). Specifically, her mother developed uterine cancer at age 46 years and pancreatic cancer at age 52 years, and her maternal aunt was diagnosed with colon cancer at age 60 years. Her father had prostate cancer at age 75 years, and she had no other second-degree relatives with cancer. Although the patient did not receive any specific counseling about CDH1, she underwent a 28-gene multigene panel that included CDH1 and was found to carry a likely pathogenic CDH1 variant, c.1566-2A>G. This variant had not been previously reported in the literature nor seen in any variant-tracking databases; however, CDH1 variants affecting other areas of this particular splice site were reported as pathogenic or likely pathogenic (c.1565+1G>A, c.1566-1G>C, etc) (12). Upper endoscopy and endoscopic ultrasound were both normal, and after extensive counseling our patient decided to proceed with total gastrectomy, which revealed two microscopic (<0.15 cm) foci of signet ring cell carcinoma (SRCC) and no positive lymph nodes. The patient’s sister (age 50 years) and daughter (age 23 years), who both also tested positive for the CDH1 variant, elected to undergo total gastrectomy after extensive counseling; however, both gastrectomy specimens were benign with no foci of SRCC identified despite extensive pathologic examination. Additionally, her niece and father (age 82 years with no history of gastric cancer) were both found to carry the CDH1 variant; however, at this time neither has proceeded with gastrectomy.

This case highlights several important points regarding unexpected CDH1 variants. First, based on the family history alone, which did not meet HDGC syndrome testing criteria, there would be no clear indication to perform CDH1 testing in this family, thus making this CDH1 variant truly unexpected. Second, this CDH1 variant had not been previously reported and may potentially be a lower penetrance variant; therefore, the absolute gastric cancer risk in this family is uncertain. Third, the lack of pretest counseling left this family in an unexpected situation, fraught with emotional and physical ramifications for all involved family members, as well as difficult decisions regarding whether to pursue risk-reducing total gastrectomy.

Uncertainties Associated With CDH1 Variants

Despite extensive research in the field, considerable uncertainties remain regarding CDH1 variants and their management. First, the magnitude of the gastric cancer risk for individuals with CDH1 variants who lack a family history of gastric cancer remains uncertain (11,13). In early reports, pathogenic and likely pathogenic germline CDH1 variants were shown to be clearly associated with increased risk for diffuse gastric cancer, particularly in families meeting clinical criteria for HDGC syndrome, and all CDH1 carriers had a personal or family history of diffuse gastric cancer (6,14). However, more recent studies have shown a lower gastric cancer risk (15,16), and it is likely that even the most current risk estimates for diffuse gastric cancer in CDH1 carriers still overestimate risk given the selection bias related to the inclusion of families with highly penetrant disease.

Second is the uncertainty regarding the cancer risk of specific CDH1 variants, that is, genotype-phenotype correlation. Recent work investigated whether type and location of a CDH1 variant may help stratify cancer risk (17). However, at this time there is no validated genotype-phenotype correlation that helps guide management of CDH1 families (18). Additionally, whether CDH1 families lacking diffuse gastric cancer have low-to-moderate penetrance CDH1 variants or whether other CDH1-independent genetic or environmental factors contribute to this lower penetrance is currently unclear. Furthermore, there are additional challenges for newly discovered variants without literature precedent as well as the slight possibility that a likely pathogenic CDH1 variant may in fact be incorrectly classified. Per the American College of Medical Genetics and Association of Molecular Pathology guidelines, a likely pathogenic variant carries a 90–99% probability of being pathogenic; however, this leaves up to 1 in 10 likely pathogenic variants that may not be classified correctly (19). This highlights that although the current variant classification guidelines are extremely useful in Mendelian genes that govern rare disorders, they can be difficult to apply to cancer predisposition genes, especially those with an uncertain phenotype and multifactorial etiology. This may be particularly problematic in families without gastric cancer where a likely pathogenic CDH1 variant is discovered. Ultimately, these uncertainties highlight the importance of trying to integrate all available data, including personal and family history, to quantify an affected individual’s specific cancer risk. In practice this may not be happening, as a recent study showed that for those individuals with a pathogenic variant in CDH1, the recommendation for prophylactic gastrectomy was not influenced by family history (20).

Third, there is limited understanding of the factors that promote progression of small foci of SRCC to diffuse gastric cancer in CDH1 carriers. Interestingly, the majority of CDH1 carriers will harbor foci of SRCC in their stomachs, often decades earlier than the average age of diffuse gastric cancer development (21). However, what factors ultimately lead one or more of these foci of SRCC to progress to diffuse gastric cancer remains unknown. This is especially challenging for individuals with unexpected CDH1 variants with a possible low-to-moderate penetrance phenotype, because it is unclear if and when any of these foci of SRCC will ever progress to fulminant diffuse gastric cancer. Although guidelines recommend gastrectomy in the 20s for individuals with a pathogenic or likely pathogenic CDH1 variant, this may not be the optimal timing for all CDH1 carriers.

Finally, uncertainty remains in cancer risk management for CDH1 carriers, especially those with an unexpectedly found pathogenic or likely pathogenic CDH1 variant with no family history of gastric cancer. Although breast magnetic resonance imaging and discussion about the option of preventative mastectomy is recommended based on the increased risk of lobular breast cancer, unfortunately at this time there are no
proven methods for effective gastric cancer screening for this population, primarily because of the difficulty in detecting early-onset diffuse gastric cancer and its precursor foci of SRCC (22). If screening is pursued in a CDH1 carrier, annual upper endoscopy with Cambridge protocol biopsies is recommended (7); however, studies have failed to show that endoscopic screening can reliably detect foci of SRCC (23), even with the use of advanced endoscopic imaging techniques such as chromoendoscopy (24) and endoscopic ultrasound (25). Annual endoscopic screening also uses substantial health-care resources while having no evidence that it can decrease incidence of, or mortality from, diffuse gastric cancer in CDH1 carriers. Thus, with no effective screening strategy available, the only option for cancer risk reduction is risk-reducing total gastrectomy. Total gastrectomy is associated with increased perioperative risk as well as long-term morbidity, with symptoms including dumping syndrome and weight loss, as well as nutritional and metabolic complications, including nutrient deficiencies and deterioration of bone health (21,26). Physical symptoms that persist after a total gastrectomy can also lead to reduced long-term quality of life (27). If reliable screening was available that could properly identify individuals at the highest risk of developing diffuse gastric cancer and thus those most likely to benefit from total gastrectomy, it would provide individuals with unexpected CDH1 variants with a more reasonable alternative for cancer risk management and lessen concern over discovery of an unexpected CDH1 variant. Although many cancer risk genes are included on the American College of Medical Genetics’s most recent list of 59 genes that should be reported as incidental or secondary findings, it is notable that CDH1 is absent from this list (28). The absence is likely due to the uncertainties outlined above, including the lack of effective screening available for CDH1 carriers.

Pretest Counseling and Inclusion of CDH1 on MGPT

Genetic testing for cancer susceptibility can be associated with psychosocial stress (29). However, in families meeting criteria for HDGC syndrome, testing for CDH1 is important because it can provide critical guidance to help ensure that proper risk reducing strategies are used in those at risk. However, in individuals without personal or family histories concerning for HDGC syndrome

Figure 1. Pedigree illustrating a family with an unexpected CDH1 variant. SRCC = signet ring cell carcinoma.
who may have CDH1 testing performed as part of a larger MGPT, it is imperative that individuals undergo pretest genetic counseling given the numerous uncertainties with CDH1 penetrance and management as outlined above. Specifically, pretest counseling for CDH1 should address the uncertainties in the biology of SRC2 foci and their potential and/or lack of potential to progress to diffuse gastric cancer, the lack of effective screening methods for diffuse gastric cancer, and the near global recommendation for a risk-reducing total gastrectomy as the only option for reducing gastric cancer risk when a pathogenic or likely pathogenic CDH1 variant is discovered. Furthermore, pretest counseling should also address how these uncertainties would have implications not only for the individual undergoing genetic testing but also for the individual’s family members. In our experience, some individuals who undergo MGPT without pretest counseling and who are then found to have an unexpected CDH1 variant express regret about receiving the testing results given the implications for themselves and their family, as well as potentially wishing that genetic testing had not been performed in the first place. At a minimum, these individuals wish they had affirmatively chosen to proceed with CDH1 testing.

In the age of MGPT, where numerous genes may be tested quickly and at low cost, we believe that CDH1 should be singled out during pretest genetic counseling and the sequela of finding a CDH1 mutation should be addressed with all individuals undergoing CDH1 testing. This is especially important when finding a CDH1 variant would be inconsistent with the family’s cancer phenotype. This process will ensure that all individuals undergoing CDH1 testing are aware of the implications of a positive finding for themselves as well as their families. Furthermore, if after extensive pretest genetic counseling, individuals want to proceed with MGPT for cancer risk assessment but do not want to undergo CDH1 testing, then the option to send MGPT without inclusion of CDH1 should be offered by the provider, regardless of how broad or cancer specific the intended panel is. Although as medical professionals we often strive to obtain the most information, in the case of genetic testing for CDH1, especially in the absence of a history of gastric cancer, we must provide patients with the appropriate autonomy to direct and feel comfortable with this part of their medical care.

In summary, pathogenic germline variants in CDH1 are responsible for statistically significant gastric and lobular breast cancer risk. However, differing cancer risks among CDH1 carriers remain poorly understood, which will require continued study through longitudinal follow-up and enrollment of affected families in research registries. Although discovery of a pathogenic likely pathogenic CDH1 variant is invaluable for risk stratification and management in families with HDGC syndrome, whether CDH1 is similarly useful in families when it is discovered unexpectedly is currently unclear. Given the limited gastric cancer risk-reduction strategies in CDH1 carriers as well as our evolving understanding about cancer risk associated with this gene, it is important for CDH1 testing to be performed responsibly by providing providers, with appropriate pretest genetic counseling, to ensure that individuals undergoing CDH1 testing know exactly what they may be leaping into.

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10. Schrader KA, Masciarei S, Boyd N, et al. Germline mutations in CDH1 who may have testing performed as part of a larger MGPT, then the option to send MGPT without inclusion of CDH1 should be offered by the provider, regardless of how broad or cancer specific the intended panel is. Although as medical professionals we often strive to obtain the most information, in the case of genetic testing for CDH1, especially in the absence of a history of gastric cancer, we must provide patients with the appropriate autonomy to direct and feel comfortable with this part of their medical care.

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