

Colorectal cancer patients with BRCA1 and BRCA2 mutations:

Preparing for unexpected results

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Abstract

Background: A new paradigm in genetic panel testing for hereditary colorectal cancer (CRC) has emerged. CRC association with BRCA1/2 has been suggested, but guidelines do not include CRC in Hereditary Breast and Ovarian Cancer syndrome (HBOC).

Objectives: We describe 6 patients with CRC and germline mutations in BRCA1 or BRCA2, detected by multi-gene panels, to highlight actionable findings that would have been missed by traditional CRC genetic testing.

Design/Method: 585 patients with a personal history of CRC and/or gastrointestinal (GI) polyps were tested. Variants were identified using an NGS-based cancer gene panel with CRC genes and BRCA1 and BRCA2 (henceforth referred to as BRCA). Germline variants were classified using a point-based system based on ACMG guidelines. Clinical histories from test request forms were de-identified for analysis.

Results: Hereditary cancer panel testing found Pathogenic (P) or Likely Pathogenic (LP) variants in 92 of 585 (15%) patients. Of the 92 mutation carriers, 69 (75%) had a P/LP variant in a known CRC gene (APC, MUTYH, MLH1, MSH2, MSH6, EPCAM, or PMS2), consistent with the indication, while 6 (6%) had a P/LP variant in BRCA1 or BRCA2. None of the patients with BRCA mutations reported Ashkenazi Jewish ancestry. The 4 male patients did not meet HBOC testing guidelines.

Conclusions: In this series, a substantial proportion of P/LP variants were in non-canonical CRC genes. BRCA pathogenic variants' prevalence in the general population is insufficiently elevated to account for these findings. More research is needed to link CRC and BRCA, and clinicians need to prepare themselves and their patients to deal with unexpected, actionable results.

Background

Next-generation sequencing (NGS) allows clinicians to test the known high-penetrance genes associated with CRC, or conversely, use more comprehensive panels of 30+ cancer genes, for roughly the same cost. In this case series, we describe 6 patients who presented with CRC (two of whom were early onset). None of these patients met NCCN testing criteria for Hereditary Breast and Ovarian Cancer (HBOC) syndrome, yet in each case, a multi-gene panel detected a mutation in BRCA1 or BRCA2.

Association of CRC with pathogenic variants in BRCA has been suggested (but not extensively demonstrated) and current guidelines do not include CRC as part of the phenotypic spectrum of HBOC syndrome. Nevertheless, these findings in BRCA were actionable and would have been missed by targeted colon cancer panels. We present this case series to highlight the need for clinicians to prepare for the possibility of unexpected results.

Objectives

To describe the presence of P/LPs variants in non-CRC genes identified in patients diagnosed with CRC, and discuss the ramifications of clinical management that would not otherwise be offered to CRC patients had they been identified to carry P/LP variants in canonical CRC genes, or simply fit diagnostic criteria for Lynch (HNPCC).

Design/Method

Our study included 585 consecutive patients with a personal history of CRC and/or gastrointestinal (GI) polyps as the test indication, referred for panel testing at Invitae. Genomic DNA variants were identified using an NGS-based hereditary cancer panel including known CRC genes and BRCA1 and BRCA2. Germline sequence variants and deletions/duplications were classified using a point-based system that closely adheres to ACMG guidelines. Patients' personal and family histories were obtained from test request forms and were de-identified for this analysis.

Results

Hereditary cancer panel testing (using a total of 29 cancer genes) found a Likely Pathogenic (LP) or Pathogenic (P) variant in 92 of 585 (15%) patients. Of the 92 mutation carriers, 69 (75%) had a P/LP variant in a known CRC gene (APC, MUTYH, MLH1, MSH2, MSH6, EPCAM, or PMS2), consistent with the indication, while 6 (6%) had a P/LP variant in BRCA1 or BRCA2. None of the patients with BRCA mutations (2 females and 4 males), reported Ashkenazi Jewish ancestry. Of the 6 patients, 2 males had early onset colorectal cancer, and none of the 4 males had a clinical or family history that meets current testing guidelines for HBOC syndrome (see Figures 1 and 2).

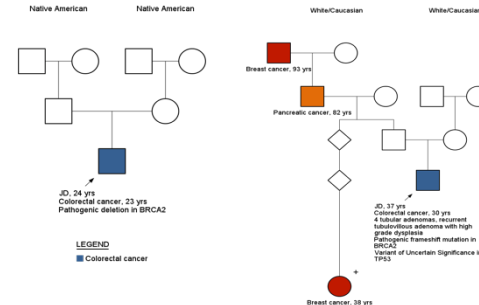


Figure 1. Male diagnosed at 23 years of age with colorectal cancer; BRCA2 mutation detected by 34 gene panel.

Figure 2. Male diagnosed at 30 years of age with colon cancer; BRCA2 mutation detected by 34 gene panel.

Of note, one of the male patients was tested for germline BRCA2 mutations as follow-up to tumor profile testing performed on colon tissue (see Figure 3). His personal and family history was not suggestive of HBOC syndrome.

Of the female patients, one presented with adenomatous colon polyps and stomach polyps, and had one first degree relative with early onset, bilateral breast cancer. Similarly, the second female patient presented with colon polyps but with no reported history of HBOC-related cancers.

Results (cont.)

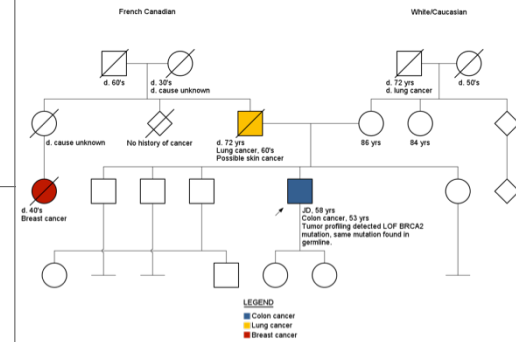


Figure 3. Male diagnosed at 53 years of age after tumor profiling revealed BRCA2 mutation.

Conclusions

In this series of patients with an indication of CRC and/or GI polyps, 24 (25%) of P/LP variants identified were in non-canonical CRC genes and, of those, 6 cases (25%) had mutations in BRCA1 in the absence of other P/LP variants.

The prevalence of BRCA pathogenic variants in the general population (1/300 to 1/800) is not sufficiently elevated to account for these findings. And thus, although the sample is not large, the findings cannot be explained by prevalence data.

Importantly, colon-specific panel testing would have been negative in these 6 individuals, and as such important preventive and risk-reducing procedures (according to NCCN guidelines) would not have been discussed with these patients.

As the phenotype of classical cancer syndromes is expanded by broad panel-based testing, it is crucial to identify and track those families that fall outside the traditional diagnostic criteria, and as such provide a novel paradigm for identifying not only the cause of cancer otherwise unexplained by routine testing, but also allow for improved prevention and risk reducing measures to be undertaken.

More research is needed to understand the relationship between BRCA and CRC, and clinicians need to prepare themselves and their patients to deal with unexpected, actionable results in genes not typically associated with CRC.