Case series of colorectal cancer patients with BRCA1/2 mutations: Finding actionable genes in patients with atypical presentations

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Background

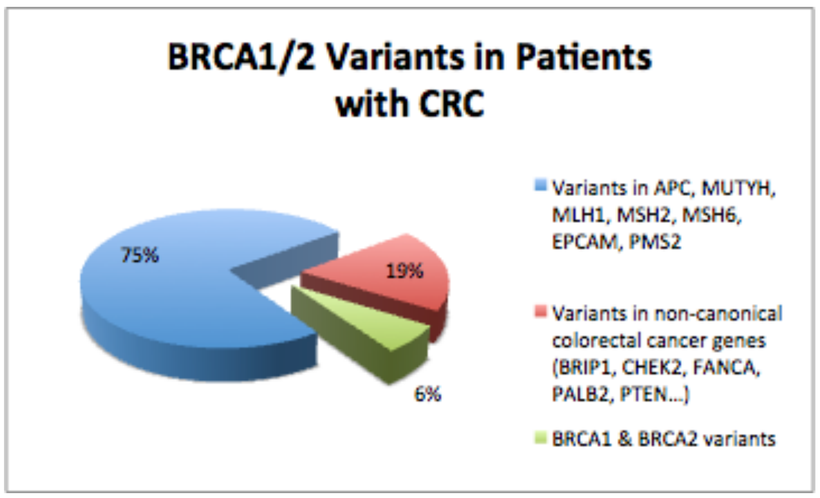
A new paradigm is emerging in genetic testing for hereditary colorectal cancer (CRC) risk. With next-generation sequencing (NGS), clinicians can choose to test 7 high-penetrance genes associated with CRC or more comprehensive panels of 30+ cancer genes for roughly the same cost. In this case series, we describe 6 patients who had unclear or overlapping features of different hereditary cancer syndromes, some of whom did not meet NCCN testing guidelines for a specific syndrome. In each case, a gene panel detected a mutation in BRCA1 or BRCA2. Association of CRC with pathogenic variants in BRCA1/2 has been suggested, but not yet extensively demonstrated. Nevertheless, these findings in BRCA1/2 were actionable and would be missed by narrowly targeted testing.

Methods

Our study included 585 consecutive patients with an indication of CRC and/or gastrointestinal (GI) polyps, referred for panel testing at Invitae. Genomic DNA variants were identified using up to a 34-gene NGS-based hereditary cancer panel; the clinician's discretion determined panel size. 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 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 high-penetrance CRC gene (APC, MUTYH, MLH1, MSH2, MSH6, EPCAM, or PMS2), consistent with the indication for testing, while 6 (6%) had an P/LP variant in BRCA1 or BRCA2.



Results (cont.)

None of the patients with BRCA mutations reported Ashkenazi Jewish ancestry. Of the 6 patients, one female and two males had a clinical or family history that meets current testing guidelines for hereditary breast and ovarian cancer (HBOC) syndrome. The remaining three patients did not have a family history suggestive of any specific hereditary cancer syndrome.

Case	Age at Dx	Indication for Testing	Germline Mutation[1]	Panel Ordered	Fam Hx of HBOC Cancers	Met NCCN Guidelines for HBOC testing
1 ♀	61	Colon polyps; Fam hx CRC	BRCA1	Custom[2]	Sister with Br Ca x2 (37yrs and 50 yrs)	Yes
2 ♂	23	Colon cancer	BRCA2	HCS[3]	None known	No
3 ♂	30	Rectal cancer, tubular adenomas x4	BRCA2	HCS	First cousin once removed with Br Ca in 30s; Male Br Ca in fam	Yes
4 ♂	58	Colon cancer	BRCA2	Custom	First cousin with br ca in 40's; Paternal GM Br Ca in 30s	Yes
5 ♀	34	Colorectal polyps	BRCA1	HCS	None reported	No
6 ♂	69	Adenocar-cinoma of GE junction at 55; colon polyps	BRCA1	HCS	Sister -melanoma at 26 yrs and Br Ca at 40 yrs	No

[1]All patients tested negative for APC, MUTYH, MLH1, MSH2, MSH6, PMS2, and EPCAM
[2]Custom panel = Hereditary Colon Cancer (14 genes) + BRCA1/2
[3]Hereditary Cancer Syndromes (HCS) panel (29-34 genes), including BRCA1/2

Family history information was limited for case 2, a 23-year-old male with CRC and a pathogenic BRCA2 variant. The pedigree below shows there was no known history of cancer (see Figure 1). Traditional testing for high-penetrance CRC genes would have missed the BRCA2 finding.

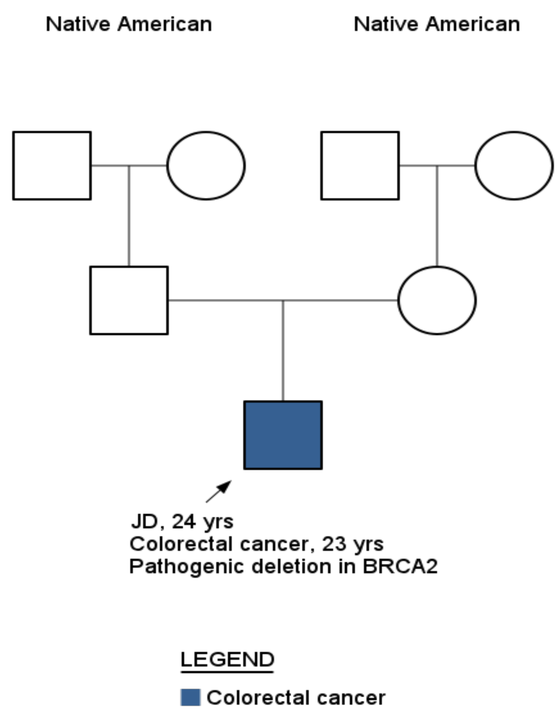


Figure 1. Male diagnosed at 23 years of age with colorectal cancer; BRCA2 mutation detected by Hereditary Cancer Syndromes panel.

Results (cont.)

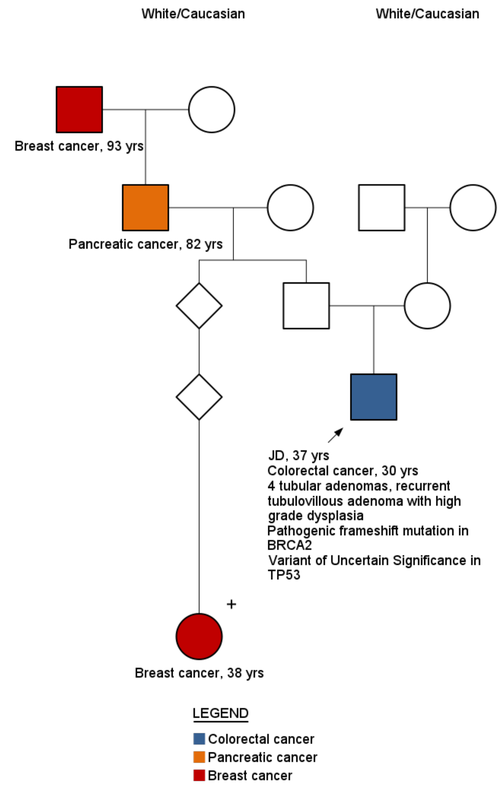


Figure 2. Male diagnosed at 30 years of age with colon cancer; BRCA2 mutation detected by Hereditary Cancer Syndromes panel.

Case 3 reported a history of 4 tubular adenomas, recurrent tubulovillous adenoma with high grade dysplasia and CRC. A pathogenic BRCA2 variant was identified. The pedigree shows the family history was remarkable for a paternal female cousin once removed with breast cancer at 38 years of age and a paternal great-grandfather with breast cancer at 93 (see Figure 2). Case 3 meets NCCN testing criteria based on the presence of male breast cancer in a third-degree relative, which was uncovered by a detailed FH that served as a guide for broader panel testing.

Conclusions

- **BRCA variants are present in CRC patients without evidence of HBOC**
- **Broad panels find actionable mutations that might be missed by targeted panels**
- **Detailed FH is a valuable guide for broader testing**
- **Multi-gene approach is useful for complex/limited FH**

While more research is needed to understand the relationship between BRCA1/2 and colon cancer, physicians need to be prepared to deal with actionable BRCA1/2 results, as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (v 2.2015). HBOC syndrome may be present in patients with CRC, particularly in those patients with atypical presentations.