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-penetration 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 no known history of cancer (see Figure 1). The remaining three patients did not have a family history suggestive of any specific hereditary cancer syndrome.

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 as pathogenic or likely pathogenic (LP) variant in 92 of 585 (15%) patients. Of the 92 mutation carriers, 59 (66%) had a P/LP variant in a high-penetration CRC gene (APC, MUTYH, MLH1, MSH2, MSH6, EPCAM, or PMS2), consistent with a family history of CRC.

Results (cont.)

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-penetration CRC genes would have missed the BRCA2 finding.

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%) were positive for a P/LP variant in a high-penetration CRC gene (APC, MUTYH, MLH1, MSH2, MSH6, EPCAM, or PMS2), consistent with the indication for testing, while 6 (6%) had a P/LP variant in BRCA1 or BRCA2.

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.