PATHOGENIC MUTATIONS IDENTIFIED IN PATIENTS WITH 6 OR MORE COLON POLYPS

Kim Grace, MS, CGC[1]; Brandie Leach, MS, LCGC[2]; John Kidd, MS[1]; Jennifer Saam, MS, CGC, PhD[1]; Johnathan Lancaster, MD, PhD[1]

1) Myriad Genetic Laboratories, Inc., Salt Lake City, UT 2) Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH

HYPOTHESIS / PURPOSE

- Testing individuals at risk for hereditary colorectal cancer has traditionally posed a challenge for clinicians.
- Personal and family histories do not always meet testing guidelines, even when the history appears suggestive to a clinician. Criteria may also be met for multiple syndromes.
- This analysis reviewed results from a hereditary cancer panel test to determine whether polyp count might have predicted genetic diagnosis.

METHODS

- Pathogenic variants (PVs), as identified by a 25-gene hereditary cancer panel, were noted for all patients for whom a minimum of six polyps had been documented.
- PVs are any variant that received a laboratory classification of Deleterious or Suspected Deleterious.
- All clinical information was obtained by health care provider report on the test request form.
- The polyp count, personal, and family cancer history were reviewed for each patient.
- Patients with PVs in Lynch syndrome genes were also reviewed using strict Amsterdam II and Bethesda criteria, which did not include ovarian cancer for Amsterdam criteria or allow testing of unaffected relatives.
- The panel included *BRAC1, BRAC2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A (p16INK4A* and *p14ARF), CDK4, TP53, PTEN, STK11, CDH1, BMPR1A, SMAD4, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD51C*, and *RAD51D*.

RESULTS

- 190/1,378 (13.8%) patients with ≥6 polyps were found to carry PVs.
- The majority of the PVs were identified in *APC* (35.0%) and *MUTYH* (8.6%) (Table 1).
  - 9/86 (10.5%) patients with a PV in *APC* or *MUTYH* had <20 polyps (Figure 1).
- 33/190 (17.4%) patients with a PV were identified as having a mutation in one of the Lynch syndrome genes.
  - 11/33 (33.3%) had ≥20 polyps (Figure 1).
  - 14/33 (42.4%) met Revised Bethesda criteria.
  - 9/33 (27.3%) met Amsterdam II criteria.
  - 17/33 (51.5%) did not meet criteria for either.
- 14 patients had mutations in other polyposis genes (*STK11*, *PTEN*, *SMAD4*, *BMPR1A*).
- 62/190 patients had mutations in genes historically not associated with colon cancer (Table 1).
  - *BRCA2* (17) was the most common in this group followed by *CHEK2* (10).
- The majority of patients with PVs in *BRCA1*, *BRCA2*, and *CHEK2* had a personal or family history of breast and/or ovarian cancer (Table 2).

TABLE 1. *Mutation Distribution in Patients with ≥ 6 Polyps*

Gene	COUNT
APC	69 (35.0%)
Biallelic *MUTYH*	17 (8.6%)
APC AND *MUTYH* TOTAL	86 (43.7%)
MLH1	8 (4.1%)
MSH2	9 (4.6%)
MSH6	8 (4.1%)
PMS2	7 (3.6%)
EPCAM	1(0.5%)
LYNCH SYNDROME TOTAL	33 (16.8%)
STK11	6 (3.0%)
SMAD4	4 (2.0%)
PTEN	3 (1.5%)
BMPR1A	1 (0.5%)
OTHER POLYPOSIS GENES TOTAL	14 (7.1%)
BRCA1	8 (4.1%)
BRCA2	17 (8.6%)
BRCA1/2 TOTAL	25 (12.7%)
ATM	9 (4.6%)
BARD1	1 (0.5%)
BRIP1	4 (2.0%)
CHEK2	10 (5.1%)
NBN	6 (3.0%)
CDKN2A (p16INK4A)	1 (0.5%)
PALB2	4 (2.0%)
RAD51C	2 (1.0%)
TP53	2 (1.0%)
OTHER GENES TOTAL	39 (19.8%)

60 patients identified as having a monoallelic *MUTYH* mutation and 10 patients identified as having a *APC* I1307K mutation were not included.
7 patients with two PVs were included, for a total of 197 PVs.

FIGURE 1. *Polyp Count by Mutation Type*

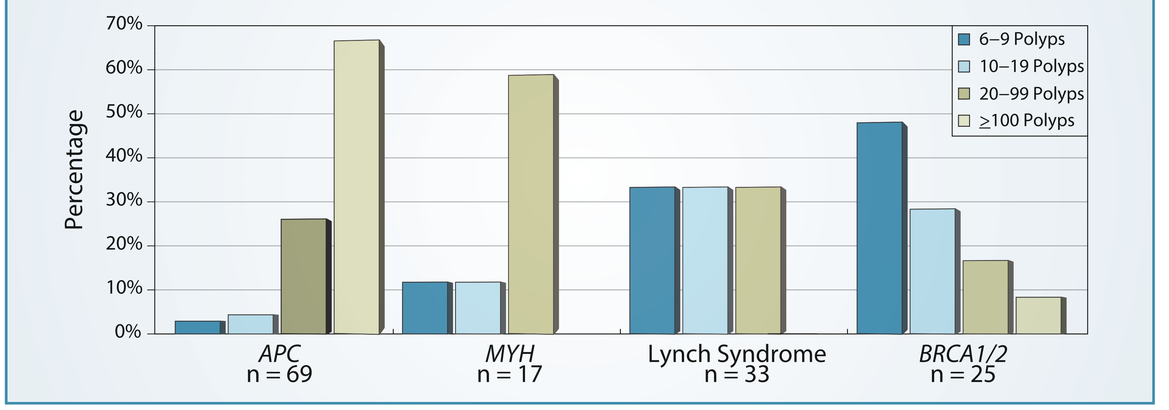

TABLE 2. *Personal and Family History*

Mutation	N	≥20 Polyps	Personal History of Breast or Ovarian Cancer	Family History of Breast or Ovarian Cancer*	Does not Meet NCCN Guidelines for HBOC
BRCA1	8	1 (12.5%)	4 (50.0%)	8 (100%)	1 (12.5%)
BRCA2	17	5 (29.4%)	12 (70.6%)	10 (58.8%)	4 (23.5%)
CHEK2	10	3 (30.0%)	4 (40.0%)	7 (70.0%)	4 (40.0%)

* ≥1 first- or second-degree relative with breast or ovarian cancer

CONCLUSIONS

- For patients with ≥6 colon polyps, testing with a 25-gene panel resulted in a 121% increase in patients identified as having a PV, compared to *APC* and *MUTYH* testing alone.
- A multi-gene cancer panel enables a practitioner to assess for multiple syndromes with a single analysis.
- Although a thorough personal and family history are very important when selecting hereditary cancer testing among patients at risk for colon cancer syndromes, this sample of patients with polyposis illustrates an advantage of a multi-gene cancer panel since polyp count may not indicate the single most appropriate hereditary colon cancer test.

REFERENCES

- Provenzale D, et al. NCCN Clinical Practice Guidelines in Oncology® Genetic/Familial High-Risk Assessment: Colorectal. V 1.2015. May 04. Available at http://www.nccn.org

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