OVERLAPPING PHENOTYPES WITH AFAP AND FAP IN PATIENTS WITH LYNCH SYNDROME GENE MUTATIONS

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BACKGROUND

- Lynch syndrome is a well-described cause of hereditary colon cancer. Amsterdam II criteria, which provides a clinical diagnosis of Lynch syndrome, excludes familial adenomatous polyposis (FAP).[1]
- FAP is caused by mutations in the *APC* gene and is defined as the presence of 100+ adenomas. The attenuated form of familial adenomatous polyposis (AFAP) can be considered when an individual has 10-99 adenomas.[2]
- While adenomatous polyps may be a part of the Lynch syndrome phenotype (as a precursor to carcinoma), the assumption is that Lynch syndrome and *APC*-associated polyposis do not have overlapping phenotypes.[3]
- This study aimed to determine the adenoma number in patients with Lynch syndrome, and whether there is a potential overlap in adenoma phenotype with FAP/AFAP.
- Overlapping phenotypes could lead to clinical confusion surrounding genetic test orders.

METHODS

- A retrospective analysis was performed on 8,202 individuals with a personal history of adenomatous polyps that had clinical genetic testing for Lynch syndrome between January 2006 and July 2013.
- All individuals included in the analysis underwent full sequence and large rearrangement analysis of *MLH1* and *MSH2*.
  - As testing enhancements were implemented, some patients also underwent full sequence and/or large rearrangement analysis of *MSH6*, *PMS2*, and *EPCAM*.
- Patient adenoma history was collected on the test request form.
- Inclusion criterion was limited to personal history of adenomatous polyps and did not depend on either personal or family history of cancer. Patients were excluded from the analysis if the test performed was either targeted mutation testing or single gene testing, presumably based on prior immunohistochemistry tumor testing.

RESULTS

- Of 8,202 patients with a personal history of adenomatous polyps that underwent Lynch syndrome testing, 610 (7.4%) were positive for a mutation.
  - Mutations were detected in patients with a wide distribution of cumulative adenomas (Table 1).
- Seventy-five (12.3%) patients with a Lynch syndrome mutation had an adenomatous polyp phenotype suggestive of either FAP or AFAP.
  - *APC* testing was completed at this same diagnostic laboratory for 19 patients - All were negative for an *APC* mutation.
  - Patients with Lynch syndrome may first present with adenomas only - 20% didn't have a personal dx of cancer (Table 2).
- The majority of patients with 10+ adenomas did meet Revised Bethesda and/or Amsterdam II criteria for Lynch testing (Figure 1).

CONCLUSIONS

- Individuals with diverse adenoma histories had similar Lynch mutation positive rates, indicating an overlapping phenotype between Lynch syndrome and FAP/AFAP.
- This overlap supports expansion of the panel of genes considered for patients with an adenoma history.

REFERENCES

1. Vasen, HFA. Clinical diagnosis and management of hereditary colorectal cancer syndromes. *J Clin Oncol* 2000;18(suppl 1):81s-91s.
2. Burt et al. Clinical Practice Guidelines in Oncology™ Colorectal Cancer Screening. Version 2.2013. Available at http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed November, 2013.
3. Jass et al. Evolution of hereditary non-polyposis colorectal cancer. *Gut* 1992;33:783-786.

TABLE 1 Similar Lynch Mutation Positive Rates in Patients with a Wide Distribution of Adenomatous Polyps

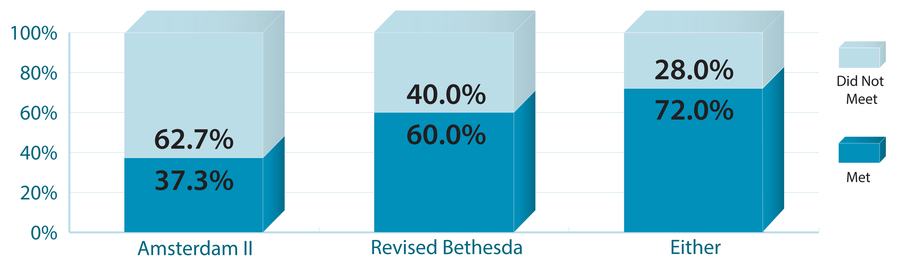
Adenomatous Polyp Count	Patient Count	Lynch Positive Patient Count	Lynch Positive Rate
1	2197	145	6.6%
2 - 5	3740	304	8.1%
6 - 9	995	83	8.3%
10 -19	710	45	6.3%
20 - 99	479	27	5.6%
100+	45	3	6.7%
Multiple	35	3	8.6%
TOTAL	8202	610	7.4%

TABLE 2 Cancer Personal Histories for Lynch Positive Patients with FAP/AFAP Adenoma Phenotypes (N=75)

Personal History of Cancer	Average Age at Dx (yrs)	Range (yrs)
Colon (N=46)	46.1	(17 - 86)
Endometrium (N=19)	47.4	(35 - 64)
Ovary (N=2)	42.0	(42 - 42)
Kidney / Renal (N=5)	59.0	(50 - 68)
Stomach / Gastric (N=2)	59.0	(58 - 60)
Bladder (N=2)	63.5	(62 - 65)
Ureter (N=3)	56.7	(40 - 65)
Duodenum (N=2)	69.0	(56 - 82)
Sebaceous Adenoma / Carcinoma (N=8)	54.7	(38 - 67)

Fifteen patients (20.0%) had a personal history of only adenomatous polyps, and no cancer diagnosis.

FIGURE 1 The Majority (72.0%) of Lynch Positive Patients with FAP/AFAP Adenoma Phenotypes Met Either Revised Bethesda or Amsterdam II Criteria



Of the 75 patients with either an FAP or AFAP phenotype, 37.3% met Amsterdam II criteria and 60.0% met Revised Bethesda criteria.
For this analysis, only first- and second-degree relatives were taken into account when reviewing the Amsterdam II criteria.

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