Genetic Testing Outcomes in Patients with Abnormal Immunohistochemistry (IHC) Staining of the Mismatch-Repair (MMR) Proteins

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BACKGROUND

- IHC staining of the MMR proteins is often used to screen for Lynch syndrome (LS) and has historically been used to guide confirmatory genetic testing.
- Abnormal IHC results are sometimes used as evidence that a variant is pathogenic.
- However, the sensitivity of IHC ranges from 50% to 90% depending on the gene.
- The aim of this study was to evaluate the overall accuracy of IHC in predicting genetic test results and determine whether such data are appropriate for use in variant classification.

METHODS

Cohort and Genetic Testing

- We assessed individuals with reported abnormal IHC who had genetic testing for all the MMR genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*) from 2006-2017 (N=670).
- Pathogenic variants (PVs) are those that received a laboratory classification of Deleterious or Suspected Deleterious.
- Benign variants are those that were classified as Polymorphism or Favor Polymorphism.
- All clinical data, including IHC results, were obtained from provider-completed test request forms.

Analysis

- Genetic results were considered concordant with IHC results based on 2017 NCCN guidelines (Genetic/Familial High Risk Assessment: Colorectal V2.2017).
- PVs detected in MMR genes not predicted to be affected are considered discordant.

RESULTS

PVs Identified by Genetic Testing

- 22.8% (153/670) of patients with abnormal IHC were positive for a PV in an MMR gene, irrespective of concordance with IHC results.
  - 92.2% of PVs were in genes predicted to be mutated by IHC results (Table 1).
  - 7.8% of PVs were in a MMR gene not predicted by IHC results (Table 1).

Benign Variants in MMR Genes Identified in Individuals with Abnormal IHC

- 110 unique rare variants were identified among the 670 patients with abnormal IHC.
- 21% (23/110) of these benign variants were originally classified as variants of unknown significance (VUS) and were later downgraded to benign based on additional evidence (Table 2).
  - If IHC were used as evidence of pathogenicity, these variants may have been misclassified as pathogenic.

Table 2. VUS in MMR Genes Consistent with IHC Results that were Downgraded to Benign

Evidence Used to Downgrade VUS	Unique Variants	
	N	%
In trans with Known PV	8	34.8%
Mutation Co-Occurrence	6	26.1%
Family History Weighting Algorithm	5	21.7%
Population Frequency	5	21.7%
Segregation Analysis	2	8.7%
Other	2	8.7%
Literature Evidence	1	4.3%
Total	23	100%

Table 1. Comparison of IHC Findings and PVs Detected in Genetic Testing (N=153)

	Concordant	Discordant
Total PVs	141 (92.2%)	12 (7.8%)
Genes with Abnormal IHC Staining		
MLH1	3 (60.0%)	2 (40.0%)
MSH2	5 (50.0%)	5 (50.0%)
MSH6	40 (100%)	—
PMS2	23 (100%)	—
MLH1; PMS2	27 (90.0%)	3 (10.0%)
MSH2; MSH6	28 (96.5%)	1 (3.5%)
MLH1; MSH6; PMS2	1 (100%)	—
MSH2; MSH6; PMS2	1 (100%)	—
MSH2; PMS2	1 (100%)	—
MSH6; PMS2	7 (100%)	—
MLH1; MSH2; MSH6	2 (100%)	—
MLH1; MSH2; PMS2	—	1 (100%)
MLH1; MSH2; MSH6; PMS2	3 (100%)	—

CONCLUSIONS

- The data presented here suggests that caution must be taken when utilizing IHC test results in guiding choice of genetic test and variant classification in order to ensure appropriate patient care.

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