Comparison of Colorectal Cancer Patients with Lynch Syndrome, Double Somatic Mutations, and *MLH1* Promoter Hypermethylation

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BACKGROUND

Colorectal cancer (CRC) demonstrating *MLH1* promoter hypermethylation (*MLH1*-hm) is generally accepted as sporadic; however, less information is available regarding outcomes and familial risk for patients with double somatic (DS) mutations. Here we describe paired tumor/germline testing results based on clinical risk factors and compare clinical characteristics of DS CRC patients to those with Lynch syndrome (LS) and *MLH1*-hm.

METHODS

647 CRC patients with classic IHC loss patterns [MLH1-/PMS2- (n=360), MSH2-/MSH6- (n=145), MSH6- (n=61), PMS2- (n=81)] underwent paired testing at a commercial laboratory. Patients were excluded for: prior germline LS and/or *MLH1*-hm testing (n=189); concurrent DS and *MLH1*-hm (n=2); DS discordant with IHC (n=3). Patients were grouped based on clinical characteristics aligning with NCCN LS testing criteria: CRC <50y (n=75); CRC <50y with additional risk factors (+RF) (e.g. family history, multiple LS-associated cancers) (n=42); CRC >50y +RF (n=108); no risk factors (CRC >50y) (n=228).

RESULTS

Regardless of IHC pattern, LS is the most likely result for patients diagnosed <50y +RF and the least likely for patients with no additional risk factors. For those diagnosed <50y or >50y +RF, LS germline mutations were identified in a majority of patients with MSH2-/MSH6- or MSH6- and a minority of patients with MLH1-/PMS2- or PMS2- (Fig. 1). DS patients have an earlier mean age of onset for first LS-associated cancer (58.85y) than *MLH1*-hm patients (66.03y), and a later age of onset than LS (52.67y) ($p<0.001$) based on ANOVA testing. Logistic regression analysis showed that when comparing DS to LS, a similar proportion have CRC <50y as their only risk factor ($p=0.117$), while significantly fewer DS have CRC <50y +RF ($p<0.001$). *MLH1*-hm are more likely than DS ($p=0.003$) or LS ($p<0.001$) to have no risk factors and are less likely to present with CRC <50y compared to DS ($p=0.015$) (Fig 2).

CONCLUSIONS

Results from this analysis revealed a clinical gradient correlated with origin of mismatch repair deficiency, in which DS lies between LS and MLH1-hm with respect to age of onset. Paired testing outcomes are correlated with clinical presentation; thus, this data can help inform testing and management decisions for CRC patients.