Tumor characteristics provide evidence for MMR variant pathogenicity

Shuwei Li, Jacob Clifford, Dajun Qian, Yuan Tian, Aaron Elliott, Hsiao-Mei Lu, Mary Helen Black

Pathogenic mutations in mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* and *PMS2*) increase risk for Lynch syndrome and other cancers. MMR deficiency may result in microsatellite instability (MSI); tumor MSI testing and protein immunohistochemical (IHC) analysis for MMR protein expression are often used alone or together to evaluate risk for Lynch syndrome in clinical screening. It has been suggested that these quantifiable tumor characteristics may be useful in assessing germline MMR variant pathogenicity. We obtained research consent and clinical information for 77,071 patients who underwent germline multigene panel testing including MMR genes in 2012-2016. Among the 3,627 patients with available MSI or IHC information, we excluded 69 with conflicting MSI/IHC status and 238 carriers of non-MMR pathogenic variants. Variant pathogenicity was assessed according to ACMG guidelines. Among the remaining 3,320 individuals with MSI (*n*=1,055) or IHC (*n*=2,954) status (*n*=689 with both), we tested association between MMR carrier status and the combined MSI/IHC phenotype using Fisher's exact test, followed by estimation of MSI/IHC likelihood ratios (LR=%pathogenic variant carriers/%non-carriers). For each variant, we computed the tumor characteristic LR (TCLR) based on the estimated MSI/IHC LRs. While typically TCLR>1 for pathogenic and TCLR<1 for benign variants, we used the TCLR>10 or <0.1 as thresholds suggestive of pathogenic or benign classification, respectively. Carriers of MMR mutations were more likely to have abnormal MSI/IHC (OR=27.3, 95%CI: 16.2-49.0). Estimated LRs for MSI/IHC unstable/abnormal and stable/normal were 3.136 and 0.115, respectively. Overall, we identified 141 pathogenic/likely pathogenic, 217 benign/likely benign, and 223 VUS/unclassified MMR variants. Among pathogenic variants, 73.0% have TCLR>1 and none have TCLR<0.1; 89.9% of benign variants have TCLR<1 and none have TCLR>10. Moreover, 15% of VUS/unclassified variants have TCLR>1 and 66% TCLR<1, suggesting that many of these may be potentially classified. While no VUS/unclassified variants have TCLR>10, 17 (8%) have TCLR<0.1, providing stronger evidence for classification as benign/likely benign. These data show that MSI/IHC-based TCLRs provide evidence for or against pathogenicity of variants in MMR genes. Used independently or in conjunction with other evidence, the TCLR may inform variant classification, and thus have important implications for genetic testing and clinical management.

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