Types and frequencies of Lynch syndrome mutations identified through multigene panel testing

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Background: Lynch syndrome (LS) is a well-known hereditary cancer syndrome, caused by mutations in the mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* and *PMS2*) and *EPCAM*. **Methods:** We retrospectively reviewed consecutive cases that had multigene panel testing including the MMR and *EPCAM* genes between March 2012 and June 2015 (N=35,214). Pathogenic and likely pathogenic MMR and *EPCAM* mutations were reviewed and statistical analyses performed. **Results:** Overall, 629 MMR and *EPCAM* mutations were identified in 621 patients; 346 (55%) were unique and 106 (17%) recurrent. Mutations in *MSH6* were most frequent (30.4%), followed by *PMS2* (25.1%), *MSH2* (22.9%), *MLH1* (20.5%), and *EPCAM* (1.1%). Among unique mutations, truncating insertion-deletion mutations (indels) and substitutions were most frequent (N=189, 54.6%), followed by non-truncating indels and substitutions (N=66, 19.1%), large deletions and duplications (del/dups; N=59, 17%), splicing (N=28, 8.1%), AUG/5'UTR (N=3, 0.9%), and synonymous mutations (N=1, 0.3%) with small indels being the most frequent sub-type (N=139, 40.2%). The proportions of truncating, large del/dup, AUG/5'UTR, and silent mutations were similar to those reported by InSiGHT (International Society for Gastrointestinal Hereditary Tumors), while our proportions of non-truncating and splicing mutations were significantly higher ($P<0.001$) and lower ($P<0.01$), respectively. Four mutations were seen more than ten times. *PMS2* c.137G>T p.S46I (N=21) is reported as a European founder mutation and *MSH2* c.1906G>C p.A636P (N=13) is a known Ashkenazi Jewish founder. *MSH2* c.942+3A>T (N=18) and *MSH6* c.3261dupC p.F1088Lfs*5 (N=16) are recurrent mutations occurring in microsatellite tracts. **Conclusions:** Mutation types and most frequently seen mutations support previous literature. While most previous studies suggest that mutations in *MLH1* and *MSH2* are the most common causes of LS, *MSH6* and *PMS2* were most common in this cohort. This may be relevant to evolving genotype-phenotype correlations. The high frequency of indels in this cohort highlights the importance of utilizing an NGS assay highly sensitive for indels in analyzing cases suspicious for LS.