Comprehensive mismatch repair gene panel screening identifies variants in patients with Lynch-like syndrome.

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Lynch-like syndrome (LLS) represents around 50% of the patients fulfilling the Amsterdam II Criteria (ACII)/revised Bethesda Criteria (BC) guidelines and is characterized by a strong family history of Lynch Syndrome (LS) associated cancers but no causative variant in one of four DNA mismatch repair genes was not identified when genetically tested for LS. Given that the phenotype of LLS is very similar to LS we reasoned that a more in-depth examination of genes associate with DNA mismatch repair (MMR) was warranted. In total 22 MMR genes were investigated using a next generation sequencing panel approach.

Next-generation sequencing data of 22 mismatch repair (MMR) genes (MSH3, PMS1, MLH3, EXO1, POLD1, POLD3 RFC1, RFC2, RFC3, RFC4, RFC5, PCNA, LIG1, RPA1, RPA2, RPA3, POLD2, POLD4, MLH1, MSH2, MSH6, and PMS2) was analyzed from 274 patients who fulfilled either the ACII or BC guidelines. Detected variants of interest were annotated and filtered using ANNOVAR and FILTUS software.

Thirteen variants were revealed in MLH1, MSH2, and MSH6, all genes previously linked to LS. Five additional genes (EXO1, POLD1, RFC1, RPA1, and MLH3) were found to harbor 11 variants of potential significance in our sample cohort, two of them being frameshift variants.

The data revealed other genes associated with the process of DNA MMR have a high probability of being associated with LLS families. These findings indicate that the spectrum of genes that should be tested when considering an entity like Lynch-Like Syndrome should be expanded so that a more comprehenisve definition of this entity can be developed.