Title Suggestions:

Importance of accurate *EPCAM* deletion characterization to prevent misdiagnosis of Lynch syndrome

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Background and Aim

Gross deletions involving the 3' end of *EPCAM* cause Lynch syndrome (LS). Prior to the introduction of NGS, *EPCAM* deletion screening was typically performed by one MLPA kit throughout the country, in which the 5'-most probe resides in exon 3. Therefore, it can be unclear whether some deletions encompass the full gene. However, full *EPCAM* deletions may not be disease-causing so accurate differentiation of deletion size has significant clinical implications.

Methods

We reviewed cases with a gross deletion of *EPCAM* identified at a single laboratory from 2011-2021 to determine how many had a known or possible full *EPCAM* deletion detected via MLPA or microarray. Amsterdam criteria II (AC) and revised Bethesda criteria (BC) were assessed in families with full and partial deletions. Data presented herein are exempt from IRB review.

Results

A total of 503 cases were identified that included an *EPCAM* deletion, 373 of which also included *MSH2.* Isolated *EPCAM* deletions were identified in 129 individuals from 91 unique families. In most families (79.1%; 72/91), MLPA indicated a definitive partial *EPCAM* deletion based on retention of the exon 3 probe. In 9 additional families (9.9% of 91), 5'UTR coverage from a microarray was available and identified a full *EPCAM* deletion. Deletion size could not be determined in 10 remaining families (11.0%). Therefore, 20.9% of families with *EPCAM* deletions identified at our laboratory may not have LS due to a known or possible full gene deletion. No families with a known full gene deletion met AC and 1 met BC while 44.7% (n=21) and 89.3% (n=42) of those with a partial deletion met AC or BC, respectively.

Conclusions

This study identifies a need for re-evaluation of a subset of individuals with EPCAM deletions reported through clinical testing. There was a stark difference in phenotype between those with a known full deletion compared to a known partial deletion, in which no individuals with full deletions met AC or BC. This supports findings that full EPCAM deletions are not pathogenic. Accurate characterization of *EPCAM* deletions is critical to prevent misdiagnosis of LS.

Keywords: 1-6 keywords

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