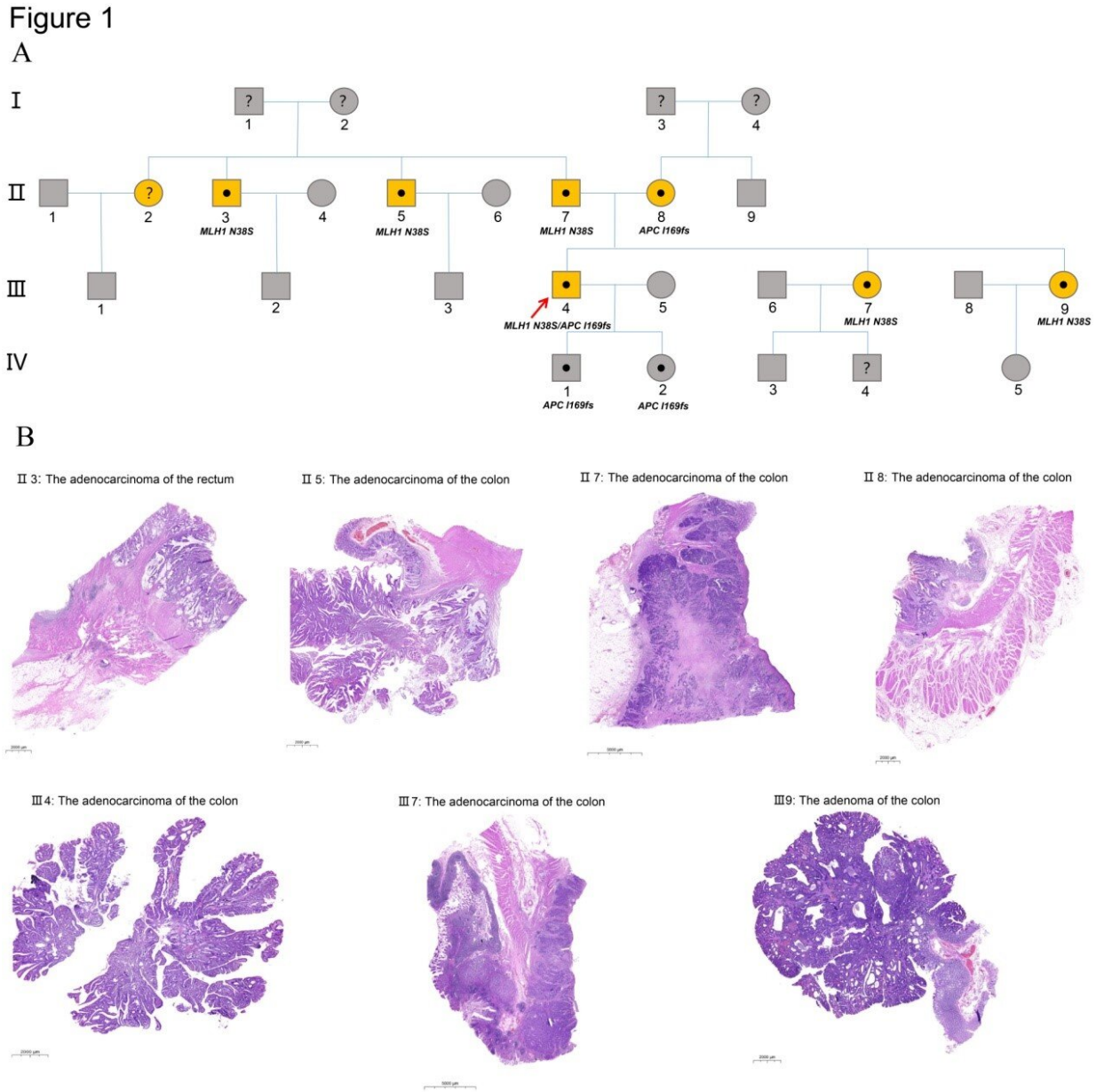
Study reveals somatic mutation profile of colorectal tumor with simultaneous APC and MLH1 germline mutations

May 4 2023, by Zhao Weiwei; Hong Bo



The pedigree of the studied family, and hematoxylin-eosin staining of colorectal adenocarcinoma or adenomas in all patients. Credit: Cheng Yunsheng

Recently, a research group from Hefei Institutes of Physical Science (HFIPS) of Chinese Academy of Sciences (CAS) and The Second Hospital of Anhui Medical University dissected, for the first time, the somatic mutation profile of familial colorectal cancer with the coinheritance of mutations in both APC and MLH1 genes.

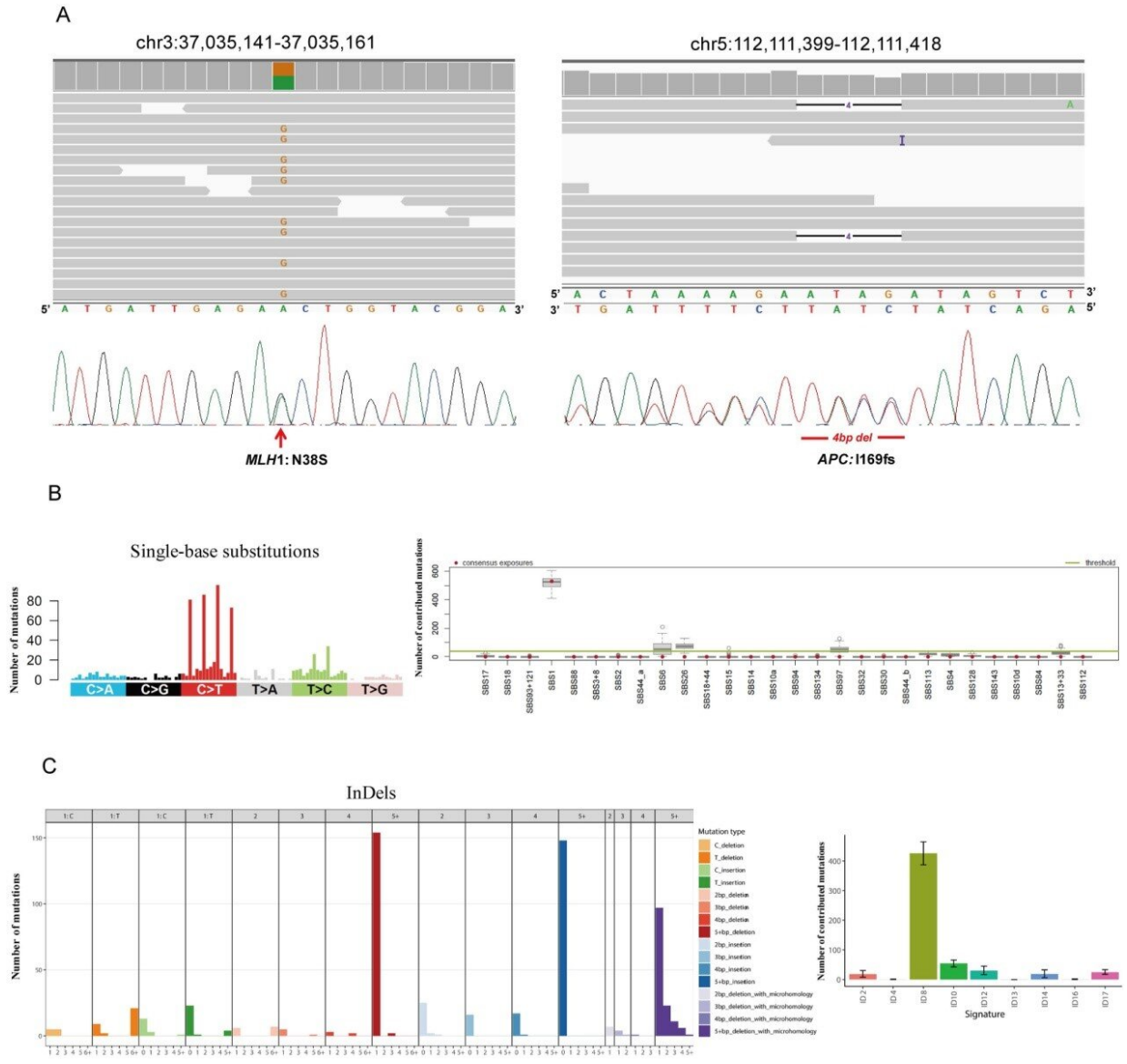
The results were published in *Genes & Diseases*.

Inherited mutations in cancer susceptibility genes account for about 10% of all cases of colorectal cancer. Germline mutations in the APC gene and the mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) cause the most frequent forms of hereditary colorectal cancer, familial adenomatous polyposis and Lynch syndrome, respectively. It is highly unusual for simultaneous mutations in both the APC and mismatch repair genes to cause hereditary colorectal cancer.

In this research, through whole exome sequencing, researchers found that a 20-year-old patient with colon cancer and multiple polyposis harbored germline mutations in both the APC and MLH1 genes. The team of researchers dug deeper into the nature of the somatic mutations present in the patient's colorectal cancer.

The significant mutation levels of C-T transitions and 5+ base Indels predominated in the patient's colorectal tumor, indicating a high somatic mutation burden. Additionally, the single-nucleotide substitution mutational signature in the patient's colorectal tumor matched the

COSMIC signature 1, which is correlated with increasing age at cancer diagnosis.



The somatic mutation signatures of the colorectal tumor with concurrent APC and MLH1 germline mutations were related to age and defective DNA mismatch repair. Credit: Cheng Yunsheng

Other matched mutational signatures (signatures 6, 26 and 97) were linked to defective DNA mismatch repair. The colorectal tumor featured many Indel mutations similar to COSMIC signature ID8, which is similarly correlated with increasing age at cancer diagnosis.

This study for the first time reported the somatic mutational profile of colorectal tumor with concurrent APC and MLH1 germline mutations. The simultaneous germline mutations in APC and MLH1 genes could accelerate the genome instability, thereby fostering early tumor onset and rapid tumor progression.

More information: Yunsheng Cheng et al, Characterization of somatic mutations of colorectal tumor in a patient with concurrent APC and MLH1 germline mutations, *Genes & Diseases* (2023). DOI: 10.1016/j.gendis.2023.02.017

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