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LETTER TO THE EDITOR

Mutational alterations of TDRD 1, 4 and 9 genes in colorectal cancers

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To the editor:

Tudor domain-containing proteins (TDRDs) play important roles in the regulation of chromatin remodeling and RNA metabolism, which are closely related to caner pathogenesis [1]. Alterations of TDRDs have been detected in many cancers. For example, TDRD9 is overexpressed in lung cancers and associated with poor clinical outcomes [2]. TDRD1 is associated with ERG overexpression that is a driver in prostate cancers [3]. TDRD5 is decreased in hepatocellular carcinoma compared to the chronic liver diseases [4]. However, alterations of TDRDs in gastrointestinal cancers have not been explored comprehensively. An earlier study found that TDRD5 was expressed in normal gastric and colonic mucosal tissues [4], suggesting a possibility that *TDRD* genes could be altered in colorectal cancer (CRC).

In the public genome database, we found that there were mononucleotide repeats in the coding sequences of *TDRD1* (one A7 and one T7), *TDRD5* (one A7 and one T7) and *TDRD9* (one T7) that could be mutation targets in the cancers with microsatellite instability (MSI) [5]. We analyzed the repeats in 78 CRCs with high MSI (MSI-H) and 75 CRCs with stable MSI (MSS) by polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP) assay as described previously [6]. Our analyses discovered frameshift mutations in the repeats (2 CRCs for *TDRD1*, 3 CRCs for *TDRD5* and 1 CRC for *TDRD9*). Importantly, the mutations were significantly different between CRCs with MSI-H (6/78: 7.7%) and those with MSS (0/75) (Fisher's exact test, $p = 0.033$). The mutations were deletions of one base within the repeats that would cause premature stop codons with termination of amino acid translation (Table 1). Next, we analyzed 16 cases of MSI-H CRCs (4 to 7 regional fragments per tumor) to detect intratumoral heterogeneity (ITH) of the frameshift mutations, which could drive cancer evolution and clinical aggressiveness [7]. We found that the ITH was present in one CRC for the *TDRD1* frameshift mutation (1/16: 6.25%) and another CRC for the *TDRD5* frameshift mutation (1/16: 6.25%). The ITH of *TDRD1* mutation was c.2319delT in one region and wild-type sequence in the other 6 regions of a CRC, while the ITH of *TDRD5* mutation was c.1907delT in 6 regions and wild-type sequence in the other one region of another CRC. We analyzed the association of the mutational ITHs and clinicopathologic parameters, but we were not able to find any significant association probably due to the small ITH cases (n = 2).

Earlier studies on *TDRD* genes revealed that they might be cancer-related genes [2–4], but such evidence on CRC was not well provided. In this study, we have analyzed CRCs and found not only frameshift mutations but also ITH of *TDRD1, TDRD5* and *TDRD9*, which together might alter *TDRD* gene functions and could possibly play a role in tumorigenesis of MSI-H CRC. It is not clear that the ITH might be either cause or consequence of genetic evolution of CRCs, which needs further validation in a larger CRC cohort.

Ha Yoon Mo and Eun Ji Choi contributed equally to this work.

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Table 1 Summary of *TDRD1, TDRD5* and *TDRD9* mutations in colorectal cancers

Gene	Wild type	Mutation	MSI status of the mutati on cases (n)	Incidence in MSI-H cancers (%)	Nucleotide change (predicted amino acid change)
TDRD1	T7	T6	MSI-H (2)	Colorectal: 2/78 (2.6)	c.2319delT (p.Phe773LeufsX11)
TDRD5	T7	T6	MSI-H (3)	Colorectal: 3/78 (3.8)	c.1907delT (p.Leu636CysfsX16)
TDRD9	T7	T6	MSI-H (1)	Colorectal: 3/100 (1.3)	c.1908delT (p.Phe636LeufsX16)

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Compliance with ethical standards

Conflict of interest None to declare.

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