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LETTER TO THE EDITOR

Inactivating Frameshift Mutations of *HACD4* and *TCP10L* Tumor Suppressor Genes in Colorectal and Gastric Cancers

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To the Editor:

HACD4 (also known as PTPLAD2; protein tyrosine kinase-like A domain-containing protein 2) belongs to a family of enzymes that catalyze the dehydration step of very long chain fatty acid synthesis [1]. Esophageal squamous cell carcinomas show downregulation of HACD4 expression that is correlated with poor patient survival [2]. Knockdown of *HACD4* increases STAT3 phosphorylation and cell proliferation [2]. In glioblastomas, the locus for *HACD4* is frequently deleted [3]. TCPL10 encoding T-complex protein 10-like, a nuclear protein with transcription regulation functions, suppresses colony formation, cell cycle progression through G0/G1 phase and cell growth in vivo in liver [4]. Together, these data suggest that both *HACD4* and *TCP10L* possess tumor suppressor gene (TSG) activities. However, the roles of *HACD4* and *TCP10L* in colorectal (CRC) and gastric (GC) cancers are not known.

About one third of CRC and GC have defects in mismatch repair that can cause microsatellite instability (MSI). TSGs are often observed to have mutations at monocleotide repeats in high MSI (MSI-H) CRC and GC [5]. There are mononucleotide repeats in *HACD4* (A8) and *TCP10L* (G7) of their coding sequences that could be mutation targets in cancers with MSI-H. In addition, it is well known that intratumoral heterogeneity (ITH) plays an important role in cancer development and progression and impedes proper diagnosis and treatment of cancer patients [6, 7]. The present study aimed to find whether *HACD4* and *TCP10L* genes harbored frameshift mutation within the repeats and ITH. For this, we studied the mononucleotide repeats in *HACD4* (A8) and *TCP10L* (G7) in 79 high MSI (MSI-H) CRCs, 45 microsatellite stable (MSS) CRCs, 34 MSI-H GCs and 45 MSS GCs by single-strand conformation polymorphism (SSCP) assay. After SSCP, Sanger DNA sequencings were performed in cancers with mobility shifts in the SSCP to confirm the mutations [8].

SSCP and Sanger sequencing identified frameshift mutations of *HACD4* in 3 cases of CRC and 1 case of GC, and *TCP10L* in 3 cases of GC. All of them were detected in CRC or GC with MSI-H, but neither in CRC nor GC with MSS. These mutations were not detected in their matched normal tissues. The *HACD4* mutations (c.689delA (p.Lys230Argfsx42)) and the *TCP10L* mutations (c.641delG (p.Gly214Valfsx26)) were recurrent in all mutated cases (Table 1). For ITH of the mutations, we studied 16 cases of CRCs with 4 to 7 regional fragments per CRC. One of the 16 CRCs (6.3%) showed the deletion mutation of *HACD4* mutations (c.689delA) in different tissue regions. No ITH of the *TCP10L* frameshift mutation was observed in the 16 CRCs. Clinical and histopathological parameters, however, could distinguish neither *HACD4* frameshift mutation (+) and (−) cancers nor *TCP10L* frameshift mutation (+) and (−) cancers.

The frameshift mutations of *HACD4* and *TCP10L* identified in this study would result in truncation of HACD4 and TCP10L proteins respectively, suggesting that inactivation of their TSG functions would contribute to tumorigenesis in MSI-H GCs and CRCs. Also, one CRC (6.3%) exhibited ITH for the *HACD4* frameshift mutation. ITH of the frameshift mutation in the CRC might suggest a possibility that there could be a mixed or ameliorated effect of the *HACD4* mutation in the affected CRC. However, we were not able to find any distinguished clinicopathologic features of *HACD4* mutation ITH-positive cancer. It

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Table 1 Summary of *HACD4* and *TCP10L* mutations in gastric and colorectal cancers

Gene	Wild type	Mutation	MSI status of the mutation cases (n)	Incidence in MSI-H cancers (%)	Nucleotide change (predicted amino acid change)
TCP10L	A8	A7	MSI-H (3)	Gastric: 3/34 (8.8)	c.641delG (p.Gly214Valfsx26)
HACD4	G7	G6	MSI-H (4)	Gastric: 1/34 (2.9) Colorectal: 3/79 (3.8)	c.689delA (p.Lys230Argfsx42)

was probably due to small number of the ITH cases. The current study identified inactivating type mutations of *HACD4* and *TCP10L* in CRC and GC, further studies are needed to define the clinical implication of *HACD4* and *TCP10L* mutations and their ITH in MSI-H cancers.

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Compliance with Ethical Standards

Conflict of Interests The authors declare no competing interests.

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