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LETTER TO THE EDITOR

Intratumoral Heterogeneity for Inactivating Frameshift Mutation of *CYB5R2* Gene in Colorectal Cancers

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To the Editor:

CYB5R2 is an enzyme involved in drug metabolism such as chemotherapeutic agents. Loss of CYB5R2 expression has been reported in many tumors including prostate, nasopharynx and brain tumors [1, 2]. Functionally, mice with CYB5R2 overexpression showed decreased tumorigenicity [2], suggesting that *CYB5R2* might be a tumor suppressor gene (TSG). However, there is no data that have analyzed whether *CYB5R2* is a TSG in colorectal cancer (CRC). About 10% of CRC show microsatellite instability (MSI) that has defects in mismatch repair [3]. In addition, intratumoral heterogeneity (ITH) plays an important role in development and progression of cancers and impedes proper diagnosis and treatment of cancers [4]. TSGs are often observed to harbor mutations at monocleotide repeats in high MSI (MSI-H) CRC. There is a mononucleotide repeat (A7) in *CYB5R2* coding sequence that could be a mutation target in cancers with MSI-H. This study aimed to find whether *CYB5R2* frameshift mutation is common and harbors ITH in MSI-H CRC. For this, we studied the A7 in 79 MSI-H CRCs and 45 microsatellite stable MSI (MSS) CRCs by single-strand conformation polymorphism and Sanger DNA sequencing [5].

We found *CYB5R2* somatic frameshift mutations in two CRCs with MSI-H (2/79, 2.5%), but there was none in those with MSS (0/45). They were a same deletion mutation (c.433delA (p.Thr145Hisfsx8)). For ITH of the mutation, we studied 16 cases of CRCs with 4 to 7 regional fragments per CRC. Two of the 16 CRCs (12.5%) showed the c.433delA mutation in different regions, indicating ITH of the *CYB5R2* mutation existed in the CRCs (Table 1). Clinical and histopathological parameters, however, could distinguish neither *CYB5R2* frameshift mutation (+) and (−) cancers, nor the ITH (+) and (−) cancers.

The *CYB5R2* frameshift mutation would result in truncation of CYB5R2 protein. Based on the previous known TSG activity of CYB5R2 [1, 2], the frameshift mutations could contribute to cancer development by inhibiting the TSG. Presence of ITH of the frameshift mutation in CRC might suggest a possibility that there could be a mixed or ameliorated effect of *CYB5R2* mutations in MSI-H cancers. However, we were not able to find any distinguished clinicopathologic features of *CYB5R2*-mutated or ITH-positive cancers. It was probably due to small number of *CYB5R2*- mutated cases. Based on our data, further studies are needed to define the clinical implication of *CYB5R2* mutation and its ITH in MSI-H cancers.

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Table 1 Intratumoral heterogeneity of *CYB5R2* mutation in colorectal cancers

Case	Regional biopsy sites							Mutation status	ITH status
	#1	#2	#3	#4	#5	#6	#7		
CRC3	WT	WT	WT	WT	WT	WT	n.d.	Wild type	Non-ITH
CRC15	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC26	WT	WT	n.d.	WT	WT	WT	WT	Wild type	Non-ITH
CRC27	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC34	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC35	c.433delA	WT	n.d.	n.d.	n.d.	WT	c.433delA	Mutation	ITH
CRC39	WT	WT	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC41	WT	n.d.	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC43	WT	WT	WT	n.d.	n.d.	WT	n.d.	Wild type	Non-ITH
CRC45	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC47	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC48	WT	n.d.	n.d.	WT	WT	WT	WT	Wild type	Non-ITH
CRC49	n.d.	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC51	WT	WT	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC53	WT	WT	c.433delA	c.433delA	WT	WT	c.433delA	Mutation	ITH
CRC55	WT	WT	n.d.	n.d.	WT	WT	WT	Wild type	Non-ITH

n.d.: not done, ITH: Intratumoral heterogeneity, CRC: colorectal cancer

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Compliance with Ethical Standards

Conflict of Interests The authors declare no competing interests.

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