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LETTER TO THE EDITOR

Low Frequent Mutation of *ARHGAP35*, a Candidate Tumor Suppressor Gene, in Gastric and Colorectal Cancers

Eun Ji Choi[1] · **Min Sung Kim**[1] · **Sang Yong Song**[2] · **Nam Jin Yoo**[1] · **Sug Hyung Lee**[1]

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To the Editor:

ARHGAP35 gene encoding glucocorticoid receptor DNA-binding factor-1 (also known as p190RHOGAP) belongs to a family of large G proteins/ GTPase activating proteins [1]. Chromosomal region encompassing *ARHGAP* gene is frequently deleted in solid tumors, including pancreatic carcinoma and glioma [2]. Activation of ARHGAP35 causes RhoA inactivation and inhibits cell invasion [3]. Rat ARHGAP35 has anti-oncogenic activities that suppress RAS-induced tumorigenesis [4]. Downregulation of ARHGAP35 expression promotes transformed growth of epithelial tumor cells [5]. Together, these data suggest that *ARHGAP35* may be a tumor suppressor gene (TSG) and its inactivation could play a role in tumor development. However, inactivating mutation status of *ARHGAP35* remains unknown in most carcinomas along with their pathologic features. In the genome database, we found that *ARHGAP35* gene had a mononucleotide repeat (A7) in its coding sequences that could be targets for frameshift mutation (loss-of-function mutation) in cancers with microsatellite instability (MSI). Frameshift mutation of genes containing mononucleotide repeats is a feature of colorectal cancers (CRC) with MSI [6].

In this study, we analyzed an A7 repeat in exon 1 by polymerase chain reaction (PCR)-based single strand conformation polymorphism (SSCP) in 79 CRCs with high MSI (MSI-H) and 45 microsatellite stable (MSS) CRCs. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products for detection by autoradiogram. The PCR products were subsequently displayed in SSCP gels. After SSCP, direct DNA sequencing reactions were performed in the cancers with mobility shifts in the SSCP as described previously [7].

On the SSCP, we observed aberrant bands of *ARHGAP35* gene in one CRC. DNA from matched normal tissue showed no shifts in SSCP, indicating the aberrant bands had risen somatically. DNA sequencing analysis also identified that the aberrant bands represented a somatic mutation. The *ARHGAP35* mutation was a heterozygous frameshift mutation (duplication of one base) in the A7 repeat (c.2834dupA) that would result in a frameshift mutation (p.Asn946GlufsX11). It was detected in the CRC with MSI-H (1/79; 1.3%), but none in those with MSS (Fig. 1).

The mutation in our study would result in a premature stop in ARHGAP35 protein and thus resemble a typical loss-of-function mutation. Provided that *ARHGAP35* gene is a candidate TSG, we can hypothesize that the *ARHGAP35* inactivating mutation might

✉ Sug Hyung Lee
suhulee@catholic.ac.kr

[1] Department of Pathology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Socho-gu, Seoul 137-701, South Korea

[2] Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

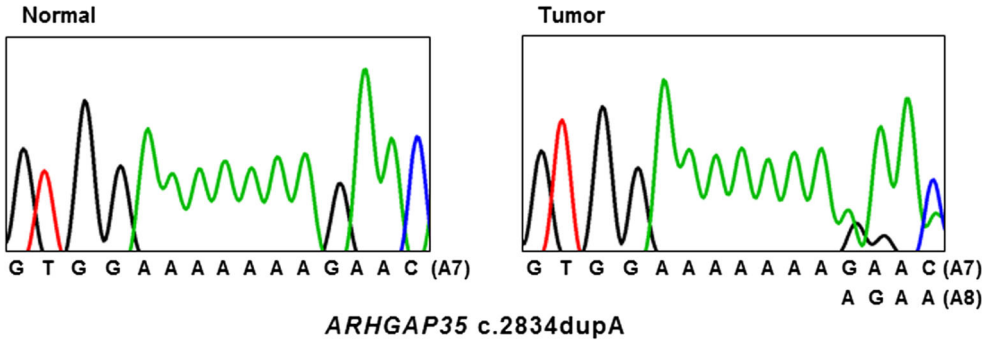

Fig. 1 Mutations of *ARHGAP35* in the mononucleotide repeat in a colon carcinoma. Direct DNA sequencing analysis show a heterozygous A deletion within the A7 repeat of *ARHGAP35* in the tumor tissue as compare to the matched normal tissue

contribute to tumor development in the affected CRC. However, all except one CRC in our study did not harbor any *ARHGAP35* inactivating mutation in the repeat. Our results indicate that inactivating mutation of *ARHGAP35* in the repeat is rare in CRC with MSI and suggest that *ARHGAP35* inactivating mutation may not play an important role in CRC development.

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