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LETTER TO THE EDITOR

Absence of *KNSTRN* Mutation, a Cutaneous Squamous Carcinoma-Specific Mutation, in Other Solid Tumors and Leukemias.

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To the Editor:

KNSTRN gene encodes the kinetochore-localized astrin/spag5-binding protein that modulates chromosome segregation during mitosis [1]. A recent genomic study identified recurrent somatic mutations of the *KNSTRN* in 19 % of cutaneous squamous cell carcinoma (SCC) [2]. Of the mutations detected, more than half of them were recurrent at a specific residue (p.Ser24Phe). In addition, the p.Ser24Phe mutation was found in other cutaneous tumors such as malignant melanomas (2 %) and actinic keratosis (19 %) [2]. Functionally, the *KNSTRN* p.Ser24Phe mutation disrupted chromatid cohesion in normal cells, correlated with increased aneuploidy in primary tumors and enhanced tumorigenesis in vivo [2]. In other reports, aberrant *KNSTRN* expression was shown to result in loss of chromatid cohesion in a non-cutaneous tumor cell line HeLa cells [1]. Also, KNSTRN is expressed in a broad range of normal human tissues [2]. These data suggest a possibility that alterations of *KNSTRN* gene might be present not only in skin but also in other tissues. Since the *KNSTRN* p.Ser24Phe mutation is considered a driver mutation with a high recurrence, it may be interesting to know whether the mutation occurs in other human tumors besides cutaneous tumors.

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For this, tumor tissues from 2229 Korean patients, including hematologic, epithelial and mesenchymal tumor from various origins, were used for this study (Table 1). Prostate and ovarian tissues were from Korea Prostate Bank and Korea Gynecologic Cancer Bank, respectively. The tumors did not include cutaneous SCC where *KNSTRN* p.Ser24Phe mutations were recurrent, because the cutaneous SCC tissues were not available in this study. For solid tumors, malignant and normal cells were selectively procured from by microdissection [3, 4]. Approval for this study was obtained from the institutional review board. We analyzed exon 1 of *KNSTRN* gene that encompassed p.Ser24Phe mutation sites by polymerase chain reaction (PCR)-based single-strand conformation polymorphism (SSCP). Genomic DNA each from tumor and normal cells was amplified by PCR with a primer pair (5′-CTCTGAGCGAACCTTCCGTA-3′ (forward) and 5′-CCGCCTGGGTTTCAAATAG-3′ (reverse); product size: 145 base pairs). Other procedures of the PCR-SSCP were described in our previous studies [3, 4]. After SSCP, direct DNA sequencing reactions were performed in the cancers with mobility shifts.

On the SSCP, all of the PCR products for *KNSTRN* exon 1 were clearly seen. However, none of the SSCP from the cancers displayed aberrantly migrating bands compared to wild-type bands from the normal tissues, indicating there was no evidence of *KNSTRN* exon 1 mutations in the tumors. To confirm the SSCP data, we repeated the experiments twice, including tissue microdissection, PCR and SSCP to ensure specificity of the results, and found that the data were consistent.

An interesting point in cancer genetics is to identify whether any mutation found in a specific tumor type is common to other types. The present study, however, detected no somatic mutations of *KNSTRN* p.Ser24Phe

Table 1 *KNSTRN* p.Ser24Phe mutations in tumors from 2229 tumors

Type of tumors	Number of tumors	*KNSTRN* p.Ser24Phe		
		Wild type	Mutation	Mutation (%)
Adulthood AML	250	250	0	0
Adulthood ALL	176	176	0	0
Childhood AML	21	21	0	0
Childhood ALL	251	251	0	0
Multiple myeloma	75	75	0	0
Myelodysplasia	68	68	0	0
Gastric carcinoma	175	175	0	0
Colorectal carcinoma	395	395	0	0
Breast carcinoma	92	92	0	0
Prostate carcinoma	265	265	0	0
Ovarian tumors	64	64	0	0
Hepatocellular carcinomas	30	30	0	0
Leiomyoma	68	68	0	0
Adenocarcinomas, lung	74	74	0	0
Squamous cell carcinomas, esophagus	61	61	0	0
Squamous cell carcinomas, larynx	44	44	0	0
Squamous cell carcinomas, lung	100	100	0	0
Squamous cell carcinomas, uterine cervix	20	20	0	0
Total	2229	2229	0	0

AML: acute myelogenous leukemia, ALL: acute lymphoblastic leukemia

in 2229 tumors from 18 tumor types. SCCs from non-cutaneous origins such as lung and uterine cervix did not harbor the *KNSTRN* exon 1 mutation. Our data indicate that the *KNSTRN* p.Ser24Phe may be specific to cutaneous tumors, but not to non-cutaneous tumor development. Discovery of the recurrent *KNSTRN* mutation provided an opportunity for developing therapeutic and diagnostic tools for targeting the recurrent *KNSTRN* mutation. Our data, however, suggest that such approaches should be limited to cutaneous tumors.

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