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LETTER TO EDITOR

Oncogenic *PTPN11* Mutations are Rare in Solid Tumors

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To the editor:

For a comprehensive elucidation of genetic alterations in high-risk neuroblastoma, Pugh et al. recently analyzed neurobalstoma tumor tissues by whole-exome and whole-genome sequencing [1]. In addition to the genes with known mutations in neuroblatoma, they found that PTPN11, a protein-tyrosine phosphatases (PTP)-encoding gene, harbored mutations at recurrent sites [1]. Protein-phosphorylation crucial for many cellular processes is activated by protein-tyrosine kinases, but inactivated by PTPs [2]. Recurrent germline *PTPN11* mutations in exons 3 and 13 are associated with Noonan syndrome characterized by multiple congenital anomalies [2]. Also, recurrent somatic *PTPN11* mutations at the same exons are reported in various types of hematologic neoplasia (high incidences in juvenile myelomonocytic leukemia and low incidences in acute lymphoblastic leukemias and acute myelogemous leukemias) [3], but not in solid tumors except neuroblastomas [1, 2]. Somatic mutations of *PTPN11* in these tumors are localized in N-SH2 (exon 3) and PTH domains (exon 13), structural alterations of which disrupt auto-inhibitory interface, generate activated PTPN11 and result in oncogenic activities [1]. Recurrent *PTPN11* mutations in neuroblastoma suggest that there might be a possibility that the *PTPN11* mutations might occur in other solid tumor as well.

In this study, we analyzed the recurrent *PTPN11* mutation sites (exon 3 and exon 13) using genomic DNA from 1,408 solid tumors and 709 hematologic neoplasia (Table 1) by polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP) assay [4, 5]. In solid tumors, malignant cells and normal cells were selectively procured from hematoxylin and eosin-stained slides using a hypodermic needle. Approval was obtained from the Catholic University of Korea, College of Medicine's institutional review board for this study. Genomic DNA each from tumor and corresponding normal cells were amplified with a primer pair covering the exon 3 (the 47th–82nd amino acids of PTPN11) and another primer pair covering the exon 13 (the 484th–592nd of PTPN11). Radioisotope was incorporated into the PCR products for detection by autoradiogram. Direct DNA sequencing reactions were performed in the cases with mobility shifts in the SSCP. To confirm the SSCP data, we repeated the PCR-SSCP twice. In the second round SSCP, we included positive controls that had been detected in the first round SSCP.

In hematologic neoplasia, PCR-SSCP analysis of *PTPN11* gene led to identification of aberrant bands in two cases. DNA sequencing analysis of the cases with aberrant SSCP bands led to identification that all of the aberrant bands represented somatic mutations. The two mutations were identified in a childhood B-cell acute lymphoblastic leukemia (p.Asn58Tyr) and an adulthood acute myelogenous leukemia M5 (p.Asp61Tyr). However, none of the SSCP from the solid tumors revealed aberrantly migrating bands compared to wild-type bands from the normal tissues, indicating there was no evidence of *PTPN11* mutation in the solid tumors analyzed. To confirm the SSCP results, we repeated the experiments twice, and found that the data were consistent.

Eun Mi Je and Youn Jin Choi contributed equally to this work.

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Table 1 *PTPN11* exons 3 and 13 mutations analyzed in 2,117 tumors

Type of cancers	Number of tumors	*PTPN11* exons 3 and 13		
		Wild type	Mutation	Mutation (%)
Adulthood AML	198	197	1	0.5
Adulthood ALL	171	171	0	0
Childhood AML	16	16	0	0
Childhood ALL	175	174	1	0.6
Multiple myeloma	75	75	0	0
Non-Hodgkin lymphoma	74	74	0	0
Non-small cell lung cancer	211	211	0	0
Gastric carcinoma	150	150	0	0
Colorectal carcinoma	367	367	0	0
Breast carcinoma	90	90	0	0
Prostate carcinoma	275	275	0	0
Ovarian epithelial tumor	16	16	0	0
Ovarian stromal tumor	47	47	0	0
Hepatoblastoma	18	18	0	0
Esophageal squamous cell carcinoma	48	48	0	0
Head/neck carcinoma	20	20	0	0
Renal cell carcinoma	7	7	0	0
Squamous cell carcinoma of skin	4	4	0	0
Gastrointestinal stromal tumor	20	20	0	0
Leiomyoma	68	68	0	0
Meningioma	9	9	0	0
Sarcoma	58	58	0	0

AML acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia

An earlier study analyzed *PTPN11* mutations in nine types of solid tumors (prostate tumors (0 %), breast tumors (0 %), gastric tumors (0 %), colon tumors (0.5 %), melanomas (10 %), astrocytomas (0 %), glioblastomas (0 %), medulloblastomas (0 %) and neuroblastomas (3.4 %)) [6]. Such variable incidences of *PTPN11* mutations led us to further analyze the mutations in other solid tumors that had not been studied for the mutations. We confirmed the previous data that prostate, breast, gastric and colon tumors did not harbor the recurrent *PTPN11* mutations. In addition, our data showed that the *PTPN11* mutations were absent in lymphomas, hepatoblastomas, renal cell carcinomas, esophageal squamous cell carcinomas, head/neck carcinomas, sarcomas, meningiomas, ovarian epithelial tumors, ovarian stromal tumors, squamous cell carcinomas of skin, leiomyomas and gastrointestinal stromal tumors. In agreement with the previous reports [1], we found two mutations in hematologic tumors with low incidences. Together with the previous reports [1–3], our results indicate that the oncogenic *PTPN11* mutations are present in hematologic neoplasia, but not in solid tumors except neuroblatomas and melanomas. Our data may provide useful information on possible clinical applications targeting *PTPN11* in cancer patients.

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References

1. Pugh TJ, Morozova O, Attiyeh EF, Asgharzadeh S, Wei JS, Auclair D, Carter SL, Cibulskis K, Hanna M, Kiezun A, Kim J, Lawrence MS, Lichenstein L, McKenna A, Pedamallu CS, Ramos AH, Shefler E, Sivachenko A, Sougnez C, Stewart C, Ally A, Birol I, Chiu R, Corbett RD, Hirst M, Jackman SD, Kamoh B, Khodabakshi AH, Krzywinski M, Lo A, Moore RA, Mungall KL, Qian J, Tam A, Thiessen N, Zhao Y, Cole KA, Diamond M, Diskin SJ, Mosse YP, Wood AC, Ji L, Sposto R, Badgett T, London WB, Moyer Y, Gastier-Foster JM, Smith MA, Guidry Auvil JM, Gerhard DS, Hogarty MD, Jones SJ, Lander ES, Gabriel SB, Getz G, Seeger RC, Khan J, Marra MA, Meyerson M, Maris JM (2013) The genetic landscape of high-risk neuroblastoma. Nat Genet 45:279–84
2. Chan G, Kalaitzidis D, Neel BG (2008) The tyrosine phosphatase Shp2 (PTPN11) in cancer. Cancer Metastasis Rev 27:179–92
3. Tartaglia M, Niemeyer CM, Fragale A, Song X, Buechner J, Jung A, Hählen K, Hasle H, Licht JD, Gelb BD (2003) Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet 34:148–50
4. Yoo NJ, Kim HR, Kim YR, An CH, Lee SH (2012) Somatic mutations of the KEAP1 gene in common solid cancers. Histopathology 60:943–52

5. Je EM, Kim MR, Min KO, Yoo NJ, Lee SH (2012) Mutational analysis of MED12 exon 2 in uterine leiomyoma and other common tumors. Int J Cancer 131:E1044–7
6. Bentires-Alj M, Paez JG, David FS, Keilhack H, Halmos B, Naoki K, Maris JM, Richardson A, Bardelli A, Sugarbaker DJ, Richards WG, Du J, Girard L, Minna JD, Loh ML, Fisher DE, Velculescu VE, Vogelstein B, Meyerson M, Sellers WR, Neel BG (2004) Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res 64:8816–20