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Analysis of driver somatic mutations in heterotopia of pancreas, spleen, liver and adrenal tissues

To the Editor:

Heterotopia, also known ectopic tissue, is defined as the presence of a particular tissue type in an abnormal site. In humans, heterotopia can originate from many organs, including pancreas, adrenal and spleen [1]. Although most heterotopic tissues are incidental, they can present with nonspecific symptoms and develop benign or malignant tumors that may result in diagnostic difficulties [2]. Several hypotheses have been suggested to explain the occurrence of heterotopia, including congenital (misdirection during embryogenesis) and acquired (abnormal regeneration or genetic alteration) theories [2]. For the latter, duodenal gastric heterotopia is known to frequently carry β-catenin mutation [3]. Also, deep infiltrating endometriosis, a heterotopia of endometrial tissue, harbors somatic driver mutations of *KRAS*, *ARID1A* and *PIK3CA* [4]. As an extension of these hypotheses, we attempted to test other commonly occurring heterotopias to determine if they would harbour somatic alterations.

In the present study, we analyzed 49 cases of heterotopic pancreas, adrenal, spleen and liver that had no histologic evidence of neoplastic changes (Table 1). Archival paraffin-embedded formalin-fixed tissues were cut and examined histologically under microscope by a pathologist. They consisted of 29 pancreas, 10 adrenal, 9 spleen and 1 liver heterotopias. The pancreas heterotopias were further subdivided according to the classification of Heinrich [5]: type 1, composed of all elements of normal pancreas parenchyma; type 2, containing ductal and acinar cells without islets; type 3, composed only of ductal cells. Two cases of spleen heterotopia had 3 physically detached splenic nodules in each case and all of the 6 nodules were analyzed in this study. This study was approved by the institutional review board at the Catholic University of Korea, College of Medicine. In this study, we analyzed somatic mutation in the 49 heterotopias by Ion AmpliSeq-based next generation sequencing (NGS) using a cancer panel (OncoChase, ConnectaGen, Korea) targeting 95 cancer-related genes (Supplementary Table 1). Of the 49 heterotopia cases analyzed, 41 cases were analyzed by the cancer panel sequencing, another 2 cases by whole-exome sequencing (WES) and the other 6 by both. The NGS analyses with the cancer panel and WES were performed according to the procedures described previously [6,7]. Coverages of cancer panel sequencing depth were X264-2541 (median X798), while those of WES were X38-112 (median X77).

Libraries of the DNA samples from heterotopias of the 49 patients were successfully made and subsequently analyzed by the panel sequencing and WES. Of note, however, in neither of the panel sequencing nor WES we did not detect any somatic mutations (Supplementary Figure 1). Next, we analyzed somatic copy number alterations (CNAs) based on read depth difference in the WES data between heterotopias and matched normal tissues as described [7], but we did not observe any CNAs in the heterotopia genomes (Supplementary Figure 1). None of the multiple heterotopic spleens in two patients harbored somatic alterations.

Initially, the aim of this study was twofold, first to demonstrate somatic alterations in heterotopia and second to identify alterations according to the tissues of origin and subtype (pancreas heterotopia). However, we did not identify any somatic alterations in the 49 cases irrespective of tissue types and subtypes. We were not able to find any somatic mutations with a relatively high sequencing depth in the cancer panel for driver genes and with a wider range of genes in WES. Our data is not in agreement with data from other heterotopias (duodenal gastric heterotopia and endometriosis) that show somatic alterations. Taken together, our results suggest that somatic alteration status in human heterotopia may be different depending on the tissue types and that some may result from acquired mechanisms and others could result from non-acquired (e.g. misdirection during embryogenesis). Discovery of driver mutation in duodenal gastric heterotopia and endometriosis provided a reasonable explanation for the tumor-like features of heterotopia. Our data, however, suggest that there could be diverse mechanisms for human heterotopia development.

Table 1
Case summary for the heterotopia analyzed in this study.

Case	Histologic diagnosis (Subtype of pancreas heterotopia by Heimlich[a])	Diameter (mm)	Location	Sequencing[b]
EP1	Heterotopic pancreas (2)	5	Stomach	P
EP2	Heterotopic pancreas (1)	10	Stomach	P
EP3	Heterotopic pancreas (1)	8	Free peritoneal mass	P
EP4	Heterotopic pancreas (2)	8	Stomach	P
EP5	Heterotopic pancreas (1)	5	Free peritoneal mass	P
EP6	Heterotopic pancreas (2)	14	Small intestine	P
EP7	Heterotopic pancreas (2)	8	Duodenum	P
EP8	Heterotopic pancreas (2)	17	Duodenum	P
EP9	Heterotopic pancreas (1)	15	Free peritoneal mass	P, WES

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Table 1 (*continued*)

Case	Histologic diagnosis (Subtype of pancreas heterotopia by Heimlich[a])	Diameter (mm)	Location	Sequencing[b]
EP10	Heterotopic pancreas (1)	16	Free peritoneal mass	P, WES
EP11	Heterotopic pancreas (1)	5	Free peritoneal mass	P, WES
EP12	Heterotopic pancreas (3)	17	Stomach	P, WES
EP13	Heterotopic pancreas (2)	10	Small intestine	P
EP14	Heterotopic pancreas (1)	7	Free peritoneal mass	P
EP15	Heterotopic pancreas (1)	5	Free peritoneal mass	P
EP16	Heterotopic pancreas (1)	9	Stomach	WES
EP17	Heterotopic pancreas (1)	15	Free peritoneal mass	WES
EP18	Heterotopic pancreas (1)	10	Free peritoneal mass	P, WES
EP19	Heterotopic pancreas (1)	15	Free peritoneal mass	P, WES
EP20	Heterotopic pancreas (1)	7	Stomach	P
EP21	Heterotopic pancreas (3)	5	Stomach	P
EP22	Heterotopic pancreas (2)	10	Small intestine	P
EP23	Heterotopic pancreas (3)	7	Small intestine	P
EP24	Heterotopic pancreas (2)	5	Duodenum	P
EP25	Heterotopic pancreas (2)	15	Stomach	P
EP26	Heterotopic pancreas (2)	3	Stomach	P
EP27	Heterotopic pancreas (2)	5	Stomach	P
EP28	Heterotopic pancreas (2)	10	Duodenum	P
EP29	Heterotopic pancreas (2)	5	Stomach	P
EA1	Heterotopic adrenal gland	1	Ovary	P
EA2	Heterotopic adrenal gland	3	Fallopian tube	P
EA3	Heterotopic adrenal gland	2	Fallopian tube	P
EA4	Heterotopic adrenal gland	2	Fallopian tube	P
EA5	Heterotopic adrenal gland	3	Fallopian tube	P
EA6	Heterotopic adrenal gland	1	Fallopian tube	P
EA7	Heterotopic adrenal gland	3	Ovary	P
EA8	Heterotopic adrenal gland	3	Fallopian tube	P
EA9	Heterotopic adrenal gland	2	Ovary	P
EA10	Heterotopic adrenal gland	10	Free pelvic mass	P
ES1	Heterotopic spleen	40	Free peritoneal mass	P
ES2	Heterotopic spleen	6	Free peritoneal mass	P
ES3	Heterotopic spleen	7	Free peritoneal mass	P
ES4	Heterotopic spleen	6	Free peritoneal mass	P
ES5	Heterotopic spleen	10	Free peritoneal mass	P
ES6	Heterotopic spleen	7, 10, 12	Free peritoneal masses (n = 3)	P
ES7	Heterotopic spleen	10	Free peritoneal mass	P
ES8	Heterotopic spleen	7, 8, 9	Free peritoneal mass(n = 3)	P
ES9	Heterotopic spleen	7	Free peritoneal mass	P
EL1	Heterotopic liver	7	Free peritoneal mass	P

[a] Type 1, composed of all elements of normal pancreas parenchyma; type 2, containing ductal and acinar cells without islets; type 3, composed only of ductal cells.
[b] P: cancer panel, WES: whole-exome sequencing.

Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152461.

References

[1] R.A. Willis, Some unusual developmental heterotopias, BMJ 3 (1968) 267–272.
[2] A.A.S.R. Mannan, M. Vieth, A. Khararjian, B. Khandakar, D. Lam-Himlin, D. Heydt, et al., The outlet patch: gastric heterotopia of the colorectum and anus, Histopathology 73 (2018) 220–229.
[3] M. Nakagawa, R. Kitazawa, T. Kondo, K. Ninomiya, M. Okita, R. Haraguchi, et al., Duodenal gastric heterotopia, sporadic or fundic gland polyp-associated, frequently carries β-catenin mutation, Virchows Arch. 465 (2014) 253–256.
[4] M.S. Anglesio, N. Papadopoulos, A. Ayhan, T.M. Nazeran, M. Noë, H.M. Horlings, et al., Cancer-associated mutations in endometriosis without cancer, N. Engl. J. Med. 376 (2017) 1835–1848.
[5] S.H. Bromberg, C. Camilo Neto, A.F. Borges, M.I. Franco, L.C. França, N. Yamaguchi, Pancreatic heterotopias: clinicopathological analysis of 18 patients, Rev. Col. Bras. Cir. 37 (2010) 413–419.
[6] S.Y. Yeon, S.H. Jung, M.S. Kim, Y.J. Chung, S.H. Lee, Targeted sequencing of burn scar-related squamous cell carcinomas identified PIK3CA amplification, Pathology 50 (2018) 568–571.
[7] S.H. Jung, M.S. Kim, S.H. Lee, H.C. Park, H.J. Choi, L. Maeng, et al., Whole-exome sequencing identifies recurrent AKT1 mutations in sclerosing hemangioma of lung, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 10672–10677.

Seung Hyun Jung[1]
Cancer Evolution Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Sun-Young Jun[2]
Departments of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Sun Shin
Departments of Microbiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Seung-Mo Hong
Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Sang Yong Song
Department of Pathology, Sungkyunkwan University College of Medicine, Seoul, Republic of Korea

Nam Jin Yoo
Departments of Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Yeun Jun Chung*
Departments of Microbiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
E-mail address: yejun@catholic.ac.kr.

Sug Hyung Lee*
Departments of Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

* Corresponding author at: Integrated Research Center for Genome Polymorphism, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Socho-gu, Seoul, 137-701, Republic of Korea.

* Corresponding author at: Department of Pathology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Socho-gu, Seoul, 137-701, Republic of Korea.

[1] These two authors contributed equally to this work.

[2] These two authors contributed equally to this work.