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Correspondences

Whole-exome sequencing of chondroid hamartoma of lung identified no driver mutations

To the Editor,

By definition, a hamartoma is disorganized but a benign mass composed of cells indigenous to the involved site. The literature describes several examples of hamartomas, including hemangioma, Peutz-Jeghers polyp of the bowel, colonic hamartoma polyp, lung (chondroid) hamartoma, melanocytic nevi and splenic hamartoma. While thought to be a developmental malformation, many hamartomas in fact have clonal genetic alterations that are acquired through somatic mutations such as *TSC2* mutations in angiomyolipomas and *BRAF* mutations in melanocytic nevi, suggesting their neoplastic natures [1,2]. The most common hamartoma, pulmonary chondroid hamartoma (PCH), occur in the lungs, where 5–8% of all solitary lung nodules and about 75% of all benign lung tumors are hamartomas [3]. Histologically, they show a mixture of cartilage, connective tissue, and fat cells. They frequently produce respiratory complaints and radiologic abnormalities that sometimes make difficulties distinguishing them from malignancies [3].

There have been debates on the nature of the PCH (i.e., hamartoma vs. benign tumor) [4]. A high frequency of rearrangements of *HMGI(Y)* genes has been identified in PCH [5], suggesting the neoplastic nature of PCHs. Hence, based on the notion that the pattern of somatic mutations is tumor type-specific in many cases, PCHs might harbor somatic mutations as well as the rearrangements [5]. In the present study, we attempted to identify somatic mutations by using next-generation sequencing (NGS)-based whole-exome sequencing that allows for the interrogation of thousands of variants from multiple genes within a given tumor sample at the same time.

We analyzed three PCHs (two (HAMAR1 and HAMAR2) with formalin-fixed paraffin-embedded (FFPE) tissues and one (HAMAR3) with frozen tissue). HAMAR1, HAMAR2 and HAMAR3 were from 58-year-old woman (5.0 cm in diameter at right lower lobe), 68-year-old woman (1.8 cm in diameter at right upper lobe) and 60-year-old woman (1.8 cm in diameter at right upper lobe), respectively. They did not show any medical problems except the incidental PCHs. Histologically, the PCHs consisted mainly of hyaline cartilage and other mesenchymal components including fat (Fig. 1). Chondroid portions of the PCHs and adjacent normal alveolar tissues were selectively procured from hematoxylin-stained sections by micro-dissection. Purities of the PCH cells from the microdissection were approximately 70%. DNA from the PCH and corresponding normal tissues was sequenced by whole-exome sequencing using the Agilent SureSelect Human All Exome 50Mb Kit (Agilent Technologies, Santa Clara, CA) and analyzed by MuTect and SomaticIndelDetector as described in our previous study [6].

In whole-exome sequencing, coverages of the sequencing depth for tumor and normal samples were 153X and 158X, respectively. A total of 16 non-silent somatic mutations (2 in HRMA1, 5 in HRMA2 and 9 in HAMR3) (Fig. 2A) were identified in the PCH genomes. To address whether the mutations found in our study were causally implicated in the development of PCHs, we queried 609 cancer-related genes from the Cancer Gene Census [7], but identified only two genes (*DCC* and *HDX*). At a variant level, the *DCC* p.P767A in HAMAR2 and *HDX* p.R334Q in HAMAR3 (Fig. 2B) had been identified in the Cancer Gene Census. Next, we analyzed somatic copy number alterations (CNAs) based on the read depth difference in the whole-exome sequencing data between PCHs and matched normal tissues as described elsewhere [6], but we did not observe any CNAs in the PCH genomes (data not shown).

The previous information supporting that PCH may be a neoplastic disease [4,5], led us to analyze somatic mutations in the coding genes by whole-exome sequencing. In this study, we found that the PCHs harbored few somatic mutations. Moreover, only two gene mutations (*DCC* and *HDX*) were previously reported in other cancers (the Cancer Gene Census). *DCC* gene encodes a netrin 1 receptor that interacts with the tyrosine kinases Src and focal adhesion kinase FAK. The protein is known to behave as a tumor suppressor and frequently mutated or downregulated in colorectal and esophageal carcinomas [8]. Cancer-related functions for HDX have not been reported. However, non-recurrence of the *DCC* and HDX mutations in our PCHs suggests that these mutations, if any, may not play an important role in PCH development. In summary, our data suggest that PCH might be a neoplastic disease with somatic alterations rather than a developmental disease. However, our data also suggest that other genetic alterations such as gene rearrangements may be responsible to PCH development.

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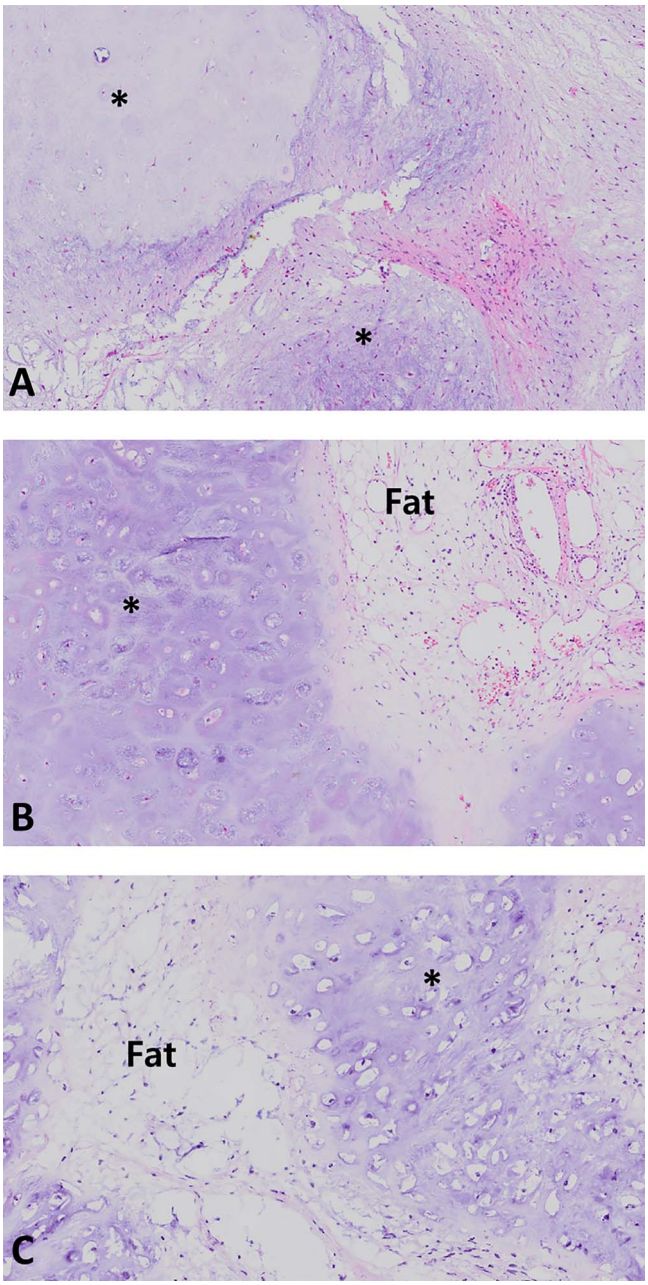

Fig. 1. Histology of pulmonary chondroid hamartomas used in this study. Hematoxylin and eosin staining of the hamartomas (A: HAMAR1, B: HAMAR2, C: HAMAR3) show chondroid (*) and fat (Fat) tissues.