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Molecular genetic differences in accordance with pathophysiology and histology between primary and secondary hyperparathyroidism targeted by next-generation panel sequencing

Yu Ah Hong[1], Ki Cheol Park[2], Bong Kyun Kim[4], Jina Lee[4], Woo Young Sun[4], Hae Joung Sul[3], Yoon Kyung Chang[1], Suk Young Kim[1], Soyoung Shin[5], Joonhong Park[5]
[1]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[2]Department of Clinical Research Institute, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[3]Department of Pathology, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[4]Department of Surgery, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of
[5]Department of Laboratory Medicine, The Catholic University of Korea, Daejeon St. Mary's Hospital, Korea, Republic of

Objectives: Secondary hyperparathyroidism (SHPT) is a common complication in patients with chronic kidney disease, and is characterized by excessive serum parathyroid hormone levels and parathyroid hyperplasia (PH). Several genes have been known to the pathogenesis of sporadic parathyroid adenoma (PA), a representative phenotype of primary hyperparathyroidism (PHPT). However, the molecular genetic pathogenesis of SHPT remains uncharacterized.

Methods: To better understand the differences of genetic alterations as a potential marker of discrimination for hyperparathyroidism between PHPT and SHPT, a next-generation sequencing (NGS) consisting of known 42 genes associated to parathyroid tumors was conducted using DNA extracted from formalin-fixed paraffin-embedded parathyroid tissues after parathyroidectomy.

Results: Among total 46 samples diagnosed as PHPT (N = 25) or SHPT (N = 21), data analysis of the NGS resulted in 23 nonsynonymous somatic variants in exons or splice sites in the 18 patients. The frequently mutated genes were *ASXL3* (17%, 4/23), *CDC73* (17%, 4/23), *EZH2* (13%, 3/23) and *MTOR* (9%, 2/23) in all parathyroid tumors. Fifteen of 25 patients with PHPT (60%) had one or more mutations, whereas 3 (21%) of 21 patients with SHPT had only one mutation (P = 0.002). Known driver mutations, *CCND1* and *CDC73,* associated with parathyroid tumorigenesis were identified only in PHPT (33%, 5/15), whereas none (0%, 0/3) in SHPT. Fifteen of 28 patients with PAs (54%) had one or more mutations, whereas 3 (17%) of 18 patients with PH had one mutation only (P = 0.015). Likewise, *CCND1* and *CDC73* were identified only in PA (33%, 5/15), whereas none (0%, 0/3) in PH. Each one patient with *ASXL3, CIT* and *HGF* gene mutation was identified in SHPT.

Conclusions: Our results suggest that the molecular genetic abnormalities of SHPT have distinct from those known for PHPT. These findings may be helpful in further analysis of the mechanisms underlying SHPT development.