中文題目：鈣離子感受器新生突變所致之低尿鈣高血鈣症

英文題目：Sporadic Hypocalciuric Hypercalcemia Caused by *De Novo* CaSR Mutation

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Background:

Hypercalcemic disorders with hypocalciuria are caused primarily by chronic thiazide or lithium use, acquired antibody to the calcium-sensing receptor (CaSR), familial hypocalciuric hypercalcemia (three types: type 1 (CaSR), type 2 (GNA11) and type 3 (AP2S1)) or sporadic type. It is crucial to distinguish among these causes due to different treatment strategy.

Methods:

A 51-year-old man was referred because of hypercalcemia of unknown cause for > 5 years and progressive decline in eGFR. Family and personal history were non-revealing. There were no obvious symptoms related to hypercalcemia but easy fatigue, constipation and deteriorating renal function. Laboratory testing revealed hypercalcemia (12.5 mg/dL; range, 8.6-10.2) with hypocalciuria (spot urine Ca/Cr ratio was 0.019 in mg/dl/mg/dl, 24-hour urinary calcium excretion was 32 mg/day), and inappropriately elevated iPTH (65 pg/mL; range, 10.0-69.0). Parathyroid and abdominal sonography was normal. Direct sequence analysis of the relevant genes inclusive of CaSR, GNA11and AP2S1 showed a heterozygous missense T>A nucleotide substitution at c.1661, resulting in an amino acid change I554N in the extracellular domain of CaSR. I554 is well conserved in all species and this novel mutation is not inherited from his parents. In addition, this CaSR gene mutation was not found in 200 healthy subjects and should be pathogenic based on the predictive tools via PROVEAN and Polyphen2 score. Calcimimetics with cinacalcet (25 mg daily) reduced his serum calcium concentration to 11.2 mg/dL and iPTH level to 9.7 pg/mL, coupled with an increased urine calcium excretion (spot urine Ca/Cr ratio to 0.06) and eGFR four months later.

Conclusions:

Genetic diagnosis for idiopathic or sporadic hypocalciuric hypercalcemia is warranted. Calcimimetics by sensitizing the CaSR to calcium rather than parathyroidectomy can be used to treat symptomatic or moderate to severe hypercalcemia patients with loss of function mutation in CaSR.