Dear editor,

We are pleased to receive the revision letter on our manuscript entitled "Cutaneous nodules and a novel GNAS mutation in a Chinese boy with pseudohypoparathyroidism type Ia: a case report" (ID: 51342). We are so grateful for the reviewers and their kind suggestions. We have studied the comments and found they are of great help on improving the quality of our manuscript. We have revised the manuscript by highlighting the revised portions in red. The point-by-point response was listed below. We really hope the revised manuscript is now qualified for publication. If there is additional question, please do not hesitate to contact us.

The responds to the comments are as flowing:

Comment 1: Please better describe the mechanism leading to PTH resistance in the kidney in PHP1a:

Response: Thanks very much for your kind suggestion. The GNAS gene is located on chromosome 20q13, which consists of 13 exons and 12 introns. The product of the GNAS gene is the Gsα, which is an important component of the cAMP/protein kinase. PTH mainly couples with Gsα through the PTH receptor to form a complex that activates adenylate cyclase and promotes the generation of cAMP, thereby regulating the cell response. GNAS is a complex imprinted gene encoding Gsα that exhibit exclusively maternal or paternal expression. Maternal allele in GNAS gene is the only source of Gsα in the kidney (the paternal allele is normally silenced in this tissue). In PHP Ia, mutations in the maternal GNAS allele results in marked reduction of Gsα levels, leading to failure to elicit an appropriate increment in urinary cAMP and phosphate excretion following exogenous PTH infusion and PTH resistance. Because the target organs (i.e., in the kidney and bone) do not respond to PTH, hypocalcemia feedback stimulates excessive parathyroid secretion of PTH. We have added more discussion about this issue in the revised discussion.

Comment 2: The authors present a case of hereditary PHP1a and describe a new mutation. Please present a supplementary table with other GNAS mutations previously described. What is the percentage of cases of sporadic PTH1a?

Response: Thank very much for your kind suggestion. We have added a supplementary table showed PHP Ia cases with GNAS mutations previously described. We could not be determined the percentage of cases of sporadic PHP Ia because of the underlying bias to report chiefly on identified mutations, and conclusion of the percentage of cases of sporadic needs to be determined by population studies. However, the percentage of cases of sporadic PHP Ia has been estimated to be approximately 20%–40%, based on some of the larger mutation analysis studies [Ahrens et al., 2001; Linglart et al., 2002; De Sanctis et al., 2003; Adegbite et al., 2008; Elli et al., 2013]. Thank you for your suggestion again.

Comment 3: Please better explain heterotopic ossification in PHP1a, concerning its location and mechanism (hypercalcemia versus GNAS mutation induced osteogenic differentiation of stromal cells derived from adipose tissue while inhibiting their adipogenic differentiation).

Response: Thank very much for your kind suggestion. We have added the explaination in the discussion, as follow:

"The GNAS-related heterotopic ossification involves aberrant differentiation of mesenchymal stem cells or early progenitors located in the dermis or subcutaneous fat. In human mesenchymal stem cells, there was a decrease in Gsα expression with osteogenic differentiation and antisense oligonucleotides, and protein kinase A inhibition led to increased expression and DNA binding of the osteoblast-specific Runx2/Cbfa1. Additionally, with decreased Gsα expression or protein kinase A inhibition, Runx2/Cbfa1 protein was serine phosphorylated and ubiquitinated less. Reduction of Gsα protein levels caused osteogenic differentiation and inhibition of formation of adipocytes.

With best regards,

Sincerely,

Fang Hong