

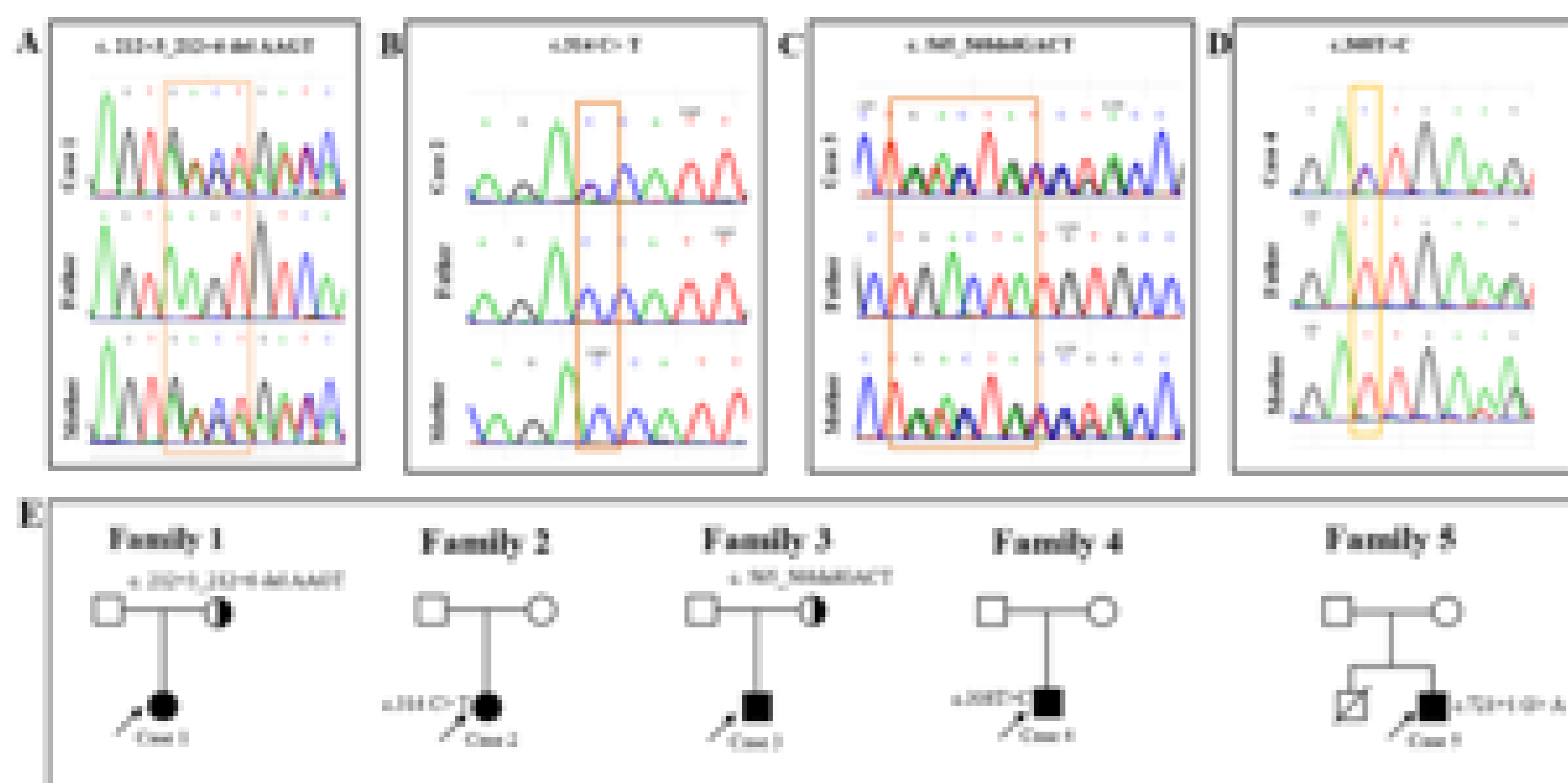
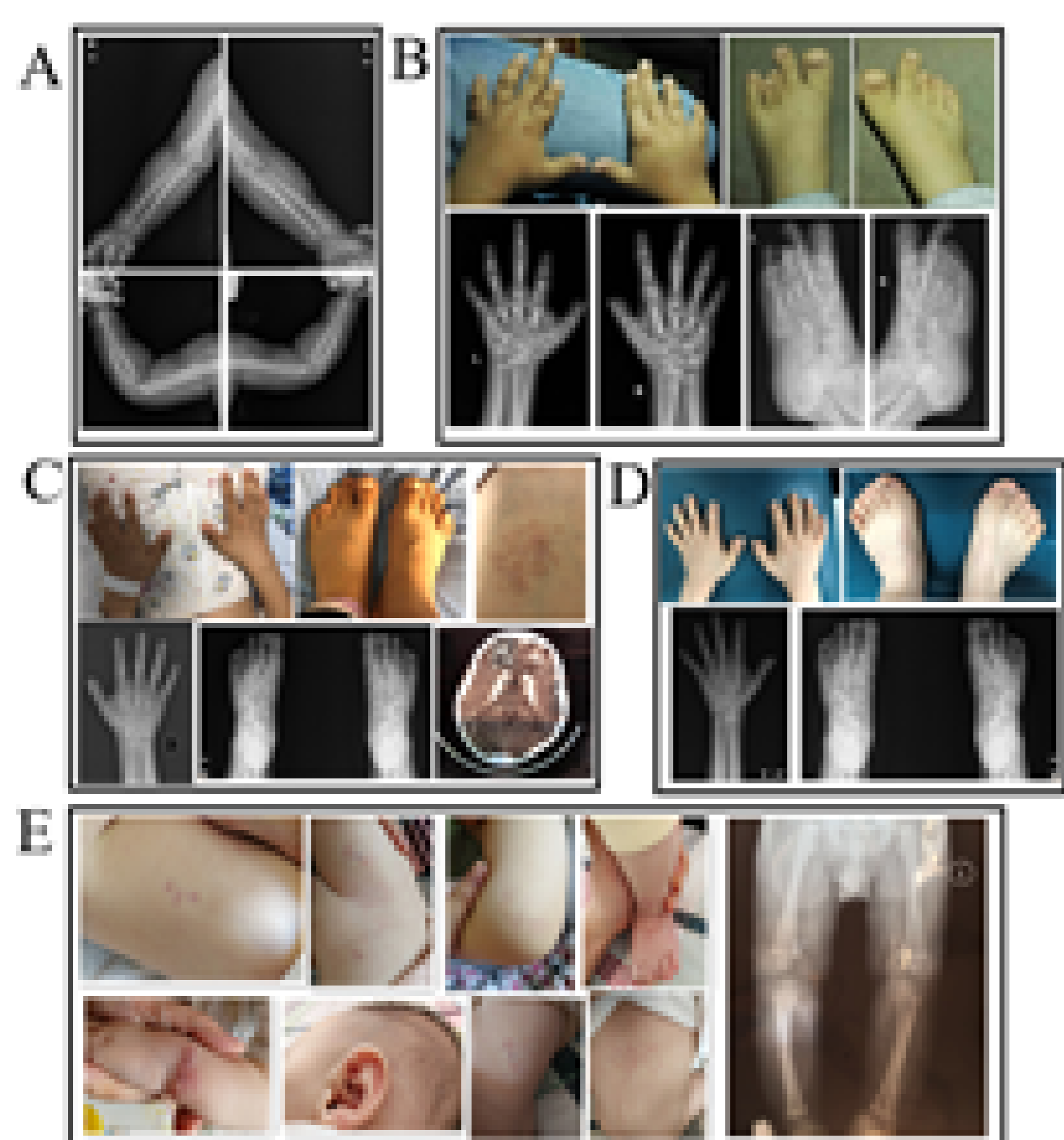
◆ **Background** Inactivating mutations of the GNAS (gene encoding the alpha-subunit of Gs) gene involving exon 1-13 which encode the alpha-subunit of the stimulatory G protein (Gsa) are associated with several syndromes, including pseudohypoparathyroidism (PHP), pseudopseudohypoparathyroidism (PPHP) and progressive osseous heteroplasia (POH).

◆ **Method** We collected clinical information of the patients, performed the targeted next generation sequencing and further verified with Sanger sequencing. The standards and guidelines from American College of Medical Genetics and Genomics was used to classify and interpret the pathogenicity for each genetic variant.

◆ **Result** The diagnosis of PPHP was made in case 4. In case 5, POH was taken into consideration. All the five patients were found to carry the possibly causative variants, among which two variants including a missense mutation (c.314C>T) and a splicing mutation (c.721+2 G>A) have never been reported in patients before.

Table 2. Clinical, laboratory, and imaging findings of five patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Female	Female	Male	Male	Male
Birth					
Weeks	Term	Term	Term	32w	36w
Birth weight (g)	2,900	2,800	3,500	1,610	2,000
Birth length (cm)	Unknown	50	Unknown	35	39
At diagnosis					
Age	2½y	11½y	11½y	10½y	10m
Height (cm)	91 (+0.5SD)	137.8 (-2.21 SD)	133 (-2.2SD)	139.5 (-2.08SD)	67 (-2.76 SD)
Weight (kg) SDS	20 (+4.9SD)	36.85 (-0.33 SD)	36.5 (-0.48SD)	24.2 (1.82SD)	6.8 (-2.82 SD)
BMI (kg/m ²)	24.152 (obese: >18.9)	19.406	20.634 (overweight: >20.1)	14.43	/
AHO phenotype					
Short stature	No	Yes	Yes	Yes	No
Brachydactyly	No	Yes	Yes	Yes	No
Ectopic ossification	Yes	No	Yes	Yes	Progressive
Obesity	Yes	No	Yes	No	No
Round face	Yes	Yes	Yes	No	No
Intellectual disability	No	No	Yes	No	No
Hormone resistance					
PTH resistance	Yes	Yes	Yes	No	No
PTH	87 pg/ml (15.0-65.0) †	124.3 pg/ml (15.0-68.3) †	14.93 pmol/L (1.6-6.9) †	4.45 pmol/L (1.6-6.9)	44.5 pg/ml (10.0-69.0)
Calcium (mmol/L)	2.70 (2.25-2.80)	2.32 (2.20-2.80)	1.25 (2.25-2.80) †	2.44 (2.25-2.80)	2.37 (1.9-2.6)
Phosphorus (mmol/L)	2.19 (1.45-2.10) †	1.66 (1.45-2.10)	>4.20 (1.45-2.10) †	1.49 (1.45-2.10)	1.88 (1.2-1.9) †
TSH resistance	Yes	No	Yes	No	/
TSH	5.72(0.34-5.60) †	4.70(0.35-4.94)	8.84(0.34-5.60) †	2.99(0.34-5.60)	/
FT4	11.71(7.86-19.20)	13.51(9.01-19.05)	7.25(7.86-19.20) †	12.88(7.86-19.20)	/
FT3	6.27(3.8-9.8)	3.78(2.63-5.70)	4.29(3.8-9.4)	6.44(3.8-9.4)	/
IGF-1 (ng/mL)	114.0	486	150	161.0	/
FSH/ LH (mIU/mL)	11.54/0.58	/	6.74/2.23	3.60/2.67	/
ACTH (3.0-46.0 pg/mL)	29.5	/	12.1	21.2	/
25-OHD (>10.0 ng/mL)	16.97 †	Unknown	18.84 †	19.01 †	20.4 †
Other findings					
Brain MRI or CT	Normal	/	Calcification	Calcification	Normal



◆ **Conclusion** Our study expanded genotypic and phenotypic spectrum of the GNAS related disorders.