

CASE REPORT

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# GNAS mutation is an unusual cause of primary adrenal insufficiency: a case report

Yajie Tong, Dongmei Yue, Ying Xin and Dan Zhang\*

## Abstract

**Background:** Primary adrenal insufficiency in children has non-specific and extensive clinical features, so the diagnosis of its etiology is complex and challenging. Although congenital adrenal hyperplasia is the most common cause, more and more other genetic causes have been identified. *GNAS* mutation is easily overlooked as a rare cause of primary adrenal insufficiency. Here we firstly report a neonatal case of primary adrenal insufficiency caused by *GNAS* mutation.

**Case presentation:** A boy was diagnosed with congenital hypothyroidism 10 days *post-partum* and treated immediately. He also had persistent hyperkalaemia and hyponatraemia with elevated adrenocorticotropic hormone. At 70 days after birth, he was transferred to our hospital on suspicion of congenital adrenal hyperplasia. Physical examination found no other abnormalities except for growth retardation. Laboratory examination revealed increased aldosterone and normal cortisol, 17-hydroxyprogesterone, and androstenedione levels. Abnormally elevated parathyroid hormone was accompanied by normal blood calcium. Genetic assessment found a *de novo*, heterozygous c.432 + 1G > A variant in *GNAS*.

**Conclusions:** We report this case to highlight that *GNAS* mutation is an unusual cause of primary adrenal insufficiency. The combination of primary hypothyroidism and /or pseudohypoparathyroidism will provide diagnostic clues to this condition.

**Keywords:** *GNAS* mutation, Primary adrenal insufficiency, Congenital hypothyroidism, Pseudohypoparathyroidism, Case report

## Background

Primary adrenal insufficiency (PAI) is a rare and potentially life-threatening disease in children. Due to the non-specific and extensive clinical features, the etiological diagnosis of PAI becomes challenging. PAI in childhood is mostly caused by monogenic diseases, and congenital adrenal hyperplasia (CAH) is the most common etiology [1–3]. However, other non-CAH genetic etiologies have been gradually established, such as *NR5A1/SF-1*, *NROB1/DAX-1*, *ABCD1* and *PEX1*. The *GNAS* gene

encodes the alpha-subunit of the G protein ( $G\alpha$ ) which mediates the signalling of numerous peptide hormones such as parathyroid hormone (PTH), thyroid stimulating hormone (TSH), growth hormone-releasing hormone (GHRH), adrenocorticotropic hormone (ACTH), and gonadotrophins. A maternally derived *GNAS* mutation causes the Albright hereditary osteodystrophy (AHO) phenotype (short stature, obesity, round face, subcutaneous ossifications, brachydactyly, mental deficits, and intrauterine growth restriction), with multiple hormone resistance (MHR). However, paternally derived mutations may lead to only AHO without hormone disorders [4]. A large number of reports have confirmed that *GNAS* mutations can cause pseudohypoparathyroidism (PHP), congenital hypothyroidism (CH) and growth

\*Correspondence: zhangdan\_0309@163.com

Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, P. R. China



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hormone deficiency (GHD) due to hormone resistance. However, conclusions about whether *GNAS* mutations cause ACTH resistance and PAI are inconsistent. Here we report for the first time a neonatal case of PAI caused by *GNAS* mutation, indicating that *GNAS* mutation is a potential and unusual cause of PAI.

### Case presentation

The patient from a nonconsanguineous family was a premature boy with a gestational age of 36 w and a birth weight of 1.9 kg. After birth, he was diagnosed with congenital hypothyroidism in a local hospital and treated immediately (L-thyroxine 25 µg/q.d p.o.). Furthermore, hyperkalaemia and hyponatraemia were noted during the same admission and persisted after discharge without treatment. At the same time, serum ACTH, renin, and aldosterone levels were elevated (Table 1). At 70 days *post-partum*, he was transferred to our hospital on suspicion of CAH. On physical examination, he was found to weigh 2.8 kg (<3rd percentile), without hypotension, skin pigmentation, and signs of AHO. His external genital development was normal. Hypothyroidism had been corrected with L-thyroxine treatment. Test results for the presence of thyroid auto-antibodies were negative, and ultrasonography scan showed no goitre. Hyperkalaemia and hyponatraemia were confirmed. Serum calcium and 25-hydroxyvitamin D3, blood glucose, and renal function were normal. On hormonal assessment, elevated ACTH and aldosterone levels and a normal basal cortisol level were detected. The follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone concentrations were matched with ‘mini-puberty’ (Table 1). The 17-hydroxyprogesterone (17-OH-P) and androstenedione levels and adrenal ultrasonography scan were normal. After intravenous infusion of normal saline, serum potassium decreased to slightly higher than normal, and serum sodium rose to normal, such that hydrocortisone was not used. After obtaining the parents’ informed consent, genomic DNA of the baby and his parents was genetically tested.

After being discharged from our hospital, the child returned to his local hospital for a follow-up examination. Thyroid function was well controlled, but hyperkalaemia and hyponatraemia persisted. At the age of 6 months, the child came back for re-examination. He weighed only 5.3 kg (<3rd percentile) and had normal blood pressure and neuromotor development. Growth was slow, although euthyroid with levothyroxine, persistent hyperkalaemia, hyponatraemia, and increased aldosterone suggested that there was still cortisol insufficiency. Elevated serum PTH with normal serum calcium and slightly elevated phosphate levels indicated resistance to PTH. Renal function and 25-hydroxyvitamin

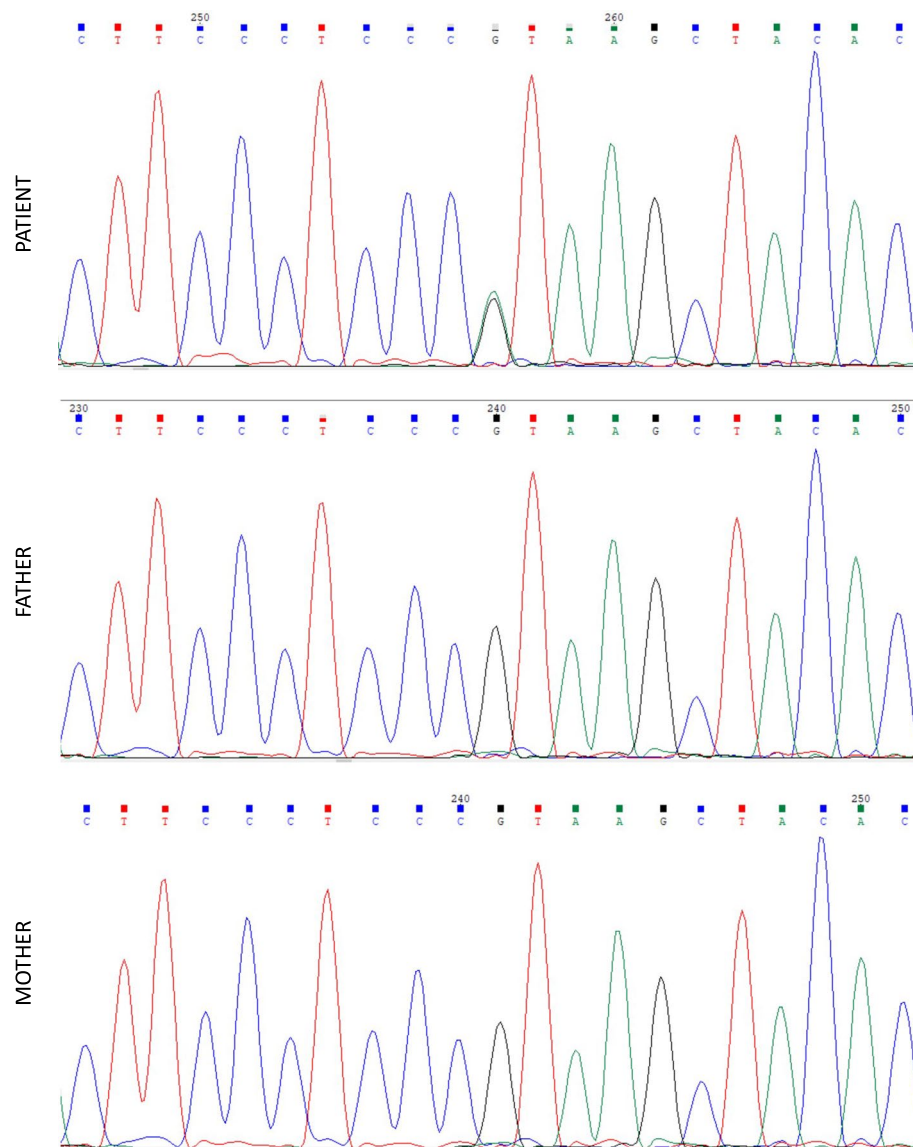
**Table 1** Laboratory evaluations at diagnosis and follow-up visits

Age	Investigation	Result	Normal Range
10 days	TSH	58.43 uIU/ml	0.3–5.7
	FT <sub>4</sub>	6.8 pmol/L	10–28
20 days	serum potassium	6.7 mmol/L	3.5–5.5
	Serum sodium	131 mmol/L	135–145
	ACTH (8:00)	20.56 pmol/L	1.6–13.9
	Renin	49.5 pg/mL	4–24
	aldosterone	959.77 pg/mL	10–160
70 days	serum potassium	6.13 mmol/L	3.5–5.5
	Serum sodium	127.7 mmol/L	136–145
	Serum calcium	2.26 mmol/L	1.9–2.6
	Serum phosphate	1.94 mmol/L	1.2–1.9
	ACTH (8:00)	111.8 pg/mL	7.2–63.3
	cortisol	10.00 µg/dL	6.02–18.4
	aldosterone	380.1 pg/mL	30–160
	LH	7.20 mIU/mL	
	FSH	3.23 mIU/mL	
	testosterone	2.24 ng/mL	
6 months	17-OH-P	5.42 ng/mL	3.6–13.7
	androstenedione	1.10 ng/mL	0.6–3.1
	serum potassium	6.62 mmol/L	3.5–5.5
	Serum sodium	129 mmol/L	136–145
	Fasting glucose	5.17 mmol/L	3.9–6.11
	ACTH (8:00)	34.34 pg/mL	7.2–63.3
	cortisol	7.64 µg/dL	6.02–18.4
	aldosterone	478.2 pg/mL	70–300
	LH	0.53 mIU/mL	
	FSH	1.57 mIU/mL	
	testosterone	0.14 ng/mL	
	Serum calcium	2.38 mmol/L	1.9–2.6
	Serum phosphate	1.95 mmol/L	1.2–1.9
	PTH	135.4 pg/mL	12–88
IGF-1	26.93 ng/mL	15–305	

TSH thyroid stimulating hormone, FT<sub>4</sub> free thyroxine, ACTH adrenocorticotropic hormone, LH luteinizing hormone, FSH follicle-stimulating hormone, 17-OH-P 17-hydroxyprogesterone, PTH parathyroid hormone, IGF-1 insulin-like growth factor-1

D3 remained normal. Serum LH, FSH, and testosterone levels were consistent with his age. Serum insulin-like growth factor-1 (IGF-1) concentration was at a low value in the normal range (Table 1).

Next generation sequencing of the patient’s DNA revealed a *de novo* heterozygous c.432 + 1G > A variant in *GNAS* (Fig. 1). It is a splicing mutation affecting the canonical splice donor site of intron 5 and is likely to result in loss of the donor splice site. According to the ACMG guideline, this variant is considered to be pathogenic. Literature review indicated that this variant had been previously described to be related to AHO [5]. To



**Fig. 1** The heterozygous c.432 + 1G > A mutation in the *GNAS* gene was detected in the patient's lymphocytes, but was absent in the parental blood samples

date, only five other cases with the same mutation have been reported, of which three patients had the mutation in the paternal allele and exhibited features of AHO but had no hormone resistance [5, 6]. The other two patients' clinical phenotypes and biochemical and endocrine characteristics were not described in detail by the authors [7, 8]. Our case is the first report that this mutation causes MHR. Since only inactivating mutations that occur in the maternal allele can cause MHR, it is speculated that the de novo mutation of our case occurred in the maternal allele.

## Discussion and conclusions

In this report we present a patient with PAI and primary hypothyroidism in the neonatal period, genetic assessment revealed a heterozygous variant in *GNAS* as an underlying defect. *GNAS* is located on chromosome 20q13.2–13.3 and is a complex imprinted gene. Owing to tissue-specific imprinting, in some tissues (such as renal proximal tubule, thyroid, pituitary, and gonads), paternal alleles are not expressed, so loss-of-function mutations of maternal alleles can lead to decompensated Gs $\alpha$  protein inactivation then result in resistance to PTH, TSH, GHRH, and gonadotrophins. However, in most tissues,

because of biallelic *GNAS* expression, a heterozygous mutation is not sufficient to significantly interfere with gene function. Paternal mutations can cause AHO, possibly owing to haplo-insufficiency of *Gsα* in bone tissue [9].

Cases with *GNAS* mutations have diverse clinical phenotypes, and hormone resistance can be detected at different stages of life with large individual differences [10, 11]. The onset of PTH resistance is usually delayed and may not be discovered until childhood, adolescence, or even adulthood. This latency of PTH resistance may be due to a gradual development of paternal *Gsα* silencing in the maternally imprinted tissues [12]. Similar to previous cases [13], our patient had normal serum calcium with an inappropriately raised PTH level, excluding secondary hyperparathyroidism caused by renal insufficiency and vitamin D deficiency. This indicates the emergence of PTH resistance, and long-term follow-up is required to monitor the serum calcium level.

Besides PTH, resistance to other hormones may also be seen. Among them, TSH resistance is the most common and usually the first to be discovered. It manifests as an elevated TSH with normal or slightly low FT<sub>4</sub>, usually in the absence of goitre and anti-thyroid antibodies. Elevated TSH may be detected at neonatal screening and diagnosed as congenital hypothyroidism [14], just like that in this case. It may also be discovered in infancy or even in childhood and adolescence.

Although corticotropin-releasing hormone (CRH) and ACTH function through *Gsα* receptors, there are inconsistent conclusions about whether *GNAS* mutation can cause adrenal insufficiency. Ridderskamp et al. [15] believe that PHP patients can be accompanied by ACTH resistance, as they detected hypocortisolism in an adult PHP case. This opinion was supported by three other reports which found elevated ACTH levels or an exaggerated ACTH response to CRH in PHP patients [16–18]. Chaubey et al. [19] also reported a case of *GNAS* mutation with primary adrenal insufficiency, although the author believes that the adrenal insufficiency was idiopathic. Our patient developed hyperkalaemia, hyponatraemia, and increased ACTH during the neonatal period and grew slowly, even with normal thyroid function control. CAH was once suspected, but the child had no clinical manifestations of elevated androgen; 17-OH-P and androstenedione were normal, aldosterone was increased, and adrenal ultrasonography scan was normal. The diagnosis of classic CAH, congenital adrenal dysplasia, and adrenal haemorrhage was not supported. Combined with the results of genetic testing, the condition was attributed to adrenal insufficiency caused by ACTH resistance. However, some other reports indicate normal adrenal responsiveness to

ACTH/CRH in patients with PHP [20, 21]. It is speculated that the absence of ACTH resistance may be related to the biallelic expression of the *GNAS* gene in the adrenal gland. Previous studies on pituitary, thyroid, and gonadal samples have revealed significant inter-individual variation with respect to the degree of paternal *Gs* expression [22, 23]. If there is a similar situation in the adrenal gland, the variable degree of paternal *Gs* silencing in the adrenal gland may be a possible explanation why ACTH resistance is less frequently encountered. In addition to the residual *Gsα* function and imprinting mechanism, other modification factors, such as environmental factors and cofactors of the cAMP coupling pathway, may also affect the clinical phenotype of patients with *GNAS* mutations. Further studies are required to explain the individual phenotypic variability among these patients.

About two-thirds of PHP patients are reported to develop GH deficiency, secondary to GHRH resistance [11, 21, 22, 24]. GH deficiency and the premature fusion of the epiphyses result in the patient's short stature. Studies have shown that rhGH replacement therapy before puberty can increase the growth rate and maximally improve the final adult height [9]. Our case had growth retardation, and the IGF-1 level of the patient was at a low value in the normal range. The possibility of combined GHRH resistance could not be excluded. After adrenal insufficiency has been corrected, close monitoring of growth velocity and IGF-1 level is necessary to further evaluate the GH level.

As hypogonadism can also be seen in PHP due to gonadotropin resistance [11], we also need to pay attention to delayed or incomplete sexual maturation during follow-up in our patient.

In conclusion, the causes of PAI are complex and diverse. Due to considerable overlap in clinical and biochemical characteristics of PAIs of different etiology, genetic detection is often required for accurate cause diagnosis. The specific genetic diagnosis of PAI is not only conducive to early diagnosis and reasonable treatment, but also extremely valuable for predicting prognosis and potential comorbidities. Our case suffered from PAI and primary hypothyroidism during the neonatal period, genetic testing confirmed that *GNAS* mutation is the cause. Sharing this case can remind pediatricians not to ignore that *GNAS* mutation is an unusual cause of PAI. The combination of primary hypothyroidism and /or PHP will provide clues to the etiological diagnosis of PAI.

#### Abbreviations

PAI: Primary adrenal insufficiency; CAH: Congenital adrenal hyperplasia; *Gsα*: Alpha-subunit of the G protein; PTH: Parathyroid hormone; TSH: Thyroid

stimulating hormone; GHRH: Growth hormone–releasing hormone; ACTH: Adrenocorticotropic hormone; AHO: Albright hereditary osteodystrophy; MHR: Multiple hormone resistance; PHP: Pseudohypoparathyroidism; CH: Congenital hypothyroidism; GHD: Growth hormone deficiency; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; 17-OH-P: 17-hydroxyprogesterone; IGF-1: Insulin-like growth factor-1; CRH: Corticotropin-releasing hormone.

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### Authors' contributions

Y.J. T. and D.Z. planned the study. Y.J. T. analyzed the data and wrote the manuscript. D.M.Y. and Y.X. collected the clinical data. D.Z. revised the manuscript. All authors discussed the results. The author(s) read and approved the final manuscript.

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### Availability of data and materials

The gene sequencing data of *GNAS* is stored in NCBI Sequence Read Archive (SRA) (accession number: SRR20281056).

### Declarations

#### Ethics approval and consent to participate

Written informed consent was obtained from the parents for providing a blood sample for genetic testing and publication of this case report. Approval was obtained from the ethics committee of Shengjing Hospital of China Medical University.

#### Consent for publication

Written consent for publication was obtained from the patient's legal guardian.

#### Competing interests

The authors declare that they have no competing interests.

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