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# Atypical Presentation and Course of ACTH-Independent Cushing's Syndrome in Two Families

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## What is already known on this topic?

Primary pigmented nodular adrenocortical disorder (PPNAD), which is rarely seen children while it is the most prevalent cause of adrenocorticotrophic hormone (ACTH) independent Cushing's syndrome, is typically a micronodular disease and mainly associated with Carney complex (CNC). CNC is a rare autosomal dominant syndrome, characterized by pigmented lesions of the skin and mucosa, cardiac, cutaneous and other myxomas and multiple endocrine tumors.

## What this study adds?

The findings of reported families provide information for a better understanding of the genetic pathogenesis, diagnosis and clinical management of CNC. Analytic variability in ACTH assays should be kept in mind during interpretation of ACTH levels. One case developed Hodgkin lymphoma five year after adrenalectomy, this association was not previously reported with CNC. Two cases had macronodules contrary to what is generally seen in cases with PPNAD.

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## ABSTRACT

Primary pigmented nodular adrenocortical disease (PPNAD) is a rare genetic disease mainly associated with Carney complex (CNC), which is caused by germline mutations of the regulatory subunit type I-alpha of the cAMP-dependent protein kinase (*PRKAR1A*) gene. We report three cases suffering from CNC with unique features in diagnosis and follow-up. All cases had obesity and a cushingoid appearance and exhibited laboratory characteristics of hypercortisolism. However biochemical and radiological examinations initially suggested Cushing's disease in one case. All of the cases were treated surgically; two of them underwent bilateral adrenalectomy at once, one of them had unilateral adrenalectomy at first but required contralateral adrenalectomy after nine months. Contrary to what is usually known regarding PPNAD, the adrenal glands of two cases (Case 2 and 3) had a macronodular morphology. Genetic analyses revealed pathogenic variants in *PRKAR1A* (Case 1: c.440+5 G>A, not reported in the literature; cases 2 and 3: c.349G>T, p.V117F). One case developed Hodgkin lymphoma five year after adrenalectomy, this association was not previously reported with CNC. The findings of these families provides important information for a better understanding of the genetic pathogenesis, diagnosis, and clinical management of CNC. Hodgkin lymphoma may be a component of CNC.

**Keywords:** Cushing's disease, cancer, myxoma, lentigo, PEG precipitation, macronodule

## Introduction

Endogenous Cushing's syndrome (CS) in children is rare, with an incidence of 1-1.5 per million population per year. Adrenocorticotrophic hormone (ACTH)-independent CS accounts for 15-20% of endogenous CS (1). Bilateral nodular adrenocortical diseases have been detected in 1-2% of these patients, resulting in ACTH-independent CS (2). In primary pigmented nodular adrenocortical disease (PPNAD), both adrenal glands are involved, and there are small, brown-black nodules separated by the atrophic adrenal cortex. Nodules are typically smaller than 1 cm and demonstrate micronodular hyperplasia (3). Carney complex (CNC) is a rare autosomal dominant syndrome characterized by pigmented lesions of the skin and mucosa, cardiac, cutaneous, and other myxomas, and multiple endocrine tumors, the most common of which is PPNAD (4). CNC is caused by mutations in the *PRKAR1A* (OMIM 188830) coding for the regulatory subunit type I-alpha ( $R1\alpha$ ) of protein kinase A (PKA). To establish a diagnosis of CNC, a patient must exhibit two of the disease's manifestations or exhibit one of these manifestations and have an affected first-degree relative or an inactivating *PRKAR1A* mutation. No direct correlation has been identified between all *PRKAR1A* mutations and the various phenotypes to date (5).

The present report describes three cases of PPNAD. Two of the cases were distantly related, and we present two pedigrees involving cases and currently healthy *PRKAR1A* mutation carriers. The cases had unique diagnostic and follow-up features. To the best of our knowledge, this report presents the first CNC case who developed Hodgkin lymphoma during follow-up.

## Cases

Case characteristics are shown in Table 1 and pedigrees in Figure 1.

## Case 1

The proband was an 11-year-old girl. She presented to our institution with weight gain over the preceding two years. She was pubertal. The family history revealed no consanguinity. On physical examination, her height, weight, and body mass index (BMI) were 132.5 cm [-1.5 standard deviation score (SDS), 44.8 kg (0.92 SDS), and 25.5 (+1.8 SDS)], respectively. Moon face, abdominal adiposity, buffalo hump, acne, and stria were evident. The hormonal assessment showed a suppressed plasma ACTH in the presence of high morning serum cortisol and an altered circadian cortisol level. The hormonal and clinical signs indicated ACTH-independent CS. A computed tomography (CT) scan of the adrenals revealed bilateral micronodular hyperplasia (shown in Figure 2A). PPNAD was suspected, and bilateral adrenalectomy was performed. Hydrocortisone and fludrocortisone were initiated. The histopathological findings showed numerous cortical hyperplastic nodules (less than 4 mm), compatible with PPNAD (Figure 3A). She progressively lost weight, and signs of CS regressed. The molecular genetic analysis of *PRKAR1A* identified a heterozygous splice site mutation within exon 4a (c.440+5 G>A), which was pathogenic according to the American College of Medical Genetics and Genomics criteria and which was not reported in the medical literature. This variation has not been associated with any protein alterations. Nevertheless, the occurrence of a different variation within the same identical exon (c.440+5 G>C) was reported to result in a premature stop codon (TGA) and modification of the secondary structure of the  $R1\alpha$  domain (6). Regarding CNC, cardiac examination and thyroid ultrasound (US) were normal, and there were no signs of skin lesions. Other pituitary hormone levels were normal. Genetic analysis of her mother (44 years old) and maternal aunt (35 years old) was performed, and they had the same variant in *PRKAR1A* without any symptoms or signs of CNC. Her father and other family members could not undergo genetic analysis

	Case 1	Case 2*	Case 3*
<b>Gender</b>	Female	Female	Female
<b>Age (years)</b>	11	16	12
<b>Serum cortisol (µg/dL)</b>			
Morning, basal	17.8	30	25
Midnight (at 23:00)	15	NA	19
Morning, after 1 mg dexamethasone	17.8	13.8	13
<b>24 h UFC (µg/m<sup>2</sup>/day, NR&lt;70)</b>	NA	207	233
<b>ACTH (pg/mL, NR 0-63)</b>	<5	<1	<5
<b>Adrenal CT scan</b>	Symmetrical, bilateral nodular hyperplasia (bilateral micronodular)	Asymmetrical (L>R) bilateral nodular hyperplasia (left side macronodular)	Asymmetrical (L>R), bilateral nodular hyperplasia (left side macronodular)
<b>PRKAR1A variant</b>	c.440+5G>A	c.349G>T	c.349G>T
<b>IGF-1 (ng/mL, NR 143-506)</b>	NA	215	203
<b>DHEA-S (µg/dL, NR 25-460)</b>	NA	169	345
<b>Echocardiography</b>	Normal	Normal	Minimal hypertrophic IVS
<b>Thyroid ultrasound</b>	Normal	Normal	Normal

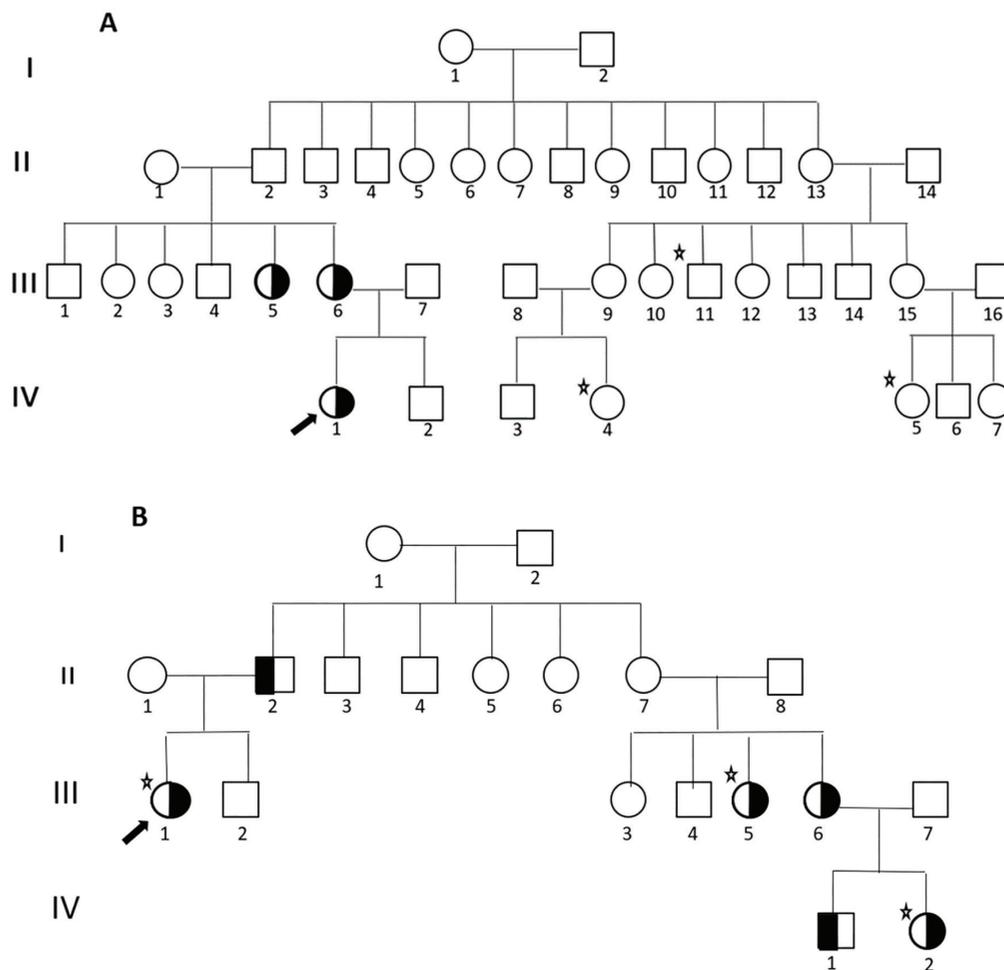
\*Cases 2 and 3 were distant relatives.  
UFC: urinary free cortisol, NR: normal range, CT: computed tomography, IGF-1: insulin like growth factor-1, DHEA-S: dehydroepiandrosterone-sulfate, L: left, NA: not available, R: right, IVS: interventricular septum

because of social reasons. Reportedly, subjects III.11, IV.4, and IV.5 were diagnosed with CS and had an adrenalectomy. At the age of 16 years, the patient developed persistent cervical and supraclavicular lymphadenopathy associated with weight loss and was diagnosed with nodular sclerosing type Hodgkin lymphoma five years after adrenalectomy. At the most recent follow-up of Case 1, she was 17 years and 8 months old; her physical examination was normal with weight of 45 kg (-1.75 SDS), height of 150 cm (-2.21 SDS), BMI of 20 kg/m<sup>2</sup> (-0.25 SDS), and other manifestations of CNC were not present.

## Case 2

This case was a 16-year-old girl who presented with a 4-year history of significant weight gain, hirsutism, and irregular menstrual periods. Pubertal development was already complete, with spontaneous menarche starting at 12 years. The family history revealed no consanguinity. On physical examination, her height, weight, and BMI were 147.5 cm (-2.58 SDS), 85.6 kg (3.29 SDS), and 39.5 (3.83 SDS), respectively. She displayed striae, moon face, abdominal adiposity, buffalo hump, acne, and hirsutism. There were no lentigines or blue nevi on skin examination. Serum and 24-hour urinary cortisol levels were high. At first, plasma ACTH level (Siemens, a solid phase, two-site enzyme chemiluminescent system, IMMULITE® 2000 XPI) was found to be 14 pg/mL (normal, 7-63 pg/mL). Pituitary magnetic resonance imaging revealed an adenoma (4 mm). High dose

dexamethasone suppression test revealed unsuppressed ACTH level of 10.6 pg/mL. Clinical and biochemical incompatibility suggested ACTH interference and ACTH level was undetectable after polyethylene glycol precipitation (PEG). Furthermore, ACTH level was undetectable (<1 pg/mL) when measured with a different analytical platform (Roche Cobas E411 Diagnostics, a solid-phase, two site electrochemiluminescence immunoassay platform). Adrenal CT scanning showed bilateral nodular lesions characteristic of hyperplasia, which were more prominent and macronodular in the left adrenal gland (shown in Figure 2B). Bilateral adrenalectomy was performed. Hydrocortisone and fludrocortisone were initiated. The histopathological findings showed PPAD with bilateral micro- and macro-nodules (greater than 10 mm), while revealing no discernible signs of necrotic or hemorrhagic regions (shown in Figures 3B and 4). The molecular genetic analysis of the *PRKAR1A* gene identified a heterozygous, previously reported c.349G>T (p.V117F) which was pathogenic according to the ACGM criteria. Additional investigations for CNC features were negative. Her mother, father, and brother underwent genetic analysis and only her father had the same variant but was asymptomatic. At the most recent follow-up of Case 2, she was 21 years and 6 months old, her blood pressure was normal without any medication but she was obese (weight: 72.5 kg, height: 149 cm, BMI: 32.4 kg/m<sup>2</sup>). Other manifestations of CNC were not present. The size of pituitary adenoma had not changed during follow-up.



**Figure 1.** Pedigrees of the two families with PPNAD. Half-filled squares and circles represent heterozygous variant carriers. Individuals who were reported to have Cushing syndrome and underwent an adrenalectomy are indicated with a star. (A) Case 1 is subject IV.1 (c.440+5 G>A). Genetic analyses were made in subjects II.1, III.5, III.6, and IV.1. (B) Case 2 is subject III.1 (c.349G>T) and Case 3 is subject IV.2 (c.349G>T). Genetic analyses were made in subjects II.1, II.2, III.1, III.2, III.5, III.6, III.7, IV.1, and IV.2  
PPNAD: primary pigmented nodular adrenocortical disease

### Case 3

Case 3 was a 12-year-old girl who presented to another institution complaining of hirsutism, significant acne, and weight gain over the preceding two years. Her parents were second cousins. On physical examination, her height, weight, and BMI were 146 cm (-1.16 SDS), 102.4 kg (4.68 SDS), and 48 (+4.5 SDS), respectively. Pubertal development was Tanner stage 3, without menarche. She displayed striae, a moon face, abdominal adiposity, and a buffalo hump, and there were no lentigines or blue nevi on skin examination. She had persistent hypertension and was receiving treatment with enalapril, spironolactone, and valsartan. Hormonal assessment showed a suppressed plasma ACTH in the presence of high serum cortisol with increased levels of 24-hour urinary free cortisol (UFC). Adrenal CT evaluation revealed bilateral nodular lesions, which were more prominent on the left (shown in Figure 2C). She underwent left-side adrenalectomy

at the same institution. However, her clinical picture and hypercortisolism did not improve, and she was referred to our center. Hormonal assessment showed a suppressed plasma ACTH level in the presence of high serum cortisol. A right-side adrenalectomy was performed at our institution nine months after the first surgery. Hydrocortisone and fludrocortisone were initiated. Histopathological assessment revealed bilateral micro- and macro-nodular hyperplasia. *PRKAR1A* analysis detected the same mutation as in Case 2 (c.349G>T, p.V117F). Her mother and brother had the same variant without any symptoms or signs of CNC. Her maternal aunt, who had the same *PRKAR1A* mutation, was diagnosed with ACTH-independent CS. Her adrenal CT revealed bilateral adenoma (right 25x27 mm, left 10x10 mm). She underwent a right adrenalectomy in another center, and histopathological assessment revealed adrenocortical oncocytoma. At the most recent follow-up of Case 3, she was 14

years and 4 months old, her blood pressure was normal without any medication, but she was obese [weight: 93.7 kg (+4.2 SDS), height: 152.5 cm (-1.59 SDS), BMI: 40.2 kg/m<sup>2</sup>(+4.2 SDS)] and had hirsutism. Other manifestations of CNC were not present.

### Follow-up

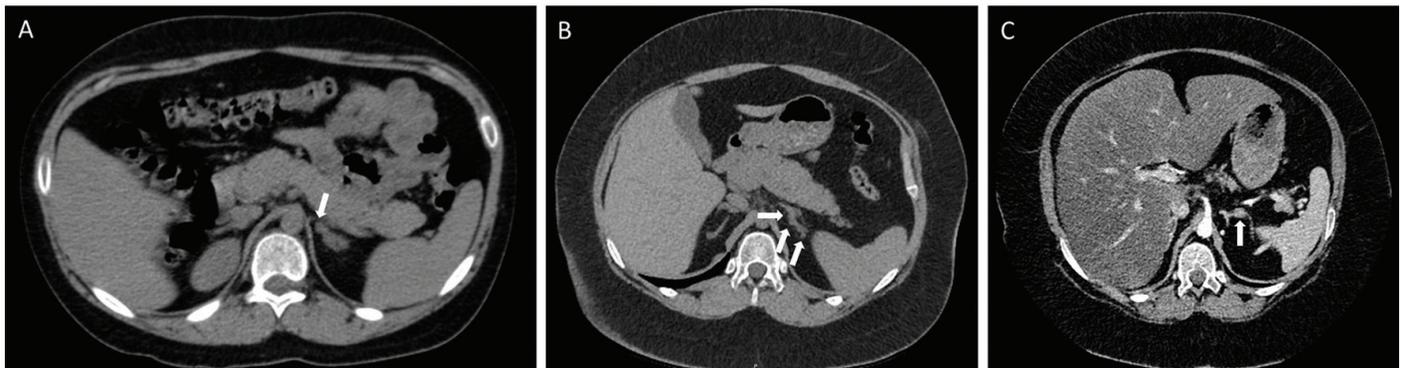
We recommended annual laboratory and imaging evaluations for both affected subjects and the asymptomatic carriers, with an echocardiogram for cardiac myxoma, a thyroid US for thyroid nodules, a testicular US for boys, and the measurement of insulin-like growth factor-1 and prolactin beginning in adolescence to screen for pituitary overactivity. For asymptomatic carriers, an annual measurement of 24-hour UFC excretion was planned. At the time of writing, no additional characteristics of CNC have been identified in either affected subjects or asymptomatic carriers (7).

### Discussion

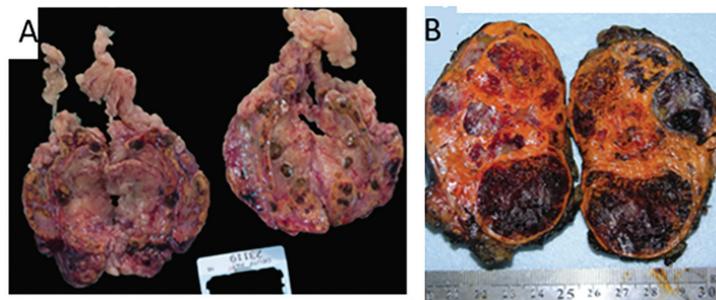
The diagnosis of CS is not straightforward and so approximately 2.5 to 3 years of delay are reported in the literature (8). The diagnosis of CS was further complicated in Case 2 due to a

falsely unsuppressed ACTH level. Available ACTH assays exhibit considerable differences in terms of sensitivity and lead to a wide variability in ACTH measurements, especially when low concentrations of ACTH are present. In the presented case, measurement of the ACTH level was initially conducted with a kit that was reported to fail in detecting low ACTH levels in 19% of cases in a multicenter study (9,10). Treatment of plasma and serum samples with PEG has been shown to precipitate immunoglobulins, including heterophile antibodies. Falsely high values are prevented, and the true level may be measured (10,11). Thus, a PEG procedure was performed using our patient's serum, and an undetectable ACTH level was demonstrated. This finding was confirmed by measurement on a different analytical platform. Regardless of their sensitivity and specificity, immunoassays are susceptible to occasional analytical errors. An astute clinician should keep in mind the potential for interference in cases where there is a discrepancy between clinical and laboratory findings.

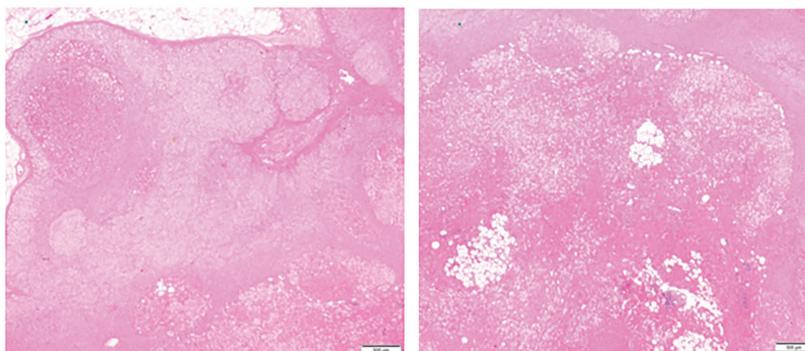
A contrast-enhanced CT scan should be the next diagnostic step after hormonal evaluation in patients with ACTH-independent CS (1). The appearance of the adrenal glands on imaging in



**Figure 2.** Adrenal CT images showing numerous adrenal nodules of varying sizes: A) Case 1, B) Case 2, and C) Case 3  
CT: computed tomography



**Figure 3.** Gross view of a resected adrenal glands showing nodular changes. A) Case 1, B) Case 2. Multiple tan-brown nodules [A] micronodules, B) macro and micronodules] were seen in the cortex



**Figure 4.** Histopathological images of the adrenal of Case 2. Nodules are composed of clear and compact cells with variable lipid. No mitotic figures or atypical cells were present

patients with PPNAD is often initially interpreted as normal, which differs from other ACTH-independent disorders where relatively large tumors are easily seen. It is important that the clinician and radiologist have expertise in evaluating radiological findings in these cases. Nodules are typically less than 1 cm in size (micronodules) (12). However, histopathological evaluation of the adrenal glands in cases 2-3 demonstrated macronodules. Contrary to what is generally known, macronodular appearance may rarely be detected in cases of PPNAD. A report of 11 patients with PPNAD due to *PRKAR1A* variants found one patient (26 years of age) with macronodules (2.5 cm), while three (between 25 and 55 years of age) of four patients with PPNAD without a *PRKAR1A* mutation had macronodules (3). An 18-year-old female who had a monoallelic (c.102G>A) germline *PRKAR1A* mutation was reported to have macronodular PPNAD. In addition, a somatic mutation in *PRKAR1A* (16-bp deletion of the acceptor splice site of exon 4B, IVSdel-17→-2) was found in the macronodule. This somatic mutation was not present in the tissue adjacent to this nodule, in the left adrenal, or in leukocyte DNA (13). The exact etiology of macronodules in PPNAD is unclear, but in general, somatic *CTNNB1* mutations are suggested to play a role in the formation of macronodules by accumulation of  $\beta$ -catenin (5).

The variant in Case 1 (c.440+5 G>A) was also present in her asymptomatic mother and maternal aunt, while individuals III.11, IV.4, and IV.5 within this family were reported to have CS and underwent adrenalectomy. However, as these patients reside in another country, we were unable to gather additional clinical and genetic information about them. Typically, the overall penetrance of CNC in individuals with a pathogenic *PRKAR1A* variant exceeds 95% by the age of 50 years. However, certain splice site variants may lead to a milder phenotype or reduced penetrance of CNC (5). To date, there is only one report in the literature of the *PRKAR1A* variant detected in cases 2 and 3, and in these cases, the adrenal phenotype was highly variable (14). According to this report, the c.349G>T splice site mutation is

predicted to lead to exon 4 skipping, and the resulting frameshift would lead to a premature stop codon. The *PRKAR1A* mutation was found in three asymptomatic individuals within this familial cohort, who did not exhibit any clinical signs associated with CNC. The authors concluded that the c.349G>T variation has low penetrance, resulting in incomplete clinical expression. The absence of CNC symptoms in asymptomatic carriers might be related to both the young age of the carriers and the low penetrance of some variants in *PRKAR1A*.

Of note, Case 1 developed Hodgkin lymphoma during follow-up. *PRKAR1A* is the gene encoding the type 1A regulatory subunit of PKA, which modulates various events during cell proliferation in combination with cAMP, and deregulation of these effector molecules is associated with the development of different cancers via multiple pathways (15). Functionally, loss of *PRKAR1A* is associated with excess PKA signaling in tumors from patients, although the exact mechanism by which this aberrant signaling causes tissue-specific tumorigenesis is unknown (16). Patients with a *PRKAR1A* mutation were more likely to develop other cancers, including growth hormone-secreting pituitary tumors, gonadal tumors, and thyroid neoplasms, at an earlier age (8). However, Hodgkin lymphoma has never been reported in the context of CNC, despite the fact that PKA is obviously involved in the regulation of the immune system (17). To the best of our knowledge, there is only one animal study suggesting this association. In a mouse model of CNC, mice with antisense-*PRKAR1A* expression were found to have B-cell lymphoma, but the *PRKAR1A* knock-out mice did not develop such a proliferative disease. In addition, *PRKAR2A*-knockout mice (absence of another PKA subunit) developed lymphoma (16). In view of this experimental evidence, we suggest that the *PRKAR1A* mutation in Case 1 may have played a role in the development of her Hodgkin lymphoma.

In summary, our study broadens the genotypic and phenotypic spectrum of *PRKAR1A* mutations associated with CNC. For the first time, the coexistence of PPNAD and lymphoma in humans has been reported. We believe that the findings from these families provide important information for a better understanding of the genetic pathogenesis, diagnosis, and clinical management of CNC.

#### Ethics

**Informed Consent:** Informed consent was obtained.

#### Footnotes

#### Authorship Contributions

**Concept:** Kübra Yüksek Acınlıklı, Sezer Acar, Ahu Paketçi, Özgür Kırbiyık, Mert Erbaş, Özge Besci, Gözde Akın Kağızmanlı, Deniz Kızmazoğlu, Oktay Ulusoy, Erdener Özer, Kutsal Yörükoğlu, Ayhan Abacı, Handan Güleriyüz, Ece Böber, Korcan Demir, **Design:** Kübra Yüksek Acınlıklı, Sezer Acar, Ahu Paketçi, Özgür Kırbiyık, Mert Erbaş, Özge Besci, Gözde Akın Kağızmanlı, Deniz Kızmazoğlu, Oktay Ulusoy, Erdener Özer, Kutsal Yörükoğlu, Ayhan Abacı, Handan Güleriyüz, Ece Böber, Korcan Demir, **Data Collection or Processing:** Kübra Yüksek Acınlıklı, Korcan Demir, **Analysis or Interpretation:** Kübra Yüksek Acınlıklı, Korcan Demir, **Literature Search:** Kübra Yüksek Acınlıklı, Korcan Demir, **Writing:** Kübra Yüksek Acınlıklı, Korcan Demir.

**Conflict of Interest:** One author of this article, Korcan Demir, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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