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The clinical characteristics and pathogenic variants of primary pigmented nodular adrenocortical disease in 210 patients: a systematic review

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Aims: Primary pigmented nodular adrenocortical disease (PPNAD), as a rare kind of Cushing's syndrome, is frequently misdiagnosed. To get a better understanding of the disease, we analyzed the clinical characteristics and pathogenic variants of PPNAD.

Methods: Databases were searched, and the pathogenic variants and clinical manifestations of patients were summarized from the relevant articles.

Results: A total of 210 patients in 86 articles were enrolled with a median age of 22 and a female-to-male ratio of 2:1. Sixty-six (31.43%) patients were combined with Carney complex (CNC) and 94.29% were combined with osteoporosis/osteopenia. Among 151 patients who underwent genetic testing, 87.42% (132/151) had pathogenic variants. Six gene mutations (*PRKAR1A*, *PDE11A*, *PRKACA*, *CTNNB1*, *PDE8B*, and *ARMC5*) were detected in the patients. The most common mutation was PKAR1A, accounting for 79.47% (120/151). There was a significant correlation between *PRKAR1A* pathogenic variant and spotty skin pigmentation in CNC concurrent with PPNAD ($p < 0.05$). Among pregnant patients with PPNAD, those without surgical treatment and with bilateral adrenalectomy suffered from a high-risk perinatal period. However, patients with unilateral adrenalectomy presented a safe perinatal period.

Conclusions: For young patients with Cushing's syndrome, especially female patients with spotty skin pigmentation and osteoporosis/osteopenia, PPNAD should be considered. Unilateral adrenal resection may be considered as an option for women with fertility needs. In view of the difficulty of PPNAD diagnosis, genetic testing before surgery might be a reasonable option.

Patients with PPNAD with spotty skin pigmentation should consider the *PRKAR1A* pathogenic variant and pay attention to CNC.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42023416988.

KEYWORDS

PRKAR1A, Cushing's syndrome, clinical characteristics, pathogenic variants, primary pigmented nodular adrenocortical disease

1 Introduction

Primary pigmented nodular adrenocortical disease (PPNAD), as a subclass of bilateral micronodular adrenocortical disease, is a rare but an important cause of endogenous Cushing's syndrome (CS) especially in children and young adults. Characterized by small, black and brown pigmented micronodules in the adrenal cortex, PPNAD can be combined with the "complex of myxomas, spotty skin pigmentation, and endocrine overactivity," or Carney complex (CNC) (cPPNAD) (1). Meanwhile, 10%–20% of patients with PPNAD can also occur in patients without CNC [denoted as isolated PPNAD (i-PPNAD)] (2). Pathologically, the diagnosis of PPNAD is mainly based on histological findings, which displays multiple adrenocortical nodules with cytoplasmic pigmentation and inter-nodular cortical atrophy. However, radiology may underestimate the presence of bilateral adrenal gland involvement in patients with PPNAD due to the discrete nodular formations (sizes < 1 cm). These micronodules are often cortisol-producing and composed of lipid-poor cortical cells; therefore, hypercortisolism in PPNAD can be overt, subclinical, cyclic, or atypical (3, 4). All these make the diagnosis of PPNAD difficult. In addition, cPPNAD is causally related with inactivating mutations of the regulatory subunit type 1A of the cAMP-dependent protein kinase (*PRKAR1A*) gene and yet unknown defect(s) in other gene(s). PPNAD is a rare autosomal dominant disorder with variable penetrance and uncertain genotype/phenotype correlation. Delineation of a genotype–phenotype correlation for patients with PPNAD is essential for understanding potential gene functions and providing counseling and preventive care. In this review, we summarize the clinical features, pathogenic variants, and recent progress in investigation and therapy of PPNAD.

2 Subjects and methods

2.1 Data sources and study patients

Five electronic databases (i.e., PubMed, Web of Science, Embase, the China National Knowledge Infrastructure, and Wanfang) were used to search for relevant studies with the following terms: "PPNAD" or "iPPNAD" or "familial isolated primary pigmented nodular adrenocortical disease" or "isolated primary pigmented nodular adrenocortical disease" or "primary pigmented nodular adrenocortical disease" or "micronodular adrenal disease". Analyses of pathogenic variants and clinical features were conducted from inception to 12 September 2023. We selected studies in the English or Chinese language. Eligible studies met the following criteria: (1) PPNAD diagnosed by pathology after adrenalectomy according to the 2022 WHO classification of adrenal cortical tumors {PPNAD is composed of multiple beaded pigmented micronodules (<10 mm, often 2–5 mm). PPNAD is characterized by multiple subcentimeter micronodules composed of eosinophilic adrenocortical cells with different pigment deposits. Atrophy of the intertubercular cortex is commonly observed. Micronodules were positive for CYP11B1, confirming cortisol production (5)}. (2) The pathogenic variant sites were described. (3) The main clinical data of the patients were described. The flow diagram of the search process is provided in Figure 1.

The following data were extracted from the eligible studies: (1) country, (2) sex, (3) age at diagnosis of PPNAD, (4) pathogenic variant, (5) treatment, (6) clinical features, and (7) complication of CNC. Diagnostic criteria of CNC are shown in Table 1. The CNC diagnostic criteria were based on the criteria proposed by Stratakis et al. (1).

Liddle GW was the first person using dexamethasone to assess CS in 1960. The original low-dose dexamethasone suppression test (LDDST) and high-dose dexamethasone suppression test (HDDST) were named Liddle tests, which were widely used in the evaluation of CS (6).

2.2 Statistical analysis

The epidemiological and clinical characteristics, and laboratory indexes of patients were described utilizing simple summary statistics. Fisher exact tests were used to test for association between qualitative variables. All tests were two-sided, and p-values < 0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 26 for Windows (SPSS). Since certain data in some patients were missing, the total number of patients was mentioned in each analysis.

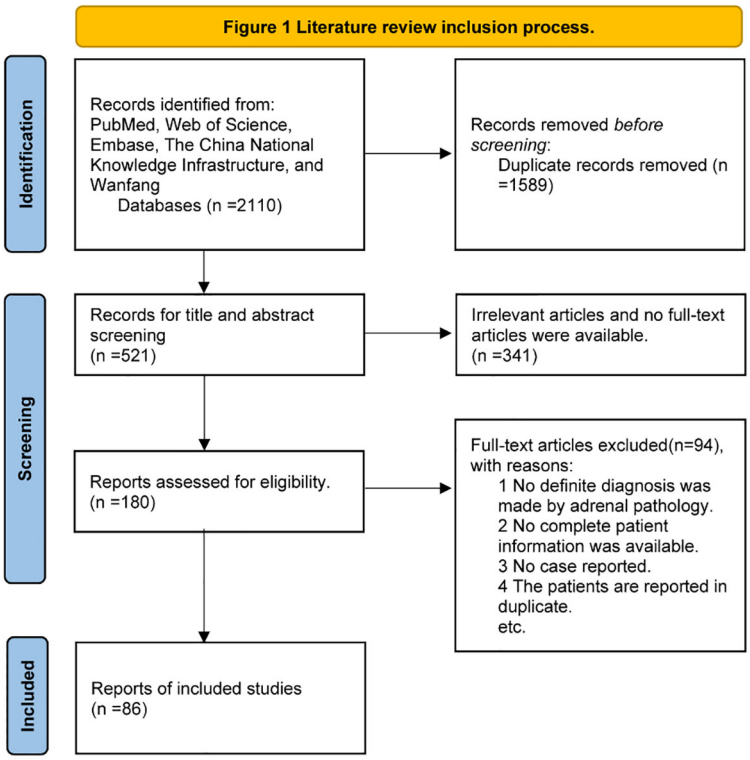

FIGURE 1
Literature review inclusion process.

TABLE 1 Diagnostic criteria for CNC*.

1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, and vaginal and penile mucosa)
2. Myxoma (cutaneous and mucosal) #
3. Cardiac myxoma#
4. Breast myxomatosis# or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
5. PPNAD# or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test
6. Acromegaly due to GH-producing adenoma#
7. LCCSCT# or characteristic calcification on testicular ultrasonography
8. Thyroid carcinoma# or multiple, hypoechoic nodules on thyroid ultrasonography, in a young patient
9. Psammomatous melanotic schwannoma#
10. Blue nevus, epithelioid blue nevus (multiple)#
11. Breast ductal adenoma (multiple)#
12. Osteochondromyxoma#
Supplemental criteria:
1. Affected first-degree relative
2. Inactivating mutation of the PRKAR1A gene

*To make a diagnosis of CNC, a patient must either (1) exhibit two of the manifestations of the disease listed or (2) exhibit one of these manifestations and meet one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the PRKAR1A gene).
#With histologic confirmation.

3 Results

3.1 Epidemiological characteristics

Eighty-six articles including 210 patients were enrolled. The top three countries were France (65/210, 30.95%), China (43/210, 20.48%), and Canada (27/210, 12.86%). The patients were distributed in 23 countries on six continents. Europe has the highest number of cases (87/210, 41.43%), followed by Asia (64/210, 30.48%), North America (47/210, 22.38%), Africa and Oceania (8/210, 3.81%), and South America (4/210, 1.90%) (Table 2; Figure 2). A total of 26 patients were from 11 families, and the others were considered as sporadic.

3.2 Clinical features

The ages of patients ranged from 1 to 61 years old, with a median of 22 (quartiles 14–28), and 71.88% (151/210) of patients were 10–30 years old at diagnosis of PPNAD. Among them, female patients were 144 (144/210, 68.57%), with a female-to-male ratio of 2:1.

The clinical data are shown in Figure 2. In addition, BMI at diagnosis was only available for 56 patients, among which the prevalence of obesity (BMI ≥ 30 kg/m^2) was 14.29% (8/56), overweight (BMI: 25–29.9 kg/m^2) was 30.36% (17/56), and normal weight was 51.79% (29/56) with a median of 24.45 (quartiles 22.29–26.48) kg/m^2. In addition, 28 patients had

TABLE 2 The detailed information of patients with PPNAD.

Continent	Percentage	Patients (%)
Europe	French	65 (30.95)
	Belgium	7 (3.33)
	Poland	5 (2.38)
	Portugal	3 (1.43)
	Greece	2 (0.95)
	The United Kingdom	2 (0.95)
	Germany	1 (0.48)
	Serbia	1 (0.48)
	Austria	1 (0.48)
Asia	China	43 (20.48)
	Japan	6 (2.86)
	India	4 (1.90)
	Thailand	3 (1.43)
	Turkey	3 (1.43)
	Korea	2 (0.95)
	Iran	2 (0.95)
	Israel	1 (0.48)
North America	Canada	27 (12.86)
	The United States	20 (9.52)
Oceania	Australia	4 (1.90)
South America	Brazil	4 (1.90)
Africa	*	3 (1.43)
	Ethiopia	1 (0.48)
Total	23	210 (100)

*People of African descent.

growth retardation, aged 1 to 19 years old with a median of 11 (quartiles 9–12). Clinical manifestations were not available in all patients, which included mainly osteoporosis or low bone mineral density (33/35, 94.29%), hypertension (81/120, 67.50%), and weight gain (71/120, 59.17%).

A total of 66 (66/210, 31.43%) patients were cPPNAD and had details of the diagnosis of CNC, with 40 (40/66, 60.61%) being women, 47 (47/66, 71.21%) having spotty skin pigmentation with a typical distribution, 19 (19/66, 28.79%) having cutaneous or cardiac myxomas, and 7 (7/40, 17.50%) having multiple breast nodules or carcinoma. Particularly, one patient with PPNAD only showed spotty pigmentation of the skin, with suspected CNC (7).

3.3 Laboratory investigations

ACTH data and normal criteria were available in 98 patients, 77 (77/98, 78.57%) of whom had low or undetectable ACTH, and 21 (21/98, 21.43%) were within the lower limit of the normal range of ACTH levels.

Seventy-one patients mentioned diurnal cortisol changes, among which 70 (70/71, 98.59%) lost their cortisol circadian rhythm. Moreover, regarding the dexamethasone suppression test, 31 patients were tested for urinary cortisol after high-dose dexamethasone test or Liddle test, and all (31/31, 100%) of them showed no significant suppression or even paradoxical increase. Plasma cortisol showed similar results and was not suppressed in all the patients with low-dose dexamethasone and high-dose dexamethasone inhibition tests.

Plasma dehydroepiandrosterone sulfate (DHEA-S) was available in 28 patients, normal in 11 (11/28, 39.29%) patients, decreased in 14 (14/28, 50.00%), and elevated in 3 (3/28, 10.71%) patients. Plasma growth hormone (GH) was provided in 13 patients, which was normal in 7 (7/13, 53.85%), decreased in 2 (2/13, 15.38%), and elevated in 4 (4/13, 30.77%) patients.

3.4 Pathogenic variants

A total of 151 patients underwent genetic testing, and 132 (132/151, 87.42%) patients found pathogenic variants. Six different mutations, *PRKAR1A*, *PDE11A*, *PRKACA*, *CTNNB1*(*β- catenin*), *PDE8B*, and *ARMC5*, were identified. The most common mutation was *PKAR1A*, accounting for 79.47% (120/151) of cases; the second most common was *PED11A* mutation, found in 26.49% (40/151) of cases, while other mutations were relatively rare. A total of 33 patients had both *PRKAR1A* and *PDE11A* mutations (Tables 3, 4).

The family genetic history was recorded in 30 cases; the pathogenic variants of 10 cases (10/30, 33.33%) were from their fathers, those of 13 cases (13/30, 43.33%) were from their mothers, and those of the remaining 7 cases were not from their parents. Among the 21 cases with mutated *PRKAR1A* gene, 11 (11/21, 52.38%) were inherited from the mothers and 6 (6/21, 28.57%) were from the fathers. Among the six cases with mutated *PDE11A* gene, three (3/6, 50%) were inherited from the mothers and two (2/6, 33.33%) were inherited from the fathers. The geographic distribution of gene mutation is shown in Figure 2.

The proportion of spotty skin pigmentation with a typical distribution in patients with cPPNAD with or without *PRKAR1A* gene mutation is presented in Figure 3. Spotty skin pigmentation was presented in 33 patients (33/45, 73.33%) with *PRKAR1A* gene mutation. There was no patient who presented with spotty skin pigmentation without *PRKAR1A* gene mutation. There was significant correlation between *PRKAR1A* gene mutation and spotty skin pigmentation with a typical distribution in cPPNAD ($p < 0.05$).

3.5 Treatment

The treatment regimens were recorded for 122 patients. A total of 62 patients (62/122, 50.82%) underwent bilateral adrenalectomy, 41 patients (41/122, 33.61%) underwent unilateral adrenalectomy, and 15 patients (15/122, 12.30%) underwent two-stage bilateral

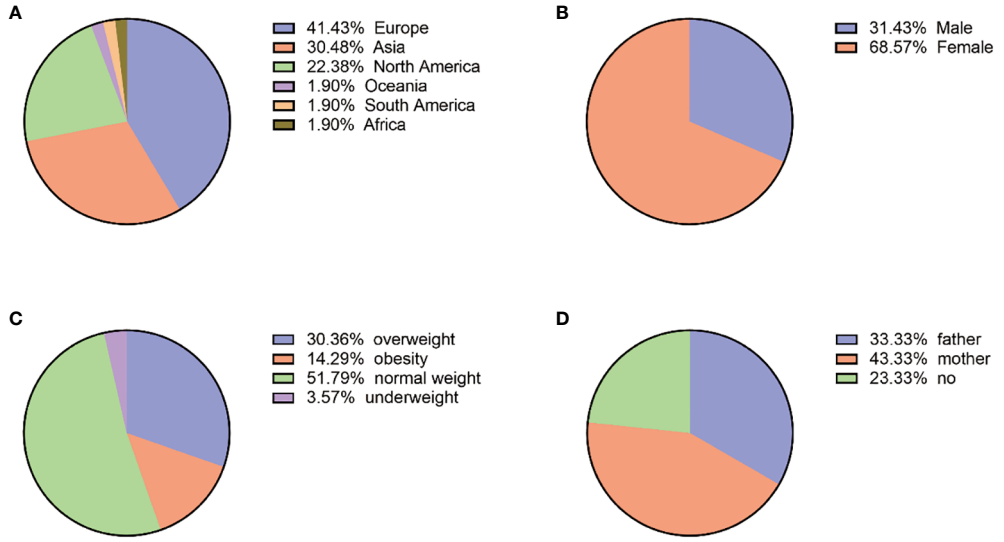

FIGURE 2
(A) Geographical country distribution. **(B)** Gender distribution. **(C)** BMI (N:56). **(D)** Mutated genes from parents (N:30).

adrenalectomy (since unilateral adrenalectomy could not control the cortisol elevation, the other side of the adrenal gland was removed). Three patients (3/122, 2.46%) underwent unilateral total adrenalectomy and contralateral subtotal adrenalectomy, and one patient (1/122, 0.82%) underwent unilateral subtotal adrenalectomy.

Regarding the fertility status of four patients with PPNAD, notably, a 31-year-old woman with cPPNAD without adrenalectomy developed severe perinatal preeclampsia and gave birth to a baby girl with moderate respiratory distress syndrome (50). Moreover, a 28-year-old woman with CS secondary to cPPNAD had a successful pregnancy 3 years after bilateral adrenalectomy, but the perinatal period was not uneventful because of the need for hormone replacement (51). There were two women with PPNAD who had difficulty in pregnancy and gave birth to healthy babies after unilateral adrenalectomy with an uneventful perinatal period (31, 52).

Here are the following suggestions for choosing which side of the adrenal gland to remove. The side with more cortisol secretion with adrenal venous sampling (AVS) was selected (53, 54), the side with the larger volume with the use of 3D radiologic imaging volume analysis to compare the adrenal size was selected (55), the side with the highest uptake with 131-cholesterol removal radionuclide scan of adrenal gland was selected (56), and the side showing obvious unilateral adrenal nodules with CT or MRI scan was selected (56).

4 Discussion

The present study is the first systemic review to investigate the different clinical features and pathogenic variants of PPNAD in 23 countries on six continents. Our study showed that most of the patients with PPNAD were between 10 and 30 years old (71.88%), with a female-to-male ratio of 2:1. Of the patients with PPNAD, 94.29% had osteoporosis or osteopenia. Moreover, almost all patients lost the cortisol circadian rhythm (98.59%), and both plasma and urinary cortisol cannot be suppressed in all patients tested with both low-dose or high-dose dexamethasone and Liddle test (100%). In terms of genetic mutations, six different gene mutations, *PRKAR1A*, *PDE11A*, *PRKACA*, *CTNNB1*(*β-catenin*), *PDE8B*, and *ARMC5*, were identified. In particular, there was significant correlation between *PRKAR1A* gene mutation and spotty skin pigmentation with a typical distribution in cPPNAD ($p < 0.05$). More than half of the patients underwent bilateral adrenalectomy, and 33.61% of the patients underwent unilateral adrenalectomy.

Abnormal bone metabolism and growth retardation are more common in PPNAD compared to other causes of CS (57, 58). In our study, the age of patients with growth retardation was 1 to 19 years old, which may be secondary to early onset and prolonged exposure to hypercortisolemia, impairing growth and delaying skeletal maturation. Moreover, *PRKAR1A* gene mutation might lead to abnormal osteoblast differentiation (59–61). The main reason for the unsatisfactory height after treatment is the lack of catch-up growth. To solve this problem, children with PPNAD should be tested for GH and IGF-1 in time after surgery. If GH is insufficient, the application of human GH is encouraged. Early treatment and a longer remaining growth period contribute to the achievement of ideal adult height (62). There are also four patients with acromegaly due to GH-producing pituitary adenoma in our study, which together form CNC. Thus, patients with PPNAD should be highly suspected of pituitary adenoma if there is an increase in GH.

In our study, we found a total of six different gene mutations, *PRKAR1A*, *PRKACA*, *PDE11A*, *PDE8B*, *ARMC5*, and *CTNNB1* (*β-catenin*). Early studies had demonstrated that the development,

TABLE 3 Geographic distribution of genes.

Gene (patients)	Continent	Patients (%)
PRKAR1A (120)	Europe	75 (62.50%)
	North America	24 (20.00%)
	Asia	15 (12.50%)
	Africa	4 (3.33%)
	South America	2 (1.67%)
PDE11A (40)	Europe	32 (80%)
	North America	6 (15%)
	Asia	2 (5%)
PDE8B (2)	Asia	1 (50%)
	North America	1 (50%)
PRKACA (2)	Asia	2 (100%)
CRNNB1(2)	North America	2 (100%)
ARMC (1)	Asia	1 (100%)

proliferation, and function of adrenocortical cells are mainly regulated by the cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway (63, 64). In particular, *CTNNB1* (*β-catenin*) gene mutation only occurs in the greater adrenal tubercle, but as a somatic mutation, it may also be involved in secondary tumors based on primary hyperplasia (34, 40). Although *PRKAR1A* gene mutation is a supplemental criterion for CNC diagnosis, the diagnosis of CNC cannot be ruled out if *PAKAR1A* gene mutation is not detected. Genetic testing results of *PRKAR1A*, *PRKACA*, or *PDE11A* mutations are helpful for the diagnosis of CNC (11). I-PPNAD may be closely related to C. 709(-7–2) del6 or *M1V* mutation of *PRKAR1A* (65–67). As a genetic modifying factor for the development of testicular and adrenal tumors in patients with germline *PRKAR1A* mutation, *PDE11A* is probably a phenotype modifying gene but not a causative gene. Therefore, *PDE11A* mutation might indicate the occurrence of PPNAD and other types of adrenal tumors (42, 68). *ARMC5* constitutional variant was reported "nonsense" in an Asian patient with PPNAD, but the P536A is a missense variant, and frequent especially in an Asian population (MAF = 0.002) (48). Some cases of corticotropin-independent macronodular adrenal hyperplasia often appear to be with inactivating mutations of *ARMC5* (69, 70). Therefore, patients with PPNAD with *ARMC5* gene mutation might combine with macronodular adrenal hyperplasia.

The study showed that the correlation between spotty skin pigmentation and *PRKAR1A* gene mutation was analyzed in patients with cPPNAD. The results showed that there was significant correlation between *PRKAR1A* gene mutation and spotty skin pigmentation in patients with cPPNAD. This is consistent with the findings of Jerome Bertherat et al. (71). PKA signaling promotes melanogenesis in melanocytes by phosphorylating CREB, which results in increased MITF transcription and subsequent increased expression of tyrosinase, TRP-1, and TRP-2. *PRKAR1A* deficiency produces large amounts of melanin and presents as darkly pigmented cutaneous papules or nodules (72). Therefore, the occurrence of spotty skin pigmentation in patients with CS should be highly suspicious of cPPNAD and *PAKAR1A* gene mutation.

Among all the patients included in this review, no mutated genes were reported in 19 cases. The reason is partly due to the limited gene sequence template selection, and the other is the somatic events. The tumor specimen might not obtain the corresponding tissue and was contaminated by the surrounding tissue. In case of somatic events, laser-captured micro-dissected cells can be used (36), and blood tissue can also be tested for genetic mutations to identify germline or somatic mutations.

Patients with PPNAD presented with an ACTH-independent form of CS, characterized by decreased or undetectable ACTH levels, elevated serum cortisol concentrations with loss of circadian rhythm, and paradoxical increase in UFC excretion after HDDST (Liddle test), with a maximum specificity of 100% (6, 39, 73, 74). Stratakis et al. found that all patients with PPNAD had a 100% or greater increase in urinary free cortisol excretion on day 6 of the Liddle test (6). The paradoxical rise in serum cortisol levels following Liddle's test implied that glucocorticoids can locally regulate adrenocortical steroidogenesis in the majority of PPNAD. In at least some PPNAD tissues, aberrant coupling of the glucocorticoid receptor (GR) to the cAMP–PKA pathway instead of GR overexpression may be the culprit for the dexamethasone-induced rise in cortisol production (31). Different from the pathological features of isolated micronodular adrenocortical disease (i-MAD), PPNAD has small nodular staining and internodular atrophy, and the cortex was clearly segmented (75, 76). However, adrenal tissue acquisition was invasive, and a patient with a psychiatric disorder concealed a history of exogenous cortisol intake, while laboratory findings were consistent with PPNAD, leading physicians to misdiagnose and remove the normal adrenal gland (77). In the future, PPNAD gene mutation diagnosis due to blood might be the first choice for diagnosis and next-generation sequencing (NGS) should be preferred (22).

DHEA-S is a specific and stable marker of adrenal androgen secretion, which may also be a good predictor of risk for postoperative adrenal insufficiency, and ACTH plays an important role in its regulation (78, 79). Circulating DHEA-S levels are significantly reduced in patients with CS due to adrenocortical adenomas (78). However, in our study, patients with PPNAD can have a higher level of DHEA-S than normal, when combined with pituitary adenoma (21) or adrenal carcinoma (19). Therefore, if there is abnormal increase in DHEA-S, attention should be paid to whether it is complicated with other types of adrenal tumors and pituitary tumors.

Clinical management is also a complex issue to be discussed for patients with PPNAD. Xu et al. reported that 12 of 13 patients with PPNAD had clinical and laboratory remission of CS after unilateral adrenalectomy (56). Regarding the fertility status of four women with PPNAD, a woman without adrenalectomy developed severe perinatal preeclampsia and gave birth to a baby girl with moderate respiratory distress syndrome (50). Furthermore, a woman experienced a not uneventful perinatal period after bilateral adrenalectomy due to the need for hormone replacement (51). There were two women with PPNAD who gave birth to healthy

TABLE 4 Mutations in patients with PPNAD.

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
1	*PRKACA*	chr19p13.2p12			Copy duplication	Somatic	Xu Yuying (8), 2023
2	*PRKACA*		c.95A>T				Wan Shuang (9), 2022
3	*PRKAR1A*		c.709-16(IVS7)_c.709-11 (IVS7)del TTATTT				
4	*PRKAR1A*		c.491_492delTG	p.Val164fsX4		Germline	Yuya Tsurutani (10), 2022
5	*PDE11A*	Exon 11	c.1921A>G	p.Lys641Glu	Missense		Qian Sun (11), 2022
6	*PRKAR1A*	Exon 6	c.543_544del	p.Glu181Aspfs*6	Protein-truncating		Sofia H. Ferreira (12), 2019
8	*PRKAR1A*		c.487–488delAC				Andreas Kiriakopoulos (13), 2018
9	*PRKAR1A*	Intron 3	c.349–5_349–4insT				J. Fu (14), 2018
		Intron 4a	c.440 + 5 G>C		Deletion of exon 4a		
		Intron 6	c.708 + 134_708 + 135insCT				
		Intron 7	c.770–24G>A				
		Intron 8	c.892–34G>T				
10	*PRKAR1A*	Exon 5	c.502G > A	p.168Gly>Ser			Lan Ling (15), 2017
	PDE11A	Exon 20	c.2763_2764insTCC	p.Ser921_Pro922insSer			
11	*PRKAR1A*		c.671delG	p.G225Afs*16	Frame shift		Laura C. Hern´andez-Ram´ırez (16), 2017
12	*PRKAR1A*		del184–237				Delphine Vezzosi (17), 2015
13	*PRKAR1A*		c.709 (-8–3)delATTTTT				
14	*PRKAR1A*		c.502 + 1G>A				
15	*PRKAR1A*		c.63_64CG>GA				
16	*PRKAR1A*		c.46C>T	p.R16X		Germline	Shih-Chen Tung (18), 2012
17	*PRKAR1A*	Exon 2	c.95_96delAA	p.Lys32Argfs*12	Frame shift		Emilie Morin (19), 2012
18	*PRKAR1A*	Intron 3	c.349 G>T		Frame shift		Helen L. Storr (20), 2010
19	*PRKAR1A*	Exon 2	(A29A)CGG→GCA				Christian Urban (21), 2007
		Exon 3	c.286C>T	R96X	Nonsense		
		Intron 7	c.769 + 524G>T				
		Intron 7	c.770–24A>G				

(Continued)

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TABLE 4 Continued

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
		Intron 9	c.974–102A>T				
20	*PRKAR1A*		c.682C>T	p.Arg228Ter		Germline	Crystal D. C. Kamilaris (22), 2021
			c.974–2A>G				
21	*PRKAR1A*		c.488delC	p.Thr163MetfsX2	Frame shift		Catherine D Zhang (23), 2019
22	*PRKAR1A*		c.709 (-7–2) del6				Aglaia Kyrilli (24), 2019
23	*PRKAR1A*		c.46C>T	p.Arg16X			Amit Tirosh (25), 2017
24	*PRKAR1A*		c.101_105delCTATT	p.Ser34fsX9			
25	*PRKAR1A*		c.496C>T	p.Gln166X			
26	*PRKAR1A*		c. 491–492delTG	p.Val164AspfsX5			
27	*PRKAR1A*		c.125dupG				Katarzyna Pasternak-Pietrzak (26), 2018
28	*PRKAR1A*		c.15dupT				
29	*PRKAR1A*	Intron 7	c.709–7_709–2del6				Constanza Navarro Moreno (3), 2018
30	*PRKAR1A*		c.1A>G	p.Met1Val			
31	*PRKAR1A*	Intron 7	c.709–7_709–2del6				
32	*PRKAR1A*		g.114213T>G				Sira Korpaisarn (27), 2017
			c.709–5T>G				
34	*PRKAR1A*		c.49G>T	p.E17X			Ryohei Mineo (28), 2016
35	*PRKAR1A*	Exon 3	243–252ACTCGTAGAGdel		Frame shift	Germline	R. M. G. da Silva (29), 2011
36	*PRKAR1A*	Exon 8	c.709(-7–2)del6 deletion				Thekla Poukoulidou (30), 2014
37	*PRKAR1A*		Q28X		Protein-truncating		Johannes Hofland (31), 2013
38	*PRKAR1A*		c.439A>G	p.S147G		Germline	J. Anselmo (32), 2012
39	*PRKAR1A*	Intron 2	c.177 + 3 A>G				Marcia C. Peck (33), 2010
40	*PRKAR1A*		c.693insT	p.Arg232X		Germline	Mimi Tadjine (34), 2008
41	*PRKAR1A*		c.1 A > G	p.Met1Val		Germline	
42	*PRKAR1A*		c.101–105delCTATT	p.Ser34fsX9		Germline	
43	*PDE11A*		171delTfs41X			Germline	

(Continued)

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TABLE 4 Continued

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
44	*PRKAR1A*		c.891 + 3 A > G			Germline	
45	*PRKAR1A*		c.438 A > T	p.Arg146Ser		Germline	
46	*PRKAR1A*		c.682C > T	p.Arg228X		Germline	
47	*PRKAR1A*		c.709-(5–107) del103			Germline	
	CRNNB1		T41A			Somatic	
48	*CRNNB1*		S45P			Somatic	
49	*PRKAR1A*		c.502 + 5delG			Germline	
50	*PRKAR1A*		c.491–492delTG	p.Val164fsX4		Germline	
51	*PRKAR1A*		IVS1–2 A>G				Paul Byron Bandelin (35), 2008
52	*PRKAR1A*	Exon 2		p. Y21X	Codon stop	Germline	Madson Q. Almeida (36), 2008
53	*PDE8B*		c.914A>C	p.His305Pro			Anelia Horvath (37), 2008
54	*PDE11A*			R804H			Anelia Horvath (38), 2006
55	*PRKAR1A*	Exon 8	IVS+3G>A				Isabelle Bourdeau (39), 2003
56	*PRKAR1A*		88A>G				
57	*PRKAR1A*		211 C>T				
58	*PRKAR1A*	Exon 1B	102 G>A		Cryptic splice site, partial exon skipping	Germline	Lionel Groussin (40), 2002
		Exon 4B	IVS del (-17→-2)		Exon skipping		
59	*PRKAR1A*	Exon 8	933 ins A		Frame shift	Germline	
60	*PRKAR1A*	Exon 2	196 C>T		Stop codon	Germline	
61	*PRKAR1A*	Exon 7	IVS del (-7→-2)		Exon skipping	Germline	
62	*PRKAR1A*	Exon 2	172 del 11 bp		Frame shift	Germline	
63	*PRKAR1A*	Exon 5	c.503G>T	p.Gly168Val		Germline	Haremaru Kubo (41), 2022
64	*PDE11A*		(919C)→(R307X)				J. Aidan Carney (42), 2010
65	*PDE11A*		1655_1657delTCT/ insCCfs15X				
66	*PRKAR1A*		c.974–1G>A				Rossella Libè (43), 2010
	PDE11A		c.2618T>C	I873T	Missense		

(Continued)

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TABLE 4 Continued

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
67	*PRKAR1A*		c.502 + 1G>A				
	PDE11A		c.2599C>G	R867G	Missense		
68	*PRKAR1A*		c.1083delA				
	PDE11A		c.2180A>G	Y727C	Missense		
69	*PRKAR1A*		c.491–492delTG				
	PDE11A		c.171Tdel	T58PfsX41	Codon stop		
70	*PRKAR1A*		c.891 + 3A>G				
	PDE11A		c.2599C>G	R867G	Missense		
71	*PRKAR1A*		c.528–531delGATTins11				
	PDE11A		c.2632A>G	M878V	Missense		
72	*PRKAR1A*		c.682C>T				
	PDE11A		c.2599C>G	R867G	Missense		
73	*PRKAR1A*		c.769 + 5G>C				
	PDE11A		c.1045G>A	A349T	Missense		
74	*PRKAR1A*		c.709(-7–2)del6				
	PDE11A		c.919C>T	R307X	Codon stop		
75	*PRKAR1A*		c.709(-7–2)del6				
	PDE11A		c.2411G>A	R804H	Missense		
76	*PRKAR1A*		c.709(-7–2)del6				
	PDE11A		c.2180A>G	Y727C	Missense		
77	*PRKAR1A*		c.891 + 3A>G				
	PDE11A		c.2632A>G	M878V	Missense		
78	*PRKAR1A*		c.763–764delAT				
	PDE11A		c.2180A>G	Y727C	Missense		
79	*PRKAR1A*		c.550(-9–2)del8				
	PDE11A		c.2411G>A	R804H	Missense		
80	*PRKAR1A*		c.845–846 ins A				

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TABLE 4 Continued

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
	PDE11A		c.2411G>A	R804H	Missense		
81	*PRKAR1A*		c.709(-5–107)del 103				
	PDE11A		c.2180A>G	Y727C	Missense		
82	*PRKAR1A*		c.709(-7–2)del6				
	PDE11A		c.1142G>T	E382X	Codon stop		
83	*PRKAR1A*		c.279–282delTAGG				
	PDE11A		c.2180A>G	Y727C	Missense		
84	*PRKAR1A*		c.440 + 1G>A				
	PDE11A		c.171Tdel	T58PfsX41	Codon stop		
85	*PRKAR1A*		c.865 G>T				
	PDE11A		c.2180A>G	Y727C	Missense		
86	*PRKAR1A*		c.491–492delTG				
	PDE11A		c.2411G>A	R804H	Missense		
87	*PRKAR1A*		c.738T>G				
	PDE11A		c.824C>A	S275X	Codon stop		
88	*PRKAR1A*		c.353–365del13				
	PDE11A		c.2180A>G	Y727C	Missense		
89	*PRKAR1A*		c.709(-7–2)del6				
	PDE11A		c.652C>T	L218F	Missense		
90	*PRKAR1A*		c.502 + 1G>A				
	PDE11A		c.2180A>G	Y727C	Missense		
91	*PRKAR1A*		c.43–58del16				
	PDE11A		c.2632A>G	M878V	Missense		
92	*PRKAR1A*		c.491–492delTG				
	PDE11A		c.2180A>G	Y727C	Missense		
93	*PRKAR1A*		c.642dupT	p.Val215CysfsX18	Codon stop		Ali A. Ghazi (44), 2021
94	*PRKAR1A*	Exon 2	c.171–172insT	p.L57FfsX70			Safak Akin (45), 2017

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TABLE 4 Continued

No.	Gene	Region	Mutation	Amino acid	Mutation type	Somatic/Germline	Author
95	*PRKAR1A*	Exon 2		C18G	Missense		Ran Hui (46), 2014
96	*PRKAR1A*	Exons 4A and 4B		S147N			Gu Yan-yun (47), 2004
97	*ARMC5*		c.1606C>G	p.P536A	Nonsense		Zhu Mingqiang (48), 2021
99	*PRKAR1A*		c.753 del AT				Patricia de Cremoux (49), 2008
100	*PRKAR1A*		c.846 ins A				
101	*PRKAR1A*		c.502C+1 G>T				
102	*PRKAR1A*		c.708C+1 G>T				
103	*PRKAR1A*		c.109 C>T				

babies after unilateral adrenalectomy with an uneventful perinatal period (31, 52). According to the included pregnant women, it is recommended that pre-pregnant women with PPNAD should undergo unilateral adrenalectomy to correct hypercortisolemia before pregnancy, and hydrocortisone can be given during delivery as a preventive measure (51, 52).

For patients who failed to effectively control elevated cortisol before or after adrenalectomy, ketoconazole, metyrapone, mitotane, and trilostane are effective in correcting hypercortisolemia through inhibition of steroidogenesis. Fluconazole has recently been proposed as a safer alternative to ketoconazole (80). After unilateral adrenalectomy, an individualized approach with close follow-up can lead to good clinical outcomes; dexamethasone stimulation test and adrenal MRI can be used for postoperative monitoring of PPNAD; if CS recurs during follow-up, contralateral adrenalectomy should be performed, followed by lifelong glucocorticoid therapy (56).

Among patients with cPPNAD, 28.79% were associated with cardiac or cutaneous myxoma, which is the most lethal manifestation of CNC and requires vigilant preoperative examination by a cardiologist and careful postoperative follow-up. Myxomas alter valve function through outflow obstruction and valve growth and pose an embolic threat to the brain and other organs (81). The incidence of embolism was 18% in the isolated atrial myxoma group and 40% in the recurrent myxoma group; CNC should be considered in all patients with cardiac myxoma; CNC is more common in patients with recurrent cardiac myxomas, and often involves two or more cavities. Testing for mutations in patients with isolated myxomas or multiple myxomas at atypical sites and screening for mutations in their immediate relatives may help establish an early diagnosis of the disease and implement appropriate clinical follow-up to detect recurrence in these patients (82).

PPNAD is the most common endocrine tumor in CNC, and in order to detect other complications of CNC in time, especially life-

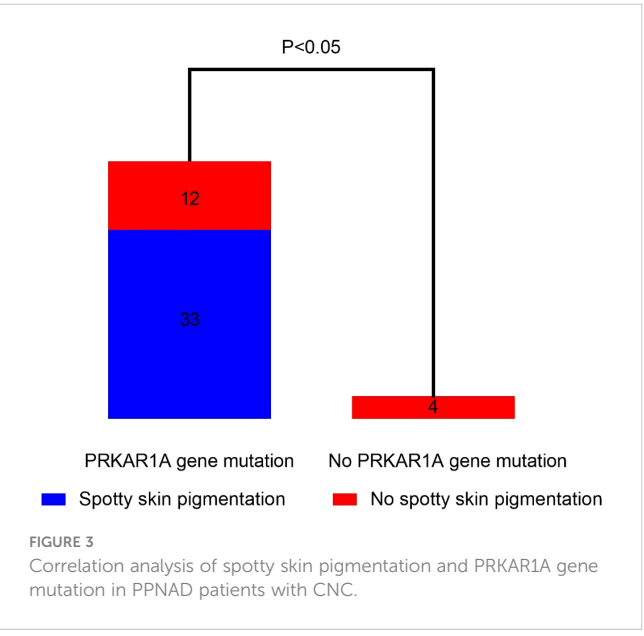

FIGURE 3
Correlation analysis of spotty skin pigmentation and PRKAR1A gene mutation in PPNAD patients with CNC.

threatening cardiac myxoma, pediatric patients should have an annual follow-up examination, which should include echocardiography, thyroid ultrasound, and pituitary function examination, and twice a year if myxoma is found. Oral glucose tolerance, thyroid hormone release, and pituitary function tests can detect growth-hormone-producing pituitary adenomas early in children before clinical symptoms (such as acromegaly) appear. Adolescent patients should also be closely monitored for abnormal changes in growth rate and pubertal status caused by large cell calcifying Sertoli cell tumors (LCCSCT) (21, 83, 84). In addition, testicular ultrasound examination is recommended for men, and abdominal and pelvic ultrasound examination and breast imaging are recommended for female patients (1, 85). One patient had a cPPNAD with bilateral papillary thyroid carcinoma occurring 11 years apart. Thus, follow-up means decades (86).

Our study has several limitations. Firstly, because of the long incubation period of comorbidities in CNC, there may be bias in the diagnosis of CNC in some patients who do not yet have comorbidities. Secondly, the limited number of pregnant patients treated by unilateral adrenalectomy (n:2) is another limitation. Although the number of pregnant women included is small, this article included pregnant women with bilateral adrenalectomy, unilateral adrenalectomy, and no surgery, to comprehensively understand the conditions of the perinatal. Thirdly, when analyzing the characteristics of patients with PPNAD, there are cases with insufficient clinical information, which prevented us from analyzing the characteristics of some rare mutations. Furthermore, there may be a selection bias in this study because many patients with PPNAD did not undergo genetic testing. The mechanisms by which different mutations lead to different clinical features and whether the mutated gene detected is the pathogenic gene of PPNAD remain unclear. Further studies are needed to explain the molecular mechanism of PPNAD more precisely.

Our systematic review, despite the above limitations, is, to our knowledge, the most comprehensive review on patients with PPNAD published to date and provides clinicians with vital information on the common presentation features that may help with the diagnosis and highlight management options. In particular, our study analyzed special groups of pregnant women and children, summarized treatment options and prognosis from the included patients, and summarized treatment options for these groups. Moreover, laboratory tests were also analyzed in detail, and patient tests for PPNAD with other endocrine tumors were analyzed. This study contributes to a comprehensive understanding of PPNAD, including clinical manifestations, laboratory findings, treatment, prognosis, and follow-up.

In conclusion, our study is the first systematic review to investigate the different clinical features, pathogenic variants, and treatments of PPNAD. For the young patients with CS, especially female patients with growth retardation, spotty skin pigmentation, and osteoporosis/low bone mineral density, PPNAD should be considered. For treatment, unilateral adrenalectomy is recommended, especially in women who are preparing for pregnancy. In view of the trauma and difficulty of pathology in PPNAD diagnosis, genetic testing before surgery might be a reasonable option. Patients with PPNAD with spotty skin pigmentation should consider *PRKAR1A* gene mutation and pay attention to CNC. In the future, both short- and long-term evaluations of the complications of PPNAD need to be carried out.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JS: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. LD: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. LH: Data curation, Writing – original draft. HF: Data curation, Writing – original draft. RL: Writing – original draft. JF: Writing – original draft. JD: Writing – review & editing. LL: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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