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# Corticotropinoma as a Component of Carney Complex

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Known germline gene abnormalities cause one-fifth of the pituitary adenomas in children and adolescents, but, in contrast with other pituitary tumor types, the genetic causes of corticotropinomas are largely unknown. In this study, we report a case of Cushing disease (CD) due to a loss-of-function mutation in *PRKARIA*, providing evidence for association of this gene with a corticotropinoma. A 15-year-old male presenting with hypercortisolemia was diagnosed with CD. Remission was achieved after surgical resection of a corticotropin (ACTH)-producing pituitary microadenoma, but recurrence 3 years later prompted reoperation and radiotherapy. Five years after the original diagnosis, the patient developed ACTH-independent Cushing syndrome, and a diagnosis of primary pigmented nodular adrenocortical disease was confirmed. A *PRKARIA* mutation (c.671delG, p.G225Afs\*16) was detected in a germline DNA sample from the patient, which displayed loss of heterozygosity in the corticotropinoma. No other germline or somatic mutations of interest were found. As corticotropinomas are not a known component of Carney complex (CNC), we performed loss of heterozygosity and messenger RNA stability studies in the patient's tissues, and analyzed the effect of *Prkar1a* silencing on AtT-20/D16v-F2 mouse corticotropinoma cells. No *PRKARIA* defects were found among 97 other pediatric CD patients studied. Our clinical case and experimental data support a role for *PRKARIA* in the pathogenesis of a corticotroph cell tumor. This is a molecularly confirmed report of a corticotropinoma presenting in association with CNC. We conclude that germline *PRKARIA* mutations are a novel, albeit apparently infrequent, cause of CD.

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**Freeform/Key Words:** Cushing disease, genetics, pituitary tumor, protein kinase A, Carney complex

Loss-of-function germline mutations of the *PRKARIA* gene are the main genetic cause of primary pigmented nodular adrenocortical disease (PPNAD) and Carney complex (CNC) [1]. Pituitary disease is not a rare finding in CNC, but, although the majority of patients develop subclinical hypersomatotropinemia and/or hyperprolactinemia, only few develop tumors that require surgery; clinically relevant hyperprolactinemia is infrequent [2, 3]. No other types of

Abbreviations: CD, Cushing disease; CNC, Carney complex; KD, knockdown; MRI, magnetic resonance imaging; PPNAD, primary pigmented nodular adrenocortical disease; SD, standard deviation.

pituitary adenomas have been detected to date in this context. We present a case of Cushing disease (CD) subsequently followed by corticotropin (ACTH)-independent Cushing syndrome in a patient carrying an inactivating *PRKARIA* germline mutation, providing evidence for the role of this gene in corticotroph tumorigenesis.

## 1. Case Report

A 15.3-year-old African-American male presented with a 6-year history of progressive growth deceleration [height: 136.7 cm/−3.9 standard deviation (SD)] and weight gain (weight: 92.2 kg/+2.23 SD, body mass index 49.3 kg/m<sup>2</sup>+2.99 SD). He had a history of nephrolithiasis diagnosed 18 months before. In the year before his admission, he developed striae; hyperpigmentation of the upper torso, arms, and face; excessive corporal hair; easy bruising; and headaches. During his initial workup, he was diagnosed with hypertension, central hypothyroidism, osteopenia, multiple vertebral compression fractures, bilateral avascular hip necrosis, and retroperitoneal and intraspinal lipomatosis. Sexual development was adequate for his age (Tanner V for pubic hair and genitalia).

A diagnosis of ACTH-dependent hypercortisolemia was established on the basis of elevated midnight serum cortisol (27.5 μg/dL), 24-hour urinary free cortisol (306.8 μg/24 h), and ACTH (53.05 ng/mL) levels. This was confirmed by the response to CRH stimulation, although the patient failed to suppress to the high-dose dexamethasone test. Additional results are included in [Table 1](#). No lesion was identified in the pituitary magnetic resonance imaging (MRI), but bilateral inferior petrosal sinus sampling demonstrated a high central-to-peripheral ACTH ratio, compatible with CD. The patient underwent transsphenoidal surgical exploration and resection of a pituitary microadenoma; the pathology report confirmed a corticotropinoma ([Fig. 1](#)). Remission was achieved, and, after discharge on glucocorticoid replacement therapy, the patient experienced substantial improvement of his symptoms. Recurrence of hypercortisolemia with a possible pituitary lesion by MRI prompted surgical reintervention 3 years later, but no adenomatous tissue was identified. Due to persistent hypercortisolemia, the patient was treated with radiotherapy and placed on ketoconazole and appeared in remission. He was lost to follow-up for 2 years; during that time his disease progressed, causing uncontrolled hypertension, headaches, and weight gain, as well as further complications (hypokalemia, nocturnal orthopnea, and urinary and fecal incontinence). A new diagnostic workup ruled out recurrent CD, but identified ACTH-independent hypercortisolemia with multiple small nodular bilateral adrenal lesions. Genetic testing identified a frameshift variant in the *PRKARIA* gene. Careful clinical examination revealed numerous lentiginosities on the face, oral mucosa, and bulbar conjunctive [[Fig. 1\(a\) and 1\(b\)](#)], and calcifications compatible with large-cell calcifying Sertoli cell tumors by ultrasonography. No myxomas were identified in the echocardiogram or cardiac MRI. The patient underwent bilateral adrenalectomy, and PPNAD was confirmed [[Fig. 1\(c\)](#)]. Because CD is not a known component of CNC, we investigated a possible role for *PRKARIA* loss-of-function in corticotroph cell tumorigenesis.

## 2. Materials and Methods

Materials and Methods are presented as Supplemental Material.

## 3. Results

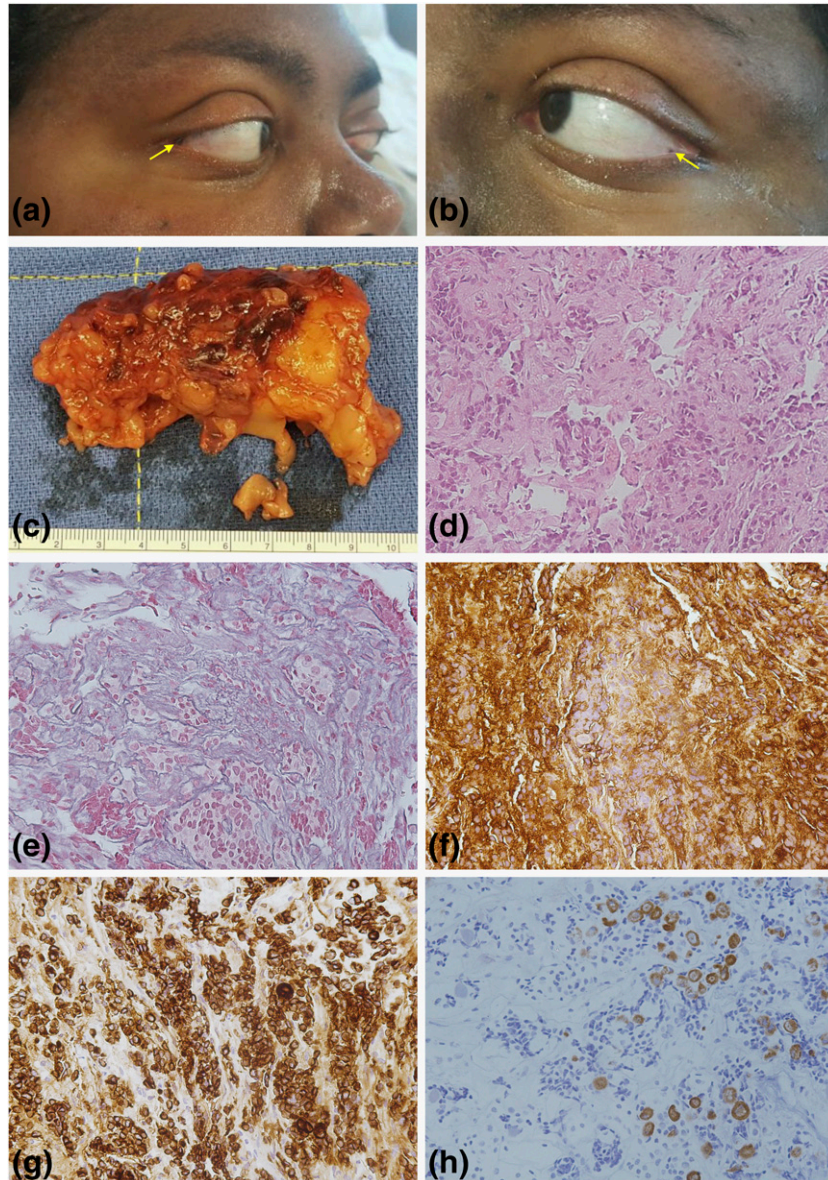
### A. A *PRKARIA* Variant Is Associated With a Corticotropinoma in the Setting of CNC

Genetic testing demonstrated a heterozygous frameshift variant of the *PRKARIA* gene (c.671delG, p.G225Afs\*16), not previously reported in the public databases or in CNC and/or PPNAD [[Fig. 2\(a\)](#)]. No other variants of interest in *PRKARIA* were identified among 97 other pediatric CD patients screened. Mutations in known pituitary disease-causative genes (*AIP*, *MEN1*, *CDKN1B*, *GPR101*) and in selected genes involved in the pituitary–adrenal axis (*POMC*, *GR*, *MC2R*, *MC3R*, *BRG1*, *CRH*, *CRHR1*, and *CRHR2*) were ruled out by manual

**Table 1. Additional Hormonal Measurements at Presentation**

Basal Hormones		
Parameter	Result	Reference
Insulin	15.4 $\mu$ U/mL	6–27
TSH	0.16 $\mu$ U/mL	0.4–4
Free T4	0.9 ng/dL	0.8–1.5
T4	5.1 $\mu$ g/dL	4.5–12.5
T3	88 ng/dL	90–215
FSH	<0.1 U/L	1–11
LH	0.2 U/L	1–8
Free testosterone	1.5 ng/dL	7.4–22.6
Androstendione	186 ng/dL	65–210 for Tanner V
Dehydroepiandrosterone	2 ng/mL	<6.6
Deydroepiandrosterone sulfate	1.75 ng/dL	0.8–5.6
IGF1	120 ng/dL	171–814 for Tanner V
Midnight salivary cortisol	0.54 $\mu$ g/dL	0.01–0.09
Dynamic Tests		
8 mg Dexamethasone Suppression Test		
Time Point	Parameter	Result
Basal	Cortisol	29.3 $\mu$ g/dL
Final		31.9 $\mu$ g/dL
CRH Stimulation Test		
Time Point	Parameter	Result
–5 min	ACTH	45.7 pg/mL
	Cortisol	28.8 $\mu$ g/dL
0	ACTH	51.7 pg/mL
	Cortisol	28.2 $\mu$ g/dL
15 min	ACTH	58.5 pg/mL
	Cortisol	33.8 $\mu$ g/dL
30 min	ACTH	66.5 pg/mL
	Cortisol	30.6 $\mu$ g/dL
40 min	ACTH	66.6 pg/mL
	Cortisol	27.9 $\mu$ g/dL
Bilateral Inferior Petrosal Sinus Sampling		
Time Point	Parameter	Result
–5 min	ACTH, RPV	40.7 pg/mL
	ACTH, LPV	4446 pg/mL
0	ACTH, peripheral	38.8 pg/mL
	ACTH, RPV	34.9 pg/mL
	ACTH, LPV	3545 pg/mL
3 min	ACTH, peripheral	35.7 pg/mL
	ACTH, RPV	476 pg/mL
	ACTH, LPV	2958 pg/mL
5 min	ACTH, peripheral	35.5 pg/mL
	ACTH, RPV	300 pg/mL
10 min	ACTH, LPV	2737 pg/mL
	ACTH, peripheral	33.3 pg/mL
	ACTH, RPV	359 pg/mL
	ACTH, LPV	2905 pg/mL
	ACTH, peripheral	31.8 pg/mL

Abbreviations: FSH, follicle-stimulating hormone; IGF1, insulin-like growth factor1; LH, luteinizing hormone; LPV, left petrosal vein; RPV, right petrosal vein; TSH, thyrotropin.



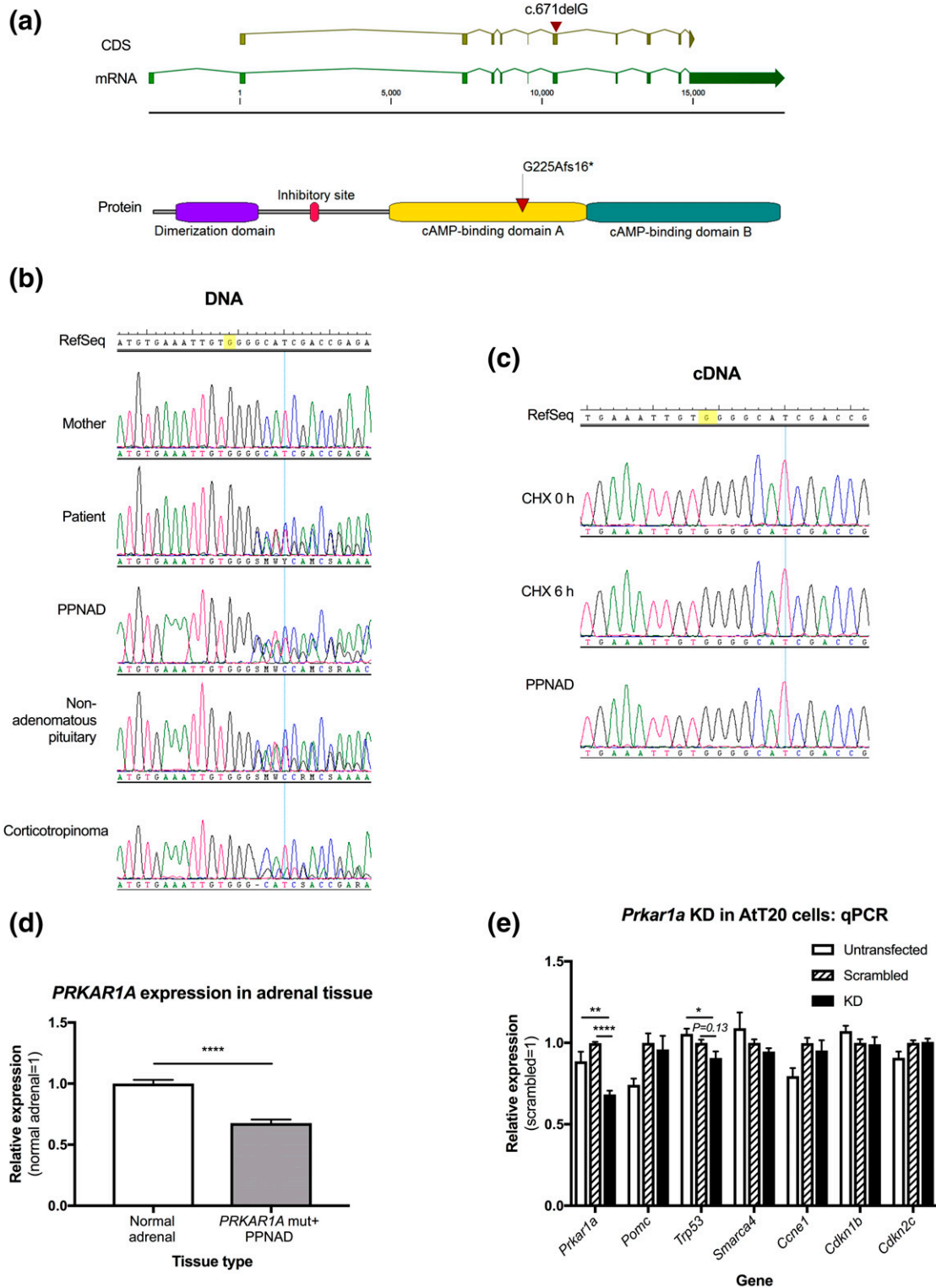
**Figure 1.** Clinical and histopathological presentation. (a and b) Small epicanthal lentiginos were observed in this patient. (c) The surgical specimens of bilateral adrenalectomy displayed the characteristics of PPNAD, and such diagnosis was later confirmed by histopathological examination. (d) Hematoxylin–eosin staining (20 $\times$ ) of the corticotropinoma tissue. The tumor was a microadenoma measuring approximately 6  $\times$  4  $\times$  2 mm, with Crooke’s cells surrounding the neoplastic tissue. (e) Breakdown of the reticulin network (20 $\times$ ), (f) as well as strong and diffusely positive ACTH staining (20 $\times$ ), was demonstrated. (g) Extensive positive immunostaining for CAM5.2 was identified (20 $\times$ ). (h) Keratin 20 immunostaining was found in some areas containing Crooke’s cells (20 $\times$ ). These images were compatible with a diagnosis of Crooke’s cell adenoma.

check of whole-exome sequencing raw data. Previous Sanger sequencing and deletion testing had excluded *AIP* and *MEN1* gene defects in this and additional patients with CD [4].

#### *B. Loss-of-Function of PRKAR1A p.G225Afs\*16 Is Due to Messenger RNA Instability*

Compared with the peripheral blood-extracted DNA, the corticotropinoma presented loss of heterozygosity at *PRKAR1A*, with clear predominance of the mutant allele [Fig. 2(b)]. At the





**Figure 2.** Role of *PRKAR1A* in corticotroph cell tumorigenesis, and in PPNAD. (a) The frameshift *PRKAR1A* gene (NG\_007093.3) variant c.671delG, p.G225Afs\*16 affects the exon 7 of the reference transcript (NM\_002734.4, the first exon is not translated). The surrounding region encodes the first of two cyclic adenosine monophosphate-binding domains in the protein, which are crucial for its regulatory function. (b) The germline mutation identified in the patient was not present in the mother. As a sample from the father was not available, we could not determine whether the mutation was inherited from the father or if it appeared as

a *de novo* event. The PPNAD and nonadenomatous pituitary (obtained from the second surgery) tissues were heterozygous for such mutation. However, loss of heterozygosity was identified in the corticotropinoma tissue, with a 72% to 82% predominance of mutant DNA in the chromatogram peaks measured. (c) In samples from lymphoblastoid cells before and after the treatment with cycloheximide and in the PPNAD tissue, only the wild-type allele was detected. Given that these tissues did not display loss of heterozygosity at the DNA level, the homozygosity for the wild-type allele should be explained by nonsense-mediated messenger RNA decay. Unfortunately, we did not achieve rescue of the mutant allele during the cycloheximide experiment performed. (d) Compared with a normal adrenal tissue sample, the PPNAD specimen displayed significantly reduced *Prkar1a* expression (mean:  $1 \pm 0.02$  vs  $0.68 \pm 0.01$ ,  $P < 0.0001$ ). (e) We achieved 30% *Prkar1a* KD compared with the scrambled control (mean:  $0.68 \pm 0.02$  vs  $1 \pm 0.01$ ,  $P < 0.0001$  KD). Compared with the untransfected cells, *Trp53* expression was reduced in the KD experiment (mean:  $1.05 \pm 0.03$  vs  $0.91 \pm 0.1$ ,  $P = 0.0130$ ), and there was a trend for lower *Trp53* in the KD cells compared with the scrambled control (mean:  $1 \pm 0.05$  vs  $0.91 \pm 0.1$ ,  $P = 0.13$ ). No other significant differences in the expression of cell cycle markers were found among experimental conditions.

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messenger RNA level, only the wild-type allele was detected in the PPNAD tissue and lymphoblastoid cells, supporting messenger RNA instability, and cycloheximide treatment was insufficient to rescue the expression of the mutant allele [Fig. 2(c)]. *PRKAR1A* expression was significantly reduced in the PPNAD tissue, compared with normal adrenal [Fig. 2(d)]. As expected from other *PRKAR1A* mutations in CNC, our data support nonsense-mediated RNA decay as the mechanism for loss-of-function.

### C. Effects of *Prkar1a* Gene Silencing on Corticotroph Cell Function and Proliferation

Under 30% *Prkar1a* knockdown (KD), *Pomc* expression was increased in both the scrambled control and the KD experiment; only the former reached statistical significance [Fig. 2(e)]. A trend for lower *Trp53* expression was found in the KD compared with the scrambled control. No significant changes were observed in the expression of other markers of cell cycle progression.

## 4. Discussion

Since its first description by Carney and collaborators in 1985, ~750 cases of CNC have been reported [5, 6]. This infrequent, autosomal dominant syndrome (Mendelian Inheritance in Man: 160980 and 605244) of multiple endocrine neoplasia and cardiocutaneous manifestations is caused by inactivating mutations in the *PRKAR1A* gene (17q24.2) in 73% of the cases, and by deletions of the 17q24.2-q24.3 region in 6% of the patients [1, 7]. A triplication of the *PRKACB* gene at the somatic level was identified as the cause of disease in a single patient, whereas other cases are linked to an uncharacterized defect in 2p16 [8, 9]. More than half of the cases display familial presentation, with almost full penetrance [10]. No germline or somatic *PRKAR1A* mutations have been identified in sporadic pituitary adenomas [4, 11, 12].

Pituitary disease in CNC consists of single or multiple somatotroph or mammosomatotroph adenomas, occasionally surrounded by areas of hyperplasia [13–15]. However, a number of such adenomas in patients with CNC are histologically pleomorphic [16, 17], and mice with *Prkar1a* and *Rb1* haploinsufficiency develop intermediate lobe tumors [18]. Thus, although *Prkar1a* complete deficiency in mouse growth hormone-releasing hormone receptor-expressing pituitary cells undoubtedly leads to tumors expressing growth hormone, prolactin, and thyrotropin [19, 20], the data point to the possibility of *PRKAR1A* deficiency predisposing to other pituitary tumors as well.

A single patient with CNC possibly having CD has previously been reported [21]. She was first seen at the age of 3 years with Cushing syndrome and high ACTH levels, although a pituitary tumor was never proven. She was treated with metyrapone and mitotane and eventually cured of her disease. Twenty-three years later, she was reported as a patient with CNC with apparently normal circadian rhythm and cortisol secretion, although biochemical

data were not presented; the patient had the most commonly identified germline *PRKARIA* mutation (c.491\_492delTG, p.V164Dfs\*5) [1, 21].

The consequence of loss-of-function of the *PRKARIA* gene is deregulated activation of the cyclic adenosine monophosphate pathway due to uncontrolled catalytic subunit activity [6, 22]. This is true for all *PRKARIA* mutations causing CNC, even those that are expressed [3, 10, 23, 24]. The mutation described in this patient appears to act the same way, and loss of heterozygosity in the pituitary tumor further strengthens its causative association.

In conclusion, we describe the association between a new *PRKARIA*-inactivating mutation and a corticotropinoma in a patient with CNC. This is a documented case with a clinical-genetic association. No other *PRKARIA* defects were found in a large cohort of patients with CD screened previously [4] and now. Germline *PRKARIA* mutations are a notable, although infrequent, cause of CD may now be included among the genetic defects that predispose to CD, albeit rarely.

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