A Novel Mutation of *PRKAR1A* Caused Carney Complex in a Chinese Patient

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Primary pigmented nodular adrenocortical disease (PPNAD) causes adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome (CS), which is the most frequent endocrine manifestation of Carney complex (CNC).[1] In the disease process of PPNAD, both presadrenal glands are involved and feature small brown-black nodules separated by the atrophic adrenal cortex. Endocrine lesions in CNC include testicular neoplasms, PPNAD, growth hormone (GH) and prolactin-producing pituitary tumors, and thyroid cancer.[2] It is a genetically heterogeneous autosomal dominant disease. Mutations of the regulatory subunit type 1A of the cAMP-dependent protein kinase (*PRKAR1A*) gene are found in nearly 60% of individuals with CNC, whereas an uncharacterized gene at the CNC2 locus on chromosome 2p16 is similarly implicated in disease pathogenesis.[2] Here, we present the case of a Chinese young girl with PPNAD.

A 15-year-old girl was admitted in November 2012 due to Cushingoid appearance for three years, the weight increase of 10 kg, and headache in the proceeding 1 year. She was diagnosed with hypertension and received amlodipine 5 mg/d for antihypertension treatment before admission. The patient also complained blurred vision, visual distortion, intermittent nausea, and vomiting. What's more, she had primary amenorrhea. The patient's height and weight were 145 cm and 45 kg, respectively, and her blood pressure was 150/90 mmHg (1 mmHg = 0.133 kPa). Physical examination showed moon face, buffalo hump, central obesity, striae over the abdomen, and hirsutism over the upper limbs. Laboratory results showed that her liver function and renal function were normal, the level of serum potassium was low (3.27 mmol/L), fasting plasma glucose was 6.18 mmol/L and glucose level after oral glucose tolerance test 2 h was 17.29 mmol/L. The endocrine studies revealed adrenal CS. During the 2-day high-dose dexamethasone suppression test, the level of cortisol (8 A.M.) was measured. The cortisol levels of 8 A.M., 4 P.M., and 0 A.M. were 29.63 μg/dl, 26.26 μg/dl, and 36.82 μg/dl, whereas the ACTH levels of 8 A.M., 4 P.M., and 0 A.M. were 1.18 pmol/L, 3.67 pmol/L, and 1.01 pmol/L. The cortisol levels could not be suppressed after both low-dose dexamethasone suppression test and high-dose dexamethasone suppression test. Her plasma GH concentration and insulin-like growth factor level were normal. Her thyroid function was normal except that thyroid-stimulating hormone (TSH) was low (0.109 μU/ml). Her levels of FSH and LH were both low (1.15 U/L, 0 U/L, respectively). Her rennin-angiotensin-aldosterone system was normal. Chromosome examination showed G banding (level of 400) with karyotype 46, XX. The result of adrenal computed tomography indicated that adrenal medial branch and lateral branch had multiple small adrenal nodules with soft tissue density [Figure 1a and 1b]. The result of pituitary magnetic resonance imaging (MRI) suggested pituitary micro-adenoma [0.4 cm × 0.5 cm; Figure 1c]. Ultrasonography indicated infantile uterus and ovaries, normal thyroid, no cardiac myxoma. The result of MRI on the eye and optic nerve was normal. Results of the eye examination by the oculist showed visual acuity of the right eye was −0.15 and left eye only can perceive hand moving; the ocular pressure of the right eye was 39.2 mmHg, and that of the left eye was 46.4 mmHg. There was no exudation and hemorrhage in the retina. The

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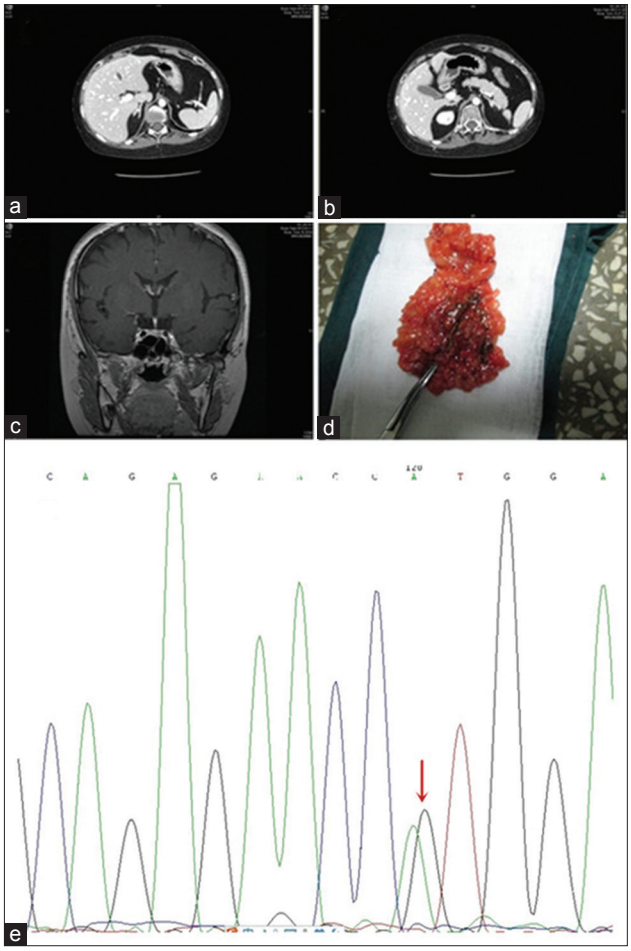

Figure 1: Results of adrenal computed tomography (a and b), pituitary magnetic resonance imaging (c), and the adrenal appearance after the patient received laparoscopic left adrenalectomy (d); A 88 A to G mutation changes the initiator ATG to a GTG codon of *PRKAR1A* gene in this patient (e).

patient was diagnosed as secondary glaucoma. The patient received laparoscopic left adrenalectomy and 1 month later she received the right adrenalectomy partially [Figure 1d]. After left adrenalectomy, the level of serum potassium was 4.33 mmol/L, the level of cortisol (8 A.M.) decreased from 29.1 ug/dl to 19.1 ug/dl, and the level of ACTH increased from 1.99 pmol/l to 5.44 pmol/l. Her level of TSH increased from 0.109 μU/ml to 0.274 μU/ml. Cushingoid features of the patient began to disappear thereafter. The patient's weight decreased 5 kg and her blood pressure was 110/70 mmHg after the right adrenalectomy. The ocular pressures of the right and left eyes were 19.2 mmHg and 21.0 mmHg, respectively. Adrenal pathology was also consistent with PPNAD, which indicated adrenocortical nodular hyperplasia, partly consist of transparent cytoplasm cells, partly by the abundant cytoplasm eosinophilic cells, with visible pigment in the cell.

A diagnosis of CNC was highly suspected for this patient; therefore, sequencing of the *PRKAR1A* gene from peripheral blood leukocytes was undertaken. Direct sequencing of all 11 exons of *PRKAR1A* of this patient identified a 88 A to G mutation, which changes the initiator ATG to a GTG codon, abolishes the translational start codon but does not introduce a premature stop codon [Figure 1e]. This specific mutation has been previously identified in *PRKAR1A* among individuals with CNC,[3] supporting a causal association with the patient's diagnosis of CNC. Sequencing of *PRKAR1A* gene in the patient's parents and her elder sister did not identify any mutation.

Mutations in *PRKAR1A* are causative.[4] Sequence analysis of the PRKAR1A coding region, available on a clinical basis, has a mutation detection rate of approximately 60%. Since the first description of CNC, numerous individuals with CNC have been reported from all ethnic groups and presenting with varying numbers, combinations, and severity of manifestations. To date, a total of 117 different *PRKAR1A* mutations have been identified (see *PRKAR1A* Mutation Database) in 387 unrelated families of diverse ethnic origin; they are summarized by Horvath.[3] Treatment of PPNAD and CNC is the treatment of manifestations. The routine intervention for CS is bilateral adrenalectomy or partially. Patient, in this case, received left adrenalectomy and right adrenalectomy partially and then most manifestations were recovered, and the laboratory examination and the cortisol levels and the ACTH levels remained normal. It was recommended to screen the family members of CNC patients. Fortunately, in this case, sequencing of *PRKAR1A* gene in the patient's parents and the patient's elder sister did not identify any mutation. Further study of the functional consequences of the mutations needs to be done in the future.

Declaration of patient consent

The author certifies that they have obtained all appreciate patient consent forms. In the form, the patient/patient' guardians have given their consent for their images and other clinical information to be reported in the journal. The patient/patient' guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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