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Case Report:

Clinical and molecular genetic analysis of a Chinese family with congenital X-linked adrenal hypoplasia caused by novel mutation 1268delA in the *DAX-1* gene*

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Abstract: Congenital X-linked adrenal hypoplasia (AHC) is a rare disease characterized by primary adrenal insufficiency before adolescence and by hypogonadotropic hypogonadism (HHG) during adolescence. In this paper, we present a Chinese family with AHC. Two brothers, misdiagnosed with adrenal insufficiency of unknown etiology at the age of 9, were correctly diagnosed with AHC when delayed puberty, HHG, and testicular defects were observed. We investigated the clinical features and identified the dosage-sensitive sex reversal AHC critical region of the X chromosome gene 1 (*DAX-1*) mutation in this kindred. Direct sequencing of the *DAX-1* gene revealed that the two siblings have a novel mutation (1268delA) of which their mother is a heterozygous carrier. This mutation causes a frameshift and a premature stop codon at position 436, encoding a truncated protein. It is important to increase knowledge of the mutational spectrum in genes related to this disease, linking phenotype to genotype.

Key words: Congenital X-linked adrenal hypoplasia, Primary adrenal insufficiency, Hypogonadotropic hypogonadism
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1 Introduction

Congenital X-linked adrenal hypoplasia (AHC; OMIM 300200) is a kind of uncommon disease characterized by primary adrenal insufficiency early in life and by hypogonadotropic hypogonadism (HHG) during adolescence (Zanaria *et al.*, 1994). It is estimated to have an incidence of 1 in 12 500 births. The disease is caused by mutations of the nuclear receptor subfamily group B member 1 (NROB1), which is also known as the dosage-sensitive sex reversal AHC critical region of the X chromosome gene 1 (*DAX-1*), on chromosome Xp21.3-p21.2.

The *DAX-1* gene comprises two exons separated by a 3.4-kb intron and encodes a 470-amino acid orphan nuclear hormone receptor (Guo *et al.*, 1996). The amino terminus comprises three and a half copies of a repeated motif but lacks a typical zinc finger DNA-binding domain, whereas the carboxyl-terminal domain displays high homology to the ligand domain of nuclear receptors. The carboxyl terminus comprises three and a half alanine/glycine-rich repeats of a 65–70-amino acid motif that is implicated in protein-protein interactions and may bind to the hairpin loop structure in DNA. *DAX-1* is expressed in the three layers of the adrenal glands, the gonads (Sertoli and Leydig cells in the testis, and theca and granulosa cells in the ovary), the ventromedial hypothalamus, and pituitary gonadotrope cells (Guo *et al.*, 1995). *DAX-1* is a general repressor of steroid biosynthesis that acts predominantly by inhibiting the activity of steroidogenic factor-1 (also known as

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NR5A1), which mediates transcription of many genes in the steroid biosynthetic pathway, including steroidogenic acute regulatory protein, 3β-hydroxysteroid dehydrogenase, and *P450scc* genes (Ito *et al.*, 1997). *DAX-1* also inhibits its own transcription and luteinizing hormone (LH) β subunit transcription activities, and reduces the expression of gonadotropin releasing hormone (GnRH) (Li *et al.*, 2010).

More than 147 different mutations in *DAX-1* have been described (Phelan and McCabe, 2001), most of which are nonsense or frameshift mutations that cause premature truncation of the protein. Most of the missense mutations are located within the carboxyl-terminal half of the protein and relatively few have been reported at the amino terminus. However, mutation of the *DAX-1* gene is not routinely detected in patients with primary adrenal insufficiency. This maybe lead to misdiagnosis of AHC. In this report, we describe a family with two siblings suffering from "primary adrenal insufficiency" and delayed puberty AHC, in which a novel *DAX-1* gene mutation (c.1268delA p.His423Leufs*14) was detected.

2 Case report

2.1 Clinical characteristics

The proband, II-1 (Fig. 1), was the product of a full term, normal, spontaneous delivery on Feb. 18, 1989. He presented at 9 years of age with recurrent fatigue, nausea, vomiting, poor food intake, and weight loss. At that time, hyperpigmentation was noted on physical examination. He was diagnosed with primary adrenal insufficiency and started treatment with 20 mg hydrocortisone, which alleviated the symptoms and hyperpigmentation.

In his teenage years, II-1 presented with delayed puberty. He was admitted to our hospital when he was 18 years old. At that time, his height was 155.0 cm and his weight was 46.0 kg. His systolic and diastolic blood pressures were 100 and 60 mmHg, respectively. Physical examination revealed no pubic hair, no gynecomastia, and a low testicular volume (left 2.0 cm× 1.1 cm, right 2.1 cm×0.9 cm). There were some hyperpigmented macules on the lips and oral mucosa. Laboratory tests showed elevated serum adrenocorticotropic hormone (ACTH) at 8:00 a.m. (548.0 pg/ml, reference range 0–46 pg/ml; chemiluminescence)

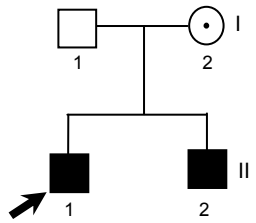

Fig. 1 X-linked inheritance of the congenital adrenal hypoplasia

The proband (II-1), indicated by the arrow, had the phenotypic spectrum of X-linked AHC including adrenocortical insufficiency, hypogonadotropic hypogonadism, and testicular defects. II-2 was the younger brother of the proband and had symptoms similar to those of his brother. The two patients' father (I-1) and mother (I-2) had both undergone normal puberty without any symptoms of adrenal insufficiency. Square=male, circle=female, black=patient, white=normal, dot in the circle=heterozygous carrier

with a decreased cortisol concentration (1.0 μg/dl, reference range 5–25 μg/dl; chemiluminescence). Serum sodium and potassium concentrations were 135.0 and 4.2 mmol/L, respectively. Computerized tomography (CT) of the abdomen revealed small adrenal glands. Magnetic resonance imaging (MRI) of the pituitary gland did not show any definite abnormality. During hospital admission, during an arginine (30 g intravenously (i.v.)) test, his growth hormone (GH) rose to 30.0 ng/ml at 30 min, suggesting a normal GH reserve. Investigations revealed low serum testosterone (below the limit of detection of 20.0 ng/dl), and LH (0.9 mIU/ml) and follicle stimulating hormone (FSH; 3.8 mIU/ml) were at the low end of the normal range (LH 1.4–7.2 mIU/ml, FSH 1.5–14.0 mIU/ml). On human chorionic gonadotropin (hCG; 2000 U, intramuscularly (i.m.) once) stimulation testing, testosterone rose to a peak of 47.4 ng/dl at 48 h after injection of hCG. A presumptive diagnosis of HHG was made. II-1 started therapy with hCG (2000 U, i.m. twice weekly) and his serum testosterone reached 102.0 ng/dl (reference range of adult: 262–1593 ng/dl) two weeks later. However, the size of his testicles did not increase (left 1.8 cm×0.8 cm, right 2.1 cm×0.7 cm).

Five years later, at 23 years of age, his serum testosterone had decreased to 41.8 ng/dl despite hCG treatment. This suggested the presence of a testicular defect. The patient discontinued hCG and started testosterone therapy. Because his ACTH at 8:00 a.m. was always higher than 1250.0 pg/ml, even with the

administration of 20 mg hydrocortisone every 12 h, 0.375 mg dexamethasone before sleep was used instead of hydrocortisone in the afternoon.

Patient II-2 (Fig. 1), the younger brother of the proband, was also the product of a full term, normal, spontaneous delivery, on Mar. 26, 1990. He was diagnosed with primary adrenal insufficiency at 8 years of age because he had symptoms similar to those of his brother (fatigue, nausea, hyperpigmentation) and he began treatment with 20 mg hydrocortisone. His height increased by 2 cm per year. He also presented with delayed puberty.

He was admitted to our hospital when he was 23 years old, complaining of nausea, fatigue and dizziness and loss of the weight nearly 5.2 kg without taking hydrocortisone in one week. At that time, the patient was 172.0 cm tall and weighed 48.0 kg, and his systolic and diastolic blood pressures were 100 and 60 mmHg, respectively. Physical examination revealed no pubic hair, no gynecomastia and a low testicular volume (left 1.8 cm×0.7 cm, right 2.1 cm× 0.9 cm). There are a few hyperpigmented macules on the lips and oral mucosa. The primary adrenal insufficiency was diagnosed by elevated serum ACTH (1250.0 pg/ml) with a low cortisol concentration of less than 1.0 μg/dl in the morning. Serum sodium concentration was 135.0 mmol/L and potassium concentrations 4.2 mmol/L. His serum aldosterone level was 124.2 ng/dl (reference range 30–100 ng/dl) and his plasma renin activity was greater than 24.0 ng/(ml·h) (reference range 0.15–2.33 ng/(ml·h)) in the supine position. His basal serum testosterone concentration was less than 20 ng/ml, but increased to 80 ng/ml 72 h after daily injections of 2000 U hCG. His basal FSH and LH were 2.1 mIU/ml and 0.7 mIU/ml, respectively, at the low end of the normal range. On GnRH stimulation testing (100 μg gonadorelin; Ferring GmbH, Kiel, Germany), his testosterone level was always less than 20.0 ng/dl. At 120 min, his FSH level had risen from 2.1 mIU/ml to a peak of 8.7 mIU/ml, and his LH level from 0.7 mIU/ml to a peak of 4.1 mIU/ml. These findings suggested incomplete HHG. Serum levels of thyroid hormone, prolactin, and GH were normal. His bone age remained markedly delayed at 15 years. CT of the abdomen showed atrophic adrenal glands (Fig. 2). Increasing the dose of hydrocortisone up to 30 mg/d improved his clinical symptoms rapidly.

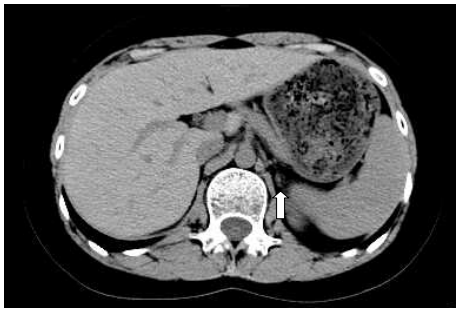

Fig. 2 Computerized tomography (CT) of abdomen of II-2
CT revealed small adrenal glands as indicated by the arrow

The patients' father (I-1) and mother (I-2) had both undergone normal puberty without any symptoms of adrenal insufficiency.

2.2 Direct sequencing of the *DAX-1* gene

After obtaining written informed consent, blood samples were taken from individuals I-1, I-2, II-1, and II-2 and leukocyte DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen, Stanford, USA). Both of the *DAX-1* (NC_000023, complementary DNA (cDNA), NM_000475) exons and their flanking intronic sequences were amplified at 95 °C for 5 min using the following sets of forward and reverse primers: exon 1 forward, 5'-GAG GTC ATG GGC GAA CAC-3'; exon 1 reverse, 5'-TGC TGA GTT AGT CAC GAT TTC T-3'; exon 2 forward, 5'-AGC AAA GGA CTC TGT GGT-3'; exon 2 reverse, 5'-GAG CTA TGC TAC CTG TTG-3'.

Polymerase chain reaction (PCR) was performed in a final volume of 50 μl with a reaction system containing 200 ng genomic DNA, 20 pmol of each primer, 200 μm deoxynucleotide triphosphates, 1.5 mmol/L $MgCl_2$, and 2.5 U Taq polymerase (Sangon, Shanghai, China). Exon 1 was amplified by an initial denaturation at 95 °C for 5 min, followed by 28 cycles of denaturation at 94 °C for 30 s, annealing at 53 °C for 30 s and elongation at 72 °C for 1.5 min, with a final extension at 72 °C for 10 min (Xiao *et al.*, 2007). Exon 2 was amplified by an initial denaturation at 95 °C for 5 min, followed by 28 cycles of denaturation at 94 °C for 30 s, annealing at 53 °C for 30 s and elongation at 72 °C for 30 s, with a final extension at 72 °C for 10 min (Xiao *et al.*, 2007). Direct sequencing was performed using fluorescent dideoxynucleotides on an ABI Prism 3700 DNA analyzer (Sangon, Shanghai, China).

Direct sequencing of all coding exons of the *DAX-1* gene and their flanking intronic sequences demonstrated that the proband (Fig. 3c) and his younger brother (Fig. 3d) had the same mutation in exon 2, comprising a single adenine deletion at position 1268. This nucleotide deletion results in a frameshift and a premature stop codon at position 436 (c.1268delA p.His423Leufs*14). The mutated gene encodes a truncated protein missing a large portion of the terminal region corresponding to the ligand binding domain (LBD). This mutation position is represented graphically in Fig. 3.

Further analysis of the family members showed that the patients' father was normal (Fig. 3a) and their mother was a heterozygous carrier (Fig. 3b). By comparison with the Human Gene Mutation Database, this mutation in the *DAX-1* gene was found to be a novel mutation associated with AHC.

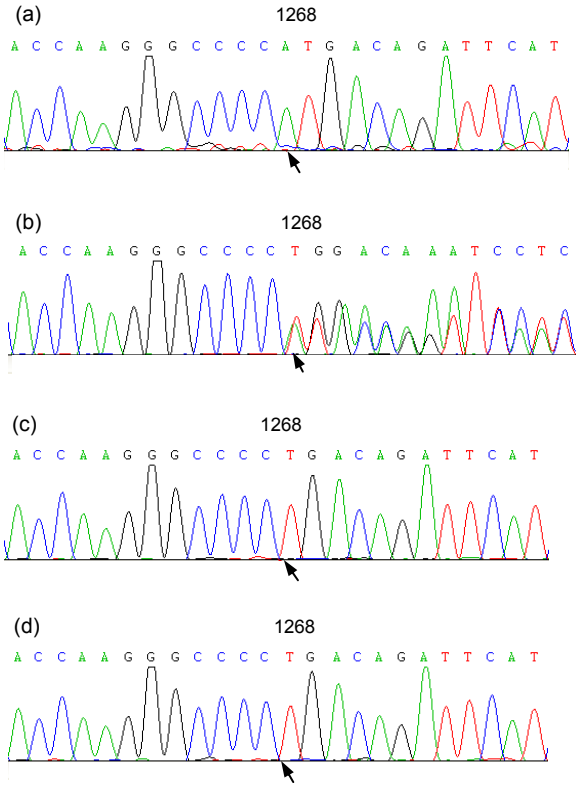

Fig. 3 Sequence analysis of exon 2 of the *DAX-1* gene
(a) Proband's father, normal; (b) Proband's mother, heterozygous carrier; (c) Proband; (d) Proband's brother. Direct sequencing of exon 2 shows a deleted peak (arrow) at nucleotide position 1268 in the proband and his brother, overlapping peaks due to a heterozygous single base pair deletion in his mother (arrow)

3 Discussion

AHC has been classified into four types according to its clinical manifestations (Burke *et al.*, 1988): type 1 is a sporadic form associated with pituitary hypoplasia; type 2 is an autosomal recessive form; type 3 is an X-linked cytomegalic form associated with HHG; and type 4 is an X-linked form associated with glycerol kinase deficiency, psychomotor retardation, and Duchenne's muscular dystrophy in most patients. The present sibling cases characterised by primary adrenal insufficiency and HHG appear to be compatible with the most common type of AHC, type 3. Note that AHC presenting with adrenal sufficiency should be differentiated from 21-hydroxylase deficiency or Addison's disease secondary to multiple etiologies. CT of the adrenal glands is useful. Patients with 21-hydroxylase deficiency always have adrenal hyperplasia; however, adrenal atrophy is common in those with AHC. Distinguishing these disorders is important, because they differ in their clinical course, steroid replacement therapy, prognosis, and genetic counseling. For example, mutation of the *DAX-1* gene can inhibit the glucocorticoid receptor and thus routine doses of hydrocortisone cannot inhibit ACTH (Zhou *et al.*, 2008). These patients always need higher doses of hydrocortisone or a small dose of dexamethasone at night.

AHC tends to occur before adolescence. The typical clinical manifestations of adrenal insufficiency include feeding difficulty, vomiting, dehydration, and low blood pressure. Hypoglycemia always is the first symptom of X-linked AHC. If left untreated, the adrenal insufficiency is rapidly due to acidosis, hyperkalemia, even shock. Affected males often exhibit delayed puberty due to HHG. Primary adrenal insufficiency can occur at any time in life, including the neonatal period, infancy, and childhood. The clinical symptoms are similar to those of AHC. Delayed puberty due to adrenal insufficiency is extremely uncommon. Thus, some AHC patients are wrongly diagnosed with adrenal insufficiency of unknown etiology before puberty. In the patient reported here, the delayed onset of adrenal insufficiency at 8–9 years of age and mild symptoms led to a wrong diagnosis of primary adrenal insufficiency of unknown etiology. In China, Chang *et al.* (2011) screened 25 boys with primary adrenal insufficiency

for mutations of the *DAX-1* gene. *DAX-1* gene mutations were found in 40.0% of the subjects, in 62.5% of those with impaired sex development, and in 100% of those with a family history. Given these results, we should pay more attention to the genetic diagnosis of "primary adrenal insufficiency", especially in patients with a familiar history. AHC should be considered in the differential diagnosis of patients exhibiting unexplained late-onset adrenal insufficiency with incomplete HHG, and *NROB1* gene analysis should be performed.

DAX-1 has a crucial role in the development and function of the reproductive axis at multiple levels. *DAX-1* increases GnRH expression in the presence of steroidogenic factor 1 (SF-1) in a dose-dependent manner, whereas mutated *DAX-1* does not (Li *et al*., 2010). Thus, HHG in AHC could be caused by GnRH downregulation attributable to *DAX-1* mutation. The present siblings had low levels of testosterone, FSH, and LH, supporting this theory. However, after the proband was treated with hCG, his testosterone level did not reach the normal male range and his testicular size did not increase, suggesting that this patient has a testicular defect. Studies using a *DAX-1* deficient mouse model have provided evidence that *DAX-1* is necessary for proper testicular development and function, suggesting a role beyond that of simply an "anti-testis" factor (Iyer and McCabe, 2004). *DAX-1* is also expressed in Sertoli cells (Tamai *et al.*, 1996), and male Ahch (Dax1) knockout mice exhibit disordered spermatogenesis and infertility (Yu *et al.*, 1998). As *DAX-1* has multiple roles, different approaches to counseling and treatment are needed for patients with *DAX-1* mutations compared with those with hypothalamic forms of HHG, such as Kallmann syndrome (Seminara *et al.*, 1998).

Muscatelli *et al*. (1994) was the first to demonstrate that mutation of the *DAX-1* gene is associated with AHC. In China, the first patient was diagnosed in 2007. To date, 25 cases from 21 families with AHC have been reported (Xiao *et al.*, 2007; Yang *et al*., 2007; Gong *et al.*, 2009; Xu *et al.*, 2009; Fu *et al.*, 2010; Chang *et al.*, 2011; Wang *et al.*, 2011; Zhang and Nie, 2011). Nineteen mutations are novel. *DAX-1* gene mutations have been shown to comprise fifteen frameshift, three nonsense, and three missense mutations, similar to the distribution observed in other countries. In our patients, the *DAX-1* mutation (c.1268delA p.His423Leufs*14) was located at the end of the LBD. This region is homologous to the LBD of other nuclear receptors and contains an activation function 2 transactivation domain, which mediates ligand binding, dimerization and nuclear localization (Iyer and McCabe, 2004). The siblings exhibited delayed onset at 8 years of age with mild symptoms, similar to a patient with the nearby mutation Ins428I (Fu *et al.*, 2010), suggesting that mutations at this location produce a truncated protein that retains most of its functions.

In conclusion, we described two siblings with AHC caused by a new *DAX-1* gene mutation (c.1268delA). This case extends the phenotypic spectrum of X-linked AHC to include HHG, delayed onset of adrenocortical insufficiency, and testicular defects.

Acknowledgements

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Compliance with ethics guidelines

Zhe ZHANG, Ye FENG, Dan YE, Cheng-jiang LI, Feng-qin DONG, and Ying TONG declare that they have no conflict of interest.

The protocol for sequencing the *DAX-1* gene was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, China. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Written informed consent was obtained from all members of the family for being included in this study. Informed consent for minors was obtained from their parents.

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中文概要

题　目：伴 *DAX-1* 基因新突变的先天性肾上腺发育不良家系报道

目　的：X 连锁的先天性肾上腺发育不良（AHC）是一种罕见疾病，主要表现为肾上腺皮质激素的严重缺乏和低促性腺激素型性腺功能不全。该研究的目的在于加强对该病临床表现和分子缺陷的认识。

创新点：不仅完整记录了该家系的临床特征，而且在基因水平加以证实，完善了疾病的基因突变图谱，有助于早期诊断，为基因型与临床表型间相互关系的研究奠定基础。

方　法：*DAX-1* 基因的测序法。

结　论：*DAX-1* 基因外显子 2 的 1268 位腺嘌呤缺失导致一个新的移码突变。该疾病为 X 连锁隐形遗传。

关键词：先天性肾上腺发育不良；*DAX-1* 基因；移码突变