

# Adult-onset X-linked adrenal hypoplasia congenita caused by a novel mutation in DAX1/NR0B1: A case report and literature review

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**Abstract.** Adrenal hypoplasia congenita (AHC) is a rare X-linked recessive disease caused by mutations in the nuclear receptor subfamily 0, group B, member 1 (NR0B1) gene, which is also referred to as dosage-sensitive sex-reversal, adrenal hypoplasia congenita, in the critical region of the X chromosome, gene 1 (DAX1). This gene is expressed in the hypothalamus, anterior pituitary and steroidogenic tissues, including the gonads and adrenal cortex. Adult-onset forms of X-linked AHC are a significant cause of concern. In the present study, the case of a 21-year-old male who exhibited adrenal insufficiency and hypogonadotropic hypogonadism was described. The patient initially presented with nausea, vomiting, fatigue and dizziness. The laboratory results demonstrated that the patient had hyponatremia, a low basal cortisol concentration and increased adrenocorticotrophic hormone levels. Molecular genetic examination revealed a novel frameshift mutation (c.1005delC, p.V336Cfs\*36). Following steroid supplementation, the patient's vomiting, fatigue and dizziness rapidly improved. To the best of our knowledge, the present study was the first case report of adult-onset X-linked AHC with this novel frameshift mutation. Furthermore, the present study highlighted differences in the clinical presentation of adult-onset forms of X-linked AHC. This may therefore alert medical professionals to the need to perform genetic analysis for DAX1 mutations in adolescents and adults with primary adrenal insufficiency and hypogonadotropic hypogonadism.

## Introduction

Adrenal hypoplasia congenita (AHC) is a rare X-linked recessive disease caused by mutations in the nuclear receptor subfamily 0, group B, member 1 gene (NR0B1), which is also referred to as dosage-sensitive sex-reversal, adrenal hypoplasia congenita, in the critical region of the X chromosome, gene 1 (DAX1). The DAX1 gene is located on the short arm of chromosome X (Xp21.3-p21.2) and is primarily expressed in the hypothalamus, anterior pituitary and steroidogenic tissues, including the gonads and adrenal cortex, and it has a crucial role in the development and function of these tissues (1). Primary adrenal insufficiency is usually the initial sign of AHC and it most frequently presents in infancy or early childhood, with a median age of 3 weeks at presentation (2). Furthermore, absent or arrested pubertal development due to hypogonadotropic hypogonadism (HH) is a hallmark of the disease, which leads to the absence of secondary sexual characteristics, severely reduced testicular volume and micropenis (3). A high variability in adrenal and gonadal manifestations has previously been observed, including delayed-onset primary adrenal insufficiency, precocious puberty in early childhood and extreme pubertal delay in heterozygous female carriers, thus expanding the complex nature of X-linked AHC.

Adult-onset forms of X-linked AHC are increasingly reported, as primary adrenal insufficiency begins later in adulthood (age, ≥18 years), and this type of X-linked AHC is less detrimental than the childhood-onset one. Compared with classical AHC, only a small number of reports regarding adult-onset forms of X-linked AHC have been published (4-14) and the underlying mechanisms of this atypical phenotype have remained to be fully elucidated. In the present study, a case of adult-onset X-linked AHC with a frameshift mutation, which is novel, was described.

## Case report

A 21-year-old male initially was referred to the First Hospital of Jilin University (Changchun, China) in September 2020 with nausea, vomiting, fatigue and dizziness, which were progressively worsening over an 8-day period. The patient was otherwise normal until the age of 14 years, when he

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failed to undergo puberty. However, this was self-reported by the patient, and he did not present to the hospital for personal reasons. A physical examination indicated that the patient exhibited a decreased testicular volume (bilateral, 5 ml), a small penis (3.5 cm) and a shrill voice, and had no beard or pubic hair (Tanner stage 2). Whole-body skin pigmentation was first observed by the patient two years earlier. A closer examination revealed hyperpigmentation of the oral mucosa and nail bed. The height of the patient was 175 cm and the patient's BMI was 20.25 kg/m<sup>2</sup>. The patient's blood pressure was 90/55 mmHg and the heart rate was 110 beats/min. Various laboratory parameters measured are presented in Table I. Thyroid function tests demonstrated increased thyroid-stimulating hormone levels (6.806  $\mu$ IU/ml); however, free triiodothyronine and free thyroxine levels were normal. Hypothalamus-pituitary-gonad (HPG) axis evaluation determined that the patient had low testosterone levels of 0.72 nmol/l [normal range (NR), 5.03-23.11 nmol/l] and basal serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels of 2.03 IU/l (NR, 0.9-10.9 IU/l) and 0.76 IU/l (NR, 2.8-6.8 IU/l), respectively. The peak LH level was 0.3 IU/l (NR,  $\geq$ 12 IU/l) and the peak FSH level was 1.6 IU/l following the gonadotropin-releasing hormone (GnRH) test (100  $\mu$ g intravenous gonadorelin). The basal cortisol concentration was 30.29 nmol/l (NR, 240-619 nmol/l), whereas the adrenocorticotrophic hormone (ACTH) concentration was 440.4 pmol/l (NR, 1.6-13.9 pmol/l). Blood test results demonstrated that the patient had hyponatremia (sodium level, 129 mmol/l; NR, 137-147 mmol/l), markedly increased plasma renin activity (>500  $\mu$ IU/ml), low aldosterone levels (below the lower limit of detection; <0.97 ng/dl) and normal serum potassium levels. The serum prolactin concentration was 968.30 mIU/l (NR, 87-392 mIU/l), the insulin-like growth factor-1 level was 48 ng/ml (NR, 128-464 ng/ml) and the growth hormone level was normal. Furthermore, MRI of the pituitary gland demonstrated that the patient had a relatively small pituitary gland (height, 3 mm; NR, 4-7 mm). An adrenal CT scan was also performed but the results did not demonstrate any abnormalities. The bone age of the patient was 7 years and the epiphyseal line was visible. Furthermore, the chest X-ray was normal and there was no evidence of tuberculosis.

DAX1 is responsible for X-linked AHC characterized by primary adrenal insufficiency and HH (1). Based on the aforementioned physical examination and laboratory results, genetic analysis of the DAX1 gene (1) was then performed. Written informed consent was obtained from the patient and the patient's family. The present study was performed in adherence to the tenets of The Declaration of Helsinki and was approved by the Ethics Committee of the First Hospital of Jilin University (Changchun, China). Genomic DNA was extracted from leukocytes by a CWE9600 Blood DNA Kit (CoWin Biosciences) according to the manufacturer's protocol. The DAX1 (NC\_000023, cDNA, NM\_000475) exons were amplified by PCR using specific primer pairs: Forward, 5'-CCGACACTCTCCTGATCACTG-3'; reverse, 5'-AAG TACTTGCCCTGCTTCCA-3', which were designed and synthesized by BGI Tech Co. Ltd. PCR was performed using 50  $\mu$ l volumes containing 200 ng genomic DNA, 200  $\mu$ M dNTPs, 20 pmol of each primer, 1.5 mM MgCl<sub>2</sub> and 2.5 U of Taq polymerase (TsingKe Biological Technology). PCR

Table I. Endocrinologic characteristics of the proband.

Test	The proband	Reference range
8 am Cortisol, nmol/l	30.29	240.0-619.0
8 am ACTH, nmol/l	440.4	1.6-13.9
Basal LH, IU/l	0.76	2.8-6.8
Basal FSH, IU/l	2.03	0.9-10.9
Testosterone, nmol/l	0.72	5.03-23.11
Renin activity, $\mu$ IU/ml	>500	2.8-39.9
Aldosterone, ng/dl	<0.97	3.0-23.6
Prolactin, mIU/l	968.30	87-392
GH, ng/ml	0.11	0.02-1.23
IGF-1, ng/ml	48	128-464
TSH, $\mu$ IU/ml	6.806	0.35-4.94
FT3, pmol/l	5.27	2.43-6.01
FT4, pmol/l	13.87	9.01-19.05

ACTH, adrenocorticotrophic hormone; LH, luteinizing hormone; FSH, Follicle stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone; FT3, free tri-iodothyronine; FT4, free thyroxine.

was performed using a Bio-Rad T100 instrument (Bio-Rad Laboratories, Inc.) at 95°C for 10 min, 35 cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 45 sec, followed by elongation at 72°C for 5 min. The revealed variants were confirmed by Sanger sequencing of PCR products (Mygenostics Co. Ltd). The ClinVar ([www.ncbi.nlm.nih.gov/clinvar/](http://www.ncbi.nlm.nih.gov/clinvar/)), Human Gene Mutation Database (HGMD; [www.hgmd.cf.ac.uk](http://www.hgmd.cf.ac.uk)) and Genome Aggregation Database (gnomAD; <http://gnomad.broadinstitute.org>) were used to obtain the variants' information, including gene information, variant consequence, minor allele frequency, altered protein function and related disease information. Genomic positions refer to the Human Genome February 2009 assembly (GRCh37/hg19; [www.ncbi.nlm.nih.gov/assembly/GCF\\_000001405.13/](http://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.13/)). The molecular genetic examination of the proband revealed a novel frameshift mutation leading to a deletion of one base pair at nucleotide 1,005 in exon 1 (c.1005delC). The mutation resulted in a valine-to-cysteine frameshift mutation in codon 336 and introduced a premature stop codon at position 372 (p.V336Cfs\*36). According to the American College of Medical Genetics and Genomics Standards Guidelines (15), this variant is classified as likely pathogenic. Detection of this novel mutation confirmed the diagnosis of adult-onset X-linked AHC. As expected, the mother of the patient was a heterozygous carrier of the same mutation and the patient's sister was also heterozygous for the mutation. The father had the normal allele (Fig. 1).

Based on the clinical findings and laboratory results, a diagnosis of primary adrenal insufficiency was established. Oral hydrocortisone (30 mg/d) and testosterone undecanoate (40 mg/d) were prescribed. Following steroid supplementation, the patient's vomiting, fatigue and dizziness rapidly improved. After two months of treatment, the patient's serum testosterone concentration increased from 0.72 to 1.73 nmol/l. Furthermore, the basal cortisol concentration was 31.8 nmol/l and the ACTH concentration was 440.4 pmol/l. The patient

Table II. Cases of adult-onset X-linked adrenal hypoplasia congenita (all patients were male) caused by nuclear receptor subfamily 0, group B, member 1 mutations in the literature.

First author, year	Age at diagnosis, years	Presentation	Mutation	Family history	Fertility	(Refs.)
Tabarin <i>et al</i> , 2000	28	PAI (fatigue, nausea, abdominal pain, dizziness, body weight loss) HH (low testicular volume, impaired libido, sparse facial, thoracic and pubic hair)	c.1316T>G p.Ile439Ser	Heterozygous mother	Not mentioned	(7)
Sekiguchi <i>et al</i> , 2007	18	PAI (mild skin pigmentation) HH (small testes)	c.915delG p.Glu305Hisfs67	Affected younger brother	No children	(14)
Raffin-Sanson <i>et al</i> , 2013	19	PAI (fatigue, sore throat, dizziness) HH (oligospermia)	A nonsense mutation W39X	Affected brother and young nephew	Father to two children	(5)
Ozisik <i>et al</i> , 2003	20	PAI (nausea, fatigue and hyperpigmentation) HH (small testes, azoospermia)	A nonsense mutation Q37X	No family history	Not mentioned	(11)
Kyriakakis <i>et al</i> , 2017	30	PAI (hyperpigmentation, hyponatremia) HH (small left testis, ejaculatory failure, azoospermia)	c.836C>T p.Pro279Leu	No family history	Infertility	(6)
Kyriakakis <i>et al</i> , 2017	19	PAI (hyperpigmentation) HH (low libido)	c.775T>C p.Ser259Pro	Affected brother	No children	(6)
Guclu <i>et al</i> , 2010	22	PAI (hyperpigmentation, weakness) HH (small testes, eunuchoidal habitus)	A nonsense mutation W39X	Affected elder brother	Not mentioned	(12)
Oh <i>et al</i> , 2017	28	PAI	c.706A>G p.Ser259Pro	Affected brother and maternal cousin	Normal	(4)
Hasegawa <i>et al</i> , 2021	28	PAI (general fatigue, sustained fevers and skin hyperpigmentation) HH	c.884A>T p.Leu295His	Affected elder brother	Not mentioned	(8)
Vargas <i>et al</i> , 2020	41	PAI (salt craving and hyperpigmentation) HH (decreased testicular volume, decreased libido and erectile dysfunction)	c.1133A>G p.Tyr378Cys	Affected brother and maternal uncle	Not mentioned	(9)
Vargas <i>et al</i> , 2020	36	PAI (dizziness, fatigue and hyperpigmentation) HH (oligoasthenoteratozoospermia)	c.1133A>G p.Tyr378Cys	Affected brother and maternal uncle	Father to a healthy son	(9)
Vargas <i>et al</i> , 2020	64	PAI (refractory hypotension, nausea and hyperpigmentation) HH (decreased testicular volume, decreased libido and erectile dysfunction)	c.1133A>G p.Tyr378Cys	Affected nephews	Father to a healthy son	(9)
Gerards <i>et al</i> , 2017	38	PAI (fatigue, dizziness, nausea, vomiting and skin pigmentation) HH (impaired libido, small testes, gynecomastia, reduced pubic hair, azoospermia)	c.64C>T Q22X	Affected maternal male cousins	No children	(13)
Mantovani <i>et al</i> , 2002	28	HH (small testes, eunuchoidal habitus)	A missense mutation p.Tyr380Asp	No family history	Not mentioned	(10)

Table II. Continued.

First author, year	Age at diagnosis, years	Presentation	Mutation	Family history	Fertility	(Refs.)
Present study	21	PAI (fatigue, dizziness, nausea, vomiting and skin pigmentation) HH (small testes and no pubic hair)	c.1005delC, p.V336Cfs*36	Heterozygous mother and sister	Not married and no fertility requireme nts	-

PAI, primary adrenal insufficiency; HH, hypogonadotropic hypogonadism.

continued the aforementioned treatment under the guidance of an endocrinologist.

## Discussion

The DAX1 gene encodes for a protein that is an orphan member of the nuclear receptor superfamily. Compared with other members of the nuclear receptor superfamily, the amino-terminus of DAX1 lacks a characteristic zinc-finger DNA-binding domain (16). Exon 1 encodes the amino-terminal region, which contains 3.5 repeated sequences of ~66–67 amino acids, each of which harbors an LXXLL motif, which is implicated in protein-protein interactions. The carboxyl-terminal region is a homologue of the nuclear receptor ligand binding domain (LBD) and is encoded by exons 1 and 2 (17). To date, >200 different mutations in the DAX1 gene have been described, most of which are frameshift or nonsense mutations that cause premature truncation of the protein. Most missense mutations cluster at the carboxyl-terminal region of the NR0B1 protein and relatively few missense mutations occur in the amino-terminal region. This may be due to the function of protein-protein interaction domains harboring repeated LXXLL being redundant (16). To the best of our knowledge, there are only 14 DAX1 mutations present in adulthood (Table II). Of these, 10 are missense mutations clustered within the LBD (4–10) and three are nonsense mutations at the amino terminus (Fig. 2) (11–13). Only one frameshift mutation, which causes delayed-onset X-linked AHC, has previously been reported (14). In the present study, the mutation identified in the patient was a novel frameshift mutation, which, to the best of our knowledge, has not previously been reported. Structural and functional analysis indicated that amino acids 314–352 of the LBD of DAX1 attached to the loop connecting helices H5 and H7, which is relatively loose in the LBD. Large deletions in this region do not alter the subcellular localization or the corepressor function of DAX1 (18). Changes in this region may be associated with milder phenotypes; however, a frameshift mutation c.999\_1000insCTCA, p. Leu335ThrfsX389) has been previously reported in a pediatric male patient with classic early-onset AHC (19). These findings suggested an effect of modifier genes or environmental factors on the clinical presentation of AHC.

A normal basal cortisol level should not exclude the diagnosis of X-linked AHC. The response to synacthen (an ACTH analogue) stimulation, which is useful in assessing the adrenal reserve, is usually impaired. In a previously reported

case, the diagnosis of covert compensated primary adrenal failure is important for the clinical monitoring of endocrine and reproductive functions and for early treatment prior to an adrenal crisis (10). The diagnosis of delayed-onset X-linked AHC is challenging in early adolescence, as the clinical manifestations may be similar to the constitutional delay of growth and puberty (20). Sequencing of DAX1 makes it possible to diagnose atypical X-linked AHC with no evident adrenal insufficiency (16). Male family members unexpectedly died in adolescence or adulthood, which suggests that undiagnosed adrenal crisis may be a leading cause of early death (9). Female relatives (sisters, nieces and maternal aunts) of the proband should also be provided with genetic testing. Furthermore, their pubertal development and HPG axis should be assessed, as they may potentially be heterozygous carriers or may also be affected by the disease (21–23). A limitation of the present study was that there was no access to other maternal relatives of the proband. Genetic testing of only the parents and sister of the proband was performed, and there may be other potential patients and carriers of X-linked AHC in the patient's family.

Patients who present with adrenal insufficiency require effective management with steroid supplementation. In a previous case, the elder brother of the proband died unexpectedly after intensive physical activity with no timely initiation of steroid supplementation (12). Therefore, raising awareness of glucocorticoid dose adjustment during illness, including respiratory and gastrointestinal infections, or stress, is of great importance (17). It is widely accepted that testosterone replacement is effective in stimulating virilization for pubertal and adult patients who suffer from HH (16). Exogenous gonadotrophin or pulsatile GnRH has been used to induce fertility in affected males; however, attempts to induce spermatogenesis have been unsatisfactory. Despite elevated serum gonadotrophin, testosterone and an enlarged testicular volume, semen characteristics frequently remain unchanged (7,11). A DAX1 knockout mouse model previously demonstrated that the DAX1 protein serves an essential role in the integrity of the seminiferous tubule epithelium. Furthermore, a primary defect in spermatogenesis may be caused by disruption of DAX1 expression (24), which is also supported by human studies. A low serum inhibin B level, despite elevated serum FSH levels, also indicates primary Sertoli-cell dysfunction independent of gonadotrophin insufficiency (25). Only 4 of 14 reported patients with adult-onset of X-linked AHC were fertile. A patient

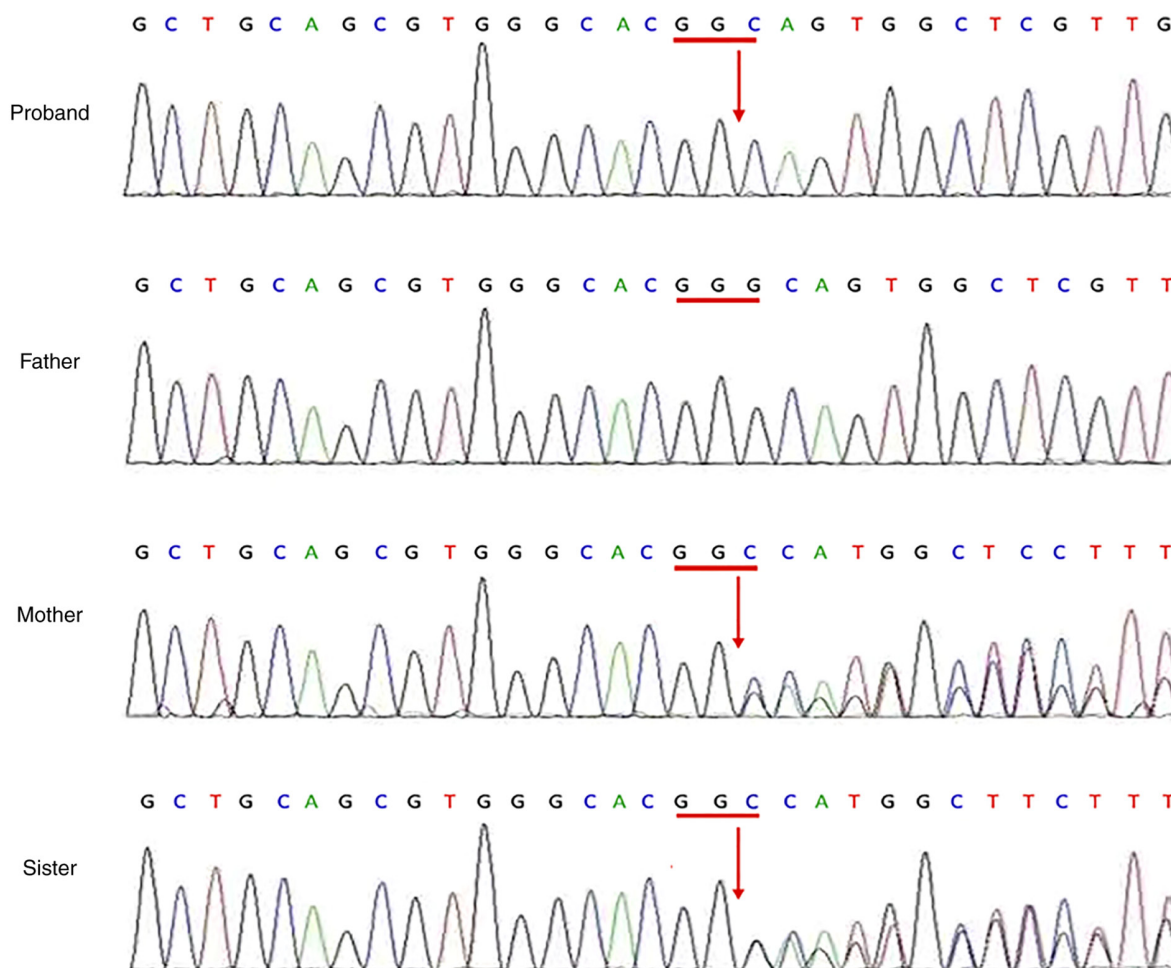


Figure 1. Partial sequence of the X chromosome, gene 1 from the proband and the proband's family. The base change c.1005delC that leads to the frameshift mutation p.V336Cfs\*36 is presented. The proband's mother and sister were heterozygous for this mutation, whereas the father has the normal allele. All the above were obtained by reverse Sanger sequencing.

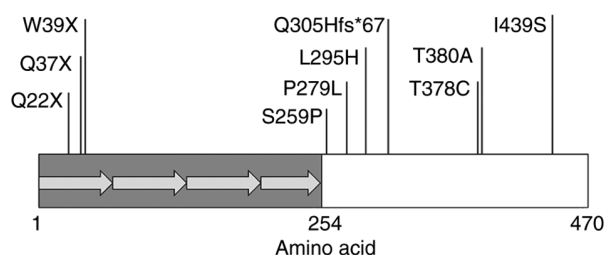


Figure 2. Overview of the nuclear receptor subfamily 0, group B, member 1 mutations in adult-onset X-linked adrenal hypoplasia congenita. The arrows indicate 3.5 repeated sequences of ~66-67 amino acids.

with adult-onset adrenal insufficiency and normal gonadotrophic function produced a healthy son following *in vitro* fertilization and a second healthy son after spontaneous conception (5). Spontaneous fertility has also been reported in the kin of an affected patient who had experienced very late-onset AHC, the patient's affected uncle and affected brother produced children prior to a diagnosis of X-linked AHC (9). The majority of patients with AHC face infertility, varying from low libido and erectile dysfunction to oligospermia or azospermia. However, an assisted reproduction technique using testis sperm extraction and intracytoplasmic

injection has been used in a patient with X-linked AHC and azospermia following repeated courses of gonadotropin therapy. This therefore highlights the potential for producing children that do not have the disease (26).

In conclusion, the present study, described for the first time a case of adult-onset X-linked AHC with a novel frameshift mutation (c.1005delC, p.V336Cfs\*36). Structural and functional analysis indicated that changes in 314-352 amino-acids of the LBD of DAX1 may be associated with delayed-onset adrenal insufficiency. For this atypical phenotype of X-linked AHC, correct diagnosis and timely treatment are important. The present study indicated that the genetic analysis of DAX1 mutations should be performed in adolescents and adults with primary adrenal insufficiency and HH.

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## Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

## Authors' contributions

YW and XX conceived the study and drafted the manuscript. YW, XL, YG and JH contributed to clinical data collection, analysis and manuscript editing. YG and XL confirm the authenticity of all the raw data. XX and YG supervised the work. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The Ethics Committee of the First Hospital of Jilin University (Changchun, China) approved the study.

## Patient consent for publication

Informed written consent was obtained from the patient and the patient's family for publication of this report and any accompanying images.

## Competing interests

The authors declare that they have no competing interests.

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