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CASE REPORT

Recognizable type of pituitary, heart, kidney and skeletal dysplasia mostly caused by *SEMA3A* mutation: A case report

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Abstract

BACKGROUND

The *SEMA3A* gene, which is located at 7q21.11, is involved in hypothalamic neuron migration, heart development, kidney development, and skeleton metabolism. Mutation of the *SEMA3A* gene is associated with Kallmann syndrome 16 with or without a normal sense of smell. In addition, two case reports showed that mutation of the *SEMA3A* gene could cause short stature, low gonadotropin, hypogonadism, thoracic deformity, a high scapula, rib and lower limb deformity, facial deformity (long face, epicanthic folds, backwards ears), and arterial malformation.

CASE SUMMARY

We reported the case of a 26-year-old Chinese man who was admitted because of short stature. Physical examination showed that he had many abnormal symptoms, including a short neck, facial moles, knee valgus, transverse palm, continuous grade 5/6 murmurs in the pulmonary auscultation area, no whiskers, or pubic hair, no Adam's apple, short penis and cryptorchidism. Radiological examination showed pituitary, gonad, heart, kidney and skeletal dysplasia. The laboratory tests revealed low growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone and estrogen. Clinical whole-exome detection showed that our patient, unlike previously reported patients, has a new *SEMA3A* gene mutation (c.950A>G). Now, his height has increased by 3 cm. In addition, he has a good appetite and reduced subcutaneous fat over 3 mo of recombinant human growth hormone injections therapy. Unfortunately, he refuses further treatment about gonad.

CONCLUSION

Patients who come to a hospital because of their short stature must undergo gene detection if they have other simultaneous abnormal phenotypes.

Key words: Pituitary dysplasia; Heart dysplasia; Kidney dysplasia; Short stature;

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Core tip: The *SEMA3A* gene is involved in hypothalamic neuron migration, heart development, kidney development, and skeleton metabolism. Mutation of the *SEMA3A* gene was associated with short stature, low gonadotropin, hypogonadism, thoracic deformity, a high scapula, rib and lower limb deformity, facial deformity (long face, epicanthic folds, backwards ears), and arterial malformation in cases reported before. Here, we report a patient who exhibited pituitary, heart, kidney and skeletal dysplasia caused by new mutation of the *SEMA3A* gene (c.950A>G).

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INTRODUCTION

The *SEMA3A* gene is located at 7q21.11 and has a length of 496947 bp. *SEMA3A* is a member of the semaphorin family and encodes a protein with an Ig-like C2-type (immunoglobulin-like) domain, a PSI domain and a sema domain called semaphorin-3A. Semaphorin-3A is important in the development and migration of hypothalamic neurons. It is secreted by neurons and their surrounding tissue and guides migrating cells to their correct destination following very precise paths, sends out axons, and reacts to specific chemical environments. In addition, as a dual regulator of osteoclasts and osteoblasts, semaphorin 3A is involved in the balance of bone homeostasis by the *SEMA3A*/*NRP1* axis and the Wnt/β-catenin signaling pathway[1]. Semaphorins are needed in kidney development because they regulate ureteric bud branching, vascular morphogenesis, and podocyte-endothelial crosstalk[2]. *SEMA3A*-knockout mice exhibited an abnormal electrocardiograph pattern and were prone to ventricular arrhythmias and sudden cardiac death[3]. Therefore, *SEMA3A* is important in maintaining normal heart function.

SEMA3A mutations often appear in patients with Kallmann syndrome[4]. In addition, patients with mutation of the *SEMA3A* gene exhibiting short stature, low gonadotropin, hypogonadism, thoracic deformity, high scapula, rib and lower limb deformity, facial deformity (long face, epicanthic folds, backwards ears), arterial malformation, and a normal sense of smell have been reported[5]. We report a patient who exhibited pituitary, heart, kidney and skeletal dysplasia caused by new mutation of the *SEMA3A* gene.

CASE PRESENTATION

Chief complaints

A 26-year-old Chinese man complained of short stature.

History of present illness

The 26-year-old patient, who was his parents' first child, was 50 cm in length and weighed 3.3 kg when he was born at 40 wk of gestation. His growth rate gradually slowed down beginning at the age of 12. Now, he is 133 cm tall (< -2.0 SD) with a 65 cm long upper half and 68 cm long lower half and weighs 35 kg (< -2.0 SD), with 130 cm finger spacing.

History of past illness

No disease in the past.

Personal and family history

His sister is of normal height and physical development. The patient was born normally without ischemia and hypoxia. His mother's height is 156 cm, and his

father's height is 155 cm. The predicted height of the boy was calculated to be below the mid-parental height of 162 cm.

Physical examination upon admission

His abnormal symptoms are a short neck; facial moles; knee valgus; transverse palm; continuous grade 5/6 murmurs in the pulmonary auscultation area; no whiskers, or pubic hair; no Adam's apple; a penis length of approximately 2 cm; a penis circumference of 3 cm and cryptorchidism (Figure 1A).

Laboratory examinations

The patient's liver and kidney function, cortisol rhythm and thyroid function were normal. He completely lacked growth hormone, as shown through hypoglycemia challenge, a levodopa test and IGF-1 determination. His 25-hydroxyvitamin D was 11.3 ng/mL (low). Sex hormone assessment showed that the levels of luteinizing hormone (LH), follicle-stimulating hormone, testosterone and estrogen were all below normal. The peak LH level in a GnRH excitation test was 1.92 nmol/L (< 5 nmol/L). The peak testosterone level in a delayed human chorionic gonadotropin excitation test was 0.91 ng/mL (< 10 ng/mL). Conventional karyotyping after GTG-banding at a 500-band resolution showed a normal male karyotype (46, XY). Chromosomal microarray analysis showed no abnormalities.

Written informed consent for clinical whole-exome detection was obtained from the patient. All of the 3583 genes identified by the OMIM database were identified by high-throughput sequencing. Clinical whole-exome detection was offered by BGI in Shenzhen, Guangdong Province.

The results of clinical whole-exome detection are shown in Table 1. The diseases related to the *LHCGR, HSPG2*, and *PKDIL1* genes were autosomal recessive. *ANCA* gene-related exfoliative osteochondritis, short statue, early onset arthritis and vertebral hypoplasia exhibited autosomal dominant inheritance. *SEMA3A* gene-related hypogonadotropic hypogonadism with or without olfactory loss exhibited autosomal dominant inheritance.

Imaging examinations

His bone age was 15 years old (Figure 1E). Dual-energy X-ray bone density assessment showed that the T (lumbar spine) was -5.3 SD below the mean and T (left hip joint) was -2.4 SD below the mean. Pelvic magnetic resonance imaging (MRI) (Figure 1C, D) showed the following: (A) Pelvic genitourinary dysplasia, in which (1) The prostate and bilateral seminal vesicles were not clearly shown; (2) The bilateral groin had soft tissue nodules and testicular hypoplasia; and (3) Penile dysplasia was observed; and (B) A pelvic bone that was not closed. In addition, abdominal ultrasound suggested left renal hypoplasia. Cardiac ultrasound suggested aortic dysplasia with moderate reflux. Pituitary MRI suggested pituitary dysplasia (Figure 1B).

FINAL DIAGNOSIS

LHCGR, HSPG2, PKDIL1, ANCA and *SEMA3A* are all heterozygous mutation. So *ANCA and SEMA3A* gene mutations might be related to the symptom shown by our patient. However, *ANCA* gene mutation could not cause the previously reported gonadal and cardiac dysplasia. Therefore, we focused on *SEMA3A* as the pathogenic gene. So final diagnosis is *SEMA3A* mutation, growth hormone deficiency, short stature, hypogonadotropic hypogonadism, heart dysplasia, kidney dysplasia and skeletal dysplasia.

TREATMENT

The patient was treated with recombinant human growth hormone injections (0.15 U/kg, GenSci, Changchun, Jilin Province). He refuses further treatment about gonad.

OUTCOME AND FOLLOW-UP

Now, his height has increased by 3 cm. In addition, he has a good appetite and reduced subcutaneous fat over 3 mo of recombinant human growth hormone injections therapy. We will continue to observe his height, bone density and gonads.

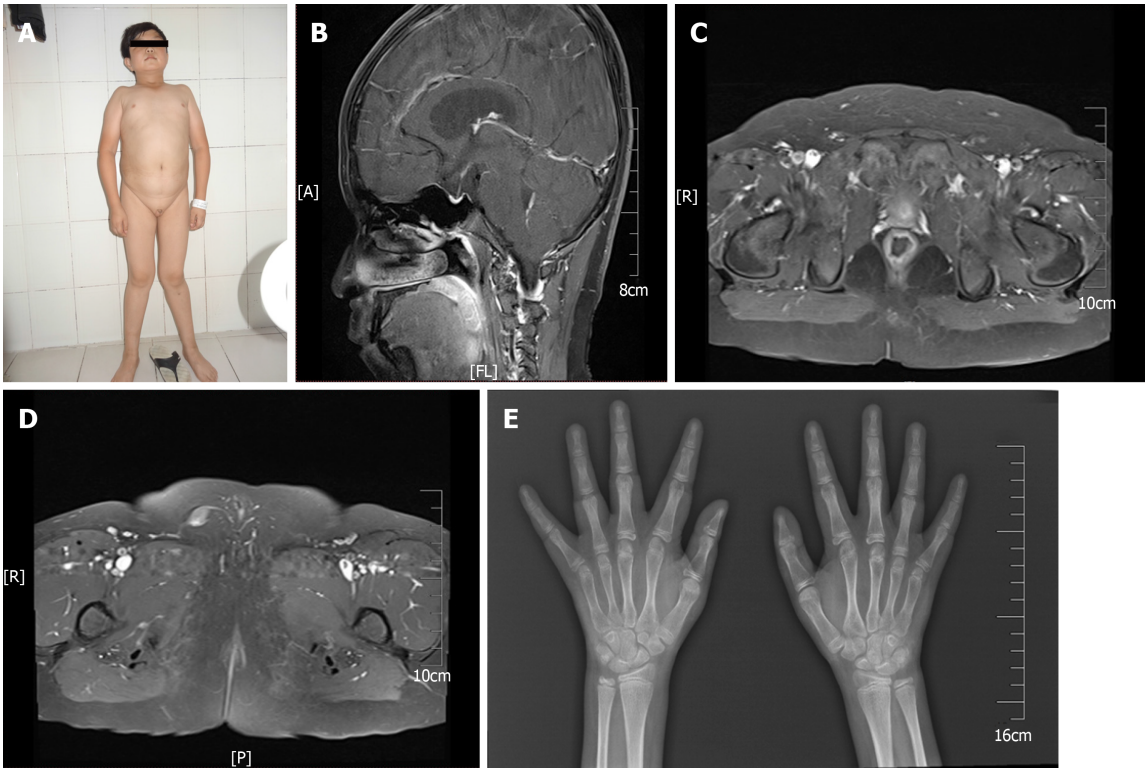

Figure 1 Clinical findings and radiographic abnormalities in a patient with a heterozygous *SEMA3A* gene mutation (c.950A>G). The patient was 26 years old. A: He exhibited a short neck; facial moles; knee valgus; transverse palm; continuous grade 5/6 murmurs in the pulmonary auscultation area; no whiskers,or pubic hair; no Adam's apple; short penis and cryptorchidism; B: Pituitary magnetic resonance imaging (MRI) showed pituitary dysplasia; C, D: Pelvic MRI showed the following: (1) Pelvic genitourinary dysplasia, in which (1) The prostate and bilateral seminal vesicles were not clearly shown; (2) The bilateral groin had soft tissue nodules and testicular hypoplasia; and (3) Penile dysplasia was observed, and (B) a pelvic bone that was not closed; E: Left wrist orthotopic X-ray (bone age of 15 years).

DISCUSSION

Two similar case reports have been published before. The *SEMA3A* genotype of the first case reported in 2013 included a compound-heterozygous de novo in-frame mutation in exon 9 (c.945_949delinsTACATCTTCTAATG; p. Phe316_Lys317-delinsThrSerSerAsnGlu), a 150-kb deletion, the retention of intron 8, and a premature stop codon after 348 amino acids[6]. The *SEMA3A* genotype of the second case reported in 2018 included a homozygous c.607C>T [p.(Arg203*)] mutation in exon 6[5]. All patients not only exhibited short statue, facial dysmorphism and skeletal system anomalies but also had cardiovascular, urogenital, hearing, olfactory, visual, motor development and cognitive development defects. There were some differences between our patient and the two patients presented previously (Table 2). First, the *SEMA3A* genotype in our patient is c.950A>G. Second, examination of our patient showed a complete lack of growth hormone, but this was not mentioned during the examination of the other two patients. Our patient's short statue was perhaps caused by not only a lack of growth hormone but also vitamin D deficiency. Third, our patient has normal cognitive function and works in an electrical factory. Finally, he has kidney hypoplasia. Semaphorins are needed in kidney development because they regulate ureteric bud branching, vascular morphogenesis, and podocyte-endothelial crosstalk[5]. Thus, *SEMA3A* gene mutation might result in kidney hypoplasia. In contrast, *SEMA3A* overexpression could promote foot process effacement, glomerular basement lamination, and endothelial damage in vivo and disrupt autonomous podocyte shape by downregulating nephrin and inhibiting αvβ3 integrin[7]. Excess *SEMA3A* also promoted severe diabetic nephropathy[8]. No genes related to pituitary dysplasia were discovered in whole gene exome detection. Pituitary dysplasia might occur mainly because of defective hypothalamic neurons.

CONCLUSION

At present, short stature gets more and more attention. But we should make a clear diagnosis through gene detection if they have other simultaneous abnormal phenotypes.

Table 1 Clinical whole-exome detection results

Gene	Sequence	Nucleotide change/mutation	Amino acid change	Gene subregion	Heterozygous	Chromosome location	Variant type
ACAN	NM_013227.3	c.6798G>A	p.Pro22666=	EX12	Heterozygous	Chr15: 89402614	VUS
LHCGR	NM_000233.3	c.911G>A	p.Cys304Tyr	EX10	Heterozygous	Chr2: 48921399	VUS
HSPG2	NM_005529.5	c.1216C>T	p.Pro406Ser	EX11	Heterozygous	Chr1: 22211645	VUS
PKD1L1	NM_138295.3	c.2842T>G	p.Phe948Val	EX18	Heterozygous	Chr7: 47925647	VUS
SEMA3A	NM_006080.2	c.950A>G	p.Lys317Arg	EX9	Heterozygous	Chr7: 83640383	VUS

VUS: Variant uncertain significace.

Table 2 Summary of patients' clinical presentations and comparison to the published patients

Ethnicity	Patient 1	Patient 2	Patient 3
	Asian	Turkish	Southern German
Mutation	c.950A>G (p.Lys317Arg) in exon 9, heterozygous	c.607C>T [p.(Arg203*)] in exon 6, homozygous	c.945_949delinsTACATCTTCTAATG ; p.Phe316_Lys317-; delinsThrSerSerAsnGlu in exon 9, de novo, in-frame; 150-kb deletion, intron-8 retention, premature stop codon after 348; amino acids, compound-heterozygous
Gender	Male	Male	Male
Gestational age (wk)	40	41	37
Age at examination	26	8	6
Birth weight and length	Weight: unknown; Length: unknown	Weight: 3720 g (P50-P75; 0.19 SDS); Length: 50 cm (P10-25; -1.25 SDS)	Weight: 2910 g (P25-P50; -0.92 SDS); Length: 48 cm (P10-P25; -0.43 SDS)
Mother's and father's heights	156 cm, 155 cm	154 cm, 174 cm	159 cm, 174 cm
Short statue	+	+	+
Facial dysmorphism	Facial moles, transverse palm	Long face; epicanthic folds; mildly low-set, backwards; rotated ear; bilateral retrolobular notches; long philtrum	Long face; epicanthic folds; mildly low-set, backwards, rotated ear; dolichocephaly; prominent forehead; broad nasal root; rounded nasal tip; long philtrum; thin lips; high palate; crossbite with crowded teeth
Skeletal system	Short neck, knee valgus	High-positioned scapulae, lateral clavicle hook, restricted mobility of the shoulder joints, arched rib deformation, mild upper thoracic; scoliosis, widely spaced nipples, camptodactyly of the second and third fingers, flexion contracture of the right knee with patellar luxation	Sloping shoulders, broad and asymmetric thorax, flattened vertebrae in the upper thoracic region, mild funnel chest, kyphosis, hyperlordosis, widely spaced nipples, camptodactyly, of the third left finger,relatively large first toe
Cardiovascular	Aortic dysplasia with moderate reflux	Arteria lusoria	Patent foramen ovale, nearly closed with 6 yr
Urogenital	No prostate, bilateral seminal vesicles, testicular hypoplasia and cryptorchidism, micropenis	Micropenis	Micropenis
Hearing	Normal	Mild conductive hearing impairment	Susceptible to upper airway and middle ear infections until 2 yr of age
Olfaction	Normal	Normal	Normal
Vision	Normal	Myopia	Hyperopia
Motor development	Normal	Delayed, walking independently at 3.8 yr	Delayed, walking independently at 21 mo
Cognitive development	Normal	Reduced performance and verbal score with a full scale IQ of 55 (at 6 yr)	Average performance and full scale IQ, verbal IQ in the lower average; range (at 5 yr)
Kidney	Hypoplasia	Normal	Normal
Growth hormone	Lacking	Unknown	Unknown
Sex hormone	Lacking	Unknown	Unknown

IQ: Int

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