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Case report

Novel mutation in the *IGHMBP2* gene in spinal muscular atrophy with respiratory distress type 1: A case report

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ABSTRACT

Background: Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare autosomal recessive hereditary disease. Immunoglobulin μ-binding protein 2 (*IGHMBP2*) gene mutations are the main cause of SMARD1.
Case presentation: Here we describe a female infant with SMARD1 carrying heterozygous mutations in *IGHMBP2* genes, *c.1334A > C(p.His445Pro)* and *c.1666C > G(p.His556Asp),* which were inherited from both parents. Clinical presentations included frequent respiratory infections, respiratory failure, distal limb muscle weakness, and fat pad found at the distal toe.
Conclusions: c.1666C > G(p.His556Asp) is a novel site mutation in *IGHMBP2*. This case expanded knowledge on the genetic profile of SMARD1 and it provides a basis for genetic testing of parents and for genetic counseling to assess the risk of fetal disease.

1. Background

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a form of spinal muscular atrophy that is characterized by respiratory distress with an onset between age 6 weeks and 6 months, accompanied by phrenic paralysis, distal muscle weakness, and intrauterine growth retardation [1,2]. This condition is caused by mutations in the immunoglobulin μ-binding protein 2 (IGHMBP2) gene, which is located on chromosome 11q13.2- q13.4. IGHMBP2 gene is widely distributed in nerve cells, and its mutation can cause damage to motor neurons and innervation muscle fibers 1.IGHMBP2 gene mutations in patients with SMARD1 are mainly point mutations such as single-base replacements, insertions, and deletions. More than 60 point mutations have been found, which are located in the helicase domain of IGHMBP2[3,4]. This article describes a female infant with SMARD1 who had compound heterozygous mutations in the IGHMBP2 gene. The mutation of c.1334A > C(p.His445Pro) has been reported previously; however, c.1666C > G(p.His556Asp) is a novel mutation that has not been reported before. This case broadens the genetic spectrum of SMARD1 and provides a rationale for genetic testing of parents and a medical consultation to estimate the risk of fetal illness.

2. Case presentation

A female, Chinese infant was born at full term by cesarean section in Yunnan, China.She was born at 41 weeks with a birth weight of

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Abbreviations

IGHMBP2 immunoglobulin μ-binding protein 2
SMARD1 spinal muscular atrophy with respiratory distress type 1

Table 1
Family clinical information.

Sample source	Sample number	Main clinical features
Patient	22C621107	Birth weight was less than the 10th percentile, respiratory distress occurred 2 months and 6 days old, muscle strength and tone of the limbs were reduced, knee and achilles tendon reflexes were absent, and intrauterine growth restriction, tremors in her facial-expression and tongue muscles, and toe fat pad were present.
father	22C621106	No clinical phenotype
mother	22C621105	No clinical phenotype

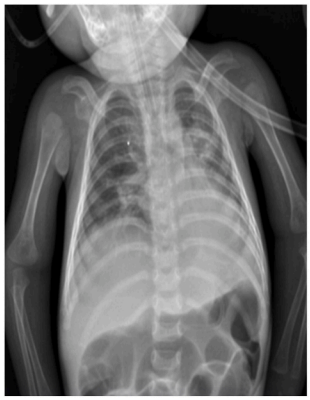


Fig. 1. The results of the chest X-ray.

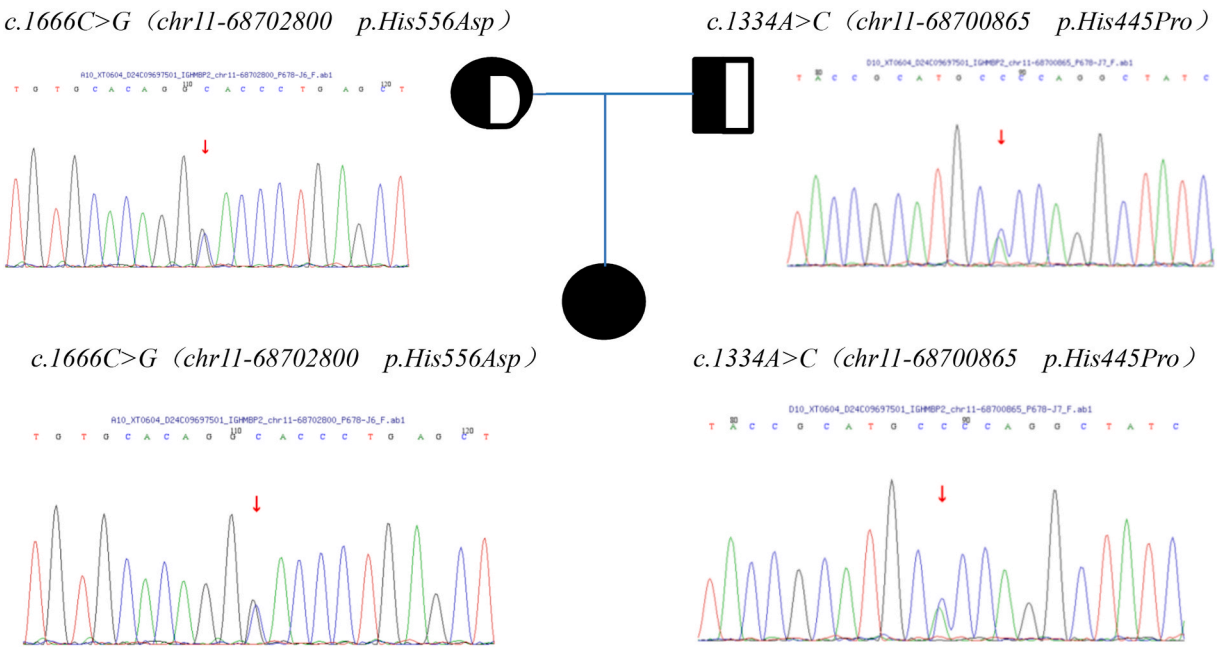


Fig. 2. The proband had a compound heterozygous variation of *IGHMBP2* gene *c.1334A > C(p.His445Pro)* and *c.1666C > G(p.His556Asp)*from her father and mother respectively.

Table 2
Genetic test results.

Gene	Chromosome position	Transcript/ exon	Nucleotide/ amino acid	Hom/ Het	Normal frequency	Prediction	ACMG pathogenicity analysis (score)	Disease/ Phenotype (genetic pattern)	Source of variation
IGHMBP2	chr11:687 00865	NM_0021 80.3; exon 9	*c.1334A > C (p. His445Pro)*	Het	0.0003994	Detrimental	Pathogeni c	1. Autosomal recessive distal spinal muscular atrophy 1 (AR) 2. Charcot-Marie-Tooth Disease (AR)	Father
IGHMBP2	chr11:687 02800	NM_0021 80.3; exon 12	*c.1666C > G (p. His556Asp)*	Het		Possibly benign	Uncertain	1. Autosomal recessive distal spinal muscular atrophy 1 (AR) 2. Charcot-Marie-Tooth Disease (AR)	Mother

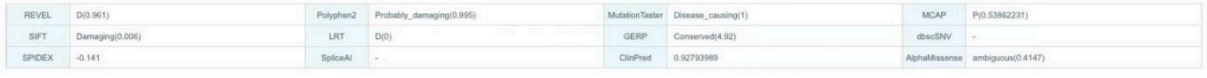
Note: Het: Heterozygous, Hom:Homozygous, ACMG:American College of Medical Genetics and Genomics guidelines,AR: Autosomal recessive inheritance.

2.9 kg, which was greater than the 3rd percentile and less than the 10th percentile. Her mother had no history of asphyxia rescue, fetal movement, or oligohydramnios during pregnancy. The infant cried after birth and was breastfed with no signs of poor feeding. There was no family history. When she was 2 months and 6 days old, she developed progressive dyspnea after a respiratory infection, requiring tracheal intubation and ventilator-assisted ventilation. The child is now 7 months old and to date the ventilation cannot be discontinued even after infection control was implemented.

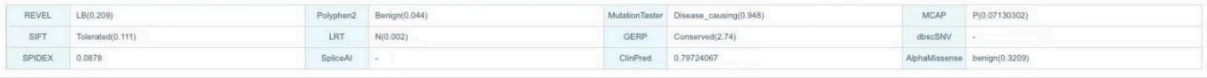
The infant's weight(4kg) and height(57cm) were all at below three standard deviations. She was alert, active, and able to follow, and fix on, visual and sound stimuli. She showed minimal tremors in her facial-expression and tongue muscles. None of her accessible cranial nerves were abnormal and she had normal hearing and vision. She exhibited flexion and adduction of the elbow joint at 90° for both upper limbs, limited extension of the bilateral knee joints, 90-degree dorsiflexion of the left ankle back, and 60-degree dorsiflexion of the right ankle back. Muscle strength and tone of the limbs were reduced. Knee and Achilles tendon reflexes were absent. No signs of sensory loss were found in physical examination.A fat pad was visible at the second and fifth toes of both feet. The main clinical features are shown in Table 1.

Laboratory examinations, including plasma creatine phosphokinase, serum ammonia levels, lactate levels in serum and cerebrospinal fluid, blood sugar, electrolyte, renal function, coagulation, and urine organic acid levels were all within the normal ranges. Her chest radiograph showed pneumonic changes but the X-ray did not show diaphragm eventration (Fig. 1). There were no abnormalities in the brain and neck computed tomography examination, electrocardiogram, electroencephalogram, echocardiography, or abdominal ultrasound examinations.

The infant inherited compound heterozygous mutations in the *IGHMBP2* gene from her parents, *c.1334A > C(p.His445Pro)* and *c.1666C > G(p.His556Asp)*. Her mother had the heterozygous *IGHMBP2* mutation c.1666C > G(p.His556Asp), and her father had the mutation c.1334A > C(p.His445Pro) in the IGHMBP2 gene (Fig. 2,Table 2). Her parents were confirmed as carriers of IGHMBP2 gene mutations and had no clinical symptoms.



A：The gene locus of *c.1334A>C(p.His445Pro)* was analyzed by protein function prediction software



B：The gene locus of *c.1666C>G(p.His556Asp)* was analyzed by protein function prediction software

Fig. 3. The protein function prediction software predicted the results(A and B).

3. Discussion and conclusions

SMARD1 is a neuromuscular disease caused by mutations in IGHMBP2 [5]. Grohmann et al. [6] detected the *IGHMBP2* gene in 29 children with SMARD1, and found 24 missense mutations, 20 nonsense mutations, 10 frame shift mutations, and 2 shear site mutations. There have also been case reports of inversions of intron 10 and 14 and deletion of large fragments of exon 2 of the *IGHMBP2* gene [7]. However, there is considerable heterogeneity in clinical presentation among patients with SMARD1. At present, the relationship between the SMARD1 phenotype and *IGHMBP2* genotype is not well understood [8].

Here we described a case of an infant from the Yunnan Plateau region. She had SMARD1 and caried heterozygous mutations in *IGHMBP2*, *c.1334A > C(p.His445Pro)* and *c.1666C > G(p.His556Asp),* which were inherited from her father and mother, respectively.

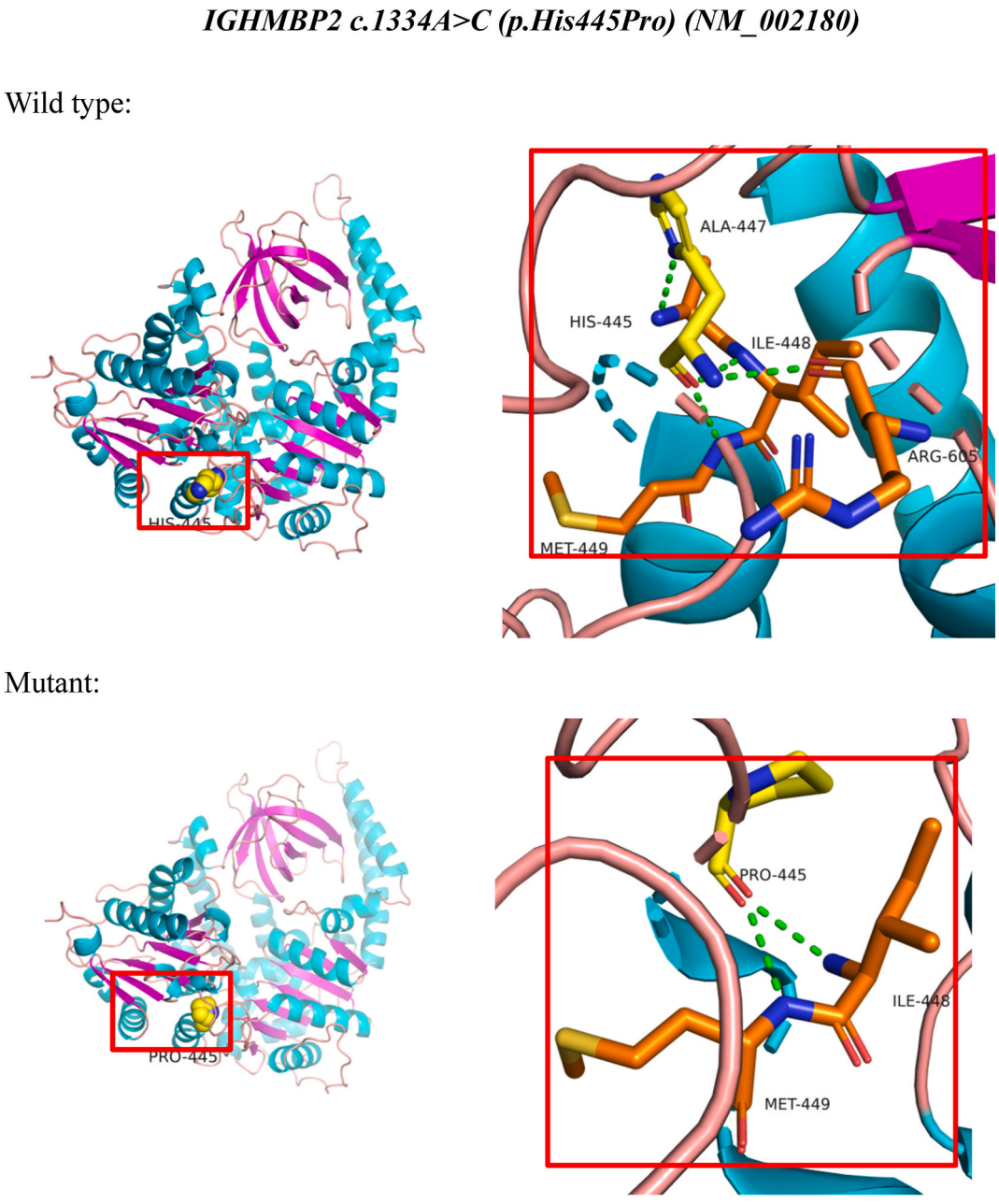


Fig. 4. The 3D structures of *c.1334A > C(p.His445Pro)* and *c.1666C > G(p.His556Asp)*
Note: In the cartoon structure in the figure, blue represents the α-helix, purple represents the β-strands, and pink coil represents the loop structure. The diagram shows the hydrogen bond observed as a stick-like structure, where each color represents a different atom, yellow-C atom, gray-H atom, blue-N atom, red-O atom, orange-s atom, and the dotted green lines represent hydrogen bonds.

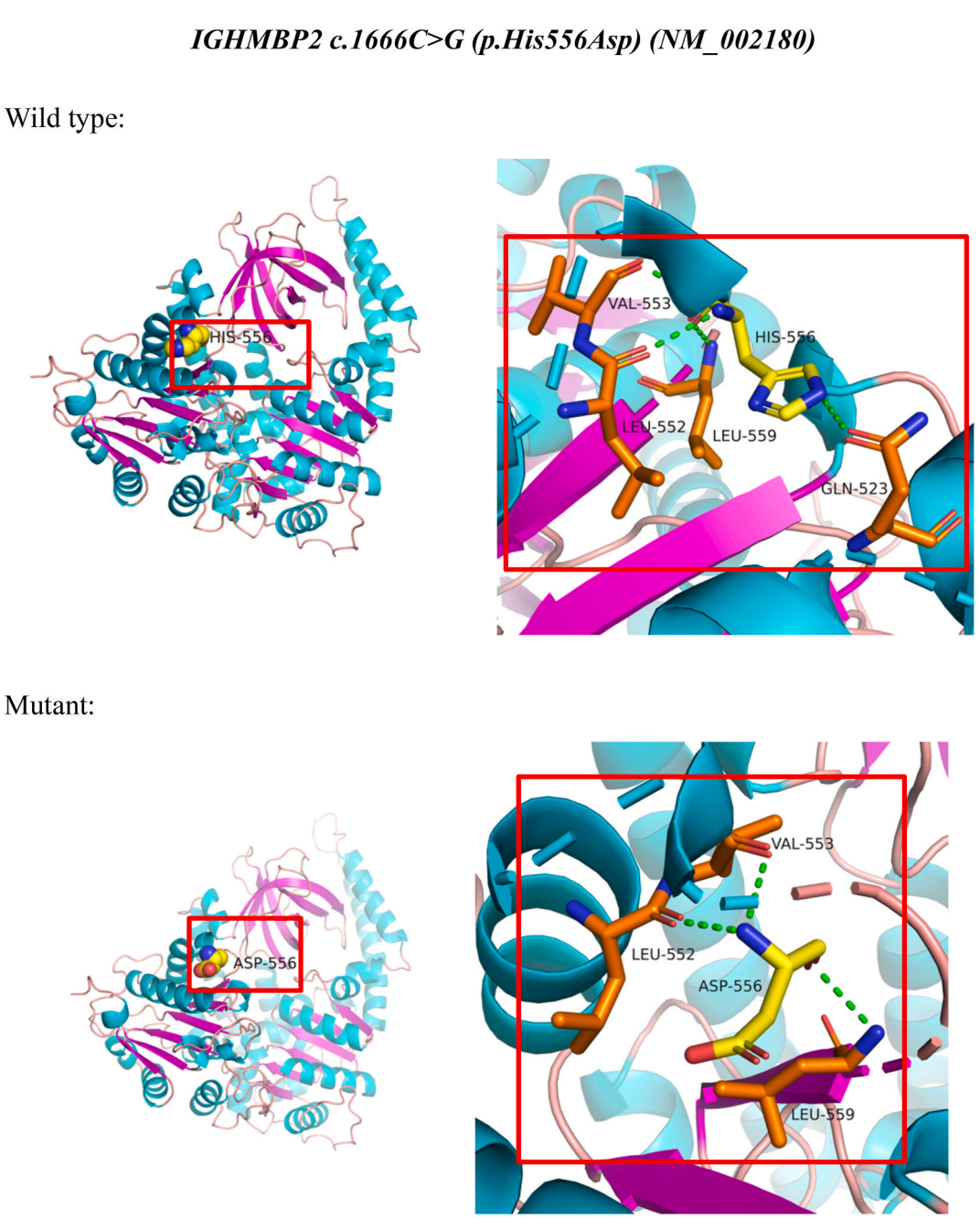


Fig. 4. (*continued*).

Table 3
SMARD1 diagnostic criteria (Pitt et al., 2003).

1.Low birth weight below the 3rd centile.
2.Onset of symptoms within the first 3 months of life.
3.Diaphragmatic weakness either unilaterally or bilaterally.
4.Ventilator dependence within less than one month from onset with inability to wean.Absence of either dysmorphology or other conditions.

The pathogenic mutation *c.1334A > C(p.His445Pro)* is a missense mutation that changes amino acid 445 from histidine to proline. According to the American College of Medical Genetics and Genomics guidelines, this mutation may contribute to SMARD1. This mutation site *c.1334A > C(p.His445Pro)* in *IGHMBP2* has been reported previously for SMARD1 [9]. The other mutation, *c.1666C > G (p.His556Asp)*, is also a missense mutation that changes amino acid 556 from histidine to aspartic acid. This missense mutation has not been reported in patients with SMARD1 previously, and has not been documented in the Human Gene Mutation Database. Based on the analysis using multi-protein function prediction software, the *c.1334A > C (p.His445Pro)* mutation was predicted to be detrimental and the *c.1666C > G (p.His556Asp)* mutation was predicted to be possibly benign(Fig. 3,Fig. 4). The infant's parents did not have clinical manifestations, in line with recessive inheritance. The infant had clinical features of SMARD1 [10] (Table 3): respiratory distress occurred between 6 weeks and 6 months after birth, muscle strength and tone of the limbs were reduced, knee and achilles tendon reflexes were absent, and intrauterine growth restriction, tremors in her facial-expression and tongue muscles, and toe fat pad were present. The site *c.1666C > G(p.His556Asp)* reported here is a novel *IGHMBP2* gene mutation. However, it's pathogenic mechanism needs to be further studied in more patients.

In conclusion, we report a novel mutation in a patient with SMARD1, *IGHMBP2 c.1666C > G(p.His556Asp),* and the interaction between *c.1666C > G(p.His556Asp)* and the other mutation *c.1334A > C(p.His445Pro)* may be responsible for SMARD1 presentation in this patient. Finding the *IGHMBP2* locus *c.1666C > G(p.His556Asp)* expanded the genetic profile of SMARD1 and offers a basis for genetic testing of parents and medical counseling to assess the risk of fetal disease.

4. Patient's consent

Informed consents were obtained from the patient's parents to publish this case report.

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jicai Zhu: Writing – original draft. **Minming Ma:** Data curation. **Xiaofang Chen:** Data curation. **Caiyun Xiong:** Data curation. **Yan Ju:** Data curation. **Tang Chunhui:** Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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