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CASE REPORT

Missense mutation in *DYNC1H1* gene caused psychomotor developmental delay and muscle weakness: A case report

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Abstract

BACKGROUND

The *DYNC1H1* gene encodes a part of the dynamic protein, and the protein mutations may further affect the growth and development of neurons, resulting in degeneration of anterior horn cells of the spinal cord, and a variety of clinical phenotypes finally resulting in axonal Charcot-Marie-Tooth disease type 20 (CMT20), mental retardation 13 (MRD13) and spinal muscular atrophy with lower extremity predominant 1 (SMA-LED). The incidence of the disease is low, and it is difficult to diagnose, especially in children. Here, we report a case of *DYNC1H1* gene mutation and review the related literature to improve the pediatrician's understanding of *DYNC1H1* gene-related disease to make an early correct diagnosis and provide better services for children.

CASE SUMMARY

A 4-mo-old Chinese female child with adducted thumbs, high arch feet, and epileptic seizure presented slow response, delayed development, and low limb muscle strength. Electroencephalogram showed abnormal waves, a large number of multifocal sharp waves, sharp slow waves, and multiple spasms with a series of attacks. High-throughput sequencing and Sanger sequencing identified a heterozygous mutation, c.5885G>A (p.R1962H), in the *DYNC1H1* gene (NM_001376) of the proband, which was not identified in her parents. Combined with the clinical manifestations and pedigree of this family, this mutation is likely pathogenic based on the American Academy of Medical Genetics and Genomics guidelines. The child was followed when she was 1 year and 2 mo old. The magnetic resonance imaging result was consistent with the findings of white matter myelinated dysplasia and congenital giant gyrus. The extensive neuro-

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genic damage to the extremities was considered, as the results of electromyography showed that the motor conduction velocity and sensory conduction of the nerves of the extremities were not abnormal, and the degree of fit of the children with severe contraction was poor. At present, the child is 80 cm in length and 9 kg in weight, with slender limbs and low muscle strength, and still does not raise her head. She cannot sit or speak. Speech, motor, and mental development was significantly delayed. There is still no effective treatment for this disease.

CONCLUSION

We herein report a *de novo* variant of *DYNC1H1* gene, c.5885G>A (p.R1962H), leading to overlapping phenotypes (seizure, general growth retardation, and muscle weakness) of CMT20, MRD13, and SMA-LED, but there is no effective treatment for such condition. Our case enriches the *DYNC1H1* gene mutation spectrum and provides an important basis for clinical diagnosis and treatment and genetic counseling.

Key Words: *DYNC1H1*; Mental retardation; Muscle weakness; Medical exome sequencing; Case report

Core Tip: The dynein cytoplasmic1 heavy chain 1 gene-related diseases include Charcot-Marie-Tooth disease type 20, mental retardation 13, and spinal muscular atrophy with lower extremity predominant 1, all of which are inherited in an autosomal dominant manner. A novel mutation, c.5885G>A (p.R1962H) in the *DYNC1H1* gene, led to overlapping phenotypes (seizure, general growth retardation, and muscle weakness) of those three diseases and expanded the *DYNC1H1* gene mutation spectrum. And there is no effective treatment for such condition.

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INTRODUCTION

DYNC1H1-related diseases include axonal Charcot-Marie-Tooth disease type 20 (CMT20), mental retardation 13 (MRD13), and spinal muscular atrophy with lower extremity predominant 1 (SMA-LED), all of which are inherited in an autosomal dominant manner. The clinical symptoms of CMT20 are mainly peripheral neuropathy, distal limb muscle weakness, muscle atrophy, difficulty walking, and hyporeflexia, and may be accompanied by high arch feet and foot drop[1]. The clinical symptoms of MRD13 are mainly mental retardation, epilepsy, and brain abnormalities such as thin corpus callosum, abnormal basal ganglia, cerebellar hypoplasia, spastic paralysis of limbs, abnormal gait, and abnormal facial appearance, most of which are newly described variants[2]. The clinical symptoms of SMA-LED are mainly symmetric proximal muscle weakness and muscle atrophy, especially in the lower limbs, walking delay, and mild cognitive delay[3]. Mutation in the *DYNC1H1* gene (OMIM: 600112) is considered closely associated with all of them. The *DYNC1H1* gene encodes cytoplasmic dynein 1 heavy chain 1, which contains a motor domain and a stem domain[4]. It is involved in a variety of cellular functions, such as the shuttle of cell components to the negative end of microtubules and many aspects of mitosis. These functions enable the dynein motor complex to play an important role in neurogenesis and migration[2]. In this paper, we will review and analyze the clinical data and genetic test results of one child with *DYNC1H1* gene mutation and review the relevant literature to summarize the clinical phenotype and the key points of diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A female, 4 mo old, was admitted to the hospital due to hypoplasia (Figure 1).

History of present illness

Physical examination revealed a slow response, no obvious gaze with no follow-up, no eyesight, no smile, no recognition of the mother, head drooping, hands with clenched fists, adducted thumbs, symmetrical limbs, fully stretched limbs, high hips, and low head. She raised the head and back when laid on her back. She was unable to turn over, seated fully forward, seated upright, and pointed feet. Both of her lower limbs were unable to support her weight. The muscles of the limbs were tense. The internal adductor angle was 30°, the popliteal angle was 60°, the foot dorsiflexion angle was 20°, and the Vojta posture reflex showed abnormal reflexes due to poor head, neck, and trunk extension. The grip and embrace reflexes were present, and the bilateral knee tendon reflex was elicited. Normal children raise their heads at 4 mo of age, and they can stand up independently, will turn their heads and look for it when they hear the sound, can be amused, and will also make a first babble. However, the patient in our case had attention deficit disorder and delayed motor performance.

History of past illness

The baby was delivered at 41 wk of gestation, amniotic fluid was turbid, birth weight was 3250 g, and she had weak crying and vomiting, with a weak hugging reflex, and was transferred to the neonatal department for hospitalization.

Personal and family history

Both parents were healthy (G1P1) without a family history of the disease and consanguinity was denied.

Physical examination

Physical examination revealed a slow response, no obvious gaze with no follow-up, no eyesight, no smile, no recognition of the mother, head drooping, hands with clenched fists, adducted thumbs, symmetrical limbs, fully stretched limbs, high hips, and low head. She raised the head and back when laid on her back. She was unable to turn over, seated fully forward, seated upright, and pointed feet. Both of her lower limbs were unable to support her weight. The muscles of the limbs were tense. The internal adductor angle was 30°, the popliteal angle was 60°, the foot dorsiflexion angle was 20°, and the Vojta posture reflex showed abnormal reflexes due to poor head, neck, and trunk extension. The grip and embrace reflexes were present, and the bilateral knee tendon reflex was elicited (Figure 1).

Laboratory examinations

Peripheral blood samples (2 mL) were obtained from the proband and her parents. DNA was extracted using a standard phenol-chloroform protocol. Medical exome sequencing (MES) was performed using the lllumina NovaSeq 6000 system with an average sequencing depth of 200 × as previously described[5]. Sanger sequencing was performed to verify the mutation. The pathogenicity of the variant was classified according to the guidelines of the American Academy of Medical Genetics and Genomics (ACMG)[6].

Imaging examinations

Magnetic resonance imaging (MRI, Phiilips, 1.5 T, Achieva) of the brain showed that the cortex of the cerebral hemispheres was thickened, and the sulcus gyrus was reduced. The corpus callosum was short and widened on both sides of the ventricle, the shape was not natural, the transparent septum was shown, and the subarachnoid space of the frontotemporal area was slightly wider on both sides.

FINAL DIAGNOSIS

In this case, MES analysis, which included 5177 disease-associated genes, was performed. Detailed genetic testing methods and data interpretation methods can be found in our previous article[7]. The average coverage depth was 249 ± 85 ×, 99.7% of which were higher than 10 ×, and 99.5% of which were higher than 20×. A hetero-

Figure 1 Clinical phenotypic characteristics of the proband. A: Adducted thumbs, symmetrical limbs, and permanently stretched limbs; B: No obvious gaze and high hairline; C and D: High arch feet.

zygous mutation, c.5885G>A (p.R1962H), was detected in *DYNC1H1* (NM_001376). *DYNC1H1* gene sequence analysis showed a G>A change at chr14: 102474582 involving the replacement of an arginine at position 1962 by histidine (Figure 2). Sanger sequencing results showed that none of the parents carried this mutation, indicating a *de novo* variant. No copy number variants in this gene were detected. This *de novo* variant has not been reported in the peer-reviewed literature. The mutation located in this region is an important domain (motor domain) of the protein. Multiple computational analyses predicted that this variant likely affected the structure and function of the protein. A variant at the same amino acid location, c.5885G>A (p.R1962C), has been reported in patients with cortical developmental malformations, microcephaly, and lower extremities involving spinal muscular atrophy[8]. The clinical manifestations along with the segregation evidence make this a likely pathogenic variant, according to the ACMG Guidelines[6]. *DYNC1H1* gene-related diseases are CMT20, MRD13, and SMA-LED.

TREATMENT

The current treatment for patients with *DYNC1H1* gene related disease is mainly supportive, aiming to provide nutritional and respiratory support as needed, and to treat or prevent the complications of muscle weakness. The prognosis of the disease is poor.

OUTCOME AND FOLLOW-UP

We plan to continue to follow the child's disease progression. This diagnosis permitted proper genetic counseling with associated risk assessment.

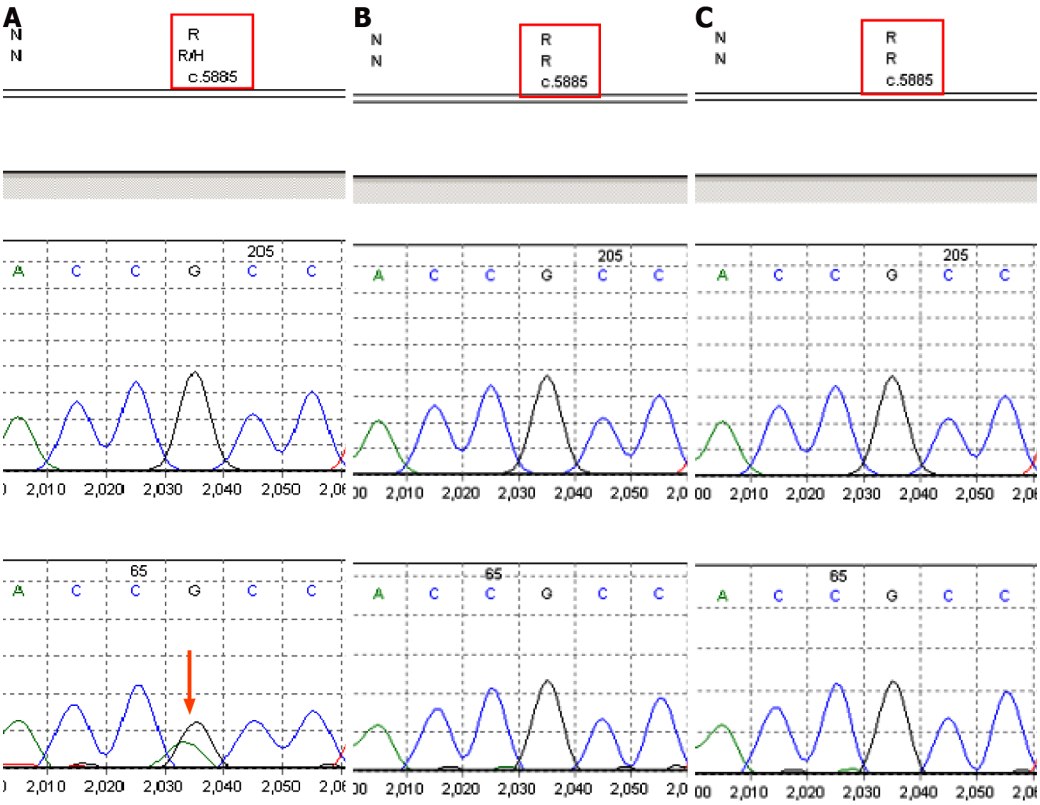

Figure 2 Sanger sequencing for detection of mutation. A: Dynein, cytoplasmic 1, heavy chain 1 gene sequencing map of the child with c.5885G>A (p.R1962H) mutation; B: Father without mutation; C: Mother without mutation.

DISCUSSION

The heterozygous variant c.5885G>A (p.R1962H) in the *DYNC1H1* gene detected in this case is a novel *de novo* variant. The *DYNC1H1* gene is located at 14q32.31, which encodes a large key subunit of the cytoplasmic dynein complex[2]. *DYNC1H1* mutations were first reported by Weedon *et al*[9] using whole exome sequencing in a large pedigree of Charcot-Marie-Tooth. A missense mutation in the *DYNC1H1* gene, the first known cause of SMA-LED, has only been reported in a few families[9]. In 2012, Harms *et al*[10] tentatively found that a tail mutation of the *DYNC1H1* gene was responsible for the rare SMA-LED. The proband was of a pedigree with lower limb weakness, bilateral congenital hip dislocation, and clubfoot as a child; the proband's father and brother had similar symptoms with congenital hip dislocation and clubfoot, and they also had significant proximal muscle atrophy in their lower limbs; the family was suggested to have an autosomal dominant disorder; MES detected a heterozygous missense variant in exon 8 of the *DYNC1H1* gene, c.1809A>T (p.E603D)[11]. Four patients had a strong phenotype-genotype correlation, with early childhood onset of mainly lower extremity muscle weakness and weight loss, slow progression, and late-onset of mild upper extremity proximal muscle weakness, and genetic analysis revealed a heterozygous missense mutation in the *DYNC1H1* gene, c.751C>T (p.R251C)[12] (Table 1). The *DYNC1H1* gene not only caused axon movement and neuron migration defects, but also promoted nerve development by enhancing myelination through zebrafish model experiments. All those four patients had normal nerve conduction results and no evidence of peripheral neuropathy[13]. Mutations in the *DYNC1H1* gene may cause defective neuron migration, leading to malformations in cortical development[14].

Moreover, the clinical features observed for the *DYNC1H1* gene mutation c.5885G>A (p.R1962H) were similar to those previously described for the same amino acid site variation (c.5884C>T, p.R1962C). Heterozygous *DYNC1H1* c.5884C>T (p.Arg 1962Cys) variants have been reported in three unrelated individuals with neurodevelopmental disorders (Table 1). It was first reported that a 19-year-old boy with normal head intellectual disabilities had focal seizures from 2 mo to 8 years old, mainly in the posterior gyrus[2]. A 4-year-old boy with epileptic encephalopathy with a *de novo* heterozygous mutation had seizures, growth retardation, autism spectrum disorders,

Table 1 Clinical features of gene mutation patients with *DYNC1H1* gene mutation

Patient	Age (yr)	Sex	Main clinical manifestations	Mutation	Ref.
A four-generation family with 23 members affected	-	-	Pes cavus at birth; delayed motor milestones; lower limb weakness; speech delay; learning difficulties	Heterozygous; c.917A>G, p.His306Arg	[9]
I 2	82	Female	Lower limb muscle wasting and weakness; walked with a waddling gait	Heterozygous; c.1809A>T, p.glu603Asp	[11]
II 1	60	Male	Lower limb muscle wasting and weakness; had learning difficulties and epilepsy		
II 2	59	Male	Bilateral talipes equinovarus, congenital hip dislocation, and scoliosis; lower limb weakness and difficulty walking		
II 3	58	Male	Bilateral talipes equinovarus and congenital hip dislocation requiring surgeries; bilateral pes cavus, wasting of muscles (particularly quadriceps), reduced reflexes, but normal sensation in the lower limbs and walked very slowly with a waddling gait		
III 1	32	Male	Similar features as #II 3		
III 2	30	Male	Similar features as #II 3		
Patient 1	15	Female	Middle East. Twenty months: Delayed walking and early predominant weakness in the lower extremities. Investigations showed normal creatine kinase levels and nerve conduction study findings, and needle electromyography suggested neuronal degeneration. Brain MRI: Mild ventricular dilatation. Muscle biopsy from right vastus lateralis: Neurogenic atrophy with pathological fibre-type grouping and fatty infiltration in the muscle fascicles. At 15 yr old, walked independently with waddling and needed support to rise from floor. Longer distance travel: Wheelchair. At present, mild proximal upper limbs weakness; mild intellectual disabilities	*De novo* heterozygous; c.751C>T, p.Arg251Cys	[12]
Patient 2	16	Female	Chinese. At birth: Clubfeet; 2 years old: Delayed walking; 7 years old: Pes cavus, significant lower limb muscle wasting and weakness, absent knee jerks but preserved ankle jerks, positive Gower sign, mild proximal muscle weakness in the upper extremities with preserved reflexes. Mildly elevated creatine kinase level (255 U/L, normal reference: < 154 U/L). Muscle biopsy from the right deltoid: Type 2 fibre atrophy. Needle electromyography: Chronic denervation. 12 years old: Mild scoliosis with Cobb's angle of 14 degrees from T12 to L5. Attention deficit and hyperactivity disorder with dyslexia. 14 years old: Walk independently but required to use a walking stick for long distance travel. Leg muscle MRI: Selective muscle involvement and no deterioration when repeated 1.5 yr later. 18 years old: Knee tightness increase; scoliosis and motor performance stable. Brain MRI: Mild ventricular dilatation		
Patient 3	8	Male	Chinese. At birth: Club feet. 2 years old: Started walking and fell easily. Normal to mildly elevated creatine kinase levels (CK148 - 216 IU/L: normal reference: < 163 IU/L). Muscle biopsy from left quadriceps reported predominant type 1 fibres with rare scattered atrophic fibres. Brain MRI: Mildly dilated lateral ventricles and a left posterior fossa arachnoid cyst. 7 years old: Positive Gower sign and predominant lower limbs weakness and atrophy with absent knee jerks and decreased ankle jerks. Mild shoulder girdle weakness with preserved reflexes. Needle electromyography: Chronic denervation. 8 years old: Selective muscles involvement. 11 years old: Attention deficit disorder and motor performance remained stable with knee and tendoachilles tightness		
Patient 4	21	Male	Caucasian. At birth: Left clubfoot. 27 mo old: Walked led by hand. Right quadricep muscle biopsy: Predominant type 1 fibres surrounded by fat and fibrosis. Needle electromyography: Neurogenic pattern. Urinary and faecal incontinence problem. 6 years old: Predominant weakness and atrophy of both legs, more pronounced on the left side. His knee jerks were absent but the ankle jerks were preserved. He could walk up to a 100-m distance. 8 years old: Muscle ultrasound: Abnormal echogenicity of the quadriceps and bicep brachii. Mild grade intellectual disabilities and autism with hyperactive behaviour. Over the next few years: Lower limb weakness increased and upper extremities proximal weakness. Twelve years old: Walk with walking stick. 21 years old: Walk up to several meters and required a wheelchair for long distance travel. Pronounced muscle atrophy of the legs and marked contractures at both knees. Repeated brain MRI: Small right-sided posterior fossa arachnoid cyst		
Family 10	4	Male	Parental nonconsanguinity; Seizure onset; 3 mo: Focaltonic/opisthotonic posturing. IS (6 mo) to multiple types. EEG: MEA + AB, Severe DD, ASD, focal pachygyria	Heterozygous; c.5884C>T, p.Arg1962Cys	[15]
Case 4	7	Female	Prenatally believed to have isolated mild ventriculomegaly but with additional postnatal findings; ventricular width: 12.0 mm; MRI: Sinuous malformation; intellectual disability, impaired psychomotor development; follow-up sonograms: Regression to normal	Heterozygous; c.5884c>T; p.Arg1962Cys	[16]

IS: Infantile spasms; EEG: Electroencephalogram; ASD: Autism spectrum disorder; AB: Abnormal background; DD: Developmental delay; MEA: Multi-electrode arrays; MRI: Magnetic resonance imaging.

and focal brain hyperfunction 3 mo later[15]. A 7-year-old woman with mental disability, psychomotor development impairment, prenatal history of ventricular

enlargement, and sinus malformation[16]. The *in vitro* motility assays showed that *DYNC1H1* mutation (p. R1962C) inhibited dynein activity, dynein's core mechanochemical properties, and did not produce any movement of microtubules along the glass surface[4] (Table 1). In our case, considering the children's growth and development stage, some pediatric disease clinical phenotype will gradually change or begin to appear according to the development of child nervous system. Therefore, we conducted a preliminary follow-up of the child. The child is currently 1 year and 2 mo old, 80 cm in length, and 9 kg in weight, with slender limbs and low muscle strength, and still cannot raise her head, sit, or speak. Speech, motor, and intelligence development is low, accompanied by seizures. MRI of the brain showed that the cortex of the cerebral hemispheres was thickened, the sulcus gyrus was reduced, and nodular protrusions were seen on part of the brain surface. The frontal lobe was the most obvious. Part of the myelin sheath showed slightly longer T1 and longer T2 signals, and multiple spots with shorter T2 and shorter T1 signals were seen in the frontal medulla. The corpus callosum was short and widened on both sides of the ventricle, the shape was not natural, the transparent septum was shown, and the subarachnoid space of the frontotemporal area was slightly wider on both sides. The clinical manifestations of the children are consistent with the symptoms of the *DYNC1H1* gene mutation, and we will follow the children in the future. Because there is currently no effective treatment for the disease, the prognosis of such children is poor. We will follow the life of the child every 1-2 years. In particular, we will monitor muscle and intellectual development by muscle and brain MRI examination, and carry out symptomatic treatment and interventions.

However, for this *de novo* mutation, Sanger sequencing could not rule out the possibility of low-level mosaicism in the parents of the proband. Therefore, it is recommended to select a high overage next generation sequencing method to evaluate the source of variation and the risk of offspring reoccurrence. At the same time, in this case, the mother of the child had no clear indications for prenatal diagnosis during pregnancy, but for couples who have given birth to such children, genetic counseling and prenatal diagnosis are required for the next pregnancy to avoid the birth of such children.

CONCLUSION

We herein report a *de novo* novel variant of *DYNC1H1* gene, c.5885G>A (p.R1962H), leading to overlapping phenotypes (seizure, general growth retardation, and muscle weakness) of CMT20, MRD13, and SMA-LED. And there is no effective treatment for this disease. Our case enriches the *DYNC1H1* gene mutation spectrum and provides an important basis for clinical diagnosis and treatment and genetic counseling.

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