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Case Report

A Childhood-Onset Nemaline Myopathy Caused by Novel Compound Heterozygote Variants in the Nebulin Gene

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Abstract

Congenital myopathies are clinically and genetically heterogeneous disorders, which often remain genetically undiagnosed for many years. Here we present a 20-year-old patient showing gradually deteriorated proximal muscle weakness and rod-shaped structures found in muscle fibers was suspected of having nemaline myopathy. Whole-exome sequencing and subsequent Sanger sequence analysis for the patient revealed a pathogenic mutation in *NEB* gene c.21522+3 (IVS 144) A>G and c.23722 (exon 165) A>T. Based on genetic analyses, we identified two novel, compound-heterozygous variants in the *NEB* gene, which cause a childhood-onset nemaline myopathy.

Keywords: Congenital myopathy; Nemaline myopathy; *NEB*; Next Generation Sequencing

Introduction

Nemaline Myopathy (NM) is a hereditary muscle disorder with a wide range of severity. The most common clinical symptoms include early-onset muscle weakness of proximal limb, neck flexors, weakness of respiratory muscles [1]. NM was historically defined by the muscle biopsy finding of nemaline rods [2].

Mutations in 12 genes have been associated with NM. The most common mutations are *NEB* (encoding nebulin) [3,4] and *ACTA1* (skeletal muscle α-actin) [5,6], other mutant genes including *TPM2* (β-tropomyosin) [7], *TPM3* (α-tropomyosin) [8,9], *KBTBD13* (Kelch repeat and BTB domain-containing protein 13) [9], *CFL2* (cofilin-2) [10], *KLHL40* (Kelch-like family member 40, KLHL40) [11], *KLHL41* (Kelch-like family member 41, KLHL41) [12], *LMOD3* (leiomodin-3) [13], *MYPN* (myopalladin) [14], *TNNT1* (troponin T1) [15,16] and *TNNT3* (troponin T3) [17].

Homozygous or compound heterozygous mutation in the nebulin gene on chromosome 2q23 is responsible of NM [18]. *NEB* gene encodes nebulin, a giant cytoskeletal protein that plays a role in specifying and maintaining the length of actin thin filaments in striated muscle [19]. Here, we report a case of NM in a 20-year-old boy using next-generation sequencing.

Case Report

A 20-year-old male patient presented in the clinic complaining of a longstanding history of weakness since early childhood. He reported that he never gained the ability to run. Symptoms were progressive, so that he had difficulty in climbing stairs. He denied any history of muscle pain and stiffness. There was no history of diplopia, shortness of breath, or change in urine color. The weakness was not fluctuating and not associated with dysphagia or facial weakness. He has one sister and one brother, both of them died when they were infants with unknow cause. Both parents did not report neuromuscular symptoms and were normal upon clinical examination (Figure 1).

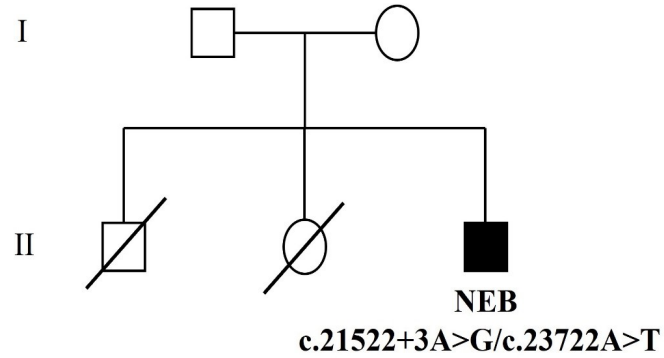

Figure 1: Results of DNA sequence. Pedigree symbols. Square: male; circle: female; unfilled: unaffected or unknown; filled: affected; a diagonal line through a symbol, death.

Table 1: List of found variants in our patient.

Gene	Site	Sequence variants	State	ACMG evidence of pathogenicity
NEB	Exon165	c.23722A>T (p.R7908*) Chr2:152362712	Het	VUS
	IVS144	c.21522+3A>G - chr2:152389953	Het	Likely Path

Het heterozygote, *Likely Path* likely pathogenic, *VUS* variant of uncertain significance, *ACMG* American College of Medical Genetics

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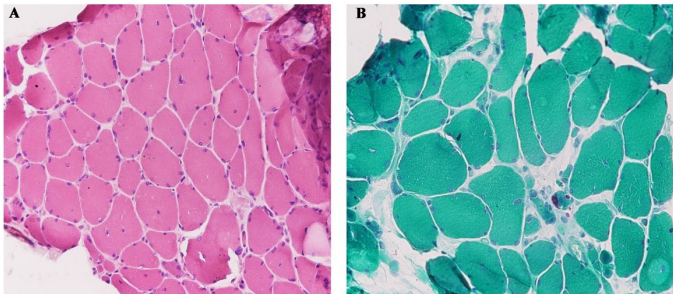

Figure 2: Left quadriceps femoris muscle biopsy from our patient by conventional microscopy. Hematoxylin and eosin (H&E) staining (×100) showed presence of abundant rods (dark pink substance), a wide variation in fiber size, as well as occasional atrophic small round fibers in certain parts (A). Modified Gomori trichrome staining (×100) reveals frequent subsarcolemmal dark nemaline rods which also aggregate in the intermyofibrillar spaces (B).

Table 2: Summary of NM with *NEB* mutations: present study and review of literature.

Mutation site	Ethnicity	References
A homozygous mutation in NEB intron 122	Lebanese	[30]
c.20131C > T; c.674C > T	Unknown	[33]
c.1999-2A>G; c.1999-2A>G	Unknown	[35]
c.6915+1G>T; c.14910+3G>C	Unknown	[36]
c.8501delA; c.1674+2T>C	Brazilian	[24]
c.24189_24192dup; c.20466+2T>A	Brazilian	[24]
c.24304_24305dup; c.24304_24305dup	Brazilian	[24]
c.8889+1G>A; c.6869_6870insTGC	Brazilian	[24]
c.22170G>A; c.24579G>C	Brazilian	[24]
c.24735_24736del; IVS122:c.191028_19102-4del	Brazilian	[24]
c.23601_23602del; c.2835+5G>C	Brazilian	[24]
c.23878_23881dup; c.25405-1G>C	Brazilian	[24]
c.1623delT; duplication of exons 82 to 105	Brazilian	[24]
c.3648del; del exon 29	Brazilian	[24]
c.5343+5G>A; c.5343+5G>A	Brazilian	[24]
c.21076C>T; c.24192_24193insTCAA	Brazilian	[24]
c.19944G>A; c.16423A>T	Brazilian	[24]
c.5343+5G>A; c.2943G>A	Brazilian	[24]
c.21522+119C>G; c.21522+119C>G	Algerian	[37]
c.23122-1G>C; c.21522+3A>G	Chinese	[34]
c.14837dupA; c.3758C>A	Chinese	[34]
c.21522+3A>G; c.11164C>T	Chinese	[34]
c.21522+3A>G; c.4417C>T	Chinese	[34]
c.21522+3A>G; c.23233-1G>T	Chinese	[34]
c.21522+3A>G; c.5343+1G>A	Chinese	[34]
c.21417+3A>G; c.20360_20361insA	Chinese	[23]
c.21793C>T; c.21417+3A>G	Chinese	[23]
c.21417+3A>G; c.5574_5575ins	Chinese	[23]
c.4189C>T; Exon 82 duplication	Chinese	[23]
c.1623delT; c.21417+3A>G	Chinese	[23]
c.21417+3A>G; c.19211delT	Chinese	[23]
c.13669C>T; c.2311-2A>C	Chinese	[23]
c.19944G>A; c.6029del	Chinese	[23,38]
c.7818delG; c.24579G>A	Chinese	[23,38]
c.17367G>A; c.21417+3A>G	Chinese	[23]
c.21417+3A>G; c.12019-10G>A	Chinese	[23]
c.21417+3A>G; c.18917G>A	Chinese	[23]
c.21605G>C; c.5789A>T; c.613A>T	Chinese	[23]
c.21417+3A>G; c.8479C>T	Chinese	[23]
c.21417+3A>G; c.1263dupA	Chinese	[23]

On examination, he had a symmetrical face with no ptosis, ophthalmoplegia, or dysmorphic characteristics. No muscle wasting or fasciculations in the tongue or extremities were observed. Inspection of skeletal muscle and testing of muscle strength showed atrophy and weakness of the proximal and distal leg muscles (hip extensors and knee flexors: 3/5; foot extensors: 4/5). There was no rigid spine, axial atrophy or scapula alata.

Serum creatine kinase levels and vitamin D levels were normal. Imaging of the spinal cord showed no abnormalities. Echocardiography and pulmonary function tests were normal. Electromyography revealed myopathic potentials with normal nerve conduction evaluation for right upper and lower extremities. A first skeletal muscle biopsy revealed typical nemaline rods in the modified Gomori-trichrome-stain (Figure 2).

Whole-exome sequencing and subsequent Sanger sequence analysis for the patient revealed a pathogenic compound heterozygous variant in *NEB* gene c.21522+3 (IVS 144) A>G and c.23722 (exon 165) A>T (Table 1). Unfortunately, his parents didn't have genetic testing. He was diagnosed with autosomal recessive nemaline myopathy with two novel pathogenic variants in the *NEB* gene.

Discussion

The NM constitute a large proportion of the congenital or structural myopathies. The causative genes are at least twelve, encoding structural or regulatory proteins of the thin filament, and the clinical picture as well as the histological appearance on muscle biopsy vary widely.

Among these known genes, mutations in the *NEB* gene are the most common cause of autosomal recessive NM, corresponding to around 50% of the cases [20]. This gene is huge, with 183 exons spanning 249 kb of the genomic sequence, and encodes the nebulin protein of approximately 600–900 kDa [19,21,22]. Therefore, the molecular study of this gene was a great challenge in previous years. We collected more than 80 NEB mutation pattern with literature review (Table 2). More recently, with the advance of next-generation sequencing methodologies, the screening of the NEB gene has been applied in larger cohorts of NM patients, and more mutations have been identified. Yin et al reported that *NEB* gene mutation was the most common mutation in a 16 NM patient cohort, in which splicing change c.21522 +3A > G is hotspot mutation in Chinese NM patients (33742414). Another cohort including 48 NM patients found that *NEB* was the most frequent causative gene in this Chinese cohort, followed by *ACTA1*. Notably, one *NEB* splicing mutation, c.21417+3A>G causing exon 144 splicing was found in 52.9% of *NEB* variant-carrying patients [23]. In Brazilian patients, the most common mutations are also *NEB*. Therefore, previous study suggested that considering the high frequency of *NEB* mutations and the complexity of this gene, NGS tools should be combined with CNV identification, especially in patients with a likely non-identified second mutation [24].

Autosomal recessive mutations in *NEB* encoding nebulin were reported to cause NM in 1999 [25]. Romero et al. first reported a case with core-rod myopathy caused by *NEB* gene mutation that showed generalized hypotonia and required immediate intubation and resuscitation at birth [26]. However, clinical phenotypes of NM caused by *NEB* mutations are variable [27-29]. Some patients have shown mild symptoms and began walking in the normal milestone range or up to 3 years of age

c.4352delC; c.1470+5G>T	Chinese	[23]
c.21417+3A>G; c.16465A>G	Chinese	[23]
c.24209_24212dupTGTT; c.183_184ins	Chinese	[23]
c.7212T>G; c.21417+3A>G	Chinese	[23]
c.18187C>T; c.21417+3A>G	Chinese	[23]
c.6195dupG; c.21417+3A>G	Chinese	[23]
c.8394T>G; c.21417+3A>G	Chinese	[23]
c.5924C>T; c.10976A>G; c.24650G>A	Chinese	[23]
c.21417+3A>G; c.36G>T	Chinese	[23]
c.22037A>T; c.21417+3A>G	Chinese	[23]
c.24314_24317dupTGTT; c.19732-3C>A	Chinese	[23]
c.21417+3A>G; c.19751T>G	Chinese	[23]
c.15187dupC; c.8350G>A	Chinese	[23]
c.21485A>C; c.8434C>T; c.2017T>C	Chinese	[23]
c.24375_24378del; c.18340delA	Chinese	[23]
c.23246_23249delAGTA; c.24182_24185dupAACA	Chinese	[23]
c.7653C>G	Chinese	[23]
c.2859T>G	Chinese	[23]
c.20131C>T	Chinese	[23]
c.3567 + 1G>A; c.6734dupA	Chinese	[38]
c.3255+1G>T; c.7165delA	Chinese	[39]
c.24372_24375dup	Caucasian	[28]
c.2310+5G > A; c.17779_17780delTA	Unknown	[40]
c.19653G>A; c.25441C>T	Unknown	[41]
c.18676C>T; c.9812C>A	Chinese	[42]
c.20131C>T; c.9046C >T	Japanese	[32]
c.20131C>T; c.23161A >T	Japanese	[32]
c.8899A>C; c.23908_23911del	Italian	[43]
c.1896+2T>C	Italian	[43]
c.17737-2A>T; c.21423delA	Unknown	[19]
c.24559C>T; c.19429-381_19429-379delinsA	Italian	[43]
c.7310G>A	Italian	[43]
c.22936C>T	Unknown	[19]
c.21840+313_22266 + 5del	Italian	[43]
c.7309C>T	Italian	[43]
c.11086A>C; c.17779_17780delTA	Unknown	[40]
c.10872+1G>T; c.21622A>C	Unknown	[44]
Deletion of exons 14–81 and one-copy loss of exons 82–89	Unknown	[45,46]
c.1152+1G>T; c.11318_11319del	Unknown	[47]
c.20131C>T; c.22924delT	Japanese	[31]
c.21522+3A>G; c.12148G>T	Chinese	[48]
c.23722A>T; c.21522+3A>G	Chinese	Current

[27-29]. However, Rocha et al found a homozygous mutation in *NEB* intron 122 causing foetal nemaline myopathy with arthrogryposis during early gestation [30]. Previous study reported a *NEB*-related adult NM patient presenting slowly progressive distal myopathy with respiratory and heart failure. She had a known missense variant of c.20131C > T [31,32], and a novel variant of c.674C>T in *NEB* [33]. In the present study, we report a childhood-onset NM patient, with suspected positive family genetic history. Whole-exome sequencing and subsequent Sanger sequence analysis for the patient revealed a pathogenic compound heterozygous variant in *NEB* gene c.21522+3 (IVS 144) A>G and c.23722 (exon 165) A>T. Yin et al reported that splicing change c.21522+3A>G is hotspot mutation in Chinese NM patients [34]. After searching all the literatures, we found that mutation of c.23722 (exon 165) A>T has not been reported yet.

Conclusion

We reported one individual with NM carried new *NEB* mutation. The results of our study help to expand the mutation spectrum of *NEB* and enrich the clinical knowledge of this disorder. We suggest that *NEB* be included in a carrier screening panel in Chinese patients with congenital myopathies.

Author Statements

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