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DETAILED GENOMIC ANALYSIS OF CONGENITAL MYOPATHIES: A CASE SERIES

Genetics

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ABSTRACT

Background: Congenital myopathies are a heterogeneous group of inherited neuromuscular disorders characterized by early-onset hypotonia, muscle weakness, and distinctive structural abnormalities in skeletal muscle. Advances in genomic sequencing technologies have significantly expanded the genetic spectrum and improved diagnostic precision. **Objective:** To describe the clinical features and genomic findings in a cohort of infants with suspected congenital myopathy and analyze genotype–phenotype correlations. **Methods:** This retrospective case series included six infants presenting with early hypotonia and motor developmental delay who underwent whole exome sequencing. Clinical data, neuroimaging findings, and genomic variants were analyzed. Variants were classified according to American College of Medical Genetics (ACMG) criteria. **Results:** Six children (four males and two females) were included. Consanguinity was present in four families. Pathogenic or likely pathogenic variants were identified in three cases involving NEB, TNNT1, and KY genes, consistent with nemaline and myofibrillar myopathies. Two patients harbored variants of uncertain significance in COL6A2 and DYNC1H1, while one case remained genetically unresolved despite extensive genomic testing. Orthopedic abnormalities such as clubfoot were observed in two patients, and neuroimaging findings were largely nonspecific. **Conclusion:** This case series highlights the genetic heterogeneity of congenital myopathies and demonstrates the diagnostic utility of whole exome sequencing. Early genomic diagnosis facilitates accurate disease classification, prognosis, and genetic counseling.

KEYWORDS

congenital myopathy, nemaline myopathy, whole exome sequencing, infantile hypotonia, neuromuscular disorders

INTRODUCTION

Congenital myopathies are a diverse group of inherited neuromuscular disorders characterized by early onset muscle weakness and distinctive histopathological abnormalities in skeletal muscle fibers[12]. Traditionally, these disorders were classified based on characteristic structural findings on muscle biopsy, including nemaline rods, central nuclei, and core lesions[2].

Over the past two decades, advances in molecular genetics have substantially expanded the understanding of congenital myopathies. More than 40 genes have now been implicated, highlighting the remarkable genetic heterogeneity underlying these disorders[3]. The major subtypes include nemaline myopathy, centronuclear myopathy, core myopathy, and myofibrillar myopathy, each associated with specific genetic mutations and clinical phenotypes[45].

Clinically, congenital myopathies often present during infancy with generalized hypotonia, delayed motor milestones, feeding difficulties, respiratory compromise, and skeletal abnormalities such as clubfoot or scoliosis[6]. However, considerable phenotypic overlap exists between different genetic subtypes, making clinical diagnosis challenging.

Next-generation sequencing technologies, particularly whole exome sequencing (WES), have revolutionized the diagnostic approach to congenital myopathies by enabling comprehensive genomic analysis and identification of pathogenic variants across multiple genes[37]. This genomic approach has significantly improved diagnostic yield and facilitated genotype–phenotype correlations.

In this study, we describe the clinical and genetic spectrum of congenital myopathies in a cohort of infants evaluated using whole exome sequencing and highlight important genotype–phenotype correlations.

METHODS

Study design

This retrospective case series was conducted at a tertiary pediatric neurology center. Medical records of infants evaluated for suspected congenital myopathy between 2023 and 2026 were reviewed.

Inclusion criteria

Children were included if they had:

- Early-onset hypotonia
- Motor developmental delay
- Clinical suspicion of congenital myopathy
- Whole exome sequencing performed

Data collection

Clinical data collected included:

- Demographic characteristics
- Consanguinity
- Clinical features
- Neurological examination
- Neuroimaging findings
- Genetic testing results

Genetic analysis

Genomic DNA was analyzed using whole exome sequencing. Identified variants were classified according to ACMG guidelines as pathogenic, likely pathogenic, variant of uncertain significance, or benign.

Ethical considerations

The study was conducted in accordance with institutional ethical guidelines. Patient identifiers were removed to maintain confidentiality.

RESULTS

Demographic characteristics

Six children with suspected congenital myopathy were included. The median age at presentation was 10 months (range 8–12 months). Four patients were male and two were female. Consanguinity was reported in four families.

Clinical presentation

All patients presented with generalized hypotonia and delayed motor milestones. Additional clinical features included:

- External ophthalmoplegia and facial weakness (1 patient)
- Bilateral clubfoot (2 patients)
- Dysmorphic facial features (1 patient)
- Respiratory involvement (1 patient)

Neuroimaging findings were largely nonspecific and included mild white matter abnormalities or normal MRI findings.

Genetic findings

- Whole exome sequencing identified pathogenic or likely pathogenic variants in three patients.
- A homozygous deletion in the KY gene was identified in one patient, consistent with myofibrillar myopathy type 7.
- A homozygous nonsense variant in TNNT1 (p.Gln224Ter) was detected in another patient, confirming severe infantile nemaline myopathy.
- Compound heterozygous pathogenic variants in NEB were identified in one patient, establishing the diagnosis of nemaline myopathy type 2.
- Two additional patients harbored variants of uncertain significance in COL6A2 and DYNC1H1, genes associated with collagen VI-related myopathies and dynein-related neuromuscular disorders respectively.
- One patient remained genetically unresolved despite combined

nuclear and mitochondrial genome analysis.

Diagnostic yield

The overall molecular diagnostic yield in this cohort was 50% (3/6 cases).

DISCUSSION

Congenital myopathies represent a genetically and clinically heterogeneous group of neuromuscular disorders. Historically, diagnosis relied heavily on muscle biopsy and histopathological classification. However, the increasing availability of genomic sequencing has transformed the diagnostic landscape[3,6].

In the present case series, nemaline myopathy-related genes were the most frequently identified genetic causes, consistent with previous studies that report NEB mutations as one of the most common etiologies of congenital myopathy[10].

Mutations in TNNT1 are known to cause severe infantile nemaline myopathy characterized by early hypotonia and progressive muscle weakness[8]. The identification of a truncating TNNT1 mutation in our cohort aligns with previously reported severe phenotypes.

The detection of a homozygous KY gene deletion highlights the importance of copy number variant analysis in exome sequencing pipelines. KY-related myopathy is rare but increasingly recognized as part of the congenital myopathy spectrum[3].

Variants in COL6A2 are associated with collagen VI-related disorders, including Bethlem myopathy and Ullrich congenital muscular dystrophy, which demonstrate a broad phenotypic spectrum[4]. Similarly, DYNC1H1 variants have been linked to a range of neuromuscular disorders including congenital myopathy and spinal motor neuron disease[7].

One patient in our cohort remained genetically undiagnosed despite exome sequencing. Previous studies report diagnostic yields ranging from 40–60%, suggesting that unresolved cases may involve deep intronic variants, structural rearrangements, or novel disease genes[10].

Overall, our findings emphasize the importance of genomic testing in infants presenting with hypotonia and suspected congenital myopathy.

CONCLUSION

This case series demonstrates the clinical and genetic heterogeneity of congenital myopathies. Whole exome sequencing enabled identi-fication of pathogenic variants in half of the cases, with nemaline myopathy genes representing the most frequent genetic cause. Early genomic diagnosis is crucial for accurate classification, prognosis, and genetic counseling. Further studies integrating genomic and functional analyses are needed to improve diagnostic yield.

Key Messages

What is known

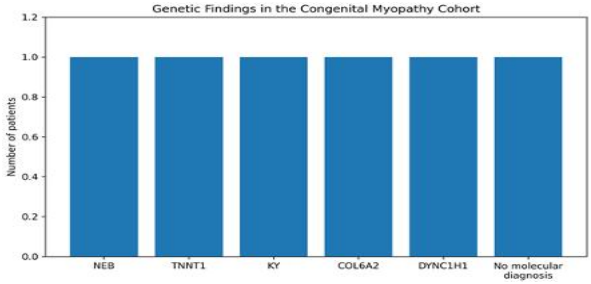
- Congenital myopathies are genetically heterogeneous neuromuscular disorders presenting with infantile hypotonia.
- Next-generation sequencing has improved diagnostic accuracy.

What this study adds

- Nemaline myopathy genes were the most common genetic cause in this cohort.
- Whole exome sequencing provided a diagnostic yield of 50%.

Clinical implications

- Early genomic testing should be considered in infants with unexplained hypotonia.



REFERENCES

1. Gineste C, Laporte J. Therapeutic approaches in different congenital myopathies. Curr Opin Pharmacol. 2023;68:102328.
2. Goebel HH, Stenzel W. A brief history of the congenital myopathies – the myopathological perspective. Neuromuscul Disord. 2023;33(12):990-995.
3. Onnée M, Malfatti E. The widening genetic and myopathologic spectrum of congenital myopathies (CMYOs): a narrative review. Neuromuscul Disord. 2025;49:105338.
4. Phadke R. Myopathology of congenital myopathies: Bridging the old and the new. Semin Pediatr Neurol. 2019;29.
5. Buono S, Monseur A, Menuet A, Robé A, Koch C, Laporte J, et al. Congenital myopathies – centronuclear myopathies. Neuromuscul Disord. 2021;31:S58.
6. North KN, Wang CH, Clarke N, Jungbluth H, Vainzof M, Dowling JJ, et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord. 2014;24(2):97-116.
7. Radke J, Stenzel W, Goebel HH. Recently identified congenital myopathies. Semin Pediatr Neurol. 2019;29:83-90.
8. Piteau SJ, Rossiter JP. Congenital myopathy with cap-like structures and nemaline rods: Case report and literature review. Pediatr Neurol.
9. Rodríguez Cruz PM, Sewry C, Beeson D, Jayawant S, Squier W, McWilliam R, et al. Congenital myopathies with secondary neuromuscular transmission defects. Neuromuscul Disord. 2014;24(12):1103-1110.
10. Maggi L, Scoto M, Cirak S, Robb SA, Klein A, Lillis S, et al. Congenital myopathies – clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. Neuromuscul Disord. 2013;23(3):195-205.