



## Letter to the Editor: New Observation

# Congenital Myopathy Due to Pathogenic Missense Variant in the *MYBPC1* Gene

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Congenital myopathies are a heterogeneous group of genetic disorders characterized by muscle weakness and classified based on the histopathological findings on the muscle biopsy. Due to recent advances in genetic testing technologies and next-generation sequencing, an increasing number of genes have been associated with various neuromuscular phenotypes and histologic expressions.<sup>1</sup>

Our patient is a 49-year-old male of Jamaican descent, born to nonconsanguineous parents, who presented with muscular weakness since birth. He was born preterm at 36 weeks gestational age and was admitted to the hospital for observation for hypotonia at birth. He was noted to have upper extremity tremors, which persisted into adulthood. During infancy, he had significant delays in gross motor milestones. During childhood, he had trouble keeping up with his peers. All other developmental milestones, including social development and fine motor function, were normal. There were no ocular or bulbar symptoms. He had improved strength throughout puberty.

He reported significant decline in motor function after age 36, with progressive proximal weakness, contractures in the ankles and knees, and required a cane for ambulation. At the age of 43, he developed chest pain. Cardiac MRI done in 2022 showed multifocal non-ischemic myocardial fibrosis with mildly reduced systolic function.

His clinical examination showed diffuse atrophy of the muscles in the lower extremities, with weakness in hip flexion (4/5) and shoulder abduction (4/5). He had lordotic posture with flexion contractures at the hips, knees, and ankles. He had postural and kinetic tremors in the upper extremities. His nerve conduction studies were normal. Needle EMG showed a mixed myopathic and neurogenic process. Serum CK and lactate were normal. Muscle biopsy of the right vastus lateralis revealed central cores in type I

fibers, consistent with congenital myopathy and central core disease. Genetic testing revealed normal microarray and whole exome sequencing (WES).

His daughter exhibited a similar phenotype. She was born full-term but displayed hypotonia, tremors, and motor weakness at birth and noted delay in gross motor milestones. However, her strength improved during puberty. Clinical examination revealed widespread muscle atrophy in the extremities, with 4/5 power in the limbs. She also exhibited a lordotic posture, scoliosis, and postural and kinetic tremors in the upper extremities. Needle EMG showed myopathic potentials.

Clinical WES in his daughter, with inclusion of her parents as part of a trio in 2019, was negative; however, research-based whole genome sequencing of the patient and his daughter in 2022 identified a heterozygous pathogenic variant in the *MYBPC1* gene (c.788T > G; p. Leu236Arg) in both. The presence of this variant was confirmed in both individuals at the genetics laboratory that performed their previous WES and were classified as pathogenic according to ACMG criteria. The *MYBPC1* variant was not reported on the original WES due to unknown association with the family's phenotype. The WES for the daughter and her parents was reported in January 2019, before the creation of the OMIM entry for congenital myopathy 16 (linked to *MYBPC1*) in August 2019.

The MyBP-C family comprises three isoforms: slow skeletal (sMyBP-C), fast skeletal (fMyBP-C), and cardiac (cMyBP-C) proteins encoded by *MYBPC1*, *MYBPC2*, and *MYBPC3* genes. Mutation in the *MYBPC3* gene causes an autosomal dominant inherited cardiomyopathy with incomplete penetrance, the most prevalent cause of familial hypertrophic cardiomyopathy.<sup>2</sup>

*MYBPC1* gene encodes a protein expressed in the slow-twitch skeletal muscle sarcomeres that modulate muscle contractility and recruits muscle-type creatine kinase to myosin filaments, aiding in

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**Table 1:** Summary of cases associated with heterozygous MYBPC1 mutation presenting with myopathy and tremor

Individual	Onset	Inheritance pattern/ inherited form	Ethnicity	Gender	Clinical presentation	MYBPC1 variation	Contractures	Cardiac involvement
Individual 1	Birth	Autosomal dominant/ De novo	Caucasian	Female	Hypotonia at birth, delayed gross motor development, feeding difficulties, tremors of extremities and tongue, dysmorphic facies, normal cognitive development.	c.788T > G (p.Leu263Arg)	No	Absent
Individual 2	Birth	Autosomal dominant/ De novo	Caucasian	Male	Hypotonia at birth, delayed gross motor development, feeding difficulties, hypersomnolence, stridor, tremors of extremities, face and trunk, dysmorphic facies, normal cognitive development.	c.776T > C (p. Leu259Pr)	No	N/A
Individual 3	Birth	Autosomal dominant/ Paternaly inherited	Asian	Female	Hypotonia at birth, delayed gross motor development, feeding difficulties, tremors of extremities and tongue, dysmorphic facies, lordotic gait, epilepsy, normal cognitive development.	c.788T > G (p.Leu263Arg)	No	N/A
Individual 4	Birth	Autosomal dominant/ De novo	Asian	Male	Hypotonia at birth, delayed gross motor development, tremors of extremities and tongue, dysmorphic facies, normal cognitive development.	c.788T > G (p.Leu263Arg)	No	N/A
Individual 5	Infancy	Autosomal dominant/ Maternally inherited	Caucasian	Male	Hypotonia at infancy, delayed gross motor development, tremors of extremities, skeletal abnormalities, normal cognitive development	c.742G > A (p.Glu248Lys)	Yes	N/A
Individual 6	N/A	Autosomal dominant/ De novo	Caucasian	Female	Hypotonia at infancy, delayed gross motor development, tremors of extremities, skeletal abnormalities, normal cognitive development	c.742G > A (p.Glu248Lys)	Yes	N/A
Individual 7	N/A	Autosomal dominant/ Maternally inherited	Caucasian	Male	Hypotonia at infancy, delayed gross motor development, tremors of extremities, skeletal abnormalities, normal cognitive development	c.742G > A (p.Glu248Lys)	Yes	N/A
Individual 8	N/A	Autosomal dominant/ Paternaly Inherited	Caucasian	Female	Hypotonia at infancy, delayed gross motor development, tremors of extremities, skeletal abnormalities, normal cognitive development	c.742G > A (p.Glu248Lys)	Yes	N/A
Individual 9	Childhood	Autosomal dominant/ De novo	Caucasian	Female	Myalgias, cramps, muscle weakness, tremors of extremities and tongue, dysmorphic facies, normal cognitive development	c.739T > C, (p.Tyr247His)	Yes	Absent
Individual 10	N/A	Autosomal dominant/ Maternally Inherited	Caucasian	Male	Muscle weakness, tremors of extremities, dysmorphic facies	c.739T > C, (p.Tyr247His)	Yes	N/A
Individual 11	N/A	Autosomal dominant/ Paternaly Inherited	Caucasian	Female	Muscle weakness, tremors of extremities, dysmorphic facies	c.739T > C, (p.Tyr247His)	Yes	N/A
Individual 12	Infancy	Autosomal dominant/ Paternaly Inherited	Caucasian	Male	Muscle weakness, tremors of extremities	c.739T > C, (p.Tyr247His)	Yes	N/A
Individual 13*	Birth	Autosomal dominant/ De novo	Black	Male	Hypotonia at birth, delayed gross motor development, tremors of extremities, lordotic gait normal cognitive development, worsening after 36 years of age*	c.788T > G, (p.Leu236Arg)	Yes	Present*
Individual 14*	Birth	Autosomal dominant/ Paternaly inherited	Black	Female	Hypotonia at birth, delayed gross motor development, tremors of extremities, lordotic gait and scoliosis, normal cognitive development,	c.788T > G, (p.Leu236Arg)	Absent	Absent

muscle contraction.<sup>3</sup> Shashi et al. recently reported a novel association of MYBPC1 with hypotonia, myogenic tremors, and skeletal muscle weakness in four patients from three families, showing gradual clinical improvement. Facial dysmorphisms with hypotonic facies have also been reported due to the above mutation. The patients had either the p. Leu263Arg variant (in three individuals) or the p. Leu259Pro variant (in one individual) in MYBPC1, both identified as de novo heterozygous mutations.<sup>4</sup> A similar phenotype due to a dominant missense variant in the MYBPC1 gene in two independent, three-generation families has been described due to c.739T > C p.(Y247H) and c.742G > A p.(E248K) mutations manifesting as congenital myopathy and mild to severe congenital hypotonia, with persistent high-frequency tremors. Additional manifestations previously described include improved congenital hypotonia, normal cognition, myalgias, abnormal gait, skeletal abnormalities including mild contractures, scoliosis, lordosis, spinal rigidity, and thoracic asymmetry. Weakness and tremors tended to progress slowly during childhood and adolescence, followed by stability in early adulthood at a moderate level of disability, preserving ambulation.<sup>5,6</sup> In our review, cardiac manifestations in this condition have not been described.

MYBPC1 has also been associated with several myopathic disorders, including autosomal dominant distal arthrogryposis and autosomal recessive lethal congenital contracture syndrome.<sup>7</sup>

Similarly, our patient presented with hypotonia, muscle weakness, and tremors at birth. Research-based whole genome sequencing identified a heterozygous pathogenic variant in the MYBPC1 gene (c.788T > G; p. Leu236Arg) in our patient and his daughter, heterozygous pathogenic variant in the MYBPC1 gene (c.788T > G; p. Leu236Arg). This is a relatively new and rare disorder, which has not been fully characterized. It is unclear if our patient's cardiac manifestation is due to his MYBPC1 variant. We suspect that it may be an unreported feature of the disease (see Table 1). Thus, we suggest that it is important to perform cardiac screening in patients who present with a similar phenotype. The patient reported significant progression of his neuromuscular phenotype recently. This is an atypical feature, as weakness is believed to stabilize in early adolescence.

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"We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

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## References

1. D Cassandrini, Trovato R, Rubegni A, Lenzi S, Fiorillo C, Baldacci J, Minetti C, Astrea G, Bruno C, Santorelli FM, Italian Network on Congenital Myopathies. Congenital myopathies: clinical phenotypes and new diagnostic tools. *Ital J Pediatr.* 2017;43:101. DOI: [10.1186/s13052-017-0419-z](https://doi.org/10.1186/s13052-017-0419-z).
2. Ho CY, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation.* 2018;138:1387–98. DOI: [10.1161/CIRCULATIONAHA.117.033200](https://doi.org/10.1161/CIRCULATIONAHA.117.033200).
3. Ackermann MA, Kontogianni-Konstantopoulos A. Myosin binding protein-C slow: an intricate subfamily of proteins. *J Biomed Biotechnol.* 2010;2010:652065. DOI: [10.1155/2010/652065](https://doi.org/10.1155/2010/652065).
4. Shashi V, Geist J, Lee Y, et al. Heterozygous variants in MYBPC1 are associated with an expanded neuromuscular phenotype beyond arthrogryposis. *Hum Mutat.* 2019;40:1115–26. DOI: [10.1002/humu.23760](https://doi.org/10.1002/humu.23760).
5. Stavusis J, Lace B, Schäfer J, et al. Novel mutations in MYBPC1 are associated with myogenic tremor and mild myopathy. *Ann Neurol.* 2019;86:129–42. DOI: [10.1002/ana.25494](https://doi.org/10.1002/ana.25494).
6. Geist Hauserman J, Stavusis J, Joca HC, et al. Sarcomeric deficits underlie MYBPC1-associated myopathy with myogenic tremor. *JCI Insight.* 2021;6:e147612. DOI: [10.1172/jci.insight.147612](https://doi.org/10.1172/jci.insight.147612) Published 2021 Oct 8.
7. Markus B, Narkis G, Landau D, Birk RZ, Cohen I, Birk OS. Autosomal recessive lethal congenital contractural syndrome type 4 (LCCS4) caused by a mutation in MYBPC1. *Hum Mutat.* 2012;33:1435–8. DOI: [10.1002/humu.22122](https://doi.org/10.1002/humu.22122).