

Novel truncating mutations of *MYO18B* causing congenital myopathy in a Swiss patient

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Congenital myopathies (CMs) are a group of rare inherited myopathies most commonly presenting in infancy with hypotonia and weakness. They have been classified on the basis of distinctive myopathologic features. Mutations in more than 25 genes can cause CM.¹

Recently, truncating mutations of *MYO18B* have been found to cause nemaline myopathy with cardiomyopathy or Klippel-Feil syndrome (KFS).^{2–4} KFS is characterized by the presence of congenital synostosis of some or all cervical vertebrae.

Here, we report the sixth known patient with CM due to 2 novel truncating mutations of *MYO18B*. Unlike the previously reported patients, our Swiss patient has neither KFS nor cardiomyopathy.

The patient was the third child to healthy nonconsanguineous German mother and Swiss father. The patient's elder siblings were not affected. The patient had delayed motor development. He was able to walk at 1.5 years. Generalized muscle weakness and atrophy were observed since early infancy. He presented at our department at 47 years and reported a slow progression of his muscle weakness. On clinical examination, he had the following dysmorphic features: low-set ears, micrognathia with small teeth, thin lips, high-arched palate, short stature, and bilateral pes planus. He was operated because of strabismus in childhood. He had facial weakness, nasal speech, bilateral steppage gait, mild proximal upper and lower limb weakness, and pronounced distal leg weakness. There were no contractures, nor rigid spine. Tendon reflexes were diminished. There were no cognitive, sensory, coordination, or bladder disturbances. The CK level was normal. Heart ultrasound and Holter ECG were unremarkable. Lung function tests disclosed restrictive respiratory impairment. Needle EMG showed myopathic changes without fibrillation potentials or myotonic discharges. Brain MRI was normal. X-ray of the neck did not find KFS.

We suspected CM and proceeded with next generation sequencing panel (supplementary material, links.lww.com/NXG/A271). We found 2 new frameshift mutations of *MYO18B*: NM_032608.6:c.3880_3884delAGGAA/p.(Arg1294Glyfs*34) and NM_032608.6:c.112_121delATTAAGCAAC/p.(Ile38Trpfs*18).

The new variants were confirmed using targeted Sanger sequencing. The patient is compound heterozygous for the mutations. His mother carries p.(Ile38Trpfs*18) heterozygously, and his father is a heterozygous carrier of p.(Arg1294Glyfs*34). His asymptomatic sister carries p.(Arg1294Glyfs*34) heterozygously.

The newly identified mutations segregate with disease phenotype and were not found in the current public databases (gnomAD, ESP5400, and G1000).

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Table Reported patients with *MYO18B*-related congenital myopathy

Case	Age at report/last follow-up	Ethnic origin/consanguinity	<i>MYO18B</i> mutation	Dysmorphic features	KFS	Myopathy/floppy infant	Heart involvement
Alazami et al., 2015 ³	14 y	Saudi Arabian/+	c.6905C>A p.(S2302*) homozygous	+	+	+	nd
Alazami et al., 2015 ³	12 y	Saudi Arabian/+	c.6905C > A p.(S2302*) homozygous	+	+	+	nd
Malfatti et al., 2015 ²	Newborn, deceased at 4.5 mo	Portuguese/+	c.6496G>T p.Glu2166* homozygous	+	nd	+	+
Schieffer et al., 2019 ⁴	3 y 8 mo, deceased at 4 y 9 mo	European/-	c.6768delG p.(Leu2257SerfsTer16) and c.6660_6670del11 p.(Arg2220Serfs*74)	+	+	+	nd
Brunet et al., 2020 ⁵	16 mo/1 y	Afghan/+	c.6433C>T p.(Arg2145*) homozygous	+	+	+	Small PFO, minimal mitral regurgitation
Our case	47 y	Swiss and German/-	c.3880_3884delAGGAA p.(Arg1294Glyfs*34) and c.112_121delATTAAAGCAAC p.(Ile38Trpfs*18)	+	-	+	-

Abbreviations: + = yes; - = no; KFS = Klippel-Feil syndrome; nd = no data; PFO = patent foramen ovale.

Our patient demonstrates similar phenotype as the previously reported patients²⁻⁵ (table). However, he has no KFS. In contrast to the Portuguese patient,² our patient did not have cardiomyopathy. Of interest, he demonstrated predominant distal weakness. All previously reported patients presented at birth as floppy infant with general weakness. Apparently, the predominant distal weakness is not a common feature or at least is not characteristic at the beginning.

It had been speculated that cardiomyopathy could be mutation-specific because truncated myosin 18B protein was found in muscle extracts from the patient reported by Malfatti et al., whereas the mutation in Saudi patients was shown to involve nonsense-mediated messenger RNA decay.^{2,3} However, the frameshift mutations of another *MYO18B* patient without cardiomyopathy did not undergo nonsense-mediated decay,⁴ casting doubt about this hypothesis.

MYO18B (myosin XVIIIIB) represents an unconventional myosin family protein. Deficiency of Myo18B caused an embryonic lethality in mice accompanied by the disruption of myofibrillar structures in cardiac myocytes.⁶ Zebrafish models of Myo18B loss-of-function mutants revealed that Myo18B is essential for coordinating the integration of preformed thick and thin filaments into the sarcomere.⁷ Based on these data, it is not surprising that the muscle and cardiac involvement is caused by Myo18B deficiency in humans. Because KFS was found in at least 4 *MYO18B* mutant patients, *MYO18B* might also play a role in somite segmentation.

All previously reported mutations are located in the C-terminus in the second large unknown domain of Myo18B. The novel mutation p.(Ile38Trpfs*18) is located in the N-terminus. N-terminal unique domain of Myo18B is crucial for its localization to F-actin.⁶ Our second mutation p.(Arg1294Glyfs*34) is located in the myosin head domain containing a guanosine triphosphate/adenosine triphosphate binding site.

The 2 unique N- and C-terminal extension distinguish Myo18B from the conventional myosins. Of interest, apart from p.(Arg1294Glyfs*34), all reported disease-causing mutations cluster in these 2 domains with still unclarified function.

Our case further supports that loss-of-function mutations of *MYO18B* lead to CM with facial dysmorphism but are not uniformly associated with KFS. This suggests that *MYO18B* should be included in gene panels for CM. Our case demonstrates the delay in diagnosing CM because of the slow progression and mild symptoms, as previously reported.¹ Finding additional patients and analyzing muscle biopsies would be helpful to clarify still largely unknown *MYO18B* function.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Violeta Mihaylova, MD, PhD	University Hospital and University of Zurich, Switzerland	Data collection, draft preparation, and interpretation of data
Fabian Chablais, PhD	Genetica, Human Genetics and Genetic Counselling Unit, Zurich, Switzerland	Molecular genetic analyses and interpretation of data
Yvan Herenger, MD	Genetica, Human Genetics and Genetic Counselling Unit, Zurich, Switzerland	Molecular genetic analyses and interpretation of data
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Appendix (continued)

Name	Location	Contribution
Hans Heinrich Jung, MD	University Hospital and University of Zurich, Switzerland	Interpretation of data and revised the manuscript for intellectual content

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