Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Electrophysiological Characterization of a *MYH7* Variant with Tremor Phenotype

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Abstract: Background: The concept of a myopathy with associated tremor ("myogenic tremor") in humans has been previously described for specific *MYBPC1* (Myosin-Binding Protein C) variants. Here we report for the first time an individual with tremor who was found to have a de-novo likely pathogenic variant in Myosin Heavy Chain 7 (MYH7).

We provide a detailed electrophysiological characterization of the tremor syndrome in a human individual with a myopathy and this pathogenic MYH7 variant to provide further insight in the phenotypic spectrum and pathomechanism of myogenic tremors in skeletal sarcomeric myopathies.

Methods: Electromyographic recordings were obtained from facial muscles, as well as bilateral upper and lower extremities.

Results: 10 to 11 Hz activity was observed in the face and extremities during recordings with muscle activation. There were intermittent episodes of significant left–right coherence that would modulate across muscle groups throughout the recording, but no coherence between muscles at different levels of the neuraxis.

Conclusions: A possible explanation for this phenomenon is that the tremor originates at the sarcomere level within muscles, which is then picked up by muscle spindles and leads to activating input to the neuraxis segment. At the same time, the stability of the tremor frequency does suggest the presence of central oscillators at the segmental level. Thus, further studies will be needed to determine the origin of myogenic tremor and to better understand the pathomechanism.

In 1988, a progressive tremor syndrome was recognized in a group of piglets. The tremor in the pigs was described as high-frequency (14–15 Hz), affecting forequarters when standing or moving that ceased at rest.[1]

A pathogenic variant on chromosome 7 (p.Ala1440_Ala1441ins ProAla) compromising the *MYH7* (Myosin Heavy Chain 7) gene was subsequently described to be the disease-causing in the piglets.[2,3] The *MYH7* gene (OMIM: 160760) codes for a beta-cardiac myosin heavy chain, a type of myosin expressed in both heart and skeletal muscle, where it is expressed mostly in type 1 fibers.[4]

The concept of a myopathy with associated tremor ("myogenic tremor") in humans has been previously described by our group for specific *MYBPC1* (Myosin-Binding Protein C) variants in two unrelated three-generation families. In that article, we proposed a myopathic origin for the tremor, arguing that *MYBPC1* is a regulator of myosin to thin-filament binding kinetics known to influence cross-bridge cycling, while it is not known to function in the central nervous system. Therefore, we proposed a mechanism of peripheral origin in which the sarcomere would produce possibly sarcomeric contractions that would activate the stretch reflex leading to the synchronization and oscillation of the effector muscle.[5] In support of this hypothesis, there are clinical descriptions for additional genes in which pathogenic variants have been associated with possible postural or

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action tremor like manifestations as part of the phenotype, such as in *MYH2*, *MYL2*, *TNNT1*, *NEB*, *and TPM3*, although formal characterization of the tremor has been limited.[6]

Here we report an individual who was found to have a de-novo likely pathogenic variant in *MYH7* clinically manifesting with a distinct phenotype of childhood onset rigid-spine myopathy, respiratory insufficiency, in the setting of mild muscle weakness, and a tremor syndrome. We present detailed electrophysiological characterization of this tremor to provide further insight in the phenotypic spectrum and pathomechanism of myogenic tremors in skeletal sarcomeric myopathies.

Methods

For the genetic analysis, a singleton genome sequencing was pursued to identify the underlying genetic cause of the patient's symptoms.

An electrophysiological study to characterize the tremor was performed using surface electromyography (EMG) and accelerometry. Details on the recording methodology can be found in the Appendix S1.

Results

Clinical Case

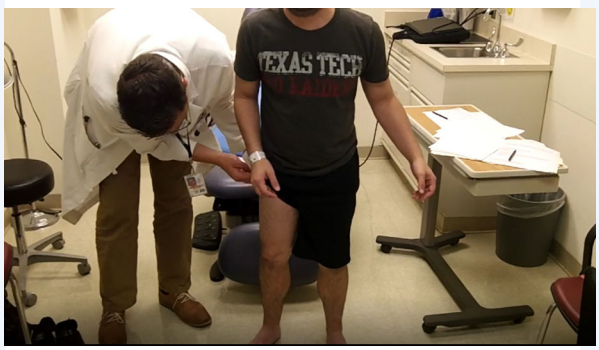
A 26-year-old male with a diagnosis of childhood onset rigid spine myopathy first noticed symptoms during junior high school when he had trouble turning his body during sports. His complaints of axial stiffness and rigidity prompted him to seek evaluation and ultimately led to the genetic diagnosis. The patient also described a progressive action activated tremor first noticed during his early teenage years that mainly affects his arms and legs and is worse on the left side. It was present during physical activity, particularly any activity when the arms or legs are extended. He also noted that the tremor is worse when he is tired or hungry. He denied any tremor at rest. He also has a facial tremor, which, like the tremor in the extremities, was notable during activation of facial muscles. Alcohol calms his hand tremor but evokes no change in the leg tremor.

He has a positive family history of tremor, with his paternal grandfather also having tremor. However, his father has not experienced tremor. His family history was negative for any muscle disorders or history of myopathy. He has two unaffected sisters, aged 30 and 22 years. Other than his underlying myopathy, he has a history of asthma starting at the age of 12 years, but without a need for treatment since age 15. He also had a history of asymptomatic mitral valve prolapse. Aside from difficulty bending over and riding a bike due to the axial stiffness and rigidity, the patient remains independent in his daily activities. He works as an engineer and lives with his wife. He has no children.

The neurologic exam showed normal cranial nerves, except for a clearly observable facial tremor during perioral muscle activation (smiling, opening of the mouth). Muscle bulk was increased in his neck and lower legs bilaterally, with bilateral calf hypertrophy posture was hyperlordotic. There was normal tone in the extremities. Strength was mildly reduced distally in the hands, fingers, and foot flexion/extension (MRC 5-), with otherwise full-strength proximally, with the exception of mild neck extension weakness (MRC 4). Reflexes were not clearly elicitable in all extremities, and there was no Babinski sign.

On movement exam, rapid alternating hand movements were normal on the right, slow, and irregular on the left. There was significant bilateral postural (symmetric, amplitude 1–3 cm) and left-hand kinetic tremor (1–3 cm) during finger-to-nose maneuver, with no kinetic tremor on the right. There was no resting tremor or worsening of tremor amplitudes towards reaching a goal during upper limb movements bilaterally, and no other signs of ataxia of the trunk or extremities. Spiral drawing was more affected on the left than the right due to tremor. The legs showed a high-amplitude tremor bilaterally (amplitude 5 cm, left > right) during posture against gravity. There was no visible nor palpable tremor while standing in a normal position, however, standing on toes elicited a noticeable tremor in the lower extremities. The Essential Tremor Rating Assessment Scale (TETRAS) was 22.5 (maximum 52, with higher values indicating higher tremor severity). The tremor was slightly irregular without entrainment or distractibility (Video 1).

A muscle ultrasound was also performed, which showed mild atrophy and some granular increase in echogenicity, most notable in the bilateral tibialis anterior (Mod Heckmatt Grade 2-3). Routine nerve conduction studies were normal, and EMG showed myopathic features and no features of denervation.



Video 1. Video captures a portion of the clinical exam, including standing flat footed and on tip toes, as well as walking and head turning. In addition, video of the electrophysiological study is also included, including rest, posture with arms supported, posture with arms and legs extended against gravity, and facial tremor.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13664

Genetic Analysis

A heterozygous *MYH7* (NM_000257.4): c.4451T>C; p.(Leu1484Pro) variant was identified, which is not present in GnomAD v3 and is predicted to be damaging per various in-silico prediction tools (MutationTaster: disease causing; CADD Prediction: 33).[7] The variant was confirmed by targeted Sanger sequencing in the patient, and it was confirmed to be de novo, ie, not inherited from either parent. The p.(Leu1484Pro) *MYH7* variant has not been previously reported in patients with a myopathy. The variant is located in exon 32 of *MYH7*, impacting the coiled coil region of the myosin tail. Other pathogenic variants in this exon are known to clinically manifest mostly as Laing distal myopathy.[8] Based on the American College of Medical Genetics and Genomics guidelines for the interpretation of sequence variants,[9] the c.4451T>C; p.(Leu1484Pro) *MYH7* variant is classified as likely pathogenic (PS2, PM2, PP3).

Electrophysiological Study

In the upper extremities, there was no significant rest tremor. During posture of both hands against gravity with supported arms, there was a bilateral 10–11 Hz tremor with EMG correlate (Fig. 1) that did not change in frequency with progressive weight loading of 1, 1.5, and 2 pounds (0.45, 0.68, 0.91 kilograms). Tremor at a similar frequency was also seen intermittently in the face. There was also a 5 Hz component that was present only on the accelerometers (see Fig. 1) and disappeared during weight loading.

When the patient was asked to extend his lower extremities against gravity a similar 10–11 Hz activity was observed in the quadriceps (Fig. 1). The same frequency was also observed when the patient was asked to contract his facial muscles. During recordings with muscle activation, the quadriceps, lower limb, upper limb, and the facial muscles showed episodes of significant left–right coherence (Fig. 2), but no coherence between muscles at different levels of the neuraxis. A review of the raw EMG traces revealed that synchronization between muscles was episodic and would modulate across muscle groups throughout the recording (Fig. 3).

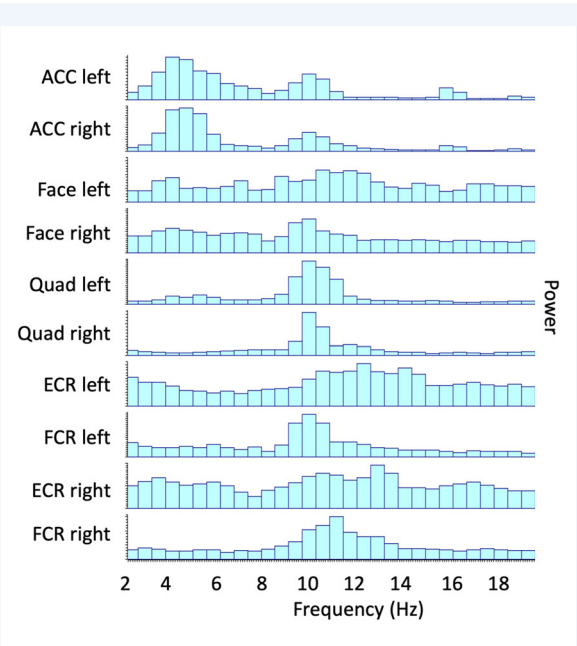


FIG 1. Tremor frequency characteristics during posture with arms supported. EMG data were rectified before processing. Both EMG and ACC data were converted into the frequency domain using a Fast Fourier Transform. Each part of the figure is power which is autoscaled to similar maximum values. A peak at about 10 Hz is seen in most traces, best defined in the quadriceps bilaterally.

Discussion

Here we report the first electrophysiological characterization of a tremor syndrome in a human individual with a myopathy and a pathogenic *MYH7* variant. Similar to the *MYBPC1* related myopathy-tremor syndrome, this patient with *MYH7* related tremor syndrome only had mild myopathic findings including axial rigidity. Interestingly, the tremor phenotype in this patient resembles the description of tremor in the animal model with an *MYH7* variant in the same general coiled-coil tail region of the protein. The presence of the 10–11 Hz component, without change during progressive weight loading, rules out the possibility of an enhanced physiological tremor.[10] We do find that the 5 Hz component is sensitive to weight loading, indicating that there is some peripheral tremor present in addition to the 10–11 Hz component. The prominent involvement of facial and leg muscles makes it unlikely that this is a case of essential tremor. Although there was family history of tremor in one grandfather, we do not have more information about the characteristics of that tremor so is difficult to derive any conclusion from that.

The only tremor other than functional tremor in which there is left–right coherence is orthostatic tremor (OT), but this type of tremor has a higher frequency (12–18 Hz).[11] The patient's tremor may share some similarities with a slow OT that has been previously described, which can have a frequency in the same range (10–11 Hz) and have right–left coherence (although the level of coherence is lower than in classic OT[12]). However, both classic and slow OT are tremors that characteristically appear only during standing, which is not the case here.

In all muscles tested the frequency was similar (10–11 Hz) but not the same. Thus, we cannot explain the tremor as coming from a single oscillator (as in OT). We did find episodes of synchrony between muscles of the same spinal segment (left–right quadriceps), but not between segments. A possible explanation for this phenomenon is that the tremor originates at the sarcomere level within muscles which is picked up by muscle spindles and leads to activating input to the neuraxis segment, as it was proposed by us in[5] for the *MYBPC1* variants. This event could then be enhanced by spinal reflexes, which would explain the observed segmental synchrony, although the absence of clearly

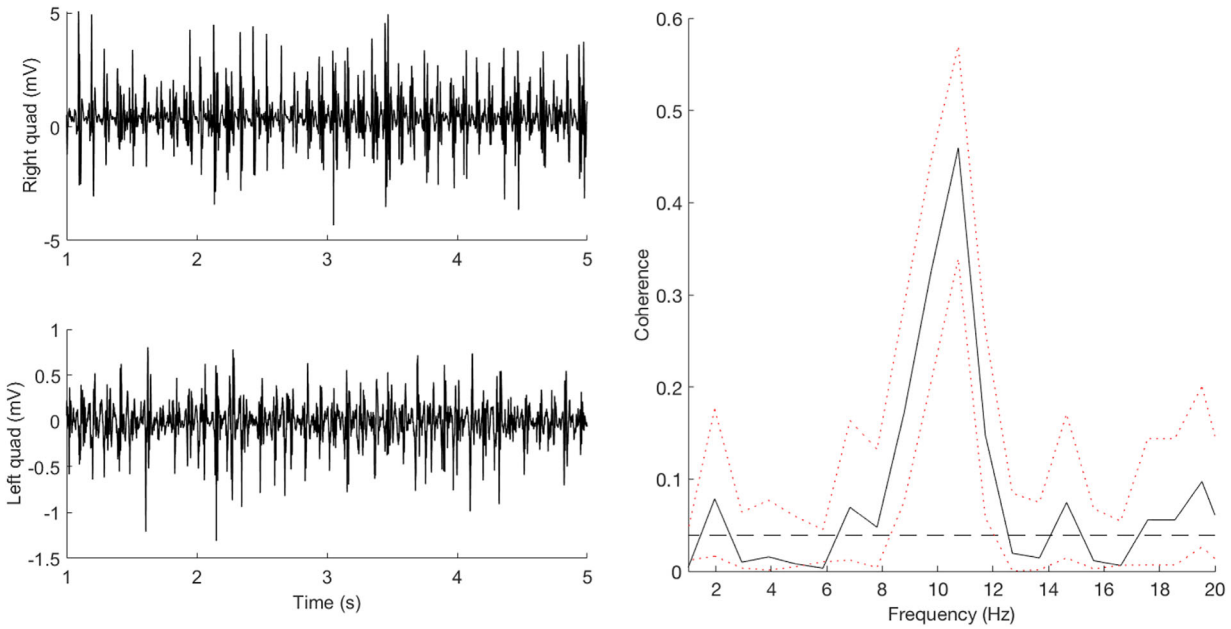


FIG 2. Raw EMG traces (left) for the left and right quad with legs raised against gravity while seated and coherence between these two muscles (right).

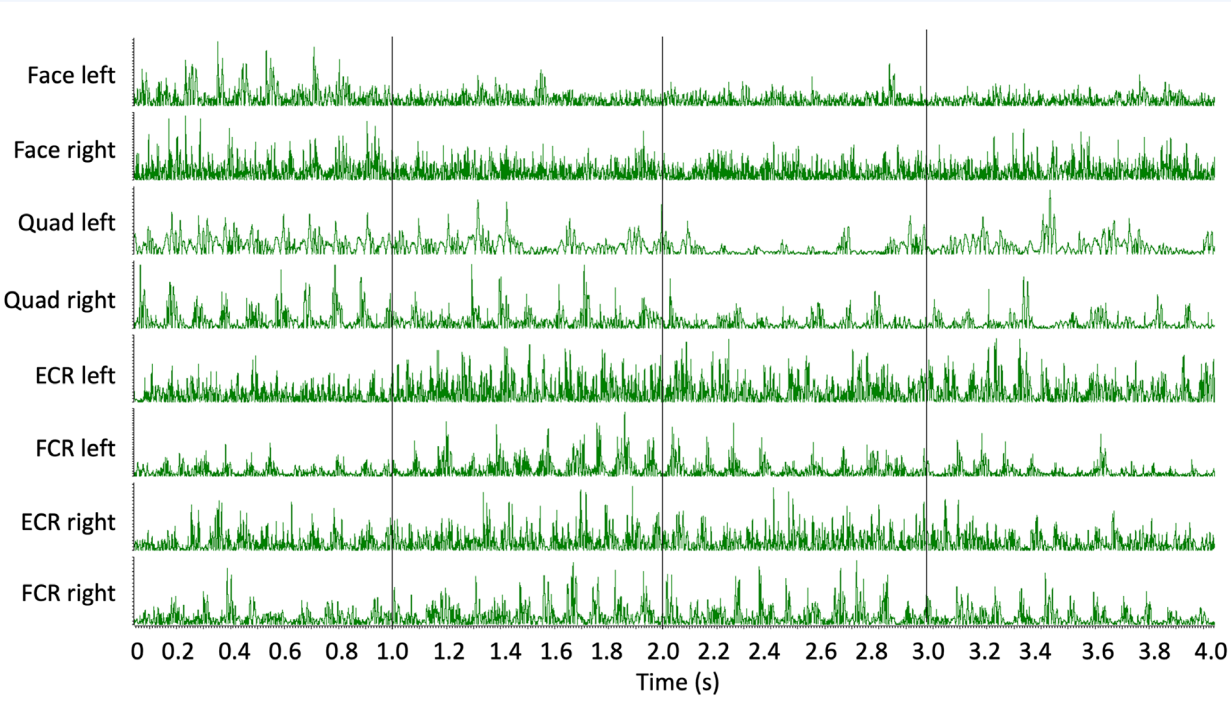


FIG 3. Raw EMG traces for all recorded muscles with arms and legs raised against gravity while seated. The vertical black bars indicate periods of 1 s.

elicitable reflexes makes this hypothesis less likely. Alternatively, the muscle input could activate a segmental generator.

Evidence to oppose the hypothesis of enhancement via spinal reflexes is the decreased tendon reflexes which argues against segmental hyperactivity, but in myopathies tendon reflexes are often decreased. In addition, routine electrophysiological studies did not show any sign of neuropathy, so that cannot be an explanation. The stability of the tremor frequency on the other hand does suggest the presence of central oscillators at the segmental level. Further studies will be needed to determine the origin of myogenic tremor and to better understand the pathomechanism and to identify avenues for therapeutic intervention.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

P.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
F.V.: 1A, 1B, 2A, 3A, 3B.
T.O.: 2A, 2B, 2C, 3A, 3B.
D.E.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
S.T.I.: 1A, 1B, 1C, 3A, 3B.
S.D.: 1A, 1B, 1C, 3A, 3B.
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K.C.C.: 1A, 1B, 1C.
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D.H.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
M.H.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

Disclosures

Ethical Compliance Statement: This study was approved by the National Institutes of Health (NIH) Combined Neurosciences Institutional Review Board. All study procedures were verbally described to the patient, and Informed consent was subsequently obtained in writing. All authors affirm that they have read and complied with the Journal's Ethical Publication Guidelines. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that to the best of our knowledge this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1. Supplementary Information