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Adult-Onset Leg Dystonia Due to a Missense Mutation in *THAP1*

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THAP1 encodes a transcription factor that contains an atypical zinc finger domain and regulates cell proliferation in the context of cell cycle progression.[1] An Exon 2 insertion/deletion frameshift mutation in *THAP 1* produces DYT 6 dystonia in Amish-Mennonites.[1] Two early, follow-up studies identified 11 additional sequence variants in familial, primarily early-onset, primary dystonia.[2] More recently, a heterogeneous collection of *THAP1* sequence variants has been associated with varied anatomical distributions and onset ages of both familial and sporadic primary dystonia. Adult-onset dystonia characteristically begins in the craniocervical or brachial areas and tends to remain confined to these regions, whereas dystonia manifesting before the age of 30 usually starts in a leg or arm and then becomes more generalized.[3] Peripheral trauma and other sensorimotor perturbations may induce dystonia in genetically predisposed individuals.[4,5] Adult-onset focal lower extremity dystonia usually involves foot inversion.[6]

A 63-year-old, right-handed American man of Danish ancestry, and without known Amish-Mennonite roots, presented with a 12-year history of gait difficulties, initially manifesting as intermittent “flopping” of his left foot and paresthesias over the lateral aspect of his left leg. He had not undergone lumbo-sacral spine surgery. Over time, the patient began to notice that his left leg would feel “tight, like a bow” while ambulating. He also found that he would “need to walk quicker to feel more stable.” Indeed, his wife has noticed that he seems to walk at a “double-step” now. He has not found other gait adaptations that will alleviate his problem nor is a diurnal variation apparent; the feeling of “tightness” in his leg is only apparent while ambulating. A couple of years before presentation, the patient retired from the post office, because of deterioration in his handwriting, associated with “shaking” and a feeling of “tightness” in his forearm and hand. The latter has not been alleviated by alcohol consumption or writing in different positions. The patient does not have much difficulty

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

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with tasks, such as eating, pouring, or dressing. His deceased father was diagnosed with "torticollis" after sustaining a neck injury at age 16, and a living, paternal aunt developed "neck shaking and twitching," allegedly after undergoing thyroid surgery in her 20s. The patient's examination was notable for mild, left L5/S1 distribution weakness. His gait revealed excessive contraction of his left hamstrings and gastrocnemius as he made a step with his left leg; having him walk backward and run did not alleviate his gait dysfunction notably (see video, segment 1). The patient had a severe writing tremor, yet only a subtle postural and action upper limb tremor, and no action tremor on pouring (see video, segments 2 and 3), suggesting that his writing tremor is likely dystonic. No adventitial neck movements or abnormal cervical or upper limb postures were evident. Electromyography revealed evidence of a relatively mild, quiescent, left L5/S1 radiculopathy. Sequencing of *THAP1* in the forward and reverse directions revealed a c.446T>C sequence variant, producing substitution of a strongly hydrophobic isoleucine residue with a threonine (l149T) in the nuclear localization signal domain of *THAP1*. The patient's paternal aunt, alluded to above, was found to harbor the same c.446T>C sequence variant. The patient has not responded to a levodopa trial and has not been interested in pursuing other treatment options, such as botulinum toxin injections.

Our patient's history of present illness, family history, neurologic and neurophysiologic examinations, and *THAP1* mutation demonstrate that adult-onset, primary dystonia may begin in a lower extremity, may not be associated with foot inversion, and reinforces that the anatomic site of onset of a primary dystonia may be influenced by trauma and/or a structural lesion, potentially producing a multifocal dystonic state.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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