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Dystonic cerebral palsy like presentation caused by a novel *TCF20* variant

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Dear Editor,

Cerebral palsy (CP) is a group of non-progressive disorders of posture and motor impairment resulting from injury to the developing brain [1]. Dystonic CP is characterized by sustained, repetitive, and patterned movements such as twisting of the trunk or the extremities. Often, there is sudden increase in tone associated with movements or emotion. Differential diagnosis of dystonic CP is broad and includes movement disorders, neurodegenerative, neuromuscular, and

neurometabolic conditions. Many inherited conditions such as Leigh syndrome, pyruvate dehydrogenase deficiency, glutaric aciduria type 1, dopa responsive dystonia, and Rett syndrome can be misdiagnosed as dystonic CP. With the availability of next generation sequencing and frequent utilization of genetic tests, many individuals with a previous diagnosis of dystonic CP will be diagnosed with an inherited slowly progressive neurodegenerative disorder or a neurodevelopmental disorder (NDD).We found a novel *de novoTCF20* variant in an 18-year-old girl with learning disability, dysarthria, ataxia, spasticity, and fluctuating dystonia. She was previously diagnosed with dystonic CP.

The patient was born to a then 33-year-old primigravida mother. There were no pregnancy complications. She was born at 42 weeks gestation by spontaneous vaginal delivery. She weighed 7 pounds 2 ounces (15^{th} centile) and was 21 inches (70^{th} centile) in length. There were no complications during the delivery. She had mild jaundice that required phototherapy. Otherwise, the neonatal period was unremarkable. The patient attained her early developmental milestones mostly on time. However, she had a mild speech delay and slurring of speech.As a toddler, her parents noticed that she had trouble getting up from a sitting position and had an abnormal gait compared to her peers. She was enrolled in early intervention services and received physical, speech, and occupational therapies. The patient went to a regular school. She was diagnosed with learning disabilities andhad an individualized education plan. Shegraduated from high school with special assistance and plans to attend a technical school. During her teenage years, she started to develop spasticity and dystonia of lower limbs. Her dystonia was more noticeable after exertion. She was referred to neurology for dystonia evaluation. MRI of the brain and spine were unremarkable. A diagnosis of dystonic CP was made. The patient was then referred to the physical medicine and rehabilitation department. She was given botulinum toxin

injections for spasticity. Due to fluctuating nature of dystonia, a genetic cause was suspected leading to genetics referral at 18 years old. At her genetics evaluation, dysarthria, and gait imbalance due to spasticity and dystonia of lower limbs were noted (Figure 1). Because of the history of learning disability and speech delays, genetic conditions such as a chromosomal structural defect ora monogenic neurodevelopmental disorder were suspected. Whole genome sequencing showed a novel *de novo*variant, c.792C>A (p.Tyr264Ter) in *TCF20*. This variant introduces a premature termination codon in exon 2 of the *TCF20* gene and is expected to result in loss of function, which is a known disease-causing mechanism for *TCF20* related NDD.This variant is pathogenic based on ACMG variant classification guidelines, as it is a nonsense variant in a gene where loss of function is disease-causing mechanism (PVS1) and is de novo in the patient with no family history of disease (PS2) [2]. In addition, this variant is absent from the gnomAD database version 4.0 (PM2) [3].The minimum on-target average read depth reported by the performing laboratory is 30X.

*TCF20*encodes a chromatin-binding protein that regulates gene expression. *TCF20* was first associated with autism spectrum disorder [4]. However, later it was found to be associated with a NDD of varying severity [5]. The core findings of *TCF20* related NDD are developmental delays, variable intellectual disability, hypotonia, structural brain abnormalities, and neurobehavioral abnormalities. Subtle but nonspecific dysmorphic facial features have been described [5,6]. In addition, movement disorders such as gait abnormalities, paroxysmal dyskinesia, tremors, and ataxia are reported in some individuals [5, 6]. Most of the patients were diagnosed in childhood. However, a few were adults at the time of diagnosis [6]. Two individuals with dystonia as the presenting clinical feature were diagnosed in adulthood [7]. One of them was 43-year-old at diagnosis. He had history of speech delay and learning disability as a child like our patient. The

other individual was 21-year-old at diagnosis. She had gait abnormality from early childhood in addition to spasticity and dystonia that worsened with stress very similar to our patient.

TCF20 was found to be essential for neurogenesis in the developing mouse brain [8]. A recent study showed that the Rett syndrome protein "MeCP2' interacts with TCF20 [9]. MeCP2 and TCF20 are highly co-expressed in neurons and regulate many neuronal genes. Movement disorders are prevalent in Rett syndrome as well. MeCP2-TCF20 interaction might explain the similarity of clinical features between Rett syndrome and *TCF20* related NDD.

Although*TCF20* related NDD is known to be associated with movement abnormalities, we have described here anindividual with a novel *TCF20* variant who was initially diagnosed with dystonic CP. The findings in our patient suggest that *TCF20* related NDD can primarily present with tone abnormalities and may be misdiagnosed as dystonic CP.

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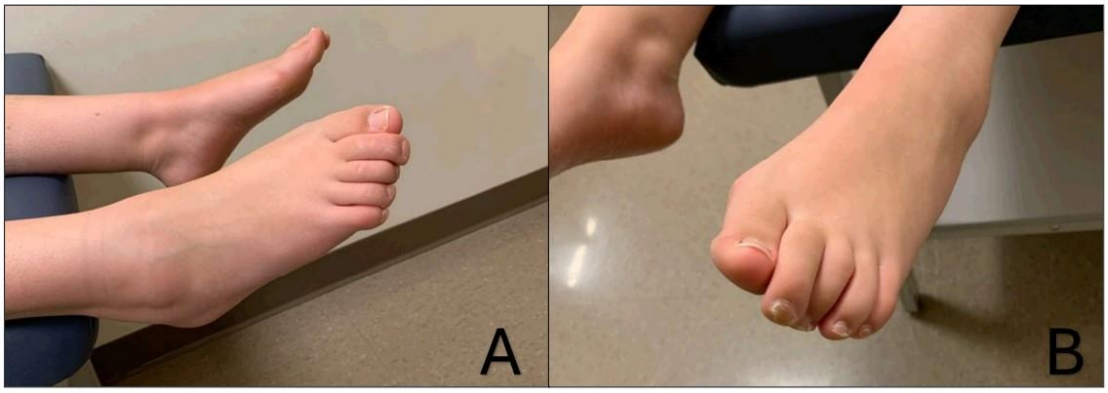

Figure 1: Flexion of right ankle (A) and toes of left feet (B) during episodes of dystonic posturing.

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