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## Letter to the Editor: New Observation

# Novel *GNB1* Variant and the Development of Spastic Diplegic Cerebral Palsy

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Cerebral palsy (CP) comprises a group of nonprogressive disorders of movement or posture of early onset and is associated with a wide spectrum of comorbidities, including but not limited to, intellectual disability, epilepsy and behavioral disorders. Historically, environmental risk factors, including premature birth, difficult delivery and preeclampsia, have been associated with CP development.[1] Recently, genetic etiologies as potential causal agents or modifiers of CP have grown in importance. A recent study where whole-genome sequencing was performed on 327 children with CP showed that 11.3% of these children had pathogenic/likely pathogenic variants and that 17.7% had variants of unknown significance.[2] *ATL1, SPAST, CACNA1* and *ATM* are among the most reported genes in individuals with CP.[3]

This case report aims to first highlight the *GNB1* variant as a potential causal agent of spastic diplegic cerebral palsy, as *GNB1* variants are more commonly associated with hypotonic features not traditionally labeled as "CP" and second to emphasize the importance of a "genotype-first" approach when diagnosing individuals with CP. This implies that genetic testing should be promptly attempted in patients with clinical features traditionally suggestive of CP, but with normal MRI studies in the absence of a readily evident acquired etiology, and perhaps considered when imaging findings do not align with a putative etiologic risk factor.

The patient is a seven-year-old female who was initially referred for specialty evaluation of spastic diplegia at the age of four. Prior to initial consultation, the patient was followed in Iran by specialists, where several investigations were conducted including a head MRI and electromyography, both of which were normal.

The patient's parents originate from Iran without evident consanguinity. Her father is known for "flat feet" but is otherwise healthy as is her mother. On the paternal and maternal sides of the family, there is no family history of seizures or neurodevelopmental disorders including CP.

The patient was born to a primigravida mother with protective serologies and no antenatal exposure to medication, alcohol, drug or tobacco. The pregnancy was uncomplicated, and the patient was born at 37 weeks of gestation via a planned elective cesarean section, as per the mother's choice. There was no history of perinatal adversity or need for resuscitation. The patient displayed mild jaundice in the neonatal period, which resolved with one day of phototherapy.

The patient walked late at the age of two and a half years. At the time of the initial referral, the patient was four years old and could ambulate independently with her shoe braces, but not without them. She could not jump nor stand from the floor independently. Fine motor development revealed that she could scribble, draw circles and feed herself. The patient said her first word prior to 12 months of age and was making short sentences by age two. At the age of four, she spoke Farsi with good comprehension and was learning French and English at daycare. Behavioral development revealed that she made good eye contact and demonstrated reciprocity with others. Cognitively, she understood complex commands and knew her numbers up to 10.

During our initial consult, general physical examination was normal except for a musculoskeletal examination of the lower limbs, which revealed mild hip flexion and adduction contractures, mild knee flexion contractures and symmetrically severe ankle plantar flexion contractures. Neurological examination revealed significant spasticity of the lower extremities with concurrent symmetric brisk reflexes graded as 3+, with positive cross adductors and spread. She had clonus in both ankles. She had decreased bulk in her calves. The patient had normal axial tone with spastic scissoring.

Based on these clinical findings, a 3 T magnetic resonance imaging (3T MRI) of the spine and the head were undertaken, which were both normal. To rule out a genetic cause, whole exome sequencing was undertaken afterward with *Prevention Genetics*. A potential pathogenic mutation was confirmed with targeted testing via *GNB1* gene sequencing with the patient identified as heterozygous for a sequence variant identified as NM_002074.4, c.158G>A, p.Gly53Glu. This variant is known to be autosomal dominant and pathogenic and has been associated with global developmental delay, intellectual disability, seizures and autism spectrum disorder. *GNB1* sequencing in either parent did not document any variants in the *GNB1* gene, thereby confirming that our patient has a *de novo* variant.[4]

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*GNB1*, or guanine nucleotide-binding protein beta 1, encodes for a G-protein β subunit (Gβ1), which complexes with the α and γ subunits to form a heterotrimeric G-protein-coupled receptor.[4] Gβ1 is highly expressed in the cranial neural plate, neural tube, spinal cord and limb buds during embryogenesis.[5] Using mice deficient in the *Gβ1* gene, it was shown that about 40% of knocked-out embryos had abnormal actin organization in the basal side of the neuroepithelium, potentially impairing neural tube closure and neural progenitor cell proliferation.[5] From these results, we hypothesize that *GNB1* pathogenic variants in humans might lead to an abnormal neural development, most likely contributing to the pathogenesis of an observed CP phenotype.

A 2018 literature review, which presented 18 patients with *GNB1* variants, reported that all but 3 of the patients within this cohort had hypotonia in infancy, which made hypotonia the most common neurological phenotype across patients with *GNB1* variants. In this cohort, a two-year-old male patient, with the same *GNB1* variant as the patient described in this case report (c.158G > A), was reported.[4] Both patients had spasticity in the lower limbs, brisk tendon reflexes, no perinatal and birth complications and a normal MRI; however, in distinction to our patient, the two-year-old was noted to have multiple dysmorphic features and axial hypotonia. Importantly, no mention of the *GNB1* variant with a p.Gly53Glu amino acid substitution as a potential contributor to the phenotype of spastic diplegic cerebral palsy was made in previously reported cases, which highlights the novelty of this described gene-phenotype association.[4]

Current clinical challenges in the diagnosis of CP include when should genetic testing be undertaken and what genes should be tested for. Our case report provides emerging support for two clinical insights: to consider a *GNB1* variant in patients with spastic diplegic features and the importance of promptly completing genetic testing as part of the diagnostic workup of CP when detailed MRI studies are normal and in the absence of an evident acquired etiology. A genotype-first approach may have drawbacks, particularly due to the limitations of our current understanding of precise disease-gene associations when interpreting genomic sequencing data. Some children may only be diagnosed years later as novel gene-phenotype variants are continuously being discovered. Despite being limited by our present genetic knowledge, it is expected that this approach will become increasingly evident in facilitating earlier diagnosis of CP and improving functional outcomes, as new disease-gene associations are continuously being described in the literature.

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**Competing interests.** None.

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