


Myoclonus-Dystonia in an Individual with a Mutation in the *GRIN2A* Gene

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Abstract

Keywords

- *GRIN2A*
- pediatric movement disorders
- hyperkinetic
- myoclonus
- dystonia

Mutations in the *GRIN2A* gene are associated with epilepsy-aphasia spectrum disorders and developmental and epileptic encephalopathies. Associations have been linked with disorders, including autism spectrum disorder and Parkinson's disease. Recently, *GRIN2A* variants have been reported as a cause of movement disorders in individuals without epilepsy, suggesting that movement disorders should be highlighted as a genetic phenotype associated with pathogenic variants in *GRIN2A*. We present a case of a male with myoclonus dystonia and without epilepsy found on whole-exome sequencing to have a c.1880G > A; p.S627N variant in the *GRIN2A* gene. Our case contributes to the expanding phenotypic spectrum of *GRIN2A*-related disorders and highlights another genetic cause of the myoclonus-dystonia phenotype. *GRIN2A* should be considered a part of the differential diagnosis of myoclonus-dystonia in individuals with developmental delay without epilepsy.

Introduction

N-methyl-D-aspartate receptors (NMDARs) consist of 2 GluN1 and 2 GluN2 subunits. The *GRIN1* and *GRIN2A-2D* genes encode the GluN1 and GluN2 subunits, respectively.¹ The GluN2A subunit of the NMDAR is expressed throughout the brain and is important for functions including brain development and synaptic plasticity.^{1,2}

Mutations in *GRIN1* and *GRIN2A-GRIN2D* have been associated with neurologic disorders.^{1,3} *GRIN2A* mutations are found in 9 to 20% of probands with epilepsy aphasia spectrum (EAS) disorders, including individuals with Landau-Kleffner syndrome (LKS) and epileptic encephalopathy with continuous spike-wave during slow-wave sleep (ECSWS).^{4–7} Individuals with *GRIN2A* mutations and epilepsy have been affected predominantly by speech and language impairment (100%),^{7–9} epilepsy (90%),^{7,9–11} and intellectual disability (38–67%).^{4,7,9,11}

In contrast, *GRIN1* and *GRIN2B* variants have been linked to severe epileptic encephalopathy syndromes, intellectual disability/developmental delay, hypotonia, cortical visual

impairment, autism spectrum disorders, and movement disorders (e.g., dystonia, chorea, and dyskinesia).^{7,12–15} GluN2 has been linked genetically with disorders including autism spectrum disorder and Parkinson's disease.^{1,2} All three genes can produce similar effects on NMDAR function.^{2,16} This suggests that these variants should be considered a part of a more extensive set of variants.^{2,16}

Recently, mutations in the *GRIN2A* gene have been reported in patients with nonepileptic neurodevelopment delay and movement disorders.^{7,9,17,18} This suggests that movement disorders should be highlighted as a genetic phenotype associated with pathogenic variants in *GRIN2A*.

We present a case of a child, with myoclonus-dystonia and tremor phenotype with a history of developmental delay and without epilepsy, who was found to have a *GRIN2A* variant.

Case Report

The patient is a 13-year-old biracial non-Hispanic male with mild global developmental delay and coordination difficulties who presented to the outpatient pediatric movement

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disorders clinic for evaluation of hyperkinetic movements described as long-standing tremors and body jerks. His past medical history was notable for receptive and expressive language delay, esotropia, febrile seizures, and attention deficit hyperactivity disorder (ADHD). He was conceived by nonconsanguineous parents. The pregnancy was complicated by preeclampsia. He was delivered by cesarean section for failure to progress. Admission to the neonatal intensive care unit was not required. Gross and fine motor skills were delayed. He sat at 8 months, crawled at 9 to 10 months, and began walking at 18 months. His first words were at 2 years of age, and he began using two- to three-word sentences at 3 years of age. Early intervention services started at 18 months with physical therapy, occupational therapy, and speech therapy. His family history was notable for progressive supranuclear palsy-like disorders, Alzheimer's disease, and migraines. Physical examination at the initial evaluation demonstrated frequent irregular myoclonic jerks primarily in the trunk and upper extremities, motor imper-sistence with arm and finger extension and dystonia with writing and walking. There were no tremors on initial examination in the movement disorders clinic. However, prior records note postural and limb kinetic tremor history of onset since toddler age. On subsequent examinations, he demonstrated both postural and limb kinetic tremor. His speech was articulate and clear, and his language was fluent and coherent. The tone and prosody were restricted. His workup included normal basic metabolic blood and urine laboratory tests, electroencephalogram, and magnetic reso-nance imaging of the brain. He underwent genetic testing with normal karyotype, chromosomal microarray, and nor-mal sequencing of the SCGE gene. Whole-exome sequencing revealed a likely pathogenic heterozygous variant in the *GRIN2A* gene (p.Ser627ASN [AGC > AAC]: c.1880 G > A in exon 10 of the *GRIN2A* gene [NM_000833.3]). He was started on carbidopa-levodopa treatment which improved dysto-nia, fine motor skills, and physical endurance.

Discussion

The glycine- (GluN1) and glutamate-binding (GluN2A-D or GluN3A-B) subunits of the NMDARs form a Ca²⁺-permeable cation channel which extracellular Mg²⁺ can block.^{1,3} Unlike *GRIN1*- and *GRIN2B*-related disorders, which are associated with movement disorders,^{2,9,12-14} *GRIN2A* mutations are considered predominantly associated with speech and language impairment, epilepsy, and intellectual disability.^{4-8,11}

Previous analyses of *GRIN2A* mutations indicate that the agonist binding domain and transmembrane domain of GluN2A are particularly intolerant to genetic variation.¹⁶ Missense mutations in the transmembrane domain pre-dominantly lead to gain of function and are associated with more severe phenotypes.^{3,9} In addition, missense mutations in the transmembrane domain may affect the formation of the ion channel, reducing inhibition by Mg²⁺.

Our patient has a history of neurodevelopmental delay, speech difficulties, and ADHD which can be present in many

Table 1 Reported cases of individuals with *GRIN2A* mutations with a movement disorder and without epilepsy

Publication	Our case	Fernández et al ¹⁷	Fernández et al ¹⁷	Nicotera et al ¹⁸	Strehlow et al ⁹	Strehlow et al ⁹	Strehlow et al ⁹	Yoo et al ¹⁹
Gender	Male	Male	Female	Male	N/A	N/A	N/A	Female
Age (y)	12	12	8	21	N/A	N/A	N/A	13
Age at onset of movement disorder (mo)	15	19	20	Early life	N/A	N/A	N/A	N/A
Age at testing (y)	9	6	2	18	N/A	N/A	N/A	9
Pathogenic variant	p.Ser627Asn	p.Ala643Asp	p.Ala643Asp	p.Glu1055Gln	p.Asn614Ser	p.Asn614Ser	p.Arg695Gln	p.Thr749Ile
Movement disorder	Myoclonus-dystonia, tremor	Generalized dystonia	Generalized dystonia, tremor	Generalized dystonia (predominantly head and neck)	Chorea, hand stereotypies	Dyskinetic movement disorder	Ataxia	Stereotyped hand movements
Speech/language	Fluent spontaneous speech with age-appropriate vocabulary and fund of knowledge; restricted prosody and tone; articulation normal	Reduced vocabulary, expressive language difficulties	Articulation difficulties	Restricted to vocalization	Aphasia	Aphasia	Dysarthria, imprecise articulation	Normal
Intellectual disability/developmental delay	Mild	Moderate	Mild	Severe	Profound	Profound	Moderate	Mild
Treatment	Carbidopa-levodopa	N/A	N/A	Clonazepam	N/A	N/A	N/A	N/A

Abbreviation: N/A, not available.

neurodevelopmental disorders. He had a history of febrile seizures and did not have epilepsy. The family reported a long-standing history of tremors and body jerks but on examination was found to have myoclonus-dystonia and tremors, highlighting the importance of a careful neurological examination, and defining the phenomenology of movements observed. The presentation of these movements and motor coordination challenges are common features in *GRIN1*- and *GRIN2B*-related disorders^{14,15} but are not usually present in *GRIN2A*.^{9,17,18} The similar features reinforce that *GRIN* variants should be considered as an extensive set of variants.²

Similarly, Strehlow et al⁹ identified movement disorders in 26.4% (19/72) of individuals with previously unreported likely pathogenic *GRIN2A* mutations. 84.2% (16/19) of individuals were found to have epilepsy and a movement disorder. Also, 56.3% of (9/16) individuals had ataxia, which was the predominant phenotype, with the remaining patients having a spectrum of dystonia, chorea, and an unspecified movement disorder. The remaining three patients did not have epilepsy and had a normal electroencephalography (► **Table 1**). Other case series have reported individuals with dystonia and gait difficulties and concurrent tremor or dyskinesia without evidence of epilepsy.^{17,18}

Upon reviewing an open-access online database (<http://www.grin-database.de/>),⁹ 1 individual out of 222 had repetitive hand movements and loss of gait without epilepsy, speech/language delay, or fine motor delay.^{9,19}

The most common phenotype reported in prior studies with *GRIN2A*-related disorders was ataxia,⁹ followed by dystonia^{9,17,18} and chorea.⁹ Individuals with myoclonus-dystonia and tremor phenotype have not been previously reported. Further studies will be important to highlight this aspect and link myoclonus and other movement disorders to *GRIN2A*.

Conclusion

Our case reinforces the association between *GRIN2A* mutations and neurodevelopmental and speech delay while expanding the phenotype to include movement disorders (i.e., myoclonus-dystonia and tremor). We suggest that *GRIN2A* variants be on the differential when seeing an individual without epilepsy with a myoclonus-dystonia phenotype.

Conflict of Interest

X.A.Q.: no conflicts of interest.

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N.S.: no conflicts of interest.

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