

Identification of a Novel Mutation in *GRIN2A* Gene with Global Developmental Delay and Refractory Epilepsy

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Abstract

We report a 2.5-year-old Turkish boy who first presented with nystagmus, lack of eye contact, and hypotonia at 2 months of age and developed refractory seizures when 6 months old. Extensive metabolic tests and imaging being noncontributory, whole-exome sequencing was carried out which revealed a heterozygote *NM_001134407.2:C.3299A>G (p.Glu1100Gly)* novel mutation in *GRIN2A* gene. Topiramate was started and seizures were rapidly brought under control. *GRIN2A* mutations may result in altered GluN2A membrane trafficking and response to glutamate. This report illustrates the clinical variability of *GRIN2A* mutations according to the age of onset of symptoms and suggests considering mutations in this gene in cases of global developmental delay, refractory epilepsy, and nystagmus.

Keywords: Epilepsy, *GRIN2A*, neurodevelopmental delay, nystagmus, whole-exome sequencing

INTRODUCTION

Genetic mutations causing epilepsy are numerous, including mutations of *GRIN2A* which encodes GluN2A, a transmembrane ligand-gated ion channel and a subunit of the N-methyl D-aspartate receptor (NMDAR).^[1] NMDARs get activated by binding of glutamate to the GluN1 and GluN2 subunits, which results in calcium influx into the cell. Hence, epilepsy develops from altered GluN2A membrane trafficking and response to glutamate caused by *GRIN2A* mutations.^[2] GluN2A has a critical role in normal neuronal development, synaptic plasticity, and memory.^[3] Furthermore, genetic associations of the *GRIN2A* gene with autism,^[4] schizophrenia,^[4] Huntington (the polymorphism in *GRIN2A* and *GRIN2B* gene has been reported^[5] as the factors that affect clinical polymorphism as well as the starting age of Huntington disease.) and Parkinson (where the risk of Parkinson disease was reported^[6] to be lowered in association with caffeine intake as well as the interaction of this association with *GRIN2A* genotype) diseases have been reported.

We describe a patient with refractory seizure develop after neurodevelopmental delay and nystagmus who was found to carry a *GRIN2A* mutation and compare with the existing clinical reports in the literature.

CASE REPORT

This study reports the case of currently 2.5-year-old Turkish boy first presented with nystagmus and global developmental delay at 2 months of age. Prenatal and perinatal histories were unremarkable. Parents were consanguineous (1st cousins) and healthy. On examination, the patient had normal weight, length and head circumference, no dysmorphic features, bilateral horizontal nystagmus (nystagmoid eye movements showing oscillations at equal speed in both directions in the horizontal plane), no eye contact with normal ophthalmological findings, hypotonia, brisk deep-tendon reflexes, and global developmental delay. At 6 months of age, seizures developed consisting of the sudden eye and head deviation followed by tonic-clonic movements of the extremities. Levetiracetam (50 mg/kg), clonazepam (1 mg/kg), and phenobarbital (5 mg/kg) were initiated consecutively with no complete control of seizures where phenobarbital level was measured as normal. His routine blood tests, metabolic tests (ammonia, lactate, blood gas, tandem-mass, urine organic acid, lysosomal tests, peroxisomal test), chromosomal analysis, and microarray results were normal. Electroencephalography obtained at that time had spike and slow wave discharges from the right parietooccipital region [Figure 1]. Magnetic resonance imaging showed a thin corpus callosum and mild brain atrophy [Figures 2 and 3]. Visual evoked potential study presented mildly prolonged P100 wave latency. Whole-exome sequencing (WES) demonstrated a

heterozygote *NM_001134407.2:C.3299A>G (p.Glu1100Gly)* novel mutation in *GRIN2A* gene which has not been reported previously. Therefore, 5 mg/kg topiramate treatment was started. However, the patient responded at 9 mg/kg topiramate. Testing of the parents showed a heterozygote mutation in the father and none in the mother. *In silico* analysis was made with DANN, GERP, LRT, MutationAssessor, MutationTaster, and PROVEAN *in silico* analysis programs and variant was predicted as pathogenic. Population frequency is zero in all populations but 1/111,601 in European population in ExAC database. There is no report on its pathogenicity and the variant was not reported in any affected person. The patient is presently seizure-free with topiramate and home mechanical ventilation.

The study was approved by the Clinical Research Ethics Committee of the Mersin University Rectorate. Informed consent was obtained following a full explanation of the treatment provided.

DISCUSSION

Advances in molecular genetics allow for the identification of responsible genes in patients with refractory seizures and developmental delay. However, genotypic and phenotypic diversity can complicate the establishment of a definite genetic diagnosis. The genes that encode NMDAR subtypes were first described in 1993.^[7] Endeley *et al.*^[8] reported cases with refractory seizures, learning disability, and neurodevelopmental disorder with heterozygous mutations in the region coding *GRIN2A* gene. Further studies on *GRIN2A* mutations often revealed refractory seizures and mental retardation. Our case differs from those above by the first manifestation being hypotonia, developmental delay, and nystagmus, seizures starting later. Venkateswaran *et al.*^[11] reported a case who presented with refractory seizures at 2-year-old whose global developmental delay and visual defect had been noticed at 14 months of age. Our case had earlier onset. Seizures uncontrolled by levetiracetam, clonazepam, and phenobarbital responded to topiramate started once *GRIN2A* gene mutation was identified. Seizures are expected to respond to topiramate because it blocks

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NMDARs and activates gamma-aminobutyric acid receptors. On the other hand, a recent study presented four patients with *GRIN2A* mutations of whom only one had improved seizure control under topiramate treatment.^[9] Our case highlights that clinical findings of NMDAR defects and *GRIN2A* mutations might have variable early and late clinical presentations.

This disorder was classified as an autosomal dominant disorder in OMIM database. There are incomplete penetrance and intrafamilial variability, even among family members who

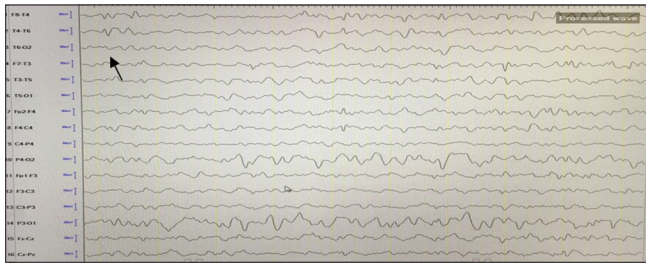


Figure 1: Spike and slow wave discharges from the right parietooccipital region

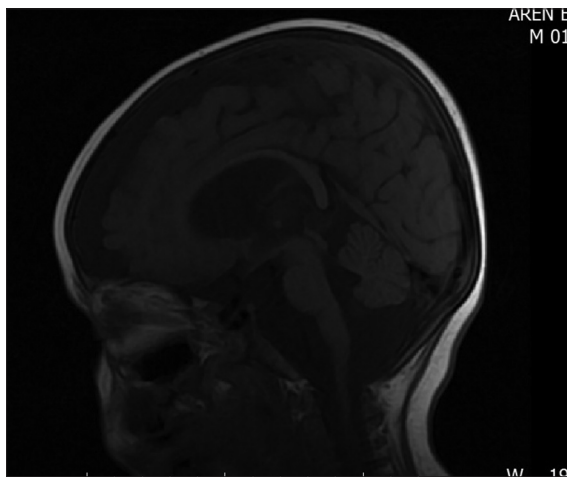


Figure 2: Sagittal view of T1-weighted image showing thin corpus callosum

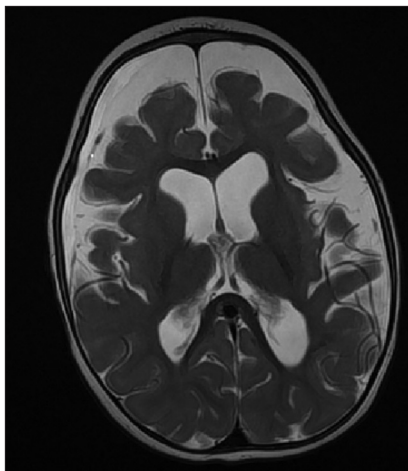


Figure 3: T2-weighted sequence, axial view showing brain atrophy

carry the same *GRIN2A* mutation.^[10-12] As in other idiopathic epilepsies, mutations were occasionally identified in unaffected relatives, suggesting incomplete penetrance. This is the reason the mutation in our patient and his father could not be classified as a “benign variant” despite the father being healthy. Further functional analyses are needed to explore the genotype-phenotype relations.

This report exemplifies the clinical presentation of *GRIN2A* mutations and the role of WES in the diagnosis of refractory epilepsy. Furthermore, it highlights that patients with *GRIN2A* mutation can present a variable clinical spectrum with respect to age of onset, nature of symptoms, and response to treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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