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A Rare Syndrome of *GRID2* Deletion in 2 Siblings

Aravindhan Veerapandiyan, MBBS[1], Stephanie Enner, BS[1], Venkatraman Thulasi, BA[1], and Xue Ming, MD, PhD[1]

Abstract

The Glutamate receptor, ionotropic, delta 2 gene codes for an ionotropic glutamate delta-2 receptor, which is selectively expressed in cerebellar Purkinje cells, and facilitates cerebellar synapse organization and transmission. The phenotype associated with the deletion of Glutamate receptor, ionotropic, delta 2 gene in humans was initially defined in 2013. In this case report, the authors describe 2 brothers who presented with developmental delay, tonic upward gaze, nystagmus, oculomotor apraxia, hypotonia, hyperreflexia, and ataxia. They were found to have a homozygous intragenic deletion within the Glutamate receptor, ionotropic, delta 2 gene at exon 2. Our patients serve as an addition to the literature of previously reported children with this rare clinical syndrome associated with Glutamate receptor, ionotropic, delta 2 deletion.

Keywords

Glutamate receptor, ionotropic, delta 2, ataxia, developmental delay, tonic upgaze

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Glutamate receptor, ionotropic, delta 2 gene located on chromosome 4q22.1 which encodes the glutamate receptor subunit delta-2 is selectively expressed in cerebellar Purkinje cells and is crucial for cerebellar functions.[1] Human phenotype associated with deletions in the Glutamate receptor, ionotropic, delta 2 gene was first described in 2013 with clinical features including cerebellar ataxia, tonic upgaze, nystagmus, and developmental delay.[2,3] The authors describe the clinical characteristics of 2 brothers with this rare syndrome.

Cases

The older brother presented at 7 years of age with developmental delay and ataxia. Developmental history was significant for the following gross motor delays: patient acquired head control at 1.5 years of age, sat without support at 3 years of age, stood with support at 6 years of age, stood without support and walked at 7 years of age. He spoke few single words at 3 years of age and 2-word phrases at 5 years of age. At the age of 7 years, he had a vocabulary of only 50 to 60 words and could use simple 3-word phrases. Currently, at the age of 9 years, he can speak longer sentences, read picture books, write his name, and use an iPad for games. He recognizes colors and alphabets, can follow simple commands, and ambulate with a walker. Neurological examination revealed frequent intermittent tonic upward gaze (Figure 1), vertical and horizontal nystagmus on eye movements, oculomotor apraxia (saccadic initiation failure and impaired voluntary pursuit), severe central hypotonia, hyperreflexia, and limb and truncal ataxia. Musculoskeletal examination revealed thoracolumbar kyphosis and scoliosis. Remainder of the physical examination was within normal limits. The younger brother presented at the age of 4 years with motor and speech delay. He could not sit independently, stand, or walk and could speak only limited single words. He spoke his first words at the age of 2 years. At the present age of 6 years, he can form 2-word phrases, follow simple commands, and ambulate with a walker. Neurological examination showed intermittent tonic upward gaze, vertical and horizontal nystagmus on eye movements, oculomotor apraxia (saccadic

[1] Division of Pediatric Neurology, Department of Neurology, Rutgers New Jersey Medical School, Newark, NJ, USA

Corresponding Author:
Xue Ming, MD, PhD, Division of Pediatric Neurology, Department of Neurology, Rutgers New Jersey Medical School, 90 Bergen Street, DOC 8100, Newark, NJ 07103, USA.
Email: mingxu@njms.rutgers.edu

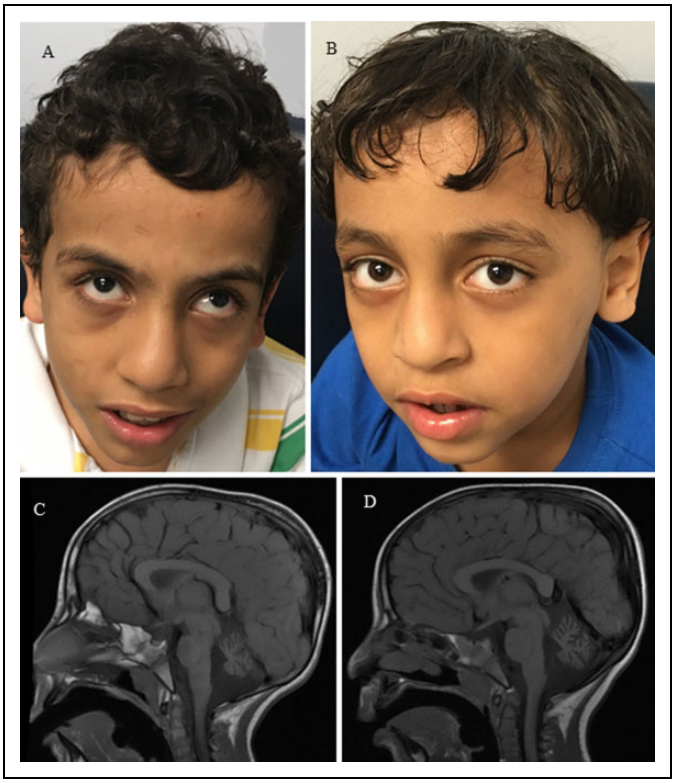

Figure 1. Older (A) and younger (B) brother showing tonic upgaze and their corresponding sagittal T1 magnetic resonance (MR) image showing cerebellar atrophy (C and D).

initiation failure and impaired voluntary pursuit), central hypotonia, hyperreflexia, and limb and truncal ataxia, however, the clinical manifestations were milder as compared to his brother. Remainder of the examination was normal.

Both brothers were born at full-term after an uneventful pregnancy to parents of Egyptian origin from the same village. They were small for their corresponding age at the time of presentation. Medical and family history was otherwise unremarkable. Electroencephalogram testing excluded seizures as possible etiology for intermittent tonic upgaze and nystagmus. Magnetic resonance imaging of the brain revealed cerebellar atrophy (Figure 1). The whole-genome single-nucleotide polymorphism microarray analysis detected a 166-kb homozygous intragenic deletion of the Glutamate receptor, ionotropic, delta 2 gene at 4q22.1 → 22.1 (93, 472, 963—93, 639, 305) involving exon 2. This was confirmed by quantitative polymerase chain reaction. Microarray analysis also revealed extended contiguous regions of allele homozygosity in chromosomes 1, 3, and 4 (33.92 Mb) and chromosomes 1, 3, 4, and 7 (71.30 Mb) in older and younger brothers, respectively, indicating distantly related parentage.

Discussion

Glutamate receptor, ionotropic, delta 2 gene deletions in humans were first described in 2013.[2,3] To the best of our knowledge, 8 patients with Glutamate receptor, ionotropic, delta 2 deletions and similar neurological presentations have been reported to date.[2-4] The homozygous deletion 4q22.1 → 22.1 involving exon 2 detected in our patients was present within a larger 16.01 Mb region of homozygotic stretch (4q21.3q24 [87, 018, 487—103, 213, 305] hmz). Mapping of the deleted region using University of California, Santa Cruz genome browser (http://genome.ucsc.edu/) indicated that Glutamate receptor, ionotropic, delta 2 is the only gene present in that deleted region.[5] Since the deleted region is within a region of homozygosity, which increases the risk of autosomal recessive disorders associated with the genes in that region, and Glutamate receptor, ionotropic, delta 2 is the only gene identified in the deleted region, the authors conclude that this deletion is responsible for the phenotype of our patients. Their asymptomatic parents were presumed to be heterozygous carriers of the deletion.

Biallelic deletions in Glutamate receptor, ionotropic, delta 2 leading to a syndrome of cerebellar ataxia and tonic upgaze were described in 4 children from 2 unrelated families.[2] Three children from a consanguineous family of Jordanian heritage had a homozygous deletion of Glutamate receptor, ionotropic, delta 2 exon 4, whereas the child from the second family of Mexican heritage had compound heterozygous deletions involving Glutamate receptor, ionotropic, delta 2 exon 2. All of the affected individuals exhibited gross motor, speech delays, truncal and appendicular ataxia, tonic upgaze, and nystagmus. Hypotonia was noted only in children with exon 4 homozygous deletion.[2] The 2 brothers described in this report with homozygous deletion involving exon 2 displayed all of these features including hypotonia.

In another study, Utine et al[3] identified homozygous partial deletion of Glutamate receptor, ionotropic, delta 2 exons 3 and 4 in 3 children in 1 large consanguineous Turkish family who presented with cerebellar ataxia, nystagmus, oculomotor apraxia, hypotonia, pyramidal signs, and developmental delay. Interestingly, these children did not exhibit tonic upgaze like our patients. In another study, homozygous deletion of exon 2 (93422866_93754032) of Glutamate receptor, ionotropic, delta 2 was described in a patient with ataxia, dysarthria, nystagmus, tonic upgaze, impaired peripheral vision, and retinal dystrophy.[4] Of note, this deletion overlaps with the deleted region in our patients. However, our patients did not have these reported visual defects.

The role of the Glutamate receptor, ionotropic, delta 2 protein in the human brain is not clearly understood. Extensive studies in mice have demonstrated that its mouse ortholog, Glutamate receptor, ionotropic, delta 2 (Grid2), is primarily expressed in cerebellar Purkinje cells and plays a critical role in synapse organization and modulation of synaptic transmission which is essential for cerebellar development and function.[1,2,6] A recent study illustrated a strikingly similar expression pattern in the developing human cerebellum, which may indicate a similar function of Glutamate receptor, ionotropic, delta 2 in humans.[2] Glutamate receptor, ionotropic, delta 2 loss-of-function mouse mutants show ataxia and mild cerebellar volume loss,[2,7] thus reiterating the clinical

manifestations seen in human counterparts with Glutamate receptor, ionotropic, delta 2 deletions. Additionally, larger spontaneous and random eye movements have been demonstrated in such mice that are comparable to nystagmus seen in humans.[2] The similar role of Glutamate receptor, ionotropic, delta 2 is further supported by an additional study that demonstrated the expression of Glutamate receptor, ionotropic, delta 2 in human and murine retina.[4]

The siblings depicted here are children of Egyptian descent with a syndrome of cerebellar ataxia and tonic upgaze associated with Glutamate receptor, ionotropic, delta 2 deletions. Our patients further add to the repertoire of phenotype associated with Glutamate receptor, ionotropic, delta 2 deletions.

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Author Contributions

AV contributed to conception and design, contributed to acquisition, analysis, and interpretation, critically revised the manuscript, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. SE and VT contributed to design, contributed to acquisition and analysis, critically revised the manuscript, and drafted the manuscript. XM contributed to conception and design, contributed to analysis and interpretation, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy

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