CLINICAL REPORT

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# 1p34.3 Deletion Involving *GRIK3*: Further Clinical Implication of GRIK Family Glutamate Receptors in the Pathogenesis of Developmental Delay

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A growing body of evidence suggests an association between microdeletion/microduplication and schizophrenia/intellectual disability. Abnormal neurogenesis and neurotransmission have been implicated in the pathogenesis of these neuropsychiatric and neurodevelopmental disorders. The kainate/AMPA-type ionotropic glutamate receptor (GRIK = glutamate receptor, ionotropic, kainate) plays a critical role in synaptic potentiation, which is an essential process for learning and memory. Among the five known GRIK family members, haploinsufficiency of *GRIK1*, *GRIK2*, and *GRIK4* are known to cause developmental delay, whereas the roles of *GRIK3* and *GRIK5* remain unknown. Herein, we report on a girl who presented with a severe developmental delay predominantly affecting her language and fine motor skills. She had a 2.6-Mb microdeletion in 1p34.3 involving *GRIK3*, which encodes a principal subunit of the kainate-type ionotropic glutamate receptor. Given its strong expression pattern in the central nervous system and the biological function of GRIK3 in presynaptic neurotransmission, the haploinsufficiency of *GRIK3* is likely to be responsible for the severe developmental delay in the proposita. A review of genetic alterations and the phenotypic effects of all the GRIK family members support this hypothesis. The current observation of a microdeletion involving *GRIK3*, a kainate-type ionotropic glutamate receptor subunit, and the neurodevelopmental manifestation in the absence of major dysmorphism provides further clinical implication of the possible role of GRIK family glutamate receptors in the pathogenesis of developmental delay.



**Key words:** GRIK3; glutamate receptor; developmental delay

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## INTRODUCTION

An emerging paradigm suggests that intellectual disability and schizophrenia are associated with microdeletion/microduplication at several specific genetic loci [Crespi et al., 2010; Malhotra and Sebat, 2012]. This association is best exemplified by the chromosome locus 16p11.2, where microdeletion/microduplication are associated with autism and schizophrenia [Weiss et al., 2008; McCarthy et al., 2009]. These studies have led to the identification of a candidate gene (*KTCD13*) that has been implicated in the cell cycle during neurogenesis [Golzio et al., 2012].

Along with abnormal neurogenesis, the pathogenesis of major neurodevelopmental and neuropsychiatric illnesses involves aberrant neurotransmission. Among the major neurotransmitters, glutaminergic and GABAergic systems play critical roles [Stawski et al., 2010; Niciu et al., 2012]. Both metabotropic and ionotropic types of glutamate receptors are known to exist: the latter has been subclassified into NMDA (*N*-methyl-D-aspartate), and kainate/

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Abbreviations: CGH, comparative genome hybridization; GRIK, glutamate receptor, ionotropic, kainate.
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AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid) receptors [Egebjerg et al., 1991]. The kainate/AMPA receptor is widely expressed in the central nervous system and is a key molecule in synaptic plasticity, an essential process for learning and memory [Bortolotto et al., 1999; Schmitz et al., 2001].

The kainate receptor (GRIK = glutamate receptor, ionotropic, kainate) is a tetrameric receptor composed of three principal subunits, GRIK1-3 (formerly GluR5-7), and two auxiliary subunits, GRIK4-5 (formerly KA1-2)[Fernandes et al., 2009]. Compared with other kainate/AMPA receptors, the GRIK3-containing kainate receptor has an atypical electrophysiological function: it has a very low affinity to kainate/glutamate because of fast desensitization [Schiffer et al., 1997; Perrais et al., 2009]. Indeed, *Grik3*$^{-/-}$ mice exhibit markedly impaired short- and long-term synaptic potentiation [Pinheiro et al., 2007]. This discrepant electrophysiological property in GRIK3 suggests that the presence of other subunits cannot compensate for defective GRIK3.

Several nucleotide polymorphisms in *GRIK3* are known to be associated with major neuropsychiatric illnesses, such as schizophrenia and recurrent major depressive disorder [Begni et al., 2002; Schiffer and Heinemann, 2007; Kilic et al., 2010]. However, the phenotypic effect of *GRIK3* deletion remains to be elucidated.

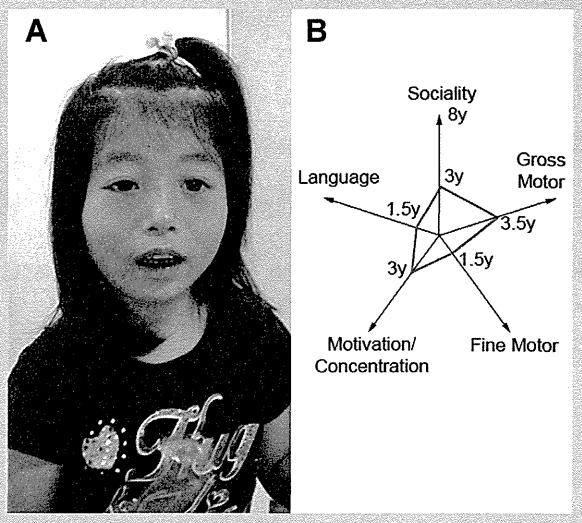


**FIG. 1. Facial appearance and multi-axial developmental assessment of the proposita. A: Photo of the proposita at the age of 6 years showing mild retrognathia and downslanting palpebral fissures. B: The proposita's developmental age for each developmental axis relative to the chronological age at assessment, that is, 8 years.**

## CLINICAL REPORT

The proposita was an 8-year-old Japanese girl born to nonconsanguineous parents. She was born at 37 weeks of gestation with a birth weight of 1,818 g (−3.0 SD) and a length of 44.5 cm (−1.9 SD). She exhibited poor weight gain during infancy and was fed via tube feeding until the age of 5 years. In addition to her failure to thrive, she exhibited severe delays in psychomotor development. She gained head control at the age of 8 months, and she walked independently at the age of 2½ years. A physical examination showed no focal neurological deficits, major physical deformities, or dysmorphisms except for mild retrognathia and slightly downslanting palpebral fissures (Fig. 1A).

At the age of 8 years, an experienced child psychologist blindly evaluated her developmental status for multiple axes, based on the Japanese standard developmental scales and a parental interview. This evaluation demonstrated marked impairment predominantly in her language and fine motor skills, compared with her gross motor skills and sociality (Fig. 1B).

### Gross Motor Development

She was able to run, but she was unable to stand on one foot. She could throw a ball, but she could not catch one. Her gross motor skills were equivalent to an age of 3.5 years.

### Fine Motor Development

She was able to pinch objects, but she was unable to stack blocks. She was barely able to complete a simple puzzle. She could scribble, but she could not draw lines. Overall, her fine motor skills were equivalent to an age of approximately 1.5 years.

### Language Development

She was able to speak four words: "bye-bye," "dada," "mama," and "good." She did not point to objects, but she chose objects and pictures that she wanted. She understood a few words using sign language. Her language development was equivalent to 1.5 years.

### Social Development

She was able to drink from a cup and to wash her hands without assistance. She could eat with a spoon and a fork but required significant assistance. She required help to brush her teeth and to change her clothes. Her social development was equivalent to approximately 3 years of age.

### Motivation/Concentration

She lacked the necessary concentration and motivation to complete tasks. We considered her attention span/concentration as being equivalent to approximately 3 years of age.

## MOLECULAR ANALYSIS

A microarray analysis using an array CGH platform (ISCA 4 × 180k; Agilent Technologies, CA) revealed a de novo 2.6-Mb deletion in 1p34.3, extending from position 34,632,258–37,241,519 (NCBI36/hg18, March 2006). The deleted interval included 44 genes (Fig. 2).

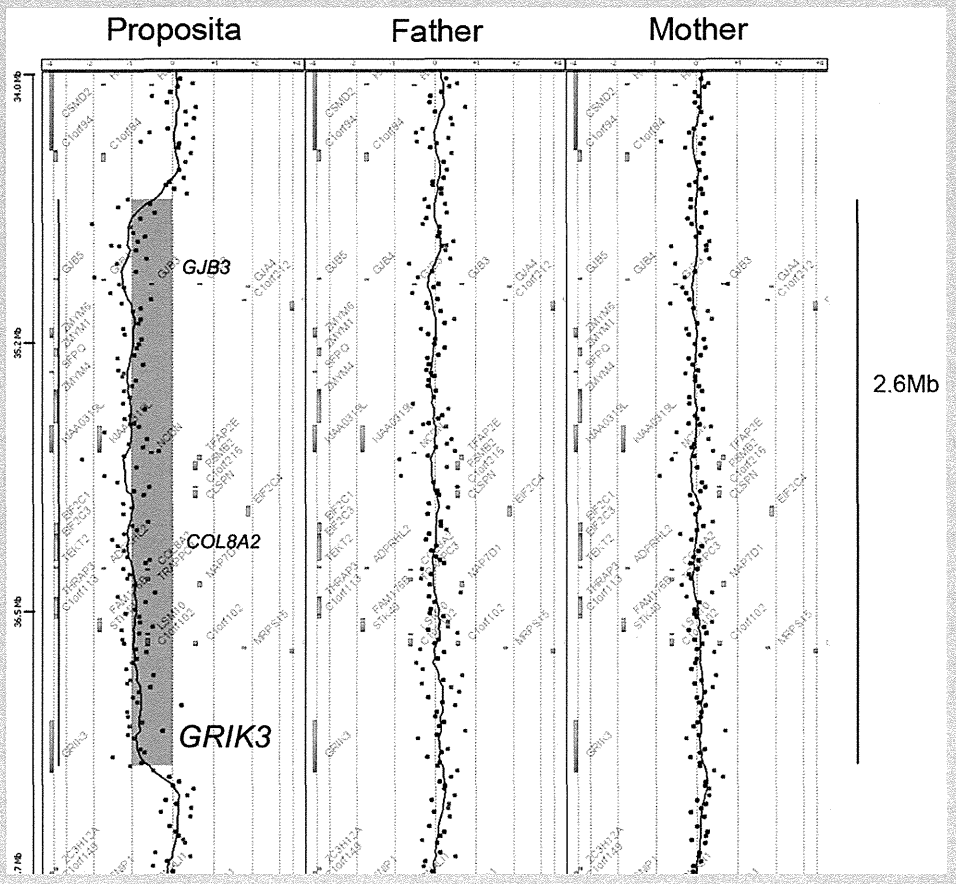


**FIG. 2. Microarray analyses of the proposita and her parents Note that the proposita (left) had a 2.6-Mb deletion (highlighted in blue). The deleted interval included *GRIK3*, *COL8A2* and *GJB3*. Neither her father (middle) nor her mother (right) had the same microdeletion, confirming that the microdeletion in the proposita was de novo.**

## DISCUSSION

A young girl with a 1p34.3 microdeletion manifested a severe developmental delay without any major recognizable dysmorphism. The 2.6-Mb microdeletion included *GRIK3*, which encodes a subunit of a kainate-type ionotropic glutamate receptor that is strongly expressed in the central nervous system [Bettler et al., 1992].

From the standpoint of the 1p34.3 microdeletion, two candidate genes for developmental delay have been previously reported. A boy with autistic spectrum disorder who had a de novo 3.3-Mb microdeletion in 1p34.2p34.3 was reported, and his autistic phenotype was attributed to *RIMS3* (OMIM 611600)[Kumar et al., 2010]. Another boy with autistic spectrum disorder had a 4.1-Mb microdeletion in 1p34.2–34.3 and exhibited a severe developmental delay, microcephaly, and facial dysmorphism. *SLC2A1* (OMIM 138140) was considered a candidate gene for his developmental delay [Vermeer et al., 2007]. Since neither *RIMS3* nor *SLC2A1* was included in the deleted interval in the proposita, the mechanistic basis for the severe developmental delay was thought to differ. Among the genes located in the deleted interval in the proposita, the biological function of the *GRIK3* gene made it the most plausible candidate for the severe developmental delay. The developmental characteristics of the proposita, which included significant deficits in language with spared gross motor function, were not incompatible with aberrant glutamate neurotransmission. This reasoning was also supported by observations in *Grik3*$^{-/-}$ mice, as these mice exhibit impaired synaptic transmission [Pinheiro et al., 2007].

We reviewed the genetic alterations of the kainate receptor family subunits, GRIK1-5, and their neuropsychiatric and neurodevelopmental manifestations (Table I). Associations between polymorphisms in each GRIK family member and major neuropsychiatric illnesses, such as schizophrenia and bipolar disorders, have been repeatedly demonstrated by multiple groups [Begni et al., 2002; Jamain et al., 2002; Pickard et al., 2006; Schiffer and Heinemann, 2007; Kilic et al., 2010; Sampaio et al., 2011; Yosifova et al., 2011; Hirata et al., 2012]. Patients with deletions of GRIK family genes and non-syndromic intellectual disability have also been reported by several authors [Pickard et al., 2006; Motazacker et al., 2007; Bonaglia et al., 2008; Haldeman-Englert et al., 2010].

TABLE I. Phenotypic Effect of Genetic Alterations of All the Kainate Receptor Subunits (GRIK Family)

| Gene name and chromosomal locus | Polymorphism and association studies with psychiatric disorders | Deletion with developmental delay/intellectual disability |
|---|---|---|
| *GRIK1* at 21q21.3 | SCZ [Hirata et al., 2012] | ID [Haldeman-Englert et al., 2010] |
| *GRIK2* at 6q16.3 | ASD [Jamain et al., 2002] | ID [Motazacker et al., 2007] |
| | OCD [Sampaio et al., 2011] | ID/PWS-like [Bonaglia et al., 2008] |
| *GRIK3* at 1p34.3 | SCZ [Begni et al., 2002; Kilic et al., 2010] | The present report |
| | MDD [Schiffer and Heinemann, 2007] | |
| *GRIK4* at 11q23.3 | SCZ, BPD [Pickard et al., 2006] | ID [Pickard et al., 2006] |
| *GRIK5* at 19q13.2 | BPD [Yosifova et al., 2011] | NR |

ASD, autisic spectrum disorder; BPD, bipolar disorder; ID, intellectual disability; MDD, major depressive disorder; NR, not reported; PWS, Prader–Willi-syndrome; SCZ, Schizophrenia.

The present report provides an additional piece of missing information regarding the neurobehavioral effects of genetic alterations in GRIK family genes, namely, the effect of a *GRIK3* deletion. It is possible that *GRIK3* represents the causative locus at 1p34 that has been implicated in a linkage study of schizophrenia [DeLisi et al., 2002] and in a genome-wide transcriptome analysis of autism spectrum disorders [Luo et al., 2012].

From a clinical standpoint, it is notable that while attempting to determine the etiology of the developmental delay, we were incidentally able to detect two causative genes for autosomal dominant late-onset diseases in the microarray analysis. Heterozygous and digenic mutations in *GJB3* and *COL8A2* could lead to autosomal dominant deafness 2B (OMIM 612644) [Xia et al., 1998; Liu et al., 2009] and two types of corneal dystrophy, that is, polymorphous posterior corneal dystrophy (OMIM 609140) and Fuchs endothelial corneal dystrophy (OMIM 136800) [Biswas et al., 2001], respectively. Since most causative mutations in *GJB3* and *COL8A2* are missense mutations, not truncating mutations, the mechanistic basis of these entities may be dominant-negative mutations, rather than haploinsufficiency. If so, the deletions of *GJB3* and *COL8A2* might not be clinically relevant.

In conclusion, we document a young girl with a microdeletion involving *GRIK3*, a kainate-type ionotropic glutamate receptor subunit. This predominant neurodevelopmental manifestation in the absence of major dysmorphism provides further clinical implication of the role of GRIK family glutamate receptors in the pathogenesis of developmental delay.

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