

Interstitial deletion within 7q31.1q31.3 in a woman with mild intellectual disability and schizophrenia

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Abstract: We report the case of a Japanese woman with an interstitial deletion within the 7q31.1q31.3 region, she presented with mild intellectual disability since infancy, and later developed characteristic psychiatric manifestations, including abnormal behavior, delusions, and hallucinations. She was diagnosed with paranoid schizophrenia (F20.0, International Statistical Classification of Diseases and Related Health Problems 10th Revision). Array comparative genomic hybridization examination revealed the deletion involving several important genes for neurodevelopment. Particularly, *FOXP2*, *DOCK4*, *MET*, and *WNT2* in this region are suggested to be related to language impairment, autistic disorders, and cognitive disorders, via the WNT pathway. In addition, the WNT signal pathway has been suggested to be implicated in the pathogenesis of psychiatric disorders such as schizophrenia and bipolar disorder. However, there is no case report regarding schizophrenia associated with a 7q31 microdeletion. We suspect that the disruptions of these one or plural genes among the interstitial deletion of 7q31.1q31.3 may be involved in the development of schizophrenia in this woman. This is the first report on schizophrenia associated with a 7q31 microdeletion.

Keywords: chromosomal microarray, psychiatric disorder, autism spectrum disorder, ASD, Wnt pathway

Introduction

Schizophrenia is the most well-known chronic psychiatric disorder, characterized primarily by hallucinations and delusions and abnormal behaviors, predominantly developing in late puberty. Although the lifetime prevalence is approximately 0.5%–1.0% in the general population and a great amount of evidence has been accumulating on its cause, including responsible genes, it has not been clearly elucidated yet.¹

The 7q31 chromosomal region is rich in genes. Within this region, there are several genes involved in neurodevelopment. These genes affected by the Wnt pathway may participate in the development of psychiatric disorders.

In this study, we describe the case of a 28-year-old Japanese woman with mild intellectual disability associated with an interstitial deletion in 7q31 region. This patient also showed the phenotypes of schizophrenia.

Patient report

Our case involved a 29-year-old female, who was described as cheerful and peaceful. Although her father and older brother are healthy, her mother succumbed to fungal pneumonia. The patient was born at 38 weeks of gestation via vaginal delivery with early membrane rupture. Her birth weight was 2,700 g. During pregnancy, maternal edema and proteinuria were observed. There was no birth asphyxia; however, the patient showed poor sucking and muscular hypotonia. Her development was delayed

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as evidenced by gaining head control at 6 months, rolling over at 18 months, and standing at 22 months. The diagnosis of intellectual disability was made at 7 years of age, because her intelligence quotient measured by the Binet–Tanaka test was 53. A neurological examination at that time confirmed the presence of psychomotor retardation. Some minor anomalies, such as a horizontal line in her palm, high-arched palate, and mandibular protrusion, were observed (Figure 1). After graduating from a special education school, she attended a workshop for the handicapped. She was active, helped her family well, and even participated in the Special Olympics.

At the age of 27 years, she suddenly became inactive and began neglecting her regular household chores. She refused to go to work and became withdrawn; she did not watch television, an activity she previously enjoyed. She was expressionless, was unkempt, and had stopped eating and bathing by herself. She suffered from insomnia, and her mood was unstable, irritable, and aggressive. She developed sluggish movements; talked to and laughed at herself; occasionally cried, shouted, and got irritated; and distressed her family.



Figure 1 The present patient, a 29-year-old female.

Laboratory tests, including thyroid function, revealed no abnormalities with the exception of a chromosomal abnormality. Brain magnetic resonance imaging demonstrated no remarkable changes, and electroencephalography revealed no paroxysmal activity. She was prescribed psychotropic drugs, but she did not use them. Thereafter, she demonstrated obsessive-compulsive, repetitive, ritualized behavior, and she was no longer able to eat, bath, and excrete by herself. She also experienced hallucinations and delusions. Some of her complaints included “some people whisper in my ears,” “someone is chasing me,” “something moves my hand,” and “something touched my feet.” Eight months later, her family reported that she behaved as a completely different person. She was diagnosed with paranoid schizophrenia (F20.0, International Statistical Classification of Diseases and Related Health Problems 10th Revision).

With family cooperation, she started medication, and her hallucinations and delusions improved following the use of risperidone (2 mg/day) and duloxetine (20 mg/day). Six months later, she began to smile and her appetite and sleep normalized. One year later she was able to eat meals by herself. At present, she can excrete by herself. Although her hallucinations, delusions, and psychomotor sluggishness have improved with medication, she continues to talk to herself and exhibits obsessive-compulsive behavior. She often throws tantrums when the order of daily activities set by her gets disturbed.

Cytogenetic examination

Conventional chromosomal G-banding revealed an interstitial deletion in 7q, described as 46,XX,del(7)(q31.3q31.3) (data not shown). Permission to analyze parental karyotyping could not be obtained. To confirm the precise deletion region, chromosomal microarray testing was performed with an Agilent 60 K Human Genome Comparative Genomic Hybridization Microarray platform (Agilent Technologies, Santa Clara, CA, USA) in accordance with previously reported methods.^{2,3} For this purpose, a peripheral blood sample was collected after obtaining written informed consent. Genomic DNA was extracted with the QIA quick DNA extraction kit (Qiagen, Hilden, Germany). The results are described as arr[hg19] 7q31.1q31.31(111,105,151-119,120,843)X1.

Discussion

In this study, an interstitial deletion in the 7q31 region was identified in a female patient with intellectual disability. In the deletion region, 25 registered RefSeq genes were

identified. The identified genes included *FOXP2*, *DOCK4*, *MET*, and *WNT2*. These genes play an important role in the function of central nervous system while affecting each other via the Wnt/ β -catenin signaling pathway. Several studies have investigated the association between Wnt/ β -catenin signaling pathway and autism spectrum disorders (ASD), and 7q31 has been considered a “hotspot” for ASD.⁴ The canonical Wnt pathway has been indicated to play a role in normal brain development and synaptic function and to affect dendrite growth and activity.^{5,6} Reportedly, Wnt and its receptors are involved in the embryonic development of central nervous system and are also highly expressed in adult brains, suggesting that their expression may affect higher brain functions and that Wnt signaling may be involved in higher brain functions. Therefore, genes affected by the Wnt pathway may be involved in the development of psychiatric disorders, such as schizophrenia or bipolar disorder.^{7,8}

Meanwhile, several previous studies have reported deletion cases similar to that reported here (Figure 2). Among them, cases with *FOXP2* deletion have mild-to-moderate

developmental delays (Table 1).^{2,9–16} *FOXP2* encodes a transcription factor comprising a polyglutamine tract and a fork-head DNA-binding domain.¹⁷ *FOXP2* protein may regulate the expression of other genes in the cortico-basal ganglia and cerebellar circuits of the brain.¹⁸ Disruptions in *FOXP2* are associated with language, autistic, and cognitive disorders.^{19,20} Therefore, developmental delay in such patients is likely to be derived from *FOXP2* haploinsufficiency. Interestingly, there is a report that *FOXP2* may also regulate *DISC1*, which has attracted the most attention as a candidate gene for schizophrenia.²¹ However, there are both positive and negative reports on the association between *FOXP2* and schizophrenia.^{22–25} Further, in several previous studies as stated above including *FOXP2* (Figure 2), schizophrenia has not been reported. *DOCK4*, a guanine nucleotide exchange factor (GEF) for Rac, is a component of the β -catenin destruction complex. *Dock4* is expressed in the rat hippocampal neurons and plays an important role in supine formation.²⁶ It has also been reported as candidate gene for autism, dyslexia, and schizophrenia.^{27–29} *MET* is the receptor for hepatocyte growth factor (HGF).

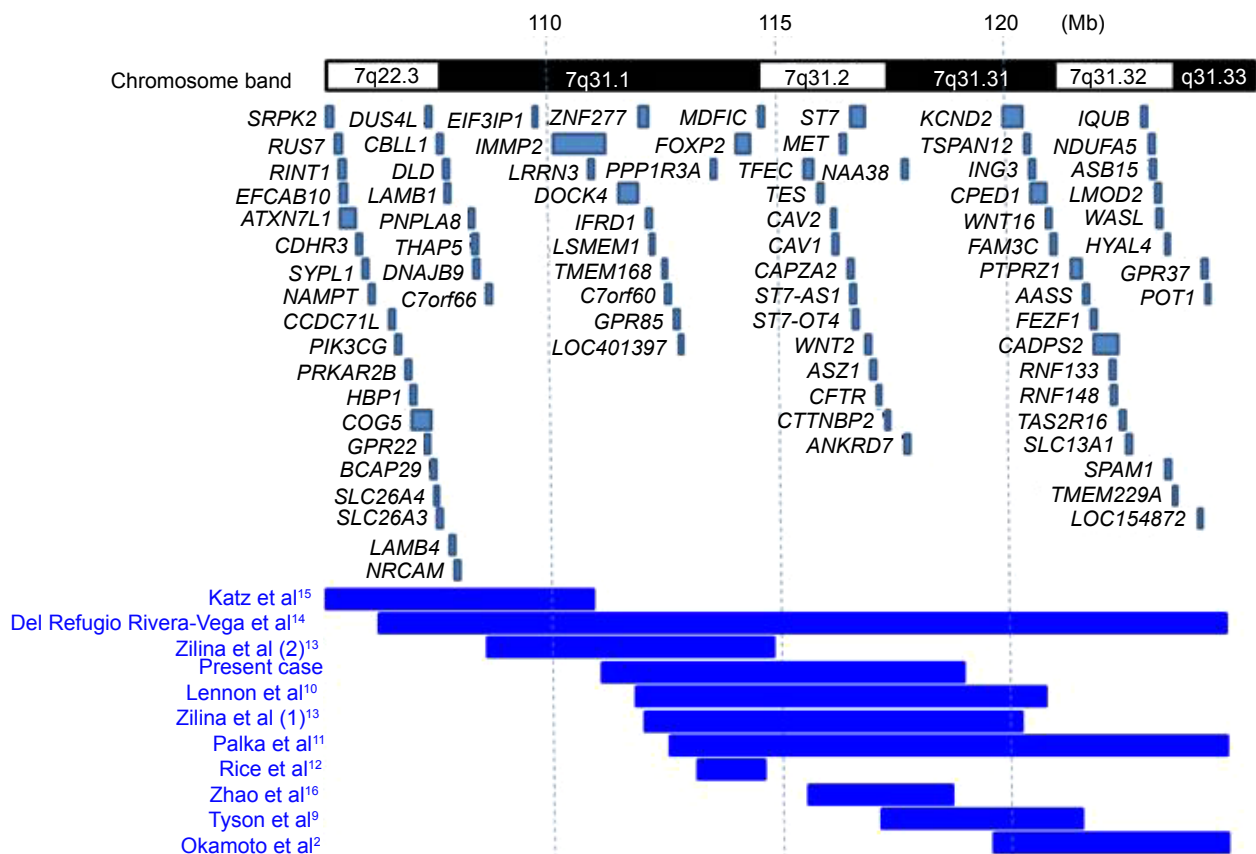


Figure 2 Genome map around 7q31 region depicting reported deletion regions.

Note: Deletion regions in previously reported patients and those in the present patient are depicted (blue bars). Genomic positions refer to build19.

Table 1 Summary of the patients with interstitial deletions in the 7q31 region

	Katz et al ¹⁵	Del Refugio Rivera-Vega et al ¹⁴	Zilina et al ¹³ (2)	Present case	Lennon et al ¹⁰	Zilina et al ¹³ (1)	Palka et al ¹¹	Rice et al ¹²	Zhao et al ¹⁶	Tyson et al ⁹	Okamoto et al ²
	2016	2015	2012	2012	2007	2011	2012	2012	2016	2004	2011
Age	3y7m	1y9m	6y	27y	7y	3y	10y	4y10m	4y	14y	3y
Gender	M	F	F	F		F	F	M	F	M	M
Growth delay	+	+	-	-	-	+	-	-	-	+	+
Developmental delay	+	Mild	+	Mild	Mod	Mod	Mild	+	+	-	-
ASD	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	+
Psychiatric symptoms	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	-
Distinctive features	+	+	+	+	+	+	-	+	+	+	+
Deletion size (Mb)	12.0	23.0	6.0	8.0	9.0	8.0	14.0	2.0	3.0	5.0	5.0
Chromosomal position							Mosaicism				
Start	q22.1	q22.3	q31.1	q31.1	q31.1	q31.1	q31.1	q31.1	q31.2	q31.2	q31.31
End	q31.1	q32.1	q31.2	q31.31	q31.31	q31.31	q31.3	q31.2	q31.31	q31.32	q31.33
Deletion region (Mb)											
Start	99	107	109	112	112	112	113	113	116	117	120
End	111	130	115	120	121	120	127	115	119	122	125
Inheritance	NT	DN	Inherited	NT	Inherited from parental-balanced insertion	Inherited	NA	Inherited	DN	NT	DN
FOXP2 involvement	-	+	+	+	+	+	+	+	-	-	-

Abbreviations: y, years; m, months; M, male; F, female; Mo, mother; Mod, moderate; ASD, autism spectrum disorder; NA, not available; NT, not tested; DN, de novo; +, positive; -, negative; Mild, mild delay; Mod, moderate delay.

HGF-MET signaling contributes to neuronal differentiation, cerebral cortex and cerebellum development, and axon growth. *MET* transcription is regulated by *FOXP2*,³⁰ and *DOCK4* and *MET* are related to the Wnt pathway through β -catenin.⁴ Finally, *WNT2* is a homologue of *WNT1*, and Wnt1 has been suggested to regulate genetic networks in midbrain dopaminergic neuron development.³¹ Wnt-1 protein has increased expression in the brains of individuals with schizophrenia.³² Similarly, *WNT2* may be associated with the development of schizophrenia.

FOXP2, *DOCK4*, *MET*, and *WNT2* are heterozygous in this case. We suspected that one possibility is that mutation or epigenetic change occurs somewhere in the contralateral allele and the disruptions of these plural genes affect each other and may be involved in the onset of schizophrenia in this patient.

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Disclosure

The authors report no conflicts of interest in this work.

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