Brain & Development 41 (2019) 452–455

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Phenotypic features of 1q41q42 microdeletion including *WDR26* and *FBXO28* are clinically recognizable: The first case from Japan

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Received 24 August 2018; received in revised form 23 October 2018; accepted 26 December 2018

Abstract

1q41q42 microdeletion syndrome has been established in 2007. Since then, more than 17 patients have been reported so far. The reported deletions showed random breakpoints and deletion regions are aligned as roof tiles. Patients with 1q41q42 microdeletion syndrome show intellectual disability, seizures, and distinctive features. Many genotype-phenotype correlation studies have been performed and some genes included in this region have been suggested as potential candidate genes. Recently, *de novo* variants in *WDR26* and *FBXO28* were identified in patients who showed consistent phenotypes with 1q41q42 microdeletion syndrome. Thus, both genes are now considered as the genes possibly responsible for 1q41q42 microdeletion syndrome. Here, the first case of a Japanese patient with a *de novo* 1q41q42 microdeletion is reported. Owing to the distinctive features, this syndrome would be clinically recognizable.

Keywords: Chromosomal microarray testing; Smallest region of overlap (SRO); Ataxic gait; Loss-of-function

1. Introduction

Until now, many chromosomal microdeletion syndromes have been established. Accumulation of genotype information enabled us to narrow critical region for such syndromes. Furthermore, massive parallel sequence accelerated to identify responsible genes in the critical regions. In 2007, a new microdeletion syndrome due to 1q41q42 microdeletion (MIM #612530) was firstly reported by Shaffer et al. [1]. Then after, many patients have been reported to show overlapping deletions [2–6]. Recently, *de novo* mutations in the genes in this region have been identified in patients with similar findings with 1q41q42 microdeletion syndrome.

Here, we report an additional patient with 1q41q42 microdeletion syndrome and compare the clinical features of patients derived from chromosomal deletions and gene mutations in this region.

2. Patient report

The female patient is 8 years at present. At 37 weeks of gestation, she was born with a birth weight of 2902 g. Her parents and an elder brother are healthy. There was

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https://doi.org/10.1016/j.braindev.2018.12.006
0387-7604/

no remarkable past history during pregnancy. She was hypotonic in early infancy. Owing to that, poor sucking and failure to thrive were shown. At 6 months, it was noted that she did not pursue moving objects. Her psychomotor development was moderately delayed; walking alone at 22 months and no meaningful word at present. At 11 months, she suffered a generalized tonic-clinic convulsion. After that, she showed Todd's paralysis. Electroencephalogram showed sporadic spikes in the bilateral frontal regions. Her epileptic seizures were intractable. Brain magnetic resonance imaging showed no definite abnormality. At present, she can understand the simple sentences people say; however, expressive language is still lacking. Due to that, she uses gesture for communication. She requires supports for all activities in daily life; including clothing, eating, and toilet habits. She shows distinctive facial features including upslanting palpebral fissures, hypertelorism, and a flat nasal bridge (Fig. 1). She shows microcephaly with occipitofrontal circumference of 45.8 cm (<3rd centile) measured at 3 years. At present, her height and weight are 111.5 cm (<3rd centile) and 17.2 kg (<3rd centile), respectively; indicating growth impairments. Ataxic gaits are exhibited. Her personality is happy and over-friendly for everybody. She is also diagnosed as having autistic spectrum disorder owing to repetitive behaviors and communication disability.

For molecular diagnosis, chromosomal microarray testing was performed after receiving written informed consent using Agilent 60 K Human Genome CGH Microarray platform (Agilent Technologies, Santa Clara, CA) as described previously [7]. A 2.2-Mb deletion was identified, represented as arr[GRCh37] 1q41q42.12(221,875,044_224,702,816) × 1. Fluorescence *in situ* hybridization analyses confirmed the result and both parents showed no deletion, indicating *de novo* occurrence (data not shown).

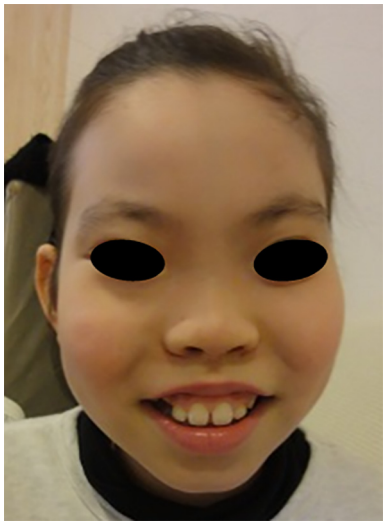

Fig. 1. Facial findings of the present patient. High forehead, brushy arched eyebrows, full cheeks, protruding upper lip, and widely spaced teeth are noted. We obtained an informed consent from patient's parents for the usage of this photo with masked eyes.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of institution. After receiving written informed consent from patients' families, we performed this study.

3. Discussion

By use of the previously reported data for 1q41q42 microdeletions, genotype-phenotype correlation studies have been performed and some potential candidate genes have been proposed. Rosenfeld et al. [8] reported 7 patients with 1q41q42 microdeletions. They paid attention to the dispatched homolog 1 gene (*DISP1*), because it is located on the smallest region of overlap (SRO). Decreased expression of *DISP1* was detected in a patient with a deletion including *DISP1*. Filges et al. [9] reported a patient with an overlapping deletion, but the deletion did not include *DISP1*.

In 2017, fifteen *de novo* variants of the WD repeat domain 26 gene (*WDR26*) were identified in patients with intellectual disability, seizures, and distinctive facial features [10]. Those clinical manifestations are consistent with that observed in patients with 1q41q42 microdeletions. Because most of the identified variants are related to loss-of-function, haploinsufficiency of *WDR26* was considered as the gene responsible for 1q41q42 microdeletion syndrome.

On the other hand, the F-box protein 28 gene (*FBXO28*) has been proposed as the candidate gene responsible for intellectual disability and seizures, owing to the identification of an additional patient with a very small 590-kb deletion, which narrowed the SRO and refined the critical region [11]. Cassina et al. [12] also suggested this proposal. In 2018, a *de novo* frameshift *FBXO28* mutation was identified in a patient with similar phenotypic features with 1q41q42 microdeletion syndrome [13]. Now, both of *WDR26* and *FBXO28* are considered as the genes responsible for 1q41q42 microdeletion syndrome.

The identified deletion in the present study was typical for 1q41q42 microdeletion, because the deleted region is overlapped with most of the deletions (Fig. 2). Both of *WDR26* and *FBXO28* are included in the deletion region. The patient's clinical manifestations; including intellectual disability, epilepsy, abnormal gait, and distinctive facial features; are consistent with that observed in patients with 1q41q42 microdeletion syndrome and a *FBXO28* frameshift mutation (Table 1). Because the combination of each facial finding of the patient is distinctive, this syndrome would be clinically recognizable. This is the first case report of 1q41q42 microdeletion syndrome from Japan.

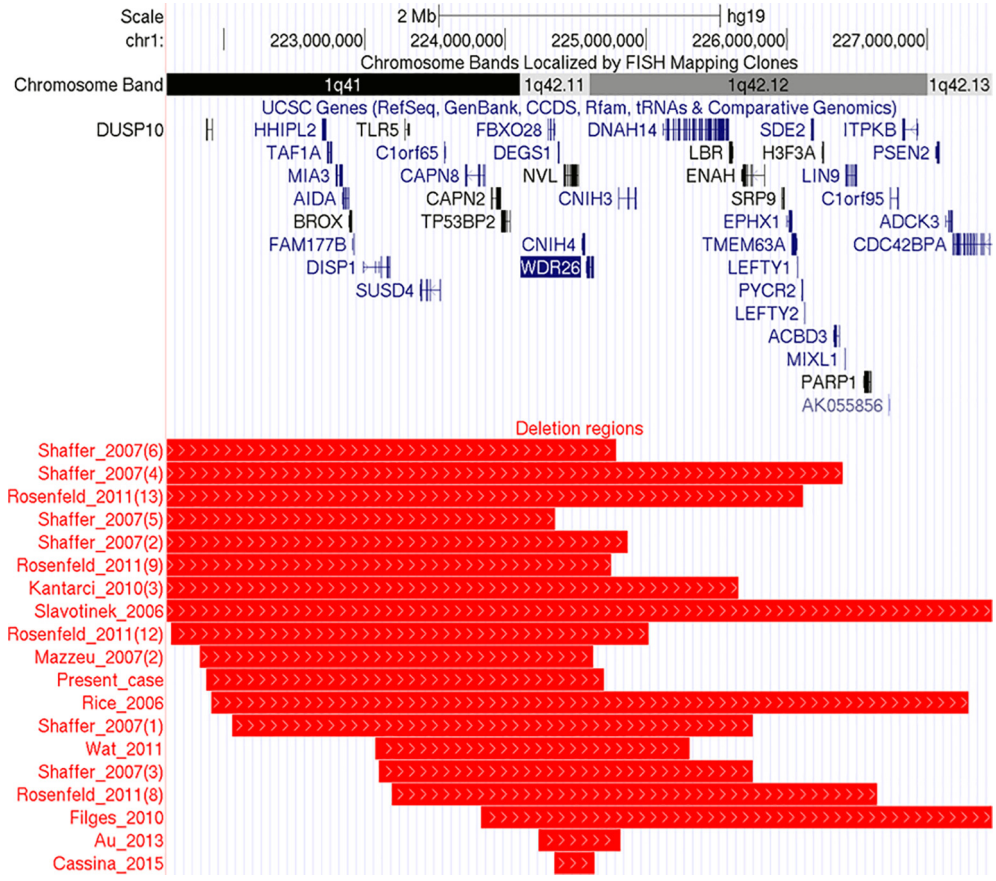

Fig. 2. Genome map and identified microdeletions in 1q41q42 region. *WDR26* and *FBXO28* are located on the smallest region of overlap. Red bars indicate the deletion region identified in patients. This map was captured from UCSC genome browser (https://genome.ucsc.edu/). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Comparison of the clinical features.

	Present patient	Patient with a *FBXO28* frameshift mutation* (n = 1)	Patients with *WDR26* mutations (n = 15)	Patients with 1q41q42 microdeletions including *WDR26* (n = 17)
Developmental delay/intellectual disability	+	+	15/15	15/15
Seizures	+	+	15/15	13/14
Brain structural anomalies	–	+	10/14	11/15
Hypotonia	+	+	9/12	5/15
Abnormal gait	+	NI	9/9	1/15
Happy and/or friendly personality	+	+	10/11	2/2
Autistic and/or repetitive behaviors or posturing	+	–	5/9	1/1
Coarse facial features	+	+	12/15	12/16
Full cheeks as a child	+	+	11/13	7/8
Abnormal eyebrows	+	+	6/15	5/12
Depressed nasal root	+	+	5/15	11/15
Anteverted nares	+	+	8/15	9/13
Full nasal tip	–	+	11/15	9/14
Prominent maxilla and protruding upper lip	+	+	13/15	7/12
Decreased cupid's bow	+	+	11/15	10/12
Widely spaced teeth	+	+	13/15	7/8
Abnormal gums	–	–	9/15	6/6

Modified from the table reported by Skraban et al. (2017).
NI, not indicated due to no walking.
* This case was reported by Balak et al. (2018).

Acknowledgements

We would like to thank the patient's family for cooperation. This research was supported by the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED), a Grant-in-Aid for Scientific Research from Health Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, Japan, and the Japan Society for the Promotion of Science (JSPS) KAKENHI (T. Yamamoto).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.12.006.

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