CASE REPORT

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16p13.11 microduplication with growth retardation and developmental disorders: a case report and literature review

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ABSTRACT

Short stature and growth retardation is a common condition in children. Genetic variations are responsible for many cases of short stature of unknown etiology. In particular, pathogenic copy number variants (CNVs) have been found in 10%–16% of children with unexplained short stature. This paper reports on a 5-year-old Japanese girl with both growth retardation and developmental delay associated with a 16p13.11 microduplication. Although the patient's mother also carries this microduplication, she did not show growth retardation and developmental delay. These cases illustrate the diverse phenotypic manifestations of 16p13.11 microduplication. Consequently, we conducted the literature review of 274 cases associated with this duplication revealed neurological disorders in approximately 70% of cases, 15.3% of these cases were associated with short stature. Diagnosis of 16p13.11 microduplication remains challenging due to its diverse symptomatology and elusive genotype–phenotype correlations. Comprehensive genetic evaluation is crucial for patients presenting with short stature and developmental disorders, underscoring the need for further investigation into the 16p13.11 microduplication to clarify its specific role and implications.

Keywords: 16p13.11 microduplication, copy number variants (CNVs), growth retardation, developmental disorders

Abbreviation:
CNVs: copy number variants

INTRODUCTION

Short stature and growth retardation is a common condition in children. Genetic variations are responsible for many cases of short stature of unknown etiology. To date, pathogenic copy number variants (CNVs) have been found in 10%–16% of children with short stature of unknown cause.[1] The 16p13.11 microduplication, a rare CNV, is known to cause several neurodevelopmental dis-

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orders, including developmental delay and intellectual disability, and autism spectrum disorders.[2] However, the clinical significance of short stature in cases with this CNV is unclear due to a lack of focus on this in previous reports. We present a case of 16p13.11 microduplication with growth retardation and developmental delay, highlighting the need for investigation of this CNV.

CASE REPORT

The patient was a 5-year-old Japanese girl. She was born at 38 weeks and 4 days of gestation with a height of 46 cm (–1.28 SD: evaluated according to height and weight, expressed in terms of standard deviation in Japanese children), weight of 2514 g (–1.17 SD), and head circumference of 31 cm (–1.57 SD). Her father presented short stature of 158 cm (–2.33 SD) and had a history of epilepsy, while the mother's height was 156 cm (–0.39 SD) and she had a past medical history of depression (Fig. 1a). The mid parental target height of the proband was

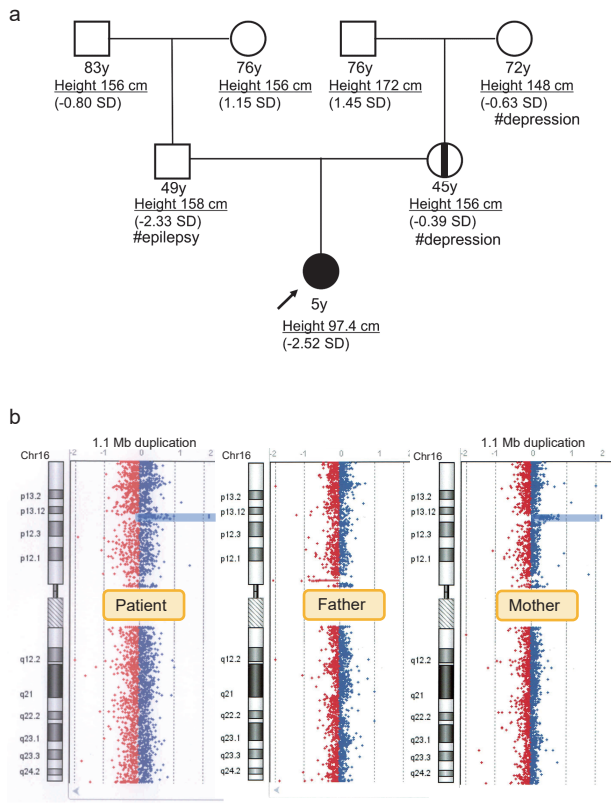

Fig. 1 Pedigree and microarray analysis

Fig. 1a: Pedigree. The arrow indicates the proband. The proband's black shading represents being affected with the trait. The mother's pedigree mark indicates an asymptomatic carrier. The father's height was 158 cm (–2.33 SD). He had a history of seizures. The mother's height was 156 cm (–0.39 SD). She had a history of depression. However, the parents did not have short stature below –2.5 SD or neurodevelopmental disorders.

Fig. 1b: Microarray analysis. The 1.1 Mb duplication at the 16p13.11 region in the patient and her mother was revealed. The patient's father did not carry this duplication.

150.5 cm (–0.57 SD). Her neck became stable at 4 months, she could sit without support at 8 months, she could crawl at 8 months, and she could walk by herself at 1 years and 5 months.

The patient was referred to our clinic at the age of 2 years due to growth retardation and neurodevelopmental delay. She had no distinctive facial features. She was unable to speak meaningful words and showed a tendency towards autism such as specific interests and repetitive behaviors. At 2 years of age, her height was 78 cm (–2.14 SD), weight was 8.1 kg (–3.18 SD), and head circumference was 44 cm (–1.8 SD). Thyroid hormone profile, plasma amino acid profile, urine amino acid profile, and tandem mass spectrometry were negative for congenital hypothyroidism and metabolic disorders. Echocardiography and brain magnetic resonance imaging (MRI) showed no abnormalities. At 3 years of age, she was unable to utter two-word sentences. Her developmental index at 4 years of age was 65 in the cognitive-adaptive domain, and 48 in the language-social domain by the Kyoto Scale of Psychological Development. She was subsequently diagnosed with autism spectrum disorder.

The patient did not present delayed bone age, and her Insulin-like Growth Factor I (IGF-1) level was normal at 83 ng/mL (normal range: 56–252). After obtaining written informed consent, we attempted a chromosomal analysis of the patient and parents. Her chromosomal G-banding indicated a karyotype of 46, XX. Array comparative genomic hybridization (array comparative genomic hybridization [CGH]), using a 4×180K CGH oligonucleotide microarray (Agilent Technologies), revealed patient's 16p13.11 microduplication {[GRCh37/hg19]:16p13.11 (15,125,829–16,229,700) ×3} involving nine genes (*ABCC1*, *CEP20*, *MYH11*, *NDE1*, *MARF1*, *MPV17L*, *RRN3*, *NTAN1*, and *PDXDC1*). Parental analysis confirmed the same duplication in her mother (Fig. 1b).

She was referred to a developmental support center where she received developmental rehabilitation therapy. Regarding her short stature, she did not meet the criteria for growth hormone therapy. She is being followed up regularly, has progressed to speak a few meaningful words, and can now communicate. Her height and weight have increased steadily to 97.4 cm (–2.52 SD) and 12.1 kg (–3.56 SD) at 5 years of age, without growth hormone therapy.

DISCUSSION

Here, we describe a case of 16p13.11 microduplication with growth retardation and developmental delay, highlighting the range of possible manifestations, including growth retardation and developmental delay, associated with 16p13.11 microduplication. We emphasize the need for comprehensive genetic evaluation in patients with short stature and developmental disorders.

In cases of short stature complicated with developmental delay, the potential association with CNVs must be considered.[3] Recently, Homma et al identified 32 pathogenic CNVs (14.0%) in 229 patients with short stature and dysmorphic features, developmental delay, and/or intellectual disability. In addition, they selected four studies from the literature involving 442 patients with unidentified short stature and detected pathogenic CNVs in 55 of them (12.4%) using microarray analysis.[1]

The 16p13.11 microduplication was not included in previous reports, we summarized 274 cases from five reports related to 16p13.11 microduplication (Table 1).[4-8] We found that the rate of de novo occurrence of this duplication was low (12/157 cases), while more than half of the carrier parents had no symptoms (17/25 cases). In 15.3% (18/117) of cases with this duplication exhibited short stature, and 66.7% (110/165) of cases had behavioral difficulties such as autism spectrum disorder or attention deficit hyperactivity disorder, and 74.7% (130/174) of cases had delayed motor or speech development.

Table 1 Clinical features of 16p13.11 microduplication in the previously reports

Author	Hamad[4]	Allach El Khattabi[5]	Ramalingam[6]	Nagamani[7]	Hannes[8]	**Total**
Year	2023	2020	2011	2011	2009	
Country	UK	France	USA	USA	Belgium	
No.	206	45	8	10	5	**274**
Male:Female (Unknown)	104:65 (37)	22:23	NA	5:5	3:2	**134:95**
Inheritance						
Inherited:de novo	101:7	31:3	4:1	7:0	2:1	**145:12**
Parent's phenotype (affected:unaffected)	NA	7:16	NA	NA	1:1	**8:17**
Growth						
Short stature	14.7% (16/109)	NA	12.5% (1/8)	11.1% (1/9)	0% (0/1)	**15.3% (18/117)**
Tall stature	2.8% (3/109)	NA	0% (0/8)	11.1% (1/9)	0% (0/1)	**3.4% (4/117)**
Microcephaly	17% (19/112)	NA	12.5% (1/8)	14.3% (1/7)	50% (1/2)	**17.1% (22/129)**
Macrocephaly	9.8% (11/112)	NA	12.5% (1/8)	0% (0/7)	0% (0/1)	**9.4% (12/128)**
Neurobehavioral						
Behavioral difficulty	62.1% (64/103)	79.4% (31/39)	62.5% (5/8)	50% (5/10)	100% (5/5)	**66.7% (110/165)**
ASD	n = 29	n = 24	n = 4	NA	NA	
ADHD	n = 17	NA	n = 2	n = 5	NA	
Delayed development	72.4% (79/109)	88.1% (37/42)	50.0% (4/8)	50% (5/10)	100% (5/5)	**74.7% (130/174)**
Motor delay	NA	n = 19	NA	n = 3	NA	
Speech delay	n = 58	n = 35	NA	n = 5	NA	

NA: not available
ASD: autism spectrum disorder
ADHD: attention deficit hyperactivity disorder

In our patient's family members, the mother carrying 16p13.11 microduplication had a medical history of depression, but interestingly she did not exhibit short stature like her daughter. The proband's short stature might be attributable to genetic inheritance from her father. This highlights the variable expressivity and incomplete penetrance of 16p13.11 microduplication. Allach El Khattabi et al clearly established that the size of the duplicated segment had no effect on the severity of the phenotype.[5] Therefore, it may be more accurate to consider the 16p13.11 microduplication as one of several potential genetic factors that, in combination with environmental influences, may contribute to the symptoms of short stature.

Determining which specific genes in the duplicated region contribute to the phenotype

remains a contentious. The 16p13.11 region contains significant genes, 13 genes in the OMIM database: *ABCC1*, *ABCC6*, *CEP20*, *MARF1*, *MPV17L*, *MYH11*, *NDE1*, *NOMO1*, *NOMO3*, *RRN3*, *NTAN1*, *NPIPA1*, and *PDXDC1*. In particular, *NDE1* is critical for neurodevelopment which has been shown to be essential for cortical development.[9] *MYH11* is associated with muscle contraction which affects the structural integrity of the myocardium.[10] *ABCC1* is associated with non-syndromic hearing loss.[11] Additionally, non-coding RNA miR-484 located on chromosome 16p13.11 is reported regulating the expression of genes and potentially influencing cell growth and metabolism related to height through pathways associated with cell proliferation.[12] Recently, mouse models of neurodevelopmental mechanisms between miR-484 showed that an imbalance in miR-484/PCDH19 expression results in dysregulated neurogenesis.[12] Further research may contribute to clarify the interactions between genes and miRNAs.

There are various issues to consider in this case, given that short stature may be associated with multiple environmental factors such as nutrition and hormones. No clear genetic factors associated with the father's short stature were identified here. Continued follow-up of the patient is necessary because new phenotypes may emerge.

CONCLUSION

In conclusion, this paper emphasizes the need for comprehensive genetic evaluation in patients with short stature and developmental disorders. Further research is needed to explore the involvement and impact of each gene within 16p13.11 microduplication on growth and development.

ETHICAL STANDARD AND INFORMED CONSENT

We took informed consent from the patient's parents. Written informed consent was obtained from the patient for publication of this case report.

AUTHOR CONTRIBUTION

Daisuke Watanabe, Hideaki Yagasaki, and Hiromune Narusawa were directly involved in the management of the patient. Daisuke Watanabe drafted the case report. All authors contributed to and approved the final draft of the report.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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