Letter to the Editor
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Identification of *SUZ12* Haploinsufficiency due to a 1.4-Mb Deletion at 17q11.2 in a Child With Overgrowth and Intellectual Disability Syndrome

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Dear Editor,

Polycomb repressive complex 2 (PRC2) is an epigenetic regulator that functions through methylation of lysine 27 of histone H3 and plays a role in transcriptional silencing [1]. Germline pathogenic variants in the genes encoding its core components, *EZH2* and *EED*, cause clinically overlapping overgrowth-intellectual disability (OGID) syndromes, including Weaver syndrome and Cohen–Gibson syndrome [2, 3]. Rare coding variants in *SUZ12*, which encodes another PRC2 core component, have been recently reported to induce clinical characteristics similar to the above two OGID syndromes [4, 5]. However, the clinical spectrum of *SUZ12*-related overgrowth has not been fully defined, as there are few reports of such cases. Additionally, all published cases involved *SUZ12* sequence variants [6]. Copy number variants of *SUZ12* are very rare, and associated phenotypes have not been described. We report a novel *de novo* 1.4-Mb deletion at 17q11.2, which includes *SUZ12*, in a child who presented with overgrowth and intellectual disability. This study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital, Bucheon, Korea (2022-08-014) and was exempted from informed consent.

A 12-year-old boy visited our hospital in October 2021 for evaluation of gait disturbance. He was the second child of healthy, unrelated parents. His siblings had no medical problems. At birth at 38 weeks of gestation, he weighed 2,250 g (<3rd percentile), with no known family history of genetic diseases. Muscular hypotonia and feeding problems were absent during the neonatal period. The patient could walk in a timely manner at the age of 13 months, but gait abnormalities, such as toe walking, were observed on both sides. His hands and feet were large; his wrists and fingers showed hyperlaxity, indicating that his joints were hypermobile beyond the normal range. At 3 years of age, his parents noticed developmental delay primarily affecting speech and coordination. At 4 years, he was diagnosed as having intellectual disability and continues to receive speech and cognitive therapy since then. Since 7 years of age, walking became increasingly difficult because of cavovarus foot deformity with Achilles tendon tightness. He presented with macrocephaly and had facial dysmorphisms (Table 1). At 12 years, his height was 165 cm (83th percentile), and he has grown by 8 cm to 173 cm (92th percentile) in the last six months. His weight increased from 50 kg (47th percentile) to 55 kg (49th percentile) during the same period. Brain magnetic resonance imaging was normal. Electromyography revealed incomplete bilateral superficial peroneal nerve lesions without axonal degeneration.

Chromosomal microarray (CMA) showed a 1.4-Mb deletion at

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Table 1. Comparison of clinical characteristics between the current patient with a copy number variant including *SUZ12* and previously reported cases with *SUZ12* sequence variants

Variable	This study	Imagawa, *et al.* (2017) [5] and (2018) [4] (N = 3)	Cyrus, *et al.* (2019) [6] (N = 10)
Genotype	1.4-Mb deletion including *SUZ12*	Sequence variants in *SUZ12*	Sequence variants in *SUZ12*
Growth parameters			
Generalized overgrowth	+	3/3	8/10
Craniofacial features			
Macrocephaly	+	2/3	6/9*
Prominent forehead	+	3/3	4/10
Round face	+	3/3	5/10
Hypertelorism	+	2/3	8/10
Downslanting palpebral fissures	+	1/3	5/10
Low or broad nasal bridge	+	0/3	9/10
Neurological features			
Developmental delay	+	2/3	8/10
Intellectual disability	+	1/3	7/9*
Musculoskeletal features			
Advanced bone age	Not determined	2/2*	3/6*
Thoracic/chest abnormalities	-	Not known	3/10
Large hands and feet	+	1/1*	6/8*
Finger camptodactyly or clinodactyly	-	1/1*	3/10
Toe camptodactyly or clinodactyly	-	2/2*	4/10
Other abnormalities	Cavovarus foot deformity, hypermobility of wrist and finger joints	Short toes, flexion disorders of fingers, cubitus valgus, etc.	Short fingers, pes planus, hypermobility of joints, coxa valga deformity, etc.
Skin and integument			
Excessive loose skin	+	0/2*	1/8*
Hypertrichosis	-	1/1*	2/10
Abdomen/genitourinary features			
Umbilical hernias	-	2/2*	2/9*
Cryptorchidism	-	Not known	4/7*

"-," absent; "+," present.
*One or several cases that could not be evaluated were excluded from the denominator.

17q11.2 defined as base positions between 29,935,893 and 31,361,994 (GRCh37/hg19) (Fig. 1A). The copy number deletion was not identified in the blood of his parents and was considered to have occurred *de novo*. The deletion resulted in the loss of 14 protein-coding genes (Fig. 1B). The only plausible gene within the deleted segment that was relevant to the patient's phenotype was *SUZ12*, which has been linked to Imagawa–Matsumoto syndrome (IMMAS). Diagnostic exome sequencing, performed simultaneously with CMA, revealed no significant sequence variants related to the patient's symptoms.

SUZ12 is a component of the PRC2 and is responsible for binding DNA and RNA via its zinc finger domain [7]. IMMAS is the least well-characterized of the OGID syndromes, with only 13 cases published to date [4-6]. Pathogenic sequence variants in *SUZ12* lead to pre- and postnatal overgrowth, facial dysmorphisms, musculoskeletal abnormalities, developmental delay, and/or intellectual disability to varying degrees [4-6]. To assess the genotype–phenotype correlation in patients with *SUZ12* sequence variants and copy number variants, we compared the clinical characteristics of our patient with those of previously reported cases (Table 1). The phenotype of our patient was similar to the clinical features of IMMAS patients with *SUZ12* sequence

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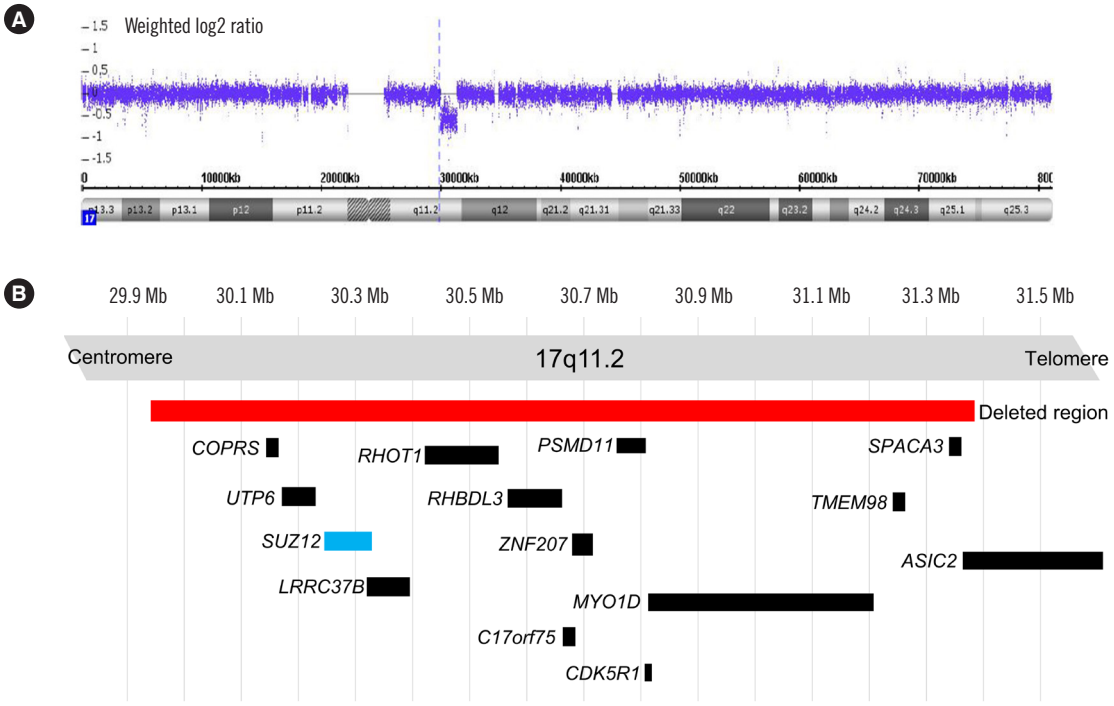

Fig. 1. Molecular investigation of our patient presenting with overgrowth and intellectual disability. (A) CytoScan Dx assay (Affymetrix, Santa Clara, CA, USA) results, including the weighted log2 ratio, revealing a 1.4-Mb deletion at 17q11.2. (B) Schematic representation of the 17q11.2 region showing the deletion as a red rectangle. *SUZ12* is shown as a blue rectangle, and the 13 other protein-coding genes are shown as black rectangles.

variants, but without prenatal overgrowth (birth weight <3rd percentile).

Deletions involving both *SUZ12* and the nearby *NF1* have been reported in 5–10% of neurofibromatosis type 1 (NF1) patients [8, 9]. NF1 patients with *SUZ12* deletion have more frequent facial dysmorphism and overgrowth than patients with variants confined to *NF1* alone, indicating that *SUZ12* haploinsufficiency contributes to the overgrowth phenotype [8]. *SUZ12* has a probability of loss-of-function intolerance score of 1.0, indicative of extreme intolerance to loss-of-function (LoF) variants in the Genome Aggregation Database [10].

In conclusion, we report the first case of a genomic deletion including *SUZ12* and the associated phenotype, which showed overlap with PRC2-related overgrowth syndrome. Further clinical reports of whole or partial *SUZ12* deletions and functional studies of LoF *SUZ12* variants would provide greater insight into the genetic mechanisms of the disorder.

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None declared.

AUTHOR CONTRIBUTIONS

Park S and Jang MA wrote the manuscript and approved the submission of the final manuscript.

CONFLICTS OF INTEREST

None declared.

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