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Case Report

# A *de novo CHD3* variant in a child with intellectual disability, autism, joint laxity, and dysmorphisms

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**Abstract**

*Background:* Chromodomain helicase DNA-binding (CHD) proteins play important roles in developmental processes. CHD3, a member of the CHD family of proteins, was reported to be a cause of a neurodevelopmental syndrome by Snijders Blok et al., but only a small number of probands have been reported.

*Case report:* The patient was a 9-year-old female with severe intellectual disability, speech impairment, autism, joint laxity and dysmorphisms. Whole exome sequencing revealed a *de novo* missense variant in *CHD3* (NM_001005273:exon18: c.2896C > T:p.R966W).

*Conclusion:* We report a case with a pathogenic variant in the *CHD3* gene. Our report indicates that *CHD3* analysis is helpful for diagnosis of the cases with neurodevelopmental disorders, joint laxity, and coarse facial phenotype.


*Keywords:* Snijders Blok-Campeau syndrome; CHD3; Intellectual disability; Joint laxity; Dysmorphisms; Speech delay

## 1. Introduction

Chromodomain helicase DNA-binding (CHD) proteins are ATP-dependent chromatin remodelers, and they play critical roles during developmental processes [1]. Numerous CHD proteins are involved in human diseases. CHD3, a member of the CHD family, had not been reported as a cause of any human diseases, but Snijders Blok et al. reported in 2018 that *CHD3* mutations caused a syndrome characterized by intellectual disability (ID), macrocephaly, and impaired speech and language [2]. Here, we report a *de novo CHD3* variant in a girl who exhibited severe ID, autism, joint laxity, impaired speech and language, and dysmorphisms (Fig. 1).

## 2. Case report

A 9-year-old female was the first child of non-consanguineous healthy Japanese parents. At birth (at 37 weeks of gestation), her weight, height, and head

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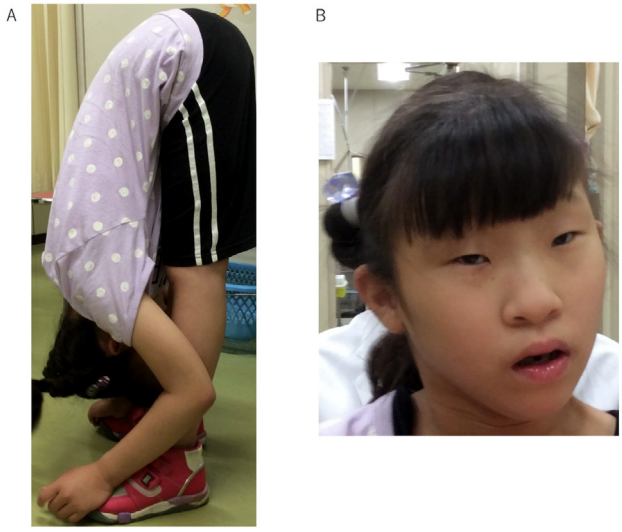


Fig. 1. A: Note joint laxity and remarkable flexibility of her body. B: Facial features of our patient at 9 years of age. Note widely spaced eyes, upslanted and short palpebral fissure, sparse eyebrows, prominent nose, epicanthus, low set ears, prominent helix, and short philtrum. We took the written permission to use the patient's photographs from the parents.

circumference were noted to be 2346 g (-0.6 standard deviations [SD]), 44 cm (-1.4 SD), and 31 cm (-1.1 SD), respectively. At the age of 4 months, strabismus was detected. Her motor developmental milestones were almost normal, but hypotonia and joint laxity were remarkable (Fig. A). She exhibited severe ID, and speech development was delayed. She spoke no meaningful words and demonstrated stereotyped and repetitive motor mannerisms. She fitted the ICD-10 criteria for autism. Brain MRI and an electroencephalogram showed no abnormality.

At the age of 9 years, her height was 124 cm (−1.5 SD), weight was 26 kg (−0.7 SD), and head circumference was 50 cm (-0.8 SD). In addition, she showed several dysmorphic features including widely spaced eyes, upslanted and short palpebral fissure, sparse eyebrows, prominent nose, epicanthus, low set ears, prominent helix, and short a philtrum (Fig. B).

Chromosome analysis in the patient revealed a normal 46, XX karyotype. Fluorescence *in situ* hybridization testing for 22q11.2 deletion syndrome was negative. Whole exome sequencing of peripheral blood DNA from the patient and both her parents was performed.

The research protocol was approved by the Ethics Committees of Sapporo Medical University School of Medicine.

A *de novo* heterozygous missense variant in *CHD3* (NM_001005273:exon18:c.2896C > T :p.R966W) was identified. This variant was not listed in the Tommo3.5KJPN database (https://jmorp.megabank.tohoku.ac.jp/202008/downloads/legacy/), PopFreqMax (ANNOVAR) database (http://www.openbioinformatics.org/annovar/). Neither of the parents carry this variant. Polyphen-2 predicted this variant to be probably damaging with a score of 1.000 (sensitivity: 0.00, specificity: 1.00) (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster predicted it to be disease-causing (http://www.mutationtaster.org/). This variant is interpreted as likely pathogenic by guidelines for the interpretation of variants by the American Collage of Medical Genetics and Genomics and the Association for Molecular Pathology [3].

## 3. Discussion

Nine CHD proteins have been identified in humans. Proteins in the CHD family are further divided into subgroups according to the presence or absence of additional domains. CHD3 is a member of the second subfamily of CHD proteins together with CHD4 [1]. Furthermore, CHD3 and CHD4 are components of the nucleosome remodeling and deacetylase (NuRD) complex that regulates gene expression in multiple tissues [4]. The NuRD complex plays an important role in embryogenesis and is required for normal development [4]. Developmental processes modulated by NuRD and some subunits including CHD3 have been linked to human genetic neurodevelopmental disorders [5]. Snijders Blok et al. reported that 35 probands with CHD3-related syndrome shared characteristic phenotypes. All of the probands had ID and speech delay/disorder, and most of them had hypotonia (75%), dysmorphisms characterized by a high, broad, and/or prominent forehead (85%) and widely spaced eyes (77%). Macrocephaly was also reported as a characteristic feature of CHD-associated syndrome [2]. Furthermore, a second cohort of *CHD3* patients was reported that all new probands had similar phenotypic presentation with Snijders Block-Campeau syndrome [6]. Among those patients, 4 patients also harbored missense mutation at amino acid codon 966, identical position to our case. CHD3 has a paired plant homeo-domain (PHD) and Zn-finger-like domain, tandem chromodomains, and an SNF2-like ATPase domain [7]. According to previous two reports, a mutation of *CHD3* has hotspots and cluster in and around the SNF-like ATPase domain [2]. The variant in our case is c.2896C > T (p.R966W), which is also around the domain. However, It was reported there was no apparent difference in phenotype between those patients with variants in hotspot region and patients with any other variant type [2,6], and the genotype-phenotype correlation for the Snijders Blok-Campeau syndrome has been still unclear. It had been revealed that CHD3 protein had three alternatively spliced transcripts encoding different isoforms by RefSeq (https://www.ncbi.nlm.nih.gov/gene/1107/). The p.R966W variant identified in

our case is the variant of shorter CHD3 isoform, transcript 2, than canonical sequences, it coincides with the p.R1025W variant of canonical CHD3 isoform which had been reported as likely pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). It has been revealed Transcript 2 of CHD3 more expressed in brain tissue, so it might be linked with the severity of ID in our case.

We identified a *de novo CHD3* pathogenic variant in a girl with severe ID, autism, joint laxity, and dysmorphisms. Since there have been few case reports on Snijders Blok-Campeau syndrome, our case could shed light on the novel association between neurodevelopmental abnormalities and *CHD3* variants, and it is important to confirm the transcript type when we evaluate the variant of *CHD3*. Our report indicates that *CHD3* analysis is helpful for diagnosis of the cases with neurodevelopmental disorders, joint laxity, and coarse facial phenotype.

## 4. Consent

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

[1] Marfella CGA, Imbalzano AN. The Chd family of chromatin remodelers. Mutat Res 2007;618(1-2):30–40.
[2] Snijders Blok L, Rousseau J, Twist J, Ehresmann S, Takaku M, Venselaar H, et al. CHD3 helicase domain mutations cause a neurodevelopmental syndrome with macrocephaly and impaired speech and language. Nat Commun 2018;9(1).
[3] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American Collage of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.
[4] Basta J, Rauchman M. The nucleosome remodeling and deacetylase complex in development and disease. Transl Res 2015;165 (1):36–47. https://doi.org/10.1016/j.trsl.2014.05.003.
[5] Pierson TM, Otero MG, Grand K, Choi A, Graham Jr JM, Young JI, Mackay JP. The NuRD complex and macrocephaly associated neurodevelopmental disorders. Am J Med Genet 2019;181 (4):548–56. https://doi.org/10.1002/ajmg.c.31752.
[6] Drivas TG, Li D, Nair D, Alaimo JT, Alders M, Altmüller J, et al. A second cohort of CHD3 patients expands the molecular mechanisms known to cause Snijders Blok-Campeau syndrome. Eur J Hum Genet 2020;28(10):1422–31. https://doi.org/10.1038/s41431-020-0654-4.
[7] Woodage T, Basrai MA, Baxevanis AD, Hieter P, Collins FS. Characterization of the CHD family of proteins. Proc Natl Acad Sci 1997;94(21):11472–7. https://doi.org/10.1073/pnas.94.21.11472.