Sotos syndrome (OMIM #117550) is an autosomal dominant overgrowth syndrome with key features of early excessive growth (e.g., both height and head circumference exceed two standard deviations [SDs] above the mean), craniofacial features (e.g., high anterior hairline, frontal bossing, downslanting palpebral fissures, hypertelorism, and pointed chin), and mild to severe learning disabilities. We describe a boy with Sotos syndrome caused by a splicing variant (c.4378+5G>A). The clinical manifestations included severe connective tissue involvement, including joint hypermobility, progressive scoliosis, pectus deformity, and skin hyperextensibility; no overgrowth was observed.

Atypical Sotos syndrome caused by a novel splice site variant

Mari Minatogawa1,2, Taichi Tsuji3,4, Mie Inaba3, Noriaki Kawakami3,6, Seiji Mizuno5 and Tomoki Kosho1,2,7,8

© The Author(s) 2022

Sotos syndrome is usually caused by haploinsufficiency of NSD1; it is characterized by overgrowth, craniofacial features, and learning disabilities. We describe a boy with Sotos syndrome caused by a splicing variant (c.4378+5G>A). The clinical manifestations included severe connective tissue involvement, including joint hypermobility, progressive scoliosis, pectus deformity, and skin hyperextensibility; no overgrowth was observed.

Human Genome Variation (2022) 9:1–4; https://doi.org/10.1038/s41439-022-00219-4

1Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan. 2Center for Medical Genetics, Shinshu University Hospital, Matsumoto, Japan. 3Department of Orthopedics, Meijo Hospital, Nagoya, Japan. 4Department of Orthopedics, Toyota Kosei Hospital, Toyota, Japan. 5Department of Orthopedics, Toyota Kosei Hospital, Toyota, Japan. 6Department of Pediatrics, Central Hospital, Aichi Developmental Disability Center, Kasugai, Japan. 7Department of Orthopedics, Ichinomiyanishi Hospital, Ichinomiya, Japan. 8Division of Clinical Sequencing, Shinshu University School of Medicine, Matsumoto, Japan. 9Research Center for Supports to Advanced Science, Shinshu University, Matsumoto, Nagano, Japan. 

Received: 11 August 2022 Revised: 20 October 2022 Accepted: 20 October 2022
Published online: 16 November 2022

© The Author(s) 2022
age, array comparative genomic hybridization and gene panel analysis of hereditary connective tissue disorders (e.g., Marfan syndrome and Ehlers–Danlos syndrome) revealed no pathogenic variants.

The proband attended a special class for physically handicapped children at an elementary school because of his severe scoliosis. Evaluation by the Wechsler Intelligence Scale for Children, 4th edition, showed that he had an IQ of 61 at the age of 11 years; thus, he was admitted to a junior high school with a special class for intellectual disabilities. He had nocturia since childhood; when he was 15 years of age, urological examinations revealed bilateral vesicoureteral reflux and a reduced bladder capacity of 180 mL. Therefore, he began oral fesoterodine therapy.

We last examined the proband when he was 16 years of age; his weight was 39.1 kg (−1.6 SD), height was 158.0 cm (−1.1 SD), and OFC was 54.0 cm (−1.4 SD). He showed craniofacial characteristics (e.g., frontal bossing, downslanting palpebral fissures, and a pointed chin) (Fig. 1G, H), skeletal features (e.g., slender build, joint hypermobility in the thumbs [Beighton score 2/9], severe scoliosis, large hands with slender fingers [Fig. 1I, J], and pes planus), and skin with softness and mild hyperextensibility but without fragility or bruissibility. Skin hyperextensibility was measured using the method by Remvig et al. (length of skin stretching ≥cutoff values in 4/5 areas). The systemic score in the revised Ghent criteria for Marfan syndrome was 7/20 (≥7 indicating systemic involvement), although he did not have aortic dilatation or ectopia lentis. He had neither overgrowth nor macrocephaly, suggesting an atypical form of Sotos syndrome.

An unknown disorder with connective tissue involvement was suspected; thus, whole-exome sequencing (WES) was performed. This study was approved by the Ethics Committee at Shinshu University School of Medicine. After written informed consent was obtained from the proband and his parents, genomic DNA was extracted from peripheral blood leukocytes and subjected to WES. Libraries were prepared with SureSelect Human All Exon kit V6 (Agilent Technologies, Santa Clara, CA, USA). Libraries were sequenced on NovaSeq (Illumina, San Diego, CA, USA) with 151-bp paired-end reads. After read quality was assessed using FastQC v.0.11.8 (https://github.com/s-andrews/FastQC), the reads were aligned to the human reference genome (UCSC hg19, NCBI build

Fig. 1 Clinical images of the proband. Facial photographs of the proband at the following ages: 1 year (A), 2 years (B), 3 years (C), 4 years (D), 8 years (E, F), and 16 years (G, H). Images of the proband's hands at the age of 16 years (I, J). A full body image of the proband at the age of 8 years (K). Radiographs of the proband's spine at the age of 2 years (L; before surgery), 5 years (M, N; after vertical expandable prosthetic titanium rib implantation), and 12 years (O; after final fixation surgery).
Although Sotos syndrome had been suspected when the proband was an infant because of intrauterine overgrowth and craniofacial features, connective tissue involvement (e.g., skin softness and mild hyperextensibility, joint hypermobility in the thumbs, and severe scoliosis) were the main clinical manifestations thereafter. We initially presumed that he had an unknown connective tissue disorder based on his substantial connective tissue-related features along with normal OFC and nonovergrowth, which are atypical for Sotos syndrome. These atypical features might be attributed to the characteristics of the detected variant, c.4378+5G>A. However, there were no data concerning detailed clinical features in a previously described patient with Sotos syndrome who had a variant at the same position (c.4378+5G>C)8. The molecular consequences of this probable splicing variant might be identified through an mRNA-based analysis, but mRNA could not be obtained from the proband. Furthermore, other gene(s) might be related to connective tissue involvement in the proband, although WES excluded variants in genes relevant to known heritable connective tissue disorders.

In conclusion, we identified a novel splice site mutation of NSD1 in a patient with atypical Sotos syndrome that included substantial connective tissue involvement without overgrowth. These observations might extend the phenotypic spectrum of Sotos syndrome.

DATA AVAILABILITY
The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figshare.hgv.3252.

REFERENCES
1. Tatton-Brown, K. et al. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. Am. J. Hum. Genet. 77, 193–204 (2005).
2. Leventopoulos, G. et al. A clinical study of Sotos syndrome patients with review of the literature. Pediatr. Neurol. 40, 357–364 (2009).
3. Kurotaki, N. et al. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat. Genet. 30, 365–366 (2002).
4. Machida, M. et al. The association of scoliosis and NSD1 gene deletion in Sotos syndrome patients. Spine 46, E726–E733 (2021).
5. Remvig, L. et al. Skin extensibility and consistency in patients with Ehlers-Danlos syndrome and benign joint hypermobility syndrome. Scand. J. Rheumatol. 38, 227–230 (2009).
6. Loeys, B. L. et al. The revised Ghent nosology for the Marfan syndrome. J. Med. Genet. 47, 476–485 (2010).
7. Pedersen-Brent, S. & Quinlan-Aaron, R. Who when and why? Detecting and resolving sample anomalies in human DNA sequencing studies with Peddy. Am. J. Hum. Genet. 100, 406–413 (2017).
8. Zlates, M. N., Ahmad, A., Bemat, J. A., Fisher, R. & Glassford, M. Genotype-phenotype analysis of 523 patients by genetics evaluation and clinical exome sequencing. Pediatr. Res. 87, 735–739 (2020).
9. Richards, S. et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. 17, 405–424 (2015).

ACKNOWLEDGEMENTS
We are grateful to the patient and his family for their cooperation. We thank Dr. T. Fujikawa; Dr. K. Nakamura, Ph.D.; Dr. K. Takano, Ph.D.; Ms. Y. Takiguchi; Ms. T. Yamaguchi; and Ms. K. Wakui, Ph.D., for their assistance. We thank Ryan Chastain-Gross, Ph.D., from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

FUNDING
This work was supported by the Initiative on Rare and Undiagnosed Diseases (IRUD) (21445007) (TK) and the Japan Agency for Medical Research and Development (AMED).
COMPETING INTERESTS
T.K. is a member of an endowed chair named “Division of Clinical Sequencing, Shinshu University School of Medicine” sponsored by BML Inc. and Life Technologies Japan Ltd. of Thermo Fisher Scientific Inc. The other authors declare no competing interests.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Tomoki Kosho.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.