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ORIGINAL ARTICLE

Clinical details of individuals with Rauch–Steindl syndrome due to *NSD2* truncating variants

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Abstract

Background: Rauch–Steindl syndrome (RAUST) is a very rare genetic syndrome caused by a pathogenic variant in *NSD2* on chromosome 4p16.3. Although *NSD2* was previously thought to be the major gene in Wolf–Hirschhorn syndrome (WHS), a contiguous gene syndrome of chromosome 4p16.3 deletion, RAUST has been found to present different facial and clinical features from WHS. In this study, we report the details of two newly diagnosed individuals with RAUST in order to better understand the molecular and clinical features of RAUST.

Methods: Whole-genome sequencing was performed on two individuals with psychomotor delay and growth failure. Detailed clinical evaluation of growth parameters, craniofacial features, electroencephalogram (EEG), magnetic resonance imaging of the brain, and developmental assessment were performed.

Results: Both individuals had de novo truncating variants in *NSD2*. One had a novel variant (c.2470C>T, p.Arg824*), and the other had a recurrent variant (c.4028del, p.Pro1343Glnfs*49). Both exhibited characteristic RAUST facial features, growth failure, and mild psychomotor delay. A novel finding of RAUST was seen in individual 2, a Chiari malformation type 1, and both showed delayed bone age. They lacked common WHS features such as congenital heart defects, cleft lip/palate, and seizures (EEG with abnormal findings).

Conclusion: We present a novel variant and clinical presentations of RAUST, expand the molecular and clinical diversity of RAUST, and improve our understanding of this rare syndrome, which is distinct from WHS. Further researches are needed on more RAUST cases and on functional analysis of *NSD2*.

KEYWORDS
loss-of-function, NSD2, psychomotor delay, Rauch–Steindl syndrome

1 | INTRODUCTION

Rauch–Steindl syndrome (RAUST) (MIM #619695) is a very rare genetic syndrome caused by a heterozygous pathogenic variant in *NSD2* on chromosome 4p16.3 (Zanoni et al., 2021). *NSD2* encodes a SET domain-containing transcriptional regulatory protein with histone methyltransferase activity that is associated with

actively transcribed regions of the genome during embryonic development. NSD2 is the principal enzyme that demethylates histone H3 at lysine 36 (H3K36me2) in most cells and tissues (Boczek et al., 2018; Zanoni et al., 2021). *NSD2*, also called *WHSC1* (Wolf–Hirschhorn syndrome candidate 1), has been considered important for the phenotype of Wolff–Hirschhorn syndrome (WHS) (MIM #194190), a contiguous gene deletion syndrome associated with a hemizygous deletion of chromosome 4p16.3 (Battaglia et al., 2008, 2015). RAUST is characterized by pre- and postnatal growth retardation, sometimes accompanied by short stature and microcephaly, dysmorphic facial features, and variable degrees of delayed motor and speech acquisition, and mildly impaired intellectual ability that can be mild. Recently, several reports have been published regarding individuals with loss-of-function variants in *NSD2*; those clinical presentations were found to overlap only partially with that of WHS. Moreover, they did not share the 'Greek warrior helmet' facial features of WHS (Barrie et al., 2019; Boczek et al., 2018; Derar et al., 2019; Hu et al., 2020; Jiang et al., 2019; Lozier et al., 2018; Zanoni et al., 2021). Although both RAUST and WHS share growth failure and psychomotor delays, there are some differences between the two syndromes. RAUST presents with a milder phenotype than WHS, and characteristic symptoms such as seizures, cleft palate, and heart disease, commonly observed in WHS, are less frequent in RAUST. Moreover, the facial features of individuals with RAUST have been reported to have sufficient specificity to distinguish it as a distinct syndrome (Zanoni et al., 2021). We presented the similarities and differences between RAUST and WHS in Table S1 (Battaglia et al., 2008, 2015; Zanoni et al., 2021). Here, we present the clinical details of two individuals of RAUST who had de novo heterozygous pathogenic variants in *NSD2*.

2 | CASE REPORT

Individual 1, a 7-year-old boy, was the second child of a healthy 42-year-old mother and a healthy 43-year-old nonconsanguineous father with no family history about psychomotor delay and growth failure. He was born via normal vaginal delivery at 41 weeks and 3 days of gestation after an uncomplicated pregnancy. His birth weight was 2876 g (−1.6 SD), his length was 47.2 cm (−1.6 SD), and his occipitofrontal circumference (OFC) was 35.0 cm (+1.0 SD). He did not show respiratory or feeding difficulties in the neonatal period but had feeding problems from infancy. At the age of 1 year and 7 months, he was referred to our clinic for a close examination of the genetic etiology of growth failure and psychomotor delay.

Individual 2, a 5-year-old boy, was the first child of a healthy 18-year-old mother and a healthy 19-year-old nonconsanguineous father with no family history about psychomotor delay and growth failure. He was delivered by cesarean section at 36 weeks and 1 day owing to umbilical cord torsion. His birth weight was 1690 g (−2.5 SD), his length was 40.3 cm (−2.3 SD), and OFC was 30.5 cm (−1.1 SD). He was referred to our clinic at the age of 1 year and 2 months for investigation of the genetic etiology of growth failure with psychomotor delay.

Individuals 1 and 2 showed relative macrocephaly, a mild triangular face, broad forehead, high anterior hairline, broad arched and laterally sparse eyebrows, full cheeks, thin and elevated nasal bridge, smooth short philtrum, prominent Cupid's bow, thick everted lower lip vermilion, protruding ears, and clinodactyly (Table 1, Figure 1). Individual 1 exhibited growth failure at age 1 year and 7 months with a SD of −2.5 SD for the height, −2.9 SD for the weight, and −0.8 SD for the OFC. Thereafter, at 3 years and 2 months, the SD of the height was −3.2 SD, that of the weight −2.2 SD, and that of the OFC −0.3 SD. At 5 years and 4 months, the SD of the height was −3.3 SD, that of the weight −2.4 SD, and that of the OFC −0.8 SD, with even more marked growth impairment and relative macrocephaly (Figure 2). An X-ray of the carpal bones at the age of 5 years and 8 months showed a delay of approximately 2 years delayed bone age (Figure 1). Individual 1 exhibited marked growth failure; however, no growth hormone (GH) deficiency was observed in the arginine-loaded GH stress test at 4 years and 3 months of age. Individual 1 had right cryptorchidism and underwent right orchidopexy at 1 year and 8 months. There was no history of seizures, but a sporadic spike wave was noted on an EEG at the age of 5 years. Individual 2 showed intrauterine growth retardation, at the age of 1 year and 2 months with a SD of −3.0 SD for height, −2.9 SD for the weight, and −1.6 SD for the OFC. At the age of 5 years and 8 months, the SD was −2.1 SD for the height, −3.2 SD for the weight, and −1.0 SD for the OFC, indicating growth failure and relative macrocephaly (Figure 2). He also exhibited delayed bone age, but no GH deficiency, and was treated with GH owing to being diagnosed with small for gestational age. He had brain MRI findings of Chiari malformation type 1 and bilateral T2WI high signals in the cerebral white matter (Figure 1). He had no evidence of seizures or epilepsy; however, an abnormal EEG was observed. He exhibited bilateral accommodative esotropia and hyperopic astigmatism.

The growth curves for individuals 1 and 2 are shown in Figure 2. In addition, we have included Table 2 detailing their development. Hypotonia was not marked, but a generalized psychomotor delay was present. Autism spectrum disorder was not evident in either individual. Moreover,

TABLE 1 Molecular findings and clinical details of the two individuals with Rauch–Steindl syndrome.

	Evaluation	Individual 1	Individual 2
Age		7 years	5 years
Sex		Male	Male
Karyotype		46, XY	46, XY
Chromosomal microarray		No pathogenic CNVs	No pathogenic CNVs
Molecular findings	Gene	*NSD2*: NM_133330: c.2470C > T, (p.Arg 824*)	*NSD2*: NM_133330: c.4028del, (p.Pro1343Glnfs*49)
	Molecular consequence	Nonsense	Frame shift
	The ACMG/AMP classification (Richards et al., 2015)	Pathogenic (PVS1, PP3, PM2, PS2)	Pathogenic (PVS1, PS3, PM2, PS2)
	ClinVar	No registration (14 September 2023)	Pathogenic (24 June 2022)
Perinatal findings	Gestational age	41w3d	36w1d
	Birth height (SD)	47.2 cm (−1.7 SD)	40.3 cm (−2.3 SD)
	Birth weight (SD)	2876 g (−1.6 SD)	1690 g (−2.5 SD)
	Birth OFC (SD)	35 cm (+1.0 SD)	30.5 cm (−1.1 SD)
Growth	Height (SD)	107.7 cm (−2.8 SD)	101.5 cm (−2.1 SD)
	Weight (SD)	15 kg (−4.1 SD)	13.3 kg (−3.2 SD)
	OFC (SD)	52 cm (−0.1 SD)	49.5 cm (−1.0 SD)
Cardiovascular	Echocardiography ECG	No congenital heart disease	No congenital heart disease
Neurological	MRI EEG	No brain malformations, no seizures, EEG abnormalities (bilateral temporal spikes)	Chiari malformation type 1, no seizures, EEG abnormalities
Endocrinological	Carpal bone X-ray, the arginine-loaded growth hormone stress test	Delayed bone age (3y3m/5y8m) no failure of growth hormone	Delayed bone age (3y/5 m) no failure of growth hormone
Otorhinological	Otorhinolaryngological examination, ABR	No hearing loss	No hearing loss
Ophthalmic	Ophthalmology examination	No ocular complications	Accommodative esotropia, hyperopic astigmatism
Urological	Echography	Cryptorchidism	NP
Oral	Oral surgery examination	No cleft palate or soft palate	No cleft palate or soft palate
Neurodevelopment	The Kyoto Scale of Psychological Development (2001) (Koyama et al., 2009)	Moderate to severe psychomotor delay At 5 years 5 months, the overall DQ was 35	Moderate to severe psychomotor delay at 5 years 7 months, the overall DQ was 37
Feeding problem		+	+
Craniofacial dysmorphia and physical characteristics		Relative macrocephaly, triangular face, broad forehead, high anterior hairline, deeply set eyes, broad arched and laterally sparse eyebrows, periorbital hyperpigmentation, full cheeks, thin and elevated nasal bridge, smooth short philtrum, prominent cupid bow, thick everted lower lip vermilion, protruding ears, and clinodactyly	Relative macrocephaly, mild triangular face, broad forehead, high anterior hairline, broad arched and laterally sparse eyebrows, full cheeks, thin and elevated nasal bridge, smooth short philtrum, prominent cupid bow, thick everted lower lip vermilion, and protruding ears, and clinodactyly

Abbreviations: ABR, auditory brainstem response; CNV, copy number variation; DQ, development quotient; EEG, electroencephalogram; MRI, magnetic resonance imaging; NP, no particular findings; OFC, occipitofrontal circumference; SD, standard deviation.

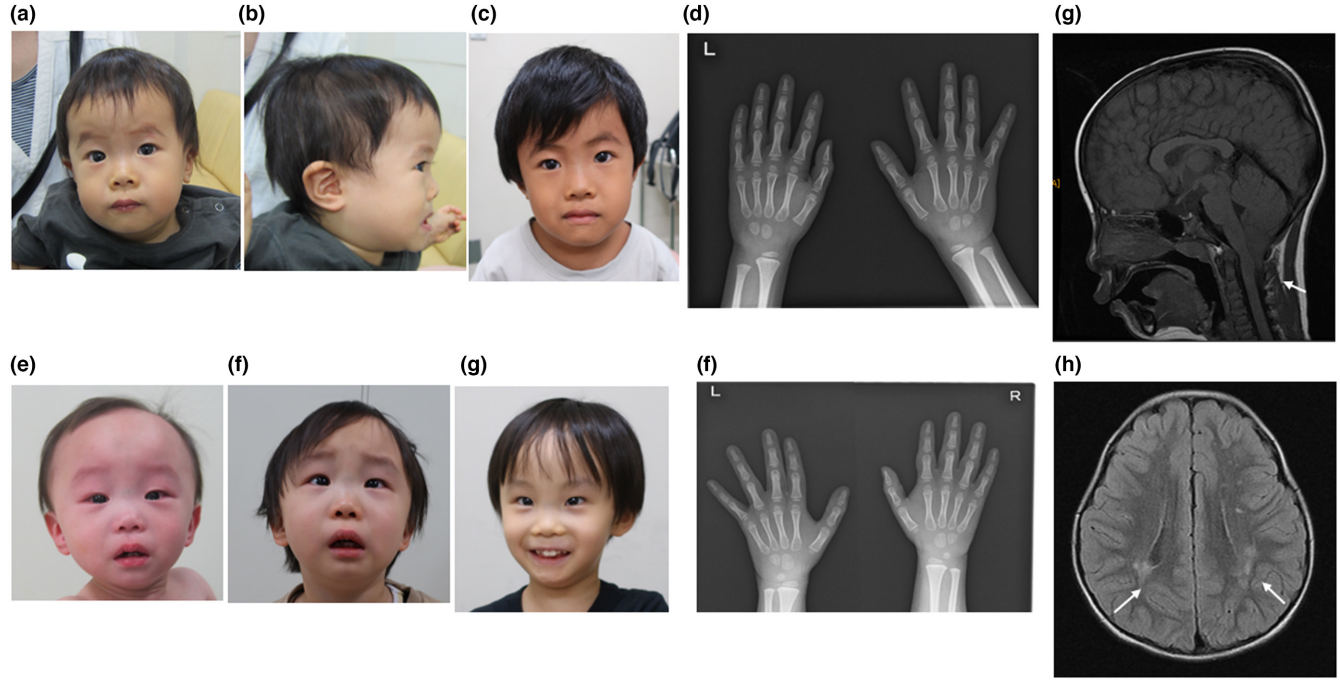

FIGURE 1 Photographs of individuals with RAUST. Note that craniofacial dysmorphic features including relative macrocephaly, mild triangular face, broad forehead, high anterior hairline, broad arched and laterally sparse eyebrows, full cheeks, thin and elevated nasal bridge, smooth short philtrum, prominent cupid bow, thick everted lower lip vermilion, and protruding ears. Both individuals do not have the 'Greek warrior helmet' facial features of WHS. Photographs of Individual 1 (a, b—1 year and 6 months, c—5 years and 8 months) and Individual 2 (e—1 year and 2 months, f—4 years and 4 months; g—4 years and 11 months). X-ray imagings of bilateral carpal bones of individual 1 (d—5 years and 8 months) and individual 2 (f—5 years). Bone age is delayed by about 2 years in both individuals. Brain MRI findings of individual 2 (g—Chiari malformation type 1, h—bilateral T2WI high signal in the cerebral white matter).

they shared a lack of interest in food and had poor feeding and low food intake during infancy and early childhood.

3 | METHODS

3.1 | Editorial policy and ethical considerations

This study was approved by the Institutional Ethics Committee (approval number 31154). Written informed consent was obtained from the parents of the patients for the genetic analysis and for the publication of their photographs.

3.2 | Genetic analysis

Chromosomal aberrations were analyzed using G-band karyotype analysis, followed by chromosomal microarray testing using the Agilent 60 K Human Genome CGH Microarray (CMA) platform (Agilent Technologies, Santa Clara, CA, USA). Trio-based whole-exome sequencing (WES) was performed. The sequence library was prepared using a Human All Exon V6 Kit (Agilent Technologies, CA, USA) or Twist Comprehensive Exome, Mitochondrial DNA Panel Spike In (Twist Bioscience, CA, USA) and sequenced using a NovaSeq with 150-bp paired-end reads. Sequence reads were aligned to GRCh38 and annotated using CompStor NOVOS and CompStor Insight (OmniTier, CA, USA). Variants with allele frequencies greater than 0.01 in gnomAD, 14KJPN (jMORP) and our in-house exome variant data were removed. Remained variants were narrowed down based on the assumed modes of inheritance, such as autosomal dominant, autosomal recessive, X-linked, and compound heterozygous inheritance. The candidate variants by WES were validated by Sanger sequencing.

3.3 | Clinical analysis

Clinical data were obtained from the chart of the individuals, and complications, growth parameters, craniofacial dysmorphia, physical characteristics, development, bone age, electroencephalogram (EEG) readings, magnetic resonance imaging (MRI) of the brain, and psychomotor development tests were evaluated in each specialty departments (Table 1). Clinical geneticists (E.N. and N.O.) examined and evaluated their physical features, including

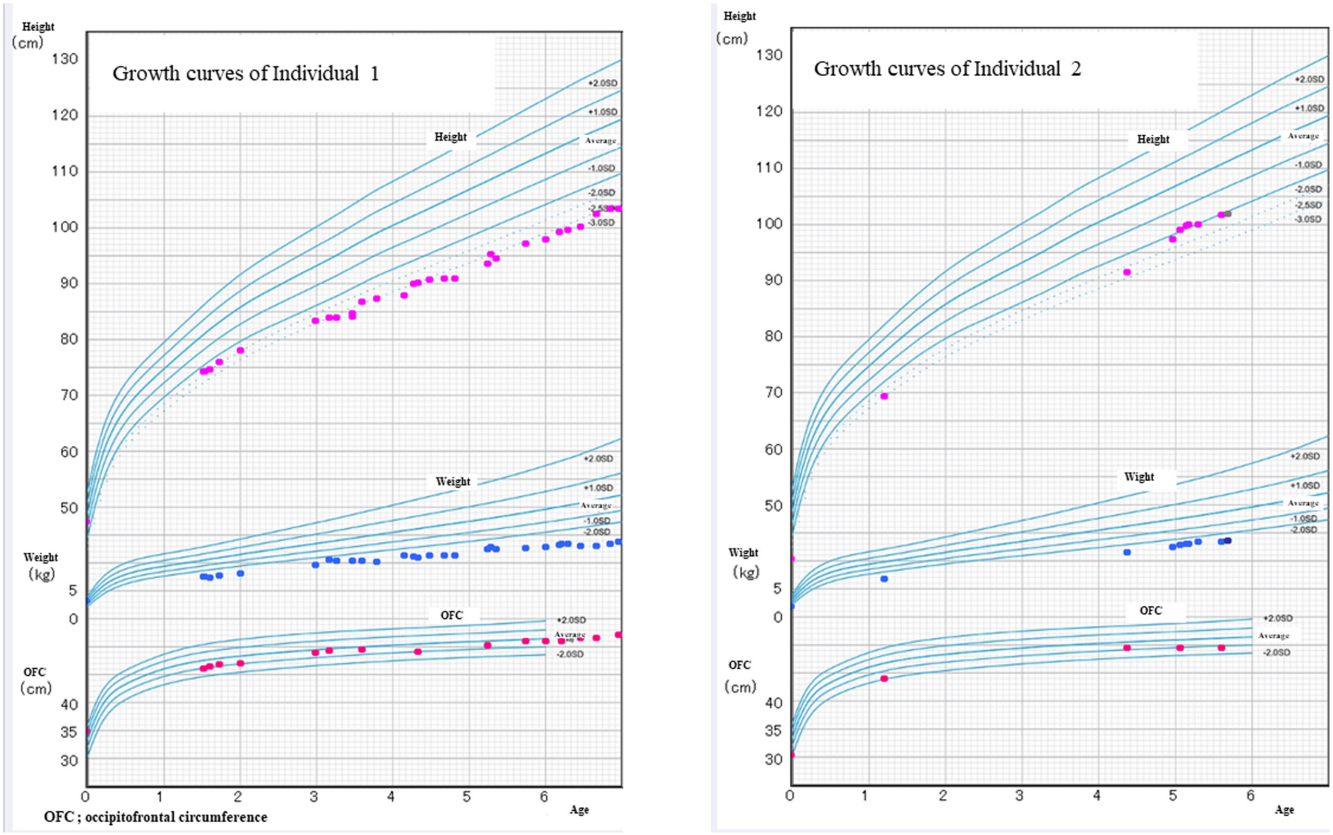

FIGURE 2 Growth curves of individuals 1 and 2.

craniofacial features. The developmental details of the milestones for the two individuals in RAUST compared to an individual with a microdeletion of 4p16.3, including part of *NSD2* (Okamoto et al., 2013), are presented in Table 2.

4 | RESULTS

4.1 | Summary of genetic findings

No chromosomal aberrations were observed in any of the individuals (Table 1). We identified a novel heterozygous nonsense variant, c.2470C>T, (p.Arg 824*), in *NSD2* (NM_001042424.3) in individual 1 (Table 1). This was confirmed de novo using their parental analysis. The allele frequency of this variant is zero in the genome aggregation (gnomAD) database (Table S2). The variant was predicted to be pathogenic using MutationTaster and FATHMM-MKL. It was also classified as pathogenic according to the guideline of the American College of Medical Genetics and Genomics (ACMG)/Association of Molecular Pathology (AMP; Richards et al., 2015) because of nonsense variants in the gene for which loss-of-function is known mechanism (PVS1), the variants had arisen de novo (PS2), the variants were absent from controls (PM2), and there was in silico evidence (PP3; Table S2). We also identified a recurrent heterozygous frameshift variant in *NSD2* (NM_001042424.3), c.4028del, (p. Pro1343Glnfs*49), in individual 2 (Table 1). This was confirmed de novo using their parental analysis. This frameshift variant was classified as pathogenic using ClinVar and was also classified as pathogenic (PVS1, PS1, PS3, PM2, PS2) according to the ACMG/AMP guidelines (Richards et al., 2015; Table S2). There were no other candidate genes in individual 1 in this study. In individual 2, *FAT4*, the causative gene for the autosomal recessive Van Maldergem syndrome 2 (MIM #615546) and Hennekam lymphangiectasia–lymphedema syndrome 2 (MIM #616006), was filtered. However, it was excluded because the clinical symptoms were not consistent and both paternal and maternal variants were classified as likely benign according to the ACMG/AMP guidelines (Richards et al., 2015; Table S2).

5 | DISCUSSION

We identified a novel and recurrent truncating pathogenic variant in *NSD2* in two individuals with growth failure and moderate psychomotor delay. *NSD2*, also known as *WHSC1*, has been considered a critical gene in WHS, 4p16.3 deletion syndrome. Recently, it has been reported

TABLE 2 Developmental details of the individuals with Rauch–Steindl syndrome (compared to the individual with 109 kb deletion of 4p16.3, including a part of *NSD2*; Okamoto et al., 2013).

Complications	Individual 1	Individual 2	Individual with 109 kb deletion of 4p16.3, including a part of *NSD2* (Okamoto et al., 2013)	Wolf–Hirschhorn syndrome (Battaglia et al., 2015, 2008)
Sex	Male	Male	Male	
	NSD2: NM_001042424.3 c.2470C > T, (p.Arg 824*)	*NSD2*: NM_001042424.3: c.4028del, (p.Pro1343Glnfs*49)	arr 4p16.3 (1,792,001–1,900,840) × 1dn	
Held head up	5 m	3 m	3 m	ND (motor milestone are delayed)
Rolled over	6 m	9 m	10 m	ND (motor milestone are delayed)
Sat up alone	10 m	10 m	12 m	ND (motor milestone are delayed)
Crawled	12 m	11 m	10 m	ND (motor milestone are delayed)
Stood with assistance		11 m	11 m	ND (motor milestone are delayed)
Walked alone	28 m	24 m	14 m	45% of individuals with WHS are able to walk by age 2–12 years, either independently or with support
Spoke first word	48 m	24 m	19 m	Only small fraction of individuals with WHS is pronounce simple sentences
First tooth	11 m	9 m	11 m	ND
The Kyoto Scale of Psychological Development (2001) (Koyama et al., 2009)	At 5 years 5 months, the overall DQ was 35	At 5 years 7 months, the overall DQ was 37	At 2 years 6 months/8 years 8 months, the overall DQ was 71/65	ND
PM (posture-motor)	DQ 37	DQ 43	DQ 123	ND
CA (cognition-adaption)	DQ 33	DQ 39	DQ 68/70	ND
LS (language-social)	DQ 37	DQ 37	DQ 65/61	ND
Autism/ADHD	−/−	−/−	−/+	+/+, with behavior problem
Feeding problem	Low interest in food, selective eating, and reduced appetite were observed.	Selective eating and fluctuations in appetite were noted	Poor appetite and lack of desire to eat were observed	44% of individuals with WHS required gastrostomy
Sleeping disorder	NP	NP	NP	+

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DQ, developmental quotient; m, months; ND, no data; NP, no particular findings.

that individuals with pathological variants in *NSD2* share common facial features lack the so-called 'Greek warrior's helmet' features specific to WHS, and their physical complications only partially overlap with those of WHS and are recognized as RAUST (Barrie et al., 2019; Boczek et al., 2018; Derar et al., 2019; Hu et al., 2020; Jiang et al., 2019; Lozier et al., 2018; Yang et al., 2023; Zanoni et al., 2021; Table S1). A detailed clinical examination of two individuals with RAUST in the present study revealed that facial features were consistent with previously reported features of RAUST (Zanoni et al., 2021). Regarding complications, neither individual had congenital heart disease, cleft lip and palate, hearing loss, or epilepsy, which are common in WHS but infrequent in RAUST, supporting prior reports (Table 1). The finding of Chiari malformation type 1 on brain MRI in individual 2 is novel and should broaden the clinical diversity of RAUST. From this detailed investigation, both individuals have no history of seizures or epilepsy, but EEG studies showed abnormalities, suggesting that careful follow-up is important. Regarding growth, previous reports showed that the SD of height in RAUST was −2.3, weight was −2.4, and head circumference was +1.1. Furthermore, individuals with truncating variants were reported to be significantly shorter than those with missense variants (Zanoni et al., 2021). In the present study, both individuals with truncating variants had a SD of height of −2.8 SD (individual 1, at age 7 years) and − 2.1 SD (individual 2, at age 5 years), consistent with results from previous studies (Table 1; Zanoni et al., 2021). Interestingly, the finding that both individuals showed growth failure but no GH deficiency is one of the new findings of RAUST. Regarding development, the median age at independent walking of both individuals was 26 months (range, 24–28 months), and the median age at beginning of single-word speech was 36 months (range, 24–48 months). Statistical tests were difficult because only two individuals were included; however, the postural-motor, cognitive-adaptive, and language-social quotients appeared to be unbiased (Table 2).The two individuals had a median developmental quotient (DQ) of 36 (range, 35–37) at the age of 5 years, indicating a moderate delay. To characterize the development of RAUST, we compared their milestones with those of individuals with a 109 kb microdeletion that partially encompasses the 5′ end of *NSD2* (Okamoto et al., 2013), WHS (Table 2, Table S2). The results suggest that the developmental characteristics are similar to those of individuals with microdeletions, but not WHS, which may also be affected by other genes. For this comparison, as a limitation, it should be noted that there are few individuals, and for WHS, the size of the deletion and the genes included in the deletion are not currently defined, and that there is very little information on the milestones and developmental details.

NSD2 encodes a nuclear SET domain-containing transcriptional regulatory protein that contains four development-related domains: a PWWP domain, an HMG box, a SET domain, and a PHD-type zinc finger domain. NSD2, a SET domain histone methyltransferase responsible for the methylation of H3K36, is expressed widely across many cells and tissues, and participates in various biological processes, including early development, cytokine signaling, the DNA damage response, and class switch recombination. (Yang et al., 2023; Zanoni et al., 2021). Loss-of-function variants in *NSD2* may potentially influence cellular senescence, energy production, cell cycle regulation, and epigenetic accuracy (Tanaka et al., 2020). To date, approximately 40 variants in *NSD2* have been identified, and both missense and truncating variants are encompass various domains rather than being concentrated in specific domains (Barrie et al., 2019; Boczek et al., 2018; Derar et al., 2019; Hu et al., 2020; Jiang et al., 2019; Lozier et al., 2018; Yang et al., 2023; Zanoni et al., 2021; Figure 3). The novel nonsense and recurrent frameshift variant in this study are located near the PHD zinc finger domain and are stop codons that may result in *NSD2* haploinsufficiency. A recent study has revealed that truncated variants in *NSD2* exhibit a methylated pattern that is highly similar to that observed in WHS. This suggests that the loss

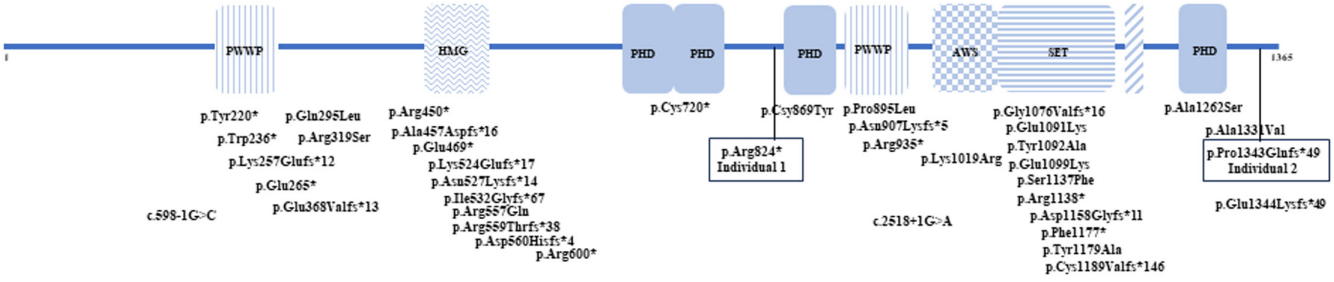

FIGURE 3 The diagram shows the structure of *NSD2*. Previously reported *NSD2* variants are shown in the *NSD2* schematic (Barrie et al., 2019; Boczek et al., 2018; Derar et al., 2019; Hu et al., 2020; Jiang et al., 2019; Lozier et al., 2018; Yang et al., 2023; Zanoni et al., 2021). The novel variants of individual 1 and the recurrent variants of individual 2 in this study are boxed.

of *NSD2* function may partially contribute to the epigenetic changes observed in WHS and that these alterations may potentially impact gene expression and development (McConkey et al., 2022).

The limitations of this study include the small number of participants and the fact that no functional studies were conducted.

In conclusion, our report on the clinical manifestations of two individuals with RAUST supports that the notion that the truncated pathogenic variant in *NSD2* confers clinical features of RAUST that are distinct from the WHS phenotype. Furthermore, the clinical diversity of RAUST was demonstrated by the presence of Chiari malformation type 1 complications, as well as the presence of EEG abnormalities and delayed bone age, common to both individuals. Still, further studies are warranted to accumulate more RAUST cases and their clinical manifestations, and to elucidate the mechanism whereby pathogenic variants in *NSD2* cause RAUST.

AUTHOR CONTRIBUTIONS

Eriko Nishi diagnosed and provided clinical data, planned the study, and wrote the manuscript. Kumiko Yanagi and Tadashi Kaname provided molecular genetic data. Nobuhiko Okamoto supervised the study. All authors reviewed the drafts and authorized the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (E.N.), upon reasonable request.

ETHICS STATEMENT

This study has been approved by the corresponding authors' Institutional Review Board.

PATIENT CONSENT STATEMENT

Informed consent has been obtained from all individuals included in this study.

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REFERENCES

Barrie, E. S., Alfaro, M. P., Pfau, R. B., Goff, M. J., McBride, K. L., Manickam, K., & Zmuda, E. J. (2019). De novo loss-of-function variants in NSD2 (WHSC1) associate with a subset of Wolf-Hirschhorn syndrome. *Cold Spring Harbor Molecular Case Studies*, *5*(4), a004044. https://doi.org/10.1101/mcs.a004044

Battaglia, A., Filippi, T., & Carey, J. C. (2008). Update on the clinical features and natural history of Wolf-Hirschhorn (4p-) syndrome: Experience with 87 patients and recommendations for routine health supervision. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *148C*(4), 246–251. https://doi.org/10.1002/ajmg.c.30187

Battaglia, A., Carey, J. C., & South, S. T. (2015). Wolf-Hirschhorn syndrome: A review and update. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *169*(3), 216–223. https://doi.org/10.1002/ajmg.c.31449

Boczek, N. J., Lahner, C. A., Nguyen, T. M., Ferber, M. J., Hasadsri, L., Thorland, E. C., Niu, Z., & Gavrilova, R. H. (2018). Developmental delay and failure to thrive associated with a loss-of-function variant in WHSC1 (NSD2). *American Journal of Medical Genetics. Part A*, *176*(12), 2798–2802. https://doi.org/10.1002/ajmg.a.40498

Derar, N., Al-Hassnan, Z. N., Al-Owain, M., Monies, D., Abouelhoda, M., Meyer, B. F., Moghrabi, N., & Alkuraya, F. S. (2019). De novo truncating variants in WHSC1 recapitulate the Wolf-Hirschhorn (4p16.3 microdeletion) syndrome phenotype. *Genetics in Medicine*, *21*(1), 185–188. https://doi.org/10.1038/s41436-018-0014-8

Hu, X., Wu, D., Li, Y., Wei, L., Li, X., Qin, M., Li, H., Li, M., Chen, S., Gong, C., & Shen, Y. (2020). The first familial NSD2 cases with a novel variant in a Chinese father and daughter with atypical WHS facial features and a 7.5-year follow-up of growth hormone therapy. *BMC Medical Genomics*, *13*(1), 181. https://doi.org/10.1186/s12920-020-00831-9

Jiang, Y., Sun, H., Lin, Q., Wang, Z., Wang, G., Wang, J., Jiang, F., & Yao, R. (2019). De novo truncating variant in NSD2 gene leading to atypical Wolf-Hirschhorn syndrome phenotype. *BMC Medical Genetics*, *20*(1), 134. https://doi.org/10.1186/s12881-019-0863-2

Koyama, T., Osada, H., Tsujii, H., & Kurita, H. (2009). Utility of the Kyoto scale of psychological development in cognitive assessment of children with pervasive developmental disorders. *Psychiatry and Clinical Neurosciences*, *63*(2), 241–243. https://doi.org/10.1111/j.1440-1819.2009.01931.x

Lozier, E. R., Konovalov, F. A., Kanivets, I. V., Pyankov, D. V., Koshkin, P. A., Baleva, L. S., Sipyagina, A. E., Yakusheva, E. N., Kuchina, A. E., & Korostelev, S. A. (2018). De novo nonsense mutation in WHSC1 (NSD2) in patient with intellectual disability and dysmorphic features. *Journal of Human Genetics*, *63*(8), 919–922. https://doi.org/10.1038/s10038-018-0464-5

McConkey, H., White-Brown, A., Kerkhof, J., Dyment, D., & Sadikovic, B. (2022). Genetically unresolved case of Rauch-Steindl syndrome diagnosed by its Wolf-Hirschhorn associated DNA methylation episignature. *Frontiers in Cell and*

Developmental Biology, *10*, 1022683. https://doi.org/10.3389/fcell.2022.1022683

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee (2015). 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. *Genetics in Medicine: An Official Journal of the American College of Medical Genetics*, *17*(5), P405–P424. https://doi.org/10.1038/gim.2015.30

Okamoto, N., Ohmachi, K., Shimada, S., Shimojima, K., & Yamamoto, T. (2013). 109 kb deletion of chromosome 4p16.3 in a patient with mild phenotype of Wolf-Hirschhorn syndrome. *American Journal of Medical Genetics. Part A*, *161A*(6), 1465–1469. https://doi.org/10.1002/ajmg.a.35910

Tanaka, H., Igata, T., Etoh, K., Koga, T., Takebayashi, S. I., & Nakao, M. (2020). The NSD2/WHSC1/MMSET methyltransferase prevents cellular senescence-associated epigenomic remodeling. *Aging Cell*, *19*(7), e13173. https://doi.org/10.1111/acel.13173

Yang, Q., Gong, D., Yi, S., Luo, J., & Zhang, Q. (2023). Case report: A de novo NSD2 truncating variant in a child with Rauch-Steindl syndrome. *Frontiers in Pediatrics*, *11*, 1064783. https://doi.org/10.3389/fped.2023.1064783

Zanoni, P., Steindl, K., Sengupta, D., Joset, P., Bahr, A., Sticht, H., Lang-Muritano, M., van Ravenswaaij-Arts, C. M. A., Shinawi, M., Andrews, M., Attie-Bitach, T., Maystadt, I., Belnap, N., Benoit, V., Delplancq, G., de Vries, B. B. A., Grotto, S., Lacombe, D., Larson, A., … Rauch, A. (2021). Loss-of-function and missense variants in NSD2 cause decreased methylation activity and are associated with a distinct developmental phenotype. *Genetics in Medicine*, *23*(8), 1474–1483. https://doi.org/10.1038/s41436-021-01158-1

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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