

RESEARCH ARTICLE

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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

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Abstract

Background: Wolf-Hirschhorn syndrome is a well-characterized genomic disorder caused by 4p16.3 deletions. Wolf-Hirschhorn syndrome patients exhibit characteristic facial dysmorphism, growth retardation, developmental delay, intellectual disability and seizure disorders. Recently, *NSD2* gene located within the 165 kb Wolf-Hirschhorn syndrome critical region was identified as the key causal gene responsible for most if not all phenotypes of Wolf-Hirschhorn syndrome. So far, eight *NSD2* loss of function variants have been reported in patients from different parts of the world, all were de novo variants.

Methods: In our study, we performed whole exome sequencing for two patients from one family. We also reviewed more *NSD2* mutation cases in pervious literature.

Results: A novel loss of function *NSD2* variant, c.1577dupG (p.Asn527Lysfs*14), was identified in a Chinese family in the proband and her father both affected with intellectual disability. After reviewing more *NSD2* mutation cases in pervious literature, we found none of them had facial features that can be recognized as Wolf-Hirschhorn syndrome. In addition, we have given our proband growth hormone and followed up with this family for 7.5 years.

Conclusions: Here we reported the first familial *NSD2* variant and the long-term effect of growth hormone therapy for patients. Our results suggested *NSD2* mutation might cause a distinct intellectual disability and short stature syndrome.

Keywords: Wolf-Hirschhorn syndrome, *NSD2* gene, Growth hormone therapy, Facial dysmorphism, Intellectual disability

Background

Wolf-Hirschhorn syndrome (WHS, MIM 194190) has been regarded as a classic contiguous gene deletion syndrome affecting 1 in 20,000–50,000 live births worldwide, with a 2:1 female/male ratio. Despite its great phenotypic variability, the minimal diagnostic criteria for WHS are defined by typical facial features, prenatal/postnatal growth retardation, developmental delay/intellectual disability (ID) and seizures [1, 2]. Other findings

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include skeletal anomalies, hypotonia, antibody deficiency, heart defects, hearing loss, urinary tract malformations, structural brain abnormalities, etc. [3]. A 165 kb Wolf-Hirschhorn syndrome critical region (WHSCR) at 4p16.3, which was commonly deleted by all WHS patients, was first described in 1997 by Wright et al. [4]. Within this critical region, the *NSD2* gene, also known as *WHSC1* (*Wolf-Hirschhorn Syndrome Candidate 1* gene), had been recognized as one of the key candidate genes for the contiguous gene deletion syndrome.

NSD2 encodes nuclear receptor-binding set domain protein 2, a histone-lysine N-methyltransferase that is believed to play a significant role in normal development [5]. Since 2018, eight patients with loss of function *NSD2* variants have been reported around the world [6–10] (Fig. 1). While most *NSD2* patients presented with overlapping yet atypical features of WHS, thus defining a novel WHS-like disorder, this gene had also been viewed as the disease gene for WHS [9]. Whether or not *NSD2* could account for all WHS phenotypes remain to be further elucidated. Herein, we reported the first familial *NSD2* case from a Chinese family with a novel *NSD2* pathogenic variant. The father had the de novo variant which was passed on to the proband daughter. We describe the clinical phenotypes of both father and daughter. We also evaluated the effectiveness of a long-term growth hormone therapy for the proband based on a 7.5-year follow-up study.

Methods

Subjects

The proband was first referred to the Pediatric Endocrine Clinic at Beijing Children's Hospital due to poor weight gain and growth delay. Written informed consents to participate were obtained from participants and the parents of the participant under the age of 16. The study was approved by the institutional medical ethics committee of Beijing Children's Hospital.

Genomic sequencing and variants analysis

DNA was isolated from peripheral blood samples obtained from patients and family members by using the GentraPuregene Blood Kit (QIAGEN, Hilden, Germany) according to the manufacturer's protocol. The SureSelect Human All Exon Kit (Agilent Technologies, Santa Clara, America) was used for whole exome capture from proband's DNA. Next generation sequencing was done using HiSeq2000 (Illumina, San Diego, America). Paired-end reads were aligned to the GRCh37/hg19 human reference sequence using Burrows-Wheeler Aligner (BWA) with the MEM algorithm. BAM files were generated by Picard. Sequence reads were recalibrated

by RealignerTargetCreator in Genome Analysis Toolkit (GATK) and sequence variants were called by GATK HaplotypeCaller.

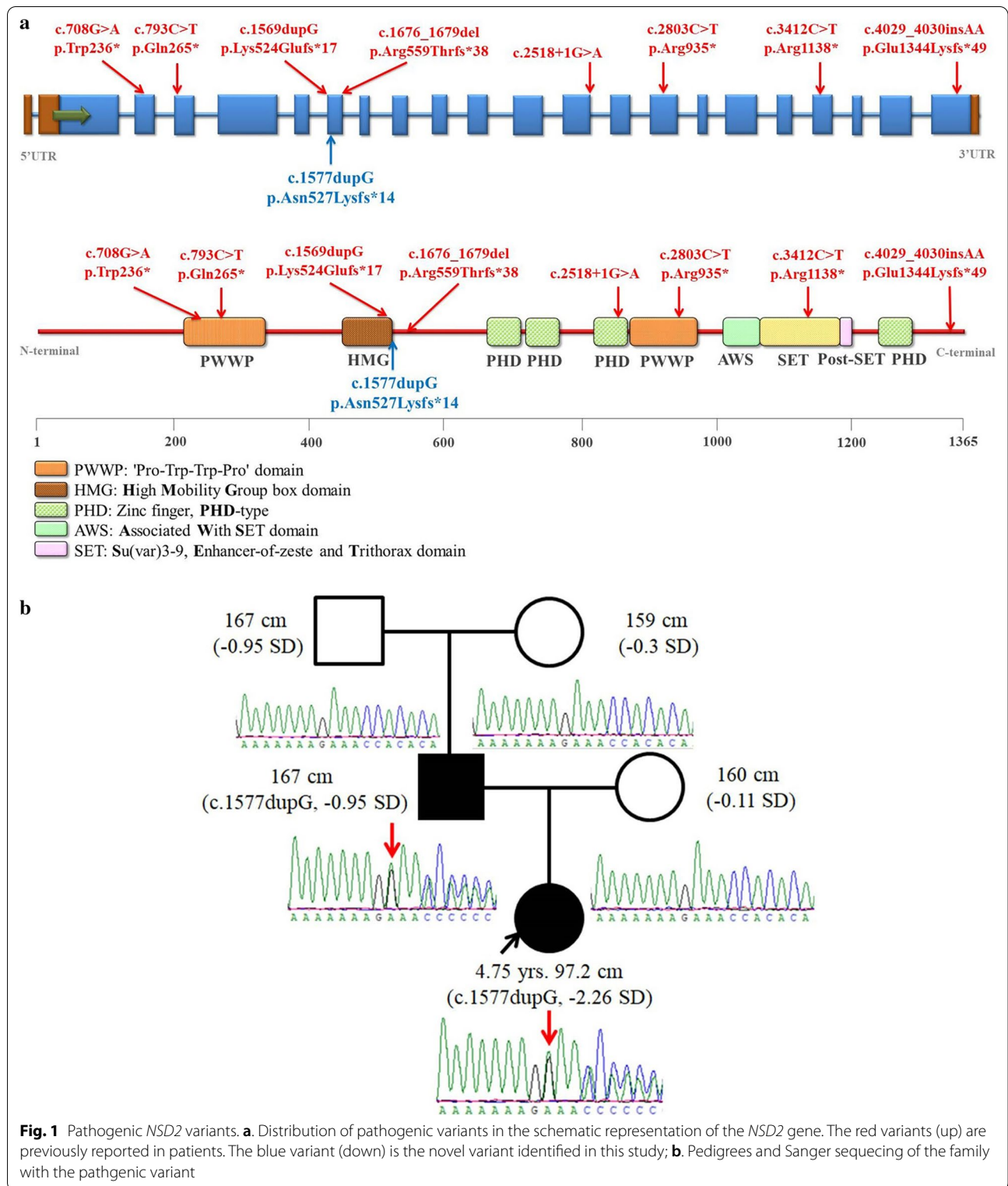
Variants were annotated and filtered by Ingenuity Pathway Analysis (<https://variants.ingenuity.com>). Common variants were filtered based on their frequency in the databases of ExAC (<http://exac.broadinstitute.org>), gnomAD (V2.11, <https://gnomad.broadinstitute.org/>) and our internal database. Rare variants were classified following the ACMG/AMP standards and guidelines [11]. All putative pathogenic variants detected by NGS were confirmed by Sanger sequencing. Additional family members were tested for the specific variants. Primer design was performed by Primer Z [12]. Products of PCR amplification (Takara Biotechnology, Co, Ltd., Dalian, China) were purified and sequenced on an ABI PRISM 3730 Genetic Analyzer (Applied Biosystems, Thermo Fisher Scientific, Inc). XHMM software was used to detect CNVs in whole-exome sequencing data as previously described [13].

Results

Clinical information

The proband was referred to the clinic at the age of 4 years and 9 months due to poor weight gain and growth retardation since birth. Intrauterine growth retardation was noticed during pregnancy. She was delivered at 33 weeks of gestation by a spontaneous premature labor. Her birth weight was 1900 g ($-3.12SD$) and birth length was 41 cm ($-5.11SD$). She could sit at 6 months, crawl at 12 months, walk at 15 months independently. She said her first word at 16 months. Her first tooth eruption was at 11 months. After birth, she was consistently shorter than normal children of the same age. Mild developmental delay was noted when she was a toddler. She went to normal primary school but she had a poor academic performance.

At her first visit at the age of 4 years and 9 months, she was 97.2 cm ($-2.26 SD$) and 11 kg ($-2.82SD$). Her head circumference was 44 cm ($<-3SD$). Her arm span was 94.5 cm and the upper to lower segment ratio was 1.15:1. She had mild intellectual delay. She presented with a thin and short stature. Her craniofacial features included microcephaly, low hairline, high-arched eyebrows, hypertelorism, epicanthal folds, hypoplastic midface, flat profile, low-set and posterior-rotated ears, relative micrognathia and long neck (Supplemental Table 1). She had normal female external genitalia. Biochemistry tests including blood electrolyte, liver and kidney function, myocardial enzymes, blood fat, thyroid function, cortisol, ACTH, glycosylated hemoglobin, sex hormones were normal. Some endocrine test results are as following: IGF-1142 ng/ml (reference range 49–283), IGF-BP3



3.45 µg/ml (reference range 1.0–4.7), and the peak value of growth hormone stimulation test is (insulin combined with arginine) 10.02 ng/ml. She had normal pituitary MRI. Her karyotype was 46, XX. Electroencephalogram

and ultrasonic cardiography were normal. Her bone age was 4 years old. Results of Wechsler Intelligence Scale for Children-IV (WISC-IV) showed an IQ 75.

Her father was 167 cm (-0.95 SD) and not known to be short as a child, her mother was 160 cm (-0.11 SD). Her father also had intellectual disability and distinct facial features (Supplemental Table 1). Her father had a seizure after a fever as a child, encephalitis was suspected, but no definite diagnosis was made. Her paternal grandfather was 167 cm (-0.95 SD) and paternal grandmother was 159 cm (-0.3 SD), and both had normal intelligence.

For both the proband and the father, the facial features did not prompt a WHS clinical diagnosis even though our patients shared other phenotypes with those previously reported individuals with *NSD2* LOF mutations. Phenotypic features and clinical data of subjects with *NSD2* loss-of-function (LOF) mutation from our report and from patients recently described in scientific literature, are summarized in Table 1 and Supplemental Table 1.

Our results proposed it might be a new intellectual disability and short stature syndrome for these patients.

Genetic findings

We identified a novel frameshift variant (NM_001042424: c.1577dupG, p.Asn527Lysfs*14) in *NSD2* in both proband and her affected father, this variant was absent from paternal grandfather and grandmother, Fig. 1). Thus it is a de novo variant for the father (Strong evidence of pathogenicity 2). This variant is located next to the C-terminal of High Mobility Group (HMG) box domain and is predicted to lead to nonsense-mediated mRNA decay (NMD) (Very strong evidence of pathogenicity 1, Fig. 1). This variant was previously unreported and absent from databases (Moderate evidence of pathogenicity 2). This is a pathogenic variant following ACMG/AMP classification guideline (1 Very Strong + 1 Strong + 1 Moderate).

Table 1 Common clinical manifestation of *NSD2* truncating mutation cases

Phenotype	Percentage in <i>NSD2</i> patients	Percentage in WHS patients
Total number of patients	10	> 300
Intellectual disability/Developmental delay	100% (10/10)	> 75%
Ear abnormal	88% (7/8)	> 75%
Hypertelorism	86% (6/7)	> 75%
High-arched eyebrows	86% (6/7)	> 75%
Wide nasal bridge	86% (6/7)	> 75%
Abnormal teeth ^a	86% (6/7)	50–75%
Hypotonia	80% (8/10)	> 75%
Intrauterine/postnatal growth retardation	80% (8/10)	> 75%
Feeding difficulties	78% (7/9)	> 75%
Microcephaly ^a	60% (6/10)	> 75%
Micrognathia ^a	57% (4/7)	> 75%
Epicanthal folds ^a	57% (4/7)	> 75%
Downturned corners of mouth ^a	57% (4/7)	> 75%
Skeletal anomalies	50% (3/6)	50–75%
Short philtrum ^a	43% (3/7)	> 75%
Stereotypies (hand washing/flapping, rocking)	33% (2/6)	25–50%
Prominent glabella ^a	29% (2/7)	> 75%
Craniofacial asymmetry ^a	29% (2/7)	50–75%
High forehead ^a	25% (2/8)	> 75%
Hearing loss	25% (1/4)	25–50%
Skin changes (hemangioma; marble/dry skin) ^a	20% (1/5)	50–75%
Genitourinary tract anomalies ^a	17% (1/6)	25–50%
Gut anomalies	17% (1/6)	< 25%
Esophagus anomalies	17% (1/6)	< 25%
Structural brain anomalies ^a	14% (1/7)	25–50%
Liver anomalies	14% (1/7)	< 25%
Seizures and/or distinctive Electroencephalogram abnormalities ^a	11% (1/9)	> 75%

WHS Wolf-Hirschhorn syndrome, HGVS Human genome variation society, NA Not Available

^a features with different incidence rates in *NSD2* and WHS patients

No pathogenic or likely pathogenic CNV were identified based on WES data using XHMM software.

Growth hormone treatment and outcome

GH therapy was initiated when she was 5 years and 2 months on the basis of short stature. Her bone age was 5 years old then. The height velocity was 5.52 cm/year before treatment. The first year height velocity after treatment was 12.5 cm/year. She was compliant with GH injections (0.15–0.17 IU/kg/day Q. N, Subcutaneous injection), and there were no complications.

The growth curve is shown in Fig. 2 and Supplemental Table 2. During GH therapy, all the monitoring indexes were normal, including biochemistry, thyroid function test, IGF-1, insulin, sex hormones (including luteinizing hormone, follicle stimulating hormone, estradiol, testosterone, progesterone, prolactin), blood routine, urine routine, HbA1C, Electroencephalogram and bone age. The proband had normal puberty when she was 10.5 years of age (breast Tanner II), and her age of menarche was 12.7 years old. The outcome of growth hormone treatment is good (Height SDS increased from -2.25 SD to -0.03 SD).

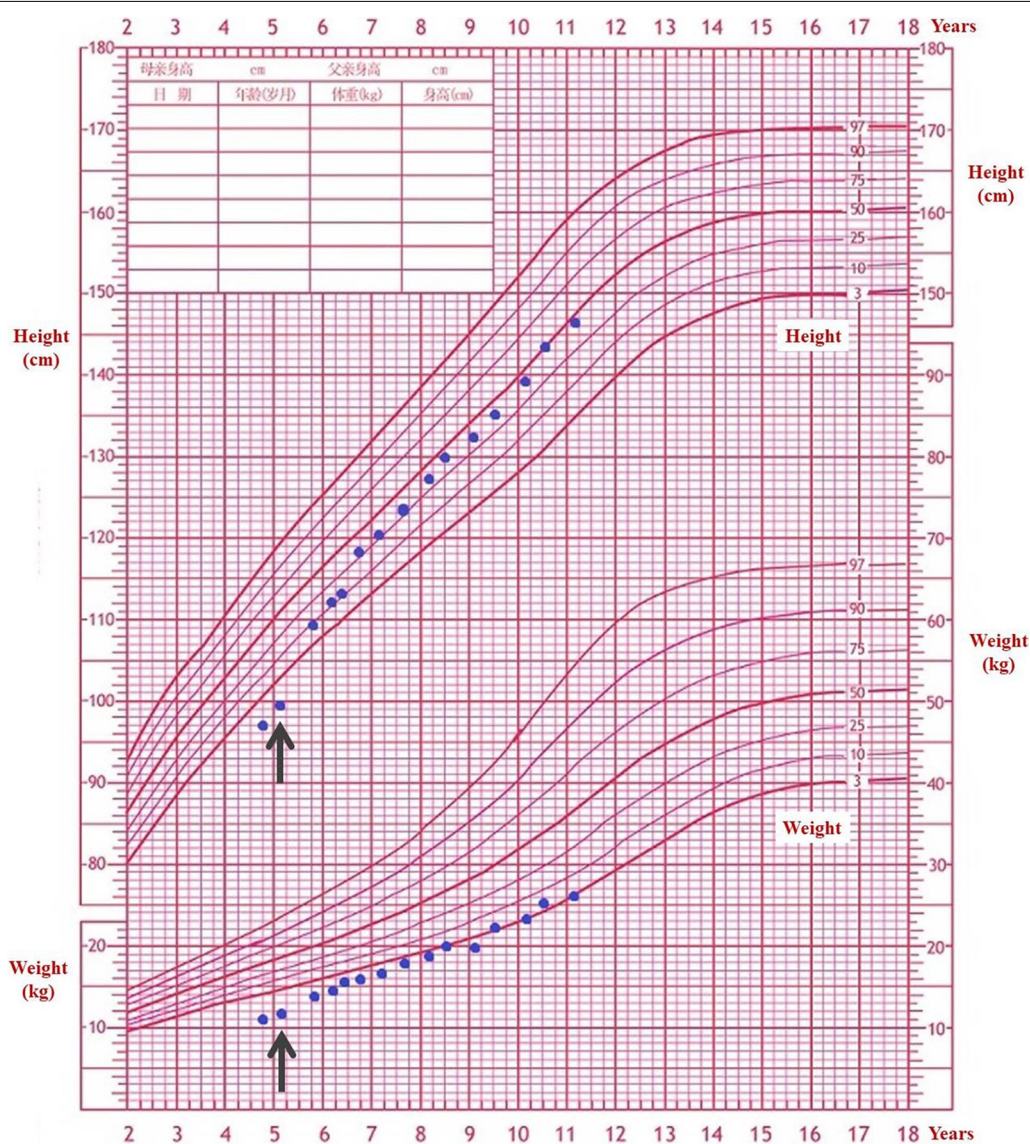


Fig. 2 Growth chart of the proband. The arrows indexed the initiation of growth hormone therapy

Discussion

WHS is a rare intellectual disability syndrome affecting 1 in 20,000–50,000 births. The phenotypes of WHS patients are variable and correlate with 4p16 deletion sizes: Patients with small deletions (<3.5 Mb) often had mild WHS, patients with a deletion of 5–18 Mb has classical WHS and patients with large deletion (>22–25 Mb) have severe phenotypes [2]. Yet all patients had typical facial dysmorphisms comprised by prominent forehead and glabella, highly arched eyebrows, hypertelorism, epicanthal folds, short philtrum, distinct mouth, and micrognathia [1, 14]. Patients with deletions involving the 165 kb WHS critical region usually exhibit these typical features of WHS [4], but individuals with LOF mutations of *NSD2* often do not present with the full WHS facial features [1, 3, 9]. They exhibited milder or less recognizable facial dysmorphism comparing to typical 4p16.3 deletion WHS patients [6, 8–10, 15]. As the phenotypes of *NSD2* patients did not meet the minimal diagnostic criteria for WHS [1, 14], a new intellectual disability and short stature syndrome has been proposed for these patients [15]. The major features (>50%) of this syndrome included intellectual disability/developmental delay, ear abnormal, hypertelorism, high-arched eyebrows, wide nasal bridge, abnormal teeth, hypotonia, intrauterine/postnatal growth retardation, feeding difficulties, microcephaly, micrognathia, epicanthal folds, downturned corners of mouth and skeletal anomalies. Other minor (25–50%) features included short philtrum, prominent glabella, craniofacial asymmetry, high forehead, strabismus, hearing loss and stereotypies (Table 1, Supplemental Table 1). Our results provided basis for the clinical diagnosis of *NSD2* patients in the future. Due to the lack of recognizable facial features of WHS in both of our patients, our findings support the notion that *NSD2* mutation is not fully responsible for all features of WHS, especially the facial features (e.g. ocular anomalies and cleft lip/palate). Other neighboring genes beyond *NSD2* mutation, as *FGFRL1* could be responsible for the development of dysmorphology [16, 17].

Growth retardation was reported in 80% of WHS [1] and *NSD2* patients (Supplemental Table 1) but short stature in WHS is not usually linked to growth hormone deficiency, thus GH supplementation is not often used for WHS patients. So far only six WHS patients underwent GH therapy [18–22] and five of them had detailed information which demonstrated a significant increase in linear height during childhood in all these patients, the longest follow-up of the treatment was 7.5 years [19]. The annual height gain ranged from 0.37 SDS/year to 0.97 SDS/year. The results of these patients showed significant increase in linear height during childhood. (Supplemental Table 3). Currently, none of *NSD2* patients had been

tested for growth hormone and none were treated with GH. The proband had normal GH stimulation test result but her height and weight were consistently lower than 3rd percentile before treatment (Fig. 2). Our proband is the first *NSD2* patient underwent GH therapy. After a 7.5-year treatment, her height increased from -2.25 SD to -0.03 SD (Fig. 2 and Supplemental Table 2). No obvious negative effects were observed and the bone age of our patient was continuously consistent with her chronological age. This study provided first case evidence for *NSD2* mutation patients to improve their height with GH therapy. It was notable that all the other reported variants in previous literature were de novo, and our research reported the first familial *NSD2* variant. In our results, even family members with the same variant had variable phenotypes (for example, the father did not exhibit short stature), indicating an incomplete penetrance on specific features. Different genetic background among family members might one of the explanations. However, more cases are needed to further demonstrate this point.

Conclusions

In summary, we reported the first familial *NSD2* cases with a novel loss of function variant. Both patients presented with main features reported in previous *NSD2* patients who presented with overlapping features of WHS. But the lack of typical facial features in our patients and in other *NSD2* patients suggested that *NSD2* gene mutation along is not sufficient to account for all WHS phenotypes. Other neighboring genes should be playing roles for the manifestation of typical facial features. The search should continue to evaluate the involvement of other genes in WHS. Our study also summarized the phenotype of *NSD2* patients and provided basis for the clinical diagnosis in the future. *NSD2* patients who had short stature can benefit from GH treatment even though GH was not deficient. The long-term GH treatment appears to be effective and safe. More cases will be needed to fully evaluate the benefit of GH treatment and define a potential novel syndrome.

Supplementary Information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12920-020-00831-9>.

Additional file 1: Table S1. Clinical manifestation comparison in WHS patients and *NSD2* truncating mutation cases.

Additional file 2: Table S2. GH therapy outcome of the proband.

Additional file 3: Table S3. Growth hormone therapy of previously reported Wolf-Hirschhorn syndrome cases.

Abbreviations

WHS: Wolf-Hirschhorn syndrome; *NSD2*: Nuclear receptor-binding set domain protein 2 gene; GH: Growth hormone; ID: Intellectual disability; WHSCR:

Wolf-Hirschhorn syndrome critical region; WHSC1: Wolf-Hirschhorn Syndrome Candidate 1 gene; BWA: Burrows-Wheeler Aligner; GATK: Genome Analysis Toolkit; WISC-IV: Wechsler Intelligence Scale for Children-IV; LOF: Loss-of-function; NMD: Nonsense-mediated mRNA decay; HMG: High Mobility Group.

Acknowledgements

Not applicable.

Authors' contributions

Conception of the study: YS, SC and CG. Study designation: XH, DW, YS, SC and CG. Patient's evaluation: DW, LW, XL and MQ. Experiments: XH, HL and ML. Data acquisition and analysis: LW, XL, MQ, XH, YS, DW and YL. First version of the manuscript: XH and DW. Revised version of the manuscript: SC, YS and CG. All authors read and approved the final version of the manuscript.

Funding

This study was partially supported by National Natural Science Foundation of China (grant number 81670713 to Chunxiu Gong, 82000745 to Xuyun Hu), the National Key Research and Development Program of China (grant numbers 2016YFC0901505 to Chunxiu Gong, 2018YFC1002501 to Yiping Shen), the "Eastern Scholar" Fund to Yiping Shen, the "Guangxi Bagui Scholar" fund to Yiping Shen, the Major Research Plan of the Provincial Science and Technology Foundation of Guangxi (grant number AB16380214 to Yiping Shen) and "YUMIAOJIHUA" Project of The Maternal & Child Health Hospital of Guangxi Zhuang Autonomous Region (grant number GXWCH-YMJH-2017005 to Yiping Shen).

The fundings participated in the design of the project, whole-exome sequencing data and patients follow-up.

Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request. Human genome version hg19/GRCh37 is available from the UCSC Genome Browser website (genome.ucsc.edu). Sequencing files are available from the NCBI BioProject database (www.ncbi.nlm.nih.gov/bioproject/679686) and Mendeley Data (data.mendeley.com/datasets/vckjp394p4/1).

Ethics approval and consent to participate

The study was approved by the institutional medical ethics committee of Beijing Children's Hospital. Written approvals, based on informed consent, for the diagnostic tests and genetic analysis were given by the patients or their parents in accordance with the Declaration of Helsinki. Written informed consents to participate were obtained from participants and the parents of the participant under the age of 16.

Consent for publication

Written informed consents for publication of clinical details and clinical images were obtained from participants and the parents of the participant under the age of 16.

Competing interests

The authors declare that they have no competing interests.

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Received: 24 December 2019 Accepted: 23 November 2020

Published online: 04 December 2020

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