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CLINICAL REPORT

The effect of growth hormone treatment in children with novel *BPTF* gene variants: A report of two cases and literature review

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Abstract

Background: Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL) is a rare neurodevelopmental disease caused by *BPTF* gene variants. To date, there are only 36 cases reported in the literature, and patients mainly presented with a developmental delay, language delay, and microcephaly. About 35% of the patients had short stature, but there had no reports published on the treatment.

Methods: The exome sequencing was performed in two probands. Sanger sequencing was used to confirm the identified variants both in probands and their parents.

Results: As for the Chinese population, we report two novel variants in *BPTF* gene (NM_004459.6: c.1133G>A, c.5941delC) causing NEDDFL from two unrelated families. Both children had short stature and responded to recombinant human growth hormone (rhGH) treatment – the first report of this therapy in NEDDFL patients.

Conclusion: Our findings broaden the genotypic spectrum of *BPTF* variants. The salutary effect of rhGH in the NEDDFL is documented.

KEYWORDS

BPTF, case report, NEDDFL, recombinant human growth hormone, short stature

1 | INTRODUCTION

BPTF gene (OMIM*601819) encodes the bromodomain PHD finger transcription factor (BPTF), the largest unit of nucleosome remodeling factor, which regulates chromatin remodeling (Stankiewicz et al., 2017). BPTF plays a key role in the differentiation of the primary germ layers and the establishment of the embryonal anterior–posterior axis (Landry et al., 2008). The *BPTF* gene is located on chromosome 17q24.2. The haploinsufficiency of human *BPTF* is known to cause neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL, OMIM#617755), which is clinically featured by intellectual disability (ID) or developmental delay (DD), language delay, and microcephaly (Glinton et al., 2021; Stankiewicz et al., 2017). Short stature is also a phenotypic component of NEDDFL.

Herein, two novel likely pathogenic variants from two families in the Chinese population are described. Treatment of their short stature with the recombinant

human growth hormone (rhGH) is novel, and the growth response was compelling.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study was conducted following the ethical standards of Fuzhou Children's Hospital of Fujian Medical University Committee on Human Research (Ethics Approval Number: 2019–21). Informed consent was obtained from the parents of both patients.

2.2 | Molecular analysis

Genomic DNA was extracted from the peripheral blood leukocytes of each patient. Blood samples from the parents were also collected. The exome sequencing was performed at Shanghai Children's Medical Center and Genokon medical Laboratory. An adaptor-ligated library was prepared using SureSelect Human All Exon Kit (Agilent Technologies) according to the manufacturer's protocol. Target regions were sequenced on an Illumina Hiseq X Ten System (Illumina). Paired-end reads were aligned to the GRCh37/hg19 human reference sequence. BAM files were generated by Picard and sequence variants were called by Genome Analysis Toolkit (GATK) Haplotype Caller.

Variants were annotated by TGex and putative pathogenic variants detected in the patients by exome sequencing were validated by Sanger sequencing. Sanger sequencing was also performed on DNA from patients' parents. Variants were classified following the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) standards and guidelines (Richards et al., 2015).

3 | RESULTS

3.1 | Clinical description

3.1.1 | Patient 1

Patient 1 was a 7.1 years old Chinese boy who presented with poor growth. He was born full-term to non-consanguineous parents with a birth weight of 2800 g and a birth length of 49 cm. There was no consanguinity. A patent foramen ovale was identified by an echocardiogram and healed naturally at the age of 6.6 years old.

On physical examination, he was short with a height of 113 cm (−2.32 SD), a weight of 17.5 kg (−2.37 SD), and a body mass index (BMI) of 13.7 kg/m^2 (−1.36 SD). He had a broad nasal tip, protruding ears, and a prominent sternum. Cardiopulmonary abdominal examinations were unremarkable. He was diagnosed with growth hormone deficiency (GHD), with a growth hormone (GH) peak of 4.39 ng/ml in both arginine and levodopa stimulation tests. Results of the Chinese Wechsler Intelligence Scale for Children (C-WISC) showed a total Intelligence Quotient (IQ) of 89 (24.8%), including a verbal IQ of 106 (67.4%) and a performance IQ of 72 (3.4%).

Bodyweight dose of 0.10–0.13 U/kg of rhGH was administered once in the evening daily by subcutaneous injection. During treatment from his 7.1 to 10.6 years at last follow-up, the gain in height was 25.6 cm (+1.63 SD, 7.3 cm per year). The growth response to rhGH is evident in Figure 1 (Li et al., 2009). The height was 138.6 cm (−0.69 SD) and weight was 30.0 kg (−0.92 SD) at his last follow-up, at the age of 10.6 years. BMI was 15.6 kg/m^2 (−0.79 SD) then.

3.1.2 | Patient 2

Patient 2 was a Chinese boy with poor growth. He was born after a normal term pregnancy with a birth weight of 2600 g and birth length of 48 cm. He was the third child born to non-consanguineous, healthy parents. He was diagnosed with glucose-6-phosphate dehydrogenase deficiency by newborn screening. At age 3, erosive gastritis was diagnosed with recurrent abdominal pain and vomiting.

His height was 89.2 cm (−4.18 SD), weight 9.8 kg (−3.05 SD) and BMI 12.6 kg/m^2 (−2.79 SD) at the age of 4.3 years. He had a broad nasal tip, protruding ears, and bilateral fifth-finger mild brachydactyly. He was also diagnosed with GHD, with a GH peak of 6.36 ng/ml in both arginine and levodopa stimulation tests. The developmental quotients (DQ) were evaluated by Gesell Developmental Schedules, with total DQ of 73.3, motor DQ 96.3, object DQ 58.9, adaptability DQ 66.9, language DQ 69.6, and social abilities DQ 74.9 (normal range of DQ: 86.0–115.0).

RhGH treatment at the dose of 0.13–0.16 U/kg continued for 4 months, from 4.3 to 4.7 years old, but subsequently discontinued due to financial constraints. At last follow-up, his height was 92.1 cm (−4.00 SD) and weight was 10.5 kg (−2.93 SD), BMI was 12.4 kg/m^2 (−2.92 SD), with height increase of 2.9 cm (+0.18 SD, 8.7 cm per year).

3.2 | Molecular analysis

In patient 1, a heterozygous c.1133G>A (p.Arg378Gln) novel missense variant was detected in *BPTF*

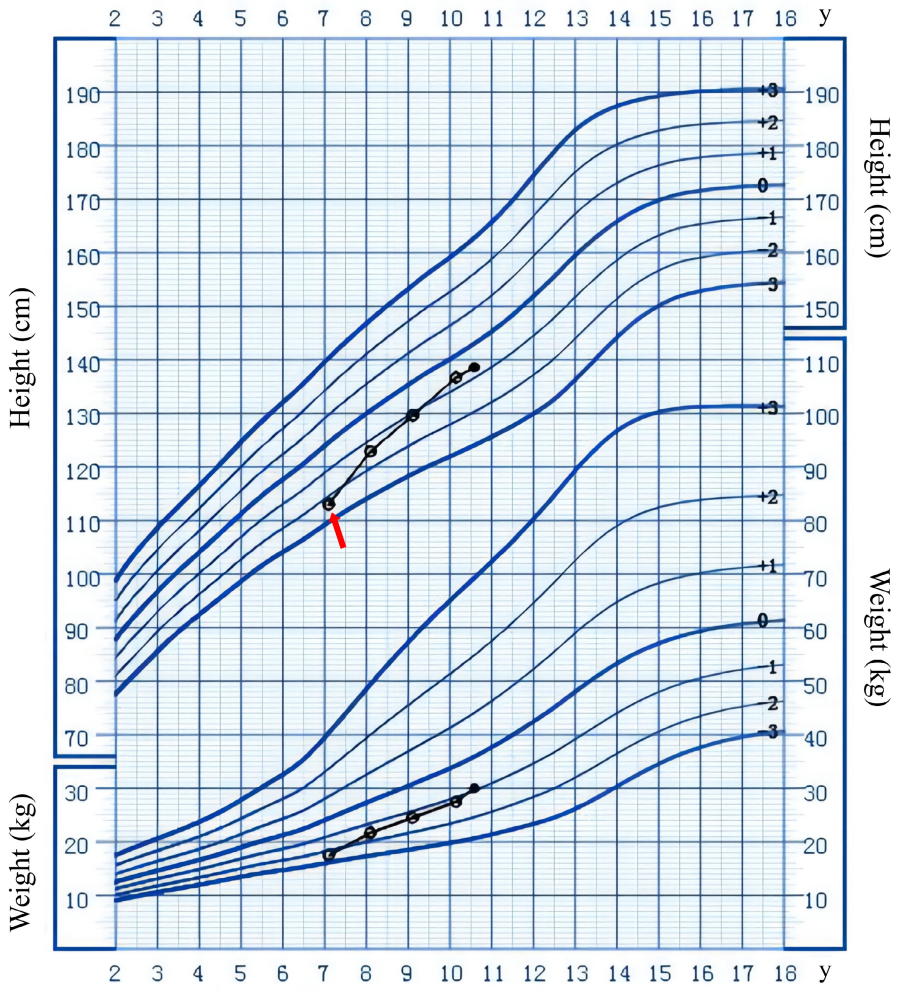

FIGURE 1 Growth curve of patient 1 during the rhGH treatment. The arrowhead indicates the initiation of the recombinant human growth hormone.

(NM_004459.6). Both parents were wild-type for this variant (Figure S1). This variant is considered to be likely pathogenic based on the ACMG/AMP standards and guidelines (Richards et al., 2015). The variant position is highly conserved (PM2_strong) (Figure S2). This genetic abnormality is assumed de novo, but without confirmation of paternity and maternity (PM6). The variant is predicted to be pathogenic by BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, LIST-S2, M-CAP, MVP, MutationAssessor, MutationTaster, and PrimateAI (PP3).

In patient 2, a heterozygous c.5941delC (p.P1981Lfs*33) novel frameshift variant was detected in *BPTF* (NM_004459.6). Both parents were wild-type for this variant (Figure S3). As in case 1, this variant is considered to be likely pathogenic based on the ACMG/AMP standards and guidelines (Richards et al., 2015), and potentially causes loss-of-function (LoF) for the *BPTF* gene for which LoF is a known mechanism of disease (PVS1_moderate). The variant is confirmed de novo in a patient with the disease and no family history (PS2). The variant is not present in databases of normal controls (PM2_supporting). Also, a hemizygous variant c.871G>A (Val291Met) was detected in *G6PD* gene (NM_000402.4). This variant was inherited from the mother (heterozygous), and considered to be pathogenic based on the ACMG/AMP standards and guidelines (PS3+ PS4+ PM1+ PP3).

In both patients, no other suspected pathogenic variants were detected in short stature or DD-related genes.

3.3 | Literature review

Thirty-six cases had been previously reported with *BPTF* variants. With the new two patients added, we summarized the phenotypic features of a total of 38 NEDDFL patients (Table 1) (Glinton et al., 2021; Midro et al., 2019; Stankiewicz et al., 2017). The major clinical manifestation were as follows: DD/ID (34/38, 89%), speech/language delay (33/38, 87%), skeletal abnormalities (23/28, 82%), motor delay (26/28, 68%), ophthalmological anomalies (17/30, 57%), moderate/severely malnutrition (18/33, 55%), brain anomalies (11/22, 50%), microcephaly (18/37, 49%), hypotonia (15/38, 39%) and short stature (12/34,

TABLE 1 Phenotypic summary of NEDDFL

Patient	1	2	Stankiewicz et al. (2017) ($n = 10$)	Glinton et al. (2021) ($n = 26$)	Total ($n = 38$)
Gender	M	M	M: F = 6: 4	M: F = 14: 11	
Age of diagnosis	7 years and 1 month	4 years and 3 months			
Growth					
Small for gestational age	−	−	3/9	5/20	8/31 (26%)
Short stature	+	+	4/10	6/22	12/34 (35%)
Moderate/severely malnutrition	+	+	5/10	11/21	18/33 (55%)
Neurological abnormalities					
DD/ID	−	+ (mild)	10/10	23/26	34/38 (89%)
Speech/language delay	−	+	10/10	22/26	33/38 (87%)
Motor delay	+	−	7/10	18/26	26/28 (68%)
Hypotonia	−	−	5/10	10/26	15/38 (39%)
Brain anomalies	−	−	6/7	5/13	11/22 (50%)
Seizures and/or EEG abnormalities	−	−	NA	6/7	6/9 (67%)
Craniofacial features					
Microcephaly	−	−	7/9	11/26	18/37 (49%)
Micrognathia	−	−	3/10	7/22	10/34 (29%)
Lateral flaring of the eyebrows	−	−	2/10	5/22	7/34 (21%)
Ocular hypertelorism	−	−	2/10	1/22	3/34 (9%)
Upslanting palpebral fissures	−	−	2/10	3/22	5/34 (15%)
Short palpebral fissures	−	−	2/10	2/22	4/34 (12%)
Epicanthal folds	−	−	1/10	5/22	6/34 (18%)
Prominent nose	−	−	3/10	7/22	10/34 (29%)
Long nasal bridge	−	−	2/10	3/22	5/34 (15%)
Broad nasal tip	+	+	1/10	2/22	5/34 (15%)
Thin upper lip	−	−	1/10	4/22	5/34 (15%)
Small mouth	−	−	1/10	1/22	2/34 (6%)
Ophthalmological anomalies	−	−	4/10	13/18	17/30 (57%)
Skeletal abnormalities	+	+	8/10	13/16	23/28 (82%)

Note: One case from Midro et al. (2019) was included in Glinton et al. (2021).

35%). A total of 31 variants were observed, classified as frameshift (15), nonsense (5), missense (4), copy number variation (4), splice (3), in-frame deletion (2). Among the *BPTF* variants identified, 24 occurred de novo and 4 were inherited from a parent, whereas the remaining 10 variants with no access to parental DNA.

4 | DISCUSSION

BPTF variants could lead to haploinsufficiency, which has been postulated to be the root cause leading to NEDDFL. This rare neurodevelopmental disease was first reported by Stankiewicz et al. in 2017 and transmitted in an autosomal dominant manner (Stankiewicz et al., 2017). To date, only 36 cases of NEDDFL have been reported. The manifestations of this disease are non-specific, and usually involve the nervous system, bones, eyes, growth, and craniofacial anatomy.

Among the multifarious clinical manifestations of NEDDFL, neurological abnormalities are predominant. Besides DD/ID, speech/language delay, motor delay, and brain anomalies, seizures and EEG abnormalities are characteristic features (Glinton et al., 2021). In addition, affected patients manifest multiple skeletal abnormalities, including distal limb defects, scoliosis and spinal anomalies, delayed bone age, and limb-length discrepancies. Ophthalmological anomalies are usually mild. Strabismus or myopia was found in 57% of the patients, and only one case with a cataract and hyperopia (Glinton et al., 2021). Moreover, 35% of the patients had variable growth failure. There were no clearly pathognomonic craniofacial features of NEDDFL, and microcephaly, micrognathia, but prominent nose may be present.

Previous studies have established that BPTF plays an important role in the formation of mesoderm, endoderm, and differentiated ectoderm lineages and is required for the establishment of the embryonal anterior–posterior axis during early development (Goller et al., 2008; Landry et al., 2008). *Bptf*-knockdown zebrafish model with *bptf* haploinsufficiency has augmented neuronal death, which may beget neurological abnormalities and microcephaly (Gilmore & Walsh, 2013; Stankiewicz et al., 2017). Ventral images from 3 days post fertilization larvae of *bptf*-knockdown zebrafish model showed a significant increase of the ceratohyal angle (Stankiewicz et al., 2017), suggesting that haploinsufficiency of *BPTF* may underlie the human craniofacial features. The forebrain-specific *Bptf* knockout mice model has recently been produced, suffered from severe cortical hypoplasia, and supported the importance role for Bptf in regulating progenitor differentiation and the activation of key cortical neuron subtype determinants (Zapata et al., 2022). The pathogenesis of skeletal abnormalities and growth delay is uncertain, but conceivably derived from the abnormalities in the embryogenetic process.

In patient 1, the growth response to rhGH was prodigious. His height increased 1.63 SD after three and a half years of treatment without side effect. Although the treatment of patient 2 lasted only 4 months, the preliminary efficacy of rhGH on him had been observed. Both cases demonstrated the efficacy and safety of rhGH treatment in NEDDFL patients, which also infers that GHD may contribute to the short stature of *BPTF* variants.

Based on the reported variants which are widely distributed within the whole *BPTF* exon regions, there are no significant correlations between variants and clinical features. Phenotypes are variable in affected pedigree (Glinton et al., 2021). Due to the important role in chromatin remodeling of BPTF, the severity of NEDDFL may be heavily influenced by additional epigenetic factors. Further studies and case reports may disclose genotype–phenotype correlations.

5 | CONCLUSIONS

In conclusion, two novel *BPTF* variants were identified in our patients, the first cases of NEDDFL in the Chinese population. Our findings broaden the genotypic spectrum of *BPTF* variants. The salutary effect of rhGH in the NEDDFL is documented, heretofore not been reported.

AUTHOR CONTRIBUTIONS

WW performed genetic analysis and wrote the manuscript. RC performed clinical investigations and revised the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Variants have been submitted into the public database ClinVar (Accession ID VCV001341680.1 and VCV001341681.1; http://www.ncbi.nlm.nih.gov/clinvar/).

The other data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

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

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