CASE REPORT

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A Novel Nonsense Mutation of *PHF6* in a Female with Extended Phenotypes of Borjeson-Forssman-Lehmann Syndrome

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What is already known on this topic?

Borjeson-Forssman-Lehmann syndrome (BFLS) is a rare X-linked disease caused by *PHF6* mutations. The features of classic BFLS include intellectual disability, developmental delay, obesity, epilepsy, characteristic face and anomalies of fingers and toes. Endocrine deregulation in BFLS has been reported but not well delineated.

What this study adds?

We report a female with a novel nonsense mutation c.673C > T (p.R225X) in the *PHF6* gene. She exhibited certain features beyond the classic BFLS, including complete deficiency of growth hormone and a horseshoe kidney. Adverse effects were elicited after growth hormone treatment in this patient, which has not been previously reported and suggests caution in the use of growth hormone in this condition. We also reviewed all the BFLS case reports and summarized data on their endocrine presentations and treatment.

Abstract

Borjeson-Forssman-Lehmann syndrome (BFLS) is a rare X-linked disease caused by *PHF6* mutations. Classic BFLS has been associated with intellectual disability (ID), developmental delay (DD), obesity, epilepsy, typical facial features and anomalies of fingers and toes. Endocrinological phenotypes and outcome of treatment in this condition remain to be delineated. Here we report a patient who exhibited complete growth hormone deficiency who responded to hormonal treatment but with adverse effects. Horseshoe kidney was present in this patient, which is also atypical in BFLS. A heterozygous nonsense mutation c.673C > T (p.R225X) of *PHF6* gene was identified in the patient, inherited from her unaffected mother. Both the patient and her mother showed highly skewed X-inactivation. We reviewed the phenotypes of all reported BFLS cases, and summarized their endocrine presentations. This first report of an Asian patient with BFLS further delineated the genetic and phenotypic spectrum of the syndrome. The adverse effect experienced by the patient suggests caution in the use of growth hormone treatment in this condition.

Keywords: Borjeson-Forssman-Lehmann syndrome, *PHF6*, X-inactivation, growth hormone deficiency, rhGH treatment, hypogonadism

Introduction

Borjeson-Forssman-Lehmann syndrome (BFLS), first described in 1962, is a rare X-linked disease (1). So far, about 33 families or sporadic cases have been reported, with 64 patients total (2,3,4). It is characterized by moderate to severe intellectual disability (ID), developmental delay (DD), obesity, epilepsy, hypogonadism, characteristic face and anomalies of fingers and toes (5). This X-linked condition usually affects males, but mild to severe symptoms are present in female carriers and most of them have highly skewed X-inactivation (6). In 2002,

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Lower et al (7) identified *plant homeodomain finger 6 (PHF6)* as the causal gene of BFLS. Since then, 29 different mutations have been reported in *PHF6* and, among these, 14 mutations were identified in affected females (2,3,4,8,9,10,11,12). All the patients and variants identified were of European ethnicity. In addition, 27 of the BFLS patients were reported to have endocrine abnormalities (10,13,14,15,16,17,18,19,20,21,22, 23,24,25). These hormonal abnormalities have not been well summarized so far.

Here we report a Chinese female with a nonsense mutation in the *PHF6* gene, inherited from her mother. Following a thorough review of all reported BFLS cases, we identified some features in this patient beyond those typical of BFLS. In addition, the endocrine aspect of BFLS patients were reviewed and summarized for the first time in the relevant literature. The genetic and phenotypic spectrum of BFLS is discussed.

Case Report

A 9 year 1 month old girl presented to the Genetic Endocrinology Clinic with complaints of ID and short stature. Her height was 123 cm [-2 standard deviation (SD)]; height age was 7 years. Her weight was 23 kg (-1.3 SD), and body mass index was 15.2 (25^{th}-50^{th} percentile). The height of her father and mother were 168 cm and 157 cm respectively, and the familial target height of the patient was 156 cm (-0.85 SD). She was born by caesarean section post-term, with no history of asphyxia. Her birth weight and body length were 4.25 kg and 50 cm respectively. Severe DD was noticed at toddler stage; she walked alone at the age of three years and could speak a few simple words at the age of five years. She presented with the typical facial features of BFLS, including coarse face, sparse hair, narrow forehead, ptosis, deep-set eyes, broad nasal tip, short nose, malformed teeth and large ears with earlobes of moderate size (Figure 1A, 1B, 1C). She had tapering fingers and fifth curved fingers bilaterally (Figure 1D). She also had flat feet and the fourth toes were shorter than the fifth (Figure 1E). Extensive hyperpigmentation was observed all over the body, but especially on the lower limbs. No secondary sexual characteristics were present at the time of examination. Breast and pubic hair were at stage B1 and P1 respectively (according to the Tanner scale).

Thyroid and liver function tests revealed normal results, but she suffered from a complete deficiency of growth hormone (see Table 1). Her stature was below the 3^{rd} percentile and her bone age was $7^{10/12}$ years. Due to the complete lack of growth hormone, recombinant human growth hormone (rhGH) injections were commenced at a dose of 0.036 mg/kg/day. However, after three weeks she developed edema in both lower extremities, and the hormonal treatment was ended.

Ultrasonography showed that she had fused kidneys at the lower end (horseshoe kidney). Brain MRI revealed periventricular leukomalacia and hyaline compartment formation. The pituitary appeared thinner than girls of the same age, though definitive measurement of the pituitary size was not performed. Her karyotype was 46,XX and chromosomal microarray did not reveal pathogenic variants. Her mother was unaffected, at least no obvious signs of symptom based on the reports of the family, though no formal evaluation was performed.

Clinical information concerning the patient was collected in Shanghai Children's Medical Center in 2012 (see Table 2). Written consent was obtained from the patient's parents.

For whole exome sequencing, genomic DNA was extracted from ethylene diamine tetra acetic acid-treated peripheral blood. Library preparation was performed on the proband with xGen Exome research panel v1.0 (Integrated DNA Technologies Inc, Coralville, Iowa, USA). The captured DNA fragments were subsequently sequenced by HiSeq 4000 (Illumina Inc, San Diego, California, USA). The data were analyzed as previously described (26). The pattern of X-chromosome inactivation in our patient and her mother was evaluated by assays of differential methylation in the genes between the active and the inactive chromosome X based on methylation-specific polymerase chain reaction (PCR) (27).

Results

The clinical features of the proband are presented in Figure 1A, 1B, 1C, 1D and 1E and Table 2. For comparison with previously reported phenotypes, we reviewed the

Table 1. Results of endocrine tests

Thyroid function			Growth hormone stimulation test (ng/mL)	
FT3	**6.99 pmol/L (3.8-9.4)**		**Arginine**	**Clonidine**
FT4	16.72 pmol/L (7.9-16.0)	0 min	1.902	0.450
TSH	3.28 uIU/mL (0.3-5.6)	30 min	0.362	0.083
IGF-1	IGF-BP3	60 min	0.122	1.005
48.5 ng/mL (84-495)	3.4 ug/mL (3.4-11.8)	90 min	0.260	0.347

TSH: thyroid stimulating hormone, IGF-1: insulin-like growth factor-1, IGF-BP3: insulin-like growth factor binding protein 3

description of a total of 20 female and 43 male BFLS patients in the literature (Table 2) and summarized the endocrinological presentations (Table 3). Whole exome sequencing revealed a heterozygous nonsense mutation c.673C>T; p.R225X (NM_001015877) of *PHF6* gene in the proband. Sanger sequencing of the proband and her parents demonstrated that the heterozygous mutation was inherited from her mother. No other variant with clinical significance was identified. Methylation-specific PCR of peripheral blood DNA indicated a highly skewed X-inactivation in the patient (98:2) and in her mother (95:5) (Figure 1F).

Discussion

BFLS is an X-linked syndrome caused by variants in *PHF6* (7,8). The most prevalent features, as observed in >80% of reported BFLS cases were: ID, delay in walking, delay in speech, coarse facies, dental abnormalities, large ears and finger deformities in females. Additionally, genital anomalies and gynecomastia have been frequently reported in male BFLS patients.

The phenotypic features of our patient largely conform to the description of BFLS based on patients of European ancestry. However, complete deficiency of growth hormone was not reported in previous cases. Our patient's height was below the 3rd percentile, which has been reported in 14% of female BFLS patients previously (3). She developed edema in the lower extremities after injection of rhGH (before the *PHF6* mutation was identified). Peripheral edema has occurred in 1:100-1:10000 of patients receiving rhGH therapy (28), possibly due to the impact on fluid homeostasis with retention of water and sodium (29). To date, a total of five BFLS patients have been reported

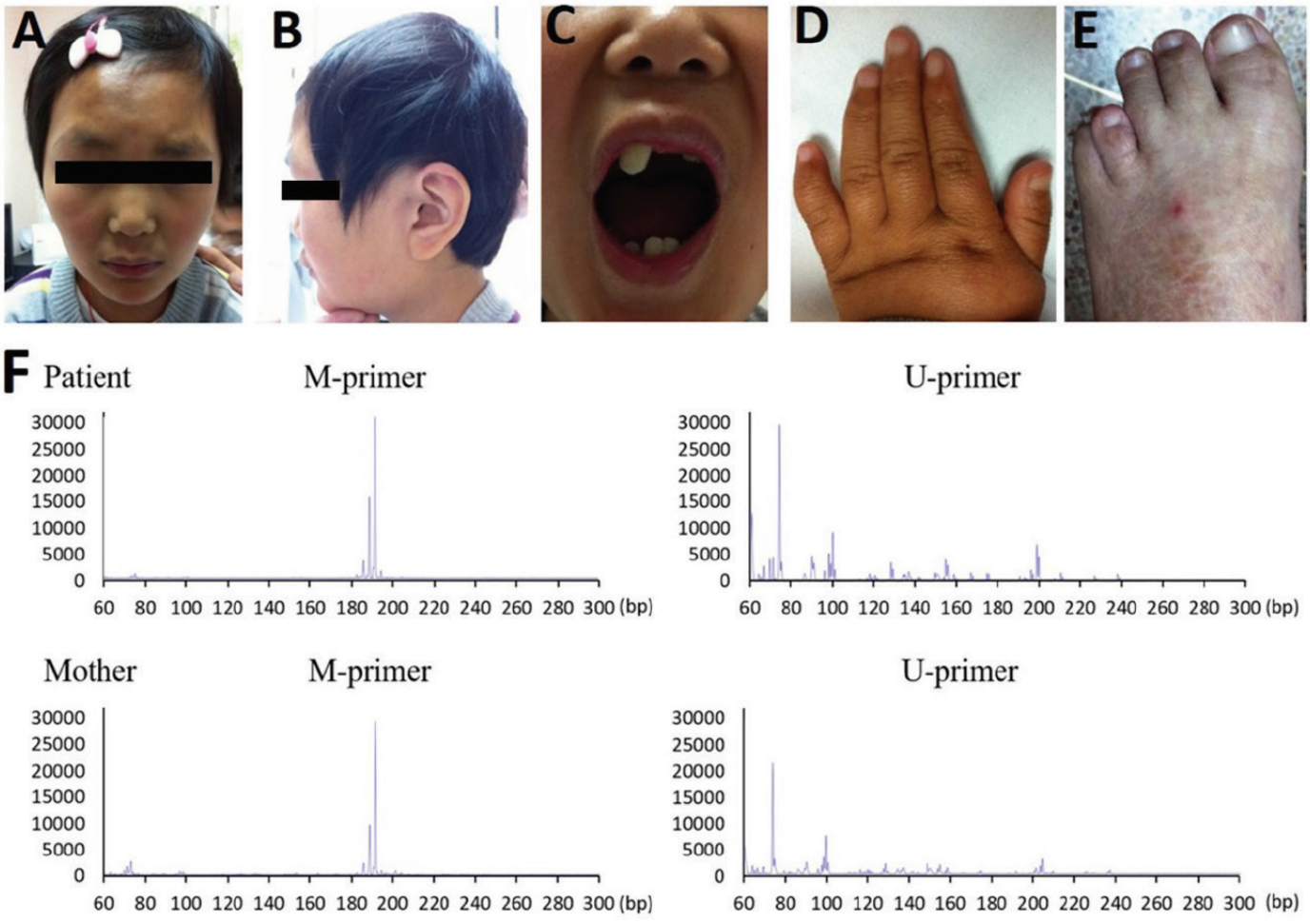

Figure 1. A, B, C, D, E, F) Pictures of our patient at age 9 years. A, B) Facial characteristics, C) Dental abnormalities, D, E) Hand and foot of the patient. The fifth fingers are short and curved, and the fourth toes are short. F) Results of the methylation-specific polymerase chain reaction assay. The inactivated X-chromosome sequence was amplified by the M-primer, the activated X-chromosome sequence was amplified by the U-primer. The result indicated a highly skewed X-inactivation in the patient (98:2) and in her mother (95:5)

Table 2. Clinical information on our patient and on reported Borjeson-Forssman-Lehmann syndrome patients

Patients	Our patient	Frequency in females	Frequency in males
Gender	Female	21 females affected (among 48 carriers)	43 males
Inheritance	Maternally inherited	9 maternally inherited 12 *de novo*	41 maternally inherited
Age	9y-1m	2y-32y	10m-59y
Growth			
Birth weight	Normal, 4.25 kg	/	/
Birth length	Normal, 50 cm	/	/
Abnormal weight	< P10	0/19 low weight 37% (7/19) obesity	3% (1/32) low weight 72% (23/32) obesity
Short stature	< P3	14% (3/21)	35% (13/37)
Abnormal bone age	+, 7y-10m	/	/
Neurological abnormalities			
Intellectual disability	+	86% (18/21)	100% (43/43)
Delay in walking	+	92% (12/13)	91% (21/23)
Delay in speech	+	91% (10/11)	92% (23/25)
Epilepsy	-	19% (4/21)	8% (3/39)
Behavioral anomalies	-	29% (6/21)	36% (4/11)
Vision anomalies	-	67% (8/12)	/
Hearing loss	-	23% (3/13)	/
Craniofacial features			
Coarse face	+	92% (12/13)	84% (27/32)
Hyperpigmentationn	+	77% (10/13)	/
Sparse hair	+	62% (8/13)	50% (5/10)
Narrow forehead	-	54% (7/13)	10% (1/10)
Ptosis	+	8% (1/13)	/
Synophrys	-	29% (6/21)	/
Deep-set eyes	+	44% (4/9)	100% (31/31)
Thick eyebrows	-	38% (8/21)	/
Arched eyebrows	-	62% (8/13)	/
Eyelid narrow	+	14% (3/21)	71% (5/7)
Broad nasal tip	+	85% (11/13)	64% (7/11)
Short nose	+	85% (11/13)	50% (4/8)
Large mouth	-	15% (2/13)	13% (1/8)
Dental abnormalities	+	92% (11/12)	100% (2/2)
Cleft palate	-	10% (2/21)	0
Large ears	+	86% (18/21)	100% (25/25)
Hirsutism	-	19% (4/21)	0
Skeletal features			
Tapering finger	+	67% (4/6)	75% (6/8)
Deformity of fingers	+	90% (9/10)	89% (8/9)
Deformity of toes	+	57% (12/21)	78% (7/9)
Viscera development			
Genital anomalies	-	19% (4/21)	92% (23/25)
Gynecomastia	/	/	97% (31/32)

Table 2. Continued

Patients	Our patient	Frequency in females	Frequency in males
Abnormal brain MRI	+	55% (6/11)	/
Cardiac defect	-	18% (2/11)	/
Renal anomalies	+	83% (5/6)	/
Skewed X-inactivation in blood	+	94% (17/18) (among patients) 88% (38/43) (among carriers)	/

y: years, m: month, +: positive, -: negative, /: not known, MRI: magnetic resonance imaging

Table 3. Summary of hormone levels in Borjeson-Forssman-Lehmann syndrome patients

Reference	Thyroid function	LH	FSH	E2	T	GH	PRL	Other
Female								
Our patient	-	/	/	/	/	↓	/	
Berland et al (13)	-	↓	↓	-	/	/	/	
Crawford et al (10)	↓	/	/	/	/	/	/	
Birrell et al (15)	↓	/	/	/	/	/	/	
Petridou et al (17)	-	-	-	/	/	-	-	
Matsuo et al (22)	-	-	-	-	/	/	/	
Robinson et al (23) #1	↓	↓	↓	↓	-	↓	↓	
Robinson et al (23) #2	↓	↓	↓	↓	-	↓	↓	
Male								
de Winter et al (14)	/	/	/	/	-	/	/	
Carter et al (16) #1	/	-	-	/	/	/	/	
Carter et al (16) #2	/	-	-	/	↓	/	/	
Birrell et al (15) #1	↓	↓	↓	/	/	↓	/	ACTH↓
Birrell et al (15) #2	↓	↓	↓	/	/	↓	/	ACTH↓
Baumstark et al (18) #1	/	-	↑	/	↓	/	/	
Baumstark et al (18) #2	/	-	-	/	↓	/	/	
Baumstark et al (18) #3	/	-	-	/	↓	/	/	
Baumstark et al (18) #4	/	-	-	/	-	/	/	
Turner et al (19) #1	-	↓	-	/	↓	/	/	
Turner et al (19) #2	/	-	/	/	↓	/	/	
Dereymaeker et al (20)	-	-	-	/	/	-	/	Cortisol-
Ardinger et al (21) #1	/	-	↓	/	↓	/	/	
Ardinger et al (21) #2	/	-	↓	/	↓	/	/	
Ardinger et al (21) #3	/	-	↑	/	↓	/	/	
Ardinger et al (21) #4	/	-	↑	/	↓	/	/	
Ardinger et al (21) #5	/	-	-	/	/	/	/	
Robinson et al (23)	-	↑	↑	-	↓	↓	↑	
Veall et al (24)	-	/	/	/	-	-	-	
Weber et al (25)	-	-	-	/	↓	/	/	Cortisol-

-: normal, ↑: increase, ↓: decrease, /: not known

LH: luteinizing hormone, FSH: follicle-stimulating hormone, E2: estradiol, T: testosterone, GH: growth hormone, PRL: prolactin, ACTH: adrenocorticotropic hormone

to have growth hormone deficiency (Table 3) and two of these presented with multiple pituitary hormone deficiency. The authors reported no improvement of stature after GH treatment (15). Considering the adverse effect in our patient, GH use in this condition may not be helpful and should be administered with caution. This is compounded by recent

research showing that *PHF6* mutation may be associated with pediatric leukemia (30).

Genital anomalies were reported in 59% (27/46) of patients. Early literature reported that hypogonadism was caused by hypophyseal dysfunction (1), but recent publications reporting a male patient with low testosterone and elevated LH and FSH, and another patient with abnormal testicular tissue, suggested that both central and gonadal deregulation may occur (23). Review of the literature reveals that the concentration of estradiol was reduced in 2/4 of the female patients and that of testosterone in 12/15 of the male patients. Gonadotrophin concentrations were found to be below reference values in 8/23 patients and hypothyroidism was reported to be present in 6/15 patients, also suggesting that both central and end-organ dysfunction may play a role in BFLS.

As reported in previous studies, hyperpigmentation is common in female BFLS patients with 10 of 13 female patients being hyperpigmented (3,13). Most of these patients were reported to have linear pigmentation in the extremities or individual spots in the armpit (3,13). However in our patient the hyperpigmentation was extensively distributed over the feet and legs. Mosaicism may be the cause for the different presentation in this case. The exact mechanism of hyperpigmentation in BFLS is unknown.

One additional feature of our patient that does not fit the description of classic BFLS is presence of a horseshoe kidney. In an earlier report, clinical phenotypes of BFLS were noted to partially overlap with the Coffin-Siris syndrome (CSS) (12), particularly in infancy among female patients (4). CSS is characterized by ID, typical facial features, hypoplasia/aplasia of the fifth digit of finger/toenail, and organ malformations including horseshoe kidney (4,12). Our patient exhibited many phenotypes overlapping with CSS, including presence of horseshoe kidney. We specifically reviewed the variants of CSS-related genes identifed in our patients, and no pathogenic variant was found. Therefore the similar phenotypes should not be attributed to CSS-related variants. It is well established that *PHF6* interacts with the nucleosome remodeling and deacetylation complex, implicated in chromatin remodeling, and thus functional interaction may exist between *PHF6* and SWI/SNF complex proteins, which are the main factors responsible for CSS (3). This may explain the overlapping features of these two syndromes.

As indicated in Table 2, the penetrance in female carriers is about 44% (21/48). 38/43 of females with *PHF6* mutations had highly skewed X-inactivation, but only 18 of them were affected. Our patient and her mother had the same genotype and similar skewing in X-inactivation. However, their clinical manifestations were quite different, suggesting mosaicism as a contributing factor to the variable expression of the phenotype (12). At the same time, this phenomenon suggests that in obligate carriers of *PHF6* mutations, the level of X-inactivation skewing measured in peripheral blood cells may not be a reliable predictor of the expression of BFLS phenotypes (5).

The limitation of this report is that the manifestation of complete GH deficiency and horseshoe kidney was based on only one patient. Reports of more cases would help to clarify the risk involved in rhGH treatment in this condition.

In conclusion, we report a female with a novel nonsense mutation c.673C > T (p.R225X) of the *PHF6* gene. The patient exhibited certain features beyond classic BFLS, including horseshoe kidney and complete deficiency of growth hormone. An adverse effect was elicited with GH treatment, suggesting caution in the use of GH in this condition. Both the patient and her unaffected mother had skewing of X-inactivation indicating that X-inactivation assay may not reliably predict the expression of BFLS phenotypes. These clinical and genetic findings may contribute to improve our understanding of BFLS and also aid in the diagnosis and genetic counseling of the condition.

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Ethics

Informed Consent: Written consent was obtained from the patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Clinical Data Collection: Yongguo Yu, Xuefan Gu, Genetic Testing and Analysis: Xia Zhang, Yanjie Fan, Xiaomin Liu, Yu Sun, Yunjuan He, Xiantao Ye, X-chromosome Inactivation Assay: Hui Yan, Design: Yanjie Fan, Yongguo Yu, Writing: Xia Zhang, Yanjie Fan, Ming-Ang Zhu.

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