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ORIGINAL ARTICLE

Chinese familial central precocious puberty with hyperuricemia due to recurrent *DLK1* mutation: Case report and review of the literature

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Abstract

Background: Central precocious puberty (CPP) is a precocious puberty due to premature activation of the hypothalamic–pituitary-gonadal axis (HPG). *MKRN3* defects are well-known causes of CPP, while *DLK1* mutations were recently identified in a few patients with CPP.

Methods: The study was approved by the Institutional Review and the scientific committee of the hospital. The clinical data were collected. Whole-exome sequencing (WES) was performed to detect causative variants. Key words 'DLK1', 'MKRN3', and "central precocious puberty" were used for literature search in PubMed, Google Scholar, HGMD, and OMIM databases.

Results: The patient, a male, whose puberty began before age nine, had significant metabolic abnormalities including overweight, hyperlipidemia, and hyperuricemia. WES detected a recurrent frame-shift mutation, NM_003836.5:c.479delC(p.P160fs*50) in *DLK1* in the patient and his father.

Conclusion: The familial *DLK1*-CPP was identified in China for the first time, which supported that short stature is predicted in patients with CPP without GnRHa treatment. Therefore, we recommend that children with *DLK1*-CPP should be treated as early as possible to improve adult height. The patient in this study had persistent hyperuricemia, further suggests that this antiadipogenic factor represents a link between reproduction and metabolism.

KEYWORDS

central precocious puberty, *DLK1*, hyperuricemia, maternal imprinting

1 | INTRODUCTION

The beginning of puberty is influenced by many factors, among which genetic factors are the most prominent (Aguirre & Eugster, 2018). The genetic contribution to pubertal timing is supported by the strong correlation between the ages that children and their parents begin puberty. Twin studies demonstrated a higher concordance of the timing of development of secondary sexual characteristics, including menarche in girls, in monozygotic compared to dizygotic twins, which also provides the basis for gene regulation of puberty onset (Dvornyk & Waqar

ul, 2012). Many studies have tried to determine the genetic factors that regulate human HPG-induced sexual development abnormalities and variants in more than 50 genes have been described in association with hypogonadotropic hypogonadism, which often lead to delayed puberty. Until recently, only a few molecular defects related to CPP were found (Roberts & Kaiser, 2020) and four genes, *KISS1*, *KISS1R*, *MKRN3*, and *DLK1*, have been described as causative for CPP (Dauber et al., 2017; Lee et al., 2020; Roberts & Kaiser, 2020). To date, loss-of-function mutations in *MKRN3* are the most common monogenetic etiology of CPP. A systematic review and meta-analysis confirmed that the prevalence of *MKRN3* mutation in patients with idiopathic CPP is 9.0% (Valadares et al., 2019), while *KISS1* and *KISS1R* are rarely known causative for CPP (Canton et al., 2021) and *DLK1* defects are only recently reported in pediatric CPP cases (Lee et al., 2020; Montenegro et al., 2020). From 2017, the first case of paternal deletion of *DLK1* found in familial CPP was reported, a total of 15 CPP cases caused by *DLK1* mutations have been identified (Dauber et al., 2017; Gomes et al., 2019; Lee et al., 2020; Montenegro et al., 2020).

In this study, we reported a familial CPP caused by frame-shifting mutation of *DLK1*. The clinical and genetic characteristics in previously reported cases reported in previous literature were summarized and compared.

2 | CASE REPORT

A 9 years and 4 months old boy came to our hospital complaining of enlarged testicles and rapid penis growth for more than 4 months. The patient was born to a non-consanguineous couple. At his birth, the patient was 2.6 kilograms in weight and 50 centimeters in length. Before age nine, he had normal development and growth. His father's puberty starts at about age 10 (growing pubic hair) and his height now is 145 cm. His mother is 154 cm in height. The clinical data of his younger sister is unavailable. The heights of many adult members in his family were remarkably lower than average (Figure 1a).

Physical examination showed the patient height of 132 cm (−0.8SD), weight of 33 kg (0.2SD), body mass index (BMI) of 18.9 kg/m^2 (1SD), and heart rate of 98 beats/min. He had no physical deformity. No skin pigmentation and café-au-lait spots, and no abnormality in the heart, lung, and abdomen. His sexual maturity was described by Tanner's stage, breast, and pubic hair in Tanner stage 1, with no armpit hair, penis measured of 4.5 × 2.0 cm and testicle volume of 8 cc.

Blood biochemical tests indicated significant metabolic abnormalities in the patient: triglyceride of 2.97 mmol/L (normal <2.3 mmol/L), serum uric acid was 458 μmol/L (90–420 μmol/L). His blood glucose, liver function, and

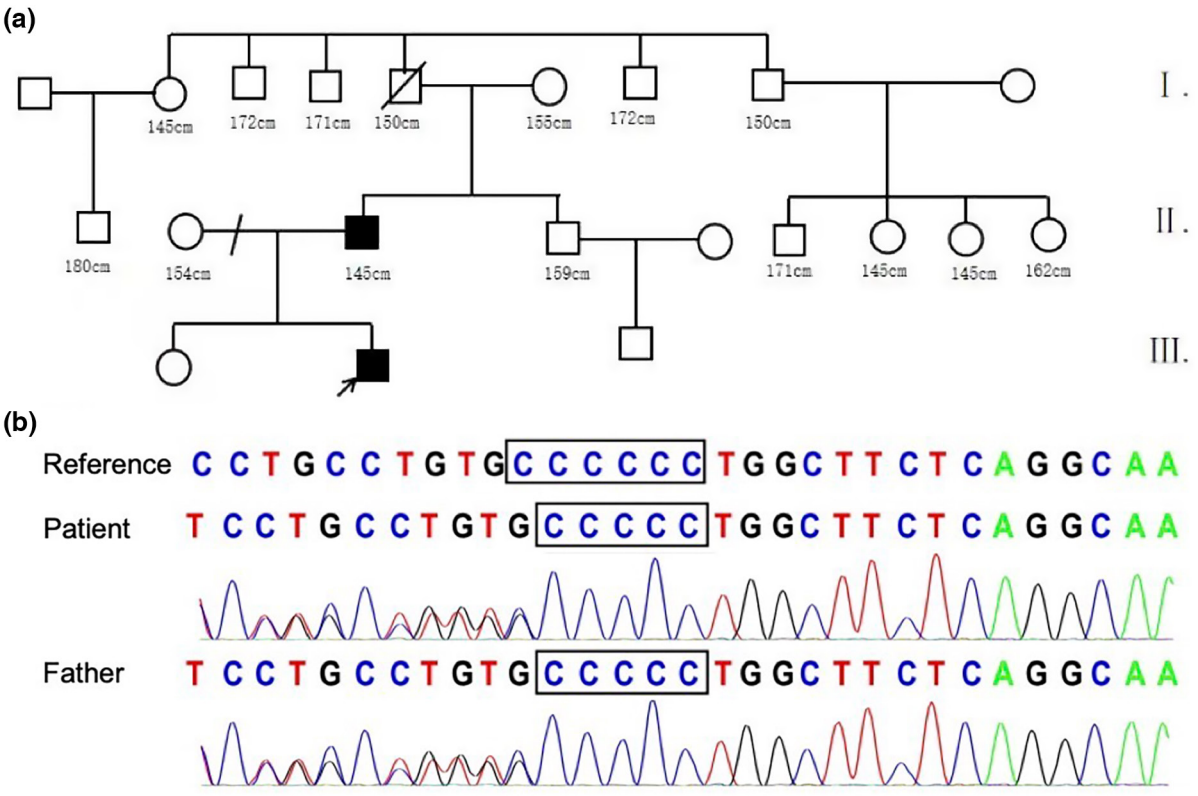

FIGURE 1 Identification of DLK1 c.479delC in the family with CPP. (a) Verification diagram of Sanger sequence (b) The black figure represents a patient diagnosed with CPP, the square represents men, the circle represents women, and the diagonal line represents death.

kidney function were normal. Endocrine-related hormone display thyroid function were normal, adrenocorticotropic hormone (ACTH) of 45.8 pg/ml (normal 0–46 pg/ml), cortisol of 14.8 ug/dl (normal 5–19.4 ug/dl), 17-hydroxyprogesterone (17-OH) of 1.49 nmol/L (normal 2.4–12 nmol/L), and testosterone of 60.77 ng/dl. The basal luteinizing hormone (LH), follicle-stimulating hormone (FSH) were 0.87 and 3.62 mIU/ml, respectively, After subcutaneous injection of triptorelin 82.5ug, the peak LH and FSH were 24.85 and 10.36 mIU/ml respectively. Color Doppler ultrasound of testis: left testicle was 2.9×2×1.5 cm, and the right testicle was 3.1×2×1.7 cm. His color Doppler ultrasound of liver, gallbladder, pancreas, spleen, urinary system, thyroid gland, and adrenal gland were normal. Magnetic resonance imaging (MRI) showed his pituitary gland was normal. Bone age was assessed (Greulich–Pyle method) in the patient indicating the age of 10 years and the predicted adult height (PAH) was 165 cm, which was calculated using the growth curve method.

In summary, before his age of 9, the patient had testicles enlarged by more than 4 cc, with LH > 5 mIU/mL, LH/FSH > 1 after stimulation with triptorelin, and the patient was diagnosed with CPP. In addition, there was no pigmentation and café-au-lait spots on the skin of the child, thyroid function, serum electrolytes, cortisol, ACTH, and 17-OH were normal, and no cystic fibrosis was found in the bone, so secondary CPP due to diseases such as thyroid disease, congenital adrenalortical hyperplasia, and McCune–Albright syndrome was not supported.

After the guardian, his father signed the informed consent, peripheral blood in the patient and his father was collected and sent to Chigene Ltd. (Beijing, China) for dual whole-exome sequencing (WES). Whole-exome library was constructed using the xGen Exome Research Panel v1.0 (IDT, Iowa, USA) and WES was performed on NovaSeq 6000 (Illumina San Diego, CA) with not less than 99% regions covered at least 10x. Raw reads were processed by fastp, followed by paired-end sequence reads were aligned to the human GRCh37/hg19 genome using the Burrows–Wheeler Aligner (BWA) software package. Single nucleic variant and short indels (≤50 bp) were called using the GATK software package. Annotations of all variants were automatically produced by an independently developed, database-based online system provided by Chigene (https://www.chigene.org, Beijing, China). The Chigene workbench includes annotating allele frequency based on public databases, the Single Nucleotide Polymorphism database (dbSNP), 1000 Genomes Project, Exome Aggregation Consortium (ExAC), Genome Aggregation Database (gnomAD), ESP, and the Chigene in-house MAFs database; causative genes and the associated clinical phenotypes were annotated based on databases including UCSC, RefGene, GENCODE, and ENSEMBL transcripts, LOVD, SWISS, Clinvitae, HGMD, OMIM, and ClinVar. Functional and conservational predictions of all the variants were performed using software packages (Provean, SIFT, PolyPhen2, MutationTaster, M-CAP, REVEL, and CADD; MaxEntScan, dbscSNV, and GTAG; GERP, phyloP, and phastCons). Pathogenicity of all the variants was evaluated and classified according to the American Academy of Medical Genetics and Genomics (ACMG) clinical practice guideline (Li et al., 2017).

Dual WES revealed a heterozygosity frameshift variant, NM_003836.5:c.479delC(p.P160fs*50), in the *DLK1* gene in the patient and his father, followed by Sanger sequencing confirmation (Figure 1b). *DLK1* c.479deCl was previously detected in a Brazilian familial CPP (Gomes et al., 2019), and it was classified as pathogenic (PVS1 + PM2 + PS4), according to the ACMG guidelines.

His father developed pubic hair at the age of 10 and was considered to have precocious puberty. Combined with the results of genetic testing, familial CPP was diagnosed. However, the guardian, his father, refused further medication. We urge the patient to control his weight and eat a low-fat, low-purine diet.

During the 1-year follow-up, the child's height increased by 11.5 cm, the testicular volume increased significantly, the pubic hair progressed from Tanner stage 1 to Tanner stage 4, and the bone age progressed by 3.6 years, indicating rapidly progressive puberty, and the child's predicted height decreased, which has reached the standard of short stature (see Table 1), At the age of 10.4 years, the triglyceride returned to normal, and the blood uric acid was 468 umol/L.

Using keywords “DLK1”, “central precocious puberty” or “CPP”, and “MKRN3”, we searched the articles in PubMed, human gene mutation database (HGMD), online human Mendelian inheritance (OMIN) database, and Google Scholar (by March 9, 2022). A total of 15 patients with CPP caused by *DLK1* mutation were previously reported in four articles (Dauber et al., 2017; Gomes et al., 2019; Lee et al., 2020; Montenegro et al., 2020). The clinical features and *DLK1*-type variation of all patients are listed in Table 2.

3 | DISCUSSION

Central precocious puberty (CPP) is an endocrine disorder with relatively high prevalence in children, which is caused by early activation of the hypothalamic–pituitary-gonadal axis (HPGA), leading to early sexual development in children. A familial CPP is defined as having two or more family members who have CPP (de Vries et al., 2004). De Vries et al. (de Vries et al., 2004) studied

TABLE 1 The main clinical data of the patient during the follow-up

Age (y)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Penis (length× diameter, cm)	Testicle volume (cc)	Pubic hair (Tanner stage)	GV (cm/y)	BA (y)	PAH (cm)
9.4	132	33	18.9	4.5×2.0	8	1	–	10	165
9.9	136.8	36	19.2	5.8×2.3	10	3	11.5	12	160.5
10.4	143.5	39.3	19.1	7.0×2.5	12–15	4	11.5	13.6	156

Abbreviations: BA, bone age; BMI, body mass index; GV, growth velocity; PAH, predicted adult height.

156 children with idiopathic CPP and they revealed that about 27% of the cases are familial, and the analysis of family map shows that it is an incomplete penetrance of autosomal dominance. A large-scale genome-wide association study showed that genetic factors were associated with 60%–80% of patients with CPP (Macedo et al., 2016). The first *DLK1*-CPP was reported in 2017. Dauber et al. (2017), using WES, found a 14 kb deletion in *DLKI* in five female patients with CPP in a Brazilian family, which led to null expression of DLK1 in the serum. Except for the three sporadic cases reported in Spain (Montenegro et al., 2020), subsequent *DLK1*-related CPP cases were reported as familial CPP and all the *DLK1* mutations were paternal inherited, indicating a maternal imprint of the *DLK1* gene (Gomes et al., 2019; Lee et al., 2020). However, a normal paternal carrier was also reported, suggesting an incomplete penetrance of *DLK1*-CPP (Dauber et al., 2017). According to literature reports, *DLK1*-related CPP tends to occur in female patients and was characterized as short stature, overweight/obesity in some patients, abnormal glucose metabolism (glucose intolerance and type 2 diabetes mellitus), dyslipidemia (hyperlipidemia, fatty liver, increased fat content) and a few have polycystic ovary syndrome. Notably, the duration of their puberty was about 2 years, suggesting that the puberty progresses rapidly in the patients. Female patients, previously reported in the literatures, who received regular GnRHa treatment all had reached normal-range adult heights. The only two male patients, reported by Gomes et al. (2019) both had short stature, in which one experienced CPP and received GnRHa treatment (intranasal spray) and the other's puberty development was undescribed (Table 2). The reasons for the increased incidence of female CPP and *DLK1*-related CPP remain unclear (Latronico et al., 2016), while some male patients with CPP could be underestimated (Valadares et al., 2019).

Short stature is a well-known consequence of untreated or late diagnosis of different forms of precocious puberty in humans. Based on a limited number of untreated patients with precocious puberty, it showed mean heights of 152 cm in girls and 156 cm in boys (Carel et al., 2004), compared to a severer phenotype (149.8 cm on average) in untreated patients with idiopathic CPP. In this study, the patient was born at a normal height, his height at diagnosis current was normal for his age. During the follow-up, without medication authorized by the guardians, his bone age progressed rapidly, and the PAH decreased, which indicated that CPP caused by *DLK1* was similar in males and females, both of them have rapid puberty progressing. In addition, without drug intervention, adults are short in stature. This view is also supported by the fact that there are many short adults in the patient ‘s family. In view of the favorable response of female patients to GnRHa treatment, early GnRHa treatment for such children should be suggested to improve adult height.

Metabolic alterations are common in *DLK1*-related CPP. Among the previously reported cases, female patients had overweight/obesity (7/13), impaired glucose tolerance or type 2 diabetes (5/13), and hyperlipidemia (3/13). The abnormal metabolic phenotype was more frequent in women carrying *DLK1* defects than in women with treated and untreated CPP (Gomes et al., 2019). Only 2 male patients have been reported in the previous literature, and it was unknown whether there was metabolic abnormality. In our study, the patient was overweight in the initial stage of diagnosis, accompanied by hyperlipidemia and hyperuricemia. After lifestyle intervention, BMI and triglycerides returned to normal, but hyperuricemia persisted, which was not reported in previously reported cases. As we all know, overweight and obese patients have an increased risk of hyperuricemia, and serum uric acid levels of children are positively correlated with BMI (Dai et al., 2021). The presence of hyperuricemia in the patient with a normal BMI suggests that hyperuricemia may be related to *DLK1* itself.

DLK1 locates on the imprinting region on the long arm of chromosome 14 (14q32.2) (Bray et al., 2008), within a locus associated with Temple syndrome, an imprinting disorder caused mainly by maternal uniparental disomy. *DLK1* is involved in regulating differentiation and cell fate determination and plays a role in many differentiation processes, especially in osteogenesis and adipogenesis (Sánchez-Solana et al., 2011). Animal and in vitro studies have shown that *DLK1* hampered adipocyte differentiation and has been considered a molecular gatekeeper of adipogenesis and the *Dlk1*-null

TABLE 2 The clinical features and mutation sites of CPP caused by *DLK1* mutation were reported

Affected family (publication)	Ethnicity	Case No.	Sex	Age of puberty start	Menarche age, years	Additional clinical features	Treatment	Adult height (cm)	BMI (kg/m^2)	Changes in nucleic acid	Amino acid changes
F1 (Gomes et al., 2019)	Brazil	1	F	5	7	Hirsutism、obesity、Type 2 DM、infertility, hypercholesterolemia、PCOS、hepatic steatosis, macromastia	Oral medication	155.7	29.2	c.594_594delC	Gly199Alafs*11
		2	F	5	7	PCOS，obesity、infertility, Type 2 DM，hepatic steatosis、macromastia	Irregular	156.7	27.2		
		3	M	NA	NA	Short stature	NA	160.5	NA		
F2 (Gomes et al., 2019)	United Kingdom	4	F	5	11	Short stature	Oral medication	146.2	21.1	c.810_810delT	Val271Cysfs*14
		5	M	5	NA	Short stature	Gnrha (intranasal spray)	147.3	NA		
F3 (Gomes et al., 2019)	Brazil	6	F	7	7	Short stature	No	145.2	13.2	c.479_479delC	Pro160Leufs*50
		7	F	7	9	Short stature、Glucose intolerance、hypercholesterolemia、obesity	No	137.8	37.7		
F4 (Dauber et al., 2017)	Brazil	8	F	5.5	12	Increased % fat mass、obesity	Gnrha	156.5	29.2	Potential donor 5′ splice region	
		9	F	5.5	12	Increased % fat mass	Gnrha	159.7	22		
		10	F	5	12	Increased % fat mass，Glucose intolerance、obesity	Gnrha	159.3	33.1		
		11	F	4.6	10.8	Increased % fat mass	Gnrha	160.5	22.1		
		12	F	NA	9–10	Type 2 DM，hypertension，hypercholesterolemia、obesity、Increased % fat mass	No	154	29.6		
Sporadic (Montenegro et al., 2020)	Spain	13	F	5.7	11.2	-	Gnrha	153.5	17.6	c.401_404＋8del	
		14	F	7	11	-	Gnrha	163.5	22	c.402C＞T	Asn134=
		15	F	6.6	11.9	Obesity, hyperandrogenism	Gnrha	158.3	27.42	g.-222 C＞A and g.-223 G＞A,	
F5 (Present study)	China	16	M	9	NA	Overweight, hypercholesterolemia, hyperuricemia	No	NA	NA	c.479delC	P160fs*50
		17	M	NA	NA	Short stature	No	145	22.4		

Abbreviations: DM, diabetes mellitus; F, female; Gnrha, gonadotropin-releasing hormone analog; M, male; NA, not applicable; PCOS, polycystic ovary syndrome.

mice had a similar phenotype of human obesity (Moon et al., 2002). Temple syndrome is also often associated with precocious puberty and metabolic abnormalities (Kagami et al., 2017). Dauber et al. (2017) suggested that loss of *DLK1* function is the cause of precocious puberty in patients with Temple syndrome and may be the cause of those patients' obesity. The high prevalence of metabolic alterations in adult females with *DLK1*-related CPP suggests that there is a connection between *DLK1* and metabolism. Hyperuricemia is significantly associated with metabolic syndrome. Some studies have found that increased fat accumulation in the liver could be induced by uric acid through endoplasmic reticulum stress and upregulation of lipogenesis, and these metabolic alterations may result in obesity. Interestingly, mature adipocytes and adipose tissues were found to be able to produce uric acid (Feng et al., 2022). It shows that hyperuricemia is closely related to fat metabolism, and the interaction between them is very complicated. The patient in this study had persistent hyperuricemia, further suggesting that this antiadipogenic factor represents a link between reproduction and metabolism.

Since Dauber et al. (2017) first reported a *DLK1*-related CPP for the first time, a total of nine genetic sites have been found variations in CPP cases (see Table 2). Most of these mutations are located in the extracellular domain and 4 (4/5) are located in exon 5, which indicates the hot region for pathogenic *DLK1* variants. Because of insufficient cases, a genotype–phenotype association needs to be investigated. To date, all identified mutations could be linked to familial or sporadic CPP. In addition, different patients from the same family may have different clinical features, suggesting a phenotypic heterogeneity. The p.P160fs*50 mutation identified in this study was predicted to result in a production of shortened transcripts and null expression of *DLK1* mutant in peripheral blood (Gomes et al., 2019), which could be explained by nonsense-mediated decay (NMD).

4 | CONCLUSION

DLK1-related CPP is hard to differentially diagnosed with other idiopathic CPP based on the clinical features, which could be only revealed by genetic tests. The familial *DLK1*-related CPP was identified in China for the first time, which supported that short stature is predicted in patients with CPP without GnRHa treatment. Therefore, we recommend that children with CPP should be treated as early as possible to improve adult height. In addition, the patient in this study had persistent hyperuricemia, which further suggests that this antiadipogenic factor represents a link between reproduction and metabolism.

AUTHOR CONTRIBUTIONS

Gaopin Yuan was the patient's physician, reviewed the literature, designed the study, and contributed to manuscript drafting; Shaofeng Liu, Xiaohong Zhang, and Tingli Chen made substantial contributions to the conception and interpretation of data. SL was responsible for revising the manuscript; all authors issued final approval for the version to be submitted.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of Quanzhou Women's and Children's Hospital. And informed consent from the patient's parents prior to conducting the exome sequencing had been obtained, including the patient's clinical details in the manuscript for the purpose of publication.

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