ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 November 16; 9(32): 9699-10051

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
November 16, 2021

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World Journal of Clinical Cases

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World J Clin Cases 2021 November 16; 9(32): 10018-10023

DOI: 10.12998/wjcc.v9.i32.10018

ISSN 2307-8960 (online)

CASE REPORT

Rare mutation in *MKRN3* in two twin sisters with central precocious puberty: Two case reports

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Author contributions: Jiang LQ and Wang CL conceived and designed the study; Jiang LQ, Zhou YQ, Yuan K performed the experiments; Jiang LQ and Zhou YQ provided clinical research; Jiang LQ wrote the paper; Jiang LQ, Yuan K, Zhu JF, Fang YL and Wang CL reviewed and edited the manuscript; and all authors read and approved the manuscript.

Supported by the key Research and Development Program of Zhejiang Province (No. 2020C03121).

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest related to this manuscript.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE

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Abstract

BACKGROUND

Caused by premature activation of the hypothalamic-pituitary-gonadal axis, there is increasing incidence of central precocious puberty (CPP), especially in girls. Makorin ring finger protein 3 (*MKRN3*), a maternal imprinted gene with a highly conserved sequence, is the most common genetic etiology associated with CPP. Approximately 50 different mutations in *MKRN3* have been found in CPP.

CASE SUMMARY

This case report involves identical twin sisters presenting with premature thelarche at the age of 6 years. The left hand bone age of both patients revealed advanced age (9 years). Pelvic B ultrasound indicated enlargement of the ovaries. Luteinizing hormone (LH) releasing hormone testing confirmed CPP. Whole-exome sequencing detected the c.841C>T mutation in *MKRN3*, leading to a single base substitution, in the twins. This mutation was inherited from the father and paternal grandmother. After 3 mo of treatment with a gonadotropin-releasing hormone analog, levels of LH, follicle-stimulating hormone, and estradiol in the proband's sister returned to normal levels.

CONCLUSION

Here, we report a rare mutation (c.841C>T) in *MKRN3* in identical twin sisters with CPP.

Key Words: Central precocious puberty; *MKRN3*; Mutation; Case report

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Core Tip: This report discusses the diagnosis and treatment of central precocious

Checklist (2016).

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Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 1, 2021
Peer-review started: July 1, 2021
First decision: July 16, 2021
Revised: July 21, 2021
Accepted: September 10, 2021
Article in press: September 10, 2021
Published online: November 16, 2021

P-Reviewer: Abubakar MS, Cimen SG
S-Editor: Wang JJ (Online Science Editor)
L-Editor: A
P-Editor: Ma YJ

puberty caused by a new Makorin ring finger protein 3 gene mutation and includes a detailed clinical and laboratory analysis of the pathogenic principle, which provided the diagnosis and led to the treatment of central precocious puberty.

Citation: Jiang LQ, Zhou YQ, Yuan K, Zhu JF, Fang YL, Wang CL. Rare mutation in *MKRN3* in two twin sisters with central precocious puberty: Two case reports. *World J Clin Cases* 2021; 9(32): 10018-10023
URL: https://www.wjgnet.com/2307-8960/full/v9/i32/10018.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i32.10018

INTRODUCTION

Precocious puberty is defined by the development of breast enlargement before the age of 8 years or menarche before the age of 10 years in girls and testicular enlargement (≥ 4 mL) before the age of 9 years in boys. Central precocious puberty (CPP) is a specific type of precocious puberty that results from premature activation of the hypothalamic-pituitary-gonadal (HPG) axis[1]. CPP has critical short-term and long-term impacts on children, including increased risks of psychosocial stress, short stature, obesity, cardiovascular disease, and type 2 diabetes in adulthood[1]. The incidence of CPP is greater in girls than in boys, though the mechanism underlying this difference is not yet understood[2]. Boys with CPP are more likely to have specific pathological factors, such as thalamic hamartoma. In contrast, 90% of cases of CPP in girls are idiopathic[3].

Genetic testing of children diagnosed with CPP has led to the identification of several pathogenic genes. Multiple genes, including makorin ring finger protein 3 (*MKRN3*), kisspeptin (*KISS1*), kisspeptin receptor (*KISS1R*), and delta-like homolog 1 (*DLK1*), are associated with CPP. Loss-of-function mutations in *MKRN3* are the most common genetic etiology contributing to CPP[4], and 115 cases of familial and sporadic CPP involving more than 20 different loss-of-function *MKRN3* mutations were reported from 2013 to 2019[5].

Herein, we report a rare mutation in *MKRN3* causing CPP in twin sisters. This is the first report of *MKRN3* gene mutation in identical twins.

CASE PRESENTATION

Chief complaints

Patient A: A Chinese girl was referred to our hospital for premature thelarche at the age of 6 years and 9 mo.

Patient B: The identical twin elder sister of patient A was previously examined at the age of 6 years and 7 mo for premature thelarche in another hospital. Premature thelarche appeared when the patient was 6 years and 4 mo old.

History of present illness

At the age of 6 years and 3 mo, patient A showed breast development and progressive enlargement; at the age of 6 years and 4 mo, patient B showed breast development and progressive enlargement. Similar to patient A, no other obvious discomfort, misuse of contraceptives, or other abnormal performance was reported.

History of past illness

The girls were born at full term weighing 2400 g and 2690 g and with a length of 48 cm (both twins). Neither patient had a history of a significant medical illness. The patients' diet was normal. The growth and development of the children prior to thelarche were similar to those of Han girls of their age.

Personal and family history

The patients were twin daughters of Han Chinese nonconsanguineous parents. There was no family history of immunodeficiency or recurrent infection. The parents had no genetic diseases. The menarche age of the mother and pubertal development of the

father were normal. The father had a height of 170 cm (-0.4 SDS) and the mother 162 cm (0.3 SDS).

Physical examination

Patient A had a height of 119.6 cm (0.04 SDS) and weighed 23 kg: Tanner stage 2 in the breasts and Tanner stage 1 in pubic hair, with no axillary hair. The height of patient B was 122.6 cm (0.8 SDS), and her body weight was 26.7 kg; she showed breast Tanner stage 2, pubic hair stage 1, and no axillary hair.

Laboratory examinations

The luteinizing hormone releasing hormone (LHRH) stimulation test for patient A indicated CPP (early stage); the peak luteinizing hormone (LH) value was 4.71 mIU/mL, the peak follicle-stimulating hormone (FSH) value was 16.48 mIU/mL, and the LH/FSH ratio value was 0.29. Laboratory results together with the typical clinical manifestations indicated CPP. The LHRH stimulation test of patient B revealed a peak LH value of 15.81 mIU/mL (Table 1).

Imaging examinations

The left hand bone age of patient A was 9 years. Pelvic ultrasound of patient A revealed enlargement of the ovary; the volume of the left ovary was 1.2 mL, while the volume of the right ovary was 1.7 mL. Pelvic ultrasound of patient B revealed larger ovaries than in patient A; the volume of the left ovary was 2 mL, and the volume of the right ovary was 3.8 mL. The left hand bone age of patient B was 9 years.

Further diagnostic work-up

We performed trio-whole-exome sequencing on genomic DNA extracted from peripheral blood of the twins and their parents. The sequencing results revealed a rare mutation in *MKRN3* in the twins resulting in the substitution of a single base (c.841C>T). The father was heterozygous for the mutation, whereas the mother carried wild-type *MKRN3*. We obtained blood samples from the grandparents, and DNA was extracted and subjected to reverse transcription polymerase chain reaction amplification. We then performed direct sequencing of the *MKRN3* target site in the proband's cDNA, which showed that the mutation was inherited from the paternal grandmother, who had normal development (Figures 1 and 2).

FINAL DIAGNOSIS

Central precocious puberty (*MKRN3* c.841C>T).

TREATMENT

Gonadotropin-releasing hormone (GnRH) analog (3.75 mg every 4 wk, subcutaneous route).

OUTCOME AND FOLLOW-UP

After 3 mo of treatment, levels of LH, FSH and estradiol (E2) decreased to normal levels.

DISCUSSION

MKRN3 is an intronless gene located in the Prader-Willi syndrome region on chromosome 15q11.2. Based on whole-exome sequencing of 40 members from 15 families diagnosed with CPP, Abreu *et al*[6] confirmed in 2013 that *MKRN3* mutation is associated with CPP.

MKRN3 is a maternally imprinted or silenced gene and is expressed only from the paternal allele. MKRN3 is a member of the Makorin family of proteins that contain special zinc-finger motifs and have a highly conserved structure among multiple species[6]. MKRN family proteins MKRN1-4 contain three CH3 zinc-finger motifs, a

Table 1 Summary of the clinical data of the two patients

	Patient A	Patient B
Age at onset (yr)	6.25	6.33
Age at referral (yr)	6.66	6.5
Weight (kg)	23	26.7
Height (cm)	119.6	122.6
Bone age (yr)	9	9
Tanner stage	B2	B2
Pubarche stage	PH1	PH1
Basal LH (mIU/mL)	0.13	N/A
Peak LH (mIU/mL)	4.71	15.81
Basal FSH (mIU/mL)	2.71	N/A
Peak FSH (mIU/mL)	16.48	N/A
Estradiol (pg/ml)	25.26	N/A
Peak LH/FSH	0.29	N/A
Uterine (mL)	2.9	5.3
Left Ovary (mL)	1.2	1.9
Right Ovary (mL)	1.7	1.8
Brain magnetic resonance imaging	Normal	Normal

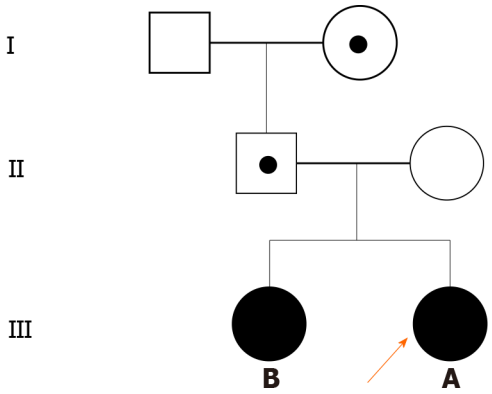

Figure 1 Pedigrees of the investigated case with *MKRN3* mutation. Square indicates male family member, circles indicate female members, the black symbol indicates clinically affected family member, the symbol with black circle indicates unaffected carrier, arrow indicates the proband, the arrow indicates the profound in this family.

characteristic RING finger domain (C2HC4 motif), and a CH motif that is rich in Cys-His. The C3H motifs are associated with RNA binding activity. The RING finger motif is present in many E3 ubiquitin ligases and is responsible for ubiquitin-ligase activity [5]. As with other Makorin family members, the transcript levels of *MKRN3* in several species are maximal during the very first developmental stages and sharply decrease over time. Previous studies showed that *MKRN3* transcripts progressively decrease in the mouse hypothalamus during the first two postnatal weeks[5]. This was further verified by reports of lower serum *MKRN3* levels in girls with CPP than in healthy girls[4-6].

CPP is caused by premature activation of the HPG axis and an increase in the amplitude and frequency of GnRH pulses. GnRH is produced in the hypothalamus and regulated by kisspeptin/neurokinin B/dynorphin (KNDy) neurons, which are critical in pulse generation, steroid negative feedback, puberty and other functions. Previous human genetic studies have demonstrated the crucial role of kisspeptin and neurokinin B in stimulating GnRH secretion; dynorphin restrains secretion of GnRH[7, 8]. One study reported that *MKRN3* selectively inhibits the promoter activity of the

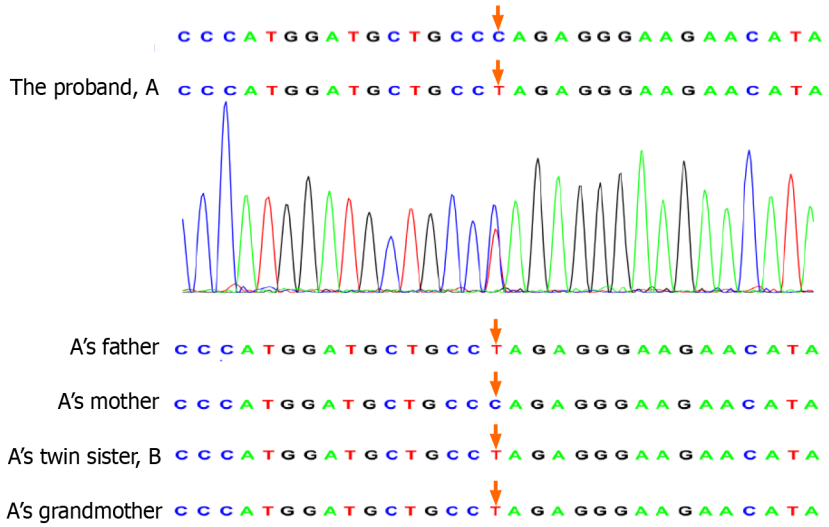

Figure 2 Whole-exome sequencing showing the novel heterozygous mutation (c.841 C>T) in *MKRN3* detected in the profound. The same mutation was covered in A's twin sister, her father and grandmother, but not A's mother.

KISS1 and *TAC3* genes, which encode kisspeptin and tachykinin-3, in the arcuate nucleus independent of its RING finger domain[8]. Liu *et al*[9] found that the RING domain of MKRN3 interacts with Nptx1, one of the earliest activated extracellular signals responding upon GnRH neuron induction when puberty begins, leading to polyubiquitination and suppression of Nptx1 activity during the initiation of puberty. Both *in vivo* and *in vitro* experiments have shown that microRNA-30 targets the 3′-untranslated region of the *MKRN3* mRNA to control pubertal initiation. Injection of microRNA-30 inhibitors during prepuberty reverses downregulation of the hypothalamic *MKRN3* protein and delays the onset of female puberty[10]. Therefore, MKRN3 is extremely essential in the initiation of puberty, and this mechanism likely underlies its association with CPP.

We identified a rare missense mutation in *MKRN3* (c.841C>T) in a 6 year and 9 mo-old girl with CPP with a twin sister who also showed premature thelarche. Whole-exome sequencing revealed that the mutation was inherited from the father, whose pubertal development was normal. The c.841C>T mutation is located in the CH motif and results in a single amino acid change in the MKRN3 protein. Thus far, 50 *MKRN3* mutations associated with CPP have been reported, including 14 frameshift mutations, 27 missense mutations, 4 nonsense mutations and 5 variants in upstream promoter or regulatory regions[3,5]. The current case is only the second report of the c.841C>T mutation in *MKRN3*[11]. Notably, this is also the first case of *MKRN3* mutation in twin sisters. It is worth noting that mutations in *MKRN3* are more common in patients from Western countries than in those from Asian countries[3], which may result from genetic differences in ethnic groups or the less frequent use of gene testing among children with CPP in Asian countries.

A systematic review and meta-analysis of the clinical features of patients with CPP carrying *MKRN3* mutations showed that *MKRN3* mutations are associated with non-syndromic CPP. Girls are more severely affected by CPP than boys and often experience pubertal initiation at an early age, with higher basal FSH levels[12]. However, no studies have investigated associations between genotypes and clinical phenotypes of CPP.

Long-acting GnRH analogs are considered the gold standard treatment of CPP, and this treatment is typically administered by intramuscular injection or subcutaneous implantation[1]. Whether GnRH is effective for CPP patients with *MKRN3* mutation has not been completely determined. A retrospective study revealed no significant differences in mean LH or target height between CPP patients with or without *MKRN3* mutations after GnRH treatment[13]. In our study, after patient B was treated with three doses of GnRH analog (3.75 mg every 4 wk), LH, FSH and E2 decreased to normal levels, without any progression of puberty signs, suggesting that the GnRH analog is effective in the treatment of CPP patients with *MKRN3* mutation.

CONCLUSION

MKRN3 mutation is the most frequent genetic etiology of CPP. Here, we report twin sisters who presented premature thelarche and were diagnosed with CPP with a rare mutation in *MKRN3* (c.841C>T).

ACKNOWLEDGEMENTS

The authors would like to thank the probands and their family for agreeing to participate in this research.

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