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CLINICAL REPORT

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Novel truncating variant of *PPM1D* penultimate exon in a Chinese patient with Jansen-de Vries syndrome

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Abstract

Background: Jansen-de Vries syndrome is a rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in the last and penultimate exons of the *PPM1D* gene. It is characterized by delayed psychomotor development, intellectual disability with speech delay, behavioral abnormalities, and dysmorphic features. Up to date, only 17 affected patients have been reported worldwide (no report in Chinese).

Methods: Here, we analyzed the clinical data and genetic test results of a Chinese patient with Jansen-de Vries syndrome admitted in our hospital in May 2019.

Results: We report a 9-month-old boy carrying a pathogenic variant (c.1254_1255del, p.(V419Qfs*14)) in *PPM1D* exon 5, which can account for his phenotype. Most of his clinical features overlap with the reported phenotype, such as growth retardation, feeding difficulties, constipation, congenital abnormalities (such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus), small hands and feet with broad forehead, low-set posteriorly rotated ears, wide mouth with thin upper lip and pointed chin; however, he also presented with additional features like hepatomegaly and left inguinal hernia.

Conclusion: This is the first published case of Jansen-de Vries syndrome in Chinese population, which will help us to enrich the clinical spectrum of this syndrome.

KEYWORDS

exome sequencing, intellectual disability, Jansen-de Vries syndrome, *PPM1D*, variant

1 | INTRODUCTION

Jansen-de Vries syndrome (OMIM 617450), also known as "intellectual developmental disorder with gastrointestinal difficulties and high pain threshold (IDDGIP)," is a rare autosomal dominant disease. In 2017, Jansen et al. firstly summarized the clinical features of 14 unrelated patients with intellectual disabilities and found that their phenotype was associated with truncating variants occurring in the last and penultimate exons of *PPM1D* (OMIM 605100) (Jansen et al., 2017). Jansen-de Vries syndrome is a neurodevelopmental disorder characterized by delayed psychomotor development, intellectual disability with speech delay, and behavioral abnormalities. Most patients have variable additional features,

including feeding and gastrointestinal difficulties, high pain threshold and/or hypersensitivity to sound, and dysmorphic features, including mild facial abnormalities, strabismus, and small hands and feet. The exact incidence rate of Jansen-de Vries syndrome is unknown, and only 17 affected patients (Jansen et al., 2017; Kuroda et al., 2019; Porrmann et al., 2018) with this syndrome have so far been reported worldwide (no report in Chinese). Here, we report a heterozygous novel variant in *PPM1D* that was identified in a child with the typical clinical features of Jansen-de Vries syndrome. This is the first published occurrence of Jansen-de Vries syndrome in Chinese population, and also the youngest patient in the world.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval number: TJ-IRB20180703) and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the parents of the patient.

2.2 | Clinical report

The proband, a 9-month-old boy, was born at 36+ week gestation to a G4P2 mother via cesarean section delivery. His birth parameters were weight 2,700 g (3rd–10th centile) and height 49.0 cm (10th–25th centile). He was fed with breast and formula milk, usually suffering feeding difficulties. At 3 months old, he underwent surgical repair for "atrial septal defect, ventricular septal defect, patent ductus arteriosus"; he suffered respiratory infection for 6 times and frequent constipation after birth. His parents are from two unrelated families, and there was no family history of inherited or metabolic diseases. His father is 170 cm tall (25th–50th centile), and his mother is 157 cm (25th centile) tall.

In the most recent evaluation, his weight was 8.85 kg (25th–50th centile), height was 67.1 cm (< 3rd centile), and occipital-frontal circumference (OFC) was 42.4 cm (< 3rd centile). He also had developmental delay and could not sit without support at 9 months. Facial features included broad forehead, low-set posteriorly rotated ears, wide mouth with thin upper lip and pointed chin. His abdomen was soft, and the liver could be touched at 3 cm below the ribs. The penis was short with bilateral testis 1 ml. His hands and feet were obviously small (Figure 1a).

Laboratory investigations revealed that there were no abnormalities in the complete blood count, renal function, serum electrolytes, and immune function examinations. Both the toluidine blue stain and methylene blue stain test were negative. The enzyme activity assay including α-L-iduronidase, α-N-acetylglucosaminase, galactose-6-sulfatase, β-galactosidase, β-glucuronidase, and iduronate-2-sulfatase was normal. Aspartate aminotransferase (AST) (46.44 U/L) and lactate dehydrogenase (LDH) (324.73 U/L) were higher than normal level. Chest X-ray showed that there was bronchitis in the lung without other abnormalities; color Doppler showed that the liver was slightly larger, left inguinal hernia.

2.3 | Whole-exome sequencing

After obtaining the informed consent from his parents, whole-exome sequencing analysis (Beijing MyGenostics Inc.) was performed on the proband and his parents. Genomic library was built using a standard library construction kit, and more than 23,000 exons were captured using the target sequence capture probe (MyGenostics, GenCap). Average coverage of all genes is greater than 97% at a 20X average depth or higher. Suspected candidate mutations were screened by comprehensively considering the genetic pattern of the disease and the clinical characterization of the patient.

3 | RESULTS

3.1 | Genetic test results

We identified a heterozygous novel variant in the *PPM1D* exon 5 (c.1254_1255del, p.(V419Qfs*14), Genome reference sequence: GRCh37/hg19) of the proband, and there was no variant at this site of his parents. The variant was confirmed by Sanger sequencing as a de novo variant (Figure 1b). According to the 2015-ACMG Standards and Guidelines (Richards et al., 2015), this frameshift variant is a pathogenic variant.

3.2 | Literature searching

Relevant studies were searched from PubMed, Web of Science, Human Gene Mutation Database (HGMD), Online Mendelian Inheritance in Man (OMIM), and some Chinese databases, such as CNKI, Wanfang, and VIP Database up to August, 2019. Our searches were based on combinations of the following index terms: Jansen-de Vries syndrome, *PPM1D* and the corresponding terms in Chinese. A total of 3 literature (Jansen et al., 2017; Kuroda et al., 2019; Porrmann et al., 2018) reports on this syndrome were retrieved. The *PPM1D* heterozygous variant (c.1254_1255del, p.(V419Qfs*14)) of this proband has not been reported in the

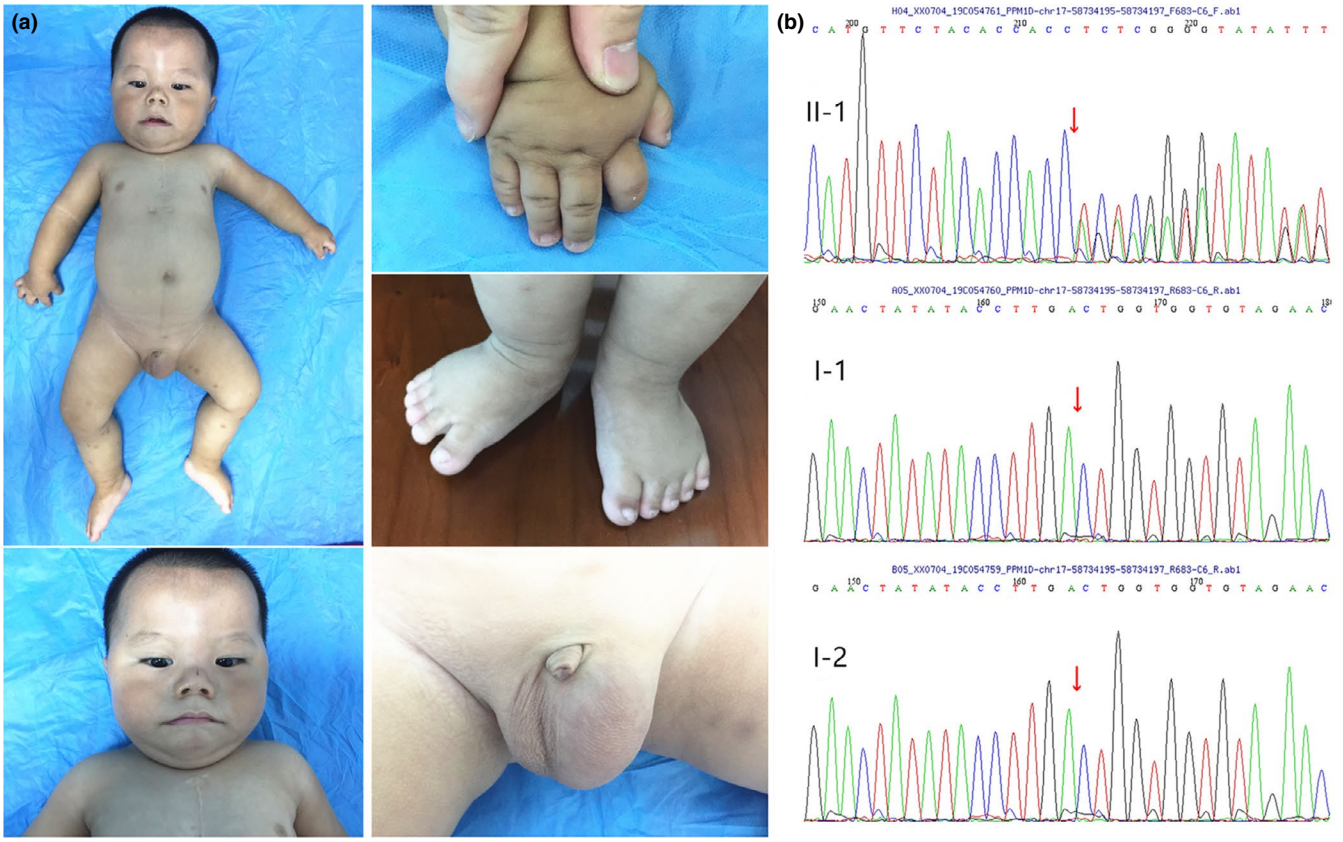

FIGURE 1 Clinical presentation and exome sequencing results of the patient. (a) The proband at 9 months old. Note his physical features, including broad forehead, low-set posteriorly rotated ears, wide mouth with thin upper lip and pointed chin as well as short penis, small hands and feet. (b) Exome sequencing results of the proband (II-1) and his parents (I-1 and I-2) (Genome reference sequence: GRCh37/hg19)

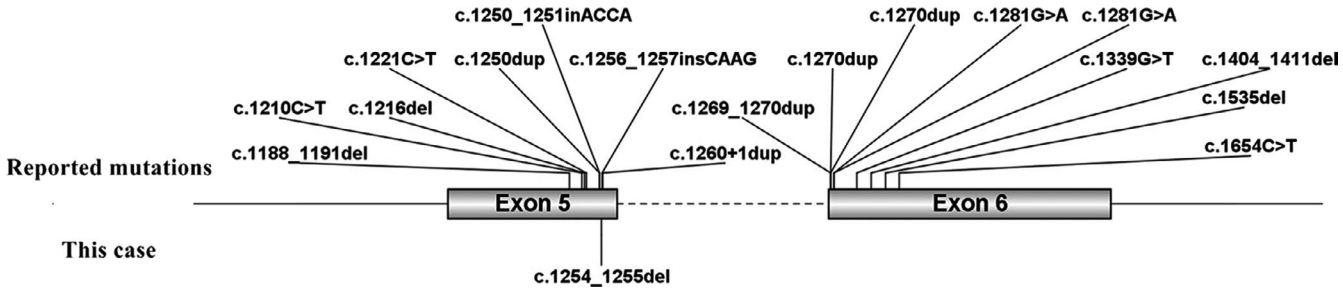

FIGURE 2 Mutations of *PPM1D* in patients with Jansen-de Vries syndrome reported in the literature and in this case

above database. The *PPM1D* variants and clinical features of Jansen-de Vries syndrome reported in the literature are summarized in Figure 2 and Table 1, respectively.

4 | DISCUSSION

Jansen-de Vries syndrome is a rare autosomal dominant disease. Up to date, only 17 affected patients have been reported worldwide (no report in Chinese) and variants in all patients were located in the last or penultimate exons (exon 5 and 6) (Figure 2). The clinical features of these reported patients are summarized as follows (Table 1): (a) growth retardation (short stature and small occipital-frontal circumference); (b) delayed psychomotor development: mild to severe intellectual disability with speech delay, hypersensitivity to sound, hypotonia, etc.; (c) special facial features, such as broad forehead, low-set posteriorly rotated ears, wide mouth with thin upper lip, and pointed chin; (d) small hands and small feet; (e)various congenital malformations: cleft lip and palate, congenital heart diseases (bicuspid aortic valve, ventricular septum defect and so on), cryptorchidism, retractile testes, small genital, laryngo-malacia, etc.; and (f) others: such as feeding difficulties, constipation, high pain threshold, vision

TABLE 1 Common clinical features of patients with Jansen-de Vries syndrome

Clinical features	This case	Reported cases	Summary
Age	9 months	2–21 years	0.75–21 years
Sex	Male	Male/Female: 8/9	Male/Female: 9/9
Height (<P3 or −2.0SDS)	+	12/16	13/17 (76.5%)
Weight (<P3 or −2.0SDS)	−	4/15	4/16 (25.0%)
OFC (<P3 or −2.0SDS)	+	4/17	5/18 (27.8%)
Intellectual disability	NA	16/17	16/17 (94.1%)
Hypersensitivity to sound	NA	9/9	9/9 (100.0%)
Broad forehead	+	11/15	12/16 (75.0%)
Low-set, posteriorly rotated ears	+	9/11	10/12 (83.3%)
Wide mouth	+	7/13	8/14 (57.1%)
Thin upper lip	+	13/15	14/16 (87.5%)
Small hands	+	13/14	14/15 (93.3%)
Small feet	+	10/11	11/12 (91.7%)
Congenital malformations	+[a]	7/15	8/16 (50.0%)
Vision problems	NA	10/15	10/15 (66.7%)
High pain threshold	NA	12/13	12/13 (92.3%)
Feeding difficulties	+	10/15	11/16 (68.9%)
Constipation	+	9/14	10/15 (66.7%)
Recurrent infections	+	5/11	6/12 (50.0%)
Hepatomegaly	+	NA	—

Abbreviation: NA, not assessable.

[a]congenital malformations in this case include the following: congenital heart diseases (atrial septal defect, ventricular septal defect, and patent ductus arteriosus), short penis, and hernia.

problems (astigmatism, myopia, strabismus, etc.), nail dysplasia, and recurrent infections.

Our patient was admitted with mental development and growth retardation for half a year. Physical examination revealed that he also had special facial features, hepatomegaly, short penis, and obviously small hands and feet. Initially, the possibility of mucopolysaccharidosis was considered (Rigoldi, Verrecchia, Manna, & Mascia, 2018). But no abnormalities in skeletal system were found, the toluidine blue stain and methylene blue stain test as well as enzyme activity assay were normal. Whole-exome sequencing analysis showed that there was a heterozygous novel variant in the *PPM1D*, which was confirmed by Sanger sequencing as a de novo variant. According to the 2015-ACMG Standards and Guidelines (Richards et al., 2015), this variant belongs to PVS1 (nonsense, frameshift variant), PS2 (both maternity and paternity confirmed, no family history, and parent–child relationship confirmed), and PM2 (low-frequency variation in the normal population database). Therefore, this frameshift variant is a pathogenic variant, which could account for the phenotype of the proband.

PPM1D (protein phosphatase, Mg2+/Mn2+-dependent 1D [MIM: 605100]), also known as WIP1, encodes for a phosphatase that belongs to serine/threonine protein phosphatase 2C (PP2C) family. PP2C negatively regulates the protein kinase cascade signaling system through dephosphorylation, participates in cell cycle processes, and assists signal transduction, gene transcription, protein translation, as well as post-translational modification (Bork, Brown, Hegyi, & Schultz, 1996; Cohen, 1989; Lu et al., 2008). *PPM1D* has previously been shown to be expressed in both mouse and human brains (Hawrylycz et al., 2012; Lein et al., 2006), but its role in nervous system development remains to be further studied. Jansen et al. (2017) pointed out that an escape from nonsense-mediated mRNA degradation, which is restricted to truncating variants occurring in the last and penultimate exons of *PPM1D*, might be the pathogenic mechanism of Jansen-de Vries syndrome. *PPM1D* amplification or gain-of-function variant can reduce the synthesis of relevant phosphatase, which affects activities of cell proliferation and thus leads to the occurrence of disease (Jansen et al., 2017; Kleiblova et al., 2013).

In conclusion, we have described a rare case of Jansen-de Vries syndrome and identified a de novo truncating variant in *PPM1D* exon 5 (c.1254_1255del, p.(V419Qfs*14)). This is the first published occurrence of Jansen-de Vries syndrome in Chinese population, and these additional reports will help us to enrich the clinical spectrum of Jansen-de Vries syndrome.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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