European Journal of Medical Genetics 66 (2023) 104807

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Jansen de Vries syndrome: Report of four new patients and review of the literature

Anna Tuiskula [a,*], Elisa Rahikkala [b,c], Andreina Kero [d], Maria K. Haanpää [d,e], Kristiina Avela [f]

[a] Department of Pediatrics, Children's Hospital, University of Helsinki and Helsinki University Hospital (HUH), Helsinki, Finland
[b] PEDEGO Research Unit, University of Oulu, Oulu, Finland
[c] Department of Clinical Genetics and Medical Research Center, Oulu University Hospital, Oulu, Finland
[d] Department of Clinical Genetics, Turku University Hospital, Turku, Finland
[e] Genomics Department, Turku University Hospital, Turku, Finland
[f] Department of Clinical Genetics, Helsinki University Hospital (HUH), Helsinki, Finland

ARTICLE INFO

Handling Editor: A. Verloes

Keywords:
Jansen-de vries syndrome
PPM1D
Intellectual disability
Short stature
Congenital heart defect
Neurodevelopmental disorder

ABSTRACT

Jansen de Vries syndrome (JDVS, OMIM: 617450) is a rare neurodevelopmental disorder associated with hypotonia, behavioral features, high threshold to pain, short stature, ophthalmological abnormalities, dysmorphism and occasionally a structural cardiac condition. It is caused by truncating variants of the last and penultimate exons of *PPM1D*. So far, 21 patients with JVDS have been reported in the literature.

Here, we describe four novel cases of JVDS and review the current literature. Notably, our patients 1, 3 and 4 do not have intellectual disability albeit they have significant developmental difficulties. Thus, the phenotype may span from a classic intellectual disability syndrome to a milder neurodevelopmental disorder. Interestingly, two of our patients have received successful growth hormone treatment. Considering the phenotype of all the known JDVS patients, a cardiological consultation is recommended, as at least 7/25 patients showed a structural cardiac defect. Episodic fever and vomiting may associate with hypoglycemia and may even mimic a metabolic disorder. We also report the first JDVS patient with a mosaic gene defect and a mild neurodevelopmental phenotype.

1. Introduction

PPM1D (protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1D [MIM: 605100]) gene encodes for a phosphatase that serves as a negative regulator of cellular stress-response pathways (Jansen et al., 2017). Pathogenic variants in *PPM1D* were first described in association with autism by Sanders et al., in 2012 (Sanders et al., 2012) and later identified as a candidate gene for intellectual disability (ID) by Lelieveld et al., in 2016 (Lelieveld et al., 2016). Jansen et al. reported the association of de novo truncating variants of the last and penultimate exons of *PPM1D* with a novel clinical ID syndrome (Jansen de Vries syndrome, JDVS [OMIM: 617450],) (Jansen et al., 2017).

PPM1D truncating variants of the fifth and sixth exons are presumed to escape nonsense-mediated mRNA decay resulting. Consequently, the resulting stable truncated PPM1D transcripts still contain functional domains but lack a nuclear localization signal. Cell lines from patients with JDVS showed a cell-growth disadvantage after irradiation suggesting these truncated *PPM1D* transcripts might compromise the cell-cycle checkpoints (Jansen et al., 2017). This finding supported a possible association between cell-cycle checkpoint genes and neurodevelopmental disorders.

In the pivotal publication of Jansen et al. most JDVS patients (N = 13/14, 93%) show mild to severe ID and behavioral problems (N = 11/14, 79%). Some are hypersensitive to sounds (7/14, 50%) and have a high pain threshold (9/10, 90%). These patients tend to have hypotonia (10/14, 71%), short stature (8/14, 57%), feeding difficulties (10/14, 71%), periods of illness with fever and/or vomiting (8/14, 57%), and problems with vision such as myopia, hypermetropia or strabismus (9/14, 64%). Jansen et al. described these patients to present with similar dysmorphic features: a broad forehead, low-set posteriorly rotated ears, an upturned nose, a broad mouth with a thin upper lip, small hands often with brachydactyly, and small feet with hypoplastic toenails (Jansen et al., 2017).

Since the first description of JDVS, seven additional patients with heterozygous de novo truncating variants in the fifth or sixth exons of

* Corresponding author. Department of Pediatrics, New Children's Hospital, P.O. Box 347, FIN-00029, HUS, Finland.
E-mail address: anna.tuiskula@hus.fi (A. Tuiskula).

https://doi.org/10.1016/j.ejmg.2023.104807
Received 7 March 2023; Received in revised form 6 June 2023; Accepted 26 June 2023
Available online 28 June 2023

Abbreviations

ADHD	attention deficit/hyperactivity disorder
ASD	atrial septal defect
CGH	comparative genomic hybridization
EEG	electroencephalogram
GER	gastroesophageal reflux
GH	growth hormone
ID	intellectual disability
JDVS	Jansen de Vries syndrome
MLPA	multiplex ligation-dependent probe amplification
MRI	magnetic resonance imaging
MRA	magnetic angiogram
NEPSY-II	test-set to assess neuropsychological development
OMIM	Online Mendelian Inheritance in Man
PDA	patent ductus arteriosus
PPM1D	protein phosphatase, Mg2+/Mn2+ dependent 1D
VSD	ventricular septal defect
WISC-IV	Wechsler Intelligence Scale For Children – IV
WPPSI-III	Wechsler preschool and primary scale of intelligence

PPM1D have been reported in literature (Kuroda et al., 2019; Porrmann et al., 2019; Li et al., 2020; Martín Fernández-Mayoralas et al., 2021; Tsai et al., 2022). These children have been described to show a phenotype and dysmorphic features resembling those first 14 patients published by Jansen et al. (2017) (Table 1) and (Fig. 2).

Here, we report three children of whom two present with a previously unpublished truncating pathogenic variant in *PPM1D* and one adult male with a novel mosaic pathogenic variant (Fig. 1). Finally, we reflect on the various clinical features of the now published 24 patients diagnosed with JDVS.

2. Clinical report

2.1. Patient 1

The patient is a 12-year-old boy who has been diagnosed with a severe language deficit, attention-deficit/hyperactivity disorder, autism spectrum disorder, and growth hormone deficiency.

The child was born to a non-consanguineous healthy Finnish couple full-term from a normal pregnancy by vaginal delivery. His Apgar score was 9 at 1min, birth weight was 3125 g/−0.3 SD and height 47 cm/−1.2 SD. Crawling on all fours and independent sitting were achieved at the age of 16 months and independent walking at the age of 20 months. He said his first words at the age of 11 months.

He was diagnosed with ADHD at the age of 7 and treated with methylphenidate. At the age of 9 years, he was diagnosed with autism spectrum disorder due to repetitive mannerisms, tic symptoms, and difficulties in social interactions. In a neuropsychological examination (WISC-IV) at the age of 11 he had a severe language deficit (index score 70) but showed average skills in perceptual reasoning (index score 91) and close to average skills in working memory (index score 85). He had difficulties in maintaining attention and a very low processing speed (index score 62). The patient is in special education, and he has difficulties especially regarding reading skills. When asked, the parents report a high threshold for pain.

At 4 years of age, he was diagnosed with growth hormone (GH) deficiency and GH treatment was initiated. Prior to treatment his height reached −2.7 SD (expected height +0.7 SD). At 12 years of age his height measurement increased to −0.8 SD and a bone age of approximately 10.5 years was observed (delayed for 1.5 years).

As an infant the child had some feeding difficulties. The child has had intermittent constipation and occasional tendency for diarrhea. At 9 years old he was examined due to episodes of nausea and vomiting. The ophthalmologist has diagnosed the patient with strong hyperopia (+7.0/+7.0) and amblyopia. At 6 years of age the left-sided hydrocele and small umbilical hernia were surgically repaired. The brain MRI showed only a small arachnoid cyst and a small Rathke's cleft cyst. The sleep EEG examination was normal. An echocardiogram performed at the age of 1 was normal.

A detailed examination of clinical geneticist (KA) revealed dysmorphic features: a protruding forehead, low-set and posteriorly rotated ears, a low nasal bridge, a wide mouth with a thin upper lip and a high and arched palate. In the extremities, hypermobile finger joints, fetal pads in fingertips, single palmar crease on the other hand, strongly fallen arches in both feet, and dysplastic toenails were observed (Fig. 1).

ArrayCGH (Agilent 180K) provided a normal result. Whole exome sequencing (HUSLAB, Helsinki, Finland) revealed a heterozygous de novo frameshift variant in exon 6 of *PPM1D* (NM_003620.4) c.1434del, p.(Cys478Trpfs*5), (hg38 g.17:60663168-C). The variant has been previously reported as an incidental finding in an infant with unilateral renal agenesis (Zhou et al., 2020). The variant was classified as a likely pathogenic (PS2, PM1) variant. The variant and patient phenotype have been submitted to DECIPHER database with open-access status (Patient 512010).

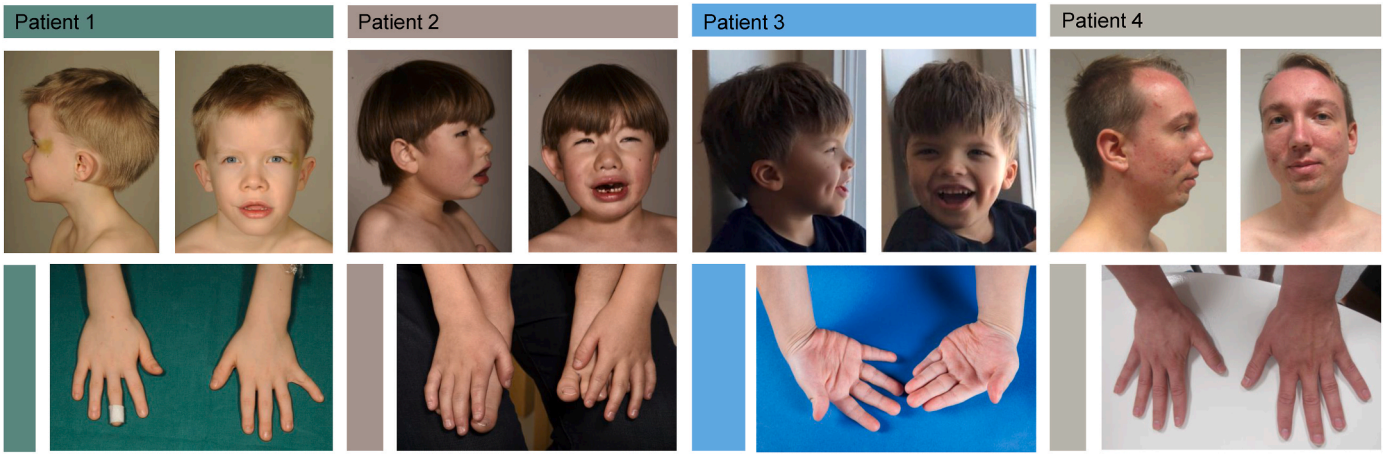

Fig. 1. Clinical characteristics of the patients. All patients share low-set posteriorly rotated ears as a common facial feature. Patient 1 shows a typical broad forehead, an upturned nose, and a broad mouth with thin upper lip. Patient 3 also has a broad forehead and a wide mouth. Patient 2 shows typical brachydactyly. Patient 3 has bilateral single palmar creases.

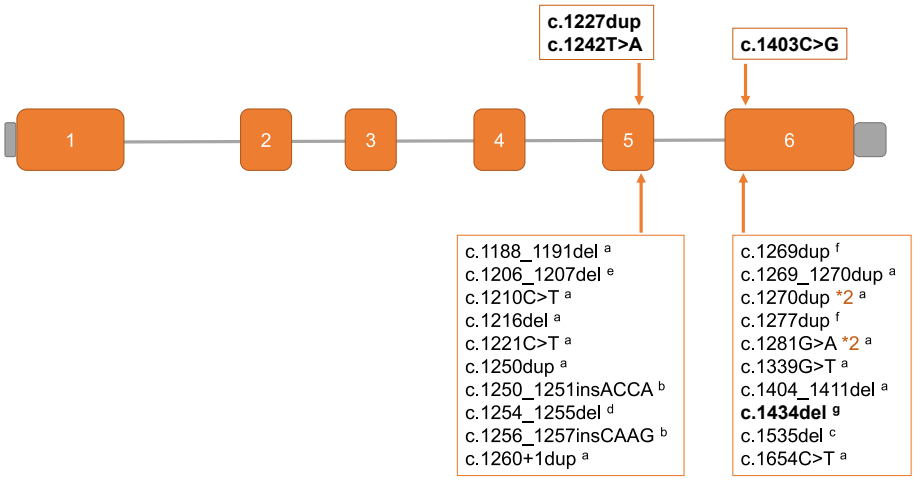

Fig. 2. Novel *PPM1D* (NM_003620.4) variants described in this report above the gene and previously published pathogenic *PPM1D* variants below the gene. [a] Jansen et al., 2017, [b] Kuroda et al., 2019, [c] Porrman 2019, [d] Li et al., 2020, [e] Fernández-Mayoralas 2021, [f] Tsai et al., 2022, [g] Zhou et al., 2020. Variants of the patients reported in this study have been bolded. Exons are to scale, introns and UTRs are not to scale.

2.2. Patient 2

The second patient is a 7-year-old boy, who has been diagnosed with intellectual disability, ventricular septal defect (VSD) and GH deficiency.

The patient was born to a healthy couple originating from Finland and Japan. He was born vaginally at full term with Apgar scores 8 at 1 min and 7 at 5 min. Birth weight was 2920 g/−2.0 SD. The child had a pneumothorax and needed a short non-invasive positive pressure ventilation treatment. The patient had hypotonia and needed a feeding tube for 2 weeks. Neonatal EEG and brain ultrasound examination were normal. The patient had micrognathia, retrognathia, a micropenis, and a small scrotum neonatally. The neonatal echocardiogram revealed a large VSD and signs of decompensation. Furosemide and spironolactone medications were used until 11 months of age. The cardiological surveillance is ongoing.

At the age of 11 months there was a suspicion of a few absence seizures, but EEG examination was normal. He started walking and said the first words at the age of 3. The patient is willing to communicate with others but is self-willed and has difficulties in maintaining attention. In a neuropsychological examination at 5.5 years of age quantification of intellectual abilities was not yet possible. Overall skills in language and perceptual reasoning were approximately at the level of a three-year-old and the patient was diagnosed with intellectual disability. He has started school in special education. His parents have not noticed the pain threshold to be atypical, but they report that the child is very sensitive to sounds.

When the patient was 6.5 years old, he was diagnosed with GH deficiency and GH treatment was started. Before treatment his height was −4.5 SD (expected height −0.5 SD). His head circumference is −3.4 SD. Before the start of GH treatment his bone age was approximately 2.5 years delayed.

The child has had chronic constipation. At 6 years of age, he had occasional vomiting and was diagnosed with gastroesophageal reflux. In the MRI of the brain the fourth ventricle seemed mildly dilated. An abdominal ultrasound examination was normal. Examinations by an ophthalmologist and audiologist were also normal.

A detailed examination of clinical geneticist (KA) revealed the following dysmorphic features: low-set and posteriorly rotated ears, a protruding left ear with smooth helix, a short philtrum and full lips. Brachydactyly, fetal pads in fingertips, and a micropenis were observed (Fig. 1).

ArrayCGH (Agilent 180K) provided a normal result. CTG repeat length in both alleles of DMPK gene were normal ruling out myotonic dystrophy type 1. Because of clinical suspicion of Kabuki syndrome, sequence and MLPA analysis of *KMT2D* and *KDM6A* were performed with normal results. Whole-exome sequencing (HUSLAB, Helsinki, Finland) revealed a heterozygous de novo frameshift variant in exon 5 of the *PPM1D* (NM_003620.4) c.1227dup, p.(Thr410Aspfs*24) (hg38 g.17:60656808–G). The variant had not been previously reported in the literature nor had it been listed in genetic databases. The variant was classified as a likely pathogenic variant (PS2, PM1). The variant and patient phenotype have been submitted to DECIPHER database with open-access status (Patient 512012).

2.3. Patient 3

Patient 3 is a 5-year-old boy, who has been diagnosed with a mixed specific developmental disorder (ICD-10 code F83).

The patient is the fourth child of non-consanguineous healthy Finnish parents. The patient was born from a normal pregnancy by vaginal delivery at term. Apgar scores where 8 at 1min, and 9 at 10 min. His birth weight was 3160 g/−0.1 SD and height 47.5 cm/−0.8 SD. He had mild respiratory stridor. After birth bilateral single palmar creases were noted. A standard GTG-banded chromosome analysis showed a normal male karyotype.

The patient has a global developmental delay. He learned to walk at the age of 18 months and could say a couple of words at that time. His speech development has been markedly delayed, he has displayed unclear speech and occasional stuttering. He is very sensitive for sounds and smells. In a psychological examination (WPPSI-III) at 5 years he had difficulties in maintaining attention and lack of motivation to tasks, which might have influenced the overall performance. His general language composite was extremely low. His performance abilities varied from extremely low to average.

At the age of 20 months the height of the patient was −3.5 SD and head circumference −0.4 SD. In further examinations an elevated alkaline phosphatase (ALP) level up to 2387 U/l (reference range 115–480 U/l) was noted. During the follow-up ALP normalized. At the age of 4 his bone age was approximately 0.5 years delayed. The patient achieved catch-up growth without growth hormone therapy and at the age of 5.5 years his height reached −1.8 SD.

The patient has been hospitalized several times due to recurrent periods of nausea and vomiting associated with hypoglycemia (blood sugar 2.6 mmol/l, reference range 4.2–6.0 mmol/l after fasting) and ketosis. The tendency to hypoglycemia was further investigated by a team of metabolic specialists, but no specific inborn error of metabolism was found. Metabolic samples were repeatedly taken in a period of acute

illness showing low plasma amino acids consistent with a prolonged fasting. Urine organic acids were consistent with a strong ketosis associated with a catabolic situation.

Ophthalmologist has diagnosed the patient with hyperopia (+3.75/3.75) and mild esophoria, and the patient wears glasses. The echocardiogram performed by a pediatric cardiologist revealed no structural cardiac abnormalities.

A detailed examination of a clinical geneticist (ER) revealed the following dysmorphic features: a prominent and wide forehead, a low nasal bridge, low-set, small and posteriorly rotated ears, a wide mouth with full lips, hypoplastic nails, and bilateral single palmar creases (Fig. 1).

Whole-exome sequencing (Centogene, Rostock, Germany) revealed a heterozygous nonsense variant in exon 5 of the *PPM1D* (NM_003620.4) c.1242T > A, p.(Cys414*) (hg38 g.17:60656823T > A). The variant is not present in the Genome Aggregation Database (gnomAD v.2.1.1, accessed on the April 20, 2022). It is predicted to be pathogenic *in silico* (Mutation Taster). Targeted Sanger sequencing of parental samples confirmed a de novo origin of the identified variant. It is classified as likely pathogenic (PS2, PM2) according to the ACMG criteria. The variant and patient phenotype have been submitted to DECIPHER database with open-access status (Patient 512013). As an incidental finding, maternally inherited *KCNH2* c.1655T > C, p.(Leu552Ser) heterozygous pathogenic variant was identified. The patient is asymptomatic but uses 2.5 mg of bisoprolol daily to prevent arrhythmias.

2.4. Patient 4

Patient 4 is a 27-year-old male, who has been diagnosed with a mixed specific developmental disorder (ICD-10 code F83). The patient is the first shared child of non-consanguineous Finnish parents. The patient was born at home from a normal pregnancy by vaginal delivery at term. Apgar scores or birth weight are unknown. The patient has a psychomotor developmental delay. He learned to walk at the age of 14 months and said his first words at the age of 2. At 6 years his speech was still unclear. The psychological examination (NEPSY-II, WISC-III) at 15 years of age showed severe deficit in language and perceptual reasoning and diagnosis of mixed spesific developmental disorder was made. EEG has been slightly abnormal, no epileptic features. He was educated in a special school and continued in a vocational school studying logistics with customized learning plan. He has been working as taxi driver and is currently studying to work as driving instructor. He lives unaided with his spouse. His spouse is currently pregnant.

Growth of the patient has followed the −2 SD curve and he has a slim body type. As a child he had microcephaly, but as an adult the head circumference is within normal range. The patient has hyperopia, and he wore reading glasses at school age.

At the age of 10 the patient was diagnosed with anaplastic anemia. A chromosomal breakage analysis showed no signs of Fanconi anemia. In a gene panel analysis from a bone marrow sample a pathogenic mosaic *PPM1D* variant was detected but no pathogenic variants related to aplastic anemia were discovered. The aplastic anemia was considered as idiopathic and treated successfully with anti-thymocyte globulin and cyclosporine. For the last few years, the disease has been in remission.

At the age of 26 the patient suffered a brain infarct with aphasia as a main symptom. The brain MRI showed an ischemic lesion in the left insular cortex. The brain MRA revealed a total blockage in the insular part of the middle cerebral artery. In a thorough investigation the etiology of the infarct remained undetermined. The brain MRI and echocardiogram did not show structural abnormalities. After the infarct the patient still showed moderate aphasia and signs of oral and verbal apraxia in the evaluation by a speech therapist. Whether the symptoms were related to the infarct remained somewhat unclear, as earlier psychological evaluations had already showed problems in verbal processing.

An examination by a clinical geneticists (MH, AK) revealed several dysmorphic features: a prominent forehead, hypertelorism and downslanting palpebral fissures, bushy eyebrows, a small chin and small hands and feet (Fig. 1).

Whole-exome sequencing (TYKS, Genomiikka, Turku, Finland) revealed a mosaic nonsense variant in exon 6 of the *PPM1D* (NM_003620.4) c.1403C > G, p.(Ser468*) (GRCh37 g.58740498C > G). The allele fraction in buccal mucosa was 14%, in blood 27% and in bone marrow 37%. The variant has not previously been reported in the literature and is reported only once in the Genome Aggregation Database (gnomAD v.2.1.1). Parental samples were not available. It is classified as pathogenic (PVS1, PM2, PP3) according to the ACMG criteria. The variant and patient phenotype have been submitted to DECIPHER database with open-access status (Patient 512014). Whole-exome sequencing did not reveal pathogenic variants known to cause brain infarct at young age.

2.5. Review of the previously reported JDVS patients

We reviewed the clinical details of both the novel (n = 4) and previously reported (n = 21) patients with JDVS (Table 1).

At the time of the published report, the patients were nine months to 27 years old and all of them were alive. 11 are female, and 14 are male. Most of the reported patients (17/23, 74%), but not all of them, showed ID. Hypotonia (16/21, 76%), a high threshold to pain (14/17, 82%) and behavioural characteristics (18/21, 86%) such as attention deficit or hypersensitivity to sounds are common features.

Most of the patients show short stature (19/24, 79%). Furthermore, the patients demonstrate feeding difficulties (15/20, 75%), GER and/or vomiting (14/19, 74%), constipation (14/20, 70%) and ophthalmological abnormalities (14/21, 67%) such as hyperopia and strabismus.

Some of the patients have a structural cardiac condition (7/NA) or minor unspecific findings on the brain MRI (11/17, 65%). Facial dysmorphisms such as a wide forehead (17/22, 77%), low-set posteriorly rotated ears (15/20, 75%) or a thin upper lip (17/22 (77%) are common.

3. Discussion

Here, we report four novel patients and review the clinical and genetic details of 21 previously published JDVS patients. Similarly to the previously published pathogenic *PPM1D* variants, all the novel variants described here are truncating variants in the last or penultimate exons of *PPM1D* (Fig. 2). The phenotype of the patients described in the current study is comparable to the phenotype described in the literature, albeit one patient with mosaicism (Table 1). Interestingly, only one of the four new patients had ID suggesting that the phenotype of JDVS extends from classic ID syndrome to a milder neurodevelopmental disability.

Previously, only three JDVS patients have been described without a diagnosis of ID (Jansen et al., 2017; Porrmann et al., 2019; Martín Fernández-Mayoralas et al., 2021). Here, we have now presented three new JDVS patients with only mild cognitive disability, albeit one of them has mosaicism. So, altogether 23% (5/22) of children with germline pathogenic variants of PPM1D do not have ID providing important information for the genetic counselling of families with a JDVS diagnosis. It must be kept in mind, that some of the patients might have been too young for the final assessment of cognition at the point of evaluation. Also, differences between countries in the follow-up and diagnosis of ID may affect this result.

In this review of clinical features of patients with JDVS, it is notable that 79% have short stature. At least four children with Jansen de Vries are described to have a significantly delayed bone age (Table 1). One of the patients described by Jansen et al. had received growth hormone treatment (Jansen et al., 2017). Both patients 1 and 2 described in this article received growth hormone treatment that seemed to accelerate their growth significantly. Patient 3 also had short stature at the age of 1.5 years. Interestingly, his growth accelerated without growth hormone therapy. Based on these findings, it might be beneficial to consult an

endocrinologist, when a child is diagnosed with JDVS and has short stature.

Seven of the children with JDVS have been described to have an otherwise unexplained cardiac condition (Table 1). Patient 2 described in this article had a VSD and needed diuretic medication. A male infant previously reported by Li et al. had ASD, VSD and PDA and needed surgical treatment (Li et al., 2020). Of the patients described by Jansen et al. one had VSD and PDA, one hypertrophic cardiomyopathy, one bicuspid aortic valve and one pericardial effusion (Jansen et al., 2017). The cardiac status has not described for all JVDS cases, so the certain percentage of cardiac structural defects is not deductible based on literature. However, it seems to be at least 7/25 (28%). Because some of the children have needed treatment for their cardiac condition, we recommend a cardiac consultation especially for all children receiving a diagnosis with JDVS.

Mild, unspecific changes have been reported in 11 of the brain MRIs of 16 patients with germline JDVS (Table 1). Because there are no findings that require specific treatment and, as the findings have been so diverse, brain MRI does not seem to be necessary for children with the genetic diagnosis of JDVS specifically. Nevertheless, brain MRIs are commonly performed as routine evaluations to determine the etiology of unclear developmental delay in children.

The initial presentation of JDVS can mimic a metabolic disorder as exemplified by patient 3 who was hospitalized numerous times due to vomiting associated with hypoglycemia. Extensive metabolic work-up including plasma and urine amino acids, urine organic acids, and blood carnitines did not show evidence of a metabolic disorder. The patient's slender build and episodic illness and vomiting associated with prolonged fasting were proposed to trigger his hypoglycemic episodes. A similar episodic illness appears to be a relatively common symptom associated with JDVS (11/25, 44%).

Even though constipation, gastroenteric reflux (GER) and feeding difficulties are frequent symptoms in the common pediatric patient population, they still seem to be overrepresented in children with JDVS (Table 1). In this review, the incidence of GER (74%), feeding difficulties (75%) and constipation (70%) are described in an incidence similar to the incidence previously reported by Jansen et al. (77%, 71%, and 62%, respectively) (Jansen et al., 2017). These symptoms can be managed with commonly used pediatric interventions. Thus, a pediatric consultation is recommended if a child with JVDS presents with these symptoms.

PPM1D variant of patient 1 (c.1434del) has been previously reported as an incidental finding in an infant with unilateral renal agenesis. Diagnostic exome sequencing was performed prenatally and during the first five months of postnatal follow-up no delay in gross motor development was observed (Zhou et al., 2020). JDVS patients have not been reported to present with congenital anomalies of the kidney and urinary tract, however some of the patients have been described to have minor genital anomalies (Jansen et al., 2017; Li et al., 2020) (also patient 2 in this report). Furthermore, it is not uncommon that mild psychomotor developmental delay is not perceptible until at 12–24 months.

Here, we report the first case with a mosaic *PPM1D* defect and respectively a mild neurodevelopmental phenotype. The mosaicism was confirmed in three separate tissues. In fact, this JDVS diagnosis was an incidental finding detected in the process of searching for the etiology of anaplastic anemia. The patient also had a brain infarct at an unusually young age. The clinical exome sequencing analysis did not reveal any causative gene defects explaining anaplastic anemia or the brain infarct. Whether these two phenotypes are associated with the *PPM1D* defect remains unclear. To our knowledge these symptoms have not been previously reported in JDVS, but it is likely that many of the patients with *PPM1D* defect still remain undetected.

4. Conclusion

The clinical phenotype of JDVS is variable and may extend from a classic intellectual disability syndrome to a milder neurodevelopmental disorder commonly associated with distinct behavioral features, short stature, gastrointestinal symptoms, well-described dysmorphic features, and, occasionally, with a structural cardiac condition.

Further clinical evaluations and reports of additional JVDS patients are warranted to assess the clinical scope of symptoms in this patient group to also optimize the adequate surveillance of the patients with JVDS.

Ethics declaration

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all parents of the patients. Written informed consent was obtained to publish patient photos.

Funding

None of the authors have conflict of interest to disclose. This study was supported by the Academy of Finland (decision number 338446) to ER.

CRediT authorship contribution statement

Anna Tuiskula: Data gathering, Visualization, Writing – original draft, Writing – review & editing. **Elisa Rahikkala:** Data gathering, Writing – original draft, Writing – review & editing. **Andreina Kero:** Data gathering, Writing – review & editing. **Maria K. Haanpää:** Data gathering, Writing – review & editing. **Kristiina Avela:** Conceptualization, Supervision, Writing – review & editing.

Data availability

The data that has been used is confidential.

Acknowledgements

We would like to thank the patients and families who participated in this study. Our sincere thanks are also extended to the psychologist Salla Kykkänen for her help with data management. The authors of this publication are members of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA). [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2023.104807.

References

Jansen, S., Geuer, S., Pfundt, R., et al., 2017. De novo truncating mutations in the last and penultimate exons of PPM1D cause an intellectual disability syndrome. Am. J. Hum. Genet. 100 (4), 650–658. https://doi.org/10.1016/j.ajhg.2017.02.005.

Kuroda, Y., Murakami, H., Yokoi, T., et al., 2019. Two unrelated girls with intellectual disability associated with a truncating mutation in the PPM1D penultimate exon. Brain Dev. 41 (6), 538–541. https://doi.org/10.1016/j.braindev.2019.02.007.

Lelieveld, S.H., Reijnders, M.R., Pfundt, R., et al., 2016. Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. Nat. Neurosci. 19 (9), 1194–1196. https://doi.org/10.1038/nn.4352.

Li, Z., Du, C., Zhang, C., et al., 2020. Novel truncating variant of PPM1D penultimate exon in a Chinese patient with Jansen-de Vries syndrome. Mol Genet Genomic Med 8 (3), e1120. https://doi.org/10.1002/mgg3.1120.

Martín Fernández-Mayoralas, D., Fernández-Perrone, A.L., Jiménez de Domingo, A., Alba Menéndez, A., Fernández-Jaén, A., 2021. [Jansen-de Vries syndrome. First case diagnosed in Spain]. Neurol Barc Spain 36 (4), 330–332. https://doi.org/10.1016/j.nrl.2020.06.006.

Porrmann, J., Rump, A., Hackmann, K., et al., 2019. Novel truncating PPM1D mutation in a patient with intellectual disability. Eur. J. Med. Genet. 62 (1), 70–72. https://doi.org/10.1016/j.ejmg.2018.05.006.

Sanders, S.J., Murtha, M.T., Gupta, A.R., et al., 2012. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 485 (7397), 237–241. https://doi.org/10.1038/nature10945.

Tsai, M.J.M., Lee, N.C., Chien, Y.H., Hwu, W.L., Tung, Y.C., 2022. Short stature leads to a diagnosis of Jansen-de Vries syndrome in two unrelated Taiwanese girls: a case report and literature review. J Formos Med Assoc Taiwan Yi Zhi 121 (4), 856–860. https://doi.org/10.1016/j.jfma.2021.12.022.

Zhou, X., Wang, Y., Shao, B., Wang, C., Hu, P., Qiao, F., Xu, Z., 2020. Molecular diagnostic in fetuses with isolated congenital anomalies of the kidney and urinary tract by whole-exome sequencing. J. Clin. Lab. Anal. 34 (11), e23480 https://doi.org/10.1002/jcla.23480.