Check for updates

Received: 20 January 2023 | Revised: 13 April 2023 | Accepted: 20 April 2023

DOI: 10.1002/ajmg.a.63226

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Jansen-de Vries syndrome: Expansion of the *PPM1D* clinical and phenotypic spectrum in 34 families

Monica H. Wojcik[1,2,3] | Siddharth Srivastava[4] | Pankaj B. Agrawal[3,5] | Tugce B. Balci[6] | Bert Callewaert[7] | Pier Luigi Calvo[8] | Diana Carli[9] | Michelle Caudle[6] | Samantha Colaiacovo[6] | Laura Cross[10] | Kalliope Demetriou[11] | Katy Drazba[12] | Marina Dutra-Clarke[13] | Matthew Edwards[14] | Casie A. Genetti[2,3] | Dorothy K. Grange[15] | Scott E. Hickey[16] | Bertrand Isidor[17] | Sébastien Küry[18] | Herbert M. Lachman[19] | Alinoe Lavillaureix[20] | Michael J. Lyons[12] | Carlo Marcelis[21] | Elysa J. Marco[22] | Julian A. Martinez-Agosto[23] | Catherine Nowak[2] | Antonio Pizzol[8] | Marc Planes[24] | Eloise J. Prijoles[12] | Evelise Riberi[9] | Eric T. Rush[25,26,27] | Bianca E. Russell[23] | Rani Sachdev[11,28] | Betsy Schmalz[16] | Deborah Shears[29] | David A. Stevenson[30] | Kate Wilson[29] | Sandra Jansen[31] | Bert B. A. de Vries[31] | Cynthia J. Curry[32]

Correspondence
Monica H. Wojcik, Division of Newborn Medicine, Department of Pediatrics and Harvard Medical School, Boston Children's Hospital, Boston, MA, USA.
Email: monica.wojcik@childrens.harvard.edu

Cynthia J. Curry, Genetic Medicine, Department of Pediatrics, University of California San Francisco/Fresno, Fresno, CA, USA.
Email: cynthia.curry@ucsf.edu

Funding information
NIH/NIMH, Grant/Award Number: R21 MH131740; NIH/NICHD, Grant/Award Numbers: K23 HD102589, P30 HD071593; NIH/NINDS, Grant/Award Number: K23 NS119666; Dutch Organization for Health Research and Development: ZON-MW, Grant/Award Number: 912-12-109

Abstract

Jansen-de Vries syndrome (JdVS) is a neurodevelopmental condition attributed to pathogenic variants in Exons 5 and 6 of *PPM1D*. As the full phenotypic spectrum and natural history remain to be defined, we describe a large cohort of children and adults with JdVS. This is a retrospective cohort study of 37 individuals from 34 families with disease-causing variants in *PPM1D* leading to JdVS. Clinical data were provided by treating physicians and/or families. Of the 37 individuals, 27 were male and 10 female, with median age 8.75 years (range 8 months to 62 years). Four families document autosomal dominant transmission, and 32/34 probands were diagnosed via exome sequencing. The facial gestalt, including a broad forehead and broad mouth with a thin and tented upper lip, was most recognizable between 18 and 48 months of age. Common manifestations included global developmental delay (35/36, 97%), hypotonia (25/34, 74%), short stature (14/33, 42%), constipation (22/31, 71%), and cyclic vomiting (6/35, 17%). Distinctive personality traits include a hypersocial affect (21/31, 68%) and moderate-to-severe anxiety (18/28, 64%). In conclusion, JdVS is a clinically recognizable neurodevelopmental syndrome with a characteristic personality and distinctive facial features. The association of pathogenic variants in *PPM1D* with cyclic vomiting bears not only medical attention but also further pathogenic and mechanistic evaluation.

For affiliations refer to page 9

 © 2023 Wiley Periodicals LLC.

KEYWORDS
cyclic vomiting, developmental delay, hypersocial personality, Jansen-de Vries syndrome, PPM1D

1 | INTRODUCTION

Jansen-de Vries syndrome (JdVS) was first delineated as a syndromic form of intellectual disability in 2017 in a cohort of 14 individuals with truncating variants in *PPM1D* (Jansen et al., 2017). All disease-causing variants in this initial cohort were found in the penultimate or last exons (5 and 6) of this gene and all were de novo (Jansen et al., 2017). Prior to this report, *PPM1D* had been identified as a candidate gene for intellectual disability due to its enrichment for de novo variants in two large cohorts of individuals with intellectual disability (Deciphering Developmental Disorders Study, 2017; Lelieveld et al., 2016). In their report, Jansen et al. describe in further detail the seven individuals reported in these larger meta-analyses (Deciphering Developmental Disorders Study, 2017; Lelieveld et al., 2016) in addition to seven new individuals. They highlight several features shared among those with pathogenic variants in *PPM1D* (Jansen et al., 2017). Intellectual disability was seen in all but one individual (though that person had learning difficulties) and other notable features included short stature, recurrent craniofacial features such as a broad forehead, a broad mouth with thin upper lip, small hands and feet, and gastrointestinal symptoms such as poor feeding, constipation, and cyclic vomiting. A particular behavioral phenotype was also noted, with an outgoing hypersocial personality, increased sensitivity to sound, nearly universal anxiety, and a high pain threshold commonly reported. Indeed, the condition was initially referred to as "intellectual developmental disorder with gastrointestinal difficulties and high pain threshold", but was later renamed Jansen-de Vries syndrome (OMIM no. 617450). The molecular mechanism is attributed to a truncated protein product that escapes nonsense-mediated decay but has lost the nuclear localization signal while maintaining the PPM-type phosphatase domain in Exon 5 (Jansen et al., 2017); thus, disease-causing *PPM1D* variants may exert their effects in a dominant negative or gain-of-function mechanism.

Since this publication in 2017, 10 additional individuals have been published (Kuroda et al., 2019; Li et al., 2020; Martin Fernandez-Mayoralas et al., 2021; Pitsava et al., 2021; Porrmann et al., 2019; Tsai et al., 2022; Zhou et al., 2020) that both reiterate and expand upon this phenotype with novel features including cleft lip and palate (one case; Porrmann et al., 2019), bladder exstrophy (one case; Pitsava et al., 2021), syndactyly (Tsai et al., 2022), and unilateral renal dysplasia with the diagnosis found on fetal exome (Zhou et al., 2020). In total, 6 of these 10 have been diagnosed by exome sequencing (ES; Li et al., 2020; Pitsava et al., 2021; Tsai et al., 2022; Zhou et al., 2020), one by genome sequencing (Martin Fernandez-Mayoralas et al., 2021) and three via a ~5000 gene panel (Illumina TruSight One; Kuroda et al., 2019; Porrmann et al., 2019). In order to further elucidate the spectrum of manifestations of this rare neurodevelopmental condition, we now report an additional 34 families with JdVS, highlighting the unique developmental and behavioral phenotype, facial gestalt, and gastrointestinal symptoms through physician reports and family interviews.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Participants 8, 23, and 30 were enrolled in the Manton Center for Orphan Disease Research's IRB-approved protocol at Boston Children's Hospital. For all other cases, informed consent to participate, including publication of photographs where relevant, was obtained at the local institution via their own institutional guidelines. Deidentified data for all patients were collected and analyzed under an IRB protocol at Boston Children's Hospital.

Individuals were identified via referral from clinicians, identification through GeneMatcher (Sobreira et al., 2015), and via connections made through the Jansen-de Vries family support group. Phenotypic data were collected via parent interview or information provided by the treating geneticists. Twenty three parent interviews (Cynthia J. Curry) were conducted via phone call, video call, or in person visits (five families). All parents provided additional information via email.

3 | RESULTS

3.1 | Demographics

We ascertained 37 individuals from 34 families, including the first report of familial cases, with two families involving an affected mother and child, a third involving an affected son, mother, and grandmother, and a fourth involving an affected father and daughter. Across the cohort, there were 27 male and 10 female individuals. Median age at ascertainment was 8.75 years (interquartile range [IQR] 5–12.25 years), with a range from 8 months to 62 years (though many families reported age at diagnosis of 2–3 years). Families were from North America, Europe, and Australia.

3.2 | Molecular diagnosis

Diagnosis was made via ES in all but two families, where the diagnosis was made by gene panel. All variants fell in xons 5 or 6 in *PPM1D* and were either frameshift variants or missense variants leading to premature termination. Two variants were recurrent, with the c.1210C > T, p.(Gln404Ter) variant observed in four separate families and the c.1280G > A, p.(Trp427Ter) variant also observed in four families. The

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

variants in these 34 families are represented in Figure 1. Variants were de novo in 30/34 families, with the remaining four families documenting autosomal dominant inheritance.

3.3 | Perinatal history

Polyhydramnios was noted in 6/34 (18%) pregnancies and gestational diabetes in 6/34 (18%) with no other salient prenatal features. Most individuals were born full term (three preterm) and anthropometric measurements at birth were generally within the normal range. Six individuals (24%) had neonatal complications including need for resuscitation at birth (five), tachypnea (two), apneic spells (one), and hypoglycemia (one). Common features noted in early infancy were hypotonia (25/34, 74%), poor feeding (two with dysphagia/choking in infancy), and constipation (22/31, 71%; Table S1).

3.4 | Growth

Growth parameters were notable for short stature (Z-score of ≤ −2) in 14/33 (42%), with only three individuals having a Z-score for height of ≤ −3 and a median Z-score for height of −1.3. Low weight (Z-score of ≤ −2) was noted in 10/35 individuals (29%) and 2 were overweight with the rest at normal weight for age and a median Z-score for weight of −0.5. Head circumference was normal in the majority with available measurements (20), with seven (35%) having a Z-score ≤ −2 (Figure 2).

3.5 | Development

Developmental milestones are described in Table S2. Motor skills were generally delayed, with median age at independent walking of 25 months (IQR 22–28.5 months). Gait was described as abnormal in several cases, with four described as walking with a wide-based gait and some experiencing frequent falls. Most individuals were able to run, some ride a bicycle, and one played ice hockey. Mild hypotonia appeared to improve with age but was often documented in older children as well. Language skills were also delayed, with a wide spectrum of ages at first words: from 12 months to 15 years, with a median of 20 months (IQR 16–33 months). Two individuals were nonverbal and one lost language at 16 years of age.

Intellectual skills varied; those who had intelligence quotient (IQ) testing (8/34, 24%) had median IQ of 70 (IQR 58.25–72.75). One person had severe intellectual disability. Eight of 29 individuals (28%) were noted to have features of autism spectrum disorder (with possible autism in one additional child), 17/29 (58%) had been diagnosed with attention deficit hyperactivity disorder (ADHD) with possible ADHD in 2. Eighteen of 28 (64%) have a formal diagnosis of anxiety and 21/31 individuals (68%) are described as hypersocial. In at least five cases, there was clinical suspicion for Williams Syndrome due to the similar personality, echolalia, perseveration, and overlapping physical exam findings such as nail hypoplasia. Other behavioral issues include aggression (8/22, 36%) and issues with impulsivity, with several children described as having "no sense of danger". Hypersexuality was a concern in some older patients. Of the affected parents or grandparents within the familial cases in our cohort, these adults had

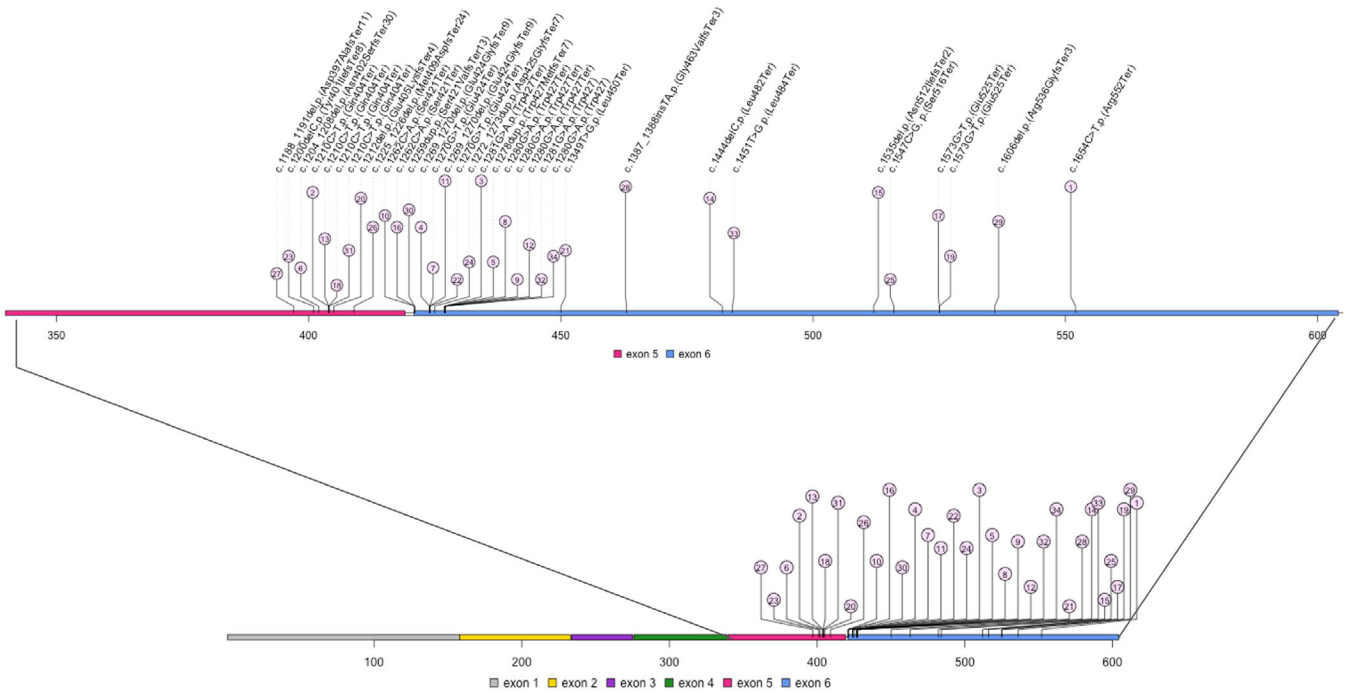


FIGURE 1 Spectrum of variants identified in *PPM1D*. Variants are identified by position in the amino acid sequence. The number within the circle indicates the case number from this series. All variants fall within exons 5 and 6 of *PPM1D*, which comprises six exons total.

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

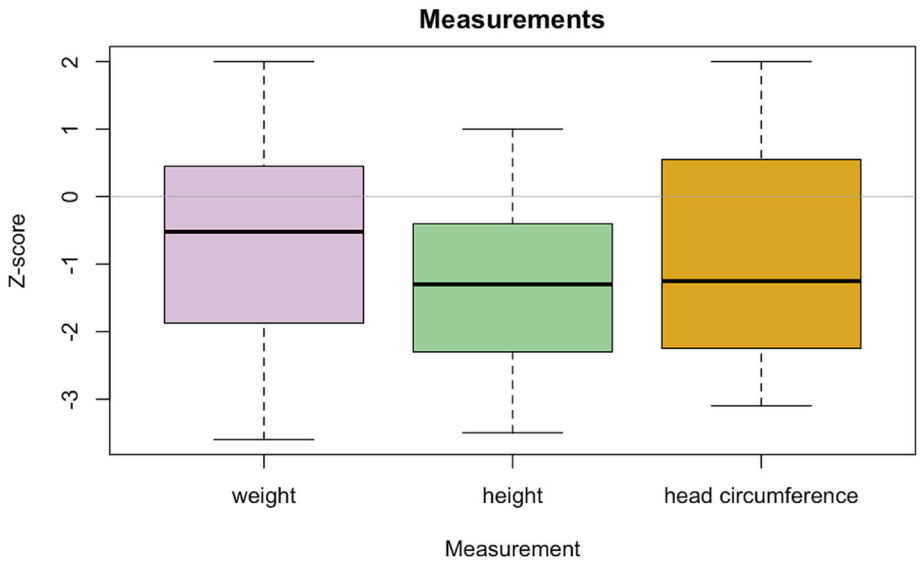


FIGURE 2 Box and whisker plot depicting the Z-score for anthropomorphic measurements at last examination. The line within the box represents the median, with the box boundaries representing the interquartile range and whiskers represent range. Data on height were available for 33 participants, weight for 35, and head circumference for 20.

some limited work experience and at least one had completed high school in regular classes. Two of the affected women ran their households, were able to drive, shop, handle money, and had other unaffected children. At least in the families reported here, fertility appears to have been normal.

3.6 | Physical examination

A common facial gestalt was noted, particularly the broad mouth with a thin and tented upper lip though these features were less noticeable after school age (Figure 3a–d). The hands were noted to be small due to short fingers (palm size normal) in 22/34 (65%) and feet were also noted to be small in 22/35 (63%) (Figure 3e). Few actual measurements were available. Nails were often hypoplastic (15/34, 44%). Common facial features include a broad forehead (27/37, 73%), thin upper lip (33/37, 89%), broad mouth (35/37, 95%), and downturned corners of the mouth (26/37, 70%; Table S1). Other occasional facial features seen included a smooth philtrum (3, 8%), midface hypoplasia (2, 5%), upturned nose (10, 27%) small/widely spaced teeth (4, 11%), hypertelorism (1), low posterior hairline and bushy eyebrows (1), everted/thick lower lip (1), deep-set eyes (1), metopic prominence (2, 5%), notched and hypoplastic alae nasi (1), underfolded pinnae with hypoplastic superior crus of the antihelix (1), high anterior hairline, high arched palate (2, 5%), broad nasal tip (1), midline nasal groove (1), small ears (2, 5%), and dental crowding (1). Face2Gene® (FDNA, Inc) research analysis also supports a specific craniofacial phenotype (Figure 4).

3.7 | Brain imaging

Brain imaging via magenetic resonance imagint (MRI) was performed in 17 individuals, with seven having a normal brain MRI and the remainder having a variety of abnormalities, including parenchymal gliosis in 2/17 (12%), and the following abnormalities each seen once: small pituitary, mega cisterna magna and mild ventriculomegaly, hippocampal rotation, shortening of the corpus callosum and inferior vermian hypoplasia, "underdeveloped" cerebellum, Chiari I malformation, corpus callosum hypoplasia, and arachnoid cyst.

3.8 | Gastrointestinal complaints

Gastroesophageal reflux disease was noted in 16 individuals with two undergoing fundoplication and three requiring gastrostomy tube feeding for weeks to months. Six patients were noted to have issues with gagging or choking on liquids and 20 had unexplained vomiting episodes with six being diagnosed with cyclic vomiting syndrome (CVS). The vomiting episodes were often associated with hypoglycemia leading to frequent emergency department visits and/or hospital admission. Extensive evaluation for metabolic/mitochondrial dysfunction in at least four of these children has been negative. Constipation was reported in 22 individuals, though this may be more prevalent than reported, and constipation tended to improve with age.

3.9 | Other health concerns

Well-controlled seizures of inconsistent types developed in two children and one had a single febrile seizure. Four individuals had recurrent migraine with vomiting, often developing after years of recurrent vomiting episodes. Four were diagnosed with growth hormone (GH) deficiency, though most were not tested. Fourteen were noted to have recurrent otitis media (including both individuals with high-arched palates) and another three had recurrent infections. Immunologic evaluations, when done, were non-diagnostic. Visual problems were noted in 17/23 individuals (74%), including hypermetropia (4/23, 17%), myopia (4/23, 17%), and strabismus (7/23, 30%). Other

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

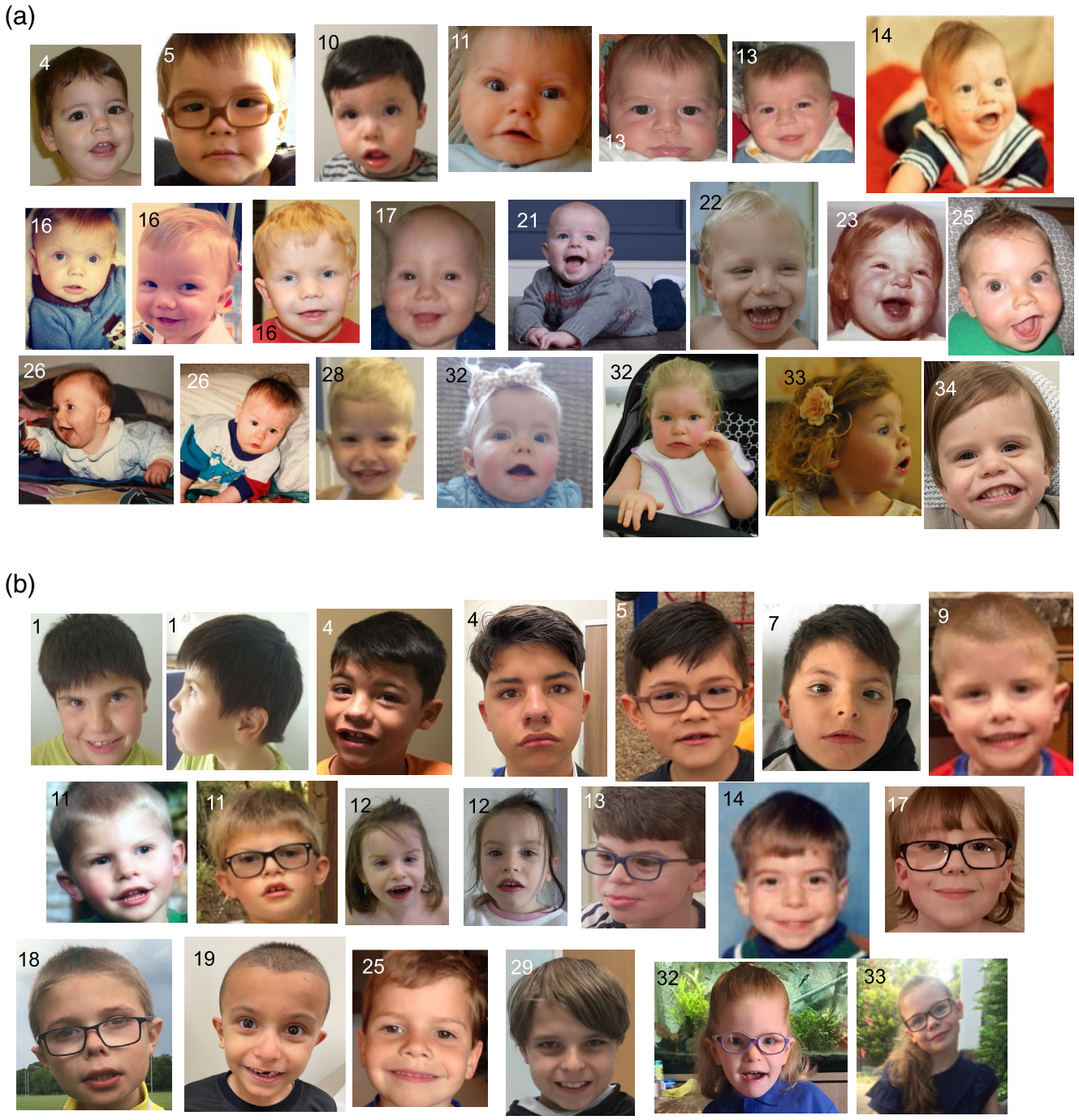


FIGURE 3 (a) In infancy and early childhood, the common facial gestalt is more easily recognizable, particularly the broad forehead and wide mouth with thin upper lip. (b) School age. (c) Adulthood. (d) Familial cases. (e) Hands and feet of affected individuals, illustrating the small size and hypoplastic nails in some.

major anomalies were rare—one person had Tetralogy of Fallot but no other cardiac anomalies were reported in this cohort.

More recently, concerns for a possible neuroinflammatory complication of this condition have emerged, with three people having unexplained developmental regression. One individual was diagnosed with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS) at age 6 (Trifiletti et al., 2022), one experienced loss of language at age 16, and one had recurrent episodes of inability to walk and regression of other skills at age 6–7. A unifying etiology for these abnormalities has not been uncovered. As somatic *PPM1D* variants have been implicated in various malignancies (Khadka et al., 2022; Machiela et al., 2019), the potential for increased cancer risk in people with JdVS has also been raised. At this time there have been no malignancies noted in this cohort, although we are aware of one child with neuroblastoma who has a pathogenic variant in *PPM1D* (S. Jansen, personal communication).

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



FIGURE 3 (Continued)

3.10 | Literature review

In order to describe the frequency of commonly noted manifestations of this condition we reviewed our 37 cases, the 10 additional individuals reported in the literature (Tsai et al., 2022) and the original 14 cases described in 2017 (Jansen et al., 2017) for a total of 61 individuals (Figure 5). Full phenotypic details were not available for all cases, particularly regarding neurodevelopmental outcomes, and certain cases were identified in the context of a broader phenotype-driven cohort such as autism and developmental delays (Coe

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

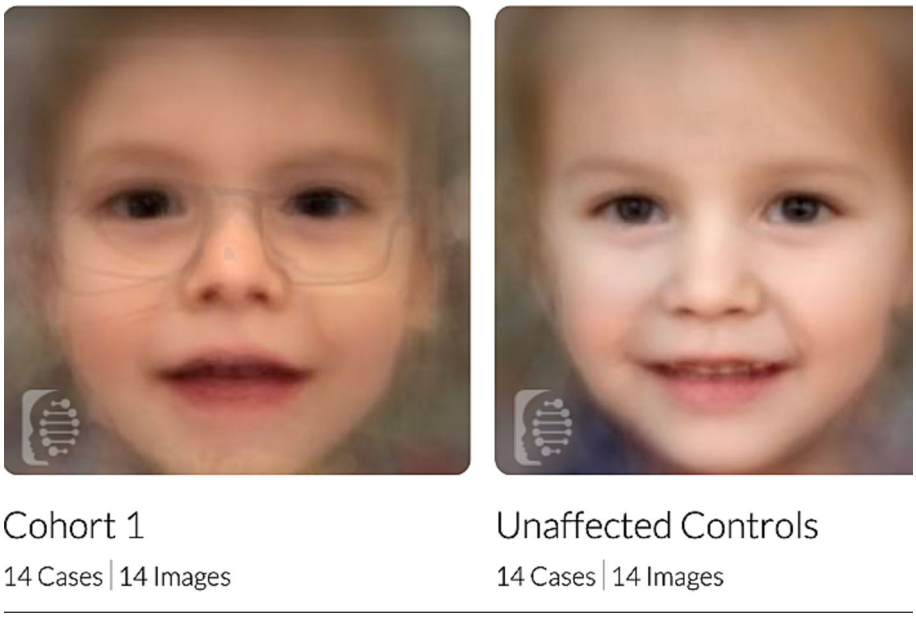


FIGURE 4 Face2Gene facial composite from a cohort of children with Jansen-de Vries Syndrome (Cohort 1) compared with controls.

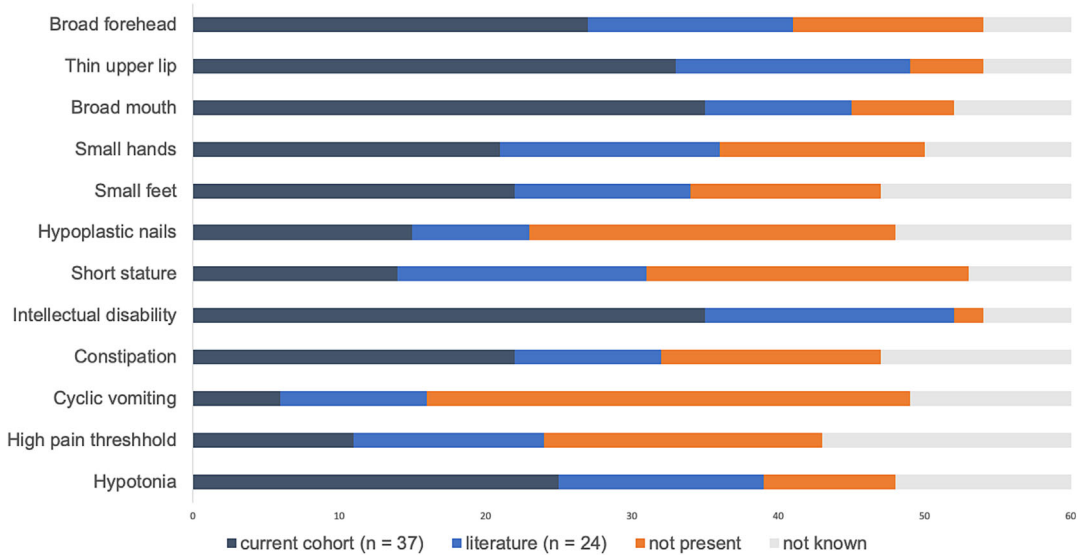


FIGURE 5 Frequency of salient features within our cohort and published literature cases. Dark blue bars represent the number of cases within our cohort, light blue bars represent cases published in the literature, orange bars represent the number without the feature, and gray bars indicate the number for whom the feature is not reported.

et al., 2019) or specific birth defects (bladder exstrophy; Pitsava et al., 2021).

4 | DISCUSSION

We describe a cohort of 37 individuals from 34 families with disease-causing variants in *PPM1D* and review the existing literature in order to further elaborate on distinctive and recurrent features of JdVS and refine the phenotype and genotypic spectrum. These results highlight the unique neurodevelopmental phenotype of this condition, a particular facial gestalt, and common medical comorbidities, with all affected individuals harboring heterozygous truncating variants in either the last or penultimate exon of *PPM1D*. The documentation of vertical transmission of JdVS in four families is consistent with autosomal dominant inheritance. As in other neurodevelopmental and chromosomal microdeletion or duplication syndromes, the ascertained probands were in general significantly more severely affected than their affected parent.

Regarding the neurodevelopmental phenotype of JdVS, a distinct personality has been described including hypersocial behavior and hyperacusis in addition to anxiety, somewhat similar to that described in Williams–Beuren syndrome (Martens et al., 2008)—though many individuals in our cohort may be too young to clearly detect either

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

hypersociality or anxiety. Global developmental delay was nearly universal, though speech delay was more prominent than motor delay. All individuals did ultimately ambulate independently with a broad range of motor skills achieved, and most were able to communicate verbally, with a range of cognitive functioning described in those who have had formal testing. Some features, such as the aggression and hypersexuality, appear to emerge in some adolescents and older patients (Martin Fernandez-Mayoralas et al., 2021). Additionally, many individuals in our cohort have been diagnosed with ADHD, and about 25% with autism-like features, as was also seen in a large neurodevelopmental cohort where one of eight described with damaging variants in *PPM1D* had autism, whereas the others were diagnosed with developmental delay or intellectual disability (Coe et al., 2019).

The physical features as described in our cohort support a unique facial gestalt for JdVS, and, indeed, a computational facial recognition model was able to discern a distinct pattern for individuals with pathogenic variants *PPM1D* compared with controls with intellectual disability (van der Donk et al., 2019). Short stature was seen in 42% of our cohort and 74% of literature cases, and small hands or feet have also been seen frequently along with hypoplastic nails. As many other features seen in JdVS such as hypotonia and feeding difficulties (particularly in infancy) are also commonly seen in other genetic neurodevelopmental disorders, additional features unique to JdVS that have been seen in multiple families include the gastrointestinal issues, particularly CVS. While CVS was only formally diagnosed in six individuals in our cohort and another 10 in the literature, this is a relatively rare and distinct condition and it is therefore unusual to see so many cases within this group; vomiting not formally described as cyclic was reported in another 13 individuals in our cohort. While also rare in our cohort, the developmental regression possibly suggestive of neuroinflammatory dysregulation and seen in three individuals in this cohort certainly bears further study.

In terms of the management following a diagnosis of JdVS, typically identified via molecular genetic testing and supported by the above clinical features, commonly addressed medical issues include anxiety, growth and short stature, vomiting, and behavioral issues such as aggression. No firm management guidelines can be universally endorsed as most reports of successes and failures are anecdotal and rely on parent reports. However, we offer the below guidance based upon our clinical experience:

1. Anxiety: This symptom seems almost universal in well-described patients and is early in onset, often by 18 months of age. It seems to intensify in school age and persists into adulthood. Helpful strategies include adherence to routine, calming techniques, learned coping strategies, meditation, and psychotherapy. Medications including selective serotonin reuptake inhibitors have been used with variable success and many families have explored using cannabidiol products with some suggestions for improvement. Further studies are indicated.
2. Growth: Short stature is frequent in JdVS and many parents have asked about GH treatment. Given the positive experiences with GH in Prader–Willi syndrome (Drabik et al., 2022), parents have extrapolated and wondered about improving hypotonia and development with early GH. Four children in our cohort have been found to be GH deficient and placed on treatment, although in at least one child no improvement in growth has been noted. No demonstrable improvement in cognition or development has been documented in the treated children. At this point, there is no evidence for empiric treatment with GH in the absence of documented GH deficiency.
3. Vomiting: Prolonged, unexpected episodes of vomiting with nausea, dehydration, and hypoglycemia have been seen in a number of children and adults with JdVS—both those with and without an official diagnosis of CVS. The etiology appears obscure, as is often the case with CVS, even in individuals without an underlying genetic disorder. Triggers have included intercurrent illness, excitement, sleep deprivation, changes in schedule, and travel. Extensive evaluations for mitochondrial or genetic metabolic abnormalities in several people with JdVS have been unrevealing. There are no universally recommended treatments although patients and physicians have used ondansetron, cyproheptadine, amitriptyline, and Coenzyme Q with variable outcomes. Early recognition and treatment with medication and, if needed, intravenous fluids are recommended for acute episodes. The CVS support group may be of assistance to families (cvsaonline.org). Results of further studies are anticipated (Pizzol et al., 2022).
4. Behavior: Most children with JdVS are outgoing, delightful, and happy children who are affectionate and much enjoyed by their families and care providers. Autistic features, when present, were usually mild and these diagnoses were based frequently on the child's lack of boundaries, and unusual social interactions with lack of the normal response to social cueing. Behavioral abnormalities ranging from meltdowns and tantrums in younger children to aggression and anger in older individuals with JdVS are common. As in other syndromes and typical children, the treatment is supportive and must be individualized. Strategies for managing hypersexuality in some older patients may be challenging. These issues are quite similar to those seen in Williams syndrome where the outgoing personality, lack of boundaries, and lack of fear or appreciation of consequences contribute to risk. Approaches such as long-term protection against pregnancy and monitoring the environment along with supportive counseling are essential. For many families affected by JdVS, enrollment in the support group, Facebook group, and WhatsApp chat has proven valuable. (https://jansen-devries.org)

The molecular mechanisms giving rise to this constellation of findings remain to be fully elucidated. In a cohort of over 10,000 people with neurodevelopmental phenotypes (ID, DD, autism), enrichment for de novo variants in *PPM1D* was observed (Coe et al., 2019). *PPM1D* is noted to be missense constrained but not loss-of-function constrained in the gnomAD database, which fits with the finding that the mechanism of disease in for JdVS entails escape from nonsense-mediated decay (Coban-Akdemir et al., 2018). PPM1D is known to be a negative regulator of p53 and other tumor suppressors, and somatic

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

variants are found in multiple malignancies (Graf et al., 2022; Khadka et al., 2022). There are several individuals with stop gain variants designated as ClinVar pathogenic/likely pathogenic in gnomAD, though at least one is present in an older individual; these may represent somatic variants acquired in the setting of clonal hematopoiesis of indeterminate potential, as has been reported with this gene, particularly in association with myelodysplastic syndromes (Panagiota et al., 2021; Zink et al., 2017) and has been previously seen in other highly penetrant, autosomal dominant conditions (Carlston et al., 2017). To our knowledge, there are no reports of individuals with JdVS and concurrent malignancies.

Overall, our findings support a distinct phenotype associated with for JdVS, with hallmark features including the facial gestalt, small hands and feet often with hypoplastic nails, the distinctive personality pattern, short stature, cyclic vomiting, moderate to severe anxiety and a high pain threshold. Disease-causing variants in our cohort fell exclusively within exons 5 and 6 of *PPM1D* as has been previously described. As ES is now recommended as a first-line test for those with intellectual disability (Manickam et al., 2021), it is likely that additional novel variants in other exons of this gene will be identified, and the clinical features seen in our cohort differentiated from the features seen with variants in other exons. To date, the features seen in those with pathogenic variants in other exons seem generally dissimilar to those seen with variants in exons 5 and 6 and should not be confused with JdVS (Trifiletti et al., 2022). Further research into the manifestations of damaging germline variants in exons 1–4 of *PPM1D* is warranted. Other areas in need of future research related to this condition include tailored treatments of common manifestations such as anxiety, short stature, and cyclic vomiting, and further investigation into the incidence and etiology of developmental regression and possible neuroinflammatory features.

AUTHOR CONTRIBUTIONS

Conceptualization: Monica H. Wojcik, Pankaj B. Agrawal, Siddharth Srivastava, and Cynthia J. Curry. *Data curation*: Monica H. Wojcik and Cynthia J. Curry. *Formal analysis*: Monica H. Wojcik and Cynthia J. Curry; *Investigation*: All authors. *Resources*: All authors. *Supervision*: Cynthia J. Curry. *Writing-original draft*: Monica H Wojcik and Cynthia J. Curry. *Writing-review & editing*: All authors.

AFFILIATIONS

[1]Division of Newborn Medicine, Department of Pediatrics and Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA
[2]Division of Genetics and Genomics, Department of Pediatrics and Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA
[3]Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, Massachusetts, USA
[4]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[5]Division of Neonatology, Department of Pediatrics, Miller School of Medicine, University of Miami and Holtz Children's Hospital, Jackson Health System, Miami, Florida, USA
[6]Medical Genetics Program of Southwestern Ontario, London Health Sciences Centre, London, Ontario, Canada
[7]Center for Medical Genetics, Pediatrics Department, Ghent University Hospital, Ghent, Belgium
[8]Pediatric Gastroenterology Unit, Regina Margherita Children's Hospital, Azienda Ospedaliera-Universitaria Città della Salute e della Scienza, Turin, Italy
[9]Department of Public Health and Pediatrics, University of Torino, Torino, Italy
[10]Clinical Genetics, Children's Mercy Hospital, Kansas City, Missouri, USA
[11]Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, New South Wales, Australia
[12]Greenwood Genetic Center, Greenwood, South Carolina, USA
[13]Division of Genetics, Department of Pediatrics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California, USA
[14]Paediatrics, School of Medicine, Western Sydney University, Hunter Genetics, Newcastle, New South Wales, Australia
[15]Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, Missouri, USA
[16]Department of Pediatrics, The Ohio State University College of Medicine, Division of Genetic & Genomic Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
[17]Department of Medical Genetics, Nantes Hospital, Nantes, France
[18]Nantes Université, CHU Nantes, Service de Génétique Médicale, Nantes, France; Nantes Université, CHU Nantes, CNRS, INSERM, L'institut du thorax, Nantes, France
[19]Departments of Behavioral Science, Medicine, and Psychiatry, Albert Einstein College of Medicine, Bronx, New York, USA
[20]Service de Génétique Clinique, Centre de Référence Maladies Rares CLAD-Ouest, ERN ITHACA, CHU Rennes, Hôpital Sud, Rennes, France
[21]Department of Human Genetics, Donders Centre for Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands
[22]Cortica Healthcare, Marin Center, San Rafael, California, USA
[23]Division of Genetics, Departments of Pediatrics and Human Genetics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California, USA
[24]Service de Génétique Clinique, University Hospital Morvan, Brest, France
[25]UKMC School of Medicine, University of Missouri Kansas City, Kansas City, Missouri, USA
[26]Division of Genetics, Children's Mercy Kansas City, Kansas City, Missouri, USA
[27]Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, Missouri, USA
[28]School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia
[29]Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[30]Division of Medical Genetics, Department of Pediatrics, Stanford University, Stanford, California, USA

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[31]Donders Centre for Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands
[32]Genetic Medicine, Department of Pediatrics, University of California San Francisco/Fresno, Fresno, California, USA

ACKNOWLEDGMENTS

The authors would like to thank the devoted parents who spent hours in interviews and in the collection of medical records, as well as the dedicated founders of the Jansen-de Vries support group.

FUNDING INFORMATION

Herbert M. Lachman is supported by the NIH/NIMH (R21 MH131740) and the NIH/NICHD (P30 HD071593) to the Albert Einstein College of Medicine's Rose F. Kennedy Intellectual and Developmental Disabilities Research Center. Monica H. Wojcik is supported by NIH/NICHD (K23 HD102589). Siddharth Srivastava is supported by NIH/NINDS (K23 NS119666). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health. Bert B. A. de vries is supported by the Dutch Organization for Health Research and Development: ZON-MW grant (912-12-109). Bert Callewaert is a senior clinical investigator of the Research Foundation-Flanders.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to report.

DATA AVAILABILITY STATEMENT

No new sequencing data were generated for the purpose of this study. Data supporting the results reported in this article are provided in the supplementary tables. Additional deidentified data may be available upon request and contingent upon a data use agreement. Please contact the corresponding author to initiate such a request.

ORCID

Monica H. Wojcik https://orcid.org/0000-0002-8162-5031
Siddharth Srivastava https://orcid.org/0000-0001-7008-1879
Tugce B. Balci https://orcid.org/0000-0002-5409-8387
Bert Callewaert https://orcid.org/0000-0002-9743-4205
Diana Carli https://orcid.org/0000-0001-5690-6504
Laura Cross https://orcid.org/0000-0003-3664-0707
Julian A. Martinez-Agosto https://orcid.org/0000-0001-6776-6949
David A. Stevenson https://orcid.org/0000-0001-8601-0020
Bert B. A. de Vries https://orcid.org/0000-0002-0000-2917

REFERENCES

Carlston, C. M., O'Donnell-Luria, A. H., Underhill, H. R., Cummings, B. B., Weisburd, B., Minikel, E. V., Birnbaum, D. P., Exome Aggregation Consortium, Tvrdik, T., MacArthur, D. G., & Mao, R. (2017). Pathogenic ASXL1 somatic variants in reference databases complicate germline variant interpretation for Bohring-Opitz syndrome. *Human Mutation*, *38*(5), 517–523. https://doi.org/10.1002/humu.23203

Coban-Akdemir, Z., White, J. J., Song, X., Jhangiani, S. N., Fatih, J. M., Gambin, T., Bayram, Y., Chinn, I. K., Karaca, E., Punetha, J., Poli, C., Baylor-Hopkins Center for Mendelian Genomics, Boerwinkle, E., Shaw, C. A., Orange, J. S., Gibbs, R. A., Lappalainen, T., Lupski, J. R., & Carvalho, C. M. B. (2018). Identifying genes whose mutant transcripts cause dominant disease traits by potential gain-of-function alleles. *American Journal of Human Genetics*, *103*(2), 171–187. https://doi.org/10.1016/j.ajhg.2018.06.009

Coe, B. P., Stessman, H. A. F., Sulovari, A., Geisheker, M. R., Bakken, T. E., Lake, A. M., Dougherty, J. D., Lein, E. S., Hormozdiari, F., Bernier, R. A., & Eichler, E. E. (2019). Neurodevelopmental disease genes implicated by de novo mutation and copy number variation morbidity. *Nature Genetics*, *51*(1), 106–116. https://doi.org/10.1038/s41588-018-0288-4

Deciphering Developmental Disorders Study. (2017). Prevalence and architecture of de novo mutations in developmental disorders. *Nature*, *542*(7642), 433–438. https://doi.org/10.1038/nature21062

Drabik, M., Lewinski, A., & Stawerska, R. (2022). Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone. *Pediatric Endocrinology, Diabetes, and Metabolism*, *28*(1), 64–74. https://doi.org/10.5114/pedm.2022.112861

Graf, J. F., Mikicic, I., & Ping, X. (2022). Substrate spectrum of PPM1D in the cellular response to DNA double-strand breaks. *iScience*, *25*(9), 104892. https://doi.org/10.1016/j.isci.2022.104892

Jansen, S., Geuer, S., Pfundt, R., Brough, R., Ghongane, P., Herkert, J. C., Marco, E. J., Willemsen, M. H., Kleefstra, T., Hannibal, M., Shieh, J. T., Lynch, S. A., Flinter, F., FitzPatrick, D., Gardham, A., Bernhard, B., Ragge, N., Newbury-Ecob, R., Bernier, R., … de Vries, B. B. (2017). De novo truncating mutations in the last and penultimate exons of PPM1D cause an intellectual disability syndrome. *American Journal of Human Genetics*, *100*(4), 650–658. https://doi.org/10.1016/j.ajhg.2017.02.005

Khadka, P., Reitman, Z. J., Lu, S., Buchan, G., Gionet, G., Dubois, F., Carvalho, D. M., Shih, J., Zhang, S., Greenwald, N. F., Zack, T., Shapira, O., Pelton, K., Hartley, R., Bear, H., Georgis, Y., Jarmale, S., Melanson, R., Bonanno, K., … Bandopadhayay, P. (2022). PPM1D mutations are oncogenic drivers of de novo diffuse midline glioma formation. *Nature Communications*, *13*(1), 604. https://doi.org/10.1038/s41467-022-28198-8

Kuroda, Y., Murakami, H., Yokoi, T., Kumaki, T., Enomoto, Y., Tsurusaki, Y., & Kurosawa, K. (2019). Two unrelated girls with intellectual disability associated with a truncating mutation in the PPM1D penultimate exon. *Brain & Development*, *41*(6), 538–541. https://doi.org/10.1016/j.braindev.2019.02.007

Lelieveld, S. H., Reijnders, M. R., Pfundt, R., Yntema, H. G., Kamsteeg, E. J., de Vries, P., de Vries, B. B., Willemsen, M. H., Kleefstra, T., Löhner, K., Vreeburg, M., Stevens, S. J., van der Burgt, I., Bongers, E. M., Stegmann, A. P., Rump, P., Rinne, T., Nelen, M. R., Veltman, J. A., … Gilissen, C. (2016). Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. *Nature Neuroscience*, *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. *Molecular Genetics & Genomic Medicine*, *8*(3), e1120. https://doi.org/10.1002/mgg3.1120

Machiela, M. J., Myers, T. A., Lyons, C. J., Koster, R., Figg, W. D., Jr., Colli, L. M., Jessop, L., Ahearn, T. U., Freedman, N. D., García-Closas, M., & Chanock, S. J. (2019). Detectible mosaic truncating PPM1D mutations, age and breast cancer risk. *Journal of Human Genetics*, *64*(6), 545–550. https://doi.org/10.1038/s10038-019-0589-1

Manickam, K., McClain, M. R., Demmer, L. A., et al. (2021). Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: An evidence-based clinical guideline of the

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*, *23*(11), 2029–2037. https://doi.org/10.1038/s41436-021-01242-6

Martens, M. A., Wilson, S. J., & Reutens, D. C. (2008). Research review: Williams syndrome: A critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry*, *49*(6), 576–608. https://doi.org/10.1111/j.1469-7610.2008.01887.x

Martin Fernandez-Mayoralas, D., Fernandez-Perrone, A. L., Jimenez de Domingo, A., Alba Menendez, A., & Fernandez-Jaen, A. (2021). Jansen-de Vries syndrome. First case diagnosed in Spain. *Neurologia (English Edition)*, *36*(4), 330–332. https://doi.org/10.1016/j.nrl.2020.06.006

Panagiota, V., Meggendorfer, M., Kubasch, A., Gabdoulline, R., Krönke, J., Mies, A., Shahswar, R., Kandziora, C., Klement, P., Schiller, J., Göhring, G., Haferlach, C., Ganster, C., Shirneshan, K., Gutermuth, A., Thiede, C., Germing, U., Schroeder, T., Kobbe, G., … Heuser, M. (2021). Impact of PPM1D mutations in patients with myelodysplastic syndrome and deletion of chromosome 5q. *American Journal of Hematology*, *96*(6), E207–E210. https://doi.org/10.1002/ajh.26162

Pitsava, G., Feldkamp, M. L., Pankratz, N., Lane, J., Kay, D. M., Conway, K. M., Shaw, G. M., Reefhuis, J., Jenkins, M. M., Almli, L. M., Olshan, A. F., Pangilinan, F., Brody, L. C., Sicko, R. J., Hobbs, C. A., Bamshad, M., McGoldrick, D., Nickerson, D. A., Finnell, R. H., … University of Washington Center for Mendelian Genomics, NISC Comparative Sequencing Program and the National Birth Defects Prevention Study. (2021). Exome sequencing of child-parent trios with bladder exstrophy: Findings in 26 children. *American Journal of Medical Genetics. Part A*, *185*(10), 3028–3041. https://doi.org/10.1002/ajmg.a.62439

Pizzol A, Adams, K. A., Curry, C., & Calvo, P. L. (2022). Is cyclic vomiting syndrome part of Jansen de Vries syndrome? Abstract presented at: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition 54th Annual Meeting, June 22–25, 2022.

Porrmann, J., Rump, A., Hackmann, K., di Donato, N., Kahlert, A. K., Wagner, J., Jahn, A., Eger, I., Flury, M., Schrock, E., Tzschach, A., & Gieldon, L. (2019). Novel truncating PPM1D mutation in a patient with intellectual disability. *European Journal of Medical Genetics*, *62*(1), 70–72. https://doi.org/10.1016/j.ejmg.2018.05.006

Sobreira, N., Schiettecatte, F., Valle, D., & Hamosh, A. (2015). GeneMatcher: A matching tool for connecting investigators with an interest in the same gene. *Human Mutation*, *36*(10), 928–930. https://doi.org/10.1002/humu.22844

Trifiletti, R., Lachman, H. M., Manusama, O., Zheng, D., Spalice, A., Chiurazzi, P., Schornagel, A., Serban, A. M., van Wijck, R., Cunningham, J. L., Swagemakers, S., & van der Spek, P. J. (2022). Identification of ultra-rare genetic variants in pediatric acute onset neuropsychiatric syndrome (PANS) by exome and whole genome sequencing. *Scientific Reports*, *12*(1), 11106. https://doi.org/10.1038/s41598-022-15279-3

Tsai, M. 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. *Journal of the Formosan Medical Association*, *121*(4), 856–860. https://doi.org/10.1016/j.jfma.2021.12.022

van der Donk, R., Jansen, S., Schuurs-Hoeijmakers, J. H. M., Koolen, D. A., Goltstein, L. C. M. J., Hoischen, A., Brunner, H. G., Kemmeren, P., Nellåker, C., Vissers, L. E. L. M., de Vries, B. B. A., & Hehir-Kwa, J. Y. (2019). Next-generation phenotyping using computer vision algorithms in rare genomic neurodevelopmental disorders. *Genetics in Medicine*, *21*(8), 1719–1725. https://doi.org/10.1038/s41436-018-0404-y

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. *Journal of Clinical Laboratory Analysis*, *34*(11), e23480. https://doi.org/10.1002/jcla.23480

Zink, F., Stacey, S. N., Norddahl, G. L., Frigge, M. L., Magnusson, O. T., Jonsdottir, I., Thorgeirsson, T. E., Sigurdsson, A., Gudjonsson, S. A., Gudmundsson, J., Jonasson, J. G., Tryggvadottir, L., Jonsson, T., Helgason, A., Gylfason, A., Sulem, P., Rafnar, T., Thorsteinsdottir, U., Gudbjartsson, D. F., … Stefansson, K. (2017). Clonal hematopoiesis, with and without candidate driver mutations, is common in the elderly. *Blood*, *130*(6), 742–752. https://doi.org/10.1182/blood-2017-02-769869

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wojcik, M. H., Srivastava, S., Agrawal, P. B., Balci, T. B., Callewaert, B., Calvo, P. L., Carli, D., Caudle, M., Colaiacovo, S., Cross, L., Demetriou, K., Drazba, K., Dutra-Clarke, M., Edwards, M., Genetti, C. A., Grange, D. K., Hickey, S. E., Isidor, B., Küry, S., … Curry, C. J. (2023). Jansen-de Vries syndrome: Expansion of the *PPM1D* clinical and phenotypic spectrum in 34 families. *American Journal of Medical Genetics Part A*, 1–11. https://doi.org/10.1002/ajmg.a.63226

15524833, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.63226 by Harvard University, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License