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Neurodevelopmental profiles of 14 individuals with phosphomannomutase deficiency (PMM2-CDG)

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Abstract

PMM2-CDG (formerly CDG-1a), the most common type of congenital disorders of glycosylation, is inherited in an autosomal recessive pattern. PMM2-CDG frequently presents in infancy with multisystemic clinical involvement, and it has been diagnosed in over 1000 people worldwide. There have been few natural history studies reporting neurodevelopmental characterization of PMM2-CDG. Thus, a prospective study was conducted that included neurodevelopmental assessments as part of deep phenotyping. This study, Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation (NCT02089789), included 14 participants (8 males and 6 females ages 2–33 years) with a confirmed molecular diagnosis of PMM2-CDG. Clinical features of PMM2-CDG in this cohort were neurodevelopmental disorders, faltering growth, hypotonia, cerebellar atrophy, peripheral neuropathy, movement disorders, ophthalmological abnormalities, and auditory function differences. All PMM2-CDG participants met criteria for intellectual disability (or global developmental delay if younger than age 5). The majority never attained certain gross motor and language milestones. Only two participants were ambulatory, and almost all were considered minimally verbal. Overall, individuals with PMM2-CDG present with a complex neurodevelopmental profile characterized by intellectual disability and multisystemic presentations. This systematic quantification of the neurodevelopmental profile of PMM2-CDG expands our understanding of the range in impairments associated with PMM2-CDG and will help guide management strategies.

KEYWORDS

congenital disorders of glycosylation, intellectual disability, neurodevelopment, neuropsychological assessment, phosphomannomutase deficiency

Tara Weixel and Dee Adedipe should be considered joint first author.

1 | INTRODUCTION

Congenital disorders of glycosylation (CDG) are a group of rare genetic disorders characterized by defects of various glycosylation synthetic pathways.[1,2] There are over 190 types of CDGs, defined by the variant gene in one of the synthetic pathways affected.[3] There is variable neurologic and multi-organ system involvement in CDGs with presentations ranging from hydrops fetalis to functional adults.

The most common type, PMM2-CDG (OMIM #212065), is an N-linked glycosylation disorder caused by pathogenic variants in *PMM2*, and approximately 1000 cases have been reported worldwide.[4] The most common pathogenic variant (c.422G>A, p.R141H) has a carrier frequency of about 1 in 70 in the northern European population. The Exome Aggregation Consortium reported a carrier frequency of 1 in 76 and can be lethal in the homozygous state.[5]

Diagnosis is typically confirmed in infancy and clinical features emerge with age.[6] The clinical presentation of PMM2-CDG is highly variable in severity and symptom profile.[4,7] Neurological involvement is characterized by early faltering growth (previously known as failure to thrive), developmental delay or intellectual disability (ID), hypotonia, movement disorders, cerebellar atrophy, seizures, stroke-like episodes, and peripheral neuropathy.[6,8] Other systemic manifestations including skeletal (e.g., osteopenia, kyphoscoliosis), hematological (e.g., risk of bleeding and thrombosis), ophthalmological (e.g., strabismus, contaracts, retinitis pigmentosa), and audiological abnormalities (e.g., sensorineural hearing loss) can further contribute to neurodevelopmental impairments.[9,10]

Developmental delay leading to ID is a significant neurological feature of PMM2-CDG. The ID found in PMM2-CDG is thought to be variable in severity, but data are limited.[1,7,11,12] Altassan et al.[4] show that a full range from mild to profound ID is present (including a small proportion that are in the borderline ID range—between average intellectual functioning and ID). The authors noted that omission of information about severity of ID in extant studies of PMM2-CDG may be explained by the severity itself; there is a lack of sensitivity of intelligence tests in this range of functional impairment.[13] For example, one prospective study evaluated 13 individuals with PMM2-CDG, however, cognitive functioning scores were obtained on less than half, with IQ scores ranging from low average (91) to moderate (40).[14] Thus, there seems to be variability and likely underestimation of ID in the more severe ranges reported, due to the large percentage of affected individuals deemed untestable. With respect to developmental milestones, attainment of motor and language milestones are not comprehensibly described in the literature.[4] A recent prospective study reported developmental milestones of 51 individuals with PMM2-CDG aged 0.75–34 years. The study reported all had development delay, but no further information (i.e., IQ scores, ID severity) was provided, and achievement of milestones were not reported.

Overall, data informing our current understanding of neurodevelopmental and neuropsychological functioning in PMM2-CDG are case studies or retrospective data reports, and current prospective studies provide limited information and/or have deemed some individuals untestable. Here, we used a hierarchical, systematic approach of testing procedures to report the neurodevelopmental profiles of individuals with PMM2-CDG within the context of related systematic involvements and establish the range in severity and presentation of neurodevelopmental impairments.

2 | STUDY PROCEDURE

Data were prospectively collected under the NIH protocol 14-HG-0071 "Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation" (http://clinicaltrials.gov, trial NCT02089789), which was approved by the National Human Genome Research Institute's institutional review board. Inclusion criteria were individuals over 1-year-old weighing more than 10 kg, with known or suspected CDG based on (1) biochemical testing or (2) a confirmed diagnosis of CDG based on enzymatic or molecular testing, and the ability to travel to the NIH. Parents or guardians provided written informed consent for minors. Each participant visited the NIH Clinical Center for an evaluation and further phenotyping including assessments in multiple body systems. For the current analyses, only participants with a molecular genetic confirmation of PMM2-CDG (via exome sequencing, whole genome sequencing, specific panels, or by targeted *PMM2* sequencing) are included.

2.1 | Participants

Fourteen participants aged 2–33 years ($M = 8.66$ years, SD = 7.72 years) with a diagnosis of PMM2-CDG comprise the sample, including eight males and one set of siblings. Ninety-three percent of participants were non-Hispanic ($n = 13$); the majority of participants were White ($n = 11$); three participants were of multiple races.

2.2 | Measures

2.2.1 | Medical history and clinical presentation

Available medical records for participants were collected and reviewed prior to study visits. In addition, a

standardized phone interview was conducted with parent(s)/guardian(s), which reviewed the participant's developmental and medical history, family history, and medications or interventions.

The clinical presentations of related systems reported include findings from evaluations related to physiatry, neurology, audiology, and ophthalmology. All information was obtained from preadmission records reviews, parent report as well as information from the NIH evaluation. Information included consultant exams, MRI and MRS brain imaging, neuropsychological testing, hearing and eye exams, nerve conduction velocity/EMG, video analysis of movement disorders, laboratory tests, overnight EEGs and sleep studies (see additional Supporting Information Methods for more information). This was done to further characterize the nuanced relationship between the multisystemic related clinical presentations relative to the neurodevelopmental profiles.

2.2.2 | Cognitive and developmental functioning

Participants were administered developmental and cognitive assessments using a hierarchical approach based on age and estimated cognitive abilities.[15] Full-Scale IQ (FSIQ) or Composite Standard Score were reported when possible, and for out-of-age range cases, the developmental quotient (DQ) was calculated [(mental age/chronological age) × 100]. Developmental and cognitive assessments administered include the Mullen Scales of Early Learning,[16] Differential Ability Scales-Second edition,[17] and the appropriate Wechsler Intelligence Scales (Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV),[18] Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V),[19] or Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV)[20]), contingent on the participant's age.

The Mullen Scales of Early Learning is a standardized developmental test normed for children from birth to 5 years, 8 months.[16] *T* scores (mean = 50, SD = 10, range 20–80) and age equivalents are computed for the five domains, Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language and an Early Learning Composite (mean = 100, SD = 15). DQ was calculated when the measure was used out-of-age range cases and if the participant was unable to achieve a *T* score (<20) on one or more domains. Nonverbal DQ included the mean of Visual Reception and Fine Motor age equivalents and Verbal DQ included the mean of the Expressive Language and Receptive Language age equivalents.

The Differential Ability Scales, Second Edition (DAS-II), Early Years is a measure of cognitive functioning for normed preschool and school age children, ages 2 years, 6 months to 17 years, 11 months.[17] DAS-II assesses verbal, nonverbal reasoning, and spatial ability. The measure provides *T* scores (mean = 50, SD = 10) for each of these domains, and a General Conceptual Ability (mean = 100, SD = 15), equivalent to FSIQ.

The Wechsler Intelligence Scales (WPPSI-IV, WISC-V, and WAIS-IV) assess cognitive ability across different ages. The assessments produce a FSIQ standard score (mean = 100, SD = 15). More information on each Wechsler Intelligence Scale administered is provided in additional Supporting Information Methods.

2.2.3 | Adaptive behavior

The Vineland Adaptive Behavior Scales, Second Edition is a semi-structured caregiver interview that assesses adaptive functioning from birth through age 90 in the areas of communication, daily living, socialization, and motor skills.[21] The measure provides standard scores for each domain and an adaptive behavior composite (ABC; mean = 100, SD = 15). One participant received the Vineland 3.[22]

2.2.4 | Milestones

Retrospective data on participants' developmental milestones from parents were collected during the standardized interview and neurodevelopmental psychological evaluation, and from record review. Parents/guardians were asked to recall if and when their child obtained various milestones (i.e., gross motor and language milestones).

3 | RESULTS

3.1 | Genetic and clinical presentation of related systems

Seven of 14 participants had the known common pathogenic variant (c.422G>A (p.R141H))[23] as one of the two pathogenic variants in this recessive disorder. Three of 14 participants had another pathogenic variant (c.710C>G (p.T237R)). The remaining pathogenic variants of the participants were each present only once among our sample (see Table 1).

Seven of the 14 participants had a history of faltering growth. Thirteen of 14 participants had cerebellar atrophy, and the remaining participant without cerebellar

TABLE 1 Genetic and clinical presentation of 14 individuals with molecularly confirmed PMM2-CDG.

Subject number	Sex	Age (years)	Allele no. 1 variant (protein)	Allele no. 2 variant (protein)	Faltering growth (Y/N)	Cerebellar atrophy (Y/N)	Peripheral neuropathy (Y/N)	Movement disorder presence (Y/N) and disorder type	Auditory defects/ sensorineural hearing loss (Y/N)
1	M	4.06	c.422G>A (p.R141H)	c.647A>T (p.N216I)	N	Y	Y	N	N
2	F	9.61	c.422G>A (p.R141H)	c.623G>C (G208A)	Y	Y	Y	Y Ataxia	Y
3	M	5.30	c.357C>A (p.F119L)	c.422G>A (p.R141H)	Y	Y	Y	Y Extrapyramidal	Y
4	M	7.49	c.422G>A (p.R141H)	c.395T>C (p.I132T)	Y	Y	Y	N	N
5	F	6.93	c.563A>G (p.D188G)	c.691G>A (p.V231M)	N	Y	Y	Y Ataxia	Y
6	M	4.10	c.559T>C (p.W187A)	c.722G>C (p.C241S)	N	Y	Y	Y Ataxia	N
7	M	3.47	c.98A>C (p.Q33P)	c.140C>T (p.S47L)	Y	Y	Y	Y Ataxia	N
8[a]	F	7.58	c.686A>C (p.Y229S)	c.710C>G (p.T237R)	Y	Y	Y	Y Ataxia	N
9	F	3.68	c.415G>A (p.E139K)	c.422G>A (p.R141H)	N	Y	Y	Y Ataxia	Y
10	M	11.03	c.323C>T (p.A108V)	c.710C>G (p.T237R)	N	Y	Y	Y Ataxia	N
11	M	2.58	c.131T>C (p.V44A)	c.422G>A (p.R141H)	N	Y	Y	Y Ataxia	N
12[a]	F	9.03	c.686A>C (p.Y229S)	c.710C>G (p.T237R)	Y	N	N	N	N
13	M	13.19	c.338C>T (p.P113L)	c.IVS3+2T>C	Y	Y	Y	N	N
14	F	33.17	c.422G>A (p.R141H)	c.710C>T (p.T237M)	N	Y	N	N	Y

Abbreviations: F, female; M, male; N, no; Y, yes.

[a]Patients 8 and 12 are siblings.

TABLE 2 Seizure findings for 14 individuals with PMM2-CDG.

Subject number	Sex	Age (years)	NIH EEG findings (normal/abnormal)	EEG findings include epileptiform activity (Y/N)	EEG findings include slowing (Y/N)	EEG findings include sharps or spikes, indicating increased risk of seizures (Y/N)	Other EEG findings	Clinical seizure presence (Y/N) and seizure type	Current seizure medication
1	M	4.06	Normal	N	N	N	–	N	None
2	F	9.61	Abnormal	N	Y	N	–	N	None
3	M	5.30	Abnormal	N	N	Y	–	N	None
4	M	7.49	Abnormal	Y	N	Y	–	N	None
5	F	6.93	Normal	N	N	N	–	N	None
6	M	4.10	Abnormal	N	N	Y	–	N	None
7	M	3.47	Normal	N	N	N	–	N	None
8[a]	F	7.58	Abnormal	N	Y	N	–	Y Absence	None
9	F	3.68	Normal	N	N	N	–	N	None
10	M	11.03	Abnormal	Y	Y	N	–	N	None
11	M	2.58	Abnormal	N	N	Y	–	N	None
12[a]	F	9.03	Abnormal	N	N	N	Runs of deltal activity during sleep	Y Tonic Clonic	None
13	M	13.19	–	–	–	–	–	Y Tonic Clonic, Myoclonic	Dilantin and Klonopin with Diastat rescue
14	F	33.17	Abnormal	N	Y	Y		Y Febrile	Diamox

Abbreviations: –, information not reported; F, female; M, male; N, no; Y, yes.
[a]Patient 8 and Patient 12 are siblings.

atrophy had mild cerebral atrophy on their MRI scan. Twelve of 14 participants had peripheral neuropathy. Nine of 14 participants had a movement disorder; eight participants had ataxia (ages 2–11 years) and one participant had extrapyramidal movement disorder (age 5 years). Results in Tables S1–S4 show normal renal and hepatic function.

While 3 of 13 participants had normal EEGs, two showed epileptiform activity and slowing of background activity suggestive of cerebral dysfunction (Table 2). Four showed only slowing. Three had sharps or spike activity and one had runs of delta activity during sleep possibly due to mini-arousals, suggestive of global cerebral dysfunction. Four of 14 participants had a history of seizures. Of these, one participant had absence seizures, one participant had tonic–clonic seizures, one participant had tonic–clonic and myoclonic seizures, and one participant had febrile seizures. Only two participants, were currently on anticonvulsant medications (Table 2). No other participants, even those with EEGs showing epileptiform activity or sharps, were on anticonvulsants.

Five of 14 participants had auditory processing defects and/or sensorineural hearing loss, with details shown in Table 1. Ophthalmology findings are reported in Table 3, and indicate findings in all 14 patients, with most common retinal degeneration/retinitis pigmentosa (= 12), esotropia or strabismus (often corrected with surgery) ($n = 13$).

3.2 | Neurodevelopmental assessment

Table 4 shows 93% ($n = 13$) had Vineland ABC scores in the low range and a profile of higher Socialization scores compared to Daily Living scores was consistent across participants. The mean communication SS was 63.86,

TABLE 3 Ophthalmological findings for 14 individuals with PMM2-CDG.

Subject number	Sex	Age (years)	Nystagmus (Y/N)	Strabismus/ esotropia (Y/N)	Cataract (Y/N)	Optic atrophy (Y/N)	Retinal degeneration/retinitis pigmentosa (Y/N)
1	M	4.06	N	Y	N	N	Y
2	F	9.61	N	Y	N	N	Y
3	M	5.30	Y	Y	N	N	Y
4	M	7.49	Y	Y	N	Y	Y
5	F	6.93	N	Y	N	N	Y
6	M	4.10	N	Y	N	N	Y
7	M	3.47	N	Y	N	N	N
8[a]	F	7.58	N	Y	N	N	Y
9	F	3.68	N	Y	N	N	Y
10	M	11.03	N	N	N	N	Y
11	M	2.58	N	Y	N	N	N
12[a]	F	9.03	N	Y	N	N	Y
13	M	13.19	N	Y	N	N	Y
14	F	33.17	N	Y	Y	N	Y

Abbreviations: F, female; M, male; N, no; Y, yes.
[a]Patients 8 and 12 are siblings.

(SD = 14.20, range = 38–83), mean Daily Living Skills SS was 57.64 (SD = 13.70, range = 34–73), and the mean Socialization SS was 67.93 (SD = 14.93, range = 43–88). Standard scores for the motor domain are only normed for individuals 7 years and younger, thus age equivalent for gross ($n = 13$) and fine motor ($n = 14$) domains were reported. Gross and fine motor skills were severely impaired, such that while age of participants ranged from 31 months (2 years 7 months) to 398 months (33 years 2 months) (mean 103.60 ± 92.76 months), age equivalents for fine motor ranged from 5 to 73 months (6 years 1 month) (mean 32.36 ± 23.51 months). Age equivalents for gross motor ranged from 1 month to 41 months (mean 12.08 ± 10.05 months). Gross motor age equivalents were lower than fine motor age equivalent for all participants.

The Mullen Scales of Early Learning ($n = 8$), DAS-II ($n = 1$), WPPSI-IV ($n = 1$), WISC-V ($n = 3$), WAIS-IV ($n = 1$) were administered to assess developmental and cognitive functioning. The mean nonverbal IQ estimate was 44.50 (SD = 21.93, range = 3.90–73.00). The average overall verbal IQ estimate was 45.19 (SD = 23.92, range = 4.34–80.35). FSIQ was less than 70 in all participants, and less than 35 (in the range to be considered severe or profound) in four patients. Given these scores and score on adaptive behavior measures, diagnoses of ID (or its equivalent of global developmental delay, which is reserved for children under 5 years), were made according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (see Table 3).[25] Severity levels are not made when the diagnosis is global developmental delay.[25] The severity level of ID in the eight participants over age 5 were mild ($n = 4$), moderate ($n = 1$), profound ($n = 2$), and unspecified ($n = 1$, due to profound motor and visual impairments including 20/270 visual acuity).

3.3 | Milestones

As seen in Table 2, only 2 of 14 participants were ambulatory and 7 of 14 cruised but did not walk independently. Mean age for gross motor milestones were as follows: rolled over = 12 months; sat alone unsupported = 24 months; crawled = 28 months; cruised (for the 7 who attained) = 51 months. Among the two ambulatory participants, the mean age of walking independently was 25 months. With respect to speech and language milestones, attainment of first words in the eight participants it was reported for ranged from 12 to 42 months, with an average age attainment of 21 months. Of the five participants reported to put two words together, the mean age of attainment was 44 months. For toilet training, only one participant attained bladder training during the day at 72 months (see Figure 1) (Table 5).

3.4 | Support services

At the time of study participation, all participants except one (the participant was 33 years of age during

TABLE 4 Neurodevelopmental assessment results of 14 individuals with PMM2-CDG.

Subject number	Age (years)	VABS Comm. SS	VABS DLS SS	VABS Soc. SS	VABS ABC SS	VABS Gross Motor AE (months)	VABS fine motor AE (months)	IQ/ DQ test	COG. nonverbal IQ/DQ SS	COG. verbal IQ/DQ SS	Full scale IQ/DQ SS	Diagnosis (severity)
1	4.06	72	73	75	62	7	14	MSEL	46.09	44.04	45.06	GDD
2	9.61	42	40	47	42	1	7	MSEL	3.9	4.34	4.12	ID (unspecified)
3	5.30	38	34	49	36	4	5	MSEL	4.71	7.06	5.89	ID (profound)
4	7.49	67	59	66	64	10	28	DAS-II	47	51	39	ID (moderate)
5	6.93	81	66	88	70	13	58	WPPSI-IV	56	59	52	ID (mild)
6	4.10	65	64	83	65	11	26	MSEL	64.99	51.79	58.39	GDD
7	3.47	69	69	75	61	6	11	MSEL	44.34	65.92	55.13	GDD
8	7.58	70	66	76	70	14	58	WISC-V	58	59	49	ID (mild)
9	3.68	83	66	81	68	13	22	MSEL	50.93	80.35	65.64	GDD
10	11.03	69	57	69	64	20	61	WISC-V	50	45	47	ID (mild)
11	2.58	66	62	70	61	5	14	MSEL	40.24	24.15	32.2	GDD
12	9.03	74	73	80	74	41	73	WISC-V	68	65	62	ID (mild)
13	13.19	42	38	43	39	12	20	MSEL	15.79	12.95	14.37	ID (profound)
14	33.17	56[a]	40[a]	49[a]	50[a]	–	56[a]	WAIS	73	63	55[b]	ID (mild)

Note: Standard score (SS) mean = 100, standard deviation = 15; severity level is not assessed in GDD.[24]

Abbreviations: –, information unknown; ABC, Adaptive Behavior Composite; AE, age equivalent; COG, cognitive; DAS-II, Differential Ability Scales, second edition, The Early Years; DQ, developmental quotient; GDD, global development delay; ID, intellectual disability; IQ, intellectual quotient; Mullen, Mullen Scales of Early Learning; SS, standard score; VABS 3, Vineland Adaptive Behavior Scales, third edition; VABS, Vineland Adaptive Behavior Scales, second edition; WAIS Nonverbal, perceptual reasoning; WAIS, Wechsler Adult Intelligence Scale, fourth edition; WISC-V, Wechsler Intelligence Scale for Children, fifth Edition; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence, fourth edition.

[a]VABS 3.

[b]Full scale WAIS IQ prorated.

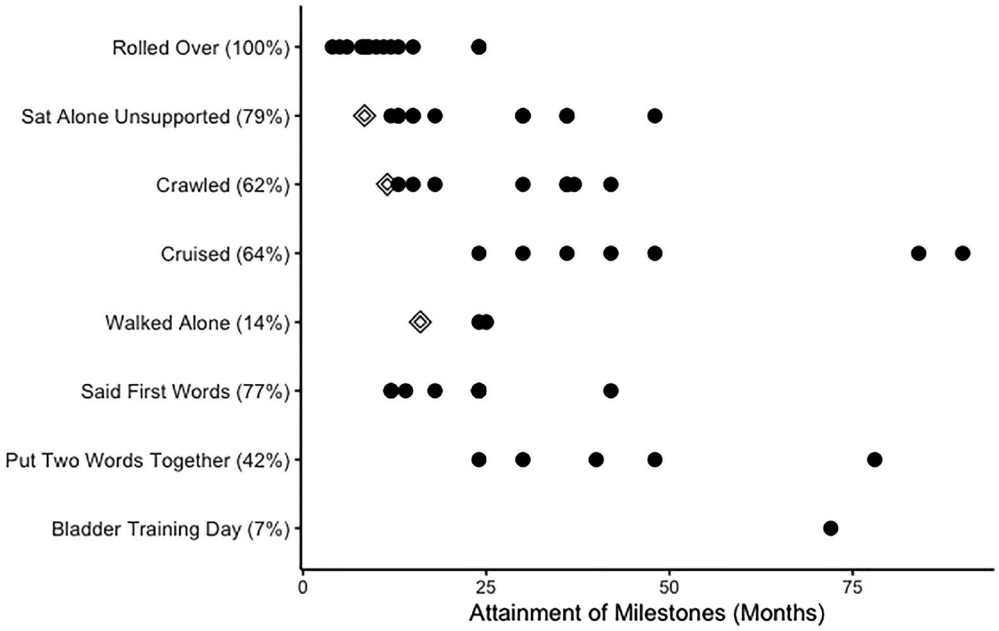

FIGURE 1 Attainment of milestones in months among individuals with PMM2-CDG. Each individual's milestone attainment is represented by a circle. The diamond denotes the 97th percentile for motor milestones indicated by the World Health Organization.[26] The percentage of individuals in the sample who attained each milestone is indicated in the parentheses following the milestone. The two individuals not shown on the figure for "said first words" were noted as delayed, but the exact age of attainment was unknown.

TABLE 5 Developmental milestones (in months) of 14 individuals with PMM2-CDG as reported by the parents.

		Gross motor					Language		Daily living skills
Subject number	Age (months)	Rolled over	Sat alone unsupported	Crawled	Cruised	Walked independently	Said first words	Put two words together	Bladder training day
1	48	6	13	18	N/R	N/R	18	N/R	N/R
2	115	12	N/R	N/R	N/R	N/R	N/R	N/R	N/R
3	63	15	N/R	N/R	N/R	N/R	–	N/R	–
4	89	24	48	N/R	84	N/R	42	78	N/R
5	83	11	30	42	42	N/R	12	48	N/R
6	49	8	13	13	24	N/R	24	N/R	N/R
7	41	–	36	36	–	N/R	A/D	N/R	N/R
8	91	24	30	36	48	N/R	24	30	–
9	44	4[a]	18	37	30	N/R	12	40	N/R
10	132	5	15	–	–	24	A/D	–	–
11	31	10	N/R	N/R	N/R	N/R	N/R	N/R	N/R
12	108	9	15	15	–	25	14	24	72
13	158	13	36	N/R	90	N/R	N/R	N/R	N/R
14	398	8.5	12	30	36	N/R	24	–	–

Abbreviations: –, information unknown; A/D, apparent delay, but age of attainment unknown; N/R, not reached.
[a]Loss of milestone.

their visit and previously received services in childhood) were receiving services including occupational, speech, and physical therapy through special education services or specialized school/program. Although one participant was homeschooled, they received occupational and speech therapy.

4 | DISCUSSION

We report on the neurodevelopmental profiles of 14 individuals with (PMM2-CDG), comprised primarily of young participants, who received systematic evaluations in a prospective study. Neurodevelopment profiles were

reported in tandem with the clinical presentations of related systemic involvement to delineate the extent to which these systems and impairments (i.e., physical and/or sensory impairments) impact neurodevelopment functioning.

Consistent with previous reports in the literature and observed in all participants in the current study, the clinical features of PMM2-CDG are multisystemic. Medical complications reported in this cohort included faltering growth and epilepsy and seizures, along with neurologic, motor, and hearing and vision impairments. The history of faltering growth in 50% of our cohort was slightly lower than the previous reports of 66.5% for faltering growth in the first year of life.[4] While one previous cohort study found 35% of participants with PMM2-CDG had epilepsy and another study found 57% had seizures,[9] our cohort found a lower rate of seizures (27%), which could be attributed to the relatively young age of the sample, missing individuals with later onset epilepsy.[8,27] Renal and liver ultrasound findings were consistent with those previously reported in the literature.[4]

Motor, physical, and neurologic impairments impacting gross and fine motor skills were observed, including a majority of participants having some type of movement disorder, consistent with prior reports.[1,8] All but one participant in the current study presented with cerebellar atrophy, consistent with previous report that found cerebellar atrophy pervasive in PMM2-CDG.[8,9] Previous cohort studies found high prevalence of ataxia (90%), comparatively, our cohort had a lower prevalence of ataxia (57%).[8] The clinical diagnosis of ataxia may be difficult to confirm before the age of 2.[11] It is important to note, cerebellar atrophy may contribute to cerebellar ataxia, a common finding among individuals with PMM2-CDG.[14,27] With 86% of the current cohort having peripheral neuropathy, it was even more prevalent than previous reports.[8,9] In addition, although peripheral neuropathy is typically diagnosed in older children and adults,[6] peripheral neuropathy was observed in younger individuals in this cohort, ages two to 13 years old.

Auditory and ophthalmologic abnormalities highlight sensory impairments found in individuals with PMM2-CDG. Thirty-six percent of the current cohort presented with sensorineural hearing loss or auditory defects, consistent with previous estimates of 8%–33% for sensorineural hearing loss in this population.[4] Every participant in this cohort had ophthalmological abnormalities; retinal degeneration and esotropia/strabismus were prominent, consistent with previous studies, but with the addition of some previously less reported ophthalmologic presentations (i.e., optic atrophy and posterior subcapsular cataract).[4]

Parental report on milestones in the study demonstrated most individuals with PMM2-CDG were significantly delayed in or lacking the attainment of motor milestones. All participants rolled over, however, fewer participants acquired later gross motor milestones such as crawling and walking; acquisitions of those skills, when accomplished, were always delayed. In fact, only 14% of participants were able to walk independently while 64% of participants cruised on average at 51 months. Results from the motor domain of the Vineland quantify and corroborate this finding of severe motor impairment.[1,4] Limited expressive language was observed; attainment of language milestones was delayed, with only 42% of the children and adults sampled able to put two words together. One or more domains of adaptive function on the Vineland were impaired and individuals received support and services such as speech, occupational, and physical therapy.

This is one of the first prospective study characterizing the neurodevelopmental profiles of PMM2-CDG where all individuals included in the study were administered a cognitive assessment regardless of impairments. Results from neurodevelopmental evaluation revealed all participants meet criteria for global developmental delay or ID. We reported variability in ID (and global developmental delay in the younger patients) in individuals with PMM2-CDG. We did find more than just a mild delay or impairment (indications that ID would be more than just mild) in close to 30% of the sample, after testing all individuals using a hierarchical approach. This is important to note, in light of previous studies that have deemed some subjects untestable, thus these findings provide confirmatory evidence for the general trends reported in the clinical guidelines published.[4] When reporting on the neurodevelopmental profile of individuals with PMM2-CDG, it is paramount that the interpretation of adaptive and cognitive functioning scores be done in conjunction with their clinical presentations of related systemic involvement. Given the multisystemic clinical presentation including medical, motor, and sensory complications, for individuals with profound ID at least, the known nomenclature—Profound Intellectual and Multiple Disabilities (PIMD)[13] should be considered.

5 | LIMITATIONS

Genetic findings from the study indicated two pathogenic variants (c.422G>A (p.R141H)) and (c.710C>G (p.T237R)) were common among participants and 16 other pathogenic variants were identified. While this study reports on the comprehensive neurodevelopmental profiles of one of the largest cohorts of PMM2-CDG to date, the sample size limited further analysis of the genotype–phenotype of the neurodevelopmental profiles

for the different observed genetic pathogenic variants of PMM2-CDG in the sample. The range of genetic variants considered with the spectrum of clinical presentations exemplify possible genotype–phenotype heterogeneity in PMM2-CDG and warrants further investigation as more affected individuals are reported. In addition, longitudinal neurodevelopmental assessments in individuals with PMM2-CDG are needed to understand the trajectory and progression of skill development in this population, and especially to more fully understand ID in this population, given how relatively young the current sample was. As found in other genetic conditions associated with neurodevelopmental disorders, neurodevelopmental testing scores, including adaptive functioning, are lower in older individuals as their trajectory further diverges from typically developing peers.[28]

It is also important to note the neurodevelopmental deficits identified has various attributions (and reciprocally has cascading effects on further development), including the cerebellar atrophy found in PMM2-CDG, the motor disability, ataxia, movement disorder, neuropathy, vision or hearing impairment, and seizure control. These various attributions are the reasons for including data on motor disability, movement disorder, neuropathy, vision impairment, hearing impairment and seizure control. Developmental profiles are impacted by other systematic involvement, along with cerebral involvement. Presenting these findings together allows for a holistic understanding of this population's developmental profile.

Another limitation of this research may involve ascertainment bias—families and patients with more severe PMM2-CDG presentations may volunteer to participate in the NIH time-intensive study, because they benefit extensively from the subsequent evaluations and recommendations provided. Conversely, families and patients with milder PMM2-CDG presentations may be satisfied with their current understanding of the patient's well-being and care routines, and thus, may perceive a time-intensive study to be less beneficial.[4,24,29]

6 | CONCLUSIONS

Overall, the findings of this study suggest that the diagnosis of PMM2-CDG is associated with ID with multiple disabilities, including neurologic, motoric, audiologic and ophthalmologic. Significant delays typically begin in infancy, with discrepancy in milestones attainment and limited evidence of loss of milestones in this cohort. The distinction of the PIMD classification comprising some of this cohort, along with every individual presenting with multisystem presentations, is an essential recognition not only for how it impacted the standardized neurodevelopmental assessments of this study, but more broadly how it impacts these individual's overall development.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conceptualization, design, data collection, analysis, and interpretation of the data, as well as the drafting and revising of the manuscript. Audrey Thurm and Lynne Wolfe supervised the project. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the National Human Genome Research Institute's institutional review board.

PATIENT CONSENT

The procedures in this study were performed in accordance with the ethical standards for medical research outlined in the Helsinki Declaration. Informed consent was obtained from all patients and/or parents included in the study. No identifying patient information is included in this article. Not applicable. This article does not contain any studies with animal subjects performed by the any of the authors.

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SUPPORTING INFORMATION

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

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