

Original Article

Clinical Features in Children with Persistent Toe Walking Who Carry Heterozygous PYGM Variants: A Cross-Sectional Study

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Abstract

Objectives: Persistent toe walking (TW) in children is often idiopathic but may conceal subtle neuromuscular or metabolic causes. This cross-sectional, retrospective study investigated clinical and genetic characteristics of children carrying PYGM variants to explore potential subclinical phenotypes among heterozygous carriers. **Methods:** Seventy-two (72) children meeting criteria for idiopathic TW were evaluated using a standardized clinical protocol and a validated 49-gene next-generation sequencing neuromuscular panel. Variants were classified as pathogenic, likely pathogenic, or of uncertain significance according to ACMG/AMP guidelines. Analyses were descriptive. **Results:** Among 1,300 screened patients, 72 were identified as PYGM variant carriers. Toe walking was bilateral in all cases, with severe dorsiflexion restriction ($\leq 5^\circ$) in 80.5%. Pes cavus was observed in 93% of patients, and muscle symptoms—pain, fatigue, or cramps—occurred in approximately one-third. VUS carriers displayed comparable, slightly milder muscle symptom frequencies than P/LP carriers. 12.5% could perform heel walking. Speech difficulties were reported in 56.9% of cases. **Conclusions:** While causality cannot be inferred, these findings suggest that heterozygous PYGM variants may contribute to subtle neuromuscular phenotypes. Genetic testing can be considered in persistent TW when clinical findings raise suspicion for an underlying neuromuscular/metabolic condition.

Keywords: Gait Disorders, Habitual Toe Walking, McArdle Disease, Pediatric Genetics, PYGM

Introduction

Toe walking is a gait abnormality characterized by absent heel strike during initial gait contact and lack of full foot contact. It is a common developmental phase in children under two years of age who are learning to walk independently^{1,2}. With etiologies varying from muscle spasticity (as in cerebral palsy)³ to congenital conditions

like a short Achilles tendon⁴, toe walking has multiple causes. It can also be associated with developmental disorders such as autism⁵ or with sensory processing differences⁶. When persisting beyond 2-3 years of age without an identifiable neurological, orthopedic, or psychiatric cause, it is referred to as idiopathic⁷. Approximately 5% of children develop idiopathic toe walking, which remains a diagnosis of exclusion⁸. The term 'idiopathic' refers to conditions where no underlying cause is known, but subtle genetic factors may still be present, as research increasingly shows that genetic predispositions play a significant role in many conditions once thought to be entirely unexplained, such as scoliosis, pulmonary fibrosis, and certain types of epilepsy^{9,10,11,12}. Recent advances in genetics have suggested possible hereditary contributions, with next-generation sequencing panels identifying up to 49 genes potentially related to toe-

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walking¹³. Among these genes, PYGM—which encodes the enzyme myophosphorylase and is implicated in McArdle disease (glycogen storage disease type V)—was found in heterozygous carriers in our clinic’s initial cohort (Emelina et al., 2024)¹⁴. McArdle disease is an inherited glycogen-storage disorder caused by myophosphorylase deficiency, which impairs skeletal-muscle glycogen breakdown. Clinical manifestations include exercise intolerance, myalgia, cramps, and, in severe cases, rhabdomyolysis¹⁵. Whereas individuals with homozygous or compound-heterozygous mutations present with classic McArdle symptoms, heterozygous carriers typically retain partial enzyme activity—about 30 to 45 percent of normal¹⁶. Although often asymptomatic at rest, carriers may show mild glycolytic dysfunction during metabolic stress. The condition follows an autosomal-recessive inheritance pattern and involves mutations in the PYGM gene located on chromosome 11q13, most commonly missense variants¹⁷. To date, more than 140 pathogenic PYGM mutations and around 40 polymorphisms have been reported, with the p. Arg50* (R50X) stop-gain mutation being the most frequent among Caucasians¹⁵. A consistent genotype–phenotype correlation has not yet been established¹⁸.

Diagnosis remains challenging, particularly in children. The ‘second-wind’ phenomenon—described by Pearson et al. (1961) as a sudden improvement after initial fatigue—is pathognomonic for GSD V but often difficult to recognize in pediatric patients¹⁹. In addition, presenting symptoms such as exercise intolerance, myalgia, and cramps are non-specific. Although genetic testing is pivotal, invasive diagnostic methods (e.g., forearm exercise tests or muscle biopsy) are often impractical in children. As a result, many cases are misdiagnosed, delaying appropriate intervention^{20,21}.

In this study, we describe clinical and genetic findings in 72 children with persistent toe walking who were found to carry heterozygous PYGM variants. The aim was to document their characteristics and explore possible genotype–phenotype patterns in a descriptive, hypothesis-generating manner.

Materials and Methods

This retrospective observational study spanned four years and investigated potential genetic factors associated with idiopathic toe walking in children. Children with persistent toe walking were referred by pediatricians for gait assessment. The study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational cross-sectional studies²².

Inclusion criteria were as follows:

1. Toe walking observed for more than 50% of daily ambulation (parent-reported or clinician-observed).
2. Completion of a targeted genetic test using a validated 49-gene neuromuscular panel.

3. Absence of diagnosed neurological, orthopedic, or developmental conditions causing toe walking such as cerebral palsy, autism spectrum disorder, tethered cord syndrome.
4. Absence of significant orthopedic deformities (e.g., limb-length discrepancy, scoliosis).
5. Children with other known genetic or metabolic disorders were excluded.
6. Patients with a history of perinatal complications or abnormal pregnancy outcomes (e.g., prematurity, neonatal hypoxia, or birth trauma) were also excluded.

All data were anonymized before analysis.

Statistical Analysis

Descriptive statistical analyses were performed using LibreOffice Calc (v.25.2.5.2) to summarize the following parameters:

- Demographic data (age, sex)
- Genetic findings (PYGM variant classifications)
- Clinical features (toe walking duration, pes cavus, muscle symptoms)

Missing data were excluded from denominator calculations.

Categorical variables were summarized as frequencies and percentages. Comparisons between variant classes (Pathogenic/Likely Pathogenic vs. VUS) were exploratory and descriptive.

Given the limited sample size, the study was not powered to perform adjusted multi variable analyses. All comparisons were therefore exploratory and descriptive.

Phenotypic Assessment

In our specialized gait analysis clinic, children are referred for evaluation after orthopedic, neurological, and other secondary causes of toe walking have been excluded in prior assessments by pediatric neurologists and orthopedics.

All clinical assessments, were performed independently by the examining physiotherapist blinded to the patients’ genetic results. Assessments were conducted once per patient and were not duplicated.

The diagnostic workflow followed the clinic’s established standardized protocol, which combines structured history taking, visual gait analysis, targeted physical examinations (Table 1).

The visual gait analysis was performed during both spontaneous walking in the clinic hallway and guided observation. A structured three-phase assessment was applied:

- (1) evaluation of overall gait symmetry,
- (2) observation of heel contact, and
- (3) assessment of hip stability and balance through the Trendelenburg sign—defined as a contralateral pelvic drop during single-leg stance—²⁴.

The range of motion of the upper ankle joint (UAJ) was

Table 1. Data Collection Framework.

Patient History	• Duration of pregnancy*
	• Mode of delivery
	• Birth weight and height
	• Speech development (delay, dysphasia)
	• Onset of walking (OoW)
Family History	• Age of onset of TW
	• Occurrence of TW in relatives
Diagnosis of TW	• Muscular and neurological diseases in the family
	• Visual gait analysis
	• Upper ankle joint examination
	• Ability to balance (Trendelenburg sign)
	• Laterality of TW (Symmetry)
	• Examination of muscular atrophy and hypertrophy of the calf muscle
Diagnosis of McArdle Disease	• Pes cavus examination
	• Anamnesis for exercise intolerance
	• Muscular weakness or cramping
	• Muscular atrophy or hypertrophy
*A normal term of pregnancy is defined as 37 to 42 completed weeks of gestation.	

measured using the neutral-zero method. The 0° position was established with the child in a supine position and the knee extended. A goniometer was centered over the lateral malleolus, with one arm aligned parallel to the fibula and the other along the fifth metatarsal bone. From this neutral position, dorsiflexion and plantar flexion were measured at their maximal range. The normal reference range was defined as 20°–0°–50° (dorsiflexion–neutral–plantar flexion)²⁵.

Speech development was evaluated through parental reports, documenting whether the child had experienced any delay or difficulty in verbal communication compared with peers of the same age. Muscle weakness and cramping were also noted by parents during anamnesis.

Pes Cavus was assessed through visual inspection of the foot arch and heel alignment while standing. A raised longitudinal arch with forefoot scarring relative to the hindfoot, and a varus heel position upon forefoot contact, were noted as indicative features²⁶.

Genetic testing

The study included only patients who underwent next-generation sequencing (NGS) panel comprising 49 genes associated with hereditary neuropathies and myopathies related to toe walking (Labor Dr. Heidrich & Colleagues, Hamburg, Germany). Children tested using other methods

(e.g., whole-exome sequencing) were excluded to ensure consistency of results. DNA was extracted from saliva using the Promega Maxwell CSC or QIAamp DNA Blood Mini Kit. Sequencing was carried out on the Ion Torrent platform (Thermo Fisher Scientific), achieving a minimum coverage depth of 30× and variant allele frequency >20%. The panel covered all coding exons and exon–intron boundaries (±10 bp). Testing was recommended as part of diagnosis, using saliva samples collected during routine clinical care.

Variants were classified using a five-tier system (benign, likely benign, variant of uncertain significance [VUS], likely pathogenic, pathogenic) following Plon et al. (2008²⁷), with automated American College of Medical Genetics and Genomics (ACMG) and Genomics and the Association for Molecular Pathology (AMP) based scoring supported by Varsome and referencing databases including ClinVar, HGMD, and gnomAD²⁸, with computational prediction (CADD, MutationTaster, PolyPhen-2, REVEL). Variant interpretations were date-stamped. Pathogenic (P), likely pathogenic (LP), and variants of uncertain significance (VUS) were included for analysis; benign and likely benign variants were excluded but are available upon request. Variant nomenclature followed Human Genome Variation Society (HGVS) recommendations.

Results

Given the descriptive design of this study, all analyses should be regarded as exploratory, intended to provide clinical and genetic insights rather than infer causality or risk associations.

Among 1,300 screened patients, 72 children carrying PYGM gene variants were selected for inclusion in this study, comprising 27 girls (37.5%) and 45 boys (62.5%). The cohort ranged in age from 1 to 13 years, with a mean age of 6 years. This represents an expansion of our previously reported preliminary cohort of 16 cases, now encompassing 33 distinct PYGM variants identified across all included individuals.

The mean reported age of onset of toe walking was 16 months, with 72% of parents indicating that the gait abnormality had been present since the initiation of independent walking. In 11% of cases, toe walking developed within the same year as walking onset, while 13.8% exhibited delayed onset more than one year later; in 2 cases, the onset was not reported.

All patients exhibited bilateral toe walking. None demonstrated a positive Trendelenburg sign, and only 12.5% were able to perform heel walking. Speech difficulties were reported in 56.94% of patients.

Family history of toe walking was reported in 52.8% of cases, most frequently among first-degree relatives (siblings or parents). In contrast, no family history of neurological or muscular diseases was reported in any patient.

Assessment of calf muscle mass was limited to visual inspection during clinical examination. As no imaging

Table 2. Overview of demographic and genetic findings among PYGM heterozygous carriers.

Patient ID	Age	Sex	Onset of Toe walking since OoW* (months)	Variant c. HGVS	ACMG Classification	Freq*	Report date
1	4	F	3	c.-20C>T	VUS	0.0112%	12.12.2022
2	9	M	OoW	c.-44_-33dup	VUS	0.0012%	07.03.2025
3	3	F	OoW	c.*59C>G	VUS	0.0008%	08.01.2022
4	8	M	OoW	c.1083C>T	VUS	0.0179%	28.11.2022
5	4	F	OoW	c.1092+6dup	VUS	0.1629%	10.10.2022
6	3	M	OoW	c.1094C>T	P	0.0711%	01.07.2021
7	2	F	OoW	c.1094C>T		0.0711%	03.06.2022
8	3	M	OoW	c.1094C>T		0.0711%	11.01.2022
9	2	F	OoW	c.1094C>T		0.0711%	08.10.2021
10	5	M	OoW	c.1094C>T		0.0711%	11.11.2024
11	11	M	24	c.1190T>C	P	0.0029%	08.07.2022
12	5	F	OoW	c.1274G>A	LP	0.0038%	08.07.2022
13	6	M	OoW	c.1315C>T	VUS	0.0017%	18.11.2021
14	6	M	OoW	c.1315C>T		0.0032%	18.05.2021
15	2	F	OoW	c.1353dup	P	0.0009%	10.01.2023
16	10	M	OoW	c.1354G>A	VUS	0.0004%	30.06.2021
17	9	F	OoW	c.1375A>G	LP	0.0005%	08.04.2022
18	10	M	OoW	c.148C>T	P	0.1452%	21.06.2023
19	8	M	OoW	c.148C>T		0.1452%	19.12.2022
20	9	F	OoW	c.148C>T		0.1452%	30.09.2022
21	2	F	OoW	c.148C>T		0.145%	09.06.2021
22	4	F	OoW	c.148C>T		0.1452%	09.01.2025
23	5	M	OoW	c.14T>C	VUS	N/A	21.03.2022
24	9	M	OoW	c.1537A>G	VUS	0.302%	31.03.2022
25	4	F	13	c.1537A>G		0.302%	04.11.2021
26	8	M	OoW	c.1537A>G		0.302%	15.10.2021
27	4	M	23	c.1537A>G		0.302%	08.10.2021
28	5	M	35	c.1537A>G		0.302%	14.02.2025
29	6	M	OoW	c.160T>G	VUS	0.0310%	25.03.2025
30	7	F	6	c.160T>G	LP	0.0310%	30.09.2022
31	3	F	12	c.160T>G		0.0310%	30.09.2022
32	2	M	3	c.160T>G		0.0310%	28.09.2022
33	8	F	OoW	c.160T>G		0.0310%	04.08.2022
34	7	F	OoW	c.160T>G		0.0310%	18.12.2024
35	3	M	OoW	c.164_168del	P	0.0007%	14.12.2022
36	2	M	OoW	c.1727G>A	P	0.0004%	14.12.2022
37	11	M	OoW	c.1805G>A	LP	0.0139%	31.03.2022
38	7	F	6	c.1827+1G>C	P	0.0004%	30.09.2022
39	3	M	OoW	c.1888G>A	VUS	0.0278%	09.08.2022
40	4	M	9	c.1957C>G	VUS	0.0923%	07.10.2021
41	13	M	OoW	c.1970-3C>T	VUS	0.0004%	17.02.2022
42	1	M	OoW	c.1970-6C>T	VUS	N/A	06.10.2020
43	11	F	OoW	c.2056G>A	P	0.0055%	07.04.2021
44	5	M	14	c.208C>T	VUS	0.00677%	18.11.2021
45	3	F	N/R	c.2218C>T	VUS	0.0004%	14.04.2021
46	12	M	21	c.2262del	P	0.0119%	19.09.2024
47	8	F	OoW	c.2280G>C	VUS	N/A	21.12.2022
48	9	M	19	c.576G>T	VUS	0.0012%	30.08.2021

Table 2. (Cont. from previous page).

Patient ID	Age	Sex	Onset of Toe walking since OoW* (months)	Variant c. HGVS	ACMG Classification	Freq*	Report date	
49	9	F	OoW	c.577G>T	VUS	0.4582%	31.07.2024	
50	12	F	12	c.645G>A	VUS/LP	0.4582%	13.06.2023	
51	8	F	OoW	c.645G>A		0.4582%	07.10.2022	
52	3	F	OoW	c.645G>A		0.4582%	25.10.2022	
53	5	F	18	c.645G>A		0.4582%	03.06.2022	
54	6	F	OoW	c.645G>A		0.4582%	18.11.2021	
55	3	F	OoW	c.645G>A		0.4582%	15.10.2021	
56	8	M	OoW	c.645G>A		0.4582%	07.09.2021	
57	8	M	OoW	c.645G>A		0.4582%	18.06.2021	
58	4	M	OoW	c.645G>A		0.3395%	13.04.2021	
59	4	M	OoW	c.645G>A		0.4582%	07.10.2024	
60	9	F	OoW	c.645G>A		0.2086%	31.07.2024	
61	8	M	OoW	c.660G>A		VUS	0.2086%	19.04.2024
62	3	M	OoW	c.660G>A			0.2086%	21.02.2024
63	11	M	23	c.660G>A			0.2086%	28.09.2022
64	6	M	N/R	c.660G>A	0.2086%		08.07.2022	
65	11	M	OoW	c.660G>A	0.2086%		08.07.2022	
66	7	M	OoW	c.660G>A	0.2086%		08.09.2021	
67	11	M	OoW	c.660G>A	0.2086%		15.10.2021	
68	3	M	OoW	c.660G>A	0.2086%		07.03.2022	
69	4	M	9	c.660G>A	0.2086%		08.01.2022	
70	4	M	OoW	c.660G>A	0.2086%		11.11.2021	
71	3	M	OoW	c.660G>A	0.20%		17.03.2021	
72	4	M	6	c.660G>A	0.2086%		07.11.2024	

*Oow= Onset of walking, P= Pathogenic, LP= Likely Pathogenic, VUS= Variant of uncertain significance, Freq= Frequencies, N/R= Not Reported.

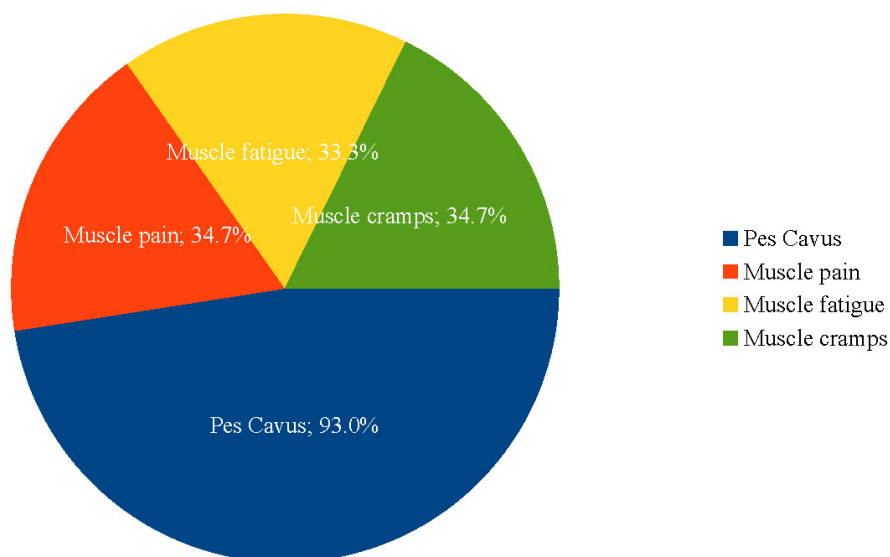


Figure 1. Distribution of Phenotypic Features Among PYGM Patients.

Table 3. Phenotypic Manifestations of the PYGM gene variants.

PYGM Variant c.HGVS	ACMG Classification	Pes Cavus	Muscle Pain	Muscle Fatigue	Muscle Cramps
c.1094C>T	P	5	3	3	3
c.1190T>C	P	1	1	1	1
c.1353dup	P	1	0	0	0
c.148C>T	P	5	1	1	1
c.164_168del	P	1	0	0	0
c.1727G>A	P	1	1	1	1
c.2056G>A	P	1	1	1	1
c.2262del	P	1	0	0	0
c.1805G>A	P	1	0	0	0
c.645G>A	VUS/LP	9	4	4	4
c.1827+1G>C	LP	1	1	1	1
c.160T>G	LP	5	2	2	2
c.160T>G	VUS	1	1	1	1
c.1274G>A	VUS	1	0	0	0
c.1375A>G	VUS	1	0	0	0
c.-20C>T	VUS	1	0	0	0
c.-44_-33dup	VUS	1	1	1	1
c.*59C>G	VUS	1	0	0	0
c.1315C>T	VUS	2	0	0	0
c.1354G>A	VUS	1	1	1	1
c.14T>C	VUS	1	0	0	0
c.208C>T	VUS	0	0	0	0
c.2218C>T	VUS	1	1	1	1
c.2280G>C	VUS	1	0	0	0
c.576G>T	VUS	1	1	1	1
c.660G>A	VUS	10	1	2	2
c.1083C>T	VUS	1	1	1	1
c.1092+6dup	VUS	1	0	0	0
c.1537A>G	VUS	4	2	2	2
c.1888G>A	VUS	1	0	0	0
c.1957C>G	VUS	1	0	0	0
c.1970-3C>T	VUS	1	1	1	1
c.1970-6C>T	VUS	1	0	0	0
c.577G>T	VUS	1	0	0	0
Total		66	24	25	25

or quantitative measurements were performed, formal results were omitted to avoid subjective bias.

With respect to upper ankle joint mobility, plantar flexion was preserved in all patients, whereas dorsiflexion was markedly restricted in the majority: 73.6% demonstrated complete limitation at 0°, 6.9% achieved up to 5°, and 5.5% reached 10–15°. Dorsiflexion was normal in one patient and unreported in another.

Table 2 presents the individual genetic and clinical data for each PYGM variant carrier, including patient demographics, onset timing, variant characteristics, and

classification details.

Because variant interpretation may evolve with emerging evidence and updated databases, the laboratory report date was included to indicate the timing of classification.

To illustrate and summarize the distribution of clinical features overlapping with those typically associated with McArdle disease, the prevalence of pes cavus, muscle pain, fatigue, and cramps among PYGM variant carriers is presented in Figure 1 and Table 3.

Discussion

This study describes the clinical and genetic spectrum of persistent toe walking, in paediatric heterozygote carriers of PYGM variants, challenging the traditional view of McArdle disease heterozygote carriers being asymptomatic. In our cohort of 72 children, we identified 33 PYGM variants with Pes cavus being present in 93% (66) of heterozygous carriers—aligning with our earlier findings and underscoring its potential as a consistent yet underreported feature in PYGM heterozygotes.

In this expanded cohort, muscle pain was reported in 34.7% of cases—lower than in our preliminary sample (50%)—while fatigue (33.3%) and cramps (34.7%) were higher (previously 25% and 6%). These frequencies exceeded the 22% prevalence of muscle discomfort reported by Núñez-Manchón et al²⁹, suggesting that mild muscle symptoms may be relatively common in this pediatric population.

The high prevalence of restricted dorsiflexion observed in our cohort aligns with existing literature suggesting a bidirectional relationship between toe walking and ankle mobility. Limited dorsiflexion can act as both a predisposing factor for toe walking—by encouraging forefoot contact during gait—and a secondary consequence of persistent forefoot loading, which contributes to contracture and tightening of the gastrocnemius–soleus complex over time^{30,31}.

Given that the majority of children in this cohort exhibited toe walking from the onset of independent ambulation, these findings underscore the importance of early clinical recognition. Family history was positive in 52.8% of cases, suggesting a potential hereditary or familial predisposition. The natural history of habitual toe walking varies considerably, and a prolonged “wait-and-see” approach may allow secondary compensatory mechanisms—such as lumbar hyperlordosis and equinus contracture—to develop over time, leading to progressive musculoskeletal pathology. In addition, children with persistent toe walking often exhibit increased effort during gait and a higher risk of falls or balance-related instability, which may further compromise motor development and daily functioning^{32,33,34}. Early identification and individualized management may therefore help mitigate these progressive musculoskeletal adaptations.

Furthermore, we are currently conducting a prospective follow-up study to evaluate treatment outcomes in children with idiopathic toe walking, using conservative approaches (e.g., physiotherapy, orthotic correction) or surgical interventions depending on each case’s description.

While not diagnostic on its own, the presence of bilateral toe walking presentation and negative Trendelenburg sign—indicator of hip abductor weakness (gluteus medius and gluteus minimus)—in all patients of our cohort, could be explored as a predictive screening feature in future prospective assessments.

Speech and language development delays have been repeatedly reported in association with idiopathic toe walking^{35,36}. In our cohort the speech-related difficulties reported during anamnesis were based solely on parental reports without formal neurodevelopmental testing, the findings should be interpreted with caution and cannot be considered diagnostic.

Limitations

Diagnosing McArdle disease (GSD-5) in pediatric populations presents inherent challenges that shaped our study design. The pathognomonic second-wind phenomenon is notoriously difficult to elicit or quantify in young children, while standard functional tests such as the non-ischemic forearm exercise test are often impractical and ethically constrained in this age group. Moreover, the high initial misdiagnosis rate reported in GSD-5 (estimated at ~90%) contributes to diagnostic delays, increasing the risk of rhabdomyolysis and renal complications.

Although genetic testing was prioritized as the diagnostic gold standard—given the >179 known PYGM variants—several constraints remained. Creatine kinase levels, which could have aided in identifying subclinical myopathy, were not systematically collected, and muscle biopsies were avoided due to their invasiveness. Methodological limitations of the NGS approach included inability to detect deep intronic variants, structural rearrangements, copy number variations, or low-level mosaicism, despite an analytical sensitivity exceeding 96% for clinically relevant variants.

At the study level, the retrospective and purely descriptive design precludes causal inference. The absence of a control group (e.g., idiopathic toe walking without PYGM variants) limits the ability to quantify association or risk. Clinical data such as speech delay, onset age, or fatigue were derived from parental reports, introducing possible recall and reporting bias. As evaluations were performed once per patient and not repeated by a second examiner, inter-rater reliability could not be assessed; however, blinding to genetic data minimized potential observer bias. Finally, the single-center setting may reduce generalizability to broader pediatric populations.

Ethics approval

This study was approved by the ethics board of the Deutschen Verbandes für Physiotherapie an der Physio-Akademie in Wremen, Germany (project number 2025-02).

Consent to participate

Written informed consent for participation and genetic testing was obtained from parents or legal guardians.

Authors' Contributions

David Pomarino: Conceptualized the study, designed the methodology, and performed primary data acquisition and analysis. Drafted the initial manuscript and coordinated revisions. The author takes responsibility for the integrity of the data analysis. Bastian

Fregien: Contributed to orthopedic phenotyping and reviewed genetic-clinical associations. Kevin M. Rostásy: Provided critical intellectual input on neurological interpretations and revised the manuscript for scientific rigor. All authors read and approved the final version of the manuscript.

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