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Persistent toe walking as a prominent feature in pediatric PMP22-Related neuropathies: A retrospective cohort study

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A B S T R A C T

Purpose: Persistent toe walking in children is often considered idiopathic; however, increasing evidence suggests that alterations in the PMP22 gene—implicated in Charcot–Marie–Tooth disease type 1 A (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)—may contribute to its pathogenesis. This study investigates the association between PMP22 variants (duplications, deletions, and point mutations) and toe walking in children, aiming to delineate their clinical and genetic characteristics.
Methods: A retrospective analysis was performed on 22 pediatric patients (mean age: 7.7 years) with persistent toe walking and confirmed PMP22 variants identified through a 49-gene next-generation sequencing (NGS) panel. In selected cases, Multiplex Ligation-dependent Probe Amplification (MLPA) was applied to confirm copy number variations. Comprehensive clinical evaluations included musculoskeletal, neurological, and developmental assessments.
Results: All identified variants demonstrated dominant inheritance. Pathogenic variants were present in 54.5 % of patients, likely pathogenic in 31.8 %, and variants of uncertain significance (VUS) in 13.6 %. Among pathogenic cases, most carried PMP22 duplications, one had a deletion, and the remainder harbored the missense variant p.(Thr118Met). The three VUS carriers exhibited comparatively milder phenotypes, such as muscle cramps, lumbar hyperlordosis, mild dorsiflexion restriction, hyporeflexia, pes cavus, and clinodactyly/brachydactyly; only one presented with tremor. Lumbar hyperlordosis (90.9 %) and pes cavus (90.9 %) were the most consistent findings.
Conclusions: Persistent toe walking may represent an early sign of PMP22-related neuropathies rather than a benign idiopathic gait pattern. The predominance of PMP22 duplications and characteristic neuromuscular features highlight the clinical utility of integrating NGS and MLPA testing for accurate diagnosis, targeted management, and genetic counseling.

Introduction

Toe walking, or equinus gait, is a common pediatric gait abnormality often classified as idiopathic when no underlying neurological, muscular, or orthopedic cause is identified [1]. Idiopathic toe walking occurs in about 5 % of children after the age of 2. If there is no spontaneous remission within six months of its onset, it becomes less likely to be idiopathic [2–5]; emerging evidence

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suggests that genetic factors, particularly mutations in the PMP22 (Peripheral Myelin Protein 22) gene, may play a significant role in the development of toe walking and associated neurological symptoms [6–9].

The PMP22 gene plays a critical role in peripheral myelin formation and nerve conduction. Different types of variants in PMP22 are associated with distinct neuropathic phenotypes. Gene duplications represent the most common cause of Charcot–Marie–Tooth disease type 1 A (CMT1A), accounting for approximately 80–90 % of all CMT1A cases. In contrast, deletions of PMP22 result in Hereditary Neuropathy with Liability to Pressure Palsies (HNPP), a disorder characterized by recurrent focal neuropathies and sensory disturbances. Furthermore, point mutations and small insertions or deletions in PMP22 have been reported in CMT1E [10–13].

Notably, 18–50 % of Charcot-Marie-Tooth (CMT) cases overall remain genetically unexplained after testing known genes, potentially due to variants in non-coding regions or undetected structural rearrangements such as insertions, inversions, or translocations [10,12,14–17].

However, the relationship between PMP22 mutations and their clinical manifestations in particular in the initial phase of the diseases in children has not been studied in detail. Beyond toe walking, patients frequently can exhibit additional neurological symptoms, such as pes cavus, distal muscle atrophy, and sensory deficits [8,18], Additionally, some patients with PMP22 mutations may present with speech and language difficulties [5,19,20].

The present exploratory, retrospective study investigates the possible association between PMP22 variants (duplications, deletions, and point mutations) and toe walking in children, while characterizing accompanying neurological and developmental features. By examining genetic and clinical correlations, we aim to emphasize the importance of genetic testing and early recognition of PMP22-related gait abnormalities to improve diagnostic accuracy and early management.

Materials and methods

The study cohort was selected from a larger clinical population of 1500 children who were referred to our specialized gait center for the evaluation of persistent toe walking. All children had been previously evaluated by their primary pediatrician, and the majority had also been assessed by pediatric orthopedists and/or neuropediatricians, yet remained without a definitive underlying diagnosis. The children then underwent targeted genetic testing with a 49-gene next-generation sequencing (NGS) panel for hereditary neuropathies and myopathies.

The final study cohort consisted of 22 children from this genetically tested subgroup who had a confirmed PMP22 variant classified as Pathogenic (P), Likely Pathogenic (LP), or Variant of Uncertain Significance (VUS) according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Inclusion criteria were presence of persistent toe walking, observed during clinical examination and reported by parents to be the child's dominant walking pattern, complete clinical gait and neurological evaluation, and a confirmed report of a P, LP, or VUS in the PMP22 gene from the 49-gene NGS panel.

Exclusion criteria were a confirmed diagnosis of a known neurological or orthopedic condition that could explain the toe walking (e.g., cerebral palsy, autism spectrum disorder, tethered cord syndrome, significant birth complications leading to encephalopathy), presence of severe orthopedic deformities such as limb length discrepancies, structural scoliosis, or severe foot deformities unrelated to a neuropathy (e.g., congenital talipes equinovarus).

Clinical Assessment

Postural and structural abnormalities:

- **Lumbar hyperlordosis:** goniometric measurement of the lumbosacral angle.
- **Pes cavus, pectus excavatum, clinodactyly, and brachydactyly:** morphological inspection

Balance and Motor Function:

- **Balance disorders: Single-leg stance (< 5 sec or needing support = failure)**
- **Motor Function: Two functional tests were administered in standing position:**

►**Heel Walking Test**

►**Foot Drop Test** (toe lifting)

Ankle Range of Motion (ROM):

- **Goniometry (neutral/0° method).**
- **Restricted** = dorsiflexion < 20° / plantarflexion < 50° [21].

Neurological Evaluations:

- **Tremor** (essential tremor):

Positioning: patients extended arms forward with palms down.

Provocation: repeated hand opening-closing.

Positive: visible rhythmic oscillations post movement.

- **Dysarthia:** (parent/caregiver-reported)

Genetic testing

Only patients who had undergone genetic testing using a targeted next-generation sequencing (NGS) panel designed to identify hereditary neuropathies and myopathies potentially associated with toe walking were included in this study. Children who had received alternative forms of genetic analysis, such as whole-exome sequencing, were excluded to ensure methodological consistency.

However, in selected cases where copy number variations (CNVs) were suspected based on NGS data, Multiplex Ligation-dependent Probe Amplification (MLPA) was subsequently performed to confirm potential duplications or deletions. MLPA was carried out using probes for the PMP22 gene (MRC-Holland), following the manufacturer's instructions. This approach allowed for detection of large copy number variants (CNVs), such as the PMP22 duplication typically associated with Charcot–Marie–Tooth disease type 1 A (CMT1A).

All participants were tested using the same commercially available 49-gene NGS panel for hereditary neuro- and myopathies (Thermo Fisher Scientific). The complete list of genes analyzed is provided in Supplementary Table 1. The panel was developed based on the Human Phenotype Ontology (HPO) database and included genes previously linked to relevant neuromuscular and neuropathic disorders.

Saliva samples were collected by the treating (neuro)pediatricians as part of the diagnostic process. DNA extraction was carried out using standard clinical protocols, and sequencing was performed on the Ion Torrent platform (Thermo Fisher Scientific, Waltham, MA, USA). The panel covered all coding exons and exon–intron boundaries (± 10 bp) [6].

Variant classification followed the American College of Medical Genetics and Genomics (ACMG) guidelines [22], assigning each variant to one of five categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign. Variant interpretations were date-stamped, as classification and allele frequency data can change over time with updated database information. Only variants categorized as pathogenic (P), likely pathogenic (LP), or VUS were included in the final analysis; benign variants were excluded but can be provided upon request.

In silico analyses were performed, for example, using the programs Mutation Taster, PolyPhen2, and/or Mutation Assessor. The following databases were used: HGMD professional (The Human Gene Mutation Database (https://portal.biobase-international.com/hgmd/pr o/gene.ph p?), LOVD -IARC (Leiden Open Variation Database, http://grenada.lume.ni/LSDB_list/Isdbs), dbSNP, ClinVar, as well as, when and as required, more specialized databases. Variants outside the analyzed areas in the examined genes (for example in untranslated, regulatory gene areas), in regions with multiple copies of high sequence homology, repeat variants as well as copy number variants of single exons or when a complete gene cannot be detected and thus cannot be excluded. In addition, mosaics with a low frequency component cannot be excluded with certainty.

The sensitivity for detecting clinically relevant variants exceeded 96 %, as confirmed by the accredited diagnostic laboratory Labor Dr. Heidrich & Colleagues, Hamburg, Germany. Documentation of internal validation is available upon request. Segregation analysis was not systematically performed due to the high cost and limited feasibility of exome sequencing.

Data collection and analysis

Clinical data were gathered through a standardized questionnaire and physical examination findings, which included information on (Table 1):

Table 1
Data Collection Framework.

Patient History	• Perinatal history • Age of bowel control • Family history of toe walking or neuropathies • Cesarean delivery
Genetic Data	• Genetic Variants • Inheritance patterns
Toe walking Characteristics	• Manifestation age of toe walking • Percentage of toe walking per day • Prevalence of persistent toe walking beyond early childhood • Progression of toe walking
Physical Symptoms and Abnormalities	• Pain localization(e.g., foot, heels, calves, back) • Muscle-related symptoms (e.g., myalgia, cramps, fatigue) • Spinal abnormalities (e.g., lumbar spine hyperlordosis) • Balance disorders • Ankle joint range of motion • Foot deformities (e.g., pes cavus) • Structural abnormalities (e.g., clinodactyly, brachydactyly, pectus excavatum) • Reflex anomalies • Presence of tremor
Developmental and Co-morbidities	• Speech and language difficulties (e.g., dysarthria) • Social development • Visual impairments • Comorbidities

Table 2
Toe-Walking Onset Patterns.

Category	Definition	N(%)	Median Delay
Immediate Onset	Toe walking began with the first steps	14 (63.6 %)	0 months
Early Post-Walking	Developed within 1–6 months after walking	3 (13.6 %)	3.5 months
Late Post-Walking	Emerged 2–5 years after walking	4 (18.2 %)	3.7 years
Exceptional Delay	Onset at 9 years post-walking	1 (4.5 %)	9 years

Statistical Analysis

Descriptive statistics were performed using LibreOffice Calc to summarize demographic, genetic and clinical characteristics of the study population. Categorical variables, such as gender, PMP22 mutation ACMG classification, and the clinical symptoms (e.g., toe walking, muscle pain, tremor), were summarized using frequencies and percentages. Genetic variants (Pathogenic, Likely Pathogenic, and Variants of Uncertain Significance) were calculated as percentages of the total study population.

Results

Study population

Twenty-two patients were included in the study, with ages ranging from 17.5 months (1.5 years) to 17 years (mean age: 7.7 years). There were 14 (63.6 %) girls and 8 (36.4 %) boys.

Toe Walking Characteristics

All 22 children started walking between 11 and 25 months (mean age: 15 months). Toe walking onset patterns were categorized in Table 2.

Toe-walking frequency categories are summarized in (Table 3).

Parental reports prior to clinical evaluation revealed variable progression patterns: approximately 22.7 % of children experienced worsening of toe walking, while the majority 59.1 % maintained stable toe walking over time. A smaller subset 18.2 % showed improvement of their condition.

Pain and Muscle-Related Symptoms

Pain was localized in specific body parts such as the feet, heels, calves, or back in 7 patients (31.8 %). Muscle related symptoms that were reported included the following findings (Table 4).

Parental and family history

In 40.9 % of cases, family members had a history of toe walking. Among these families, fathers were affected in 27.3 %, mothers in 9 %, brothers in 9 %, sisters in 4.5 %, and nieces 9 %.

Physical and neurological findings

Lumbar spine hyperlordosis was observed in 90.9 % of patients. Balance disorders were present in 45.5 % of patients. During the assessment of motor function, none of the patients were able to perform heel walking nor could they lift their toes.

Patients showed restricted ankle mobility in both feet in 90.9 %. Muscle reflexes were reduced in 22.7 % of patients, while neurological symptoms such as essential tremor were reported in 68.2 %. Structural abnormalities were also prevalent, with pes cavus observed in 90.9 % of cases and clinodactyly and brachydactyly present in 86.4 %. Additionally, pectus excavatum was noted in 36.4 % of patients.

Table 3
Frequency of Toe Walking in the study population.

Category	Percentage of patients
< ½ of the day	13.6 %
> ½ of the day	18.2 %
All day	68.2 %

Table 4
Frequency of Musculoskeletal Symptoms in Study Cohort.

Symptom	Cases Affected	Percentage
Muscle cramps	11/22	50 %
Myalgia	7/22	31.8 %
Muscle fatigue	6/22	27.3 %

Developmental and Co-morbid factors

Visual impairment was noted in 13.6 % of patients, and not reported in 1 patient, meanwhile, speech and language difficulties were present in 45.5 %. Developmental milestones varied, with voluntary bladder and bowel control achieved in 63.6 % of the cohort and challenges in social interaction observed in 22.7 % of the cohort. Only one patient underwent nerve conduction studies, which were abnormal. Cloni or Trendelenburg sign were absent in all patients.

Genetic Data

All identified variants demonstrated a dominant mode of inheritance across the analyzed cohort. Zygosity analysis showed heterozygous variants in 90.9 % of cases and homozygous variants in 9 %. Analysis of genetic variants revealed that 54.5 % of cases carried Pathogenic (P) variants, 31.8 % had likely pathogenic (LP) variants, and 13.6 % had Variants of Uncertain Significance (VUS).

Complete variant data are provided in Table 5.

In several patients with suspected copy number variation, MLPA testing confirmed large heterozygous PMP22 duplications.

A subgroup analysis was performed for patients carrying variants of uncertain significance (VUS) to better characterize their clinical presentation. Supplementary table 2 summarizes the main clinical and genetic features of these patients, including variant details, onset patterns, associated symptoms, and relevant family history.

Table 5
Variants found in PMP22 Gene.

Patie -nt ID	Age (years)	Gen.	Walking to toe -walking Interval (Months)	c. HGVS	p. HGVS	ACMG Classifi- cation	Freq. (%)	Freq. Database	Report Date
1	2	f	0	c.*33 G > A	N/A	VUS	0.0273 %	gnomAD	08.10.2021
2	10	m	106	c.*3 C > T	N/A	VUS	0.0088 %	gnomAD	14.02.2022
3	2	m	0	c.103 G > A	p.(Ala35Thr)	VUS	0.00318 %	gnomAD	15.11.2022
4	15	f	3	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	07.06.2023
5	9	f	0	c.353 C > T	p.(Thr118Met)	P	0.4020 %	gnomAD	10.01.2023
6	10	m	35	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	10.01.2023
7	8	f	0	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	19.12.2022
8	6	f	0	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	15.11.2022
				Duplication	N/A	P	N/A	-	
9	2	f	6	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	13.07.2022
10	12	m	72	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	gnomAD	01.04.2022
11	6	f	60	c.353 C > T	p.(Thr118Met)	P	0,468 %	ExAC	18.11.2020
12	16	f	2	c.353 C > T	p.(Thr118Met)	P	0,468 %	-	16.02.2021
13	5	f	6	Duplication	N/A	P	N/A	-	01.08.2022
14	11	f	2	Duplication	N/A	P	N/A	-	13.06.2023
15	2	f	0	Duplication	N/A	P	N/A	-	07.03.2023
16	11	f	0	Duplication	N/A	P	N/A	-	11.04.2022
17	17	m	25	Gene Duplication	N/A	P	N/A	-	16.06.2021
18	9	m	0	Gene Duplication	N/A	P	N/A	-	17.03.2021
19	2	m	2	Gene Duplication	N/A	P	N/A	-	16.03.2021
20	3	m	1	4 Copies	N/A	P	N/A	-	28.03.2022
21	3	f	0	Exon 2 Deletion	N/A	P	N/A	-	06.10.2020
22	4	f	2	c.353 C > T	p.(Thr118Met)	LP	0.4020 %	-	11.02.2025

Abbreviations: Gen, Gender; c. HGVS, coding DNA reference sequence standard from the Human Genome Variation Society; f, Female; m, Male; Freq, Frequency; N/A, Not Available; gnomAD, Genome Aggregation Database; ExAC, Exome Aggregation Consortium

Discussion

The heterogeneity of toe-walking patterns in our cohort suggests different etiological pathways, with more than half of the patients exhibiting toe walking as they simultaneously began their first steps, which could imply a congenital neuromuscular dysfunction. The second group, with early post-walking toe walking, may reflect a progressive contracture formation or a delayed sensorimotor integration. Finally, for the delayed-onset group, despite the low prevalence, a latent or progressive neuropathic process could be involved.

There's noticeable variability in toe-walking progression:

- **Stable course:** chronic but non-progressive, requiring long-term monitoring.
- **Deterioration:** progressive cases needing aggressive intervention.
- **Improvement:** some cases may resolve or respond to interventions, suggesting potential for management.

Next-generation sequencing (NGS) identified variants of uncertain significance (VUS) in the PMP22 gene in three patients with toe walking/pes cavus, including two non-coding and one missense variants. While these findings are documented, it is important to note that such small-scale variants are not regarded as pathogenic for PMP22-related neuropathies. MLPA testing was applied in cases where CNVs were suspected to confirm these findings. This step confirmed several PMP22 duplications, reinforcing the diagnostic utility of combining NGS and MLPA in the assessment of hereditary neuropathies.

In our cohort, all identified variants were inherited in a dominant manner, consistent with the inheritance patterns observed in PMP22-related neuropathies and other dominantly transmitted neuromuscular disorders. This uniform pattern supports a dominant mode of transmission as the main mechanism underlying the conditions studied. No evidence for recessive inheritance or atypical segregation was observed.

The high frequency of PMP22 pathogenic variants further supports a strong genetic contribution to the phenotype. Among the pathogenic variants, the majority were large duplications, consistent with the classical PMP22-related mechanism underlying Charcot–Marie–Tooth disease type 1 A (CMT1A). In addition, one patient presented with a PMP22 deletion, while the remaining pathogenic cases involved the missense variant p.(Thr118Met), which has been previously described as pathogenic in several reports.

The variant p.(Thr118Met) has been reported with different classifications across databases and publication dates, ranging from pathogenic to likely pathogenic. This variability reflects the evolving nature of genetic interpretation, as both clinical observations and allele frequency data are updated over time. For this reason, it was crucial to document the classification used contemporaneously with the patient's clinical findings, ensuring that variant interpretation remained consistent with the evidence available at the time of analysis. This principle applies not only to p.(Thr118Met) but also to other variants identified in this study.

Allele frequencies for all identified variants were primarily obtained from the Genome Aggregation Database (gnomAD). For two patients carrying the p.(Thr118Met) variant, frequency data were instead referenced from the Exome Aggregation Consortium (ExAC) database, as corresponding gnomAD data were not available at the time of analysis. The ExAC database is based on exome sequencing data from approximately 60,000 individuals, whereas gnomAD expands upon it by including both exome and genome sequencing data from over 195,000 individuals. In addition, gnomAD applies more stringent quality control measures and uses updated metrics such as the observed/expected (oe) score, replacing the pLI metric used in ExAC. Given these methodological differences, slight variations in allele frequencies between the two databases can occur. Both resources, however, are widely recognized and accepted for variant interpretation in clinical and research genetics [23].

Familial aggregation was observed, with fathers being the most commonly affected relatives suggesting paternal transmission patterns.

The near-universal presence of lumbar spine hyperlordosis suggests significant postural compensations. While the high prevalence of balance disorders points to either impaired proprioceptive integration or potential cerebellar involvement. The complete inability of all patients to walk on their heels or lift their toes demonstrates a profound dorsiflexion impairment, which, combined with the ankle joint mobility findings- where restricted mobility was more common than normal mobility – highlights chronic musculoskeletal adaptations that occur, likely reflecting long-term Achilles tendon shortening and secondary calf muscle contractures as well as fundamental weakness of dorsiflexing muscles. These motor deficits likely reflect both peripheral neuromuscular dysfunction and central control abnormalities.

The neurological abnormalities provide further insights into the underlying pathophysiology. The reflex anomalies and frequent tremors could indicate peripheral nerve dysfunction or central nervous system involvement, despite the absence of clonus or Trendelenburg sign. The structural abnormalities are particularly striking, with pes cavus strongly suggesting imbalanced muscle forces on the foot, while the high rates of clinodactyly and brachydactyly and pectus excavatum imply a potential systemic connective tissue or skeletal dysplasia component to the condition. Speech difficulties and visual impairments were reported but not systematically assessed. Whether these reflect PMP22-related neurodevelopment, secondary motor effects, or incidental findings requires prospective evaluation with standardized tools.

Collectively, these findings paint a portrait of a neurodevelopmental disorder with wide-ranging manifestations. The combination of musculoskeletal, neurological, and developmental abnormalities suggests the possibility of an underlying genetic syndrome affecting multiple systems, rather than a simple isolated gait disorder.

Elucidating the genetic basis of idiopathic toe walking enables: (1) reclassification of idiopathic origin of toe walking, (2) more accurate differential diagnosis, (3) development of targeted therapeutic strategies, ultimately improving long-term outcomes and quality of life of the affected individuals.

Future directions

1. Larger, diverse cohorts for better generalizability.
2. Genetic studies: Trio sequencing, functional variant analysis, and comprehensive testing (NGS/MLPA).
3. Epigenetic/environmental influences.
4. Longitudinal tracking of progression and treatment.
5. Multidisciplinary collaboration (neurology, genetics, and orthopedics) for improved diagnosis and management.

Limitations

While the study provides valuable insights, several limitations should be acknowledged:

1. Small cohort size limits generalizability.
2. The absence of trio sequencing prevented definitive analysis of inheritance patterns and parent-of-origin effects.
3. The absence of MLPA testing for PMP22 copy number variations (CNVs) limits our ability to conclude correlations.
4. Nerve conduction studies were performed in only a subset of patients, leaving peripheral nerve involvement incompletely characterized.

Conclusion

This study demonstrates that toe walking frequently represents an early manifestation of PMP22-related neuropathies rather than a benign developmental condition. The high prevalence of pathogenic PMP22 variants, characteristic neuromuscular findings (pes cavus, contractures, dysarthria), and significant familial recurrence supports reclassifying idiopathic toe walking as a genetically mediated disorder. These findings advocate for: 1) routine genetic testing in persistent cases enabling proper management, 2) multidisciplinary evaluation by neurology, orthopedics, and genetics teams, and 3) longitudinal studies to determine progression to classic neuropathy phenotypes. Early recognition of this association enables timely interventions and genetic counseling, transforming toe walking from a diagnostic enigma into a clinically actionable marker of hereditary neuropathies.

Authors' Contributions

David Pomarino: Conceptualized the study, designed the methodology, and performed primary data acquisition and analysis. Drafted the initial manuscript and coordinated revisions.

Kevin M. Rostásy: Provided critical intellectual input on neurological interpretations, validated clinical correlations, and revised the manuscript for scientific rigor.

Bastian Fregien: Contributed to orthopedic phenotyping, reviewed genetic-clinical associations, and approved the final version for publication.

All authors reviewed and approved the final manuscript, ensuring accountability for their respective contributions.

Ethical statement

This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. All procedures were performed in compliance with relevant laws and institutional guidelines and were approved by the ethical board of the

Deutschen Verbandes für Physiotherapie an der Physio-Akademie in Wremen, Germany (project number 2025–02).

Prior to participation, written informed consent was obtained from all subjects. The consent process included explanations of the study's purpose, procedures, and any potential implications of the results. All data collected were formally anonymized to protect participant confidentiality.

This manuscript was prepared in accordance with the International Committee of Medical Journal Editors (ICMJE) recommendations.

Study Registration: The study is registered in the German Clinical Trials Register at https://www.drks.de/DRKS00031141. Number: DRKS00031141

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Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI Deepseek was used in the writing phase of this manuscript exclusively for linguistic polishing and enhancing clarity. All scientific reasoning, data analysis, and intellectual substance remain the sole contribution of the authors. The AI was not employed in the research process itself.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gmg.2025.100082.

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Glossary

3'UTR (3′ Untranslated Region): A section of messenger RNA (mRNA) located immediately after the stop codon that is transcribed but not translated into protein. This region plays a crucial role in post-transcriptional gene regulation by influencing mRNA stability, translation, and localization, and it contains regulatory elements that bind to proteins and microRNAs (miRNAs).

ACMG Guidelines (American College of Medical Genetics and Genomics): Evidence-based standards and guidelines from the American College of Medical Genetics and Genomics that provide a framework for the practice of medical genetics and genomics. These documents cover a range of topics, including the interpretation of genetic variants, technical standards for clinical genetic labs, and clinical practice recommendations for specific conditions. They are developed by expert working groups and are used to standardize and improve the quality of genetic testing and clinical care.

Autosomal Dominant: A pattern of inheritance where only one copy of a mutated gene (on a non-sex chromosome) is sufficient to cause the disorder. An affected individual has a 50 % chance of passing the mutation to their offspring.

Autosomal Recessive: A pattern of inheritance where two copies of a mutated gene (one from each parent) are required to cause the disorder. Parents are typically carriers and are not affected.

Charcot-Marie-Tooth Disease (CMT): A group of inherited disorders that damage the peripheral nerves, leading to muscle weakness and atrophy, sensory loss, and foot deformities like pes cavus. CMT1A is commonly caused by a duplication of the PMP22 gene.

Clinodactyly: A congenital condition characterized by the curvature of a finger or toe, most commonly the little finger, which bends towards the next one.

Copy Number Variation (CNV): A type of structural genetic variation where a segment of DNA, ranging from about one kilobase to several megabases, is duplicated or deleted. PMP22 duplications and deletions are classic CNVs responsible for CMT1A and HNPP, respectively.

Dorsiflexion: the bending of the foot or hand upward toward the shin or forearm, decreasing the angle between the foot/hand and the leg/forearm.

Dysarthria: is a neurological motor speech disorder that results in difficulty speaking clearly, often described as slurred speech, due to weakness or poor coordination of the muscles used in speech production.

Equinus Gait: A walking pattern characterized by limited upward bending of the ankle (dorsiflexion), causing a person to compensate by walking with a limp or on their toes. This limitation can result from a tight calf muscle, an underlying neuromuscular condition, or long-term use of certain footwear. The compensation can lead to a range of problems, such as foot pain, arch collapse, and strain on other joints in the legs and back.

Goniometry: The measuring of the range of motion (RoM) at body joints using a goniometer, an instrument that looks like a protractor. It provides clinicians with objective, data-driven assessments of a joint's movement and is crucial for creating, monitoring, and evaluating the effectiveness of treatment plans in physical therapy and rehabilitation settings.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP): A peripheral neuropathy often caused by a deletion of one copy of the PMP22 gene. It makes nerves more susceptible to injury from compression or stretch, leading to recurrent, temporary numbness and weakness.

Heterozygous: Having two different alleles (versions) of a particular gene, one inherited from each parent.

Homozygous: Having two identical alleles of a particular gene.

Idiopathic Toe Walking (ITW): A diagnosis of exclusion for persistent toe walking in a child who has a normal neurological examination and no identifiable underlying orthopedic or neurological cause.

MLPA (Multiplex Ligation-dependent Probe Amplification): A molecular biology technique used to detect copy number variations (deletions and duplications) in DNA, often at the exon level.

Next-Generation Sequencing (NGS): A high-throughput technology used to determine the sequence of DNA or RNA. In this study, a targeted 49-gene NGS panel was used to simultaneously analyze multiple genes associated with hereditary neuropathies and myopathies.

Pes Cavus: A foot deformity characterized by an abnormally high arch that does not flatten with weight bearing.

Plantar flexion: The movement of the foot and toes downward, away from the leg, which allows you to point your toes or stand on your tiptoes.

PMP22 (Peripheral Myelin Protein 22): A gene that provides instructions for making a protein essential for the development and maintenance of the myelin sheath, the protective covering that surrounds nerve fibers. Mutations in this gene are a leading cause of inherited peripheral neuropathies.

Variant of Uncertain Significance (VUS): A genetic alteration whose association with disease risk is currently unknown. It is a classification used when there is insufficient evidence to label a variant as pathogenic or benign.