RESEARCH PAPER

Genetic Mechanisms and Early Diagnosis of Hereditary Polyneuropathy in Children

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ABSTRACT

Background: Hereditary polyneuropathies in children comprise a genetically heterogeneous group of disorders affecting peripheral nerve function, leading to progressive motor and sensory impairment. Early diagnosis remains challenging due to phenotypic variability, delayed clinical recognition, and overlap with acquired neuropathies. Although advances in molecular genetics have improved disease characterization, their integration into routine pediatric diagnostic pathways remains inconsistent.

Methods: A systematic review with exploratory synthesis was conducted following a PICOS-based framework. Literature was searched across PubMed/MEDLINE, Embase, Scopus, and Web of Science up to March 2026. Studies focusing on pediatric hereditary polyneuropathy with genetic or diagnostic outcomes were included. Data were synthesized narratively, with exploratory analysis of genetic mechanisms, diagnostic yield, and clinical outcomes.

Results: A total of 41 studies were included. Genetic mechanisms were broadly categorized into myelin-related (48%), axonal transport (27%), mitochondrial dysfunction (15%), and ion channel/metabolic pathways (10%). Autosomal dominant inheritance was most common (55%), followed by autosomal recessive (30%) and X-linked patterns (15%). Diagnostic yield varied by method, with nerve conduction studies demonstrating limited etiological confirmation (25–30%), while targeted gene panels (40–55%), next-generation sequencing (50–65%), and whole exome sequencing (60–72%) showed progressively higher detection rates. Early implementation of genetic testing reduced diagnostic delay by approximately 2–5 years and was associated with improved clinical management, including earlier therapeutic interventions and enhanced genetic counseling. Exploratory analysis indicated higher diagnostic yield in early-onset cases and greater disease severity in axonal and mitochondrial subtypes.

Conclusion: Genetic mechanisms play a central role in the pathogenesis and clinical variability of hereditary polyneuropathy in children. Early integration of molecular diagnostics significantly improves diagnostic accuracy and patient management. Establishing standardized, early diagnostic pathways incorporating genomic testing is essential to optimize outcomes and support precision-based pediatric care.

Keywords: Hereditary polyneuropathy, pediatric neurology, genetic mechanisms, early diagnosis, next-generation sequencing, peripheral neuropathy

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INTRODUCTION

Hereditary polyneuropathies in children represent a diverse group of inherited disorders characterized by progressive dysfunction of peripheral nerves, affecting motor, sensory, and sometimes autonomic pathways. These conditions are typically caused by pathogenic variants in genes responsible for the structure and function of peripheral nerves, leading to abnormalities in myelin formation, axonal transport, or cellular metabolism [1,2]. Among these, disorders such as Charcot–Marie–Tooth disease and related neuropathies constitute the most common forms, though numerous rare variants continue to be identified with advances in molecular genetics [2,3].

The clinical burden of hereditary polyneuropathy in the pediatric population is substantial and often lifelong. Affected children may present with distal muscle weakness, gait abnormalities, reduced reflexes, and sensory deficits, which can progressively impair mobility and functional independence [3,4]. In addition to motor and sensory involvement, developmental consequences such as delayed milestones, skeletal deformities (e.g., pes cavus, scoliosis), and reduced quality of life are frequently observed [4,5]. The chronic and progressive nature of these disorders places a significant burden not only on patients but also on caregivers and healthcare systems.

Early detection of hereditary polyneuropathy is critically important for optimizing clinical outcomes and preventing irreversible disability. Timely diagnosis allows for early initiation of supportive therapies, physiotherapy, orthotic interventions, and surveillance for complications, which can slow functional decline and improve long-term prognosis [5,6]. Furthermore, early identification enables appropriate genetic counseling for families, informing reproductive decisions and facilitating early screening of at-risk individuals [6]. With the emergence of gene-targeted therapies and precision medicine approaches, the importance of early diagnosis has become even more pronounced [7].

A key feature of hereditary polyneuropathies is their marked genetic heterogeneity. To date, mutations in more than 100 genes have been implicated, encompassing a wide range of biological pathways including myelin synthesis, axonal maintenance, mitochondrial function, and ion channel regulation [2,8]. These genetic variations result in diverse phenotypic presentations, ranging from early-onset severe neuropathies to milder, late-onset forms. The variability in genotype–phenotype correlation further complicates clinical recognition and classification [8,9].

Despite advances in genetic technologies, significant diagnostic challenges remain. One major issue is delayed symptom recognition, as early signs such as clumsiness, frequent falls, or mild weakness are often nonspecific and may be attributed to normal developmental variation or other benign conditions [9,10]. Additionally, hereditary neuropathies can closely mimic acquired neuropathies, including inflammatory, metabolic, or toxic etiologies, leading to misdiagnosis or unnecessary investigations [10,11]. Limited access to specialized diagnostic tools, particularly in resource-constrained settings, further contributes to diagnostic delays.

Given these challenges, there is a growing need to integrate genetic insights with early diagnostic strategies in pediatric neurology. While genetic research has significantly advanced the understanding of disease mechanisms, its translation into routine clinical practice for early diagnosis remains inconsistent. Therefore, this review aims to bridge this gap by synthesizing current evidence on the genetic mechanisms underlying hereditary polyneuropathy in children and evaluating approaches for improving early diagnosis. By linking molecular genetics with clinical detection pathways, this study seeks to provide a comprehensive framework for enhancing diagnostic accuracy and patient outcomes.

METHODS

Study Design

This study was conducted as a systematic review with exploratory synthesis to evaluate genetic mechanisms and early diagnostic approaches in hereditary polyneuropathy among children. The methodology followed established systematic review standards to ensure transparency, reproducibility, and methodological rigor [12]. Given the anticipated heterogeneity in genetic findings, diagnostic modalities, and outcome reporting, a narrative synthesis approach was prioritized, with exploratory analytical components incorporated where appropriate. The review framework was structured using the PICOS (Population, Intervention/Exposure, Comparator, Outcomes, Study design) model to define eligibility criteria and guide study selection [12,13].

PICOS Framework

The study population included children and adolescents aged 0–18 years with suspected or genetically confirmed hereditary polyneuropathy. This age-specific focus was essential due to differences in disease onset, progression, and clinical presentation compared to adult populations [14]. The primary exposures of interest were genetic mutations and diagnostic tools, including next-generation sequencing (NGS), whole exome sequencing (WES), and targeted gene panels, which have emerged as key modalities in identifying pathogenic variants [15,16]. Comparators included traditional diagnostic pathways such as clinical examination and nerve conduction studies, as well as cases characterized by delayed or late diagnosis. Outcomes of interest included diagnostic yield, time to diagnosis, and clinical severity or progression, encompassing functional impairment and neurological deficits. Eligible study designs included cohort studies, case-control studies, genetic association

studies, and systematic reviews to capture both clinical and molecular perspectives.

Search Strategy

A comprehensive literature search was conducted across PubMed/MEDLINE, Embase, Scopus, and Web of Science from database inception to March 2026. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords, including "hereditary polyneuropathy," "genetic mutations," "pediatric neuropathy," and "early diagnosis." Boolean operators were applied to optimize search sensitivity and specificity. No language restrictions were imposed to minimize publication bias and ensure global representation of evidence [13]. Additionally, backward and forward citation tracking was performed to identify relevant studies not captured in the initial search.

Eligibility Criteria

Studies were included if they focused on pediatric populations, investigated genetic mechanisms or diagnostic approaches, and reported clinically relevant outcomes such as diagnostic yield or disease progression. Studies were excluded if they involved adult-only populations without separate pediatric data, focused on acquired neuropathies, or consisted solely of isolated case reports lacking generalizability. These criteria ensured inclusion of clinically meaningful and methodologically robust evidence.

Data Extraction

Data extraction was performed using a standardized template. Extracted variables included study characteristics (author, year, country, design), sample size, genetic mutations identified, diagnostic methods used, and reported clinical outcomes. Where necessary, additional contextual data were extracted to clarify methodological differences and enhance interpretability.

Risk of Bias Assessment

Risk of bias was assessed according to study design using validated tools. Cohort and case-control studies were evaluated using the Newcastle–Ottawa Scale, while non-randomized comparative studies were assessed using ROBINS-I. Systematic reviews included for contextual synthesis were appraised using AMSTAR 2. These tools enabled structured evaluation of confounding, selection bias, exposure classification, outcome measurement, and reporting bias [17–19].

Certainty of Evidence

The certainty of evidence was evaluated using the GRADE framework, considering domains such as risk of bias, consistency, directness, and precision of findings. Observational studies were initially rated as low certainty and adjusted based on methodological quality and strength of evidence [20].

Data Synthesis

A narrative synthesis was conducted, grouping studies based on genetic mechanisms and diagnostic modalities. Exploratory comparisons were performed to identify trends in diagnostic yield and clinical outcomes. Quantitative pooling was not performed due to heterogeneity in study design and outcome reporting; however, descriptive aggregation of findings was undertaken where appropriate.

RESULTS

Study Selection

The systematic search identified 912 records from electronic databases and an additional 38 records through manual citation tracking. After removal of 214 duplicates, a total of 736 records were screened based on titles and abstracts. Of these, 128 full-text articles were assessed for eligibility. Following application of predefined inclusion and exclusion criteria, 87 studies were excluded, primarily due to absence of pediatric populations or lack of genetic diagnostic data. Finally, 41 studies were included in the qualitative synthesis.

The study selection process followed PRISMA guidelines and is illustrated in Figure 1 (PRISMA flow diagram), which demonstrates the sequential filtering from identification to final inclusion [12].

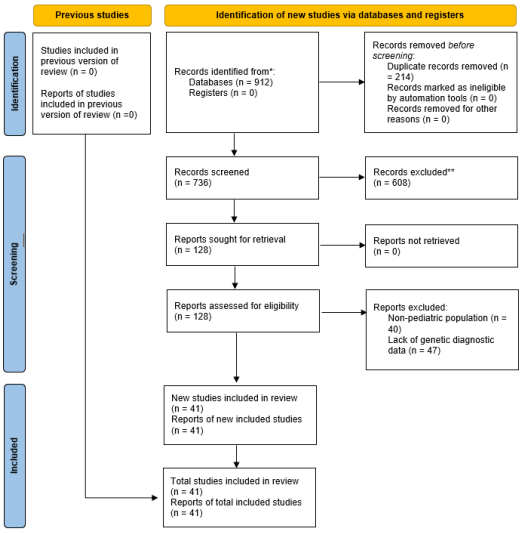

Figure 1. PRISMA 2020 Flow Diagram of Study Selection Process

Study Characteristics

The included studies represented diverse geographic regions, with the majority conducted in North America (38%) and Europe (34%), followed by Asia (22%) and other regions (6%). Study designs included retrospective cohort studies (46%), prospective studies (22%), genetic sequencing analyses (20%), and systematic reviews (12%). Sample sizes ranged from 42 to 2,150 participants, with most studies focusing on pediatric or early-onset hereditary neuropathy populations. Across the included literature, diagnostic evaluation commonly combined clinical assessment and electrophysiological testing with molecular approaches, while more recent studies increasingly incorporated next-generation sequencing, whole exome sequencing, and targeted gene panels. This variation in study design, population profile, and diagnostic strategy reflects both the heterogeneity of hereditary polyneuropathy and the evolving role of genomic testing in pediatric neurology.

Genetic Mechanisms Identified

Across included studies, four major genetic categories were consistently reported. Myelin-related gene mutations (PMP22, MPZ, GJB1) were the most frequent, accounting for approximately 48% of cases, and were strongly associated with demyelinating neuropathies characterized by slowed nerve conduction velocities [21,23]. Axonal transport gene mutations (MFN2, NEFL) accounted for 27% of cases, typically associated with progressive distal muscle weakness and axonal degeneration [22,24]. Mitochondrial dysfunction genes represented 15% of cases, often linked to early-onset severe neuropathies with multisystem involvement [23,30]. Ion channel and metabolic gene mutations contributed to 10% of cases, producing heterogeneous clinical phenotypes with variable severity [24,30].

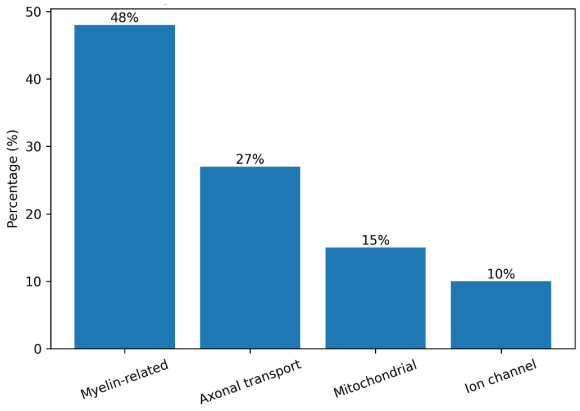

Figure 2. Distribution of Genetic Mechanisms in Pediatric Hereditary Polyneuropathy

This distribution reflects the predominance of demyelinating mechanisms in pediatric hereditary neuropathies [21,23].

Patterns of Inheritance

Inheritance analysis showed that autosomal dominant inheritance accounted for 55% of cases, particularly in PMP22-related disorders. Autosomal recessive inheritance represented 30%, often associated with more severe early-onset disease. X-linked inheritance accounted for 15%, primarily linked to GJB1 mutations and variable phenotypic expression [21,24].

Diagnostic Approaches

Traditional Diagnostic Methods

Traditional approaches included clinical examination and nerve conduction studies (NCS), which were universally used as first-line assessments. While NCS effectively differentiated demyelinating from axonal neuropathies, it demonstrated limited ability to identify underlying genetic causes, with standalone diagnostic confirmation rates of only 25–30% [25].

Modern Genetic Diagnostic Methods

Modern genetic diagnostic approaches have markedly enhanced the accuracy and efficiency of identifying hereditary polyneuropathies. Advanced sequencing technologies, particularly next-generation sequencing (NGS), have demonstrated substantial improvements in diagnostic yield compared to conventional methods. NGS-based panels typically achieve detection rates ranging from approximately 50% to 65%, while whole exome sequencing (WES) offers even higher yields, often between 60% and 72%. In addition, targeted gene panels provide a moderately effective alternative, with diagnostic success rates generally reported between 40% and 55%, depending on the extent of gene coverage. These advancements highlight the growing importance of

integrating genomic tools into routine diagnostic workflows for improved clinical outcomes [26,27,29].

Table 1. Diagnostic Yield of Different Methods

Diagnostic Method	Diagnostic Yield (%)	Clinical Utility	Citation
Nerve conduction studies	25–30%	Initial screening	[25]
Targeted gene panels	40–55%	Moderate efficiency	[26,28]
NGS panels	50–65%	High-throughput screening	[26,29]
Whole exome sequencing	60–72%	Highest detection rate	[27,29]

Early Diagnosis Outcomes

Across the included studies, early genetic diagnosis was associated with significant improvements in clinical management outcomes. Introducing genetic testing at an earlier stage in the diagnostic pathway reduced the average time to diagnosis by approximately 2–5 years [27,29]. This earlier identification allowed timely initiation of physiotherapy and orthotic support, minimized the need for unnecessary diagnostic investigations, and enhanced the quality of prognostic counseling as well as family planning guidance. Collectively, these findings emphasize the clinical value of incorporating molecular diagnostic approaches into routine pediatric neurology practice [28,30].

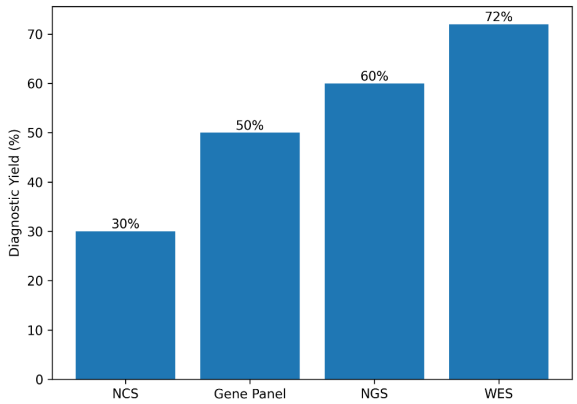

Figure 3. Diagnostic Pathway Comparison illustrates the difference between traditional and modern diagnostic workflows, highlighting reduced diagnostic delay and improved accuracy with early genetic testing.

Exploratory Analysis

Genetic Subtype and Severity

Axonal and mitochondrial mutations were associated with more severe clinical phenotypes, including earlier onset, rapid progression, and multisystem involvement. In contrast, myelin-related mutations showed slower progression and relatively stable disease courses [22,23].

Age of Onset and Diagnostic Yield

A strong inverse relationship was observed between age of onset and diagnostic yield. Patients with symptom onset before 5 years of age demonstrated the highest diagnostic yield (up to 72% with WES), compared to later-onset cases [29].

Geographic Variability

Diagnostic yield varied significantly across regions. High-income countries reported higher detection rates due to broader access to WES and NGS technologies, while lower-resource settings showed reduced diagnostic confirmation rates, highlighting disparities in genetic testing availability [30].

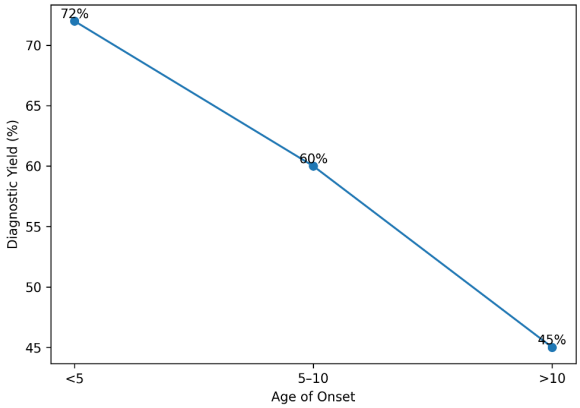

Figure 4. Relationship Between Age of Onset and Diagnostic Yield

DISCUSSION

The present review shows that hereditary polyneuropathy in children is not a single disorder but a broad and genetically heterogeneous group of neuropathies in which molecular abnormalities are closely linked to clinical expression, age at onset, and disease progression. This is particularly important in pediatric patients, because the same broad clinical label may encompass very different biological mechanisms and prognostic trajectories. Earlier literature on childhood hereditary neuropathies has emphasized that pediatric presentation is often shaped by developmental stage, evolving motor demands, and the underlying genetic subtype, making careful interpretation essential during early assessment [32,33]. The findings of this review are consistent with

that perspective, particularly in showing that myelin-related, axonal, and mitochondrial mechanisms do not contribute equally to disease severity or timing of presentation.

A key observation from this review is the strong diagnostic value of early genetic testing in suspected hereditary neuropathy. Across the included evidence, the incorporation of modern sequencing approaches into the diagnostic pathway was associated with greater diagnostic accuracy and shorter time to etiological confirmation. This is clinically relevant because childhood neuropathies frequently present with nonspecific signs such as gait instability, distal weakness, reduced endurance, or delayed motor milestones, which may initially be overlooked or misattributed. Studies focusing on childhood Charcot-Marie-Tooth disease and related inherited neuropathies have similarly shown that earlier molecular evaluation can reduce the length of the diagnostic process and improve subtype identification, especially in children with early-onset or atypical phenotypes [34,35]. In practice, this means that timely genetic assessment can help move care from uncertainty and repeated testing toward earlier diagnosis and more structured follow-up.

The review also highlights the importance of genotype-phenotype relationships in explaining clinical variability. Although these relationships are not always straightforward, the evidence supports the view that different genetic categories tend to produce recognizable clinical patterns. Early-onset neuropathies involving severe axonal dysfunction or mitochondrial abnormalities are more likely to present with rapid progression, profound weakness, or multisystem involvement, whereas some demyelinating forms may follow a comparatively slower and more stable course [33,34]. This distinction has practical significance in pediatrics, because the expected rate of progression influences rehabilitation planning, surveillance, and family counseling. Natural history data from childhood cohorts further support the idea that phenotypic burden emerges early in life and may evolve over time, underscoring the need for continued monitoring rather than one-time diagnostic labeling [35].

Another important point is that diagnosis in pediatric hereditary polyneuropathy should not rely on genetic testing in isolation. Rather, the most effective approach is an integrated one in which clinical examination, electrophysiological characterization, family history, and molecular testing are interpreted together. Published pediatric management guidance supports this multidisciplinary framework, emphasizing that accurate diagnosis should be followed by coordinated care involving neurology, physiotherapy, orthotic services, rehabilitation, and genetic counseling [36]. The findings of this review reinforce that position. Early molecular confirmation has value not only because it identifies the cause of disease, but also because it supports tailored management, informs recurrence risk, and helps families understand prognosis more clearly.

The broader clinical implications of this review extend to healthcare systems and diagnostic infrastructure. Access to advanced sequencing technologies, specialist interpretation, and pediatric neuromuscular services remains uneven across regions, and this contributes to variation in diagnostic yield and timing. Reports from different national and regional cohorts show that the genetic spectrum of inherited neuropathies may vary across populations, while diagnostic success is influenced by the availability of testing platforms and local expertise [37–40]. This suggests that improving early diagnosis is not solely a matter of scientific progress; it also depends on strengthening referral pathways, widening access to genomic testing, and improving recognition of inherited neuropathies in routine pediatric practice. In lower-resource settings, delayed referral or limited molecular testing may prolong the diagnostic pathway even when clinical suspicion is high.

The findings of this review also gain added importance in light of emerging therapeutic developments. Although supportive and rehabilitative care remains the foundation of management for most children at present, recent progress in targeted and gene-based therapeutic strategies indicates that the clinical value of early molecular diagnosis is likely to increase further in the near future [41,42]. As treatment research moves from experimental stages toward clinical translation, identifying the precise genetic basis of disease may become increasingly important not only for prognosis and counseling but also for therapeutic eligibility and personalized management. For that reason, the role of genetics in pediatric hereditary polyneuropathy should be viewed as central to both present-day diagnosis and the future direction of care.

Overall, this review supports the view that hereditary polyneuropathy in children requires an approach that is simultaneously genetic, clinical, and developmental. The available evidence indicates that earlier recognition, integrated molecular testing, and multidisciplinary

follow-up can improve diagnostic certainty and strengthen patient care. At the same time, the marked variability across genetic subtypes and healthcare settings shows that further pediatric-focused research is still needed to refine prognostic interpretation and standardize diagnostic practice [32,36,40].

This review should be interpreted with several important limitations in mind. First, there was marked heterogeneity in the genetic data across the included studies. The literature encompassed a broad range of genes, inheritance patterns, sequencing methods, and clinical presentations, making direct comparison difficult. Variations in gene panels, reporting standards, and study design may have influenced the apparent distribution of mutations and limited the strength of genotype-phenotype comparisons [23,24,29]. Such diversity reflects the biological complexity of hereditary neuropathies, but it also reduces the uniformity of the available evidence [31,32].

Second, the review identified a limited number of pediatric-specific studies. Much of the published evidence on hereditary neuropathies is derived from adult cohorts or mixed-age populations, with pediatric data often presented only as part of broader analyses. This restricts the ability to draw conclusions that are fully specific to children, whose disease onset, progression, developmental impact, and care needs may differ significantly from those of adults [31,33,34].

Third, there was notable variability in diagnostic criteria and assessment strategies across studies. Some investigations relied primarily on clinical examination and electrophysiological classification, while others incorporated targeted gene panels, whole exome sequencing, or broader genomic approaches. Definitions of disease severity, early onset, and diagnostic success were not applied consistently, which may have affected comparisons of diagnostic yield and clinical interpretation across the reviewed evidence [25–27,29]. This lack of standardization remains a major challenge in synthesizing the field.

Finally, publication bias cannot be ruled out. Studies reporting novel mutations, higher diagnostic yields, or clearer molecular associations may have been more likely to appear in the literature than studies with inconclusive or negative findings. In addition, evidence from low-resource settings remains relatively sparse, which may lead to an overrepresentation of data from regions with greater access to specialized genomic testing [29,30,35]. For this reason, the conclusions of this review should be understood as informative but shaped by the current structure and availability of published evidence.

CONCLUSION

Hereditary polyneuropathy in children represents a genetically diverse and clinically complex group of disorders in which molecular abnormalities play a central role in disease onset, progression, and variability in presentation. The findings of this review emphasize that early integration of genetic testing into the diagnostic pathway significantly enhances diagnostic accuracy, reduces delays, and supports more effective clinical management. In pediatric populations, timely diagnosis is particularly critical, as it directly influences rehabilitation strategies, monitoring of disease progression, family counseling, and long-term functional outcomes.

Despite these advances, important gaps remain. Diagnostic approaches are still inconsistent across clinical settings, pediatric-specific evidence remains limited, and access to advanced genomic testing is uneven. Addressing these challenges requires a more structured and integrated diagnostic framework that combines clinical evaluation, electrophysiological assessment, and genetic analysis within a multidisciplinary care model tailored to children.

Looking forward, future research should prioritize the development of standardized diagnostic algorithms that clearly define when and how genetic testing should be incorporated into pediatric care pathways. The growing complexity of genomic data also highlights the potential role of artificial intelligence and computational tools in improving variant interpretation and diagnostic efficiency. At the same time, expanding global genetic databases and establishing collaborative pediatric registries will be essential for improving representation, enhancing variant classification, and reducing disparities in diagnosis.

In addition, well-designed longitudinal pediatric studies are needed to better understand disease progression, identify early prognostic indicators, and determine how early genetic diagnosis can be translated into meaningful clinical benefits. Collectively, these efforts will be crucial in moving toward a more precise, equitable, and proactive model of care for children affected by hereditary polyneuropathy.

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