**ORIGINAL ARTICLE**

# Genotype Phenotype Variability and Genetic Spectrum of Inherited Neuropathies in Children

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## ABSTRACT

**Objective:** To characterize the clinical, electrophysiological, and genetic spectrum of inherited neuropathies (INs) in a pediatric cohort, with an emphasis on genotype-phenotype correlations and the role of whole-exome sequencing (WES) in genetic diagnosis.

**Study Design:** Cross-sectional observational study.

**Place and Duration of Study:** Department of Pediatric Neurology at the Children's Hospital and University of Child Health Sciences, Lahore, from January 2017 to January 2023.

**Materials and Methods:** Twenty-eight pediatric patients (≤18 years) with genetically confirmed inherited neuropathies were enrolled. Clinical, electrophysiological, and genetic assessments were conducted. Nerve conduction studies classified the neuropathies into axonal, demyelinating, or mixed subtypes. Whole-exome sequencing (WES) was performed in collaboration with the UCL Institute of Neurology, London. Statistical analysis was performed using SPSS version 26, and a p-value of 0.05 was considered significant.

**Results:** The cohort had a median symptom onset at 4 years (IQR: 2–6 years), with 96.4% consanguinity. Muscle atrophy (35.7%) and pes cavus (21.4%) were common. Electrophysiology classified the neuropathies into demyelinating (28.6%), axonal (14.3%), and mixed (46.4%) subtypes. WES yielded a 68.29% diagnostic rate, with GAN and PDXK mutations (14.3% each) being the most common.

**Conclusion:** This study highlights the genetic heterogeneity of inherited neuropathies and underscores the importance of WES for genetic diagnosis and targeted management, particularly in populations with high consanguinity.

**Key Words:** *Inherited neuropathies, Genetic testing, Whole-exome sequencing, Genotype-phenotype correlation, Consanguinity, Pediatric neuropathy*.

## INTRODUCTION

Inherited neuropathies (INs) represent a diverse group of genetic disorders affecting the peripheral nervous system, characterized by a spectrum of motor, sensory, and systemic manifestations.[1] These conditions, including Charcot-Marie-Tooth disease and hereditary sensory and motor

neuropathies, often present during childhood or adolescence and can lead to significant morbidity.[2] Understanding their genetic and phenotypic heterogeneity is essential for advancing diagnostic, therapeutic, and prognostic strategies.[3]

Advances in genomic technologies, particularly whole-exome sequencing (WES), have revolutionized the diagnosis of inherited neuropathies, enabling the identification of pathogenic variants in numerous associated genes.[4] Despite this progress, a substantial proportion of cases remains genetically undiagnosed, highlighting the complexity of these conditions and the need for comprehensive genetic and functional analyses.[5] Recent studies underscore the critical role of early genetic identification, which can guide targeted interventions and genetic counseling especially in regions with high consanguinity rates, such as South Asia and the Middle East.[6]

The phenotypic diversity of INs is equally complex, with presentations ranging from early-onset motor delays to progressive sensory deficits and systemic involvement, such as skeletal abnormalities, scoliosis, and visual and auditory impairments.[7] For instance, pes cavus and scoliosis are frequently reported, reflecting the systemic nature of these disorders.[8] Genotype-phenotype correlations have provided valuable insights, with specific mutations linked to distinct clinical manifestations.[9] Mutations in *IGHMBP2*, for example, are associated with severe motor deficits, while *OCRL* mutations are implicated in visual and skeletal abnormalities.[10] Electrophysiological studies remain a cornerstone in the diagnostic evaluation of INs, offering insights into the underlying pathology whether axonal, demyelinating, or intermediate.[11] These studies, combined with neuroimaging, have revealed central nervous system involvement in many cases, as evidenced by findings such as cerebellar atrophy and T2-weighted hyperintensities.[12] These data further emphasize the multisystemic impact of inherited neuropathies and the necessity of a multidisciplinary approach to their management.

The high prevalence of consanguinity in certain populations is a significant factor in the inheritance patterns of these neuropathies.[6] Consanguineous marriages increase the likelihood of autosomal recessive conditions, as demonstrated by the 96.4% consanguinity rate in a recent cohort study.[13] This socio-cultural context underscores the importance of incorporating genetic counseling into clinical practice in these regions.[14]

This study builds upon the existing literature by exploring the genetic underpinnings and phenotypic presentations of INs in a pediatric cohort, aiming to identify novel correlations that can inform clinical management. It also highlights the diagnostic utility and limitations of current methodologies, emphasizing the need for advanced sequencing technologies and functional studies to address the diagnostic gaps in INs research. By integrating clinical, electrophysiological, and genetic data, this research seeks to provide a comprehensive understanding of the interplay between genotype and phenotype in inherited neuropathies. These findings have implications for improving diagnostic workflows, guiding targeted therapies, and shaping public health strategies to mitigate the burden of these disabling conditions.

## MATERIAL AND METHODS

This cross-sectional study was conducted in the Department of Pediatric Neurology at the Children's Hospital and University of Child Health Sciences, Lahore. Patients with genetically confirmed pathogenic or likely pathogenic variants, along with clinical and/or electrophysiological findings of inherited neuropathies (INs), and aged below 18 years, were recruited from January 2017 to January 2023. Exclusion criteria encompassed acquired neuropathies due to chemical toxicity, metabolic disorders, immune-mediated causes, and neuropathies secondary to nutritional vitamin deficiencies. This study was approved by the Ethical Review Committee of the University of Child Health Sciences, The Children's Hospital, Lahore, under approval reference number (approval No. 753/CH-UCHS, dated 28-12-2023). All research procedures involving human participants were conducted in accordance with the Declaration of Helsinki and institutional guidelines. Informed consent was obtained from

all participants or their legal guardians. The relevant ethical committee proforma has been duly completed and is available upon request. Detailed demographic and clinical information were collected, including age, sex, consanguinity, age of symptom onset, presence of scoliosis, hearing and vision impairments, foot deformities, ambulation status, and use of mobility aids. Neurological assessments included muscle strength evaluation using the Medical Research Council (MRC) scale, along with detailed sensory evaluations. Pedigree analysis was performed for patients with a family history of neuropathies.

**Electrophysiological Testing:** Nerve conduction studies were performed using age-standardized reference values. Measurements included compound muscle action potential (CMAP), sensory nerve action potential (SNAP), and conduction velocity (CV). Patients were categorized as follows:

- **Demyelinating neuropathy:** CV <45 m/s (upper limb motor nerves)
- **Intermediate neuropathy:** CV< 45 m/s and reduced CMAP (upper limb motor nerves)
- **Axonal neuropathy:** CV > 45 m/s and reduced CMAP (upper limb motor nerves)

Electrophysiological testing limitations were noted due to the age and compliance of pediatric patients.

**Genetic Analysis:** Peripheral blood samples were collected for genomic DNA extraction from the proband, their siblings, and parents. About 3–5 ml of sample was collected in an EDTA vial. Genetic analysis was performed by WES (whole exome sequencing) in collaboration with the Department of Neuromuscular Disorders, UCL Institute of Neurology, at UCL, Queen Square, London

**Statistical Analysis:** Data were analyzed using SPSS (version 26.0). Descriptive statistics were used to summarize the demographic, clinical, electrophysiological, and genetic characteristics of the cohort. Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), based on data normality. Categorical variables were expressed as frequencies and percentages. Genotype-phenotype correlations were assessed using the chi-square test for categorical variables and the independent t-test for continuous variables, as appropriate. The diagnostic yield of whole-exome sequencing (WES) was calculated as the proportion of cases with identified pathogenic or likely pathogenic variants. A p-value < 0.05 was considered statistically significant.

## RESULTS

A total of 28 patients were enrolled in the study, comprising 53.6% males and 46.4% females. The median age at the time of enrollment was 10 years (IQR: 8–13 years), with a median age of symptom onset at 4 years (IQR: 2–6 years), as shown in fig 1. Positive consanguinity was observed in 96.4% of patients, while a minority (3.6%) reported no consanguineous background.

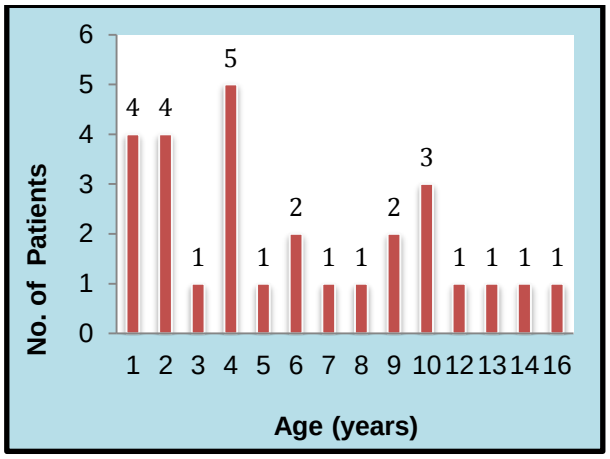


**Fig 1: Age of onset distribution in genetic neuropathy cases**

Developmental delay was documented in 25% (N=7) of patients, with motor milestones predominantly affected. Other clinical features included scoliosis 3.6% (N=1), and muscle atrophy 35.7% (N=10). Among sensory deficits, visual impairment was observed in 10.7% (N=3) and hearing loss in 14.3% (N=4) of cases. The most common skeletal abnormality was pes cavus, reported in 21.4% (N=6) of patients.

The table 1 outlines clinical, electrophysiological, and neuroimaging findings in a cohort of patients, highlighting a variety of manifestations and investigative outcomes. Among the clinical features, a significant majority 89.3% (N=25) had

siblings also affected, suggesting a strong familial component. Seizures were rare, reported in only 7.1% (N=2) of patients. Cerebellar ataxia was present in 17.9% (N=5) and sensory ataxia in 3.6% (N=1). Skeletal abnormalities were common, with pes cavus being the most frequent 21.4% (N=6), followed by combinations such as pes cavus with hammer toes 3.6% (N=1) and other deformities. Vision and speech were predominantly normal in 89.3% (N=25), although isolated cases of retinitis pigmentosa 7.1% (N=2) and hoarseness of voice 7.1% (N=2) were noted. Eye abnormalities included retinitis pigmentosa 7.1% (N=2) and nystagmus (3.6%), while sensory neural hearing loss affected 14.3% (N=4). Other notable findings included rare instances of vocal cord palsy with tracheostomy 7.1% (N=2) and respiratory muscle involvement 7.1% (N=2).

**TABLE 1: Clinical features and neuroimaging findings**

| Variables | Frequency (N) | Percentage (%) |
|---|---|---|
| **Clinical manifestations** | | |
| **Siblings also affected** | | |
| Yes | 25 | 89.3 |
| No | 3 | 10.7 |
| **History of seizures** | | |
| Yes | 2 | 7.1 |
| No | 26 | 92.9 |
| **Ataxia** | | |
| Cerebellar | 5 | 17.9 |
| Sensory | 1 | 3.6 |
| Not present | 22 | 78.6 |
| **Palpable nerves** | 0 | 0 |
| **Skeletal abnormalities** | | |
| Pes cavus | 6 | 21.4 |
| Pes planus | 1 | 3.6 |
| Scoliosis and pes cavus | 1 | 3.6 |
| Pes cavus and hammer toes | 1 | 3.6 |
| Pes cavus, hammer toes and claw hands | 2 | 7.1 |
| Self-amputation of digits | 1 | 3.6 |
| **Foot ulcers** | | |
| Yes | 2 | 7.1 |
| No | 26 | 92.9 |
| **Vision** | | |
| Normal | 25 | 89.3 |
| Affected | 3 | 10.7 |
| **Speech** | | |
| Normal | 25 | 89.3 |
| Hoarseness of voice | 2 | 7.1 |
| Nasal speech | 1 | 3.6 |
| **Eye abnormalities** | | |
| Normal | 23 | 82.1 |
| Retinitis pigmentosa | 2 | 7.1 |
| Cataract and pale optic disc | 1 | 3.6 |
| Optic disc pallor | 1 | 3.6 |
| Nystagmus | 1 | 3.6 |
| **Sensory neural hearing loss** | | |
| Yes | 4 | 14.3 |
| No | 24 | 85.7 |
| **Vocal cord palsy and tracheostomy** | | |
| Yes | 2 | 7.1 |
| No | 26 | 92.9 |
| **Involvement of respiratory muscles** | | |
| Yes | 2 | 7.1 |
| No | 26 | 92.9 |
| **Electrophysiological and neuroimaging findings** | | |
| **EMG-NCS study** | | |
| Axonal | 4 | 14.3 |
| Demyelinating | 8 | 28.6 |
| Mixed | 13 | 46.4 |
| Normal | 2 | 7.14 |
| Not available | 1 | 3.6 |
| **EEG** | | |
| Normal | 1 | 3.6 |
| Not indicated/not done | 27 | 96.4 |
| **Brain imaging (MRI Brain/CT Brain)** | | |
| Normal | 2 | 7.1 |
| Abnormal | 4 | 14.3 |
| Not indicated/not done | 22 | 78.6 |

"Giant axonal neuropathy" and "Genetic vitamin responsive neuropathy" are the most frequently reported diagnoses, each with a count of four. Several subtypes of Charcot-Marie-Tooth disease (types 2S, 4B1, and 4C) are also prevalent (figure 2).

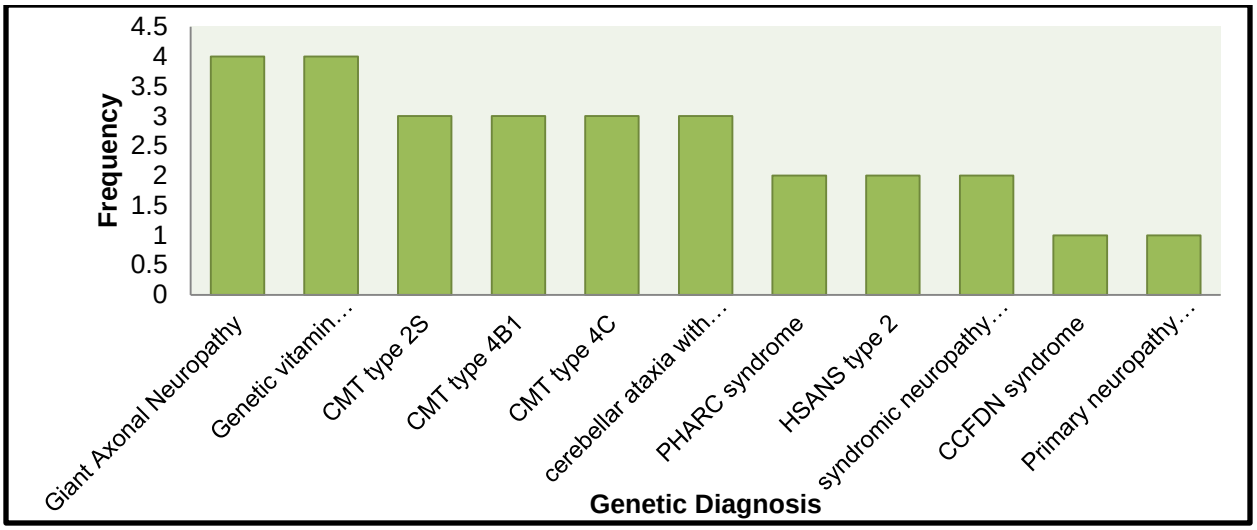


**Fig 2: Distribution of Genetic Neuropathy Diagnoses and Their Frequency**

**Electrophysiological and Neuroimaging Findings:** Electrophysiological testing classified patients into the following categories:

- Demyelinating neuropathy: 8 patients (28.6%)
- Axonal neuropathy: 4 patients (14.3%)
- Mixed neuropathy: 13 patients (46.42%)
- Normal: 2 patients (7.1%)
- Not available: 1(3.6%)

Among patients with demyelinating neuropathy, median motor conduction velocity was markedly reduced (<45m/s). Axonal neuropathy was characterized by reduced compound muscle action potential amplitudes, consistent with the clinical presentation of weakness and sensory loss.Neuroimaging revealed cerebellar atrophy in 7.1% (N=2), cerebral hypoplasia in 3.6% (N=1)and T2-weighted hyperintensitiesin centrum semiovale, periventricular white matter area in 3.6%(N=1). Among two patients with seizures EEG was performed in 1 patient and its was reported normal.

**Genetic Findings:** This study included 28 patients having pathogenic or likely pathogenic variants on genetic testing. Yield of genetic testing was 68.29%. Among these, the most common gene implicated were GAN 14.3% (N=4) PDXK 14.3% (N=4)followed by IGHMBP210.7%(N=3),MTMR210.7%(N=3), SH3TC210.7%(N=3) and SETX 10.7%(N=3) as shown in figure 3.

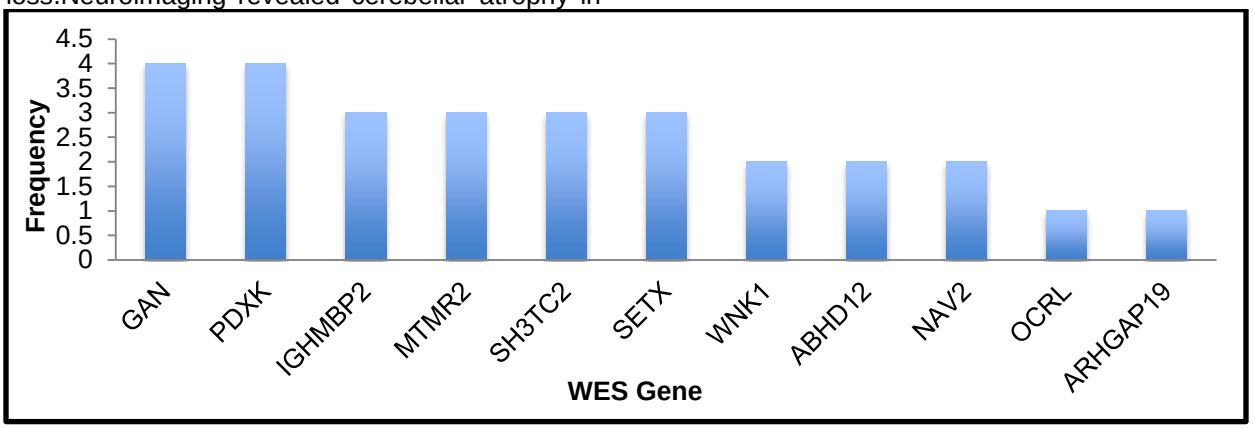


**Fig 3: Frequency Distribution of WES-Identified Genes in Genetic Neuropathy Cases**

Notably, mutations in IGHMBP2 were significantly associated with severe neuropathy, while OCRL mutations were linked to visual impairments. SH3TC2 mutations were predominantly observed in patients with scoliosis and ataxia. Vocal cord palsy and hoarseness of voice observed in MTMR2 mutation. WNK1 mutation was associated with foot ulcers and self-amputation of digits. Hearing loss and retinitis pigmentosa was observed in ABHD12 mutation (table 2).

**TABLE 2: Types of Genetic Neuropathies and their associated WES Findings, Electrophysiology, and Clinical Features**

| | Category | n/N (%) | Gene | EMG/NCS Findings | Key Clinical Features |
|---|---|---|---|---|---|
| I. | **Primary Inherited Neuropathies** | 11/28 (39.3%) | | | |
| | A. CMT | 9/28 (32.1%) | | | |
| | 1. Type 2S | 3/28 (10.7%) | IGHMBP2 | Demyelinating & Axonal | Skeletal abnormalities, muscle atrophy, neuropathic gait |
| | 2. Type 4B1 | 3/28 (10.7%) | MTMR2 | Demyelinating & Axonal | Vocal cord palsy, respiratory involvement |
| | 3. Type 4C | 3/28 (10.7%) | SH3TC2 | Demyelinating & Axonal | Scoliosis, hearing loss |
| | B. HSAN | 2/28 (7.1%) | WNK1 | Normal | Foot ulcers, Digits amputation |
| II. | **Multisystem Neuropathies** | 13/28 (46.4%) | | | |
| | A. Giant Axonal Neuropathy | 4/28 (14.3%) | GAN | Axonal | Neuropathic gait, nasal speech |
| | B. Cerebellar Ataxia | 2/28 (7.1%) | SETX | Demyelinating | Cerebellar ataxia, nystagmus |
| | C. CCFDN Syndrome | 1/28 (3.6%) | OCRL | Demyelinating | Cataracts, optic disc pallor |
| | D. PHARC Syndrome | 2/28 (7.1%) | ABHD12 | Demyelinating | Retinitis pigmentosa, hearing loss |
| | E. Other | 4/28 (10.7%) | ARHGAP19, NAV2 | Demyelinating & Axonal | Variable features, absent deep tendon reflexes |
| III. | **Vitamin-Responsive** | 4/28 (14.3%) | PDXK | Demyelinating & Axonal | Pes cavus, hammer toes, neuropathic gait |

**Genotype-Phenotype Correlations:** Patients were grouped based on the age of onset:

- **Early-onset (≤5 years):** Most commonly associated with GAN, IGHMBP2 and SH3TC2 mutations.
- **Late-onset (6–18 years):** Frequently linked to mutations in PDXK and SETX.

Among patients with cerebellar ataxia, a higher prevalence of mutations in ABHD12 and **SETX** was observed (table 2).

## DISCUSSION

This study provides valuable insights into the genetic and clinical landscape of inherited neuropathies, emphasizing the significance of genetic testing in identifying disease subtypes and their phenotypic correlations. The cohort comprised 28 patients, predominantly presenting with early-onset neuropathies, reinforcing the genetic nature of these disorders. A high prevalence of consanguinity (96.4%) suggests a strong autosomal recessive inheritance pattern,

consistent with studies conducted in populations with high consanguinity rates.[15]

The most frequently identified genetic diagnoses included Giant Axonal Neuropathy (GAN) and Genetic Vitamin Responsive Neuropathy (PDXK), each accounting for 14.3% of cases. These findings align with previous studies reporting GAN as a primary cause of severe early-onset neuropathy characterized by axonal degeneration.[16] PDXK mutations were predominantly associated with demyelinating and axonal neuropathy, manifesting as pes cavus, hammer toes, and neuropathic gait. The therapeutic implications of vitamin B6 supplementation in PDXK-related neuropathy warrant further exploration.

Charcot-Marie-Tooth (CMT) disease, particularly subtypes 2S, 4B1, and 4C, represented a significant portion of inherited neuropathies in this study. The genetic basis of CMT in our cohort was predominantly linked to IGHMBP2, MTMR2, and SH3TC2 mutations. IGHMBP2 mutations, typically associated with spinal muscular atrophy with respiratory distress (SMARD), correlated with severe neuropathy, including respiratory involvement.[17] Similarly, SH3TC2 mutations were linked to scoliosis and ataxia, a pattern observed in previous studies.[18]

Multisystem neuropathies were also prominent, with GAN being the most common. Patients with GAN exhibited nasal speech, neuropathic gait, and axonal neuropathy on electrophysiological studies. Additionally, cerebellar ataxia with neuropathy was linked to SETX mutations, highlighting the role of cerebellar dysfunction in hereditary neuropathies.18 PHARC syndrome, a rare disorder characterized by progressive neuropathy, hearing loss, and retinitis pigmentosa, was identified in one patient with an ABHD12 mutation, consistent with its known phenotypic spectrum.[19]

Electrophysiological findings classified neuropathies into demyelinating (28.6%), axonal (14.3%), and mixed patterns (46.4%). Mixed neuropathies were predominantly associated with IGHMBP2 and SH3TC2 mutations, suggesting a continuum of axonal and myelin dysfunction. Neuroimaging findings further supported genotype-phenotype correlations, with cerebellar atrophy identified in patients with SETX mutations, similar to previous reports.[18-20]

The genotype-phenotype correlations observed in this study reinforce the importance of whole-exome sequencing (WES) in diagnosing hereditary neuropathies, particularly in populations with high consanguinity. The diagnostic yield of WES in this study (68.29%) aligns with reported rates in genetic neuropathy studies.[21] The identification of pathogenic variants in genes such as WNK1 and OCRL underscores the diverse clinical presentations, including foot ulcers, self-amputation, and visual impairment, expanding the known spectrum of hereditary neuropathies.[22]

Mutations in the PDXK gene have significant clinical implications, particularly in the context of hereditary neuropathies. PDXK encodes pyridoxal kinase, a crucial enzyme in the metabolism of vitamin B6, which is essential for neurotransmitter function and neuronal survival. Deficiencies in PDXK activity lead to vitamin B6-dependent neuropathy, characterized by progressive sensorimotor dysfunction, pes cavus, hammer toes, and neuropathic gait.[23] The recognition of PDXK-related neuropathy is crucial, as affected individuals may benefit from targeted vitamin B6 supplementation, potentially mitigating disease progression and improving clinical outcomes.[24,25] Furthermore, given the demyelinating and axonal pathology observed in PDXK-related cases, early intervention with neuroprotective strategies may help preserve motor function and reduce disability. Future studies should explore the long-term benefits of vitamin B6 therapy in genetically confirmed cases, as well as the underlying molecular mechanisms contributing to disease pathology.[25]

Despite the valuable findings presented, this study has several limitations. The small sample size limits the generalizability of the results, and the absence of functional studies prevents a deeper understanding of the pathogenic mechanisms underlying the identified mutations. Additionally, long-term follow-up data were not available to assess disease progression and response to potential therapeutic interventions. Future research should focus on expanding the cohort size, incorporating longitudinal clinical assessments, and utilizing advanced genomic and

proteomic approaches to elucidate novel therapeutic targets. Investigating genotype-environment interactions and their role in disease modulation could also provide deeper insights into disease pathophysiology and potential interventions.

In conclusion, this study highlights the genetic heterogeneity of inherited neuropathies and their associated phenotypic spectrum. The strong genotype-phenotype correlations emphasize the role of genetic testing in early diagnosis, prognostic assessment, and potential therapeutic interventions. Future research should focus on expanding genetic screening, conducting functional studies of novel variants, and exploring therapeutic avenues for treatable forms such as vitamin-responsive neuropathies.

## CONCLUSION

This study highlights the genetic heterogeneity of inherited neuropathies and their associated phenotypic spectrum. The strong genotype-phenotype correlations emphasize the role of genetic testing in early diagnosis, prognostic assessment, and potential therapeutic interventions. Future research should focus on expanding genetic screening, conducting functional studies of novel variants, and exploring therapeutic avenues for treatable forms such as vitamin-responsive neuropathies.

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**Conflict of interest:**None

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