



Universiteit
Leiden
The Netherlands

Search for additional pathogenic variants to explain variation in PMP22-related neuropathies

Paassen, B.W. van; Verhamme, C.; Ruissen, F. van; Haagmans, M.A.; Dijkgraaf, M.G.W.; Visser, M. de; ... ; Weterman, M.A.J.

Citation

Paassen, B. W. van, Verhamme, C., Ruissen, F. van, Haagmans, M. A., Dijkgraaf, M. G. W., Visser, M. de, ... Weterman, M. A. J. (2025). Search for additional pathogenic variants to explain variation in PMP22-related neuropathies. *Neurology Genetics*, 11(6).
doi:10.1212/NXG.0000000000200315

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/4299670>

Note: To cite this publication please use the final published version (if applicable).

Search for Additional Pathogenic Variants to Explain Variation in *PMP22*-Related Neuropathies

Barbara W. van Paassen,¹ Camiel Verhamme,² Fred van Ruissen,³ Martin A. Haagsmans,³ Marcel G.W. Dijkgraaf,⁴ Marianne De Visser,² Frank Baas,⁵ Anneke J. Van Der Kooi,^{2,*} and Marian A.J. Weterman^{5,*}

Correspondence

Dr. van Paassen
b.vanpaassen@erasmusmc.nl

Neurol Genet 2025;11:e200315. doi:10.1212/NXG.0000000000200315

Abstract

Background and Objectives

The aim of this study was to investigate whether the considerable phenotypic variation in Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP) is due to additional pathogenic coding variants in severely affected patients, by screening a panel of neuropathy-related genes.

Methods

In this cross-sectional study, the extremes of the spectrum of 742 patients with genetically confirmed CMT1A and HNPP were selected, based on disability as assessed using the Overall Neuropathy Limitation Scale (ONLS). The ONLS data of 183 patients with CMT1A and 102 with HNPP showed a Gaussian distribution. A next-generation sequencing panel containing 177 neuropathy-related genes was tested in a selected group of 20 patients with mild CMT1A, 24 with severe CMT1A, 25 with mild HNPP, and 25 with severe HNPP.

Results

One additional autosomal dominant pathogenic variant in the *MFN2* gene was identified in a severe CMT1A case. Heterozygous pathogenic variants in autosomal recessive neuropathy-related genes were found in 2 patients with severe CMT1A and in 2 with mild HNPP.

Discussion

In our study, additional pathogenic coding variants in neuropathy-related genes did not contribute to variation in disease severity in most patients with CMT1A and HNPP. In cases with confirmed *PMP22* copy-number alterations, further genetic screening for pathogenic variants in CMT-related genes is warranted only in severe cases.

Introduction

Charcot-Marie-Tooth disease (CMT) is characterized by distal muscle weakness and wasting, foot and hand deformities, and distal sensory loss. More than 100 causative genes have been identified.¹ Autosomal dominant (AD) CMT1A is the most common subtype of CMT usually caused by a 1.5-Mb duplication on chromosome 17p11.2 that contains the gene coding for peripheral myelin protein 22 (*PMP22*), thus leading to 3 copies of the *PMP22* gene.²⁻⁴

Hereditary neuropathy with liability to pressure palsies (HNPP) is an episodic, multifocal, autosomal dominantly inherited neuropathy. The typical clinical presentation consists of recurrent painless transient pressure palsies, associated with focal motor and/or sensory

MORE ONLINE

Supplementary Material

*These authors contributed equally to this work as co-senior authors.

¹Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands; ²Department of Neurology, Amsterdam University Medical Center, the Netherlands; ³Department of Human Genetics, Amsterdam University Medical Center, the Netherlands; ⁴Department of Epidemiology and Data Science, Amsterdam University Medical Center, the Netherlands;

⁵Department of Clinical Genetics, Leiden University Medical Center, the Netherlands.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Glossary

AD = autosomal dominant; **ALDS** = Academic Medical Center Linear disability score; **AR** = autosomal recessive; **CMT** = Charcot-Marie-Tooth disease; **CMTNSv2** = CMT Neuropathy Score version 2; **HNPP** = hereditary neuropathy with liability to pressure palsies; **ONLS** = Overall Neuropathy Limitation Scale; **PMP22** = peripheral myelin protein 22.

symptoms in the territory of a single nerve. HNPP is most often caused by a 1.5-Mb deletion of the same region that is duplicated in CMT1A.⁵

Considerable intrafamilial and interfamilial phenotypic variation is known for these PMP22-related neuropathies.⁶ This suggests the presence of modifying environmental and/or genetic factors. Several severely affected patients with CMT1A and HNPP carrying pathogenic variants in other CMT genes next to the PMP22 duplication or deletion have been described, known as “double trouble.”⁷⁻¹⁰

The aim of this study was to investigate, in our cohort of patients with CMT1A and HNPP, whether severe phenotypes were caused by additional pathogenic sequence variants in neuropathy-related genes.

Methods

Patients with DNA-proven CMT1A and HNPP were approached through the physician who had requested the DNA test between 1995 and 2009. Exclusion criteria included impaired mobility due to comorbidity, diabetes mellitus, alcohol abuse, use of medications that can cause neuropathy as a side effect, renal disease, and non-White ethnicity, because of limited population frequency databases at the time of the study.

Blood tests were performed to exclude possible causes of acquired neuropathy. The study was approved by the Medical Ethical Committee of the Amsterdam University Medical Centers.

A total of 742 patients with DNA-proven CMT1A and HNPP, ranging in age from 12 to 60 years, were approached. To prevent selection bias, we approached as many patients as possible. Patients who consented to participate were interviewed by telephone to assess disease severity using the Overall Neuropathy Limitation Scale (ONLS) and the Academic Medical Center Linear Disability Score (ALDS).^{11,12} The ONLS measures limitations in the activities of arms and legs, ranging from 0 (no symptoms) to 12 (no purposeful movements). The ALDS focuses on activities of daily life, ranging from 0 (deceased) to 100 (optimal functioning). Mildly affected patients, defined as having an ONLS score of 0, 1, or 2, had to be older than 20 years because they might develop more severe symptoms over the years. Severe CMT1A was defined as an ONLS score of 5 or more, or an ONLS score of 4 with an ALDS score lower than 76. Severe HNPP was defined by an ONLS score of 4 or higher.

Sequencing of Neuropathy-Related Genes

Whole-exome sequencing (Agilent SureSelect v8) was performed on a NovaSeq 5,000 by Genomescan (the Netherlands). Sequencing was performed using paired-end reads of 150 base pairs (bp) in length (2 x 150 bp). Data were processed and mapped to the reference genome (hg19) using Illumina Dragen software v3.8. In addition to a Human Phenotype Ontology (HPO)-based analyses (mentioned further), we applied a gene panel consisting of genes associated with disorders affecting the peripheral nerves. The following genes were analyzed: AARS, ABHD12, AHNAK2, AIFM1, ALS2, ANG, ARHGEF10, ARHGEF28, ARSA, ASAH1, ATIL1, ATIL3, ATP1A1, ATP7A, ATXN2, BAG3, BICD2, BSCL2, C1orf194, CADM3, CCT5, CHCHD10, CHMP2B, COX6A1, CTDP1, DAO, DCAF8, DCTN1, DGAT2, DGUOK, DHH, DHTKD1, DNAJB2, DNMT2, DNMT1, DRP2, DST, DYNC1H1, EBP50, EGR2, EMILIN1, ELP3, EWSR1, ErbB4, FAM134B, FBLN5, FBXO38, FGD4, FIG 4, FLVCR1, FUS, GALC, GAN, GARS, GBE1, GBF1, GDAP1, GJB1, GJB3, GLE1, GNB4, GRN, HARS, HINT1, HK1, HNRNPA1, HOXD10, HSPB1, HSPB3, HSPB8, IFRD1, IGHMBP2, IKBKAP, INF2, ITPR3, JAG1, KARS, KIF1A, KIF1B, KIF5A, KLHL9, LAS1L, LITAF, LMNA, LMNB1, LRSAM1, LYST, MAPT, MARS, MATR3, MCM3AP, MED25, MME, MFN2, MORC2, MPV17, MPZ, MTMR2, MYH14, NAGLU, NDRG1, NEFH, NEFL, NEK1, NGF, NIPA1, NOTCH2NLC, NRG1, NTRK1, OPTN, PDK3, PEX1, PEX16, PEX7, PFN1, PHYH, PLA2G6, PLEKHG5, PMM2, PMP2, PMP22, PNKP, POLR3B, PRPH, PRPS1, PRX, RAB7A, REEP1, RNF170, SACS, SBF1, SBF2, SCAN, SCO2, SCN10A, SCN11A, SCN9A, SCP2, SCYL1, SEPT9, SETX, SH3TC2, SGPL1, SIGMAR1, SLC12A6, SLC5A7, SOD1, SORD, SOX10, SPAST, SPG11, SPTLC1, SPTLC2, SPTLC3, SQSTM1, SS18L1, SURF1, SYT2, TAF15, TARDBP, TBK1, TDP1, TFG, TK2, TRIM2, TRPV4, TUBA4A, TUBB3, UBA1, UBQLN2, UNC13A, VAPB, VCP, WNK1, YARS, c19orf12, and WARS.

For analysis, we used Moon software, an artificial intelligence (AI)-based suite that links genes to HPO phenotypes and prioritizes variants based on phenotypic overlap, and predicted impact on the encoded protein.¹³

Examination of a rare variant list extracted by Moon from the whole-exome analysis of the same patients yielded 473 suggestions. Most were discarded because they were associated with a much more severe AD syndrome, were hardly related to a neuropathy, were the cause of a myopathy, appeared to have a higher frequency than originally reported, or were

classified as benign or likely benign. Based on plausible suggestions by Moon, association with amyotrophic lateral sclerosis (ALS/CMT) in the disorder description by Moon, reported pathogenicity of the variant producing a (related) phenotype, reports of a complex inherited neuropathy, or involvement in motor and sensory axon degeneration, the following genes were added: *SPTBN4*, *FAM126A*, *VWA1*, *TRPM7*, *SPTAN1*, *UBA5*, *DNAJC7*, *KIAA0196*, *VPS37A*, *DIAPH3*, *SPG7*, *ANXA11*, *COA7*, *ELOVL5*, and *CYP7B1*.

Interpretation of Variants and Statistics

Moon software (Invitae, USA) was used for variant filtering using the HPO term polyneuropathy (HP: 0009830). Simultaneously, a gene panel filter was applied.

For filtering and pathogenicity scoring, the following criteria were used: coverage >7x; quality score >39; frequency below 0.5%; effect on coding and/or splicing; no conservative in-frame changes; absence in a homozygous or hemizygous state in public databases of healthy individuals; a combined annotation-dependent depletion (CADD) score of at least 20; and not reported in ClinVar as a benign or likely benign change.

All suspected variants were manually curated. Changes in adjacent nucleotides on 1 allele were counted as 1 variant, and homozygous variants were counted as 2 (2 alleles).

Differences of clinical characteristics between groups were tested with *t* test, equal variance using SPSS (IBM SPSS Statistics version 25) and Graphpad, with *p* < 0.05 considered significant. Differences between groups with identical ONLS scores were tested for significance for trends.¹⁴

Data Availability

Any data not published within the article will (after anonymization) be shared on request from any qualified investigator.

Results

Patients

Characteristics of the patients and inclusion and exclusion criteria are presented in Figure 1. Figure 2 shows the distribution of the ONLS scores of the included patients with CMT1A and HNPP. In total, 21 patients with mild CMT1A, 26 with severe CMT1A, 25 with mild HNPP, and 25 with severe HNPP were further clinically evaluated. Genetic analyses were conducted in 20 patients with mild CMT1A, 24 with severe CMT1A, 25 with mild HNPP, and 25 with severe HNPP. Three patients with CMT1A were excluded from genetic analyses because of insufficient DNA or clinical data. The clinical characteristics of the selected patients at both ends of the spectrum are provided in Table 1. These patients underwent a variety of tests, including the 10-m and 50-m timed walking tests, and were scored according to the validated Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNSv2).¹⁵

As expected, severely affected patients with CMT1A scored significantly worse compared with mildly affected patients on the 10-m and 50-m walking tests and CMTNSv2, respectively. Severely affected patients with HNPP also scored significantly worse on the 10-m and 50-m walking tests and CMTNSv2 in comparison with the mildly affected patients.

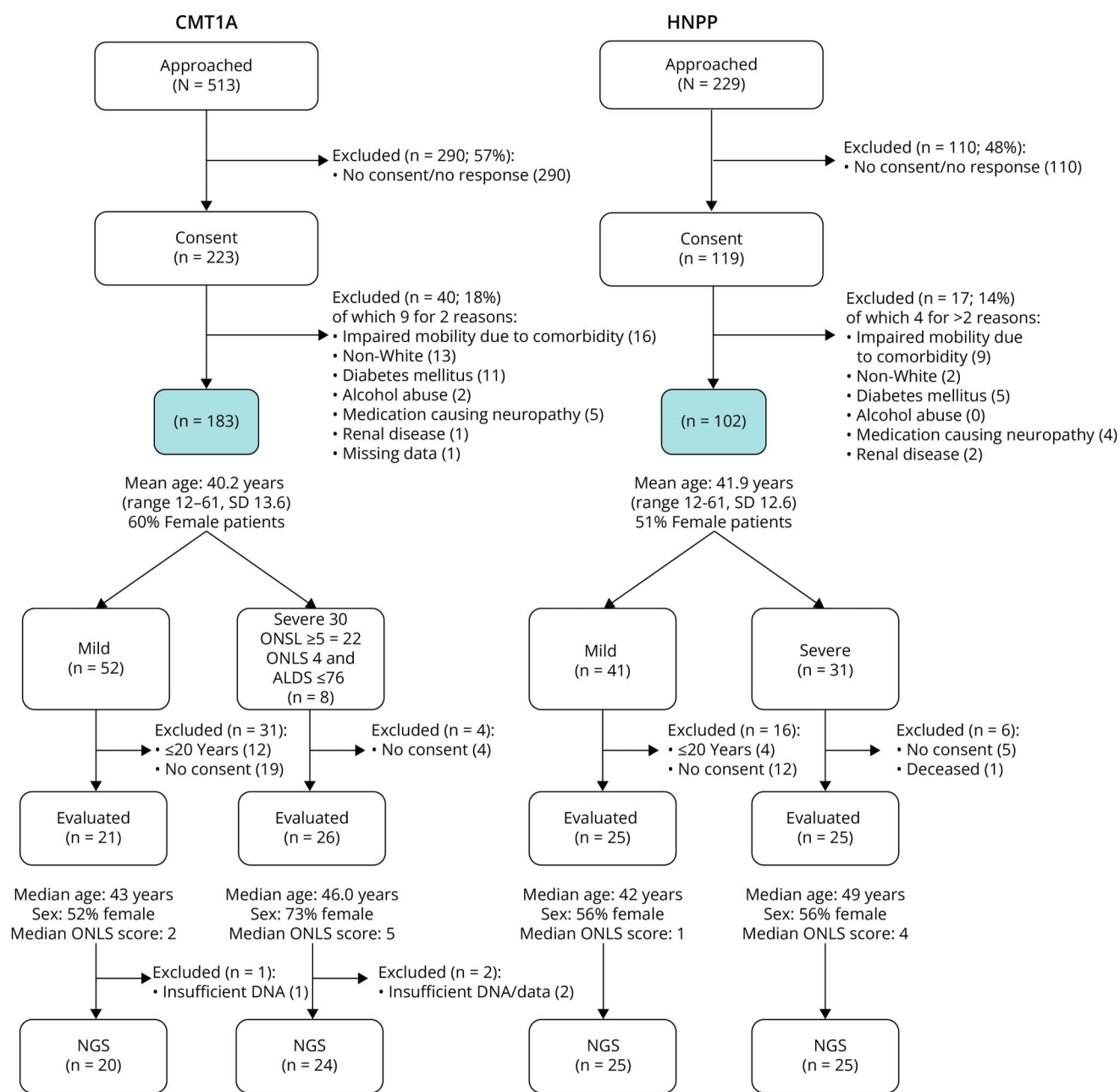
Genetic Analyses

A combined approach using the HPO term “neuropathy” and inclusion in a CMT gene panel initially yielded 670 variants; 611 were from the CMT gene panel, of which 147 were also suggested by Moon (shortlists). Other plausible suggestions by Moon, not present in the gene panel or described as associated with disease (CMT or ALS), and variants classified as pathogenic according to ClinVar causing (complex) neuropathy-related phenotypes were also included. After removal of variants based on filtering as described in the Methods section “Interpretation of Variants and Statistics,” the remaining were manually inspected using the Integrative Genomics Viewer (IGV),¹⁶ leaving 291 variants. These variants were screened for pathogenicity, excluding those with CADD score below 20, those causing in-frame protein changes that were regarded as conservative, and variants that, on closer examination, were located outside the translated region of all reference transcripts. This further reduced the number of potentially pathogenic variants to 158, which were consequently divided according to (the severity of) the disease. The final list consisted of 133 variants identified using the gene panel, and 25 variants were added based on suggestions by Moon or their description as associated with a neuropathy-related disease.

Figure 3 presents the mean number of variants per group. For CMT1A, 48 variants in the severe group (*n* = 24 patients, mean 2.00, SD 1.91) and 24 in the mildly affected group (*n* = 20 patients, mean 1.20, SD 1.06) were found. The differences in the number of variants between the severe and mild group is not significant (*p* = 0.13). Significance for a trend was only detected when comparing the number of variants in the groups with ONLS scores 1–2 with those with ONLS scores 4–5 (*p* = 0.042); however, when grouping all mild cases (ONLS scores 0–2) vs all severe (ONLS score = 4 or higher) cases, the significance was lost (*p* = 0.13) because of high variation and small numbers in the higher ONLS score groups. For HNPP, 45 variants in the severe group (*n* = 25, mean 1.8, SD 1.62) vs 41 variants in the mildly affected group (*n* = 25, mean 1.64, SD 1.05) were found. This difference was also not significant (*p* = 0.665).

Only 1 probably pathogenic and hitherto unknown sequence variant in *MFN2*, a dominant neuropathy-related gene, was found in our cohort. The heterozygous *MFN2* variant c.764T>C, p.(Ile255Thr) (NM_014874.3) was found in a patient with severe CMT1A, who had an ONLS score of 9 and was 59 years old at the time of assessment. This variant is not reported as pathogenic in literature, but in silico prediction tools and its localization in the protein suggest that it is

Figure 1 Flowchart of Inclusion and Exclusion of Patients and Their Characteristics

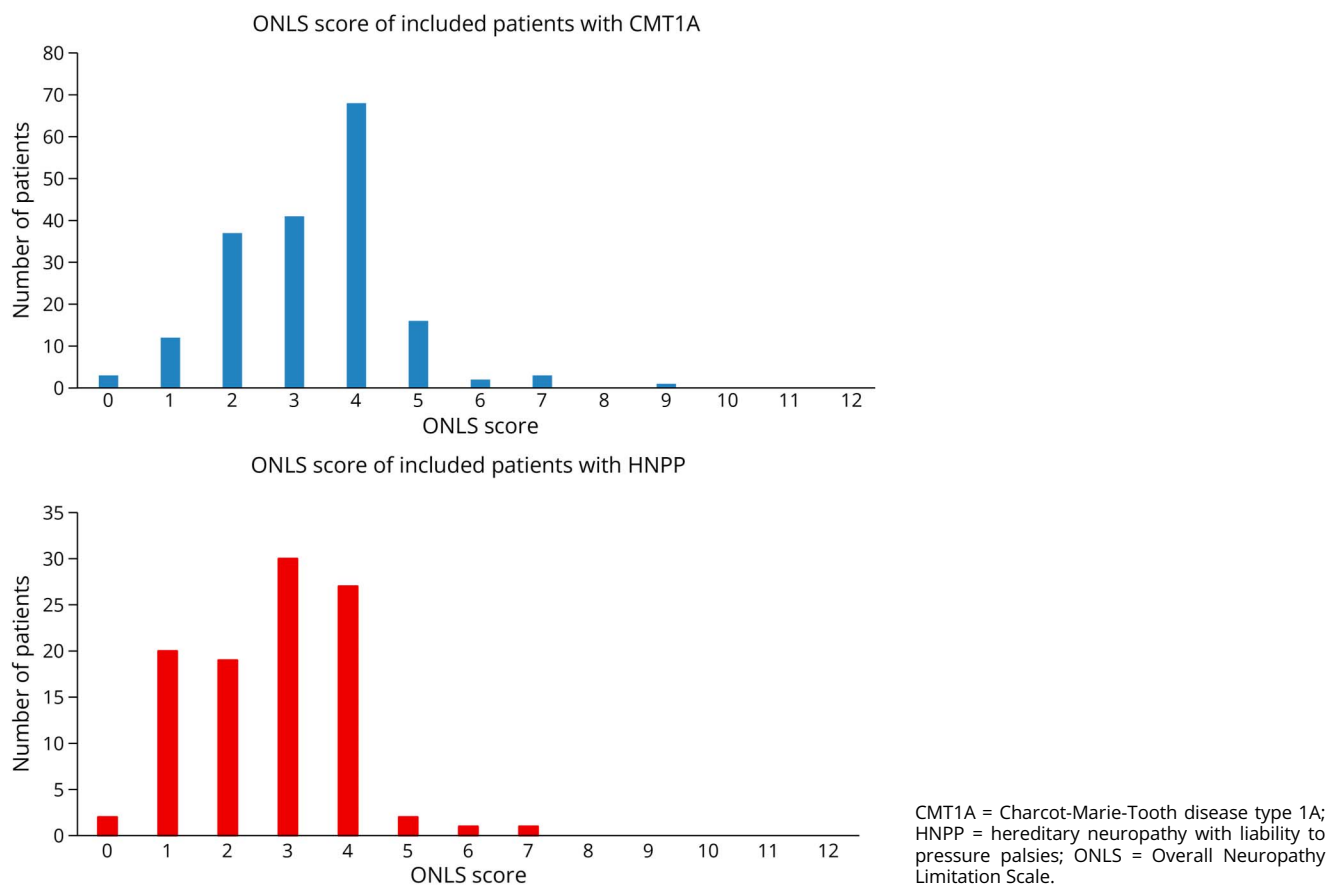


very likely pathogenic. Heterozygous sequence variants in autosomal recessive (AR) genes that were reported in ClinVar as pathogenic were found in 3 patients with severe CMT1A and in 2 patients with mild HNPP. An *IGHMBP2* c.2911_2912delAG, p.(Arg971Glufs*4) (NM_002180.2) variant was found in a severely affected patient with CMT1A, who had an ONSL score of 6. A family member with CMT1A (ONLS score 4) of this individual was also included in our study and did not carry the *IGHMBP2* variant. We found c.3325C>T, p.Arg1109* variant in *SH3TC2* (NM_024577.3) in a patient with severe CMT with an ONSL score of 5 and a *NAGLU* c.202G>A, p.Arg674His variant (NM_000263.3) in another patient with severe CMT with an ONSL score of 5. Further variants reported as pathogenic were a missense variant in

PMM2 (c.422G>A, p.Arg141His) (NM_000303.2) and a nonsense variant in the *PEX7* gene (c.875T>A, p.Leu292*) (NM_000288.3), both in patients with mild HNPP with ONSL scores of 1. All other variants identified were unclassified or classified as VUS with a CADD score >20 (eTable 1).

Discussion

In this study, we set out to test the hypothesis that severe forms of CMT1A and HNPP may be caused by additional pathogenic coding variants in neuropathy-related genes. Earlier, 4 case reports described additional pathogenic AD variants in the *PMP22* gene or other CMT genes in severely

Figure 2 Histogram of Overall Neuropathy Limitation Scale Scores, Derived From 183 Patients With CMT1A and 102 With HNPP

affected patients with CMT1A/HNPP.⁷⁻¹⁰ In our cohort, only 1 case with an additional likely pathogenic variant in a dominant neuropathy-related gene was found, suggesting that the abovementioned case reports might only concern incidental patients. This variant was detected in the most severely affected patient with CMT1A with an ONLS score of 9, demonstrating that in fact “double trouble” did occur in our CMT cohort but explained only 1 of the 24 severe cases.

We identified several heterozygous reported pathogenic sequence variants in AR genes in 3 severely affected patients

with CMT1A and in 2 mildly affected patients with HNPP. Carriers of a heterozygous pathogenic variant in AR genes are usually healthy. It is, however, possible that heterozygosity of such a pathogenic variant may modify the phenotype in a carrier with a *PMP22* duplication, although, to our knowledge, this has not been reported in CMT1A and HNPP.

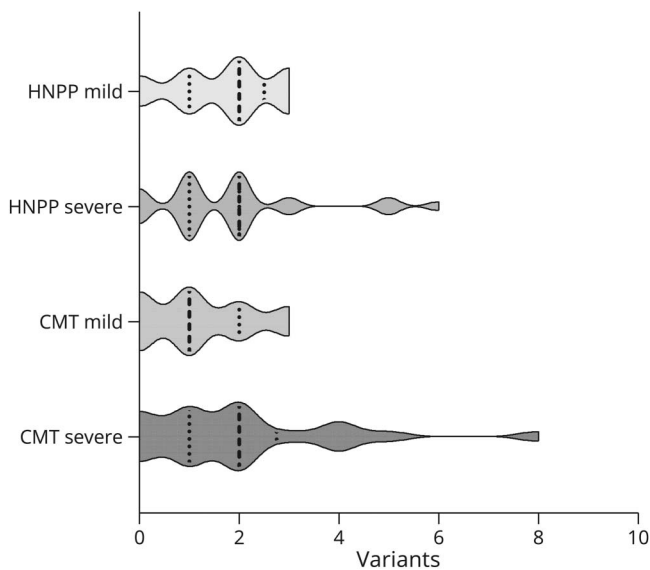
In our study, we focused on rare variants in genes with a reported association with neuropathy. The study size precludes analysis for association of common disease variants with disease severity. Variant burden of the mild and severe

Table 1 Clinical Characteristics of Patients Selected for DNA Analysis

Patient group (number)	Age at examination (y)	Female (%)	10-m walk (s)	50-m walk (s)	CMTNSv2
Mild CMT1A (21)	41.8	52	6.2	31.6	12.4
Severe CMT1A (26)	47.5	73	8.9 ^a	43.9 ^a	20.8 ^a
Mild HNPP (25)	40.4	56	5.1	25.6	5.3
Severe HNPP (25)	45.4	56	6.5 ^a	32.4 ^a	10.6 ^a

Abbreviations: CMT1A = Charcot-Marie-Tooth disease type 1A; CMTNSv2 = Charcot-Marie-Tooth Neuropathy Score version 2; HNPP = hereditary neuropathy with liability to pressure palsies.

^a $p < 0.05$ by the independent-sample t test.

Figure 3 Mean Number of Variants Found Per Group

groups was also determined by comparing the distribution of sequence variants reported as VUS, for which we suspected might affect protein function. The distribution of the sequence variants identified over the 4 CMT1A and HNPP groups was not significantly different between the severe and mild cases (Figure 3). There were severe cases without any suspected variant and mild cases with several variants. One should, however, keep in mind that our sample size is small, and that our classification of the rare variants is performed by *in silico* prediction and manual curation, with a focus on genes already associated with neuropathy. There is currently no gold standard to discriminate (probably) pathogenic variants from a suspected VUS.

It should also be kept in mind that we did not analyze for the presence of sequence variants that by themselves do not cause disease. These disease-modifying factors could not be identified in our study, because these variants are not in genes known to be associated with neuropathy or CMT at this moment. In addition, noncoding sequence variants, structural variants, mitochondrial DNA variants, or epigenetic factors are not analyzed in our study.

Another limitation of our study is the use of ONLS by telephone, because ONLS is best used when combined with direct questions to the patient and direct observation of function. It might also not be the best tool to assess severity of HNPP, given that it is an episodic disease. Despite these limitations, we used the ONLS by telephone, considering feasibility as a first screen for a large group of patients.

Despite CMT1A being a slowly progressive disease, Table 1 and Figure 1 show that the patients with mild CMT1A had a mean age of 41.8 years (median age 43 years, range 21–59) and the patients with severe CMT1A had a mean age of

47.5 years (median age 46 years, range 28–61), which was not statistically different. eFigure 1 illustrates the individual patients and their ONLS scores, showing that both groups have the same age range but that the ONLS score is clearly distinctive.

A study on the contribution of genetic variation to disease severity in CMT has identified a few modifier loci for CMT1A (971 patients), one of which was associated with clinical outcome.¹⁷ A variant in *SIPA1L2* was associated with foot dorsiflexion, but no loci were found for overall severity of disease.¹⁸ We identified only 1 pathogenic variant in a dominant neuropathy gene in a severe case. Studies on axonal CMT using exome-based gene panels found a significant higher burden of rare variants in neuropathy-related genes in patients vs controls.^{19,20} Our study group was too small to detect significant differences, although the average number of variants with a pathogenic prediction was higher in the more severely affected group.

In conclusion, screening of neuropathy-related genes in CMT1A and HNPP revealed only 1 case with a pathogenic variant in the dominant *MFN2* gene in a patient with severe CMT1A, which could explain the severe phenotype of CMT, confirming the notion that “double trouble” is rare in CMT1A and HNPP. For HNPP, no additional pathogenic variants were found. Only 5 cases with heterozygous pathogenic variants in AR-related genes were identified.

We propose to first start the genetic analysis of patients with CMT1 and HNPP using a *PMP22* duplication/deletion test. It remains to be discussed whether further screening of severe CMT1A/HNPP cases with confirmed *PMP22* copy-number alterations is useful. As long as there are no therapeutic consequences for “double trouble” cases, this has no consequences for the patient. However, the presence of a second CMT pathogenic variant has consequences for genetic counseling. Therefore, we suggest that further genetic screening for pathogenic variants in CMT-related genes is only warranted in severe cases. With the increasing use of whole-genome sequencing in genetic diagnostics, this might change as the sequencing data would then be already available.

Acknowledgment

The authors thank the patients for participating in the study and the physicians who helped with approaching the patients. Several authors of this publication are members of the Netherlands Neuromuscular Center and the European Reference Network for Rare Neuromuscular Diseases (ERN-EURO-NMD).

Author Contributions

B.W. van Paassen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Verhamme: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

F. van Ruissen: analysis or interpretation of data. M.A. Haagmans: major role in the acquisition of data. M.G.W. Dijkgraaf: analysis or interpretation of data. M. De Visser: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. F. Baas: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A.J. Van Der Kooi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M.A.J. Weterman: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

Study Funding

This study was funded by Prinses Beatrix Spierfonds, the Hague, the Netherlands, under grant number WAR08-18.

Disclosure

B.W. van Paassen, C. Verhamme, F. van Ruissen, M.A. Haagmans, and M.G.W. Dijkgraaf report no disclosures. M. de Visser consults for Novartis, Argenx, and AstraZeneca. F. Baas, A.J. van der Kooi, and M.A.J. Weterman report no disclosures. Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures.

Publication History

Received by *Neurology® Genetics* February 13, 2025. Accepted in final form August 22, 2025. Submitted and externally peer-reviewed. The handling editor was Deputy Editor Antonella Spinazzola, MD.

References

- Previtali SC, Zhao E, Lazarevic D, et al. Expanding the spectrum of genes responsible for hereditary motor neuropathies. *J Neurol Neurosurg Psychiatry*. 2019;90(10):1171-1179. doi:10.1136/jnnp-2019-320717
- Raeymaekers P, Timmerman V, Nelis E, et al. Duplication in chromosome 17p11.2 in charcot-marie-tooth neuropathy type 1a (CMT 1a). The HMSN collaborative research group. *Neuromuscul Disord*. 1991;1(2):93-97. doi:10.1016/0960-8966(91)90055-w
- Lupski JR, de Oca-Luna RM, Slaugenhaupt S, et al. DNA duplication associated with Charcot-Marie-Tooth disease type 1A. *Cell*. 1991;66(2):219-232. doi:10.1016/0092-8674(91)90613-4
- Valentijn LJ, Bolhuis PA, Zorn I, et al. The peripheral myelin gene PMP-22/GAS-3 is duplicated in Charcot-Marie-Tooth disease type 1A. *Nat Genet*. 1992;1(3):166-170. doi:10.1038/ng0692-166
- Chance PF, Alderson MK, Leppig KA, et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. *Cell*. 1993;72(1):143-151. doi:10.1016/0092-8674(93)90058-x
- van Paassen BW, van der Kooi AJ, van Spaendonck-Zwarts KY, Verhamme C, Baas F, de Visser M. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and Hereditary Neuropathy with liability to Pressure Palsies. *Orphanet J Rare Dis*. 2014;9:38. doi:10.1186/1750-1172-9-38
- Meggough F, de Visser M, Arts WF, De Coe RI, van Schaik IN, Baas F. Early onset neuropathy in a compound form of Charcot-Marie-Tooth disease. *Ann Neurol*. 2005;57(4):S89-S91. doi:10.1002/ana.20434
- Hodapp JA, Carter GT, Lipe HP, Michelson SJ, Kraft GH, Bird TD. Double trouble in hereditary neuropathy: concomitant mutations in the PMP-22 gene and another gene produce novel phenotypes. *Arch Neurol*. 2006;63(1):112-117. doi:10.1001/archneur.63.1.112
- Jerath NU, Kamholz J, Grider T, Harper A, Swenson A, Shy ME. Coexistence of a T118M PMP22 missense mutation and chromosome 17 (17p11.2-p12) deletion. *Muscle Nerve*. 2015;52(5):905-908. doi:10.1002/mus.24713
- Xie Y, Lin Z, Li X, et al. One PMP22/MPZ and three MFN2/GDAP1 concomitant variants occurred in a cohort of 189 Chinese charcot-marie-tooth families. *Front Neurol*. 2021;12:736704. doi:10.3389/fneur.2021.736704
- Graham RC, Hughes RA. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. *J Neurol Neurosurg Psychiatry*. 2006;77(8):973-976. doi:10.1136/jnnp.2005.081547
- Holman R, Weisscher N, Glas CA, et al. The Academic Medical Center Linear Disability Score (ALDS) item bank: item response theory analysis in a mixed patient population. *Health Qual Life Outcomes*. 2005;3:83. doi:10.1186/1477-7525-3-83
- James KN, Clark MM, Camp B, et al. Partially automated whole-genome sequencing reanalysis of previously undiagnosed pediatric patients can efficiently yield new diagnoses. *NPJ Genom Med*. 2020;5:33. doi:10.1038/s41525-020-00140-1
- MedCalc Software Ltd. *Two-way Chi-Squared Test*. Accessed September 16, 2024. [medcalc.org/calc/chisquared-2way.php](https://www.medcalc.org/calc/chisquared-2way.php)
- Murphy SM, Herrmann DN, McDermott MP, et al. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. *J Peripher Nerv Syst*. 2011;16(3):191-198. doi:10.1111/j.1529-8027.2011.00350.x
- Thorvaldsdottir H, Robinson JT, Mesirov JP. Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. *Brief Bioinform*. 2013;14(2):178-192. doi:10.1093/bib/bbs017
- Tao F, Beecham GW, Rebelo AP, et al. Modifier gene candidates in charcot-marie-tooth disease type 1A: a case-only genome-wide association study. *J Neuromuscul Dis*. 2019;6(2):201-211. doi:10.3233/JND-190377
- Tao F, Beecham GW, Rebelo AP, et al. Variation in SIPA1L2 is correlated with phenotype modification in Charcot-Marie-Tooth disease type 1A. *Ann Neurol*. 2019;85(3):316-330. doi:10.1002/ana.25426
- Gonzaga-Jauregui C, Harel T, Gambin T, et al. Exome sequence analysis suggests that genetic burden contributes to phenotypic variability and complex neuropathy. *Cell Rep*. 2015;12(7):1169-1183. doi:10.1016/j.celrep.2015.07.023
- Bis-Brewer DM, Gan-Or Z, Sleiman P, et al. Assessing non-Mendelian inheritance in inherited axonopathies. *Genet Med*. 2020;22(12):2114-2119. doi:10.1038/s41436-020-0924-0