Received: 14 September 2023 | Accepted: 22 December 2023

DOI: 10.1111/ene.16205

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Association of the neonatal Fc receptor promoter variable number of tandem repeat polymorphism with immunoglobulin response in patients with chronic inflammatory demyelinating polyneuropathy

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Abstract

Background and purpose: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease with humoral and cellular autoimmunity causing demyelination of peripheral nerves, commonly treated with intravenous immunoglobulins (IVIg). The neonatal Fc receptor (FcRn), encoded by the *FCGRT* gene, prevents the degradation of immunoglobulin G (IgG) by recycling circulating IgG. A variable number of tandem repeat (VNTR) polymorphism in the promoter region of the *FCGRT* gene is associated with different expression levels of mRNA and protein. Thus, patients with genotypes associated with relatively low FcRn expression may show a poorer treatment response to IVIg due to increased IVIg degradation.

Methods: VNTR genotypes were analyzed in 144 patients with CIDP. Patients' clinical data, including neurological scores and treatment data, were collected as part of the Immune-Mediated Neuropathies Biobank registry.

Results: Most patients ($n=124$, 86%) were VNTR 3/3 homozygotes, and 20 patients (14%) were VNTR 2/3 heterozygotes. Both VNTR 3/3 and VNTR 2/3 genotype groups showed no difference in clinical disability and immunoglobulin dosage. However, patients with a VNTR 2 allele were more likely to receive subcutaneous immunoglobulins (SCIg) than patients homozygous for the VNTR 3 allele (25% vs. 9.7%, $p=0.02$) and were more likely to receive second-line therapy (75% vs. 54%, $p=0.05$).

Conclusions: The VNTR 2/3 genotype is associated with the administration of SCIg, possibly reflecting a greater benefit from SCIg due to more constant immunoglobulin levels without lower IVIg levels between the treatment circles. Also, the greater need for second-line treatment in VNTR 2/3 patients could be an indirect sign of a lower response to immunoglobulins.

Jeremias Motte and Larissa Arning contributed equally.

KEYWORDS
Efgartigimod, Fc gamma receptor and transporter, *FCGRT*, genetic variation, immunoglobulin receptor

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare autoimmune inflammatory disease of the peripheral nervous system. Cellular and humoral components of the immune system are involved in the demyelination and destruction of peripheral nerves [1, 2]. CIDP is characterized by demyelination and mainly secondary axonal loss. Preservation of myelin structure and function is essential for preventing peripheral nerves from axonal damage. Therefore, adequate treatment is essential. The mainstay of therapy for CIDP includes plasmapheresis, corticosteroids, and intravenous immunoglobulins (IVIg), the latter being used in the majority of patients [3]. Although IVIg are effective in 50%–80% of CIDP patients, 30% of CIDP patients show no or only incomplete response [2, 4, 5]. Immunoglobulins can also be administered subcutaneously to treat CIDP, resulting in a more consistent plasma level of immunoglobulins [3].

IVIg administration results in supraphysiologic IgG levels that saturate the neonatal Fc receptor (FcRn). Consequently, some of the IgG antibodies are not returned to the circulation but are lysosomally degraded, resulting in reduced circulating IgG levels [6].

FcRn is encoded by the *FCGRT* gene, located on chromosome 19q13.35 [7]. Five variable number of tandem repeat (VNTR) alleles, consisting of a 37-bp-long motif (VNTR 1–5) in the *FCGRT* promoter region, result in different expression levels of mRNA and FcRn protein [8]. The VNTR 3 allele is the most common in Caucasians (92.0%), followed by the much rarer VNTR 2 allele (7.5%); all other alleles are rarely found [8]. Reporter gene analysis showed that the VNTR 3 allele is associated with an increase in *FCGRT* promoter activity when compared with the VNTR 2 allele [8]. Therefore, it has been argued that this functional polymorphism may play a role in patients treated with IgG biologics such as IVIg by influencing their efficacy via IgG pharmacokinetics [9].

Previous studies in immunodeficient patients and myasthenia gravis have shown that this VNTR polymorphism is related to the IVIg response [10, 11]. In myasthenia gravis, VNTR 2/3 heterozygous patients (associated with relatively lower expression) showed lower endogenous IgG levels and a decreased response to IVIg treatment, assuming that, in the context of high peak serum IgG levels following intravenous administration, patients with relatively lower expression genotype would experience FcRn saturation and subsequent decreased IgG recycling.

However, studies in autoimmune peripheral neuropathies like Guillain–Barré syndrome [12], multifocal motor neuropathy [13] and CIDP [14] failed to show a significant association of the VNTR polymorphism with the IVIg response. The aim of the present work was to analyze in a representative German CIDP cohort to what extent different therapeutic responses to immunoglobulins in CIDP patients can be attributed to *FCGRT* VNTR genotypes.

METHODS

Patients

Data and biosamples of CIDP patients for this study were recruited from the Immune-Mediated Neuropathies Biobank (INHIBIT), a prospective longitudinal clinical registry and biobank for patients with immune neuropathies, established in 2019 at the university hospital St. Josef-Hospital in Bochum, Germany. Patients gave written informed consent for inclusion in the study and genetic analysis. Included patients had typical CIDP or CIDP variants, and CIDP was diagnosed according to the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) criteria [15]. Patients with IgM monoclonal gammopathy or myelin-associated glycoprotein antibodies were not included.

Clinical data

Clinical data for this study on demographics, disease course, clinical scores, treatment, and treatment response were obtained from the INHIBIT registry. Functional disability was assessed using the Inflammatory Neuropathy Cause and Treatment Overall Disability Scale (ODSS) [16] and the Rasch-Built Overall Disability Scale (R-ODS) [17]. Muscle strength was assessed using the Medical Research Council (MRC) sum score [18]. Sensory deficits were recorded using the INCAT sensory sum score (ISS) [19].

Genetic analysis

Genomic DNA was isolated from blood EDTA. *FCGRT* VNTR allele sizes were analyzed by polymerase chain reaction, and the fluorescent-labeled DNA fragments were separated by capillary electrophoresis on a DNA analyzer (Applied Biosystems, ABI 3500xL).

Definition of treatment response to immunoglobulins

The therapeutic response to immunoglobulins was determined using the following parameters:

(i) In patients receiving first-line immunoglobulin therapy, the last and maximum doses of IgG used in grams per kilogram body weight per week were compared between the VNTR 3/3 and VNTR 2/3 patients.
(ii) The frequency of subcutaneous administration of immunoglobulins (as opposed to intravenous administration) was compared between the groups of patients with VNTR 3/3 and VNTR 2/3,

with subcutaneous administration suggesting that more regular application was necessary to maintain effective immunoglobulin levels.

(iii) The frequency of use of non-fist-line immunotherapies was compared between the groups of patients with VNTR 3/3 and VNTR 2/3. Non-first-line immunotherapies were divided into two groups: rituximab, cyclophosphamide, and bortezomib were defined as escalation therapy, whereas any other immunotherapy such as azathioprine, mycophenolate mofetil, or cyclosporine A was defined as second-line therapy.

Statistics

Statistical analysis was performed using Excel (Microsoft, Redmond, WA, USA, version 16.65) and IBM SPSS Statistics (IBM, Armonk, NY, USA, version 28.0.0.0). Data were compared between the groups of patients with VNTR 3/3 and VNTR 2/3. The chi-squared test was used for nominal variables and the *t*-test for linearly scaled, normally distributed variables. Probability levels (*p*-values) are indicated as statistically significant when $p < 0.05$. Absolute data are presented as mean ± SD or median ± interquartile range.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee (vote no. 18- 6534-BR of the ethics committee of the Ruhr University Bochum, Germany) and was registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien; register name: Immune-Mediated Neuropathies Biobank INHIBIT; register number: DRKS00024494; date of submission to the registry: 11 February 2021; date of first patient recruitment: 15 June 2019).

RESULTS

Data and *FCGRT* VNTR allele lengths from 144 patients were analyzed. Of these, 68 had typical CIDP, 39 had distal CIDP, 19 had multifocal CIDP, and one had sensory CIDP according to EAN/PNS criteria 2021 [15]. In total, 124 of the 144 patients were VNTR 3/3 homozygotes (86%) and 20 patients (14%) were VNTR 2/3 heterozygotes. The VNTR genotype 3/4 was detected in one patient. This patient was not included in group comparisons.

Baseline disease characteristics of the patients are shown in Table 1. The mean age was 59.9 years (±12.2) in the VNTR genotype 3/3 group and 62.9 years (±11.1) in the VNTR genotype 2/3 group. Mean disease duration from diagnosis was 6.4 years (±4.5) in VNTR genotype 3/3 patients and 8.5 years (±6.0) in VNTR genotype 2/3 patients. The mean ODSS was 3.3 (±1.9) in the VNTR 3/3 cohort and 3.3 (±1.9) in the VNTR 2/3 cohort. Patients with VNTR 3/3 status showed a mean R-ODS of 63.1 ± 20.0, whereas patients with VNTR 2/3 status showed a mean R-ODS of 69.4 ± 20.1. The mean ISS was 7.7 ± 4.7 in the VNTR 3/3 group and 7.3 ± 4.4 in the VNTR 2/3 group. The mean MRC was 72.5 ± 11.5 in the VNTR genotype 3/3 cohort and 73.1 ± 9.0 in the other cohort. Patients with VNTR 2/3 genotype had a higher proportion of female patients (40.0% vs. 21.8%) and lower body weight (76.5 ± 12.2 kg vs. 91.3 ± 19.5 kg) compared to patients with VNTR 3/3 status.

Regarding treatment, in the VNTR 3/3 group there were 20 patients who received corticosteroids. Of these, four received steroids alone, three received steroids plus immunoglobulins, and the rest received a combination of steroids, immunoglobulins, and other non-first-line immunotherapies. In the VNTR 2/3 group, there was

TABLE 1 Clinical characteristics of included patients.

Clinical characteristics	Genotype		*p*
	VNTR 3/3, *n* = 135	VNTR 2/3, *n* = 24	
Age, years	59.9 ± 12.2	62.9 ± 11.1	n.s.
Male	97 (78%)	12 (60%)	n.s.
Body weight, kg	91.3 ± 19.5	76.5 ± 12.2	<0.001
Disease duration since initial diagnosis, years	6.4 ± 4.5	8.5 ± 6.0	n.s.
Typical CIDP	60 (48%)	8 (40%)	n.s.
ODSS	3.3 ± 1.9	3.3 ± 1.9	n.s.
R-ODS	63.1 ± 20.0	69.3 ± 20.1	n.s.
ISS	7.7 ± 4.7	7.3 ± 4.4	n.s.
MRC	72.5 ± 11.5	73.1 ± 9.0	n.s.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; ISS, INCAT sensory sum score; MRC, Medical Research Council; n.s., not significant; ODSS, Inflammatory Neuropathy Cause and Treatment Overall Disability Scale; R-ODS, Rasch-Built Overall Disability Scale; VNTR, variable number of tandem repeat.

one patient on corticosteroids in combination with a non-first-line immunotherapy. We did not find a statistical connection between corticosteroid treatment and the VNTR status.

Treatment response to immunoglobulins is reduced in patients with VNTR genotype 2/3

The mean maximum dose of immunoglobulins used in patients with VNTR genotype 3/3 was 0.22 g/kg per week (±0.16), whereas it was 0.21 g/kg per week (±0.16) in patients with VNTR genotype 2/3. The difference between the groups was not statistically significant.

The mean last used dose of immunoglobulins in patients with VNTR genotype 3/3 was 0.20 g/kg per week (±0.14), whereas it was 0.19 g/kg per week (±0.12) in patients with VNTR genotype 2/3. The difference between the groups was not statistically significant.

Twelve of 124 patients (10%) with VNTR genotype 3/3 were treated with SCIg, whereas five of 20 patients (25%) with VNTR genotype 2/3 were treated with SCIg, sometimes in combination with IVIg during periods of pandemic-related global SCIg shortage. This difference between the two groups was statistically significant ($p = 0.02$), demonstrating a more frequent use of SCIg in patients with VNTR genotype 2/3 (Figure 1).

Forty-three of 124 patients (35%) with VNTR genotype 3/3 received escalation therapy with rituximab, cyclophosphamide, or bortezomib, whereas five of 20 patients (25%) with VNTR genotype 2/3 received one or more of these agents. The difference between the groups was not statistically significant.

Sixty-seven of 124 patients (54%) with VNTR genotype 3/3 had received second-line therapy, whereas 15 of 20 patients (75%) with VNTR genotype 2/3 had received second-line therapy. The difference between the two groups was almost statistically significant ($p = 0.05$; Figure 1).

Eighty-four of 124 patients (68%) with VNTR genotype 3/3 were treated with non-first-line therapy, including escalation and/or second-line therapy. In the VNTR 2/3 genotype group, 17 of 20 patients (85%) received this treatment. This difference was not statistically significant.

Table 2 gives an overview of the treatment response in both *FCGRT* VNTR genotype groups.

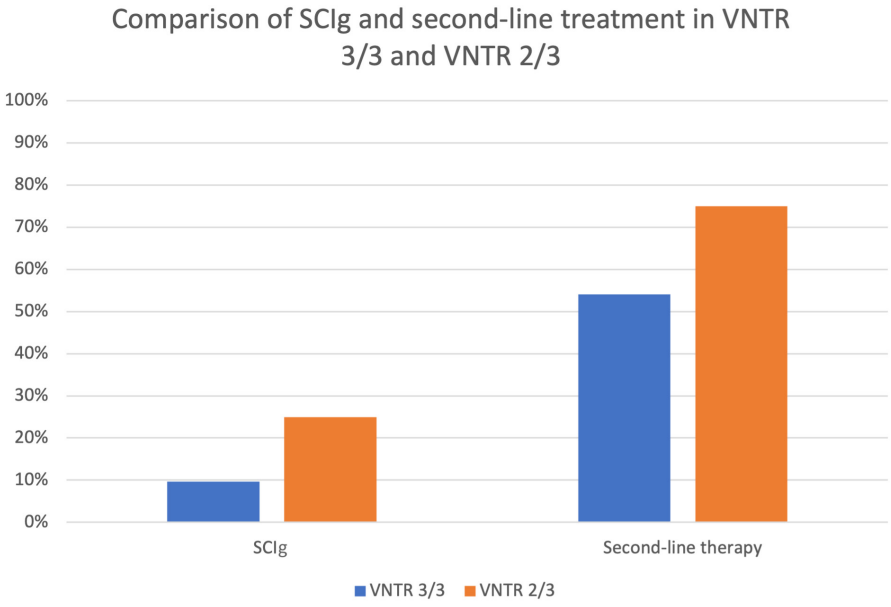

FIGURE 1 Treatment with subcutaneous immunoglobulins (SCIg) and second-line treatment was more frequent in the group with variable number of tandem repeat (VNTR) 2/3 than in VNTR 3/3.

Treatment characteristics	Genotype		
	VNTR 3/3, $n = 124$	VNTR 2/3, $n = 20$	p
Maximum IVIg dosage, g/kg per week, mean ± SD	0.22 ± 0.16	0.21 ± 0.16	n.s.
Current IVIg dosage, g/kg per week, mean ± SD	0.20 ± 0.14	0.19 ± 0.12	n.s.
SCIg, *n* (%)	12 (10%)	5 (25%)	0.017
Second-line therapy currently and/or in the past, *n* (%)	67 (54%)	15 (75%)	0.053
Escalation therapy currently and/or in the past, *n* (%)	43 (35%)	5 (25%)	n.s.
Second-line and/or escalation therapy currently and/or in the past, *n* (%)	84 (68%)	17 (85%)	n.s.

TABLE 2 Comparison of treatment characteristics of VNTR genotype 3/3 and 2/3.

Abbreviations: IVIg, intravenous immunoglobulins; n.s., not significant; SCIg, subcutaneous immunoglobulins; VNTR, variable number of tandem repeat.

DISCUSSION

IgG maintenance therapy is an established long-term treatment in CIDP that can be a continuation of IVIg or a transition to SCIg. However, there is variable response to these therapies, and in everyday clinical practice the question arises as to how therapy can best be optimized for individual patients. Therefore, a better understanding of the impact of pharmacogenetic parameters on clinical response could aid the process of tailoring Ig therapy.

In this study, we were able to demonstrate an influence of the VNTR polymorphism in the promoter region of the *FCGRT* gene on the therapeutic response to immunoglobulins in patients with CIDP. The rarer VNTR 2/3 genotype, which is associated with reduced FcRn expression and immunoglobulin recycling, was associated with more frequent administration of SCIg and second-line therapies in our cohort. Therefore, patients with a weaker response to immunoglobulins could potentially benefit from more constant immunoglobulin levels due to more frequent subcutaneous administration and from using second-line treatments.

There is a strong need for biomarkers allowing for prediction of treatment response to IVIg and future (probably high cost) treatment options. So far, such biomarkers are lacking in CIDP. Therefore, it seemed reasonable to look for genetic factors that could be responsible for response to Ig treatment and could influence Ig metabolism. Recycling of Ig by FcRn is an essential physiological mechanism to maintain constant Ig levels within the body. Thus, polymorphisms of the FcRn could be relevant for the response to IVIG due to more or less rapid degradation of Ig.

If confirmed in future studies, the VNTR genotype could be used to guide therapy decisions in CIDP toward subcutaneous administration or toward treatment other than immunoglobulins in patients with the VNTR 2/3 genotype. Hereby, the *FCGRT* genotype would potentially be a first genetic biomarker to decide for which patients second-line therapy may be appropriate.

Interestingly, the absolute dose of IVIg did not differ between patients with VNTR 3/3 and VNTR 2/3. One reason for this may be that in clinical practice, IVIg dosage is not typically increased beyond the usual level, but rather therapies other than immunoglobulins are used if there is no response to IVIg. Rajabally and Afzal have shown that IVIg dosage depends not only on treatment response but on many other factors, such as cost and availability [20]. This may mean that an inadequate treatment response at a given dose does not always lead to a further dose increase in clinical practice.

Our results are also interesting in light of the development of Fc receptor inhibitors such as efgartigimod. Efgartigimod is an antibody fragment that binds to FcRn and blocks immunoglobulin recycling, resulting in reduced circulating pathologic IgG. Efgartigimod is already approved for the treatment of myasthenia gravis [21] and is currently being investigated in a phase 2 trial in CIDP (ClinicalTrials.gov identifier: NCT04281472). According to a recent press release from Argenx, there is a 61% responder rate to efgartigimod in CIDP patients, whereby a publication of the results is not yet available. Patients with an already genetically reduced level of FcRn expression may benefit less from this therapy than patients with normal FcRn expression.

In literature, influence of VNTR polymorphism on IVIg efficacy was described in common variable immunodeficiency, where IgG rise after IVIg was higher in patients with VNTR 3/3 than VNTR 2/3 [10], and in myasthenia gravis, where the clinical response rate to IVIg in patients with VNTR 3/3 homozygosity was higher than in VNTR 2/3 patients [11]. This contrasts with studies in autoimmune peripheral neuropathies [12, 13]. In particular, Kuitwaard et al. found no association of *FCGRN* variation to response to IVIg measured by modified Rankin Scale after at least one IVIg course in CIDP [14]. A weakness of the Kuitwaard et al. study is that the clinical response was defined using the modified Rankin Scale, which is not recommended to monitor CIDP [16, 22]. Therefore, our advanced evaluation of IVIg dosage and other medications like SCIg and second-line and escalation treatment is probably more reliable. Limitations of the previous studies on Guillain–Barré syndrome and multifocal motor neuropathy have already been discussed by Dalakas and Spaeth [9]; efficacy was only assessed up to 2 and 3 weeks, reflecting response to only one IVIg cycle and not medium- or long-term response.

CIDP is not a primarily autoantibody-mediated disease like myasthenia gravis, in which IVIg therapy leads to increased degradation of endogenous pathologic antibodies, which is less effective in the case of reduced FcRn activity. However, many other effects of IVIg are relevant in CIDP, such as inhibition of complement binding, suppression of pathogenic cytokines, modulation of Fcγ receptors on macrophages, and other cellular effects [6].

A strength of our study is the relatively large number of CIDP patients recruited from the German INHIBIT registry. In this cohort, we have shown that we are dealing with a relevant percentage of genetic alterations in our CIDP patients, which is critical for many subsequent drug trials.

A limitation of our study is that patients with VNTR 2/3 genotype had lower body weight compared to patients with VNTR 3/3 status, which could be explained by the higher proportion of females in the VNTS 2/3 group. An association between body weight or gender and FcRn allele status has not been described before based on large healthy cohorts. However, lower body weight should not lead to increased use of SCIg or second-line therapies. A major limitation of our study is that we did not analyze serum IgG levels. The reasons for the more frequent use of SCIg in the VNTR 2/3 genotype therefore remain speculative, without having IgG data and specifics on why these patients were switched to SCIg and with a low number of SCIg patients in both groups. Moreover, some of the included patients received additional treatment with corticosteroids, which could strongly influence the evaluation of the treatment response. In addition, this study focused on the genetic correlation between *FCGRT* VNTR genotypes and related comorbidities in patients of self-reported German descent, and the results may not be applicable to other subpopulations due to different allele frequencies [23] and linkage disequilibrium pattern. Extended analyses will be needed for further meta-analysis.

CONCLUSIONS

In conclusion, the VNTR 2/3 genotype in CIDP patients is associated with the administration of SCIg instead of IVIg and the need for additional second-line therapies. This may reflect a need for more constant immunoglobulin administration to maintain therapeutic efficacy and a reduced response to IVIg in patients with relatively low FcRn expression. If confirmed in further studies, the *FCGRT* gene polymorphism may help guide treatment decisions in CIDP toward subcutaneous application or toward treatment other than immunoglobulins in patients with genotypes associated with relatively low FcRn expression.

AUTHOR CONTRIBUTIONS

Anna Lena Fisse: Conceptualization; methodology; software; data curation; investigation; validation; formal analysis; supervision; visualization; project administration; writing – original draft; writing – review and editing; resources. **Emelie Schäfer:** Data curation; investigation; formal analysis; visualization. **Alina Hieke:** Data curation; investigation; validation; formal analysis. **Maximilian Schröder:** Investigation; data curation; validation; formal analysis. **Rafael Klimas:** Writing – review and editing; formal analysis; validation. **Jil Brünger:** Validation; formal analysis; writing – review and editing. **Sophie Huckemann:** Validation; formal analysis; writing – review and editing. **Thomas Grüter:** Validation; formal analysis; writing – review and editing; supervision. **Melissa Sgodzai:** Validation; formal analysis; supervision; writing – review and editing. **Christiane Schneider-Gold:** Conceptualization; writing – review and editing; methodology. **Ralf Gold:** Conceptualization; methodology; writing – review and editing; resources. **Huu Phuc Nguyen:** Conceptualization; methodology; writing – review and editing; formal analysis; resources. **Kalliopi Pitarokoili:** Conceptualization; methodology; supervision; formal analysis; validation; investigation; project administration; writing – review and editing; software; data curation; resources. **Jeremias Motte:** Conceptualization; methodology; software; data curation; supervision; formal analysis; validation; investigation; writing – review and editing; resources. **Larissa Arning:** Conceptualization; methodology; software; data curation; supervision; formal analysis; validation; investigation; project administration; writing – original draft; writing – review and editing; resources.

ACKNOWLEDGEMENTS

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

C.S.-G. reports speaker and consulting honoraria from Alexion Pharmaceuticals, Amicus Therapeutics, Argenx, Bayer Vital, Hormosan Pharma, Immunovant, Janssen, Lupin Pharmaceuticals, Roche, Sanofi-Genzyme, and UCB Pharma; and a travel grant from Alexion. The other authors have nothing to declare related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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How to cite this article: Fisse AL, Schäfer E, Hieke A, et al. Association of the neonatal Fc receptor promoter variable number of tandem repeat polymorphism with immunoglobulin response in patients with chronic inflammatory demyelinating polyneuropathy. *Eur J Neurol*. 2024;31:e16205. doi:10.1111/ene.16205