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ORIGINAL ARTICLE

Genetic biomarkers for intravenous immunoglobulin response in chronic inflammatory demyelinating polyradiculoneuropathy

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Abstract

Background and purpose: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinical and electrophysiological heterogeneous immune-mediated polyneuropathy. Intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange are proven effective treatments for CIDP. The clinical response to IVIg is variable between patients and currently unexplained. Finding biomarkers related to treatment response can help to understand the diversity of CIDP and personalise treatment choice.

Methods: We investigated whether genetic variation between patients may explain some of these differences in treatment response. Based on previous publications, we selected six candidate genes that might affect immune and axonal functions, IVIg metabolism, and treatment response in CIDP. Genetic variants were assessed in 172 CIDP patients treated with at least one course of IVIg (2 g/kg). A response to IVIg was defined by ≥ 1 grade improvement on the modified Rankin Scale. Blood samples were tested for variations in *CNTN2*, *PRF1*, *FCGRT*, *FCGR2B*, *GJB1*, and *SH2D2A* genes.

Results: In univariate analysis, patients with the *FCGR2B* promoter variant 2B.4/2B.1 responded more often to IVIg than patients with the 2B.1/2B.1 variant (odds ratio [OR] = 6.9, 95% confidence interval [CI] = 1.6–30; $p = 0.003$). Patients with the p.(Ala91Val) variant of *PRF1* were less often IVIg responsive (OR = 0.34, 95% CI = 0.13–0.91; $p = 0.038$). In

Abbreviations: AUC, area under the receiver operating curve; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMT, Charcot-Marie-Tooth; IVIg, intravenous immunoglobulin; LASSO, least absolute shrinkage and selection operator; MLPA, multiplex ligation-dependent probe amplification; NK, natural killer; OR, odds ratio; PCR, polymerase chain reaction.

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multivariate analysis, both *PRF1* and *FCGR2B* showed discriminative ability to predict the chance of IVIg response (area under the curve = 0.67).

Conclusions: Variations in *PRF1* and the promoter region of *FCGR2B* are associated with the response to IVIg in CIDP. These findings, which require validation, are a first step towards the understanding of the heterogeneity in the treatment response in CIDP.

KEYWORDS

chronic inflammatory demyelinating polyradiculoneuropathy, genetic variation, intravenous immunoglobulin

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated disorder leading to limb muscle weakness, often with sensory disturbances. The majority of patients develop moderate to severe and disabling symptoms that require treatment [1]. Intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange have all been proven to be effective in CIDP [2]. Due to its rapid onset of action and lower occurrence of side effects, IVIg is often the first-choice treatment [3]. Most patients however, need long-term maintenance treatment with IVIg to maintain a stable clinical condition and to prevent (secondary) axonal nerve damage [2]. The required dosage, interval, and duration of IVIg treatment differ between patients [4].

It is not known exactly how IVIg works, why there is a large variation in the required IVIg dosage, and why IVIg is not effective in approximately one quarter of CIDP patients [3,4]. Accurate biomarkers are urgently needed to predict the response to treatment and to adjust the required treatment dose [5,6]. This may help clinicians in choosing the most effective treatment for a specific patient at the onset of the disease. Early initiation of the optimal treatment may prevent unnecessary exposure to expensive or ineffective treatment [4,7].

There are several possible explanations for why IVIg is not effective in a subset of patients with CIDP. First, patients may be incorrectly diagnosed. Several disease mimics can be difficult to distinguish from CIDP, such as paraprotein-related polyneuropathy and Charcot-Marie-Tooth (CMT) disease [8,9]. A common genetic CIDP mimic caused by changes in the *GJB1* gene is X-linked CMT disease with nonuniform nerve conduction slowing and dispersion suggesting nonhereditary demyelination [8,10]. Second, patients may have predominant axonal damage, making the disease less responsive to IVIg [7]. Axonal dysfunction may arise from disturbed axoglial interactions at the paranodes or juxtaparanodes [11]. Genetic variations in contactin 2 (*CNTN2*, also known as transient axonal glycoprotein 1), a cell-adhesion molecule expressed in the juxtaparanode, have been linked to IVIg responsiveness [11]. Axonal damage may also be related to perforin 1 (*PRF1*) gene variations, which are described more often in patients with CIDP [7,12]. Perforin 1 is important for effector functions of natural killer (NK) cells and cytotoxic T cells. Cytotoxic T cells are clonally expanded in blood and peripheral nerves of patients with CIDP [13,14]. The apparent link between axonal damage, IVIg response, and T or NK cell function in CIDP

may suggest that *SH2D2A* is another candidate genetic biomarker. *SH2D2A* encodes for T-cell-specific adaptor protein, and *SH2D2A* variants are reported to be more common in CIDP [15]. A third potential explanation for IVIg unresponsiveness in some patients is variations in genes that affect IVIg metabolism. The pharmacokinetics of IVIg differs considerably between CIDP patients, independent of the IVIg dose and interval [16]. Variation in *FCGRT*, coding for the neonatal Fc receptor that protects IgG from degradation, might influence IVIg clearance and its response [11,17–19]. Last, the effect of IVIg may depend on the functioning of the Fc receptor *FcγRIIb*, which is an inhibitory receptor and a known target of IVIg. Changes in the gene coding for *FcγRIIb* (*FCGR2B*), linked to the development of autoimmune disorders such as CIDP, have been associated with IVIg response in Kawasaki disease [20,21]. Genetic variations may explain differences in IVIg treatment response. Because large unbiased genome-wide association studies are challenging in a rare disease such as CIDP, we performed a candidate gene approach. We investigated genetic variation in *GJB1*, *CNTN2*, *PRF1*, *SH2D2A*, *FCGRT*, and *FCGR2B* in a group of CIDP patients in relation to their IVIg response. Finding biomarkers that are associated with the response to IVIg may help us to improve our understanding of the therapeutic heterogeneity in CIDP and may lead to more personalised treatment regimens for patients with CIDP.

MATERIALS AND METHODS

Patients and treatment

Data were collected retrospectively from clinical trials or medical files from CIDP patients who were diagnosed and treated at the Erasmus MC University Medical Centre between 1980 and 2018. Part of the cohort was described previously [4,22]. Patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society clinical criteria for typical and atypical CIDP [3]. Patients with an IgM monoclonal gammopathy with anti-myelin-associated glycoprotein antibodies were excluded. All included patients were treated with at least one full course of IVIg (2 g/kg). Improvement after initial IVIg treatment was defined by a clinical improvement of at least one grade on the modified Rankin Scale [23]. Patients were only included when the response to IVIg could be determined by a neuromuscular expert (P.A.v.D., B.C.J., and K.K.) and when a blood

sample was available for DNA extraction. This study was approved by the medical ethical committee of the Erasmus MC University Medical Centre in Rotterdam (MEC-2016-624).

Genetic analysis

Genomic DNA was isolated from peripheral blood in EDTA anticoagulated tubes using standard methods. The following candidate genes were investigated: *CNTN2*, *PRF1*, *FCGRT*, *SH2D2A*, *FCGR2B*, and *GJB1*.

CNTN2 and *PRF1*

CNTN2 (NM_005076.3:c.443G>A p.[Ala145 Thr]; rs2275697) and *PRF1* (NC_000010.10:g.72360387G>A p.[Ala91Val]; rs35947132) genotypes were determined by quantitative polymerase chain reaction (PCR) using fluorescently labelled primer/probe sets from Applied Biosystems. Sanger sequencing was used to validate the test using the following primers for *CNTN2* and *PRF1*, respectively: 5'-TTTGGGGGAGGGGAGAG-3' (forward), 5'-AGGC GGAAGCAGGGCACA-3' (reverse) and 5'-CAGCCGCACGCTCAGA GTG-3' (forward), 5'-ACCCCTAGCCCCAGCTCTCAC-3' (reverse).

FCGRT and *SH2D2A*

The variable number of tandem repeats ranging from one to five in the promoter region of the *FCGRT* gene (currently reported as deletion-insertion at location g.49512975 of reference sequence NC_000019.10; rs746313390) was determined by PCR amplification followed by agarose gel electrophoresis as described before [24]. For *SH2D2A* (NC_000001.10:g.156786867GA[10_24]), 200 ng of DNA was added to a master mix containing PCR gold buffer (Applied Biosystems), dNTP (20 mM), MgCl₂ (25 mM), primers, and Taq gold polymerase. Primer sequences were as follows: 5'-CTGCCCCCTCCCTCCTCAT-3' (forward) and 5'-(6-FAM) TGCCCCCTACCCCAA-3' (reverse). The PCR program consisted of 40 cycles of 95°C for denaturation, 60°C for annealing, 72°C for elongation, and 15°C for the final hold. Subsequently product lengths were determined using Gene Scan analysis. The length of the GA repeat in the promoter area of the *SH2D2A* gene is bimodally distributed; therefore, a GA repeat of ≤16 was designated as "short" and a GA repeat of >16 was designated as "long" [25].

FCGR2B

Genetic variations in the 2-kb promoter region of *FCGR2B* (NM_004001.4:c.-386G>C; rs143796418 and NM_004001.4:c.-120 T > A; rs780467580) of the *FCGR2B* gene and in the transmembrane region (NM_004001.4:c.695 T > C p.[Ile232 Thr], rs1050501)

were determined by multiplex ligation-dependent probe amplification (MLPA). The *FCGR2B* promoter variant alleles were defined as 2B.1 (c.[-386G;-120 T]), 2B.2 (c.[-386C;-120 T]), or 2B.4 (c.[-386C;-120A]). The combination c.[-386G;-120A] has never been reported in *FCGR2B*. The MLPA procedure was carried out as previously described [26,27].

GJB1

The promoter (P1 and P2) and coding region of the *GJB1* gene was sequenced using routine clinical genetic diagnostic methods. Primer sequences are available upon request.

Statistical analysis

Chi-squared tests, chi-squared tests for trend, or Fisher exact tests were used to compare the response to IVIg between patients with different clinical characteristics as well as in patients with different genetic variants. Age at start of IVIg treatment was compared between patients who responded and did not respond to IVIg as well as in patients with different genetic variants using unpaired t-test or one-way analysis of variance. A two-tailed *p*-value < 0.05 was considered statistically significant. To verify whether the genotype frequencies were in Hardy-Weinberg equilibrium, the method of Ott was used. We modelled the odds of responding to IVIg using a multivariate logistic regression model. To prevent overfitting and minimise prediction error, we used regularisation employing the least absolute shrinkage and selection operator (LASSO) method [28]. Regularisation is a statistical technique that is often applied in machine learning prediction modelling. To prevent a large number of coefficients relative to the size of the dataset leading to large variability of estimates and large errors, the LASSO method places a penalty on the absolute size of the coefficients in the likelihood function. As an added benefit, the method will also lead to more interpretable models, because the LASSO method usually sets some coefficients to zero, thereby selecting the most informative variables for the model. Cross-validation was used to find the optimal penalty factor [28]. Model performance was quantified with respect to discrimination by the area under the receiver operating curve (AUC). The AUC ranges from 0.5 to 1.0 for sensible models [29]. Statistical analysis was conducted using SPSS Statistics for Windows, version 24 (IBM; 2016) and R: A Language and Environment for Statistical Computing, version 3.5.1 (R Foundation for Statistical Computing; 2018).

RESULTS

Patient cohort

In total, 172 CIDP patients were included. Of these 172 patients, 65% were male. The median age of IVIg commencement was 55 years (range = 2-90), and the overall response rate to IVIg was

79% ($n = 136$). In this cohort 66% of the patients who improved after IVIg were male and 67% of the patients who did not improve after IVIg were male ($p = 1.0$). The percentage of acute onset CIDP was no different in the group of patients who improved after IVIg compared to the patients who did not improve (40% vs. 36%, $p = 0.69$). The age of patients when IVIg treatment was started was not different in patients who responded compared to patients who were unresponsive to IVIg (mean = 51 years vs. 55 years, $p = 0.50$). Clinical characteristics in different genotype subgroups are listed in Tables S1 and S2.

Genetic association studies

We were able to determine *CNTN2*, *PRF1*, and *FCGR2B* genotypes in all 172 patients. *FCGRT* and *SH2D2A* genotypes were defined successfully in 163 and 166 patients, respectively. All genotypes were in Hardy-Weinberg equilibrium. From 169 patients, enough DNA was available to test for *GJB1*. No disease-associated changes were observed in the *GJB1* gene in any of the 169 samples.

The response to IVIg in relation to the different genotypes is shown in Table 1. In univariate analysis, patients with the heterozygous p.(Ala91Val) variant of *PRF1* were less likely to be IVIg responsive (odds ratio [OR] = 0.34, 95% confidence interval [CI] = 0.13–0.91; $p = 0.038$). Patients with the 2B.4/2B.1 variant of *FCGR2B* were more likely to be responsive to IVIg than patients with the 2B.1/2B.1 variant (OR = 6.9, 95% CI = 1.6–30; $p = 0.003$). To analyse the contribution of all genotypes, we performed multivariate logistic regression using the LASSO penalty. Patients with missing genotype data for *FCGRT* or *SH2D2A* could not be included in the multivariate analysis; furthermore, the rare variants that only occurred in one patient were left out of this multivariate analysis. In the resulting multivariate LASSO logistic regression (Table 2; $n = 157$), the *PRF1* p.(Ala91Val) variant was negatively associated with the IVIg response (OR = 0.57), whereas the *FCGR2B* promoter 2B.4/2B.1 variant was positively associated with a response (OR = 2.56). All other covariates were shrunken towards zero. Together, *PRF1* and *FCGR2B* promoter variants showed discriminative ability (AUC = 0.67) in predicting the chance of IVIg response. Clinical characteristics such as gender, age at start of IVIg treatment, and disease course (acute onset) did not differ in genotype subgroups (Tables S1 and S2).

DISCUSSION

We determined that genetic variations in *PRF1* and the promoter region of *FCGR2B* are associated with the response to IVIg in CIDP. The p.(Ala91Val) variant of *PRF1* was negatively associated, whereas the *FCGR2B* promoter 2B.4/2B.1 variant was positively associated with a response to IVIg. Variations in *CNTN2*, *FCGRT*, and *SH2D2A* were not associated with IVIg response.

Perforin is important for cytotoxic functions of T cells, NK cells, and NK T cells [12]. Both cytotoxic T cells and NK T cells were recently reported to be elevated in the cerebrospinal fluid of CIDP

TABLE 1 IVIg response in chronic inflammatory demyelinating polyradiculoneuropathy patients with different genetic variations

Genotype	Unresponsive to IVIg, n (%)	Responsive to IVIg, n (%)	<i>p</i>
Total	36 (21%)	136 (79%)	
<i>PRF1</i> p.(Ala91Val), $n = 172$			
Ala/Ala	28 (18%)	124 (82%)	
Ala/Val	8 (40%)	12 (60%)	0.038 ^a
<i>CNTN2</i> p.(Ala145 Thr), $n = 172$			
Ala/Ala	23 (19%)	98 (81%)	
Ala/Thr	13 (27%)	35 (73%)	
Thr/Thr	0 (0%)	3 (100%)	NS
<i>FCGRT</i> VNTR, $n = 163$			
2/2	0 (0%)	1 (100%)	
3/2	5 (16%)	26 (84%)	
3/3	29 (23%)	101 (78%)	
3/5	0 (0%)	1 (100%)	NS
<i>FCGR2B</i> promoter, $n = 172$			
2B.1/2B.1	33 (26%)	95 (74%)	
2B.4/2B.1	2 (5%)	40 (95%)	
2B.4/2B.2	1 (100%)	0 (0%)	
2B.4/2B.4	0 (0%)	1 (100%)	0.006 ^a
<i>FCGR2B</i> p.(Ile232 Thr), $n = 172$			
Ile/Ile	30 (21%)	111 (79%)	
Ile/Thr	6 (20%)	24 (80%)	
Thr/Thr	0 (0%)	1 (100%)	NS
<i>SH2D2A</i> VNTR, $n = 166$			
GA≤16/GA≤16, short/short	2 (13%)	14 (88%)	
GA≤16/GA>16, short/long	15 (22%)	54 (78%)	
GA>16/GA>16, long/long	18 (22%)	63 (78%)	NS

Note:: To compare the response to IVIg between patients with different genetic variants, chi-squared tests, chi-squared tests for trend, or Fisher exact tests were used.

Abbreviations: IVIg, intravenous immunoglobulin; NS, not significant; VNTR, variable number of tandem repeats.

^aStatistically significant.

patients [30]. The variant p.Ala91Val is known to reduce the cytotoxic activity of perforin due to protein misfolding [31]. We found that CIDP patients with the p.(Ala91Val) *PRF1* variant were less responsive to IVIg. *PRF1* genetic variants are reported to be more prevalent in CIDP patients with axonal damage, suggesting a possible association with treatment response [12]. Axonal nerve damage, usually reflected by muscle atrophy and a reduced compound muscle action potential, has been associated with a poor response to IVIg in CIDP [7,11,32]. Although no systematic electrodiagnostic data were available in our cohort, axonal damage might explain the lack of IVIg response we found in patients carrying the *PRF1* variant. Whether the axonal damage itself or the variation in *PRF1* causes the lack of

TABLE 2 Multivariate logistic regression of intravenous immunoglobulin response ($n = 157$)

Genotype	OR
<i>PRF1</i> p.(Ala91Val)	
Ala/Ala (reference)	1.0
Ala/Val	0.57
<i>FCGR2B</i> promoter	
2B.1/2B.1(reference)	1.0
2B.4/2B.1	2.56

Abbreviation: OR, odds ratio.

response needs further exploration. Furthermore, genetic variation in *PRF1* was associated with a relapsing course suggesting a demyelinating form more responsive to IVIg [12]. The p.Ala91Val variant has been associated with several immune-mediated disorders such as multiple sclerosis and systemic onset juvenile idiopathic arthritis, suggesting that *PRF1* variants predispose to autoimmunity [33]. *PRF1* variants are also reported more often in CIDP compared to healthy controls, but whether CIDP patients with p.Ala91Val *PRF1* represent a different subgroup in which dysfunction of cytotoxic T cells and NK T cells leads to nerve damage that is unresponsive to IVIg needs further exploration [12].

CIDP patients with the 2B.4/2B.1 promoter genotype for *FCGR2B* were more likely to be IVIg responsive. The Fc γ R11b receptor is expressed by monocytes, macrophages, dendritic cells, and B cells and is a negative regulator of cellular activation, proliferation, and cytokine production [20]. Fc γ R11b may contribute to the therapeutic action of IVIg, because disruption of the Fc γ R11b pathway by genetic deletion or a blocking monoclonal antibody can reverse the therapeutic effects of IVIg in rodents [34]. However, it must be noted that the role of Fc γ R11b is dependent on the mouse strain and IVIg dose [35]. Our findings support the concept that Fc γ R11b is important for the therapeutic action of IVIg in CIDP, as the 2B.4 variant has been reported to induce de novo expression of Fc γ R11b on monocytes and neutrophils and may therefore lead to more effective inhibition by IVIg [27]. It is also possible that the 2B.4 haplotype promoter activity is higher than in the more common 2B.1 haplotype, resulting in increased expression [36]. Our data suggest that increased expression of Fc γ R11b is beneficial to IVIg treatment in CIDP. The cell type responsible for the Fc γ R11b-mediated beneficial effect of IVIg should be further investigated. In Kawasaki disease, another IVIg responsive immune-mediated disease, it was also shown that patients carrying the 2B.4 variant were more likely to be IVIg responsive [21]. Of note, the association between IVIg response and *FCGR2C*-ORF (data not shown), which is in linkage disequilibrium with the 2B.4 promoter haplotype [26] was less strong ($p = 0.05$; data not shown), suggesting that Fc γ R11b is more important in mediating the beneficial effect of IVIg than Fc γ R11c. In addition, we could not find an association between *FCGR2B* p.(Ile232 Thr) and the response to IVIg in CIDP. Because *FCGR2B* p.(Ile232 Thr) is well known to impact signalling through Fc γ R11b, our data suggest that the expression level or pattern of Fc γ R11b, rather than its signalling strength, is important for IVIg efficacy [37]. In addition to its role in

IVIg treatment response, Fc γ R11b is likely to influence the susceptibility to other autoimmune disorders and CIDP [20,38]. Although we did not compare the frequency of *FCGR2B* with healthy controls, it is notable that we found a lower percentage of the 2B.4/2B.1 genotype in CIDP than previous reports [20]. Similar to a study in Guillain-Barré syndrome patients, we were unable to find an association between IVIg efficacy and variation in *FCGR2B* [24].

We could not confirm the association between *CNTN2* variations and response to IVIg found in a Japanese group of patients, which may be explained by the different genetic background [11]. It is known that the allele frequency of *CNTN2* p.Ala145 Thr is higher in Europe compared to Asia (1000 Genomes Browser, accessed 28 August 2020, <https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/>) [39].

We demonstrate that genetic variations in *PRF1* and *FCGR2B* genes may partly explain the variability in IVIg response in CIDP patients. The rarity of the disease and overall good responsiveness to IVIg limits the chance of demonstrating an association between genetic variants and treatment efficacy. Also, the frequency of some of the genetic variations was low. Furthermore, we used quite a strict cutoff value of at least one grade improvement on the modified Rankin Scale for IVIg response to ensure a clear and clinically relevant improvement. It would have been interesting to know not only the initial response to IVIg, but also the dose and frequency required during maintenance treatment. Currently, hardly any genetic association studies have been conducted in CIDP to explain the variation in treatment response [11]. To our knowledge, this is the largest study investigating genetic variations in association with IVIg response in CIDP so far. Our study population seems representative of the general CIDP population regarding age, male predominance, and response rate to IVIg [2,4]. Moreover, the long follow-up of most patients improved the diagnostic certainty in our cohort, which is important because misdiagnosis of CIDP has been reported in a randomised controlled trial in 58% of treatment-unresponsive patients [40]. Limitations of our study are its relatively small sample size for a genetic study, its retrospective nature, and that our patients were mainly of European descent. Furthermore, we were unable to measure each genetic variant in all patients. The association of *PRF1* and *FCGR2B* promoter variants with the response to IVIg in CIDP found in our study needs replication in another study. The Dutch CIDP Outcome Study, an observational prospective cohort study, and the international INCbase might be good platforms to validate our results on a larger scale and to study genetic variants related to treatment response in CIDP patients from different geographical areas [41]. In addition, these studies use other outcome scales that may detect more subtle changes in the severity of the disease course and outcome. Ultimately, these pharmacogenomic studies may lead to a more personalised therapeutic approach improving the clinical outcome of patients by selecting the optimal treatment type and regimen at an early disease stage.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Krista Kuitwaard: Conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), writing—original draft (lead), writing—review & editing (equal). **Pieter A. Van Doorn:** Conceptualization (equal), data curation (equal), investigation (equal), methodology (equal), writing—review & editing (equal). **Thiziri Bengrine:** Investigation (equal), project administration (equal), writing—original draft (equal). **Wouter van Rijs:** Data curation (equal), investigation (equal), project administration (equal), writing—review & editing (equal). **Frank Baas:** Data curation (equal), investigation (equal), resources (equal), writing—review & editing (equal). **Sietse Q. Nagelkerke:** Data curation (equal), investigation (equal), resources (equal), writing—review & editing (equal). **Taco W. Kuijpers:** Data curation (equal), investigation (equal), resources (equal), writing—review & editing (equal). **Willem-Jan R. Fokkink:** Data curation (equal), investigation (equal), writing—review & editing (equal). **Carina Bunschoten:** Data curation (equal), writing—review & editing (equal). **Merel C. Broers:** Data curation (equal), writing—review & editing (equal). **Sten P. Willemsen:** Formal analysis (lead), methodology (lead), writing—review & editing (equal). **Bart C. Jacobs:** Conceptualization (equal), investigation (equal), methodology (equal), writing—review & editing (equal). **Ruth Huizinga:** Data curation (equal), investigation (equal), supervision (lead), writing—original draft (equal), writing—review & editing (lead).

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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