CIDP Antibodies Target Junction Proteins and Identify Patient Subgroups
An Autoantigenomic Approach

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Abstract

Objective
To discover systemic characteristics in the repertoires of targeted autoantigens in chronic inflammatory demyelinating polyneuropathy (CIDP), we detected the entire autoantigen repertoire of patients and controls and analyzed them systematically.

Methods
We screened 43 human serum samples, of which 22 were from patients with CIDP, 12 from patients with other neuropathies, and 9 from healthy controls via HuProt Human Proteome microarrays testing about 16,000 distinct human bait proteins. Autoantigen repertoires were analyzed via bioinformatical autoantigenomic approaches: principal component analysis, analysis of the repertoire sizes in disease groups and clinical subgroups, and overrepresentation analyses using Gene Ontology and PantherDB.

Results
The autoantigen repertoires enabled the identification of a subgroup of 10/22 patients with CIDP with a younger age at onset and a higher frequency of mixed motor and sensory CIDP. IV immunoglobulin therapy responders targeted 3 times more autoantigens than nonresponders. No CIDP-specific autoantibody is present in all patients; however, anchoring junction components were significantly targeted by 86.4% of patients with CIDP. There are potential novel CIDP-specific autoantigens such as the myelination- or axo-glial structure–related proteins actin-related protein 2/3 complex subunit 1B, band 4.1-like protein 2, cadherin-15, cytohesin-1, epidermal growth factor receptor, ezrin, and radixin.

Conclusions
The repertoire of targeted autoantigens of patients with CIDP differs in a systematic degree from those of controls. Systematic autoantigenomic approaches can help to understand the disease and to discover novel bioinformatical tools and novel autoantigen panels to improve diagnosis, treatment, prognosis, or patient stratification.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disease of the peripheral nervous system that is considered to be immune mediated.\(^1\)\(^2\) Pathogenetic antibodies directed to proteins of the region of the node of Ranvier permit the identification of a small subgroup of patients \(<10\%\) of CIDP) with particular features and therapeutic responses.\(^3\)\(^-\)\(^5\) However, in the majority of patients, no specific antibodies have been identified so far. This may be due to unsuitable identification methods or due to inappropriate hypotheses of one main antigen being targeted by the immune system. Indeed, the immune response is probably a complex process involving several antibodies and several targets with different functions in the development of the immune response and its regulation. In this case, a systemic approach may lead to a better understanding of immune-mediated diseases.\(^6\)\(^-\)\(^9\) Hence, recent methods aiming at identifying and understanding the entire repertoire of targeted autoantigens via autoantigenomics have been developed for the study of the immune response.\(^10\) Thus, instead of focusing on single autoantigens, this study takes an autoantigenomic approach pointing to the entire autoantigen repertoire in a systematic way via bioinformatical tools. To do so, sera from 43 subjects were tested with HuProt 3.1 Human Proteome arrays containing 15,798 human proteins expressed in yeast, representing about 75% of the gene-centric human proteome.

**Methods**

**Standard Protocol Approvals, Registrations, and Patient Consents**

The retrospective case-control and observational study involves the use of sera from human subjects, was approved by the ethical committee of the University Hospital of Saint-Etienne, France, and has been performed in accordance with the Code of Ethics of the World Medical Association (the Declaration of Helsinki). All participants provided written informed consent. The privacy rights of human subjects were observed. No animal experiments were conducted for this study.

**Subject Selection, Description of Population, and Serum Preparation**

We collected serum samples from 22 patients with definite CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society guidelines.\(^11\)

Selection criteria were the following: definite form of CIDP,\(^11\) age \(\geq 18\) years, and absence of severe secondary axonal degeneration according to the electroneuromyography (ENMG). Definite CIDP was either typical (typical clinical presentation, typical ENMG data) or atypical CIDP (atypical clinical presentation, typical ENMG data).\(^11\)\(^,\)\(^12\) The choice of treatment was at the discretion of the neurologist who cared for the patients.

As controls, we selected roughly age and sex-matched sera samples from 12 patients with other peripheral neuropathies (ONP), 11 of whom with an associated autoimmune context—7 Sjögren syndrome (SjS), 1 autoimmune hepatitis, 1 sarcoidosis, 1 systemic lupus erythematosus, and 1 undifferentiated connective tissue disease—and 9 healthy controls (HCs) originating from the blood donation service of the French Blood Establishment in Saint-Etienne, France. All samples were selected retrospectively. Sera were prepared and stored as previously described.\(^13\)

**Clinical Data**

For all subjects, we obtained demographic data such as age at sampling date and sex. For patients with CIDP, the following clinical data were obtained in addition: age at disease onset, course of the disease, type and topography of neurologic symptoms, type of disease’s progression (chronic evolution with or without relapse or only relapses), modified Rankin scores (mRSs) during the disease course,\(^14\) ENMG data,\(^15\) biological data (CSF proteins or monoclonal gammopathy), presence of ataxia, presence of pain, concerned nerve type (sensory or motor), onset delay (acute \(\leq 2\) months, subacute \(= 2-6\) months, or chronic \(\geq 6\) months),\(^12\) and IV immunoglobulin (IVIg) response defined as an increase of the INCAT score by \(\geq 1\) after a treatment period of 3 months.\(^16\) Because of the low number of patients treated with other immunomodulatory treatment, we did not address their response. For the comparison of IVIg responders versus nonresponders, we tested for biasing confounder effects (sampling age, delay between disease onset and sampling date, comorbidities, monoclonal gammopathy, clinical severity before treatment, and clinical presentation).

**Protein Microarrays and Definition of Repertoires**

Sera were tested on HuProt 3.1 Human Proteome microarrays (CDI Laboratories, Baltimore, MD) as described previously.\(^17\) Most of the proteins, 14,870 (94.1\%) in numbers, are full-length proteins. The full lists of resulting group-specific antigen repertoires were applied for the set of bioinformatical methods described below, aiming at a systemic understanding.
Principal Component Analyses
To compare the autoantigen repertoires of CIDP and ONP + HC, principal component analysis (PCA) was performed with the software tool from The Institute for Genomic Research, multiple experimental viewer (tigr.org/software/tm4/mev.html). PCA analysis was performed with the combined sets of intra-z values of the 3 study group-specific repertoires to identify systemic differences between them and to explore the repertoire in CIDP for potential subgroups.

Number of Targeted Antigens Per Subject
For each patient, the number of targeted antigens was counted if both of the following criteria were fulfilled: (1) intra-z score ≥2.5 and (2) inter-z score ≥4. For each study group, the corresponding other 2 study groups were used as the basis for calculating mean and SD.17

Panther Analysis: Gene Ontology Overrepresentation Test
PANTHER online software (pantherdb.org/) was applied to identify the Gene Ontology (GO) Cellular Component categories covered by the repertoires of targeted antigens (described in more detail in e-Methods, links.lww.com/NXI/A385). In the first selection steps, we selected only categories that fulfilled all of the following categories: (1) contain ≥3 targeted proteins; (2) whose number of targeted proteins is ≥5× higher for 1 of the 3 groups compared with the corresponding other 2; and (3) cover ≥4% of the CIDP or ONP repertoires. For the analysis based on the group-specific antigen repertoires, the percentage represents the frequency of targeted proteins set in relation with the repertoire size. Statistical analyses selected the categories that were significantly overrepresented in the CIDP repertoire compared with the HC repertoire.

Statistics
To show the statistical dispersion, we used the median with the 25th and 75th percentiles (abbreviated Q1–Q3 in the text) or the mean with 95% CI. For the nonparametric hypothesis tests (comparison of numbers of targeted antigens per patient), we used the Wilcoxon-Mann-Whitney test (1-sided for H1: a<b, i.e., study groups and IVIg response in the per patient), we used the Wilcoxon-Mann-Whitney test (1-hypothesis tests (comparison of numbers of targeted antigens text) or the mean with 95% CI. For the nonparametric hy-
varied from 2 to 8. As a quality control for the HuProt 3.1 protein arrays, we used the identification by the array of well-characterized autoantibodies detected by routine antibody-screening of sera for organ and non–organ-specific antibodies. Thus, gastritis autoantibody against the plasma membrane protein H⁺/K⁺-ATPase in a patient with CIDP and anti-SSA1 and SSA2 antibodies in 3 patients with OND and SjS syndrome were identified by the protein array.
The Repertoire of Targeted Antigens Identifies Subgroups of Patients With CIDP

The variation explained by the first 3 principal components (PCs) of the PCA was 23% (PC1 = 10%, PC2 = 8%, and PC3 = 5%), indicating a mild general discrimination of the 3 study groups. A subgroup of 10 patients with CIDP clustered (PCA cluster 1, blue ellipse, figure 2, A and B) apart from the ONP, HC, and the remaining 12 CIDP samples (PCA cluster 2, red ellipse, figure 2, A and B) when plotting PC2 and PC3, suggesting that these patients had a specific autoantigenome.

In the univariate model, clinical data of PCA clusters 1 and 2 were compared (table e-1, links.lww.com/NXI/A385). A younger age at onset and a higher frequency of mixed motor and sensory form of CIDP were associated with patients with CIDP of PCA cluster 1.

More Antigens Targeted in IVIg Responders

Among CIDP, the number of reactive antigens was not correlated with age at onset and sampling, sex, CIDP subtype, onset, course, pain, ataxia, maximal mRS, axonal loss or conduction blocks on ENMG, or serum-storing duration (figure 1, C–N).

However, we found on average 3 times more reactive antigens in IVIg responders compared with nonresponders (responders’ mean: 22; CI: 15.9–28.9; nonresponders’ mean: 8; CI: 2.9–12.1; p = 0.01, false discovery rate ≤0.05; figure 1B). To exclude potential confounder effects, we compared IVIg responders vs nonresponders and found no differences concerning sampling age, delay between disease onset and sampling, presence of comorbidities, monoclonal gammopathy, clinical severity before treatment, clinical presentation, and electrophysiologic data, apart from the presence of...
Anchoring Junction Proteins Were Significantly Targeted by Sera of Patients With CIDP

Two hundred seventy-five (38.4%) antigens among the CIDP repertoire, 79 (35.0%) antigens among the ONP repertoire, and 61 (38.4%) antigens among the HC repertoire were annotated to at least one of the cellular components, “Plasma membrane” and/or “Extracellular space” according to GO.

The overrepresentation analysis of cellular components with the Panther algorithm showed that the category “anchoring junction” was significantly overrepresented in the CIDP repertoire compared with the HC repertoire (figure 3A). Nineteen of 22 patients with CIDP (86.4%) had antibodies against at least one of these proteins. In average, each of the detected anchoring junction proteins was targeted by 3.6 (CI: 2.2–5.0) patients with CIDP, which is significantly more than for each of the rest of CIDP-specific non–junction proteins being targeted by an average of 2.2 patients each (CI: 2.0–2.3; difference of mean 1.4 [CI 0.002–2.8]; figure 3B). Twenty-one of 35 (60.0%) targeted anchoring junction proteins were annotated to the cellular components “Plasma membrane” (15/35, 42.9%) and/or “Extracellular region or secreted” (16/35, 45.7%) according to GO and are listed in table 1. Although expressed in a wide range of organs, most of them (19/21) are known to play roles in the nervous system or even more specifically in the peripheral nervous system (13/21). Seven of them are known to play roles in myelination or in the organization or maintenance of axo-glial structures (actin-related protein 2/3 complex subunit 1B, band 4.1-like protein 2, cadherin-15, cytohesin-1, epidermal growth factor receptor, ezrin, and radixin). Each of the CIDP-specific anchoring junction protein was targeted by 1–6 patients, and each patient reacted with 0–14 of junction proteins.

Discussion

Autoantigenomics provides the opportunity to mine systemic comprehension from autoantibody repertoires.10 Using bio-informatical tools known from proteomics,21,22 this method seeks to discover significant patterns in the repertoire of targeted autoantigens. In other words, instead of the classical approach of searching 1 single autoantibody and defining the vast rest as noise, autoantigenomics is focusing on related sets of autoantigen groups that emerge from the data set. In this study, we implemented this systemic mining for 716 CIDP-specific antigens, resulting from a quasi-proteome-wide screening of 22 patients with definite CIDP. Although seemingly low, our sample sizes are in the same range as those of similar protein microarray studies.23–25

Our approach resulted in the following main conclusions. On a systematic level, (1) the recognized repertoire of targeted antigens enables the identification of patient subgroups with differing clinical patterns and responses to IVIg; (2) anchoring junction proteins are a significant target of the CIDP-specific antibody repertoire; and (3) on a single antigen level, our approach revealed several novel interesting autoantigens that could be embarked on by the community.

The antigen repertoire specific to CIDP identified in this study contains hundreds of proteins of which only 25% were recognized
by several patients, showing that the greater part of the antibody response is individual and fingerprint-like.\textsuperscript{26} We found no specific antigen recognized by all the patients but groups of antigens that are targeted by several patients. This suggests that there is low chance of identifying 1 biomarker antibody for typical CIDP, even if the panel of antigens used in the study does not cover the totality, but only 75% of the human proteome, leaving open the possibility that this particular antigen is by chance in the missing part of the antigenome or spotted in a nonreactive conformation.

Instead, we found a complex antibody response. Of interest, this global antibody response was not produced haphazardly as it is correlated with different clinical aspects of the CIDP. Thus, using the CIDP-specific antigenome, PCA identified a cluster of 10/22 (45%) deviant patients who were younger at disease onset and more often had a mixed motor and sensory form of CIDP. Furthermore, patients who were IVIg responders targeted on average 3 times more antigens than IVIg nonresponders, and this was an independent effect. All these results, and especially those concerning the response to IVIg, were obtained with a low number of patients and need to be confirmed on a larger series. However, they are in keeping with the fact that CIDP is a heterogenous entity\textsuperscript{27} and that response to IVIg in this disease probably depends on complex

### Table 1 Anchoring Junction Proteins Associated With the Plasma Membrane or Extracellular Space

| Protein name | Known role in the nervous system | Impact on actin cytoskeleton |
|--------------|---------------------------------|-----------------------------|
| 14-3-3 protein zeta/delta | Regulates spine maturation | − |
| Actin-related protein 2/3 complex subunit 1B | Process extension and axon ensheathment during myelination; in PNS: actin cytoskeleton regulation of DRG growth cones | + |
| Annexin A6 | In PNS: scaffolding protein during membrane biogenesis and Ca\textsuperscript{2+} conductance modulation in sensory neurons | + |
| Band 4.1-like protein 2 | In PNS: axo-glial organization and maintenance in myelinated axons | + |
| Brain-specific angiogenesis inhibitor 1-associated protein 2 | Filopodia formation; dendritic branch formation; synaptic transmission | + |
| Brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1 | In PNS: biomarker for mechanical nociceptor type of DRG neurons | + |
| Cadherin-15 | In PNS: potential roles in axon/Schwann cell interactions and node of Ranvier structural maintenance | − |
| CD59 glycoprotein | Protecting from autoimmune neurologic disease and neural lesions; in PNS: deficiency can present as CIDP | − |
| Cdc42 effector protein 4 | Scaffold protein contributing to glia-neuron configuration | + |
| Cell surface glycoprotein MUC18 | Role in neuroinflammation; neurite extension | + |
| Copine-3 | In PNS: regulation of myelination | + |
| Coronin-1B | In PNS: regulation of neurite outgrowth, nociception | − |
| Cytohesin-1 | In PNS: regulation of myelination | + |
| E3 ubiquitin-protein ligase CBL | Role in microglia-mediated neuroinflammation; neuroprotective role | + |
| Epidermal growth factor receptor | Regulation of myelination via oligodendrocyte maturation; astrocyte differentiation and maturation. In PNS: regulation of neurite outgrowth, nociception | + |
| Ezrin | In PNS: node of Ranvier formation; concentrated at node of Ranvier and colocalizes with NF155 | + |
| Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 1 | In PNS: scaffolding for ion transport in DRG neurons; role in thermal nociception and acute inflammatory pain | + |
| Poly(rC)-binding protein 2 | Neuronal cell proliferation and apoptosis; in PNS: Schwann cell proliferation after nerve injury | − |
| Protein disulfide-isomerase A3 | Neuroprotective role; in PNS: supporting peripheral nerve regeneration | − |
| Radixin | Neuroblast proliferation and migration; in PNS: node of Ranvier formation | + |
| Transducin-like enhancer protein 2 | Regulation of neuronal differentiation | − |

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; DRG = dorsal root ganglia; PNS = peripheral nervous system. Categories according to Gene Ontology. Literature references in e-Methods, links.lww.com/NXI/A385.
immunologic factors specific to subgroups of patients.28 The identification of these subgroups may be helpful for treatment management and patient stratification in clinical trials.

An interesting finding is that anchoring junction proteins, although in a numerical minority in the human antigenome, are overrepresented in the repertoire of targeted antigens of CIDP. This was a general phenomenon since 86.4% of the patients with CIDP had antibodies against at least one of these proteins. The fact that each identified anchoring junction protein was on average targeted by significantly more patients with CIDP than all other CIDP-specific antigens also suggests that this is not an incidental antigen set. Anchoring junction proteins are important for maintaining the neuronal–glial cell shapes. Most of our detected anchoring junction proteins (14/21) interfere in some way with the actin cytoskeleton; 7 shapes. Most of our detected anchoring junction proteins (14/21) interfere in some way with the actin cytoskeleton; 7 are known to play a role in the myelination or axo-glial structuring process (table 1). In addition, given their roles or locations in the peripheral nervous system, 3 of these proteins (CD59 glycoprotein, Ezrin, and Radixin) have previously been discussed as potential targets for autoantibodies in de-myelinating neuropathies.29,30

Other junction31–33 or cell adhesion34–37 proteins of the nodal and paranodal region including contactin-1 and neurofascin 155 and 186 have been identified as antibody targets in subgroups of CIDP, confirming that these protein groups comprise important autoantigens in CIDP. However, in contrast to the predominantly neural proteins contactin-1 and neurofascin 155 and 186, the proteins identified in our study are—despite their roles in the nervous system—mostly widely expressed. Contactin-1 and neurofascin 155 and 186 are not on the HuProt 3.1 array. None of the 7 node of Ranvier proteins spotted on the arrays were targeted by the patients’ sera. Thus, proteins specific to the node of Ranvier are probably not the main targets of antibodies in CIDP as a whole but only in a subgroup of patients who had a specific form of CIDP or even form another disease entity (e.g., [para-]nодopathy).38

Because of the low number of only 3 anti–junction protein–negative patients, it was not possible to determine whether a specific clinical pattern is associated with the targeting of these proteins. Antibodies reacting with the nodal and paranodal regions are probably causally involved in the lesioning process by interfering with their target.5,39,40 Whether this is the case with the antibodies identified in this study is not yet determined. Although the complex specific antibody response is linked with clinical characteristics of the CIDP, it is not possible to know whether it contributes to the lesioning process or is a secondary phenomenon or a mixture of both. Regarding a diagnostic potential, each of the antibodies identifies a restricted proportion of patients, as do the known antibodies reacting with the node of Ranvier. However, several of them, alone or in combination, may be candidate biomarkers for the diagnosis of CIDP or for managing the treatment by IVIg.

In conclusion, this article describes the application of autoantigenomics, i.e., the systematic analysis of the whole autoantigen repertoire, in the neurology field. The identified candidates present novel potential antibody targets of CIDP that could be embarked on—either as single antigens or panels—by the community. The discovered set of antibodies against anchoring junction proteins may be of interest for diagnostics, prognosis, and patient stratification. At the same time, the research community interested in not only CIDP but also other inflammatory neuropathies might broaden their view from single candidates to a more systematic view of antigen repertoires. Functional or compartmental sets of targeted antigens suggest novel, more systematic tools to diagnose and understand autoimmune neuropathies.

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Appendix

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