SUPPLMENTARY METHODS

**ELISA**

Polystyrene microwells were coated with 1µg/mL of human recombinant Nfasc155 (OriGene), or 0.5µg/mL of human recombinant CNTN1 (Sino Biological Inc) at 4°C overnight. Plates were then blocked with 5% nonfat milk in phosphate buffer saline (PBS) at room temperature (RT) for 1 hour and incubated with sera diluted 1:100 in 2% nonfat milk in PBS, at RT for 1 hour. Horseradish peroxidase-conjugated goat antibody to human IgG (dilution, 1:6000; DAKO), or IgG subclasses (dilution, 1:500; Invitrogen) was added, and plates were developed with tetramethylbenzidine (Sigma-Aldrich). Plates were washed between each incubation with phosphate buffer saline (PBS), and subsequently read at 450 nm (ELx800, Biotek). Positive results were defined as those showing optical density (OD) values above the OD mean values of HCs plus three standard deviations.

**Cell-based assay**

Myc-tagged human Nfasc155 (NM\_001160331.1), Myc-tagged human Nfasc186 (NM\_001005388.2), human CNTN1 (NM\_001843.3), and human Caspr1 (NM\_003632.2) CBAs have been described in previous studies (6,10). Briefly, human embryonic kidney (HEK) cells were transfected with CNTN1, Nfasc155, Nfasc186, Caspr1, or Caspr1/CNTN1 using JetPEI (Polyplus-transfection); 48 hours later, cells were incubated with patients’ sera (diluted 1:50 in Opti-MEM) for 20 minutes at 37°C, then washed in PBS, fixed with paraformaldehyde 2% in PBS, and blocked with blocking solution (5% fish skin gelatin containing, 0.1% Triton X-100 in PBS). This step was aimed to saturate the free epitopes, and to prevent non-specific binding of the sera, and of primary and secondary antibodies. HEK cells were then incubated with primary antibodies for 1 hour: mouse anti-Myc (dilution, 1:200; Roche), rabbit anti-Caspr1 (dilution, 1:2000), or goat anti CNTN1 (dilution, 1:2000; R&D systems). Cells were then incubated with the appropriate Alexa Fluor® conjugated secondary antibodies (dilution, 1:500; donkey anti-human, mouse, rabbit, or goat IgG), or FITC conjugated mouse anti-human IgG1, IgG2, IgG3, or IgG4 (dilution, 1:500) for 30 minutes. Coverslips were washed three times in PBS, stained with DAPI, and mounted with Mowiol. The specificity of anti-Caspr1 antibodies was confirmed by testing the sera on HEK cells expressing CNTN1 or Caspr1 alone. In this latter condition, Caspr1-transfected cells were fixed and permeabilized prior to incubation with patients’ sera. Patients’ sera were found to react against Caspr1, but not CNTN1 alone.

**Immunohistochemistry on teased fibers from murine sciatic nerves**

Human (UniProtKB O94856-1, isoform 1) and mouse (UniProtKB Q810U3) Neurofascin share 95.52% identity, human (UniProtKB Q12860, isoform 1) and murine (UniProtKB P12960) Contactin-1 share 95.2%, and human (UniProtKB P78357) and murine (UniProtKB O54991) Contactin-associated protein 1 share 93.3% identify. Contactin-associated protein 1 share 93.3% identify. Anti-CNTN1 or Nfasc155 IgG4 were shown to recognize both human and rodent CNTN1 or Nfasc155, respoectively (Manso et al., 2016, Manso et al, 2019). Therefore, teased fibres from murine sciatic nerve, expressing at paranodes the Neurofascin/Contactin-1/ Contactin-associated protein 1 complex were used to screen by immunohistochemistry sera for reactivity against any component of the complex.

**Immunohistochemistry on skin biopsy**

The specimens from three patients with anti-Nfasc155 IgG4 antibodies, one patient with anti-CNTN1 IgG3/IgG4 antibodies, one patient with anti-Caspr1 IgG4, one patient with anti-Nfasc155 of undetectable isotype antibodies, and six seronegative CIDP patients were analysed at the IRCCS “Carlo Besta” Neurological Institute, Milan, Italy. All patients underwent 3-mm punch skin biopsies at one distal site of the lower limb. Biopsies were performed under local anesthesia with spry ice using sterile disposable punches. The protocol used met the recommendation of the EFNS/PNS guidelines (20).

We have used the following panel of antibodies: anti-Protein-Gene-Product 9.5 (anti-PGP 9.5; dilution 1:400; SPRING Bioscence) to visualize axons; anti-Myelin-Basic-Protein (anti-MBP; dilution 1:10; AbD Serotec) to identify myelin sheaths; anti-panNeurofascin (anti-panNfasc; dilution 1:300; Abcam), anti-Nfascin186 (anti-Nfascin 186; dilution 1:1000; Abcam), and anti-Contactin Associated Protein 1 (anti-Caspr1; dilution 1:500; Abcam) to specifically locate nodal/paranodal/juxtaparanodal structures in skin tissues from seronegative and seropositive CIDP patients. Sections were incubated with the following secondary antibodies: Alexa Fluor® DyLight 488- or 549-conjugated AffiniPure donkey anti-mouse (dilution 1:400), DyLight 488- or 549-conjugated AffiniPure goat anti-rabbit (dilution 1:400), DyLight 549-conjugated AffiniPure goat anti-chicken (dilution 1:400), Cy™5 AffiniPure donkey anti-rabbit IgG (dilution 1:300). Confocal laser scanning platform TCS SP8 microscope (Leica inc., Wetzlar -Germany) was used for double and three-channel scanning.

Nodal/internodal morphological analysis was performed by double immunofluorescence staining for MBP and Nfasc, or MBP and Caspr1 in at least two sections from each patient and in two sections from 6 HC subjects. For each section we acquired only myelinated nerve fibers with well stained nodes of Ranvier.

In patients with known serological positivity to Nfasc155, CNTN1, or Caspr1, we used antibodies to immunolocalize the specific protein. The assessment of Nfasc155 was performed by a double staining with antibodies anti-Nfasc and Nfasc186.

##### **Purification of patients’ antibodies**

##### For in vitro and in vivo studies, IgG1 and IgG4 were purified from patients’ sera and HC plasma using CaptureSelect™ affinity matrix according to manufacturer’s instructions (Life technologies), eluted with 0.1 M glycine pH 3.0. The pH was neutralized with 1:30 volume 1 M Tris pH 9.0. Fractions were dialyzed to artificial CSF (ACSF) containing 126 mM NaCl, 3 mM KCl, 2 mM CaCl2, 2 mM MgSO4, 1.25 mM NaH2PO4, 26 mM NaHCO3, and 10 mM dextrose, pH 7.4-7.5, and sterilized by filtration.

##### **Nerve incubation and injections**

##### All animal experiments were in lines with the European Community’s guiding principles on the care and use of animals (86/609/CEE), and were approved by the local ethics committee and by the “ministére de l’éducation nationale de l’enseignement supérieur et de la recherche” (APAFIS#3847-2016012610089856v5). For in vitro nerve incubation experiments, C57BL/6J mice were euthanized and the sciatic nerve quickly dissected out and transferred into oxygenated ACSF. Nerves were desheathed, cut in 1 cm segments, and incubated for 3 hours with 10 g of purified control IgG4, anti-Caspr1 IgG1, or anti-Caspr1 IgG4 in ACSF. Then, nerve segments were washed with ACSF (3 cycles of 5 min each), then fixed in 2% paraformaldehyde in PBS for 1 hour at 4°C, and processed for immunolabeling as detailed below.

##### For intraneural injections, C57BL/6J mice were anesthetized with Isovet and received a subcutaneous injection of buprenorphine for pain relief. The right sciatic nerve was exposed at the level of the sciatic notch and injected with 2 l of antibody (1 g/l) using a glass micropipette. One or three days after surgery, injected nerves were dissected out, fixed in 2% paraformaldehyde in PBS for 1 hour at 4°C, then rinsed in PBS. Axons were gently teased, dried on glass slides, and stored at -20°C. Teased fibers were permeabilized by immersion in -20°C acetone for 10 min, blocked at RT for 1 hour with PBS containing 5% fish skin gelatin and 0.1% Triton X-100, then incubated overnight at 4°C with a goat antibody against CNTN1 (dilution, 1:2000; R&D Systems). The slides were then washed several times and incubated with the appropriate Alexa Fluor®-conjugated secondary antibodies (1:500; Life Technologies). Slides were mounted with Mowiol plus 2% DABCO, and examined using an ApoTome fluorescence microscope (ApoTome, AxioObserver and AxioCam MRm, Carl Zeiss MicroImaging GmbH). Digital images were manipulated into figures with CorelDraw and Corel Photo-Paint.

##### **Cell aggregation assay**

##### HEK cells were plated in 6-well plates at a density of 500,000 cells/wells and transiently transfected using JetPEI (Polyplus-transfection) with Nfasc155 and ptdTomato-N1 (Clontech), CNTN1/Caspr1 and peGFP-N1 (Clontech), or peGFP-N1 alone. The day after, cells were trypsinized using 0.25% trypsin in PBS and suspended in 1 mL of serum free Opti-MEM medium (ThermoFisher Scientific). Cells were then mixed together in a 1:1 ratio (400,000 cells/ml) in presence of 10 µg of purified antibodies and agitated at 100 rpm for 2 hours at 37°C. 50 µl of cell suspension was then mounted between slides and coverslip, and immediately observed using an ApoTome fluorescence microscope at the 10X objective. Aggregates were defined as clusters of cells of at least 4 cells. Four experiments were performed for each condition, and a minimum of 40 cell clusters were quantified per experiments.

##### Data from in vitro and in vivo experiments were represented as mean ± S.E.M and were compared using unpaired two-tailed Student’s t-tests and by one-way ANOVA followed by Bonferroni’s post-hoc tests. Differences in group frequencies were compared using GraphPad Prism by 2 test with Yate’s correction or by Fisher’s exact test with Bonferroni’s adjustment (GraphPad Software, La Jolla, CA). P values inferior to 0.05 were considered significant.