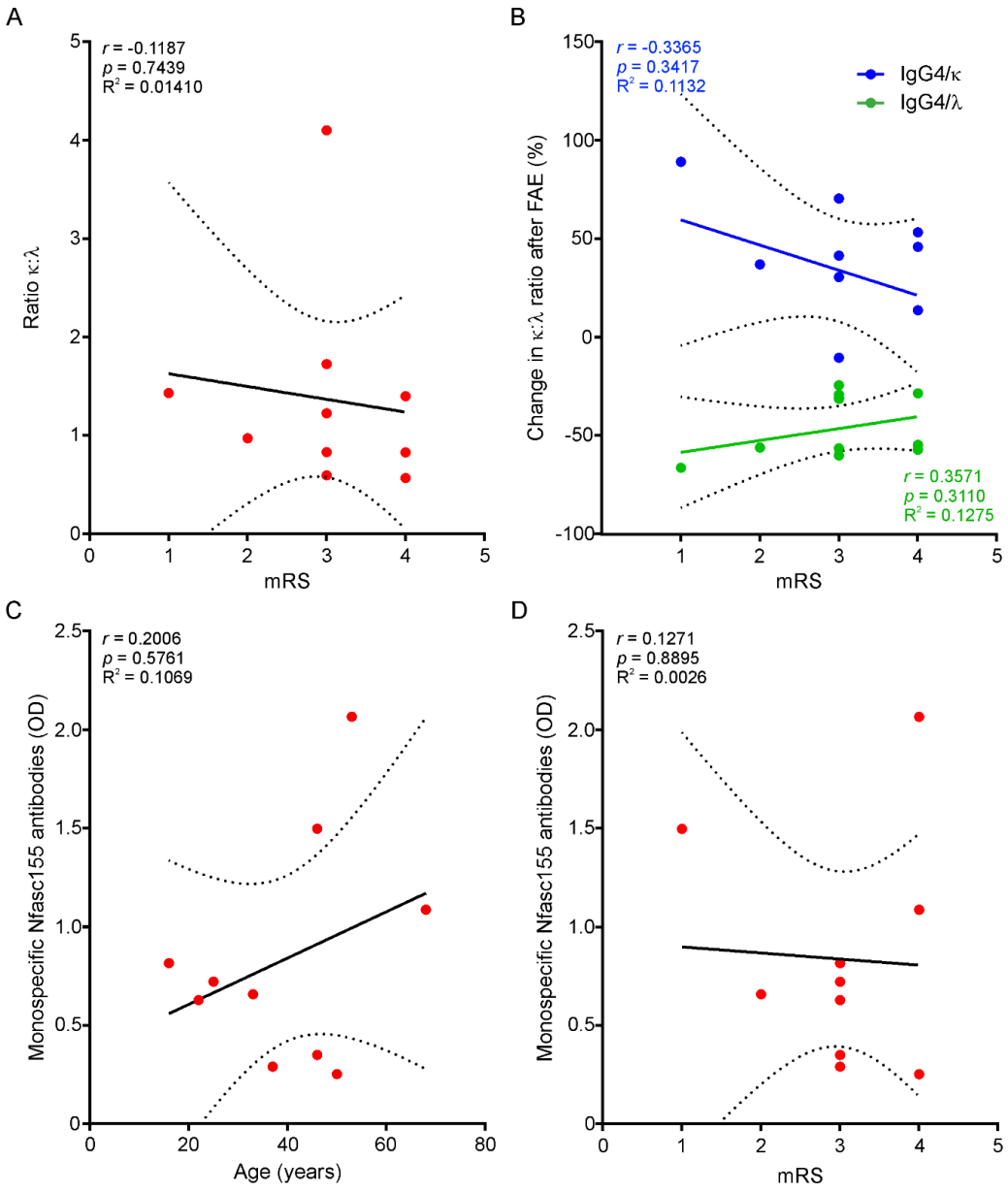
eTable 1: ratios of κ to λ light chains.

κ:λ ratios						
HC		AN +			CIDP -	
Total IgG4		Total IgG4		Anti-Nfasc155 IgG4	Total IgG4	
HC1	1,7:1	AN1	0,9:1	0.8:1	CIDP1	1,0:1
HC2	1,2:1	AN2	2,4:1	4,1:1	CIDP2	1,0:1
HC3	1,2:1	AN3	1,1:1	1,7:1	CIDP3	1,1:1
HC4	1,6:1	AN4	0.8:1	0.8:1	CIDP4	1,0:1
HC5	1,1:1	AN5	1,4:1	1.0:1	CIDP5	1,1:1
HC6	0,9:1	AN6	1,1:1	1,4:1	CIDP6	0,9:1
HC7	0,9:1	AN7	1,1:1	0,6:1	CIDP7	1,6:1
HC8	0,8:1	AN8	0,9:1	1,2:1	CIDP8	0,9:1
HC9	0,7:1	AN9	1,1:1	0,6:1	CIDP9	1,1:1
HC10	1,2:1	AN10	1,4:1	1,4:1	CIDP10	0,7:1
	1,1 ± 0,3		1.4 ± 1.0	1,2 ± 0,5		1,0 ± 0,3

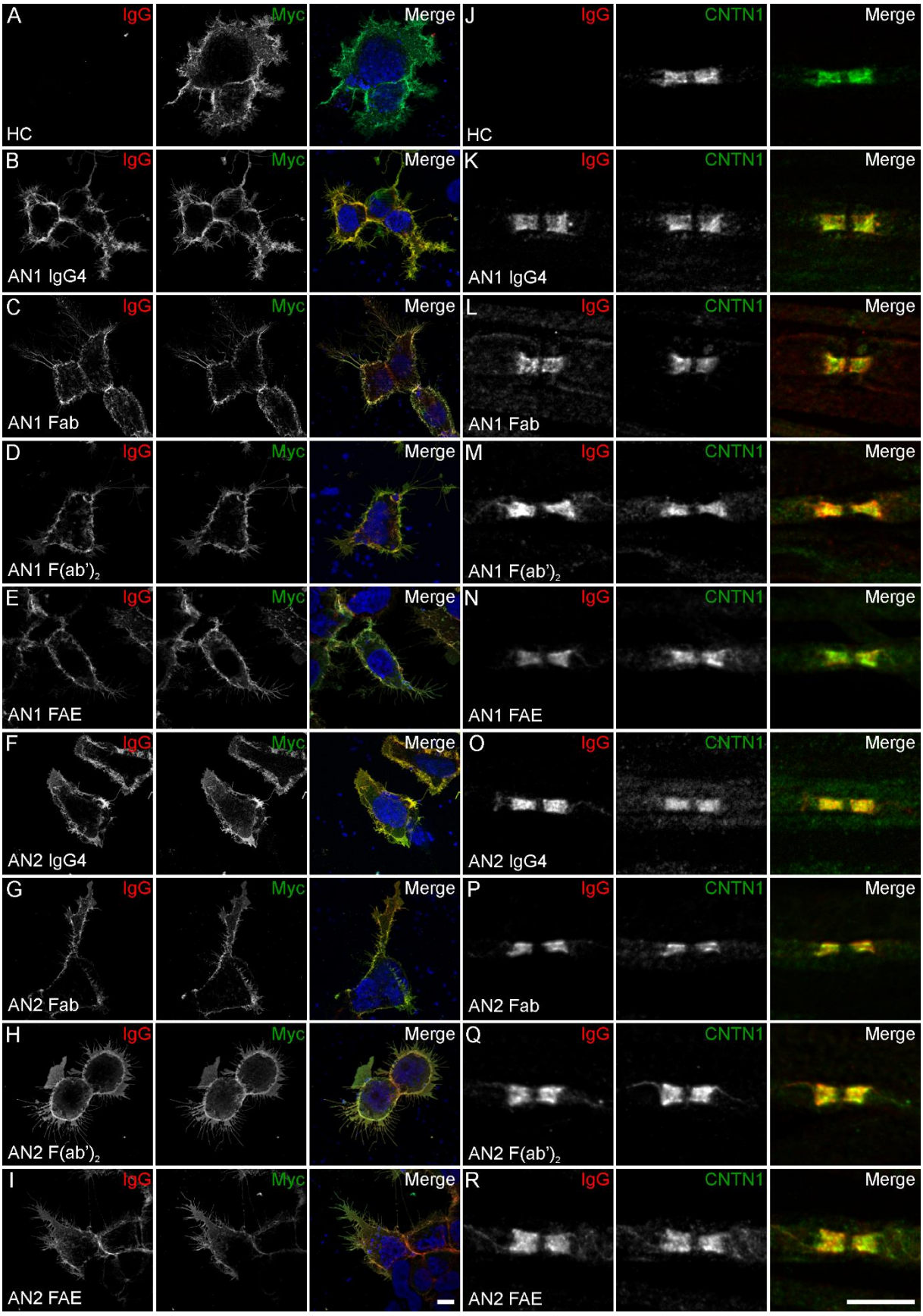
HC = healthy controls ; AN + = Nfasc155 reactive autoimmune nodopathy ; CIDP - = unreactive CIDP patients. Mean and S.D. are shown on the bottom line.

eTable 2: Percentage of change in κ/λ ratios of anti-Nfasc155 IgG4 following Fab-arm exchange with IgG4/λ or IgG4/κ.

	IgG4/λ	IgG4/κ
AN1	-24,5	70,4
AN2	-56,6	41,4
AN3	-29,2	-10,50
AN4	-28,6	45,7
AN5	-56,2	36,9
AN6	-54,8	53,2
AN7	-60,1	-31,0
AN8	-31,3	30,5
AN9	-57,1	13,6
AN10	-66,4	89,0

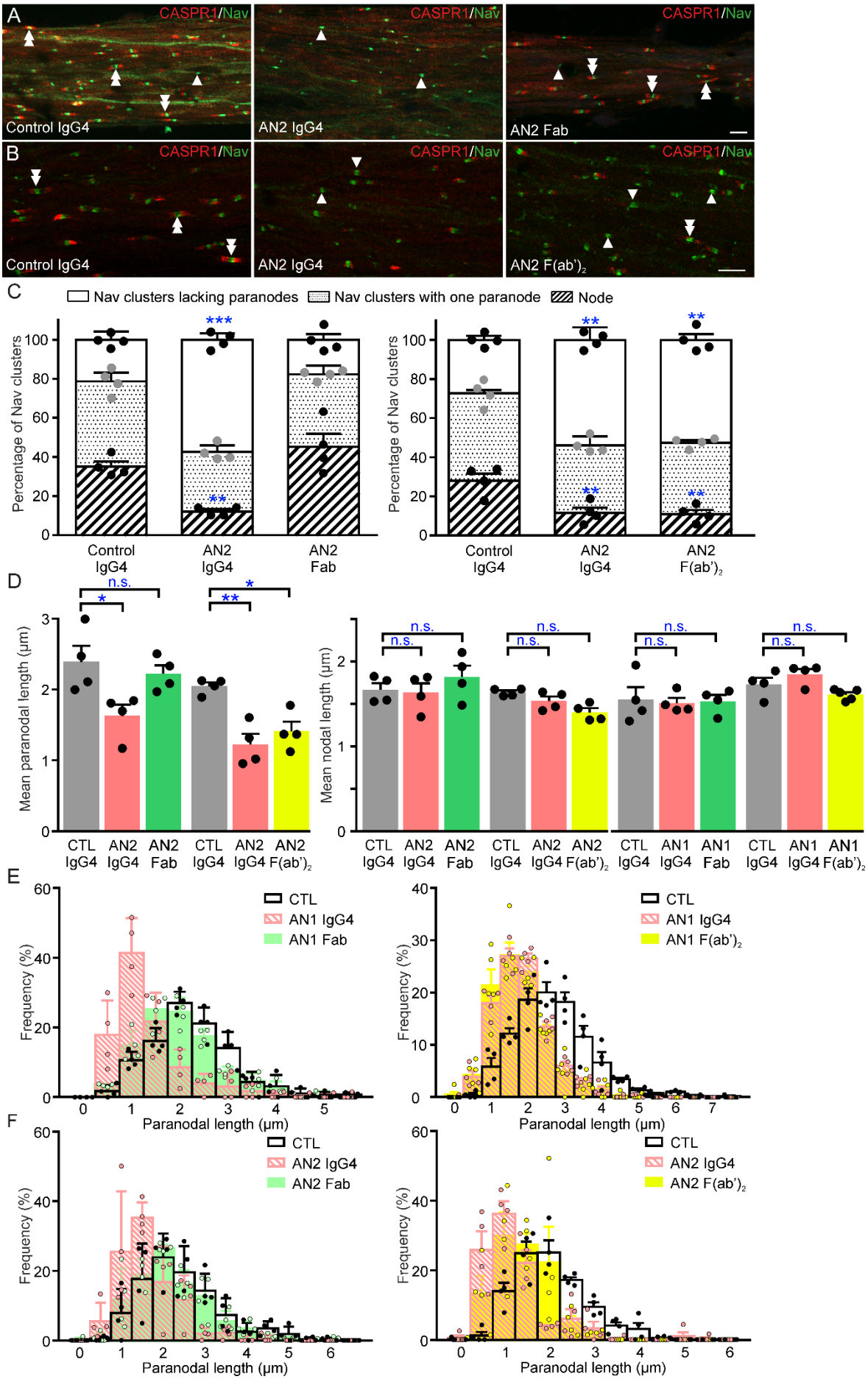


eFigure 1: Correlation between clinical features and antibody characteristics. (A-B) The clinical severity (mRS) is plotted against the ratio of κ/λ light chains of anti-Nfasc155 IgG4 (**A**) or the changes in the ratio of κ/λ light chains induced by Fab-arm exchange with IgG4/λ (green dot) or IgG4/κ (blue dot) (**B**). No significant correlation was found. **(C-D)** The levels of monospecific antibodies were plotted as a function of the age of the patients (**C**) or clinical severity (mRS; **D**). No significant correlation could be drawn. P value, Spearman's correlation coefficient (r), R square (R^2) and 95% confidence band (dotted lines) are indicated on the graph. mRS = modified Rankin Scale.

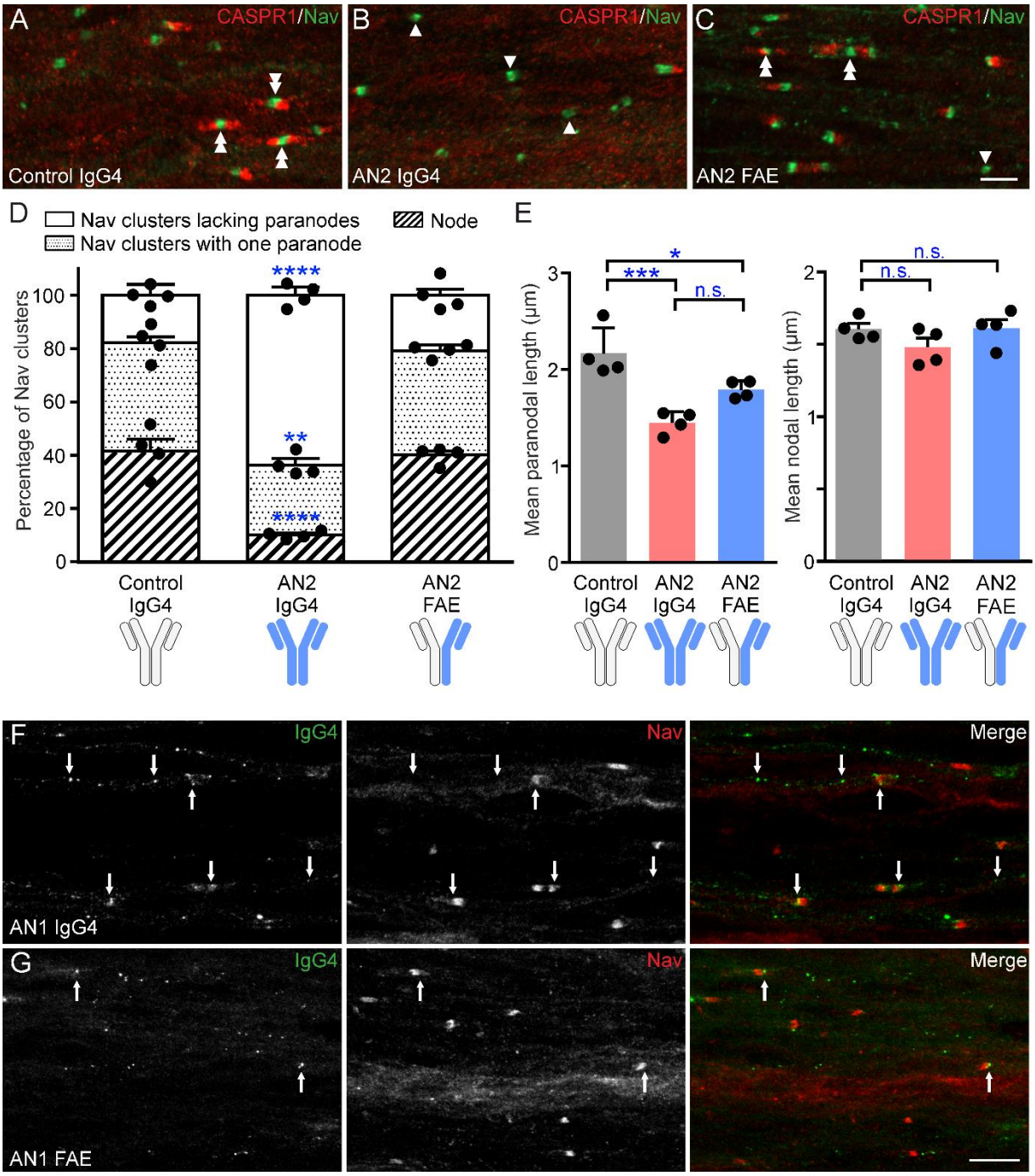


eFigure 2: Reactivity of purified native IgG4 and fragments against human Nfasc155

and paranodes. (A-I) The native IgG4, Fab fraction , $F(ab')_2$ fraction or swapped IgG4 (FAE) from two patients (AN1-2) positive for anti-Nfasc155 IgG4, but also the IgG4 fraction from a healthy control were tested on HEK cells transfected with human myc-tagged Nfasc155 as indicated. Cells were then immunostained for myc (green) and for immunoglobulin (red). Both native IgG4, Fab fragment, $F(ab')_2$ fragment and swapped IgG4 from Nfasc155 + patients recognized Nfasc155. By contrast, control IgG4 did not bind to Nfasc155. **(J-R)** These are teased rat sciatic nerves immunostained for CNTN1 (green) and the native IgG4, Fab fragment, $F(ab')_2$ fragment, or swapped IgG4 (FAE) from two patients (AN1-2) positive for anti-Nfasc155 IgG4 or the IgG4 from a healthy control (red). The native IgG4, Fab fragment, $F(ab')_2$ fragment and swapped IgG4 from these two patients presented a strong reactivity toward paranodes. The IgG4 fraction from the healthy donor did not label the paranodes. Scale bar: 10 μm.


A
CASPR1/Nav
Control IgG4
AN2 IgG4
AN2 Fab
B
Control IgG4
AN2 IgG4
AN2 F(ab')2
C
Nav clusters lacking paranodes
Nav clusters with one paranode
Node
Percentage of Nav clusters
Control IgG4
AN2 IgG4
AN2 Fab
AN2 F(ab')2
D
Mean paranodal length (μm)
Mean nodal length (μm)
n.s.
CTL IgG4
AN2 IgG4
AN2 Fab
AN2 F(ab')2
AN1 IgG4
AN1 Fab
AN1 F(ab')2
E
F
CTL
AN1 IgG4
AN1 Fab
AN1 F(ab')2
AN2 IgG4
AN2 Fab
AN2 F(ab')2
Frequency (%)
Paranodal length (μm)

eFigure 3: Bivalent F(ab')$_2$ from patient AN2's IgG4 abrogate paranode formation but not monovalent Fab. (A-B) New born rat pups received an intraperitoneal injection of 250 µg of anti-Nfasc155 IgG4, Fab or F(ab')$_2$ from patient AN2 (n = 4 animals for each condition and age). As controls, animals received 250 µg of IgG4 from healthy donors. Two days after injection, animals were sacrificed and sciatic nerve fibers were fixed. Teased sciatic nerve fibers were then immunolabeled for voltage-gated sodium channels (Nav; green) to label nodes and hemi-nodes, and for CASPR1 (red) to label paranodes. **(C)** The percentage of Nav clusters lacking CASPR1-positive paranodes (arrowheads) or with one or two flanking CASPR-1 positive paranodes (double arrowheads) were quantified, as well as the paranodal length (**D**)(n = 100-200 nodes or paranodes for each condition). The injection of native IgG4 or F(ab')$_2$ fragments from patient AN2 strongly abrogated the formation of CASPR1-positive paranodes and resulted in a higher percentage of hemi-nodes lacking paranodes (**** P<0.0001, *** P<0.001, ** P<0.005, * P<0.05 by one-way ANOVA followed by Bonferroni's post-hoc tests). The mean length of paranodes was also shorter after treatment with native IgG4 or F(ab')$_2$ fragments reactive to Nfasc155 (**** P<0.0001, *** P<0.001 by one-way ANOVA followed by Bonferroni's post-hoc tests). By contrast, the injection of monovalent Fab fragment of IgG4 did not affect the formation or the length of paranodes (**C** and **D**). The distribution of paranodal length of animals treated with Fab was not distinguishable from that of controls whereas that of animals treated with native or F(ab')$_2$ fragment of Nfasc155-reactive IgG4 was also significantly different for both AN1 (**E**) and AN2 (**F**). Scale bar: 10 µm. N.S. : non-significant. Bars represent mean and S.E.M.



eFigure 4: Fab-arm exchange decreases the pathogenicity of Nfasc155-reactive IgG4 from patient AN2. (A-C) These are teased fibers from two-day old rat pups injected at birth with control IgG4 (**A**; 250 µg per animal), IgG4 from patient AN2 (**B**; 250 µg per animal) or swapped IgG4 from patient AN2 (**C**; 1 mg per animal) that were immunostained for Nav channels (green) and CASPR1 (red)(n = 4 animals for each condition). Fab-arm exchange (FAE) was induced *in vitro* between IgG4 from patient AN2 and healthy donor IgG4. **(D-E)** The injection of native

Nfasc155-reactive IgG4 reduced the formation of CASPR1-positive paranodes and significantly decreased the mean length of paranodes. By contrast, swapped IgG4 did not significantly affect paranode formation. Nonetheless, paranodal length was significantly decreased in animals treated with swapped IgG4 (**** $P<0.0001$, *** $P<0.001$, ** $P<0.005$, * $P<0.05$ by one-way ANOVA followed by Bonferroni's post-hoc tests)(n = 100-200 nodes or paranodes for each condition). Arrows indicate Nav clusters lacking CASPR1-positive paranodes. Double arrowheads indicate Nav clusters with one or two flanking paranodes. **(F-G)** Teased fibers from two-day old pups were immunostained for Nav channels (red) and human IgG (green). Important IgG fixation was found around the nodes of Ranvier and along the myelinated axons (arrows) in animals treated with native Nfasc155-reactive IgG4. FAE with healthy donor IgG4 strongly decreased antibody fixation along nerve fibers. A few fibers showed IgG fixation near the nodes (**G**). Scale bars: 10 μm. N.S. : non-significant. Bars represent mean and S.E.M.