AUTOIMMUNE PERIPHERAL NERVE DISORDERS TC 16

Auto-antibodies in chronic inflammatory neuropathies

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Disclosure

- I. Illa has received research funds from Grifols and received speaking fees and travel grants from Grifols, Genzyme and Pfizer.
- I. Illa provided expert testimony to Alexion, UCB and Grifols.

CIDP

1. Heterogeneous group of neuropathies

2. Diagnosis based on clinical and EMG criteria

3. Response to immune therapy

European Journal of Neurology 2010, **17:** 356–363 doi:10.1111/j.1468-1331.2009.02930.x

EFNS TASK FORCE/CME ARTICLE

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society — First Revision

Members of the Task Force: P. Y. K. Van den Bergh[a], R. D. M. Hadden[b], P. Bouche[c], D. R. Cornblath[d], A. Hahn[e], I. Illa[f], C. L. Koski[g], J.-M. Léger[h], E. Nobile-Orazio[i], J. Pollard[j], C. Sommer[k], P. A. van Doorn[l] and I. N. van Schaik[m]

CIDP pathogenesis:

Synergistic interaction of cell-mediated and humoral immune responses directed against *incompletely characterized peripheral nerve antigens*.

Autoantibodies in chronic immune neuropathies

- **MYELIN GLYCOPROTEINS**

  MAG, PMP 22, P0, P2, PBM, connexin 32

- GANGLIOSIDES

  IgM GM1 MMN; CANOMAD

Table 2 Antibodies to myelin proteins and nodal antigens in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Candidate antigen	Positive sera/total tested	Ig Class	Method	Reference
Myelin proteins				
P0	6/21	IgG	Western blotting	113
	4/21		IF on normal nerve	
	6/32	IgG (3), IgA (3)	Western blotting	114
	6/36*	IgG	ELISA	115
	5/32	IgM	ELISA	116
	0/32	IgG		
	7/30*	IgG	ELISA	117
	0/20*		ELISA	118
	1/24*		Western blotting	119
	3/40*	IgG	ELISA	120
	2/40*	IgM		
P2	11/32*	IgM	ELISA	116
	4/32*	IgG		
	4/36*	IgG	ELISA	115
	4/30	IgG	ELISA	117
	3/20*		ELISA	118
PMP22	3/30*	IgG	ELISA	117
	0/24*		Western blotting	119
	7/17	Ig (3), IgM (3), pan Ig (1)	ELISA	121
	6/17		Western blotting	
	3/6*		Western blotting	122
Cx32	1/24*		Western blotting	119
MBP	2/40*	IgG	ELISA	120

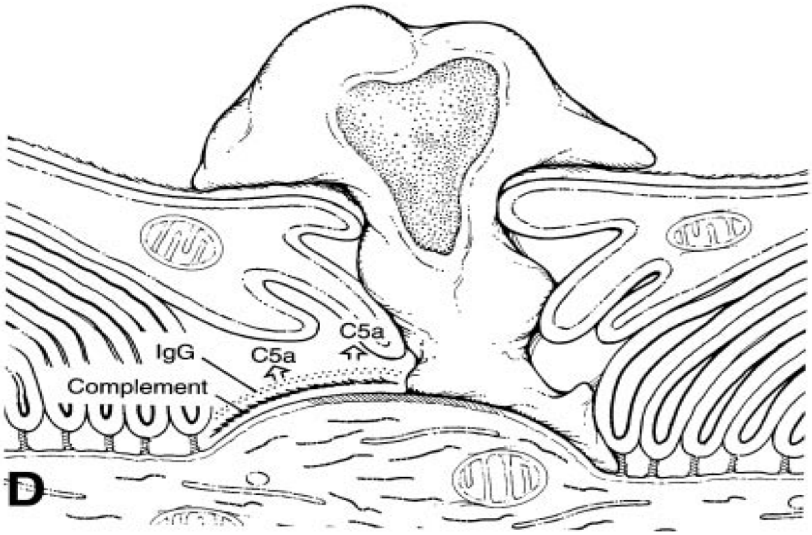
Mathey et al JNNP 2015

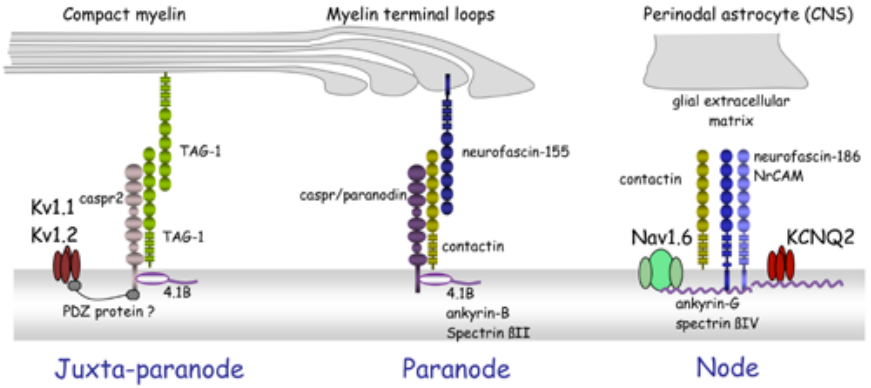
Autoantibodies in chronic immune neuropathies

- MYELIN GLYCOPROTEINS
  MAG, PMP 22, P0, P2, PBM, connexin 32
- **GANGLIOSIDES**

IgM GM1 MMN; CANOMAD

- **Antibodies directed against glycolipids** were first **detected** in the serum of patients with inflammatory neuropathies **nearly 20 years ago**.
- A number of distinct serological patterns with variable clinical and pathological associations have emerged **Acute > Chronic**.
- **Anti-GM1 antibodies are however detected in 50% of patients with multifocal motor neuropathy (MMN).**
- **CANOMAD *C*hronic *A*taxic *N*europathy *O*phthalmoplegia *M*-protein *A*gglutination *D*isialosyl antibodies.**



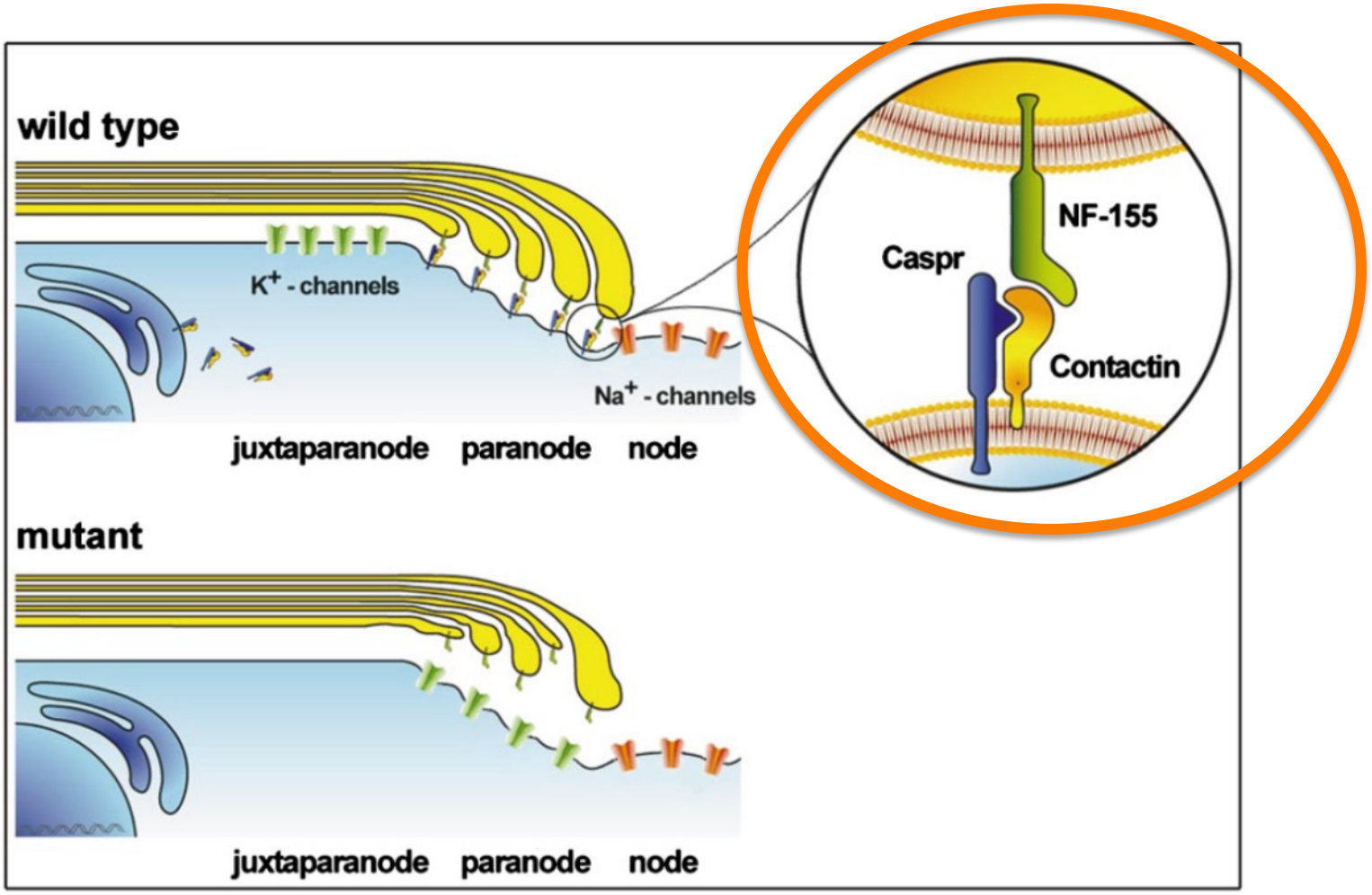


Ho TW, McKhann GM and Griffin JW
Ann Rev Neurosci 1998

Illa et al, Ann Neurol 1995; Cifuentes-DC et al, PLoSOne 2011; Pollard et al, JPNS 2012; Devaux J et al, JPNS 2012; Doppler K et al, JPNS 2013; Ng JKM et al, Neurology 2012; Querol et al, Ann Neurol 2013; Querol et al, Neurology 2014

Focus on the NODE of RANVIER

Paranodal antibodies



Antibodies to Contactin-1 in Chronic Inflammatory Demyelinating Polyneuropathy

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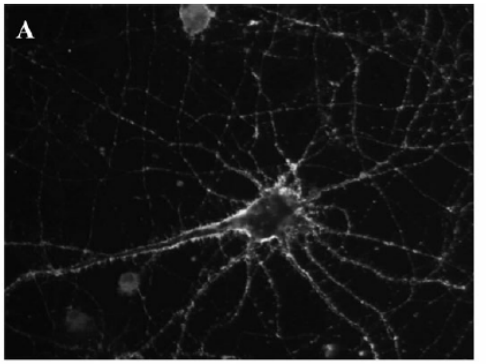
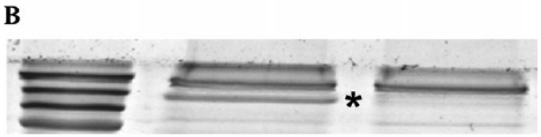
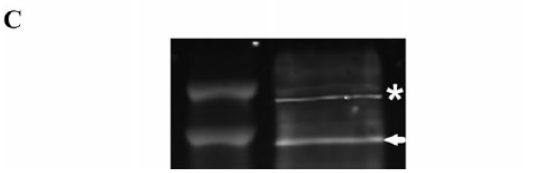
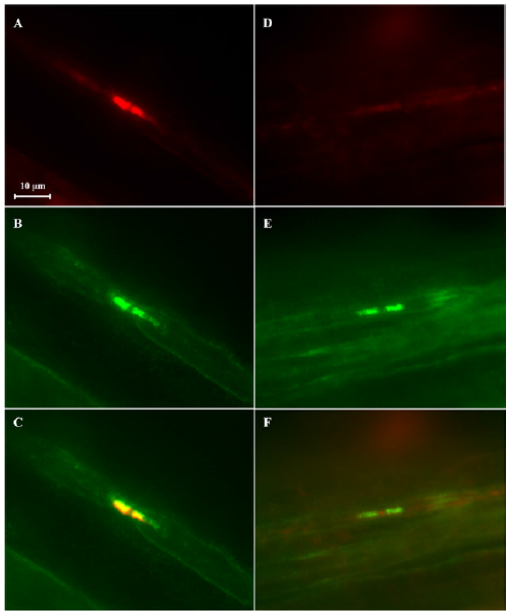
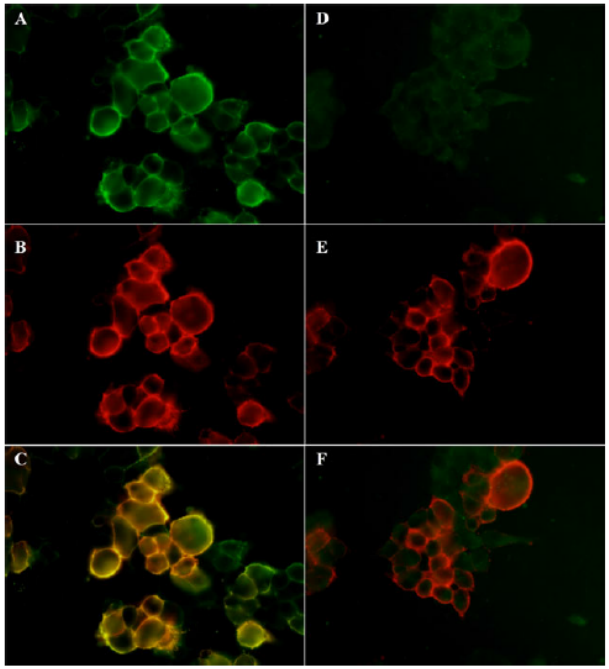
Xavier Suárez-Calvet, MSc,[1,2] Miquel Navas,[1,2] Josefa Araque, RPN,[1,2]
Eduard Gallardo, PhD,[1,2] and Isabel Illa, MD, PhD[1,2]











Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg

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Table 1 Epidemiologic, clinical, and electrophysiologic features of patients with CIDP positive for anti-NF155 antibodies

Patient	Age at onset (sex)	Symptoms	mRS score	CSF	Brain MRI	Treatments (responses)	Tremor frequency (amplitude)	NF155 titers
1	46 (M)	Rapidly progressive onset; severe weakness, predominantly distal; sensory disturbances; ataxia; severe intention tremor	4	1.5 g/L; 2 cells	Normal	IVIg (no); prednisone (no); PEx (yes)	3 Hz (9/10)	1:70,000
2	22 (M)	Chronic progressive; severe weakness, predominantly distal; sensory disturbances; ataxia; moderate intention tremor	4	4.6 g/L; 6 cells	Normal	IVIg (no); prednisone (partial); PEx (yes, partial)	6.6 Hz (2/10)	1:70,000
3	29 (M)	Chronic progressive; severe weakness, proximal and distal; sensory disturbances; ataxia; severe intention tremor	4	1.4 g/L; 7 cells	Normal	IVIg (no); prednisone (no); methotrexate (no)	4 Hz (8/10)	1:25,000
4	67 (F)	Chronic progressive; severe weakness, predominantly distal; sensory disturbances; no tremor	4	0.41 g/L; 0 cells	ND	IVIg (no); prednisone (no); cyclophosphamide (no); rituximab (no)	Not present	1:8,000

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; ND = not determined; NF155 = neurofascin 155; PEx = plasma exchange.

Conclusion: Patients with CIDP positive for IgG4 NF155 antibodies constitute a specific subgroup with a severe phenotype, poor response to IVIg, and disabling tremor. Autoantibodies against paranodal structures associate with distinct clinical features in CIDP and their identification has diagnostic, prognostic, and therapeutic implications.

Neurology® 2014;82:879–886

Clinically Homogeneous Phenotype Features

Contactin-1

- Older
- Aggressive neuropathy
- Predominantly motor
- Demyelinating features, early axonal damage
- **Poor response to IVIg**
- Response to plasma exchange
- Partial response to steroids
- **IgG4 isotype antibodies**

Ann Neurol 2013

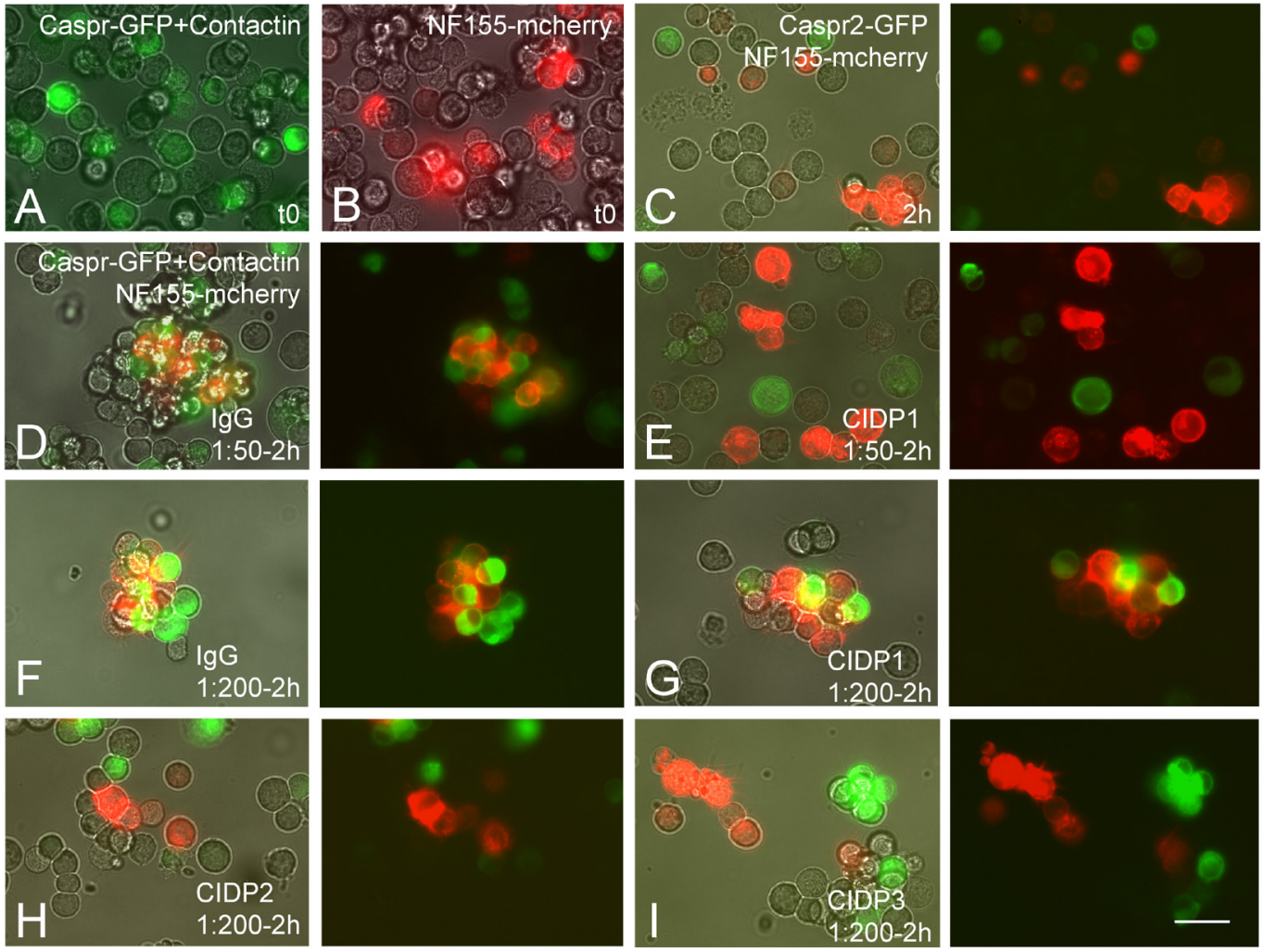
NF-155

- Predominantly distal weakness
- Ataxia
- Disabling postural and intentional tremor low frequency (3-5 Hz)
- Demyelinating features, no early axonal damage
- **Nor or poor response to IVIg**
- Response to plasma exchange
- Partial response to steroids
- **IgG4 isotype antibodies**

Neurology 2014

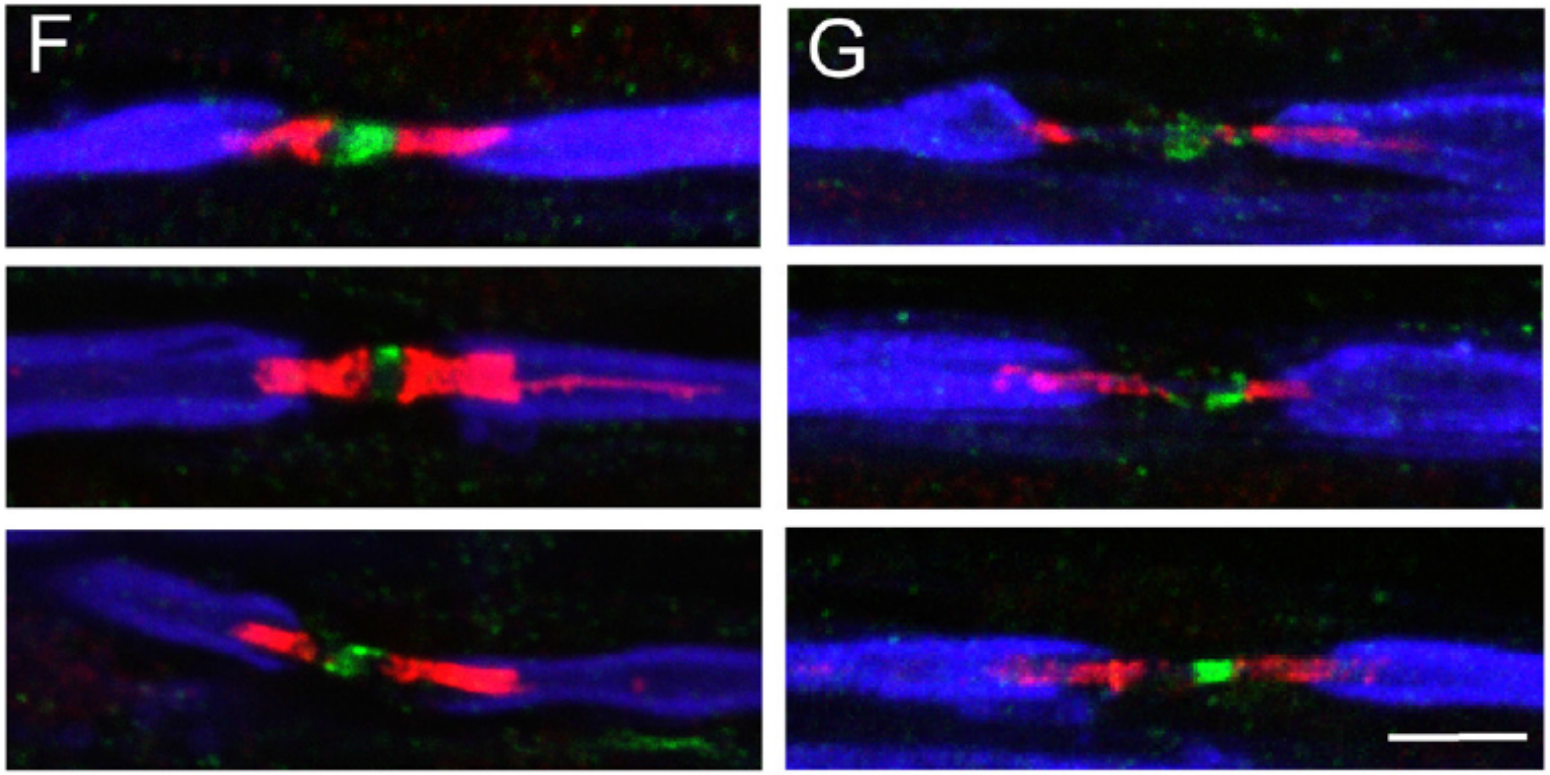
Pathogenic role of Contactin 1:

Cell aggregation assays indicate that patients autoantibodies against CNTN1 display functional blocking activity



Labasque et al, J Biol Chem 2014;289:7907-7918.

CIDP autoantibodies against contactin-1 induce paranodal alterations in myelinated DRG neurons in culture.
(DRG neuron/Schwann cell)



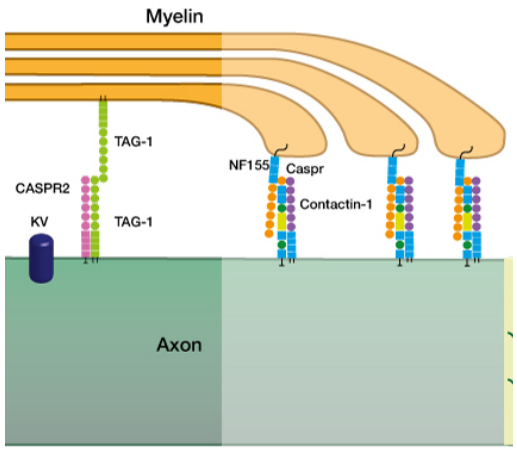
J Biol Chem 2014

Neurobiology:

Specific Contactin *N*-Glycans Are Implicated in Neurofascin Binding and Autoimmune Targeting in Peripheral Neuropathies

Marilyne Labasque, Bruno Hivert, Gisela Nogales-Gadea, Luis Querol, Isabel Illa and Catherine Faivre-Sarrailh

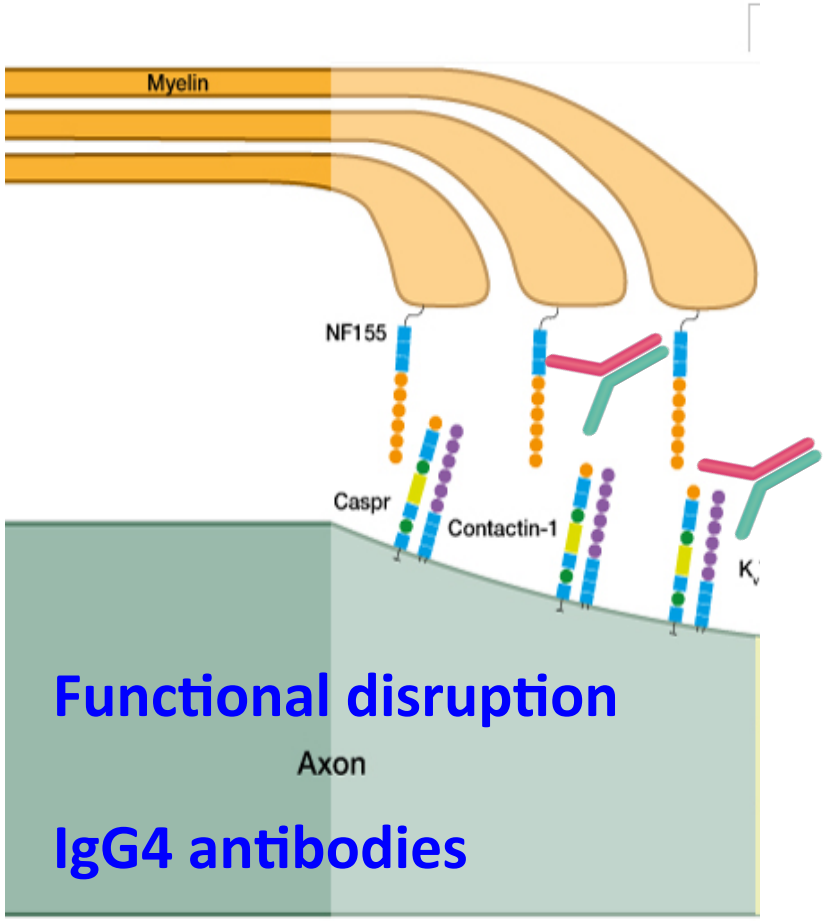
J. Biol. Chem. 2014, 289:7907-7918.



RESEARCH PAPER

Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies

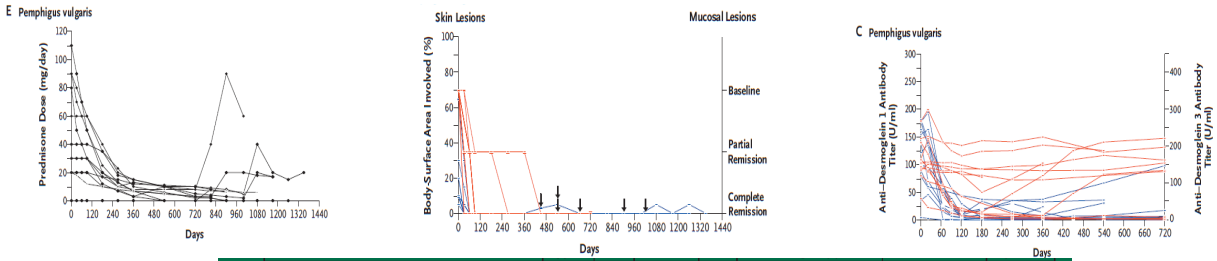
Kathrin Doppler,[1] Luise Appeltshauser,[1] Kai Wilhelmi,[1] Carmen Villmann,[2] Sulayman D Dib-Hajj,[3,4] Stephen G Waxman,[3,4] Mathias Mäurer,[5] Andreas Weishaupt,[1] Claudia Sommer[1]



Diseases mediated by IgG4-Ab respond to Rituximab

A Single Cycle of Rituximab for the Treatment of Severe Pemphigus

New Engl J Med 2007



Long-lasting treatment effect of rituximab in MuSK myasthenia

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J.L. Muñoz-Blanco, MD
C. Mazia, MD
K.R. Straasheijm
E. Gallardo, PhD
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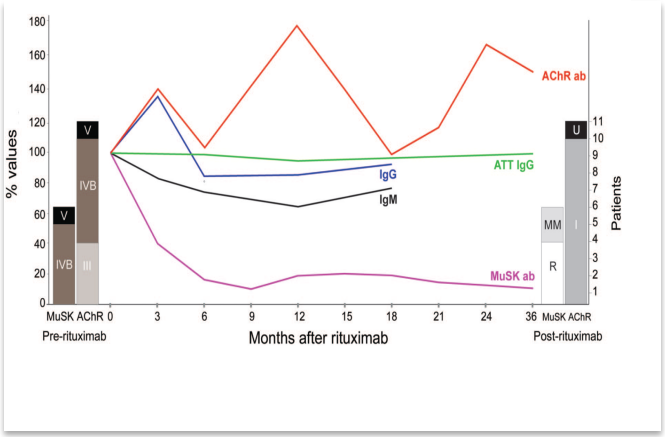
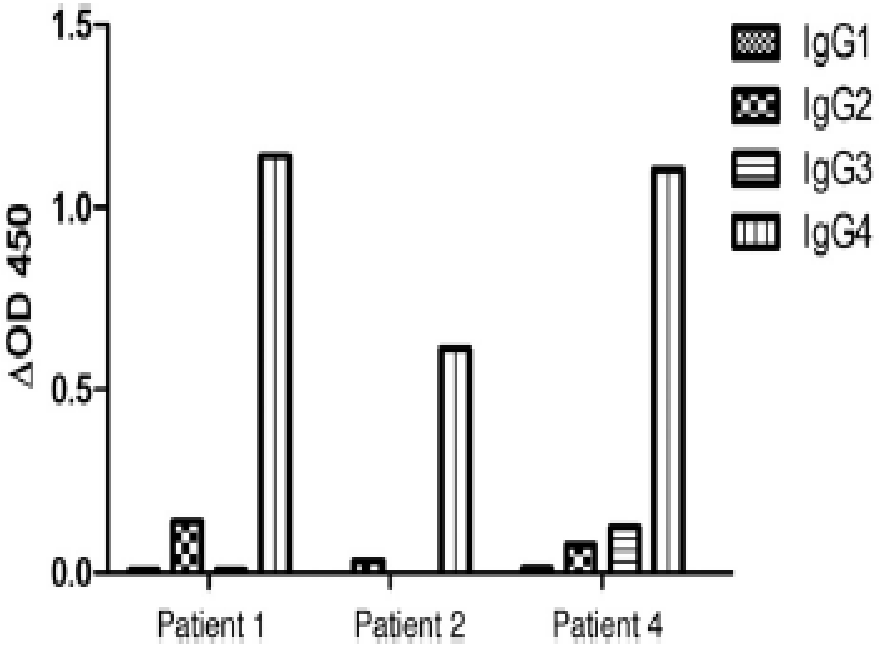
Clinical and serologic evolution after treatment with rituximab



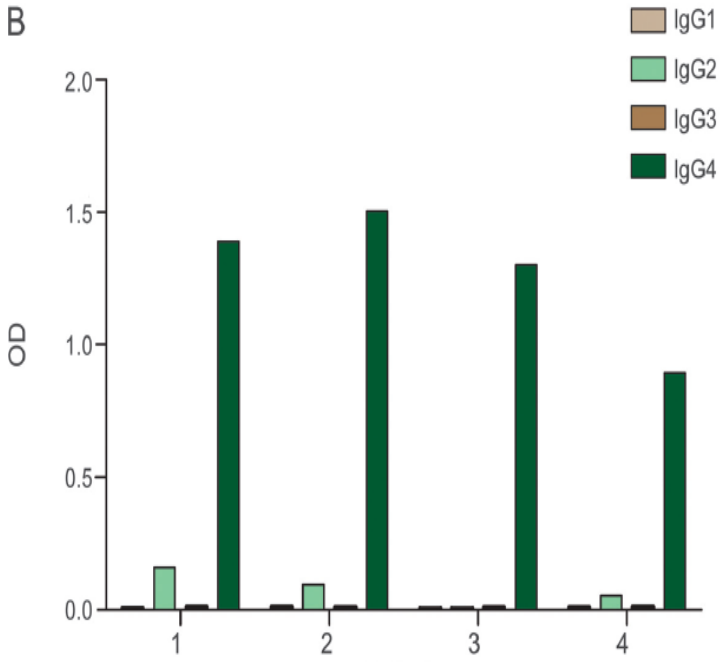
Conclusion: In view of the long-lasting benefit observed in MuSK+MG patients, we recommend to use rituximab as an early therapeutic option in this group of patients with MG if they do not respond to prednisone.

Neurology® 2012;78:189-193

IgG4



Anti-Contactin antibodies
J. Biol Chem 2014



Anti-NF-155 antibodies
Neurology 2014

RESPONSE TO RITUXIMAB OF PATIENTS WITH PARANODAL Ab. RESISTANT TO THERAPY

- **RITUXIMAB:** Patients received 375 mgr. x m2 once weekly for 4 weeks followed by 1 dose per month for two additional doses.

- **SCALES:**
  - Overall neuropathy limitations scale (ONLS) Range: 0= normal to 12= maximum disability

  - Rasch-built overall disability scale (R-ODS) Range: 0= maximum disability to 48= normal

- **ANTIBODY SAMPLES:** Blood sampling were collected prospectively every three months during the first year and every six months thereafter.

Key messages

- The node of Ranvier emerges as a target of the immune response in chronic immune neuropathies.

- Future studies will likely identify additional novel targets demonstrating the clinical and immunological heterogeneity of CIDP (? each target representing a small group).

- IgG4 antibodies against Contactin-1 or NF-155 have direct clinical and therapeutic value. Rituximab treatment is an option for patients resistant to conventional therapies.

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15.- Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins ACCEPTED N2.