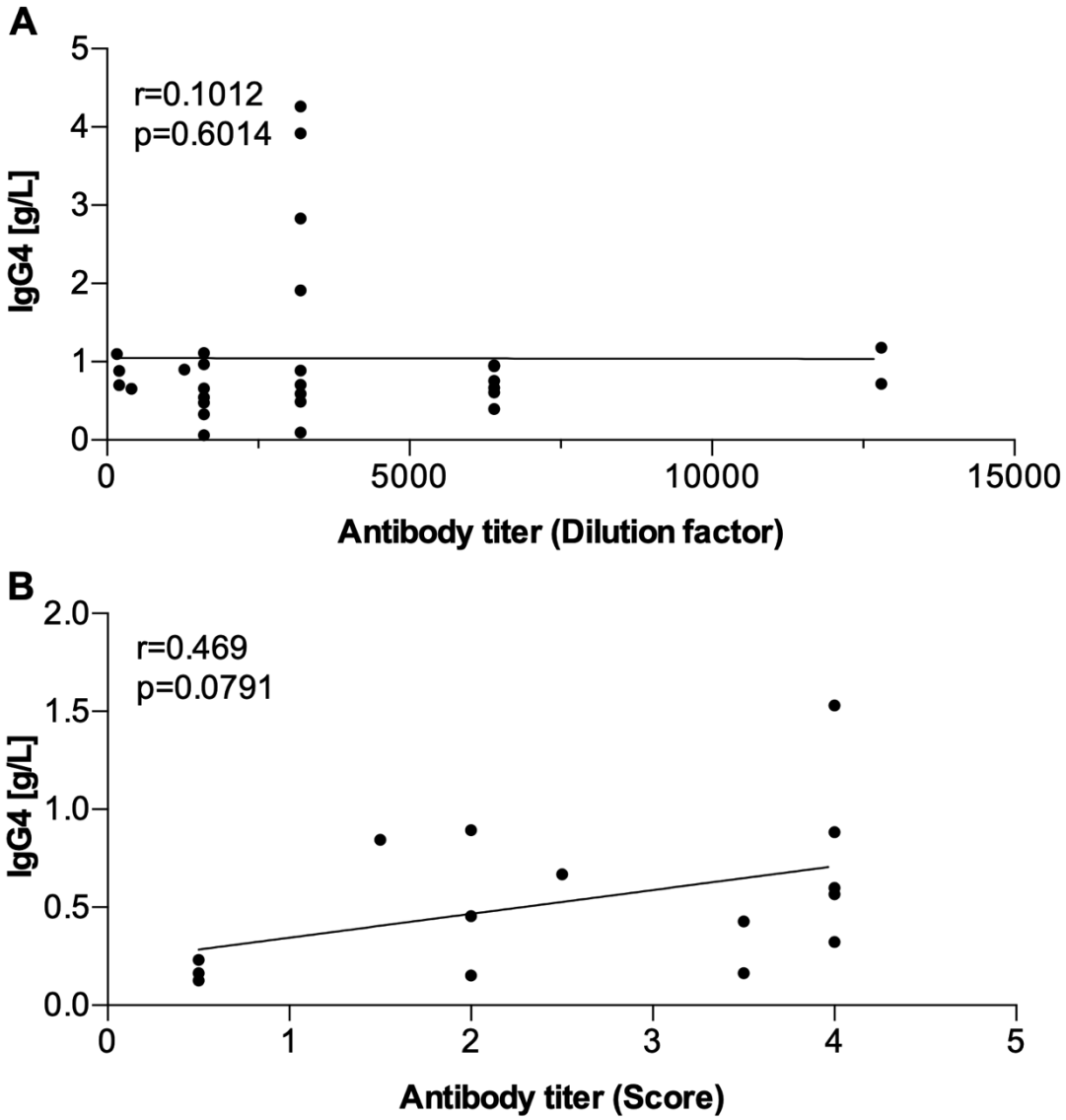
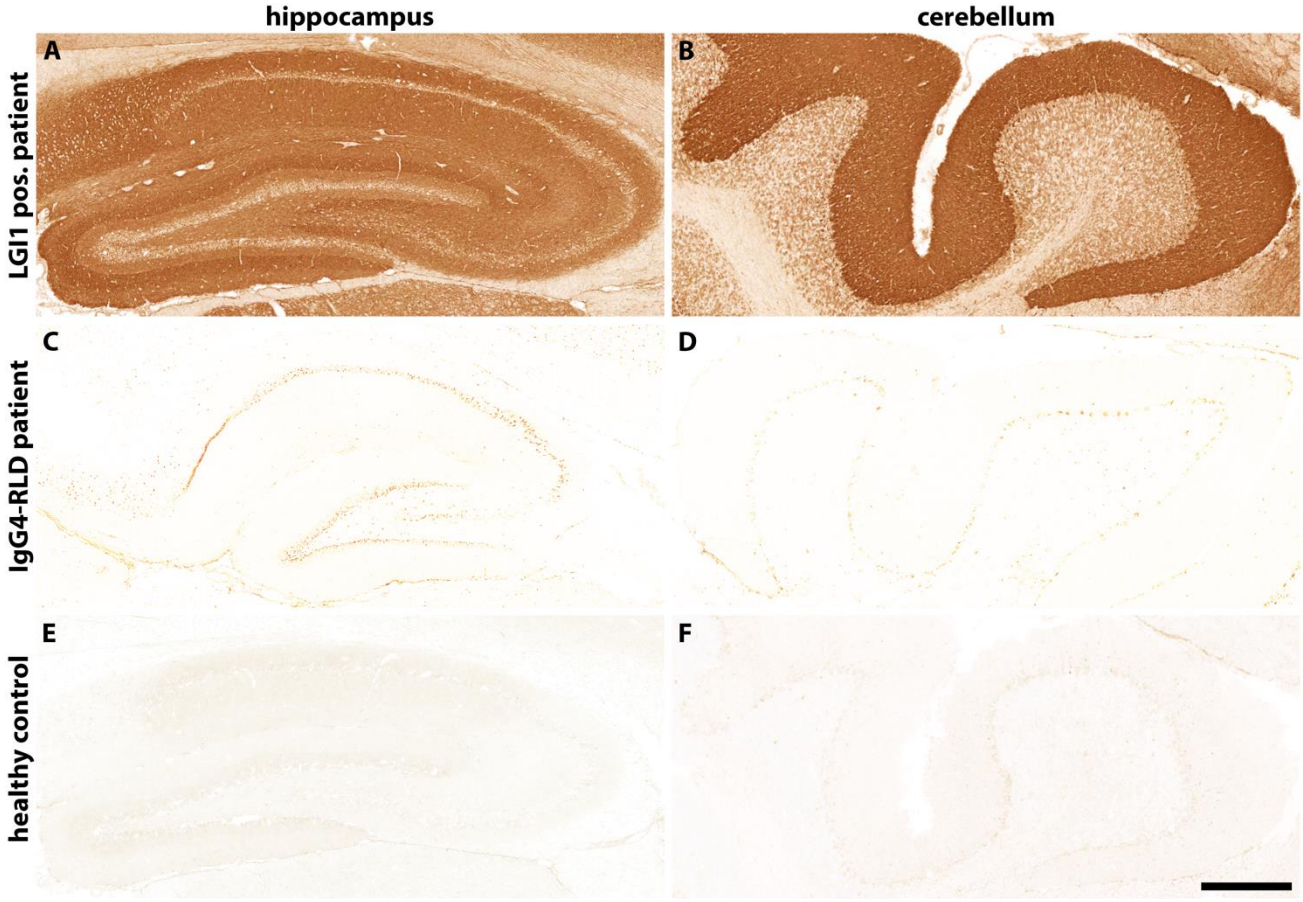
# *Supplementary Material*

**Supplementary Figure 1**




**Supplementary Figure 1: No apparent correlation between serum IgG4 concentrations and IgG4 autoantibody titers/scores could be observed. (A)** LGI1, Caspr2, NF155, CNTN1/Caspr1 antibody titers are expressed as dilution factor at which autoantibodies were still detectable. **(B)** MuSK antibody titers are determined by visual scoring of immunofluorescent signal in cell-based assay, from 0 = negative to 4 = highest intensity. Nonparametric Spearman correlation with two-tailed p-value. IgG4 = immunoglobulin type G subclass 4.

**Supplementary Figure 2**




**Supplementary Figure 2: Tissue-based assay for detection of anti-neuronal autoantibodies.** Representative image of one IgG4-AID patient positive for LGI1 autoantibodies shows a strong neuropil staining pattern in the hippocampus **(A)** as well as in the molecular layer of the cerebellum **(B)**, whereas the neuropil of an IgG4-RLD patient **(C, D)** and a healthy control **(E, F)** remains negative. IgG4-RLD = IgG4-related disease; LGI1 = leucine-rich glioma inactivated protein- 1; pos. = positive

**Supplementary Table 1: Clinical and epidemiological data of the IgG4-AID study cohort.**

AChR = acetylcholine receptor; AIE = autoimmune encephalitis; approx. = approximately; Aza = azathioprine; Caspr1 = contactin-associated protein-like 1; Caspr2 = contactin-associated protein-like 2; CIDP = chronic inflammatory demyelinating polyneuropathy; CNTN1 = contactin 1; CSF = cerebrospinal fluid; d = day; F = female; GBS = Guillain-Barré syndrome; HDMP = high dose methylprednisolone; IVIg = intravenous immunoglobulins; i.v. = intravenous; LE = lower extremities; LGI1 = leucine-rich glioma inactivated protein- 1; M = male; MG = myasthenia gravis; min = minutes; MRI = magnetic resonance imaging; mRS = modified rankin scale; MS = multiple sclerosis; MuSK = muscle-specific kinase; n.a. = not applicable; neg. = negative; NF155 = neurofascin155; pan-NF = positive for pan neurofascin antibodies (155/140/186); PLEX = plasma exchange; Prs = prednisolone; p.o. = per os; Pyr = pyridostigmine bromide; RTX = rituximab; sc = subcutaneous; UE = upper extremities.

| patient ID | antigen | age [years] | sex | age at disease onset [years] | clinical diagnosis | clinical symptoms | autoantibody titer/score | CSF [cell/µL] | oligoclonal bands | highest mRS | acute therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LGI1 #1 | LGI1 | 49 | F | 48 | AIE | MRI-neg. focal epilepsy: several episodes of blurry vision, general weakness, impaired mentation of approx. 10-15 min duration per day, approx. 7 episodes of electrifying paresthesias and generalized goose bumps of 3-4 seconds duration per day | 1:6400 | n.a. | n.a. | 1 | lamotrigine 100 mg/d |
| LGI1 #2 | LGI1 | 69 | M | 69 | AIE | anxiety, cognitive impairment, autonomic disturbance, stereotypical behavior | - | 3 | neg. | 2 | HDMP, IVIg, RTX, Prs p.o. |
| LGI1 #3 | LGI1 | 49 | M | 49 | AIE | fasciculations of the lower leg, dysesthesia of the lateral thigh area, insomnia, memory impairment | - | 2 | n.a. | 1 | HDMP, IVIg |
| LGI1 #4 | LGI1 | 63 | F | 63 | AIE | anxiety, seizures, cognitive impairment, nausea | 1:6400 | 2 | neg. | 1 | IVIg, RTX |
| LGI1 #5 | LGI1 | 54 | M | 54 | AIE | psychosis, anxiety, insomnia, social withdrawal, seizures, cognitive impairment, dyskinesia, autonomic disturbance, recurrent diarrhea for few weeks to months | 1:6400 | 2 | neg. | 2 | HDMP, IVIg, RTX, Prs p.o. |
| LGI1 #6 | LGI1 | 45 | M | 45 | AIE | psychosis | 1:3200 | 7 | neg. | 1 | HDMP, RTX, Prs p.o. |
| LGI1 #7 | LGI1 | 55 | M | 55 | AIE | reduced vigilance, cognitive impairment, autonomic disturbance | 1:3200 | 0 | n.a. | 1 | IVIg, Prs p.o. |
| LGI1 #8 | LGI1 | 62 | M | 62 | AIE | psychosis, anxiety, insomnia, social withdrawal, cognitive impairment | 1:3200 | 3 | n.a. | 2 | HDMP, Prs p.o. |
| LGI1 #9 | LGI1 | 68 | M | 68 | AIE | cognitive impairment | 1:3200 | 1 | neg. | 1 | Prs p.o. |
| LGI1 #10 | LGI1 | 62 | F | 62 | AIE | MRI-neg. focal epilepsy, cognitive impairment, depression, hallucinations, frequent subclinical temporal lobe seizures, pressing occipital headaches of location, lightheadedness, general weakness, impaired mentation, frequent trance-like episodes with formed visual hallucinations, jerking of right UE, staring gaze, oral automatisms and altered breathing pattern of few seconds duration | 1:3200 | 0 | neg. | 3 | HDMP, 2 cycles of IVIg, 4 cycles of RTX |
| LGI1 #11 | LGI1 | 59 | M | 59 | AIE | social withdrawal, autonomic disturbance, cramps, fasciculations, myokymia | 1:1600 | 13 | neg. | 1 | IVIg, Prs p.o. |
| LGI1 #12 | LGI1 | 73 | F | 72 | AIE | memory disturbances, confusion, epilepsy, inattention, hyponatremia of 118 mmol/L | 1:6400 | 0.3 | n.a. | n.a | valproate, quetiapine, HDMP, IVIg |
| LGI1 #13 | LGI1 | 68 | M | 68 | AIE | focal seizures, insomnia, memory impairment, pallhypesthesia, hyporeflexia, cognitive impairment, personality change | 1:1600 | 26 | neg. | 0 | HDMP, RTX, Prs p.o. |
| LGI1 #14 | LGI1 | 65 | M | 65 | AIE | agitation, insomnia, memory and language disturbances, confusion, epilepsy, hyponatremia of 116 mmol/L | 1:3200 | 1 | n.a. | n.a. | escitalopram 10 mg/d, sodium replacement, levetiracetam 1000 mg/d, lacosamide 200 mg/d, HDMP |
| LGI1 #15 | LGI1 | 59 | M | 59 | AIE | focal seizures, vertigo symptoms, epigastic auras | 1:6400 | 1 | neg. | 0 | HDMP, IVIg |
| Caspr2 #1 | Caspr2 | 65 | M | 65 | AIE | seizures, speech disturbance | 1:1600 | 3 | neg. | 1 | IVIg, RTX, Prs p.o. |
| Caspr2 #2 | Caspr2 | 67 | M | 66 | small fiber neuropathy | neuropathic pain | 1:400 | n.a. | n.a. | n.a | - |
| Caspr2 #3 | Caspr2 | 78 | M | 78 | AIE | limbic encephalitis | 1:1600 | n.a. | n.a. | n.a. | - |
| Caspr2 #4 | Caspr2 | 69 | M | 69 | AIE | reduced vigilance, cognitive impairment, dyskinesia | 1:6400 | 12 | n.a. | 3 | HDMP, Prs p.o. |
| Caspr2 #5 | Caspr2 | 53 | M | 53 | AIE | psychosis, memory deficits, sensory ataxia with neuropathic pain | 1:12800 | 4 | neg. | 2 | HDMP, Prs p.o. |
| Caspr2 #6 | Caspr2 | 68 | M | 68 | AIE | cognitive impairment, organic psychosyndrome | 1:12800 | 0 | neg. | 0 | HDMP, RTX, PLEX, Prs p.o. |
| Caspr2 #7 | Caspr2 + LGI1 + AChR | 69 | M | 68 | AIE | behavioral, psychiatric and cognitive disturbances, movement disorder, tremor, severe episodes of pain on the extremities | 1:3200 | 1 | neg. | n.a. | thymectomy |
| Caspr2 #8 | Caspr2 | 20 | M | 19 | AIE | agitation, confusion, dyskinesia, abnormal posture, orofacial dyskinesia, autonomic instability, sleep impairment, heteroaggressivity, auditory hallucinations, mood alteration, carrier of membranous nephropathy since 2016 | 1:1600 | 0.3 | n.a. | n.a. | no immunosuppressive therapy |
| Caspr2 #9 | Caspr2 | 32 | F | 30 | AIE | rare myokymias, fasciculations, cramps | 1:3200 | n.a. | n.a. | n.a. | thymoma (8 years ago) treated with surgery, chemotherapy and radiotherapy / no immunosuppressive therapy |
| NF155 #1 | NF155 | 24 | M | 24 | CIDP with minimal symptoms | sensory motor neuropathy of UE and LE, tremor | - | 10 | yes | 1 | IVIg |
| NF155 #2 | NF155 | 10 | M | 9 | CIDP | ataxia, tremor, sensory deficits of UE and LE | - | 21 | neg. | 5 | IVIg, RTX (two 1g doses 2 weeks apart), PLEX, Prs p.o. |
| NF155 #3 | pan-NF155/140/186 | 56 | M | 56 | GBS + MS (since 2010) + Graves' disease | tetraparesis, sensory motor deficits of UE and LE; death | 1:40960 | 1 | n.a. | 5 | IVIg, RTX (two 1g doses 2 weeks apart), PLEX |
| CNTN1 #1 | CNTN1 + Caspr1 | 75 | M | 74 | CIDP | oculomotor nerve paresis, ptosis, ataxia, diplopia, dysphagia, tetraparesis, intubation; death | 1:3200 | n.a. | n.a. | n.a. | IVIg, PLEX |
| CNTN1 #2 | CNTN1 + Caspr1 | 54 | M | 54 | CIDP | senso-motoric neurological deficits of UE and LE, sensory ataxia, dysesthesia, edema (ascites and leg edema), hypoproteinemia, hypoalbuminemia, proteinuria | - | normal (<5) | neg. | n.a. | i.v. methylprednisolone (4x 250 mg and 3x 125 mg, over 7 d), followed by Prs p.o. |
| CNTN1 #3 | CNTN1 | 72 | M | 72 | CIDP | - | 1:200 | n.a. | n.a. | n.a. | 3 cycles of IVIg |
| CNTN1 #4 | CNTN1 | 59 | M | 59 | CIDP | - | 1:200 | n.a. | n.a. | n.a. | IVIg |
| CNTN1 #5 | CNTN1 | 72 | M | 72 | acute onset CIDP | - | 1:1600 | n.a. | n.a. | n.a. | - |
| CNTN1 #6 | CNTN1 | 82 | M | 82 | CIDP | gait disorder, paresthesias in stocking-glove distribution, intention tremor, weak tendon reflexes UE, absent tendon reflexes LE | 1:160 | 5 | neg. | 4 | 2 cycles of IVIg |
| CNTN1 #7 | CNTN1 | 72 | M | 68 | CIDP | ascending paraparesis, diplopia, facial paralysis right | 1:1280 | 4 | n.a. | 0 | IVIg, RTX, PLEX |
| CNTN1 #8 | Caspr1 | 82 | M | 83 | CIDP | tetraparesis, stocking-glove distribution hypesthesia, absent tendon reflexes | 1:1600 | 6 | neg. | 5 | 3 cycles of IVIg, PLEX (1 cycle of 5 sessions), RTX |
| MuSK #1 | MuSK | 62 | F | 41 | generalized MG (initially only ocular symptoms) | - | 4 | - | - | 0 | thymectomy / Pyr, Prs, Aza |
| MuSK #2 | MuSK | 32 | F | 24 | generalized MG (initially only ocular symptoms) | ophtalmoparesis, generalized muscle weakness | 3.5 | - | - | 1 | Pyr, Prs, Aza, RTX |
| MuSK #3 | MuSK | 42 | F | 38 | generalized MG | dysarthria, dysphagia, ophtalmoparesis, ptosis, facial muscle weakness | 2.5 | - | - | 2 | RTX |
| MuSK #4 | MuSK | 44 | M | 44 | generalized MG | - | 2 | - | - | 0 | Pyr, Prs, Aza |
| MuSK #5 | MuSK, borderline | 36 | M | 34 | ocular MG | - | 2 | - | - | 1 | Prs p.o. |
| MuSK #6 | MuSK | 58 | M | 58 | generalized MG | ptosis, ophtalmoparesis, proximal muscle weakness, dysarthria, dysphagia | 2 | - | - | n.a. | Pyr, Prs, IVIg, RTX, Ibrutinib |
| MuSK #7 | MuSK | 27 | F | 27 | generalized MG | orofacial muscle weakness, dysarthria | 4 | - | - | 1 | - |
| MuSK #8 | MuSK | 40 | F | 32 | generalized MG | dysarthria, dysphagia, ophtalmoparesis, ptosis, orofacial and extremity muscle weakness, dyspnea | 4 | - | - | 2 | thymectomy / Pyr, Prs, sc IG, RTX |
| MuSK #9 | MuSK | 35 | F | 35 | generalized MG | ophtalmoparesis, dysphagia, proximal muscle weakness | 3.5 | - | - | 1 | Pyr, RTX |
| MuSK #10 | MuSK | 28 | F | 28 | generalized MG | dyspnea, dysphagia, dysarthria, proximal muscle weakness | 1.5 | - | - | 2 | thymectomy / Pyr, Prs, Aza, RTX |
| MuSK #11 | MuSK | 50 | F | 25 | generalized MG | - | 4 | - | - | 2 | thymectomy / Prs, IVIg |
| MuSK #12 | MuSK | 37 | F | 47 | generalized MG | dysarthria, dysphagia, ophtalmoparesis | 4 | - | - | 2 | Prs, RTX |
| MuSK #13 | MuSK | 57 | F | 21 | generalized MG | - | 0.5 | - | - | 2 | thymectomy / Prs p.o. |
| MuSK #14 | MuSK | 42 | F | 36 | ocular MG | - | 0.5 | - | - | 1 | Pyr, Prs p.o. |
| MuSK #15 | MuSK | 11 | F | 3 | generalized MG | - | 0.5 | - | - | 1 | thymectomy/ IVIg, Prs p.o., cyclosporine |

**Supplementary Table 2: Epidemiological, clinical, serological, and histopathological data of the IgG4-RLD study cohort.** None of the IgG4-RLD patients had an immunotherapy before blood sampling. An immunosuppressive agent was administered in 4/19 IgG4-RLD patients before blood sample taking. Increased IgG4 plasma cell infiltration indicates either the IgG4:IgG ratio and/or $IgG4^+$ cells per high power field. F = female; IgG4 = immunoglobulin type G subclass 4; IgG4-RLD = IgG4-related disease; M = male; Prs = prednisolone; p.o. = per os.

| patient ID | age [years] | sex | age at disease onset [years] | time from disease onset until blood sampling [months] | date of diagnosis [month/year] | time difference between blood sampling and date of diagnosis [months]) | acute therapy including immunosuppression and immunotherapy (before blood sampling) | clinical phenotype | serological features (IgG4 concentration [g/L]) reference value (normal: <1.35 g/L) | histopathological features (increased IgG4 plasma cell infiltration (1), storiform fibrosis (2), obliterative phlebitis (3)) |
|---|---|---|---|---|---|---|---|---|---|---|
| IgG4-RLD #1 | 76 | F | 76 | 2 | 06/2019 | -6 | Prs p.o. | IgG4-related pachymeningitis | 0.87 | (1), (2) |
| IgG4-RLD #2 | 48 | F | 48 | 7 | 05/2015 | -1 | no | IgG4-related pseudotumor orbitae | 0.90 | (1), (2) |
| IgG4-RLD #3 | 70 | M | 70 | 3 | 07/2017 | 0 | no | IgG4-related chronic sclerosing sialadenitis (parotid gland) | 17.10 | (1) |
| IgG4-RLD #4 | 62 | M | 62 | 1 | 12/2019 | -1 | no | IgG4-related pancreatitis and sialadenitis (parotid gland) | 7.03 | (1), (2) |
| IgG4-RLD #5 | 48 | F | 47 | 3 | 08/2016 | 0 | no | IgG4-related pseudotumor orbitae | 0.79 | (1), (2) |
| IgG4-RLD #6 | 64 | F | 63 | 2 | 07/2020 | 0 | no | IgG4-related chronic sclerosing sialadenitis (submandibular gland) | 0.99 | (1), (2) |
| IgG4-RLD #7 | 59 | F | 48 | 124 | 03/2015 | -4 | no | IgG4-related chronic dacryoadenitis, pancreatitis and sialadenitis | 12.10 | (1) |
| IgG4-RLD #8 | 76 | M | 75 | 7 | 12/2016 | 2 | no | IgG4-related chronic sclerosing sialadenitis (submandibular gland) | 5.22 | (1), (2) |
| IgG4-RLD #9 | 69 | F | 68 | 8 | 04/2018 | -1 | no | IgG4-related dacryoadenitis | 6.23 | no |
| IgG4-RLD #10 | 71 | M | 68 | 42 | 12/2015 | 40 | no | IgG4-related pseudotumor orbitae | 2.11 | (1), (2) |
| IgG4-RLD #11 | 50 | F | 50 | 4 | 06/2017 | -2 | no | IgG4-related pseudotumor orbitae | 0.44 | (1), (2) |
| IgG4-RLD #12 | 57 | M | 57 | 0 | 04/2019 | 0 | no | IgG4-related sialadenitis (parotid gland) | 1.04 | (1), (2) |
| IgG4-RLD #13 | 36 | F | 31 | 64 | 06/2019 | -1 | no | IgG4-related sclerosing thyroiditis | 0.44 | (1), (2) |
| IgG4-RLD #14 | 68 | M | 62 | 71 | 01/2016 | 0 | Prs p.o. | IgG4-related cholangitis, pancreatitis and sialadenitis (parotid gland) | 16.70 | (1) |
| IgG4-RLD #15 | 28 | F | 23 | 66 | 06/2020 | 0 | no | IgG4-related chronic sclerosing laryngitis | 0.98 | (1), (2), (3) |
| IgG4-RLD #16 | 14 | M | 12 | 27 | 04/2019 | -12 | Prs p.o. | IgG4-related sialadenitis (parotid gland) | 4.17 | no |
| IgG4-RLD #17 | 46 | M | 47 | -7 | 10/2020 | -12 | no | IgG4-related aortitis, pseudotumor orbitae and sialadenitis | 2.46 | (1), (2) |
| IgG4-RLD #18 | 36 | F | 36 | 8 | 12/2017 | -12 | Prs p.o. | IgG4-related pseudotumor orbitae | 0.56 | no |
| IgG4-RLD #19 | 90 | M | 90 | 0 | 03/2019 | 0 | no | IgG4-related dacryoadenitis and pseudotumor orbitae | 12.10 | no |