Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

GTPase Regulator Associated with Focal Adhesion Kinase 1 (GRAF1) Immunoglobulin-Associated Ataxia and Neuropathy

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Abstract: Background: To date, 10 patients with GTPase Regulator Associated with Focal Adhesion Kinase 1/Rho GTPase Activating Protein 26-Immunoglobulin (GRAF1/ARHGAP26-IgG) associated neurological disorders have been described, most with ataxia.

Objective: To report the clinical, oncological, and radiological associations of GRAF1 autoantibodies.

Methods: We identified 17 patients whose serum and/or cerebrospinal fluid IgG was confirmed to target GRAF1/ARHGAP26-IgG by both tissue-based immunofluorescence and transfected cell-based assay. Clinical information was available on 14 patients.

Results: The median age at neurological symptom onset was 51 years, and 8 (47%) were men. The predominant clinical features were subacute progressive cerebellar ataxia (13) or peripheral neuropathy (2). Magnetic resonance imaging brain (7 available) showed cerebellar atrophy (4, 1 also cerebrum and brainstem atrophy). Of 7 cerebrospinal fluids available for testing, 5 showed pleocytosis with oligoclonal bands in 3. Squamous cell carcinoma was observed in 3 patients (head and neck [2], lung [1]).

Conclusion: GTPase Regulator Associated with Focal Adhesion Kinase 1 autoimmunity manifests commonly with subacute ataxia and cerebellar degeneration with a potential association with squamous cell carcinoma. Peripheral neuropathy may also be encountered. Cases in this series responded poorly to immunotherapy.

Immunoglobulin-G (IgG) autoantibodies specific for ρ GTPase activating protein 26 (ARHGAP26, also known as GTPase regulator associated with focal adhesion kinase [GRAF1]) have been reported in 10 patients to date.[1–6] Neurological manifestations in decreasing order of frequency included the following: gait ataxia (gait, 7, limb 4), dysarthria (5), nystagmus (5), dizziness (3), cognitive impairment (3), depression (3), hyperkplexia (2), ocular flutter (1), oscillopsia (1), and recurrent psychoses (1). Half of the patients had a tumor, including ovarian cancer (1), breast cancer (1), melanoma (1), B cell lymphoma (1) prostate adenocarcinoma (1), and gastric adenocarcinoma (1), suggesting that this is a paraneoplastic antibody biomarker.[1–6] Here we describe the clinical and oncological associations of an additional 14 GRAF1–IgG-seropositive patients.

Methods

The Mayo Clinic institutional review board approved this study (08–06647). This is a retrospective, clinical-serological cohort study approved by the institutional review board of Mayo Clinic, with a waiver of consent for clinical data obtained as part of serologic test validation (study 08-00647). All Mayo Clinic patients whose medical records were analyzed provided written consent for medical research.

Patients

Archived specimens from 119 patients referred to the Mayo Clinic Neuroimmunology Laboratory (2011–2019) immunolabeled murine brain synapses in a pattern potentially compatible

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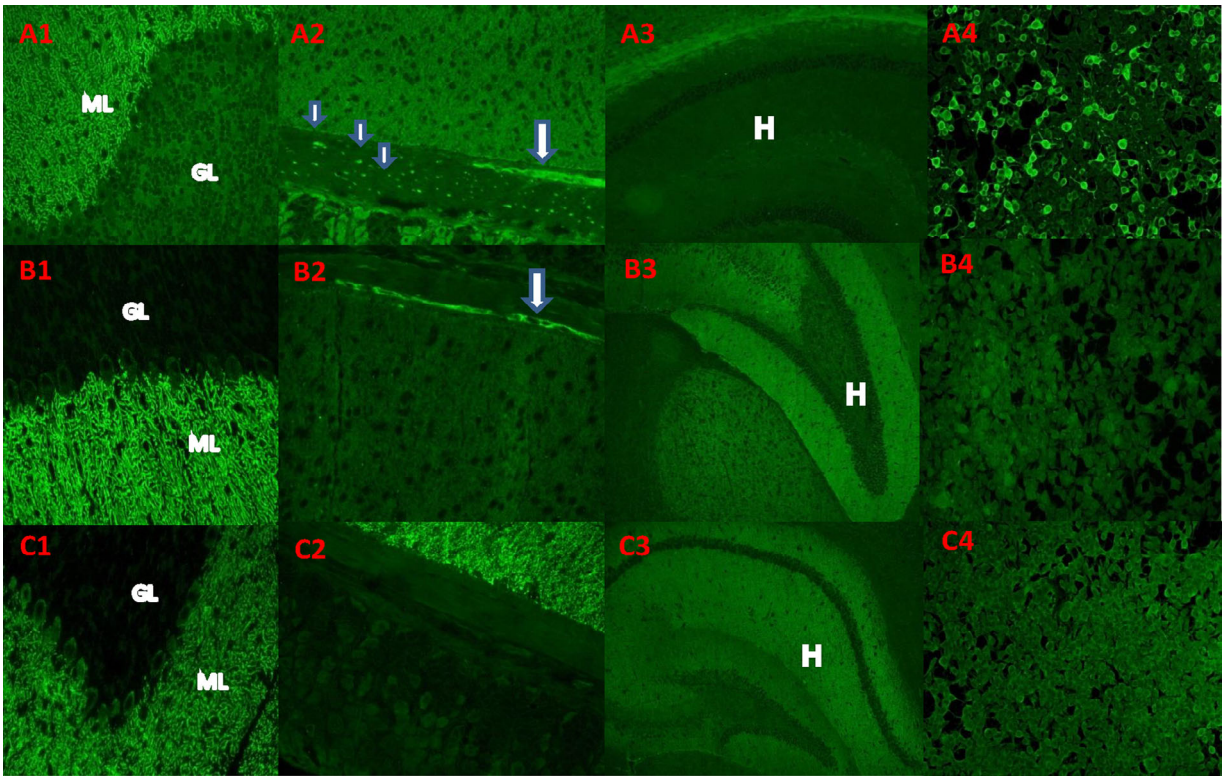

FIG. 1. Examples of "medusa-head" immunostaining pattern and IgG reactivity with ARHGAP26 (GRAF)-transfected cells. (**A**) IgG in serum of patient 5 bound to neural elements in fixed cryosectioned mouse tissues. (**A1**) Staining is prominent in the molecular layer (ML) of the cerebellar cortex in purkinje neuronal dendritic arbors and (**A2**) in the gastric smooth muscle myenteric ganglia (arrow) and nerve fibers (small arrow). (**A3**) Hippocampus was not immunoreactive. (A4) human embryonic kidney 293 (HEK293) cells transfected with ARHGAP26/GRAF were highly reactive with patient's serum IgG; interspersed nontransfected cells were not stained. (**B, C**) The medusa head–like pattern of staining observed in 104 cases lacking ARHGAP26-IgG specificity and excluded from this report: IgG in 2 such patients' sera yielded a medusa-head pattern of staining that shares some similarities with ARHGAP26-IgG, but does not bind to HEK293 cells transfected with ARHGAP26/GRAF (**B4**, **C4**). Unlike ARHGAP26-IgG, these patients' serum IgG stains hippocampus brightly (**B3**, **C3**). Patient C serum does not stain myenteric ganglia or nerve fibers in the stomach smooth muscle (**C2**).

with GRAF1–IgG (Fig. 1). Of these patients, 17 tested positive for GRAF1–IgG by cell based assay (CBA). Clinical information (limited in some) was available in 14 patients and was obtained by physician telephone interview and case record review.

Serological Testing

Specimens were evaluated by indirect immunofluorescence assay (IFA) on a composite substrate of mouse hippocampus, cerebral cortex, cerebellum, basal ganglia, thalamus, kidney, and stomach. GRAF1-specific IgG was identified by the characteristic indirect IFA cytoplasmic staining pattern (Fig. 1).

GRAF1–IgG specificity was confirmed (in all patients) molecularly by cell-based assay (CBA) on human embryonic kidney 293 cells that were transfected with GRAF1 complementary DNA fixed with 1% formalin and stored at 4°C (Euroimmun AG, Lubeck, Germany). Controls were tested on GRAF1-transfected CBA and nontransfected cells using sera from healthy adults (100), healthy children (50), patients with other antineuronal antibodies (Purkinje cell antibody type 1; 5), patients with Purkinje cell antibody type 2 (10), hypergammaglobulinemia (25), patients with multiple sclerosis (9), and patients with Sjogrens/lupus (30). Controls were also tested using cerebrospinal fluid (CSF) from healthy adults (25) and healthy children (25). Interrater agreement was 100%. Positive serum samples were titrated in doubling dilutions to ascertain the end dilution that remained positive by IFA.

All specimens underwent comprehensive paraneoplastic neural autoantibody evaluation that includes testing for cation channel antibodies (voltage-gated calcium channels [P/Q-type and N-type], voltage-gated potassium channels, and nicotinic acetylcholine receptors [muscle type and ganglionic type]); skeletal muscle striational antibodies; antineuronal nuclear autoantibodies types 1, 2 (anti-Ri), and 3; Purkinje-cell cytoplasmic autoantibodies types 1 (anti-Yo), 2, and Tr (DNER, delta/notch-like epidermal growth factor–related receptor); antiglial/neuronal nuclear antibody type 1; collapsin response-mediator protein-5 IgG; amphiphysin-IgG; and glutamic acid decarboxylase, NMDA-R

TABLE 1 *Mayo Clinic GRAF1–IgG positive cases*

Patient No./ Sex/Age	Cerebellar (Cbl) Ataxia	Peripheral Neuropathy: Small Fiber	Peripheral Neuropathy: Large Fiber	Other Symptoms/Signs	Evidence of Cancer	MRI Brain	CSF	GRAF1–IgG Serum(s) or CSF IFA Titer	Immunotherapy	Follow-Up (months)	Outcome
1/M/76	+	–	–		Peritracheal & hilar nodes FDG-avid by PET-CT	NA	Pleocytosis OCB positive	S:30720	Pulse steroid, IVIG, cyclophosphamide	5	Wheelchair bound
2/M/55	+	+	+	Severe gastroparesis	Squamous cell carcinoma in solitary node (histopathology)	Cerebral and cerebellar atrophy	Pleocytosis	S:7680	Oral steroid IVIG, PLEX	7	Wheelchair bound, GJ tube feeding
3/F/50	–	+	–	Burning feet, orthostatic intolerance and episodic diaphoresis	NA	Pituitary microadenoma	ND	S:15360	None	60	Ambulatory
4/M/47	–	–	+	–	Negative (PET-CT)	ND	ND	S:61440	PLEX	7	Ambulatory
5/F/46	+	–	–	Pseudobulbar affect cognitive dysfunction	Negative (PET-CT)	Cerebellar and brainstem atrophy	ND	S:15360	PLEX	26	Wheelchair bound
6/M/62	+	–	–	Pseudobulbar affect	Lingual tonsil and inguinal nodes FDG-avid by PET-CT	Cerebellar and cerebrum atrophy	NA	S:15360	Pulse steroid, IVIG	36	Wheelchair bound
7/F/50	+	–	–	Mild parkinsonism longtract signs LEs	None	Cerebellar atrophy	None	S:30720	None	20	Walking frame
8/F/14	+	–	–	–	Negative (PET-CT)	Normal	Pleocytic lymphocytosis, elevated protein, OCB negative	S:30720 CSF:64	Pulse steroid, IVIG, PLEX, cyclophosphamide	63	Wheelchair bound
9/F/51	+	–	–	–	Negative (PET-CT)	Unavailable	Unavailable	S:1920 CSF:128	Pulse Steroid, PLEX	0	Unavailable
10/M/63	+	–	–	–	Nasopharyngeal squamous cell carcinoma(histopathology)	Cerebellar and brainstem atrophy	Pleocytic lymphocytosis	CSF:256	Pulse steroid, IVIG, PLEX	24	Wheelchair bound
11/F/35	+	–	+	–	Unavailable	Normal	Normal	CSF:1024	Unavailable	Unavailable	Unavailable
12/M/50	+	–	–	Longtract signs LEs	Negative (PET-CT)	Normal	No pleocytosis, OCB positive, Increased protein and IgG index	S:7680 CSF: 256	Pulse steroid, oral steroid, IVIG	3	Wheelchair bound
13/F/67	+	–	–	–	Squamous cell lung cancer with retroperitoneal metastases. Remote history of mullerian fallopian tube cancer 10 years prior	Normal	Pleocytotic, elevated protein, OCB positive	CSF: 512	PLEX, IVIG	NA	NA
14/F/64	+	–	–	–	CT no solid organ malignancy. Blastic bony lesions in spine. Past history of breast cancer. PET-CT not completed	T2 hyperintensity and DWI restriction of bilateral colliculi, basal ganglia, putamen, thalamus	NA	Serum IFA positive, not titer	None	1	Rapid deterioration with coma and death within 1 mo

GRAF1, GTPase Regulator Associated with Focal Adhesion Kinase 1; IgG, immunoglobulin-G; Cbl, Cerebellar; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IFA, immunofluorescence assay; M, male; F, female; FDG, fluorodeoxyglucose; PET-CT, positron emission tomography–computed tomography; S, serum; NA, not available; OCB, oligoclonal band; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; GJ, gastro-jejunal; ND, not done; LEs, lower extremities; CT, computed tomography; DWI, diffusion weighted image.

TABLE 2 *Previously published GRAF1–IgG positive cases*

Patient No/Sex/ Age/Reference	Cbl Ataxia	Peripheral Neuropathy: Small Fiber	Peripheral Neuropathy: Large Fiber	Other Symptoms/Signs	Evidence of Cancer	MRI Brain	CSF	GRAF1–IgG Serum (s) or CSF IFA Titer	Immunotherapy	Follow-Up (months)	Outcome
1/F/33/[1]	+	NA	NA	Diplopia, depression, hyperekplexia	NA	Cerebellar atrophy	Pleocytosis, OCBs positive	S: 1:6000 CSF: 1:200	IVMP, IVIG, RTX	16 months	Cerebellar signs and hyperekplexia, stable
2/F/68/[2]	+	NA	NA	Dizziness, nausea and vomiting	Ovarian cancer	Empty sella, cerebellar atrophy	NA	S:1:32000	RTX, IVIG, cyclophosphamide	24 months	Progressive decline
3/M/38/[2]	+	NA	NA	Weight loss, nausea and vomiting	NA	Cerebellar atrophy	5 cells, OCBs positive	S:1:3200	NA	NA	NA
4/M/24/[3]	+	NA	NA	Oscillopsia, flattened affect, cognitive impairments, weight loss, headache, memory disturbances	NA	Cerebellar atrophy	OCBs positive	S:1:20000 CSF: 1:240	IVIG, PLEX	4 years	Severe gait ataxia and cognitive symptoms. Using a walking stroller at 3 years
5/F/34/[4]	–	NA	NA	Recurrent psychotic symptoms, suicidal thoughts, headache	NA	Normal	Normal	S: 1:1000 CSF: positive	IVIG	NA	NA
6/F/57/[6]	+	NA	NA	Urticaria, dizziness, abnormal eye movements	History of breast cancer, melanoma	Normal	Normal	S: 1:32	IVMP	12 months	Mild ataxia and dizziness, stable
7/F/37/[6]	+	NA	NA	Hyperekplexia, myoclonic jerks, depression, falls, dysphagia, deficits in verbal fluency	NA	Normal	OCBs positive	S: 1:100	IVMP	19 years	Wheelchair bound at 19 years
8/M/84/[5]	+	NA	NA	Emotional instability, cognitive impairment, hyperekplexia, myoclonic jerks, loss of appetite, weightloss, hyponatraemia	B cell lymphoma	Generalized atrophy	OCBs positive	S:1:1000	IVMP, PLEX	3 months	Initial mild improvement in short term memory, agitation, and depression at last follow-up
9/M/73/[5]	+	NA	NA	Poor memory	Prostate cancer	NA	NA	S:1:10000	No	NA	Death from prostate cancer
10/M/77/[5]	NA	NA	NA	Cognitive impairment	Gastric adenocarcinoma	NA	NA	S: 1:100	No	NA	NA

GRA, GTPase Regulator Associated with Focal Adhesion Kinase 1; IgG, immunoglobulin-G; Cbl, Cerebellar; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IFA, immunofluorescence assay; M, male; F, female; NA, not available; OCB, oligoclonal bands; S, serum; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; RTX, rituximab; PLEX, plasma exchange.

(N-methyl-D-aspartate receptor), GABAB-R (Gamma-aminobutyric acid B receptor), and AMPA-R (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) antibodies.

Results

A total of 17 specimens (11 sera and 6 CSF) from 17 patients were confirmed by CBA to be GRAF1–IgG positive. All 17 specimens had an identical characteristic indirect IFA cytoplasmic staining (Fig. 1). Only 1 of the control specimens tested positive for GFAP1–IgG, but by CBA only (seropositivity requires antibody detection by both IFA and CBA). GRAF1–IgG end point titers by IFA in serum ranged from 1:7680–1:61440 and CSF from 1:64–1:1024.

Of the patients, 8 (53%) were men, median onset age was 51 years (range 14–76), and median follow-up was 23 months (range 0–63). A total of 4 patients had evidence of cancer (33%), with squamous cell carcinoma being confirmed in 3.

Among the 17 patients, clinical histories were available in 14 (Table 1). Of the patients, 12 had a subacute/progressive pancerebellar syndrome (isolated in 8; patient 12) with associated large fiber neuropathy (2), autonomic neuropathy with severe gastroparesis (1), pseudobulbar affect (2), cognitive dysfunction (1), long tract signs (2), and parkinsonism (static in nature and without dysautonomia on autonomic reflex testing [making multisystem atrophy–C unlikely]) (Table 1). The 2 patients without cerebellar signs/symptoms had a small fiber neuropathy and large fiber neuropathy, respectively (patients 3 and 4). All the patients with cerebellar ataxia had a subacute onset and were progressive despite immunotherapy, except patient 8 who stabilized to premorbid function.

Cerebral magnetic resonance imaging (available in 11) showed cerebellar atrophy in 5 (patients 2, 5, 6, and 10), brainstem atrophy in 2 (patients 5 and 10), and cerebrum atrophy 2 (patients 2 and 6). Brain magnetic resonance imaging in 5 patients were normal (with a coincidental pituitary microadenoma in patient 3). CSF analysis (7 available) was inflammatory in 6: pleocytosis (5), supernumerary oligoclonal bands in 3, and a raised IgG index in 1 (Table 1).

Frequency of GRAF1–IgG Autoantibody Detection

During a 12-month period, the Mayo Clinic Neuroimmunology laboratory detected GRAF1–IgG (IFA and confirmed by CBA) in 0.004% of neurological sera submitted for paraneoplastic autoantibody evaluation (2/52,000). In comparison, approximate detection frequencies in the same period for other neuronal autoantibodies were antineuronal nuclear antibody type 1, 0.2%; Purkinje cell cytoplasmic antibody type 1 (anti-Yo), 0.08%; antineuronal nuclear autoantibodies 2/anti-Ri, 0.03%; and Purkinje cell antibody–Tr/DNER, 0.001%.

Comparison with Previously Described GRAF1–IgG Cases

There are now 24 described cases of GRAF1–IgG autoimmunity, including the 14 cases from this study. Of these, 20 (83%) had cerebellar ataxia and 8 of 18 (44%) with MRI data available had cerebellar atrophy (Table 2). Neurocognitive symptoms in 9 patients included depression, flat affect, pseudobular affect, psychosis, reduce verbal fluency, and cognitive impairment (Tables 1 and 2). Of the 24 cases, 10 had a history of malignancy (various types).

Discussion

Our observations extend the neurological spectrum of GRAF autoimmunity beyond cerebellar ataxia and provide insights into potential cancer associations. Close to one-third of patients had peripheral somatic or autonomic neuropathy (isolated or with cerebellar ataxia). The course of cerebellar ataxia was progressive and led to wheelchair dependence in all but 1 patient. Immunotherapy did not reverse the neurological disability, but stabilization was observed; however, detailed information about the timing of immunotherapy with respect to symptom onset was lacking for many patients, making it unclear whether early initiation of treatment might have reduced neurological disability.

GRAF1 binds to focal adhesion kinase, a component of the integrin signaling pathway. GRAF1 is an intracellular cytosolic protein that is expressed in a wide variety of normal tissues, including the brain, lung, gastrointestinal tract, nasopharynx, and breast. GRAF1 attenuates GTPase-mediated cellular response to integrin–extracellular matrix interaction, which include cytoskeleton organization[7,8] The finding of squamous cell carcinoma of the head and neck in 2 patients and the lung in 1 accords with the known expression of GRAF1 in epithelial tissues.[9] Furthermore, GRAF1 protein expression has been reported in head and neck cancers and ovarian cancers.

Because GRAF1–IgG is specific for an intracellular cytosolic antigen, it does not exert cell-specific cytotoxicity, but serves as a surrogate biomarker for $CD8^+$ cytotoxic T cells targeting neural cells displaying Major Histocompatibility Complex (MHC) 1-complexed GRAF1 peptides on their surface membranes.[10]

As a result of this clinical association, we recommend investigation for head and neck tumors (with attention to the nasopharynx) and lung cancer in patients who are found to be GRAF–IgG positive, ideally with a whole-body positron emission tomography–computed tomography, which identified malignancy in 4 of our cases that had negative conventional computed tomography.[11] Testing for this antibody should be considered in patients presenting with a subacute onset ataxia, especially if a paraneoplastic etiology is on the differential diagnosis.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

S.P.: 1A, 1B, 1C, 3A, 3B
N.A.: 1B, 1C, 3A
K.O.: 1B, 1C, 3A
S.H.: 1C, 3B
A.K.: 1B, 1C, 3B
V.L.: 1A, 1B, 3B
L.K.: 1B, 3B
C.P.: 1B, 3B
A.M.: 1B, 3B

Disclosures

Ethical Compliance Statement: This is a retrospective clinical-serological cohort study approved by the Institutional Review Board of Mayo Clinic with a waiver of consent for clinical data obtained as part of serological test validation (Study 08–00647). All Mayo Clinic patients whose medical charts were analyzed provided written consent for medical research. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Jarius S, Wandinger KP, Horn S, Heuer H, Wildemann B. A new Purkinje cell antibody (anti-ca) associated with subacute cerebellar ataxia: immunological characterization. *J Neuroinflammation* 2010;7:21.
2. Jarius S, Martinez-Garcia P, Hernandez AL, et al. Two new cases of anti-ca (anti-ARHGAP26/GRAF) autoantibody-associated cerebellar ataxia. *J Neuroinflammation* 2013;10:7.
3. Doss S, Numann A, Ziegler A, et al. Anti-ca/anti-ARHGAP26 antibodies associated with cerebellar atrophy and cognitive decline. *J Neuroimmunol* 2014;267(1–2):102–104.
4. Jarius S, Wildemann B, Stocker W, Moser A, Wandinger KP. Psychotic syndrome associated with anti-ca/ARHGAP26 and voltage-gated potassium channel antibodies. *J Neuroimmunol* 2015;286:79–82.
5. Bartels F, Pruss H, Finke C. Anti-ARHGAP26 autoantibodies are associated with isolated cognitive impairment. *Front Neurol* 2018;9:656.
6. Wallwitz U, Brock S, Schunck A, Wildemann B, Jarius S, Hoffmann F. From dizziness to severe ataxia and dysarthria: new cases of anti-ca/ARHGAP26 autoantibody-associated cerebellar ataxia suggest a broad clinical spectrum. *J Neuroimmunol* 2017;309:77–81.
7. Doherty GJ, Ahlund MK, Howes MT, et al. The endocytic protein GRAF1 is directed to cell-matrix adhesion sites and regulates cell spreading. *Mol Biol Cell* 2011;22(22):4380–4389.
8. Cai B, Xie S, Caplan S, Naslavsky N. GRAF1 forms a complex with MICAL-L1 and EHD1 to cooperate in tubular recycling endosome vesiculation. *Front Cell Dev Biol* 2014;2:22.
9. Regev M, Sabanay H, Kartvelishvily E, Kam Z, Bershadsky AD. Involvement of rho GAP GRAF1 in maintenance of epithelial phenotype. *Cell Adh Migr* 2017;11(4):367–383.
10. Zekeridou A, Lennon VA. Neurologic autoimmunity in the era of checkpoint inhibitor cancer immunotherapy. *Mayo Clin Proc* 2019;94(9):1865–1878.
11. McKeon A, Apiwattanakul M, Lachance DH, et al. Positron emission tomography-computed tomography in paraneoplastic neurologic disorders systematic analysis and review. *Arch Neurol* 2010;67(3):322–329.