

# Kelch-like Protein 11 (KLHL11) Antibodies in Children With Seizures of Undetermined Cause

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**Abstract.** *Background/Aim: Kelch-like protein 11 (KLHL11)-antibody may be found in paraneoplastic neurological disorders presenting with epileptic seizures. The aim of this study was to investigate the prevalence and clinical significance of KLHL11-antibody in epilepsy. Patients and Methods: Sera of 42 pediatric and 59 adult patients with seizures of undetermined cause were screened using a cell-based assay. Results: KLHL11-antibody was found in three of 168 control patients with paraneoplastic neurological disorders and four pediatric patients (4-8-year-old, 2 boys/2 girls) with seizures of unknown cause presenting with myoclonic-atonic epilepsy, generalized epilepsy or childhood epilepsy with centrottemporal spikes. In these four cases, seizures continued for 2-7 months, responded promptly and favorably to conventional anti-seizure drugs and did not recur in follow-up durations ranging between 2-5 years. Patients had normal brain MRI findings and motor-mental development before and after seizures. KLHL11-antibody was not detected in adult epilepsy patients with undetermined*

*cause, MOG antibody-positive patients and healthy controls. Conclusion: KLHL11-antibody may be detected in pediatric epilepsy patients with a relatively benign disease course.*

Antibodies targeting Kelch-like protein 11 (KLHL11) were initially identified in young men presenting with rhombencephalitis and testicular seminoma (1). However, recent studies have shown that KLHL11 antibody can be detected in patients without cancer (2-4). Moreover, the associated clinical spectrum is more heterogeneous than previously recognized and includes limbic encephalitis, psychosis, memory deficits and opsoclonus-myoclonus syndrome (2-4). Seizures are occasionally encountered in KLHL11 encephalitis at frequencies ranging from 18% to 23% (3, 4).

Antibodies directed against neuronal intracellular or cell-surface antigens are detected in a sizeable proportion of epilepsy patients of undetermined cause (5). Thus, to identify whether KLHL11 antibody belongs to the anti-neuronal antibodies associated with epilepsy, we screened adult and pediatric patients with epilepsy of undetermined cause together with disease controls using a cell-based assay.

## Patients and Methods

*Patient cohorts.* We consecutively recruited 42 pediatric patients (female/male 22/20; mean age±standard deviation 7.2±2.5; range for age 1-9 years; mean duration of epilepsy 3.6±1.9 years) admitted to our outpatient clinic with seizures of undetermined cause. Informed consent was obtained from all participants included in the study.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Istanbul University

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**Key Words:** Kelch-like protein 11, antibody, epilepsy, seizures, autoimmunity.



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Institutional Review Board; 2019-18960) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

In all patients, a detailed clinical and laboratory investigation did not yield a clue for the etiology of seizures. Patients were followed up for 28 to 64 months for definite confirmation of the undetermined cause status. Epileptic syndromes were diagnosed according to the International League Against Epilepsy (ILAE) criteria (6). All patients underwent a detailed neurological evaluation with clinical examination, seizure history and routine EEG with scalp electrodes (32 channels, noninvasive EEG monitoring with 10-20 system electrodes and ECG electrodes). In addition, all patients underwent magnetic resonance imaging (MRI) with 1.5 T or 3 T scanners. Potential underlying tumors were screened using a whole-body CT imaging only in KLHL11-antibody positive epilepsy patients. Sera of KLHL11-antibody positive patients were tested for antibodies to N-methyl-D-aspartate receptor (NMDAR),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), leucine-rich glioma inactivated-1 (LGI1), contactin-associated protein2 (CASPR2), gamma-amino butyric acid (GABA<sub>B</sub>R), glutamic acid decarboxylase (GAD), myelin oligodendrocyte glycoprotein (MOG), amphiphysin, CV2, Ma2, Ri, Yo, Hu, recoverin, SRY-Box Transcription Factor 1 (SOX1), Zic Family Member 4 (ZIC4), titin and Delta/Notch-like epidermal growth factor-related receptor (Tr/DNER) using commercial kits (Euroimmun, Luebeck, Germany). Patients with abnormal MRI features, such as tuberous sclerosis and comorbid medical conditions were excluded. None of the patients received any medication other than anti-epileptic drugs during blood sampling. CSF samples were not obtained because of the lack of parental consent. Control groups included 59 adult patients with focal seizures of undetermined cause, seven patients with epileptic encephalopathy of unknown cause, 134 negative disease controls (MOG-antibody positive patients referred to Tzartos NeuroDiagnostics, Athens, Greece), 135 patients with paraneoplastic antibodies to amphiphysin, CV2, Ma2, Ri, Yo, Hu, recoverin, SOX1, ZIC4, titin, Tr/DNER, and GAD as determined by Euroimmun kits (referred to Tzartos NeuroDiagnostics), 33 patients suspected for paraneoplastic syndrome but negative for paraneoplastic antibodies (referred to Tzartos NeuroDiagnostics) and 12 healthy controls.

**Cell culture and transfection.** HEK293 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) containing 10% Fetal Bovine Serum (FBS) and 1% penicillin-streptomycin (Invitrogen, Waltham, MA, USA) at 37°C in an atmosphere of 5% CO<sub>2</sub>. Cells were seeded on culture dishes and transiently transfected with a KLHL11 Human Tagged ORF Clone pCMV6 vector with C-terminal Myc-DDK Tag (#RC205228, Origin Technologies Inc., Rockville, MD, USA) (3.7 µg plasmid per 100 mm culture dish); or control vector, using jet PRIME kit transfection reagent (Polyplus jet PRIME, Illkirch, France).

**In-house cell-based assay.** Cells were plated in 96-well poly-L-lysine plates, fixed (4% paraformaldehyde for 15 min) and permeabilized (0.2% Triton-X-100 for 10 min). Normal goat serum (10%) was added and incubated for 30 min to block non-specific IgG binding. Transfected cells were exposed to patient serum (1 to 100, 1 to 1,000 or 1 to 3,000 dilution) or to a commercial rabbit anti-KLHL11 antibody (1 to 200 dilution; HPA044617 from Sigma Prestige Antibodies, Burlington, MA, USA) for 45 min at room temperature (RT). After washing with PBS (1X), cells were

incubated with Alexa Fluor-568 goat anti-human IgG (Invitrogen; Paisley, UK; 1 to 200) or with Alexa Fluor-568 goat anti-rabbit IgG (Invitrogen; 1 to 750) for the commercial antibody, for 45 min at RT. Images were obtained using the Olympus microscope CKX-41 and analyzed using Infinity Analyze-6.5 Lumenera software (Lumenera Corporation, Ottawa, Ontario, Canada). A serum was considered positive when 1/1,000 serum dilution produced clear positive signal. Glial fibrillary acidic protein (GFAP)-transfected HEK293 cells were used as a negative control. For further verification, co-localization of immune reactivity was tested by incubation of transfected cells with both patient sera and the commercial antibody.

**Indirect immunohistochemistry.** Indirect immunohistochemistry was performed using frozen 10-µm-thick sections of rat brain fixed in paraformaldehyde overnight, patient and control sera (1:200, overnight incubation at 4°C), secondary biotinylated anti-human IgG (1:1,000, 2 h at room temperature) and the avidin-biotin-peroxidase method (7).

## Results

**KLHL11 antibody detection.** Four of 42 (9.5%) pediatric patients with seizures of undetermined cause were found positive for antibodies to KLHL11 at 1/100 and 1/1,000 serum dilutions but not at 1/3,000 dilution. None of the patients with epilepsy had additional anti-neuronal autoimmune encephalitis and paraneoplastic syndrome antibodies. Two sera samples from 135 patients with paraneoplastic antibodies and limbic encephalitis were found to be positive for antibodies against KLHL11 at 1/100, 1/1,000, and 1/3,000 serum dilutions. These patients were also positive for anti-titin antibodies. Furthermore, one serum (of a limbic encephalitis patient) from 33 patients with suspected paraneoplastic syndrome but negative for paraneoplastic antibodies was KLHL11 antibody positive at 1/100 and 1/1,000 dilutions but not 1/3,000 dilution. All sera from the two negative control groups (12 healthy controls and 134 MOG-antibody positive patients) were found negative for antibodies against KLHL11 at all tested dilutions. All remaining 38 pediatric patients, 59 adult patients with focal seizures of undetermined cause and seven patients with epileptic encephalopathy of unknown cause were found negative for KLHL11 antibody. None of the participants' sera showed reactivity in GFAP-transfected cells (Figure 1). Serum IgG of KLHL11 antibody positive patients significantly co-localized with the commercial KLHL11 antibody on transfected HEK293 cells (Figure 2). In addition, rat brain immunohistochemistry studies showed a robust reactivity in the cytoplasm of large neurons in the brainstem, deep cerebellar nuclei (Figure 3) and hippocampus, as reported previously (2).

**Clinical features of KLHL11 antibody positive patients.** Detailed seizure, diagnostic work-up, treatment and follow-up features of KLHL11 antibody positive patients are

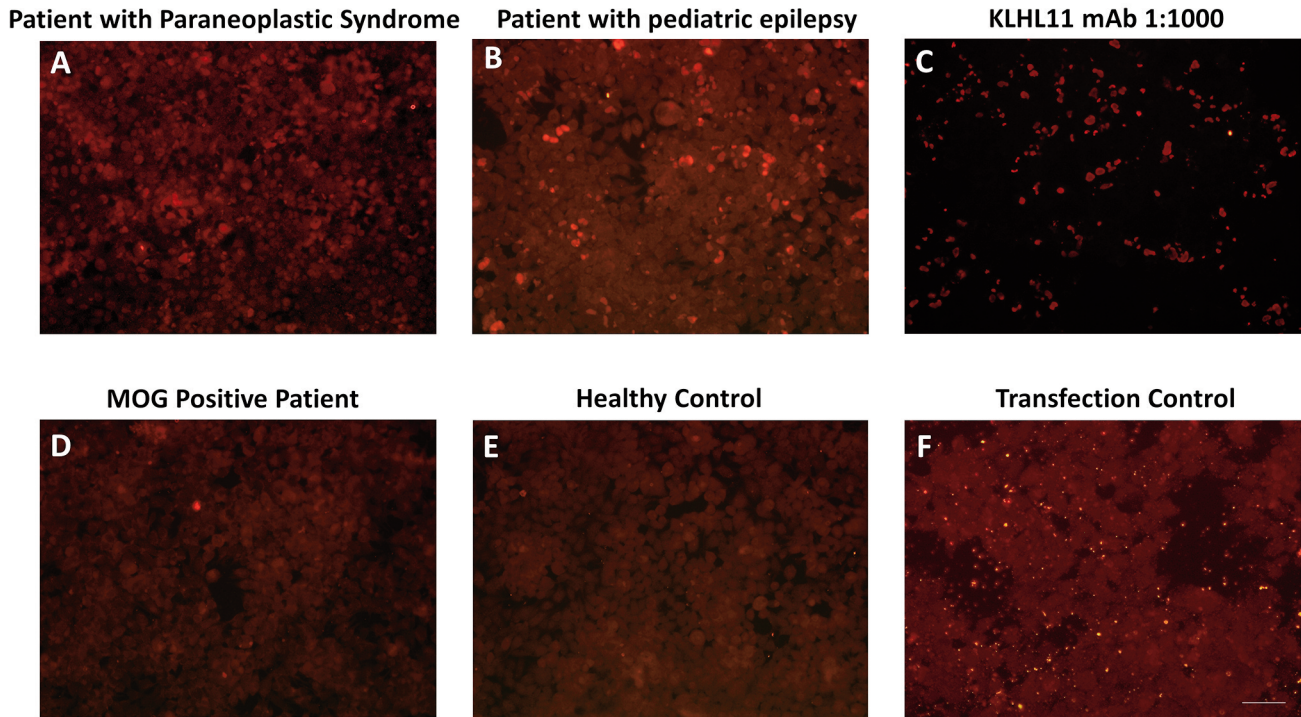


Figure 1. Cell-based assay results. Transfected HEK293 cells expressing Kelch-like protein 11 (KLHL11) antigen were incubated with sera from (A) patients with paraneoplastic neurological disorders, (B) patients diagnosed with pediatric epilepsy of undetermined cause, (D) patients with myelin oligodendrocyte (MOG) antibody-associated disease and (E) healthy controls. Transfected cells were also incubated with commercial rabbit anti-KLHL11 IgG (red, C). Some patients with (A) paraneoplastic disorders and (B) with pediatric epilepsy were found positive for KLHL11 antibody at 1/1,000 dilution, whereas (D) the patient with MOG-antibody positive sera and (E) a healthy control gave no staining at 1/100 dilution. (F) HEK293 cells expressing glial fibrillary acidic protein (GFAP) did not immunoreact with patient sera or the commercial antibody. Scale bar: 20  $\mu$ m. Note that the dot-like reactivity present in the GFAP-transfected HEK293 cells is considered as a background noise and is due to the non-specific proteins which are present in the human serum.

provided in Table I. Patients presented with focal motor, myoclonic -atonic or generalized tonic-clonic seizures. Duration of seizures ranged between 2-7 months since patients responded promptly to anti-seizure drugs. All patients were seizure-free during the follow-up period, which ranged between 2 and 5 years. None of the patients reported febrile seizures, family history of epilepsy or consanguinity or any past/coexisting disorders potentially associated with seizures. All patients had normal neurodevelopmental status and school performance before and after the seizure onset and showed normal control EEGs during the follow-up period. None of the patients tested positive for other well-characterized autoimmune encephalitis and paraneoplastic syndrome antibodies. Whole-body CT examinations were normal in all four patients.

## Discussion

In a cohort of pediatric and adult patients with epilepsy of undetermined cause, we identified four KLHL11 antibody-

positive pediatric patients, but none among the adult patients. Although seizures have been reported in KLHL11 encephalitis (3, 4), to our knowledge, KLHL11 antibody positive patients with only epilepsy have not been reported, previously. In a recent meta-analysis, an average combined prevalence of 7.6% (range=4.6-11.2% in different cohorts) of all anti-neuronal antibodies (both cell-surface and onconeurological antibodies) was reported in adult epilepsy of undetermined etiology (5). Therefore, the prevalence of KLHL11 in our pediatric epilepsy cohort (9.5%) corresponds to a sizeable proportion and suggests a putative link between KLHL11 immunity and seizure induction, at least in pediatric epilepsy.

Although our seropositive patients exhibited diverse epileptic syndromes and seizure types (focal motor, myoclonic-atonic and generalized tonic-clonic), they shared several common clinical features, such as good anti-seizure drug response, complete resolution of seizures clinically and electrophysiologically for a considerable follow-up time, normal neuroimaging features without apparent structural

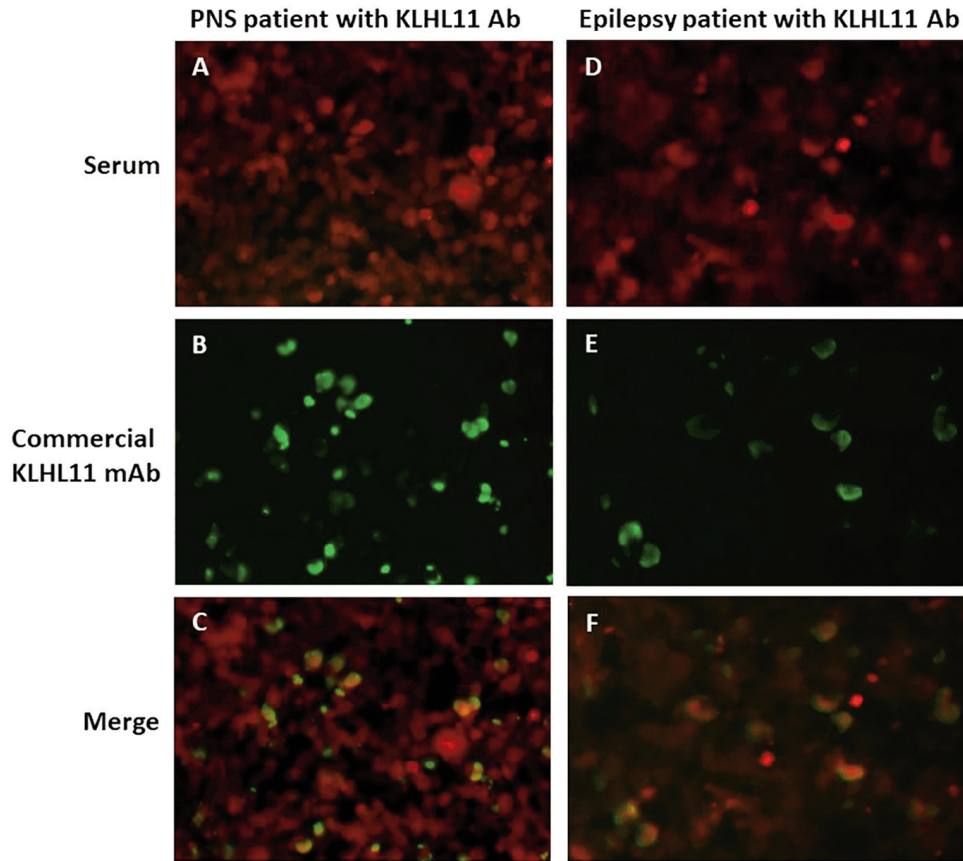


Figure 2. Co-localization studies with sera of patients and commercial Kelch-like protein 11 (KLHL11) antibody (Ab). (A, D) Reactivity (red) of sera of representative KLHL11 Ab positive patients with paraneoplastic neurological disorder (PNS) and pediatric epilepsy with HEK293 cells expressing KLHL11. (B, E) Reactivity (green) of a commercial KLHL11 Ab. (C, F) the commercial Ab shows significant co-localization with patients' antibodies (yellow). Original magnification 40 $\times$ .

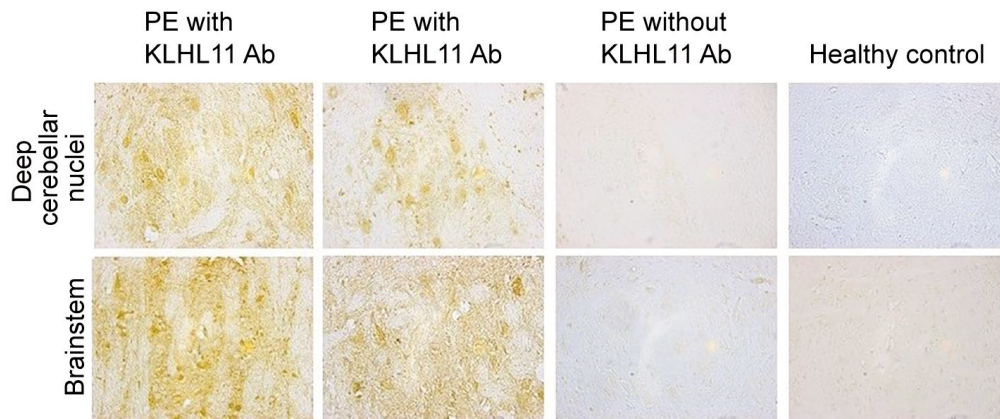


Figure 3. Immunolabeling (brown color) of frozen rat brain sections with sera of Kelch-like protein 11 (KLHL11) antibody (Ab) positive and negative pediatric epilepsy (PE) patients and a healthy control. Sera of PE patients with KLHL11 Ab show cytoplasmic staining in neurons of deep cerebellar nuclei and brainstem (leftmost two columns), whereas no appreciable immunoreactivity is observed with sera of antibody negative PE patients and healthy control (rightmost two columns; original magnification 40 $\times$ ).

Table I. Clinical characteristics of the KLHL11 autoantibody positive patients.

Age*/sex	Epileptic syndrome	AOSO	Seizure types	Seizure duration	Neurologic examination/ Cognitive impairment	EEG	MRI	ASD	ASD response/ prognosis
4/M	Epilepsy with myoclonic- atonic seizures	3	10-15 daily myoclonic- atonic seizures	6 months	Normal/ None	Bilateral spike waves, left intermittent temporal slow waves	Normal	VPA, CLB	Good No seizures in 5 years
5/M	Childhood epilepsy with centrotemporal spikes	4	Rare focal seizures of face and tongue	7 months	Normal/ None	Bilateral centrotemporal SW discharges	Normal	VPA, OXC	Good No seizures in 4 years
8/F	Childhood epilepsy with centrotemporal spikes	8	Rare focal seizures of face and tongue	3 months	Normal/ None	Bilateral centrotemporal SW discharges	Normal	VPA	Good No seizures in 2 years
5/F	GTC	5	1 GTC seizure with status and few additional GTC seizures	2 months	Normal/ None	Diffuse slow wave and SW discharges	Normal	PB	Good No seizures in 2 years

M: Male; F: female; AOSO: age of seizure onset; SW: spike wave; ASD: anti-seizure drug; GTC: generalized tonic-clonic seizures alone; VPA: valproic acid; CLB: clobazam; OXC: oxcarbazepine; PB: phenobarbital. \*Age of the patient during blood sampling.

abnormalities (*e.g.*, malformation or migration anomalies), absence of neurodevelopmental impairment before and after the seizures and absence of family history of epilepsy. These features indicate autoimmunity as an acquired etiology. In addition, occurrence of seizures in a relatively restricted time frame is congruent with the monophasic nature of autoimmune encephalitis, as commanded in the relevant clinical criteria (8). As a matter of fact, the seizure types of our seropositive patients have been described in previous reports of autoimmune encephalitis with antibodies to voltage gated potassium channel complex, GAD, NMDAR, LGI1 and Hu (9-12). Autoimmune encephalitis may also present with unilateral dominance of motor symptoms (similar to 5-year-old boy and 8-year-old girl in our cohort) and *de novo* status epilepticus (similar to 5-year-old girl in our cohort) (13, 14). Focal motor seizures observed in two of our seropositive patients were indicative of peri-Rolandic cortex involvement and such extra-limbic motor symptoms have been reported in patients with Hu encephalitis (12).

Absence of the KLHL11 antibody in adult patients with epilepsy of undetermined cause and pediatric patients with epileptic encephalopathy suggests that the emergence of KLHL11 immunity is not merely a bystander effect in response to repetitive seizures and disrupted blood-brain barrier but it is primarily involved in seizure induction. KLHL11 is ubiquitously expressed in the cytoplasm of

several neurons of the central nervous system including seizure-related regions, such as hippocampus and cortex (3). Although autoantibodies targeting intracellular antigens are not likely to display pathogenic features, KLHL11 immunity is known to be characterized by T-cell-predominant brain infiltrates (3), which may induce seizure susceptibility by enhancing neuronal network excitability (15). Furthermore, patients with KLHL11 may have additional yet uncharacterized antibodies directed to neuronal surface antigens and presence of KLHL11 antibodies might be the bystander effect of anti-neuronal autoimmunity. Notably, we have recently identified a novel cell-surface antibody to Kv5.1, a voltage-gated potassium channel subunit, in epilepsy patients with an undetermined etiology (16). Frequent coexistence of other antibodies such as those against titin (our cohort), Ma2, NMDAR and Hu antibodies (2) in KLHL11 antibody-positive patients lends support to the assertion of coexisting antibodies.

Absence of systemic tumors in our KLHL11 antibody-positive patients is congruent with absence of tumor in many recently reported patients with KLHL11 encephalitis (2-4). Notably, KLHL11 autoimmunity is associated with a strong anti-tumor immune response and regression of the underlying tumor has frequently been observed in patients with paraneoplastic KLHL11 encephalitis (3). Thus, an attractive speculation is that anti-KLHL11 antibodies might

be emerging in response to the proteins of an unnoticeable tumor. After the annihilation of this tumor by the immune system, anti-neuronal autoimmunity may develop as an undesirable side effect. This argument needs to be examined by assessing for the presence of anti-KLHL11 antibodies in a broader cohort of pediatric paraneoplastic syndrome patients with seizures.

## Conclusion

We identified anti-KLHL11 antibodies in pediatric cases with epilepsy of undetermined cause and somewhat similar clinical course. These antibodies appear to indicate a favorable response to the treatment of seizures. Future work is needed to address the potential pathogenicity of KLHL11 autoimmunity in seizure induction.

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## Conflicts of Interest

ST has shares in the research and diagnostic laboratory Tzartos NeuroDiagnostics. ST and JT have filed a patent for a cell-based method for detecting potentially pathogenic autoantibodies to neuronal nAChRs. All the other Authors declare no conflict of interest in relation to this study.

## Authors' Contributions

John Tzartos: Project administration, Supervision, Writing original draft, Review & editing, Data curation, Formal analysis. Maria Pechlivanidou, Bosveli Despoina, Elpinickie Ninou: Cell culture and transfection, Investigation, Conceptualization. Hande Yüceer, Beyzanur Yalçın: Methodology, Indirect immunohistochemistry, Formal analysis, Software. Cem İsmail Küçükali, Erdem Tüzün, Socrates Tzartos: Project administration, Supervision, Writing - original drafting, Review & editing, Data curation, Formal analysis. Dilşad Türkdoğan: Obtaining clinical data, Methodology, Formal analysis.

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