

# Unexpected findings in patients with limbic encephalitis will change disease diagnosis and classification

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New findings indicate that the target of autoantibodies that are associated with limbic encephalitis is LGI1 - a protein involved in fine-tuning of neuronal synapses. The results suggest that testing for these antibodies to LGI1 is diagnostic for limbic encephalitis, and mean that the current classification of the disease should be changed, concludes an Article published Online First and in the August edition of *The Lancet Neurology*.

Autoimmune synaptic encephalopathies are neurological disorders in which patients develop [antibodies](#) against proteins on neuronal synapses. Patients present with seizures and neuropsychiatric symptoms, such as psychosis and changes in memory, cognition, and behaviour. Such symptoms are common in patients with limbic encephalitis, an autoimmune synaptic encephalopathy previously attributed to autoantibodies against voltage-gated potassium channels.

A team lead by Josep Dalmau, University of Pennsylvania, Philadelphia, PA, USA, failed to replicate the indirect evidence on autoantibodies against voltage-gated potassium channels in limbic encephalitis so they then sought to find the true target of autoantibodies - known as the autoantigen. Blood or cerebro-spinal fluid (CSF) samples were taken from 57 patients who met criteria for limbic encephalitis and had antibodies attributed to voltage-gated potassium channels (VGKC) and compared with 148 control individuals with other neurological disorders. Most patients received [immunotherapy](#), and 78% had substantial clinical recovery.

The US and Spanish researchers used the established approach used to identify autoimmune synaptic encephalopathies, involving key steps of:

using patients' antibodies to precipitate the targeted proteins and then using other biochemical techniques to identify the autoantigen; immunologic staining to show that cell cultures expressing the autoantigen react with patients' but not controls' samples; demonstrating that this reactivity is abrogated by prior exposure to cells expressing the autoantigen; and showing that reactivity to patients' samples occurs in wild-type mice but not in those genetically engineered to lack the mouse equivalent of the autoantigen.

To the surprise of the research team, all patients tested had antibodies against LGI1 (Leucine-rich, glioma-inactivated 1 protein), but not to potassium channels. LGI1 may connect pre- and post-synaptic protein complexes for finely tuned synaptic transmission.

These findings set up the basis for a new, reliable diagnostic test to confirm clinical and brain scan findings in limbic encephalitis, say the authors, who also postulate a mechanism for the disorder. "We speculate that antibody-mediated disruption of LGI1 function causes increased excitability resulting in seizures and other symptoms of limbic encephalopathy," say Dalmau and colleagues. The findings suggest a new diagnostic classification: "the term 'limbic encephalitis associated with VGKC antibodies' should be changed for 'limbic encephalitis associated with LGI1 antibodies'", the authors recommend. Also: "We propose to include this disorder in the "autoimmune synaptic encephalopathies", they explain. Finally, the existence of a disorder related to autoantibodies against voltage-gated [potassium channels](#) remains to be confirmed.

In an accompanying Comment, Jérôme Honnorat, Hôpital Neurologique Pierre Wertheimer, Bron Cedex, France, says: "The identification of LGI1 as

the main target of voltage-gated potassium channel antibodies in patients with limbic encephalitis has many consequences for the understanding of the mechanisms that cause the main symptoms in this disease". He explains that LGI1 "is probably a key protein of synaptic organisation and thus the understanding of other neurological disorders might also improve because of these findings" and could lead to new therapeutic strategies for epilepsy, mood disorders, or even neurodegenerative diseases, such as Alzheimer's disease.

Provided by Lancet

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