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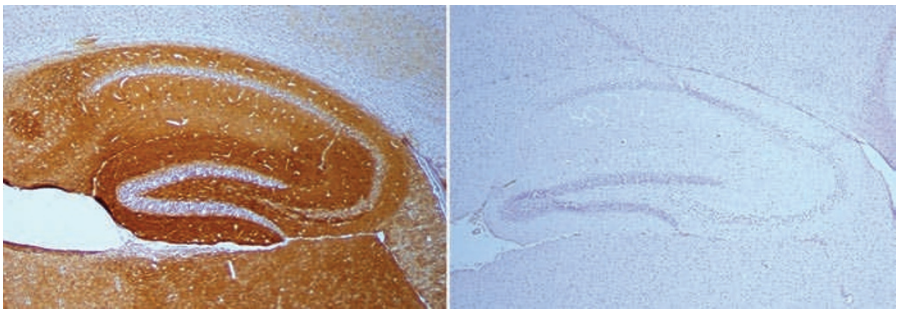
Antibodies target LGI1 rather than potassium channels in limbic encephalitis

The condition known as limbic encephalitis associated with antibodies against voltage-gated potassium channels (VGKCs) may be set for reclassification. According to a new study, such channels are not the targets of the autoantibodies found in this disorder. Rather, the study's researchers report that the antigen is, in fact, leucine-rich glioma-inactivated protein 1 (LGI1), a secreted neuronal protein that has a critical role in synaptic function.



Serum of a patient with limbic encephalitis attributed to voltage-gated potassium channel antibodies stained hippocampal sections from wild-type mice (brown staining; left) but not from *Lgi1*-null mice (right). Image provided by Prof. Josep Dalmau.

Patients who develop limbic encephalitis often experience short-term memory deficits, but can also have neuropsychiatric symptoms of varying severity, and/or seizures. Studies have indicated that one of the most common forms of this disorder is caused by autoantibodies generated against VGKCs. Such antibodies have also been associated with neuromyotonia—a peripheral nerve disorder characterized by muscle cramps and spasms—and Morvan syndrome, which shares symptoms with both of these conditions. "The fact that patients with the same antibodies could have such different symptoms raised doubts that these channels were the real target antigens," says principal investigator of the new study, Josep Dalmau. These doubts were compounded when Dalmau and his colleagues failed to see reactivity between VGKCs and antibodies from patients with one or other of these conditions in cell-based assays.

In the new study, the researchers aimed to determine the real antigen associated with VGKC antibody-related limbic encephalitis. Through careful clinical examinations, the researchers identified 57 patients with limbic encephalitis attributed to VGKC antibodies and 148 control individuals who had one of several other disorders. Serum or cerebrospinal fluid samples were collected from the study participants and examined for VGKC antibodies, which were 'confirmed' to be present if the sample was capable of immunostaining rat brain slices and hippocampal neurons, or tested positive in a ^{125}I-α-dendrotoxin radioimmunoassay. From these tests, all patients with limbic encephalitis and five controls—one with Morvan syndrome, three with neuromyotonia and one with severe encephalitis and seizures—were deemed positive for VGKC antibodies.

Immunoprecipitation experiments were conducted using sera from two patients with limbic encephalitis and 'VGKC antibodies' and one control. Mass spectrometry analysis of the immunoprecipitates revealed the presence of LGI1 in the limbic encaphalitis samples but not in the control sample, a finding that was confirmed by immunoblotting with a commercially available LGI1 antibody.

To verify the association of LGI1 with limbic encephalitis attributed to VGKC antibodies, the investigators assessed serum or CSF samples from the study participants for reactivity with LGI1 expressed in a cell line. Samples from all 57 patients with limbic encephalitis, but none of the controls, produced positive immunostaining in this assay. Moreover, in similar experiments involving co-expression of two VGKC subunits, no serum or CSF samples from patients or controls showed reactivity with these proteins.

Prior incubation with LGI1 of serum from patients with limbic encephalitis and 'VGKC antibodies' abrogated the staining of rat brain preparations, providing further evidence that LGI1 was the main antigen in these samples. This finding was supported by results in mice, in which hippocampal sections from wild-type but not *Lgi1*-null animals showed staining following incubation with serum or CSF from such patients.

In addition to identifying LGI1 as the main antigen in limbic encaphalitis previously attributed to VGKC antibodies, the researchers showed that antibodies to contactin-associated protein-like 2 were present in one patient with this disease and in some individuals with encephalitis and seizures, Morvan syndrome or neuromyotonia. Thus, "different clinical phenotypes that were difficult to explain as a result of a single immune response against VGKC are now explained by the identification of antibodies against two different molecular targets," says Dalmau.

In light of their findings, the researchers advocate reclassification of VGKC-related autoimmune diseases. They also point out that the existence of any disorder related to VGKC antibodies remains unclear.

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