



## MS & neuroinflammation

### 56087 VGKC is dead: long live LGI1- and CASPR2-antibodies. Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies

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#### Introduction

Autoantibodies against the extracellular domains of the voltage-gated potassium channel (VGKC) complex proteins, leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-2 (CASPR2), are found in patients with limbic encephalitis, faciobrachial dystonic seizures, Morvan's syndrome and neuromyotonia. However, in routine testing, VGKC-complex-antibodies without LGI1- or CASPR2-reactivities ("double-negative") are commoner than LGI1- or CASPR2-specificities. Therefore, the target(s) and clinical associations of double-negative antibodies need to be determined.

#### Methods

Sera (n=1131) from several clinically-defined cohorts were tested for IgG-radioimmunoprecipitation of <sup>125</sup>I-aDTX-labelled VGKC-complexes, <sup>125</sup>I-aDTX and <sup>125</sup>I-aDTX-labelled Kv1-subunits, live hippocampal neuron reactivity, and by cell-based assays using Kv1-subunits, LGI1 and CASPR2.

#### Results

VGKC-complex-antibodies were found in 162 of 1131 (14%) sera. Ninety of these (56%) had antibodies targeting the extracellular domains of LGI1 or CASPR2. Of the remaining 72 double-negative sera, ten (14%) immunoprecipitated <sup>125</sup>I-aDTX itself, and 27 (38%) bound to solubilized co-expressed Kv1.1/1.2/1.6 subunits and/or Kv1.2 subunits alone, at levels proportionate to VGKC-complex-antibody levels ( $r=0.57$ ,  $p=0.0017$ ). The Kv1-precipitating samples only bound to permeabilised Kv1-expressing HEK cells. These intracellular Kv1-antibodies mainly associated with non-immune disease aetiologies, poor longitudinal clinical-serological correlations, and a limited immunotherapy-response.

#### Conclusions

Double-negative VGKC-complex-antibodies are often directed against cytosolic epitopes of Kv1-subunits, and occasionally against non-mammalian aDTX. These are not neuronal-surface antibodies. They consequently lack pathogenic potential, and do not in themselves support use of immunotherapies. VGKC-complex radioimmunoassay testing should cease; antibodies against LGI1 and CASPR2 provide greater specificity and sensitivity.