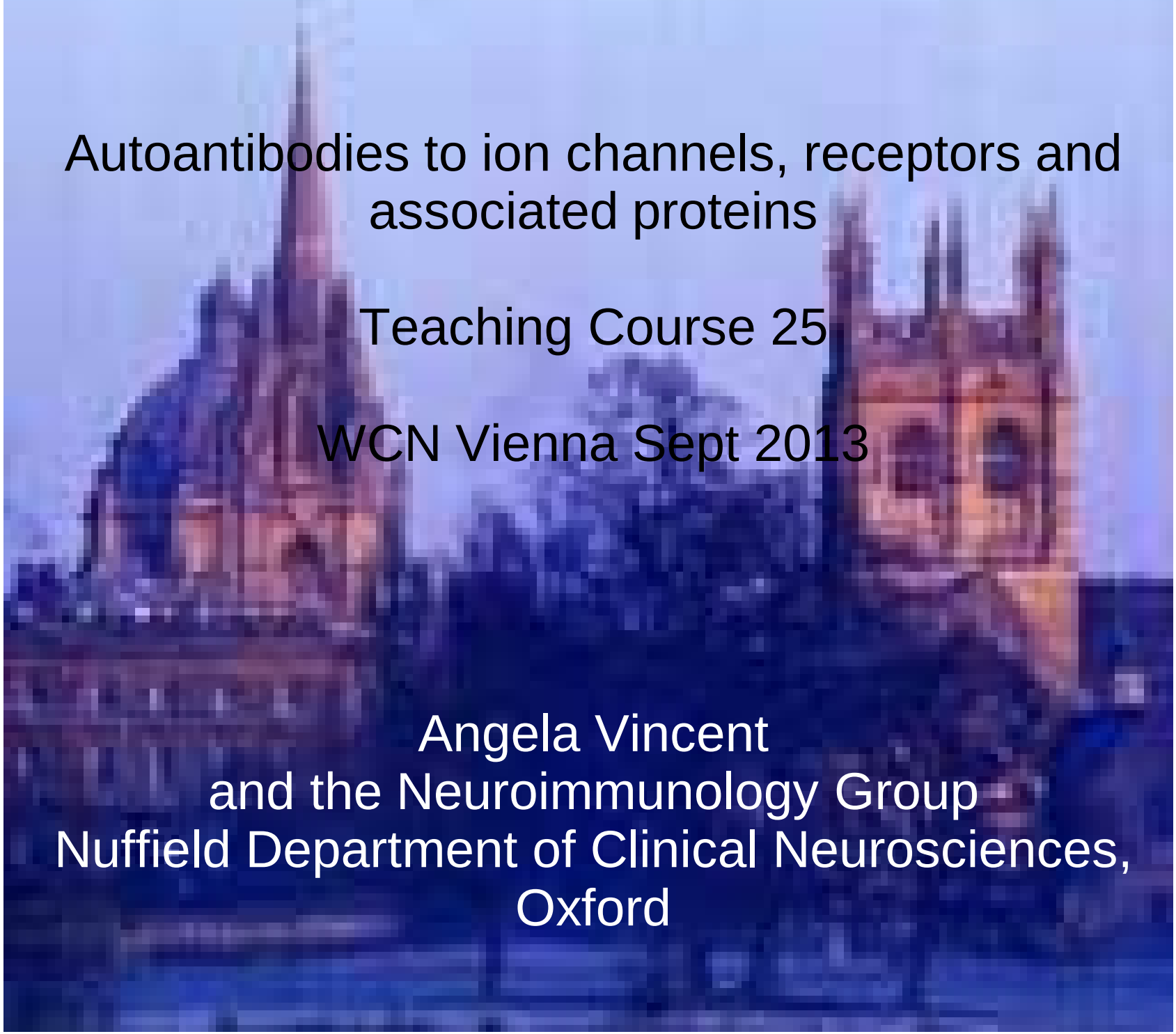


Autoantibodies to ion channels, receptors and associated proteins

Teaching Course 25

WCN Vienna Sept 2013

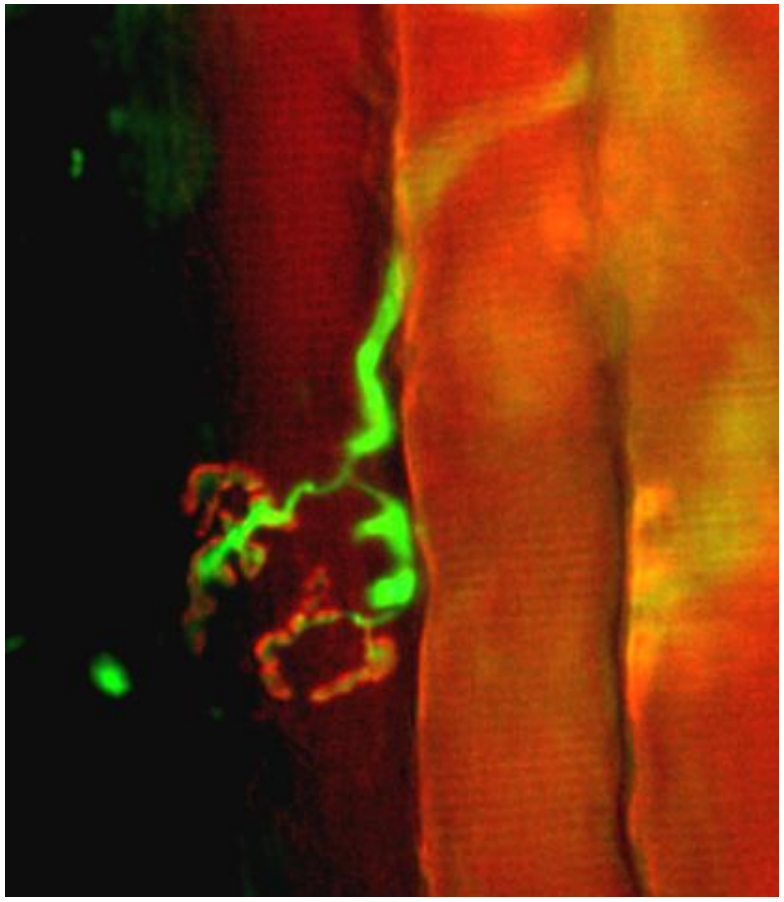
Angela Vincent
and the Neuroimmunology Group
Nuffield Department of Clinical Neurosciences,
Oxford

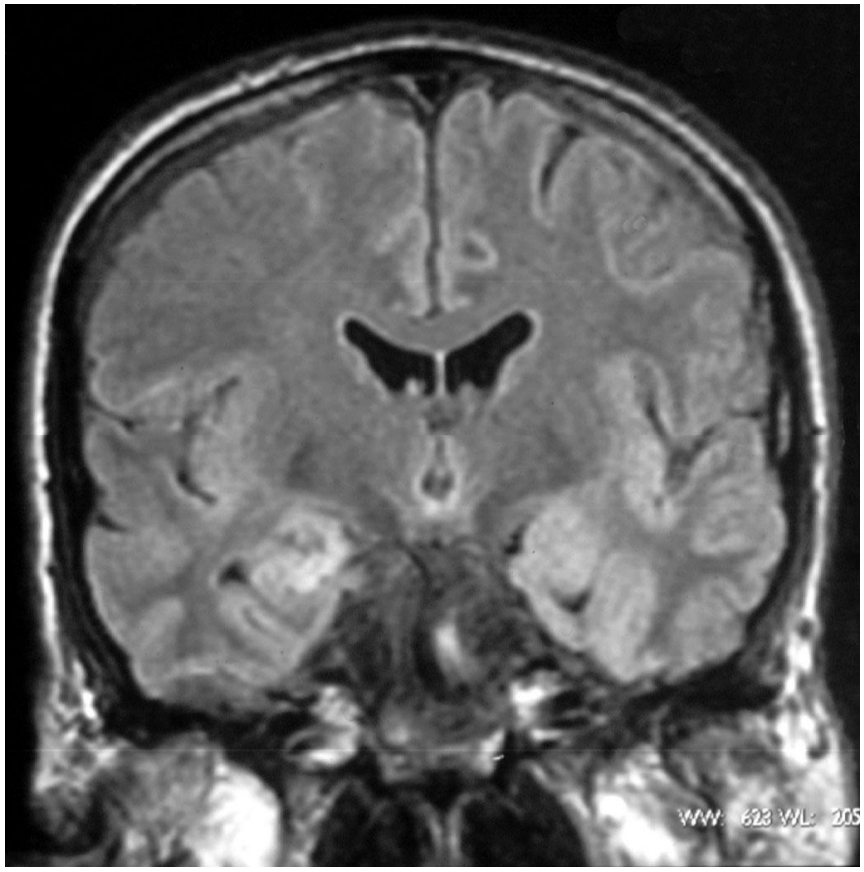
Disclosures

Angela Vincent and the University of Oxford hold patents, and receive royalties and payments for antibody tests including VGKC-complex antigens

Angela Vincent has recently received honoraria for lectures from UCB Pharma and Serono

From myasthenia to antibody-mediated CNS diseases





What myasthenia gravis taught us
Antibody-mediated diseases

Antibodies that bind to extracellular domain of membrane protein on target tissue – eg acetylcholine receptor in MG

Can be measured easily in serum

Antibodies cause loss of function

Patients can improve dramatically with immunotherapies: plasma exchange, intravenous immunoglobulins, steroids

Diseases of the CNS with specific antibodies in adults and children

Rare but immunotherapy-responsive

Most against receptors, ion channels or related proteins

Clear parallels with genetic diseases in the same or related proteins

Learning objectives

To recognise the clinical features of grey-matter antibody-mediated diseases

To appreciate the parallels with genetic disorders

To understand the pathophysiology of the diseases

To appreciate some of the treatment possibilities and challenges

Diseases of the CNS in adults and children with specific antibodies (Ab)

VGKC/LGI1 or CASPR2-Ab limbic encephalitis

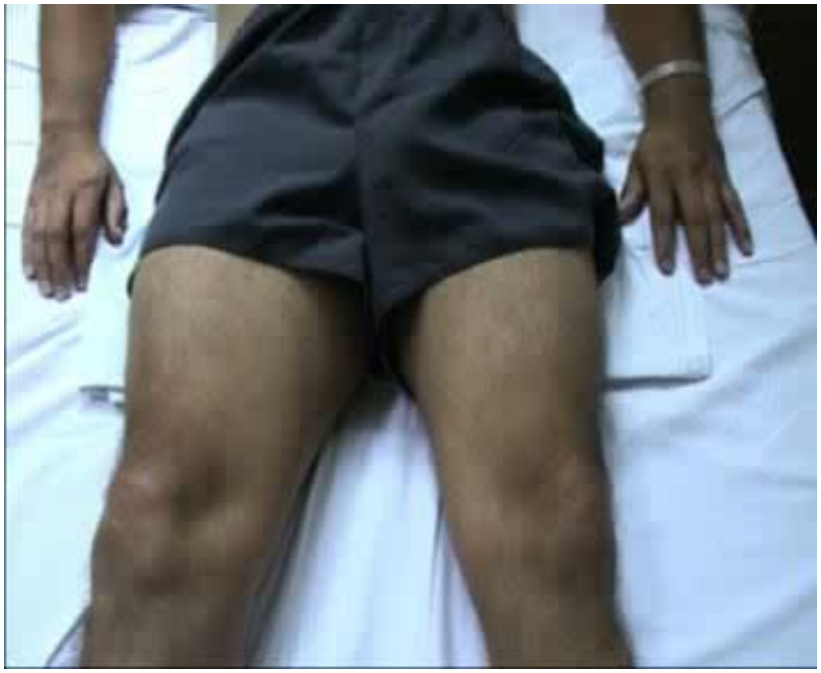
NMDAR-Ab encephalitis

GlyR-Ab encephalomyelitis

AMPAR, GABAbR, mGluRs, D2Rs, Kir4.1, DPPX

are apparently less common and these antibody targets will not be described:

Acquired neuromyotonia

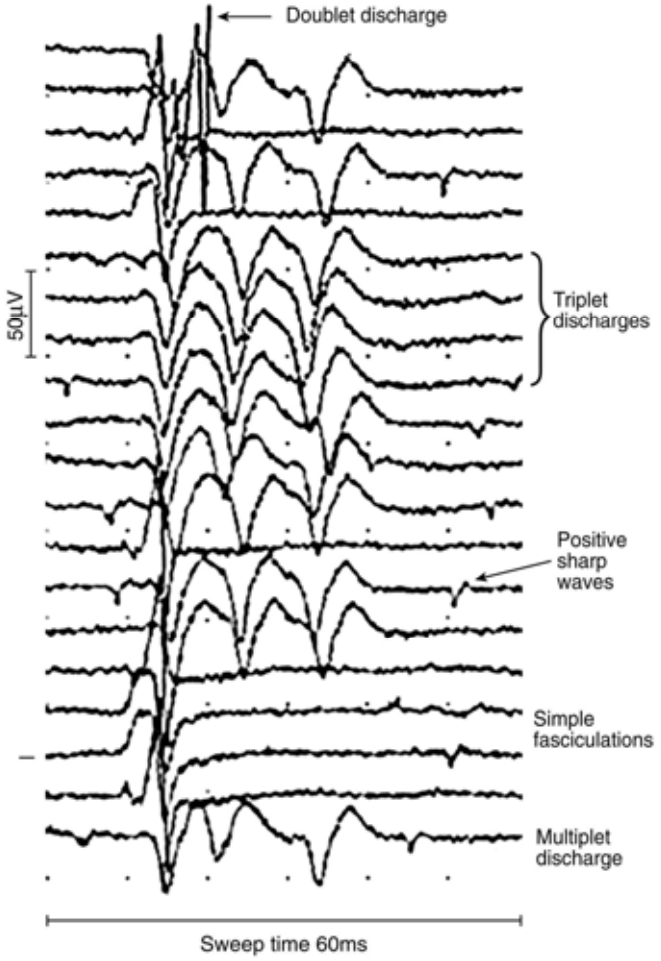


Twitching, cramps,
weakness, sweating

Spontaneous muscle
activity of peripheral nerve origin

Improves after plasma exchange
Sinha et al 1991
Turner et al 2006

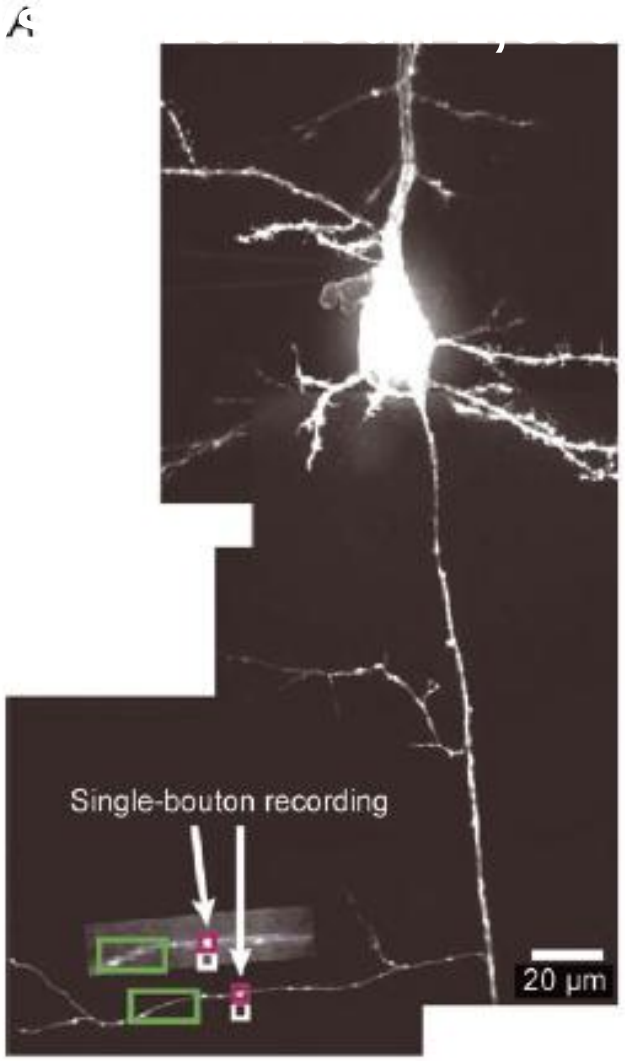
A raster display of doublet and triplet discharges with fasciculations in a representative patient with acquired neuromyotonia

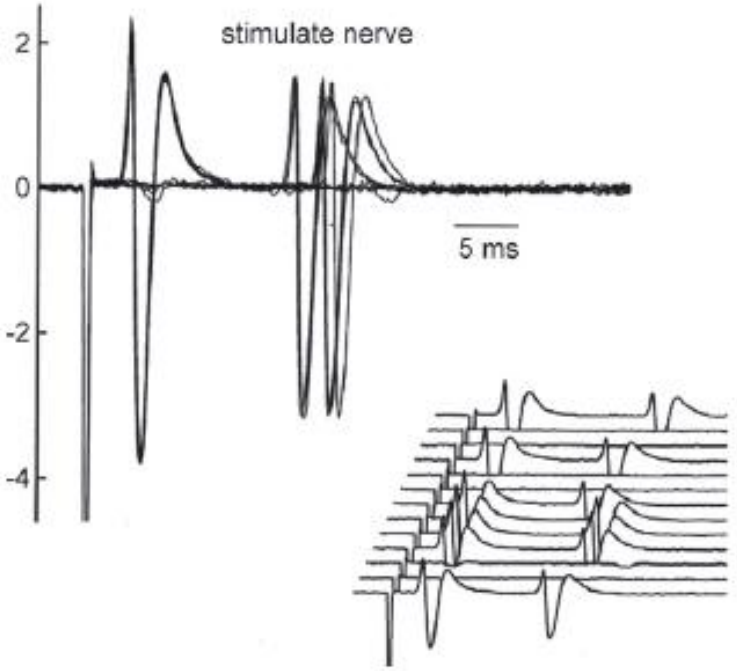


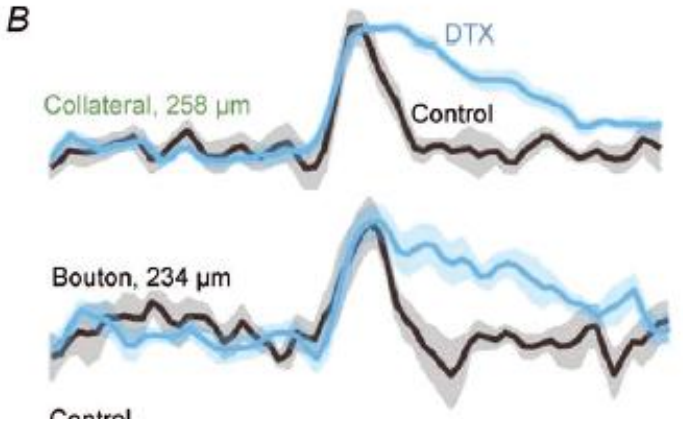
Vucic S et al. Brain
2010;133:2727-2733

Jan LY and Jan YN Review
Voltage-gated potassium channels and electrical signalling
J Physiol 2012

Dendrotoxin (DTX) blocks VGKCs, prolongs currents and causes repetitive events



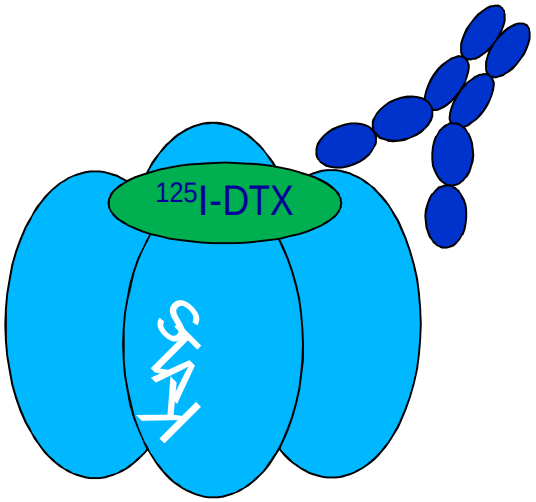




Antibodies to voltage-gated potassium channels are present in some patients with NMT

VGKC "*Shaker*" Kv1.1, 1.2 and 1.6 bind dendrotoxin

Rabbit brain digitonin extract labelled with 125I-dendrotoxin



VGKC-Ab and clinical features in 64 NMT patients
37M:27F; 12-85 years

Motor symptoms/signs N=64	Twitching Weakness, stiffness, pseudomyotonia
Sensory symptoms N=26 40%	Paraesthesia, pain
Autonomic symptoms N=21 33%	Sweating, constipation/diarrhoe, hypersecretion, tachycardia
Central symptoms N=13 20%	Anxiety, insomnia, other sleep disturbance, depression

Patient data and sera from Prof Matthew Kiernan, Sydney and Dr Osamu Watanabe, Kagoshima

VGKC-Ab and clinical features in 64 NMT patients
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Patient data and sera from Prof Matthew Kiernan, Sydney and Dr Osamu Watanabe, Kagoshima

The results of a pain survey conducted by
Mr Ron Birch in Canberra, Australia

Insomnia in Bologna

Insomnia, REMS sleep disturbance, confusion, hallucinations

76 year old man

Muscle twitching, excessive salivation and sweating

Constipation, cardiac arrhythmias

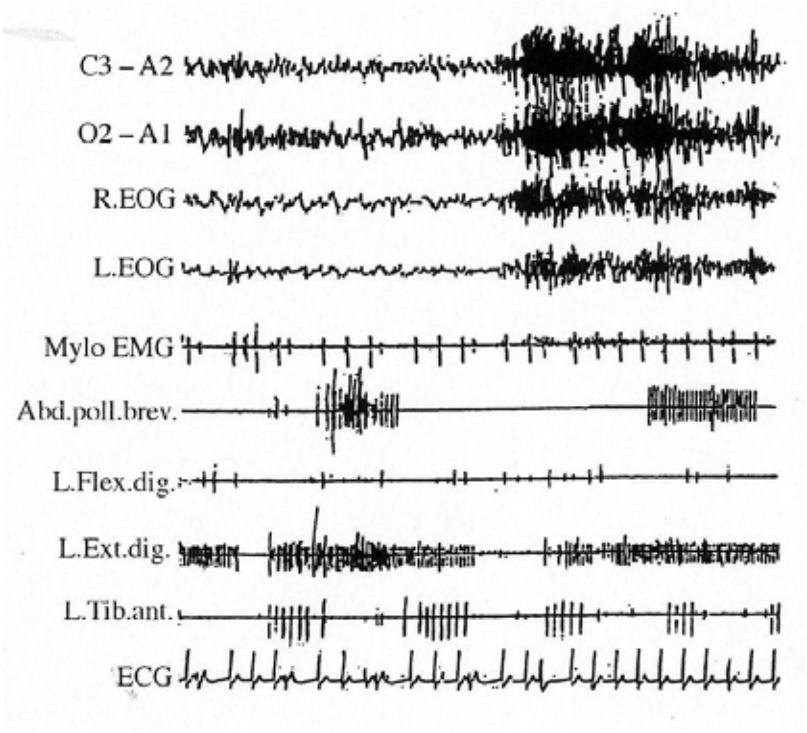
? fatal familial insomnia, ? paraneoplastic

High VGKC-complex antibodies

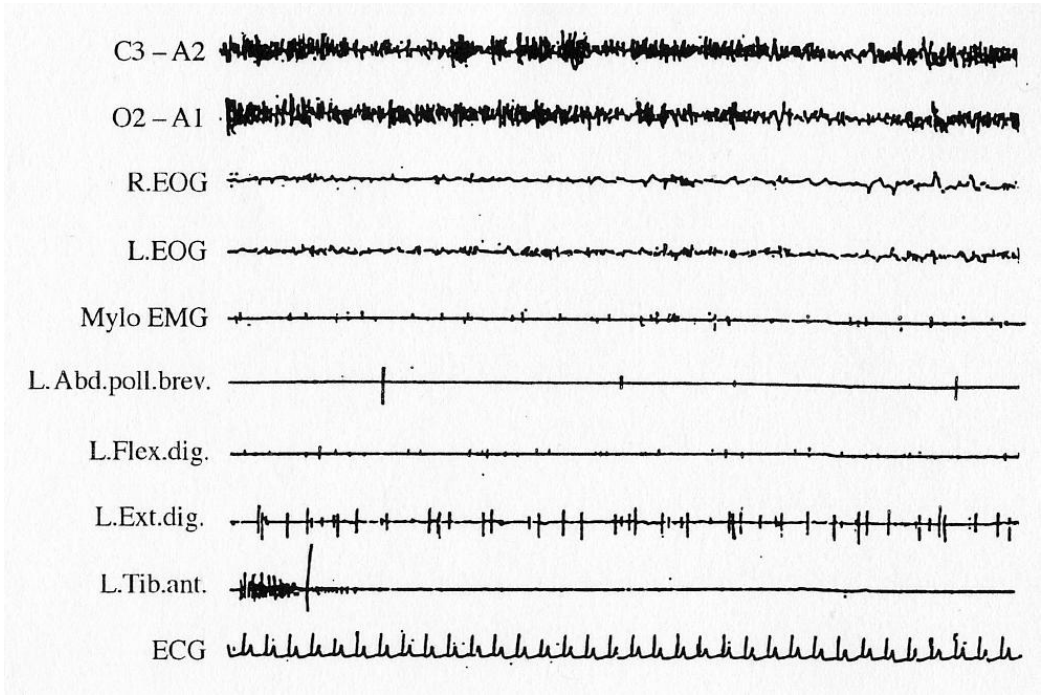
Liguori et al 2001

Morvan's syndrome - polysomnography

Before plasma exchange



After plasma exchange



Liguori R et al Brain 2001

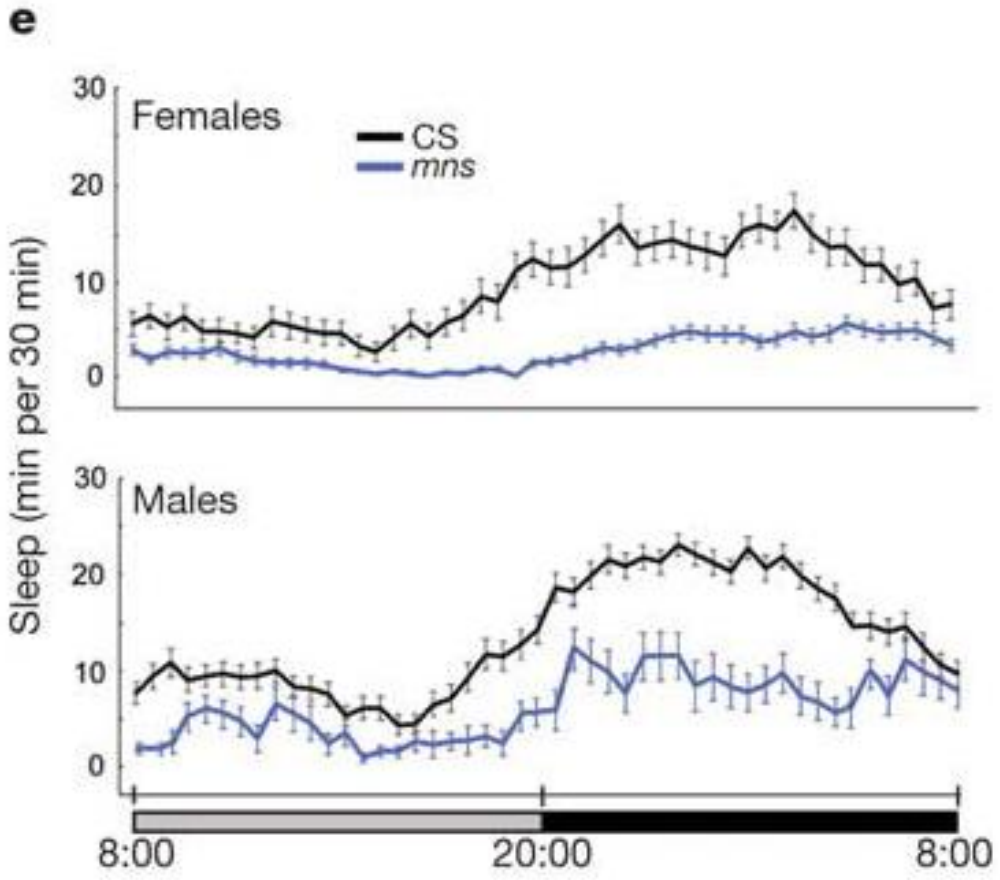
Sleep almost normal, cognition improved

29 cases and serology reviewed in Irani et al 2012

Reduced sleep in *Drosophila Shaker* mutants

Chiara Cirelli[1], Daniel Bushey[1], Sean Hill[1], Reto Huber[1], Robert Kreber[2], Barry Ganetzky[2] & Giulio Tononi[1]

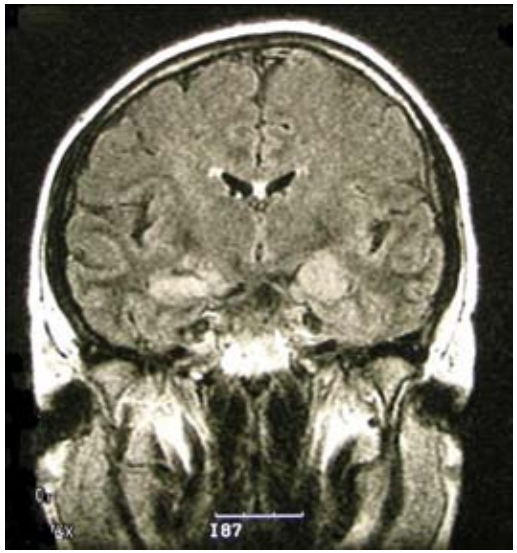
[1]*Department of Psychiatry, 6001 Research Park Blvd, University of Wisconsin Madison, Madison, Wisconsin 53719, USA*
[2]*Laboratory of Genetics, 445 Henry Mall, University of Wisconsin Madison, Madison, Wisconsin 53706, USA*



Insomniac flies with *Shaker* mutations

Cirelli et al Nature 2005

A treatable form of limbic encephalitis, mainly non-paraneoplastic



Subacute onset of memory loss, seizures and personality change

Sometimes seizures or psychosis only

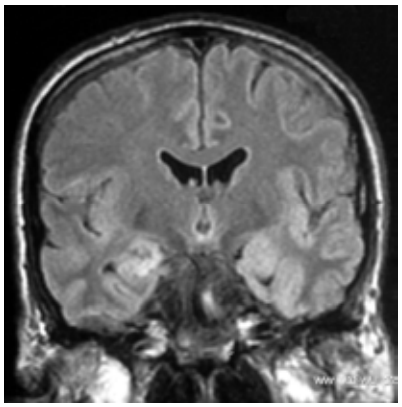
Usually high signal in medial temporal lobes on MRI

Often low plasma sodium

VGKC-complex antibodies often very high titre

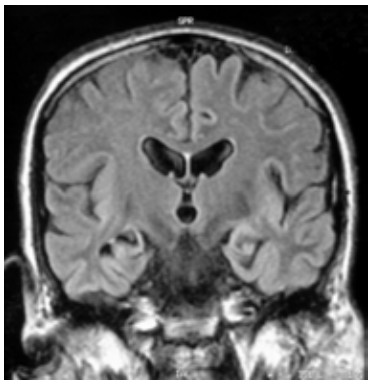
Most respond well to immunotherapies

Buckley et al 2001
Vincent et al 2004



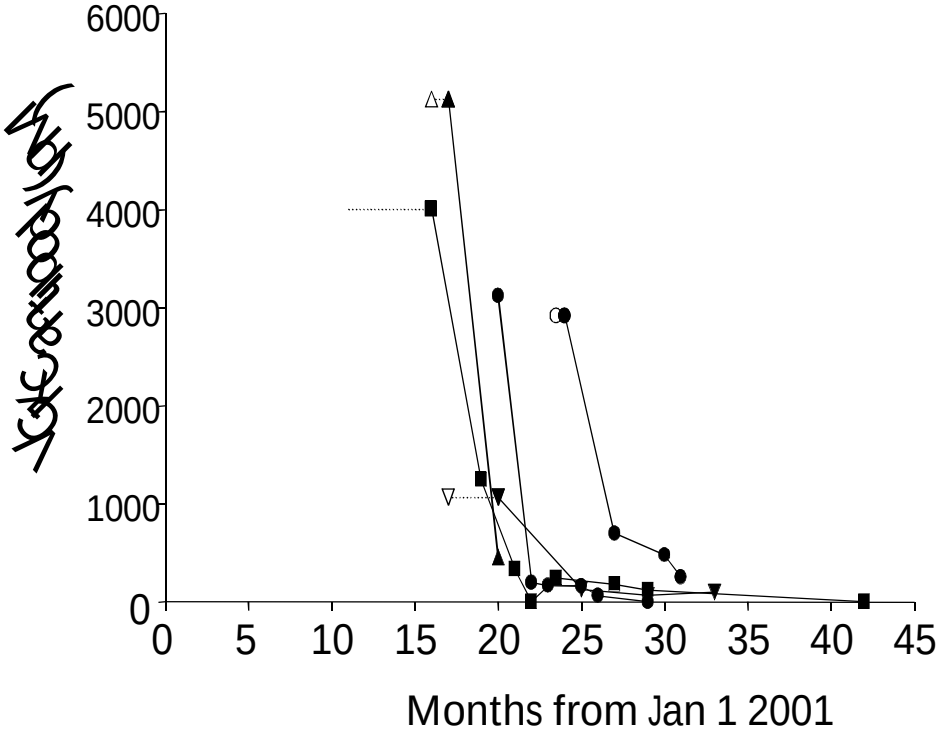
Case 2, 57 M
Vincent et al
Brain 2004

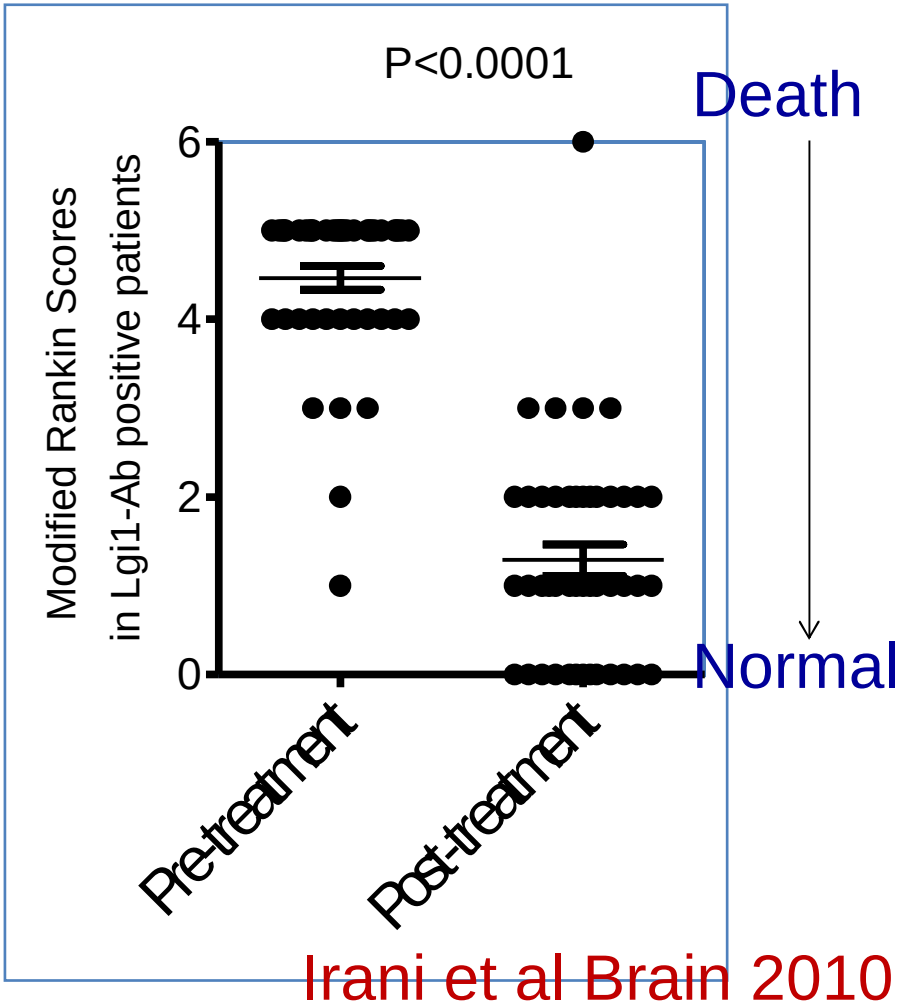
Steroids,
Pl Ex,
Ivlg



Retrospective study: Improvement in modified Rankin Scores following (variable) immunotherapies in 45 adult patients with VGKC-complex Ab limbic encephalitis

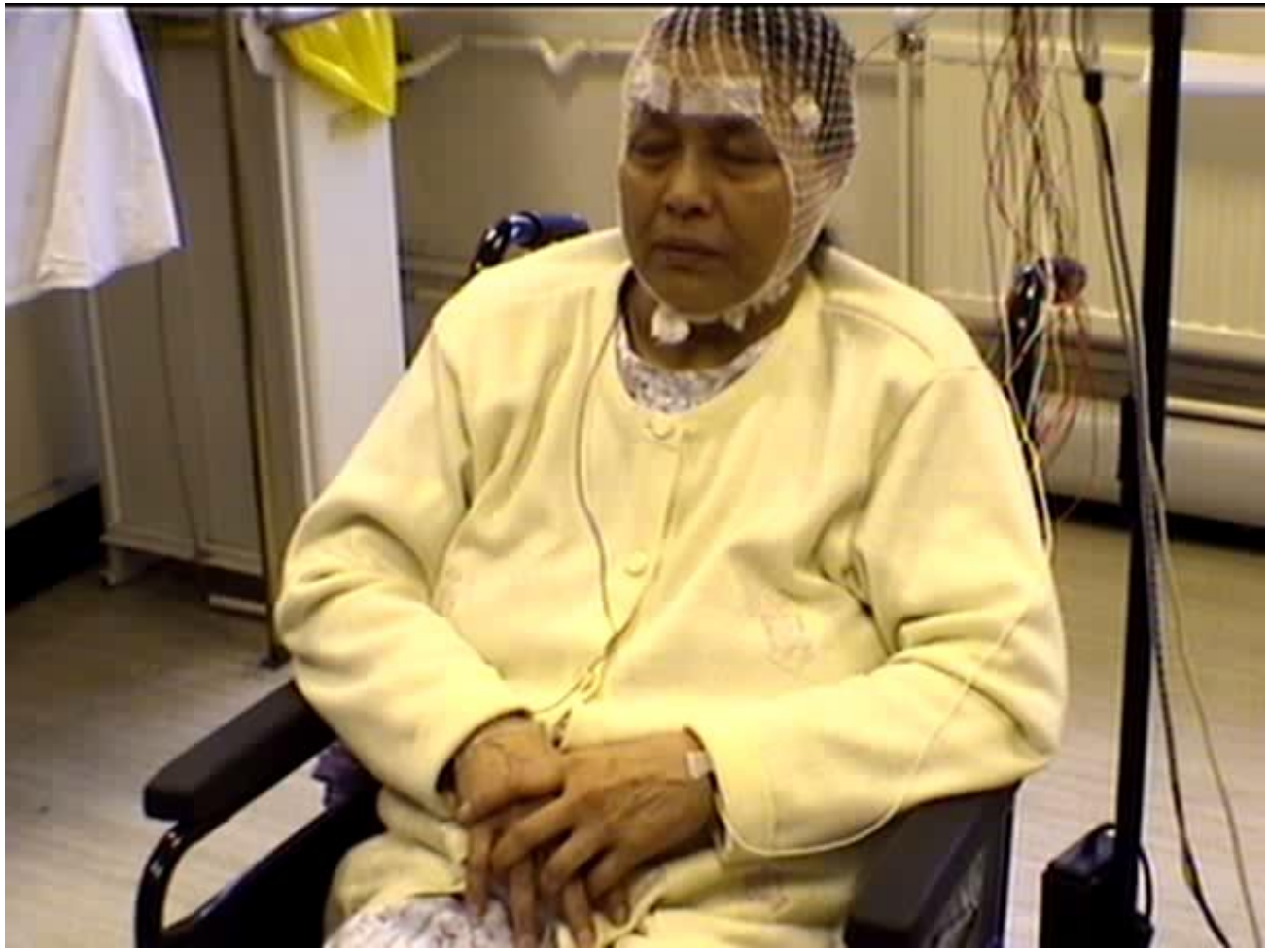
Vincent et al Brain 2004;





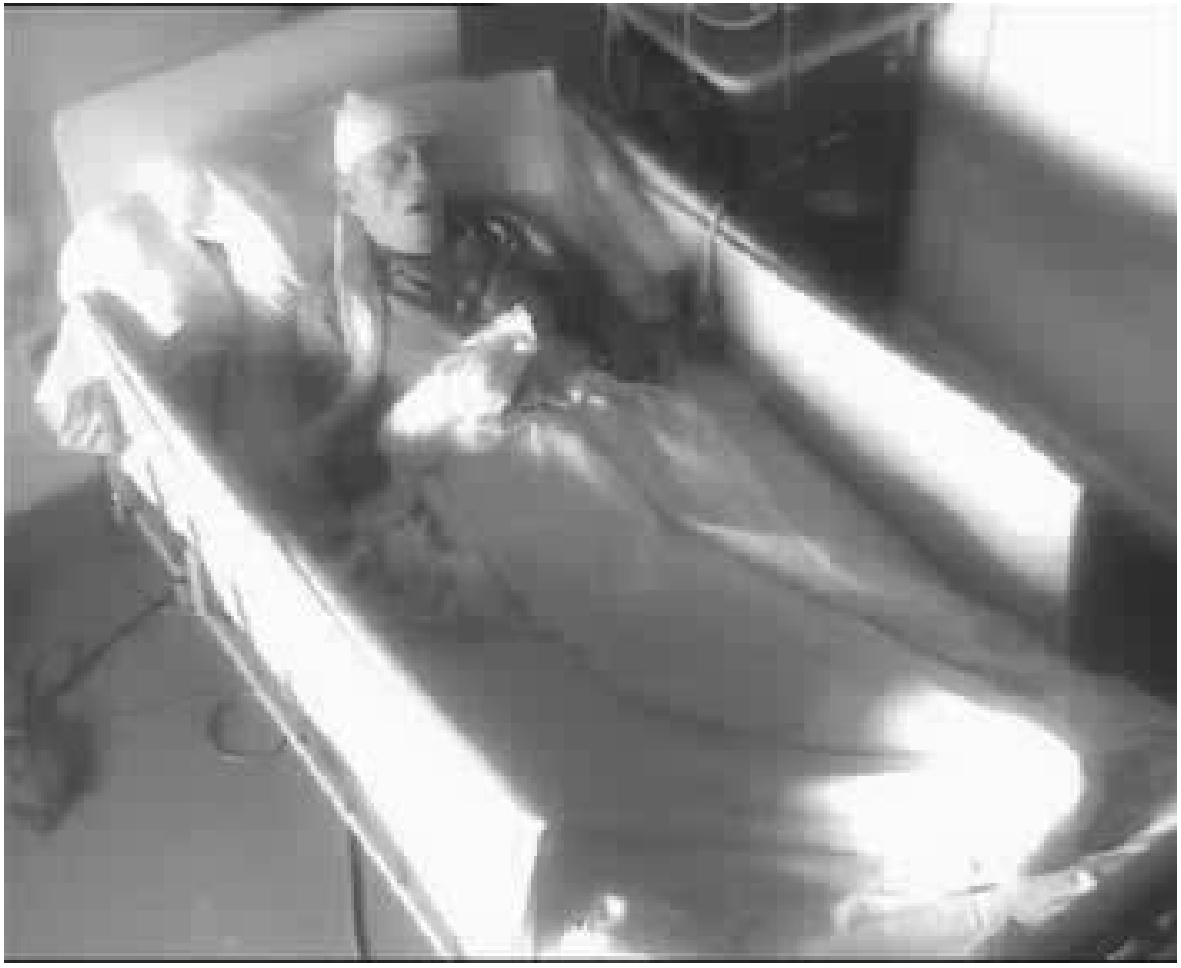
Irani et al Brain 2010

Very frequent brief dystonic seizures (FBDS) associated with high VGKC antibodies



Irani et al 2008; Irani et al Ann Neurol 2011;
Irani et al Brain 2013

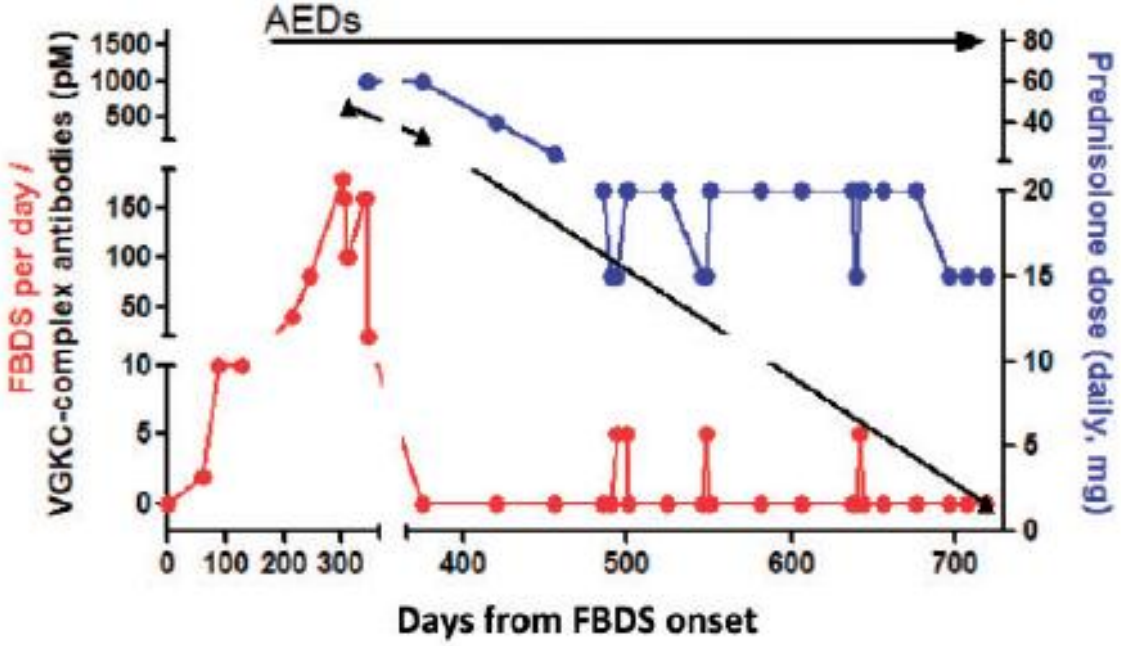
Very frequent brief dystonic seizures associated with high VGKC-complex antibodies

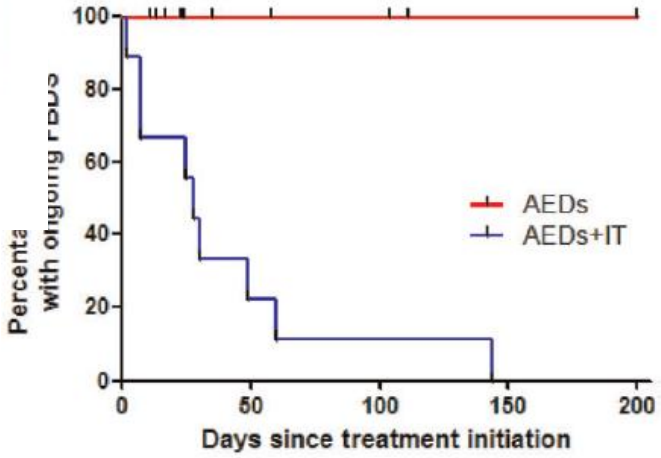


Irani et al 2008; Irani et al Ann Neurol; Irani et al Brain 2013

Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype

Sarosh R. Irani,[1] Charlotte J. Stagg,[2] Jonathan M. Schott,[3] Clive R. Rosenthal,[1] Susanne A. Schneider,[4] Philippa Pettingill,[1] Rosemary Pettingill,[1] Patrick Waters,[1] Adam Thomas,[2,5] Natalie L. Voets,[2] Manuel J. Cardoso,[3,6] David M. Cash,[3,6] Emily N. Manning,[3] Bethan Lang,[1] Shelagh J. M. Smith,[7] Angela Vincent[1] and Michael R. Johnson[8]





Faciobrachial dystonic seizures

Seen in limbic encephalitis with VGKC-complex-Abs

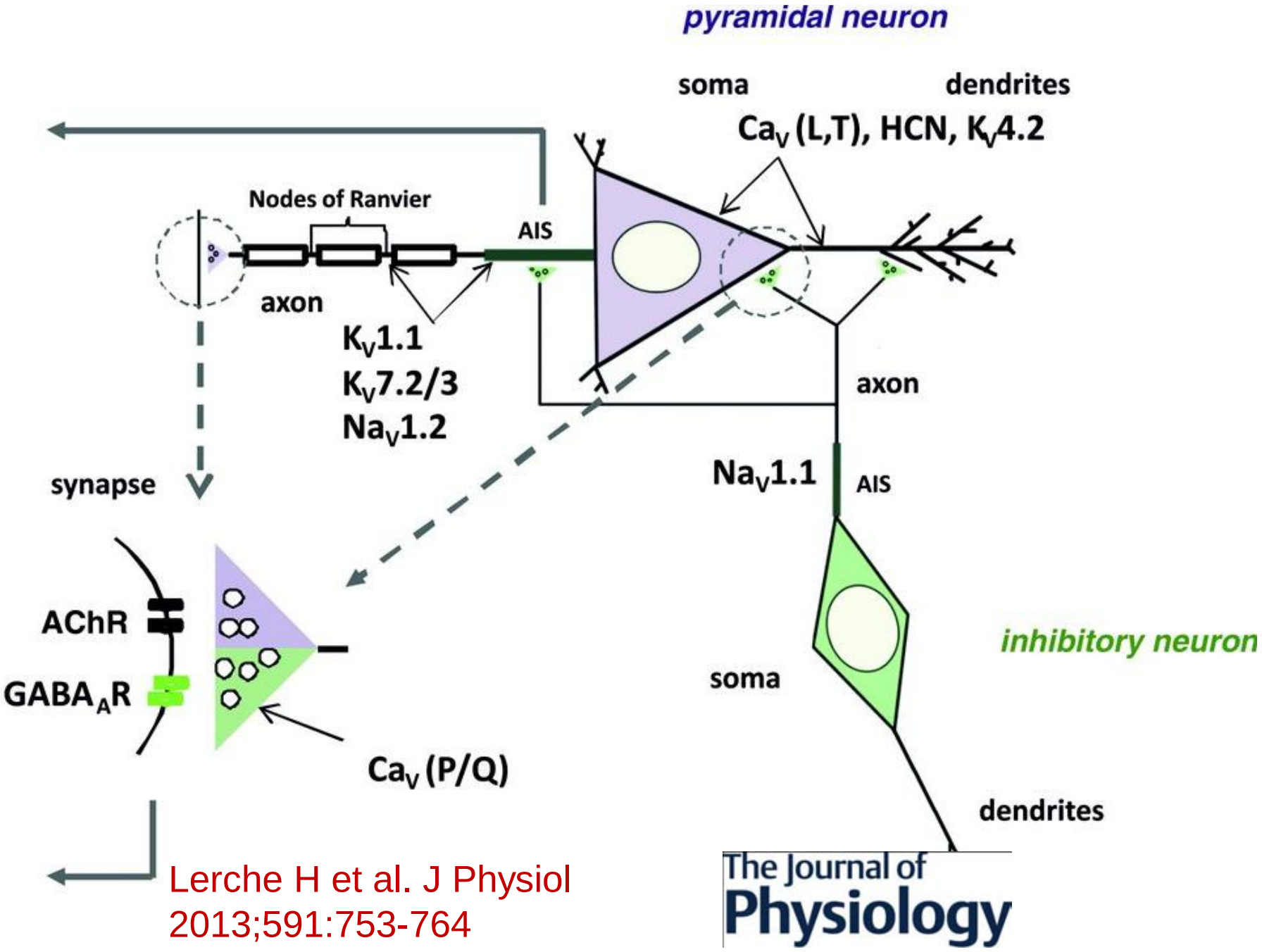
Can *precede* neuropsychiatric and MRI features of limbic encephalitis

Often poor response to AEDs and adverse reactions

Good and surprisingly fast response to prednisolone

Anglo-Australasian collaboration
Irani et al Ann Neurol 2011 and submitted for publication

Where would VGKC antibodies be acting to cause epilepsy?



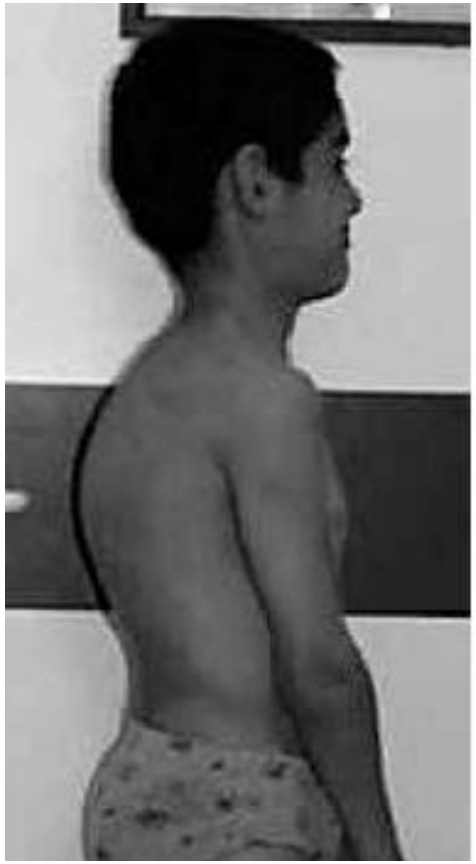
Lerche H et al. J Physiol 2013;591:753-764

The Journal of Physiology

The potassium channel enigma

Why are VGKC-complex antibodies found in so many different clinical syndromes?

Neuromyotonia
Morvan's syndrome
Limbic encephalitis
Faciobrachial dystonic seizures



One possibility is its just a reflection of the diversity of phenotypes associated with potassium channel defects

Mutations in Kv1.1 channels can cause episodic ataxia, epilepsy and neuromyotonia to different degrees

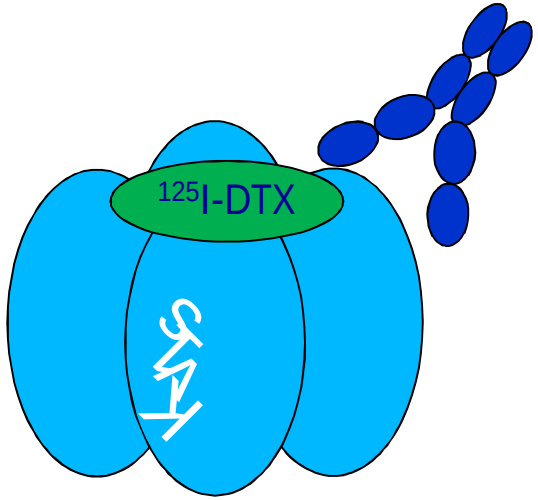
Expanding the phenotype of potassium channelopathy: severe neuromyotonia and skeletal deformities without prominent Episodic Ataxia

M. Kinali[a], H. Jungbluth[a], L.H. Eunson[b], C.A. Sewry[a,c], A.Y. Manzur[a], E. Mercuri[a,d], M.G. Hanna[*,b], F. Muntoni[a]

Measuring antibodies to voltage-gated potassium channels

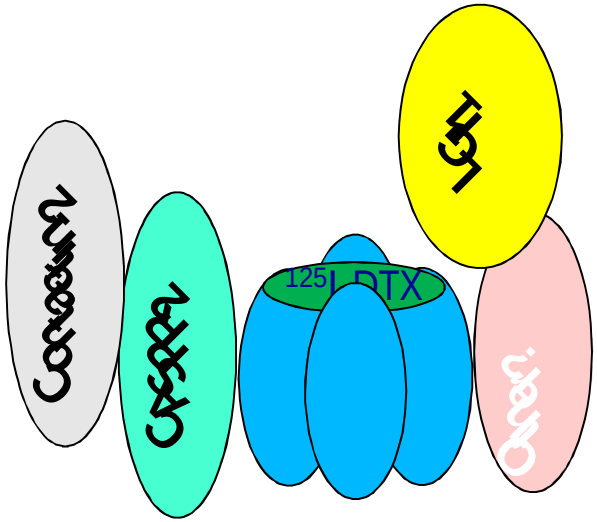
VGKC "*Shaker*" Kv1.1, 1.2 and 1.6 bind dendrotoxin

Rabbit brain digitonin extract labelled with 125I-dendrotoxin



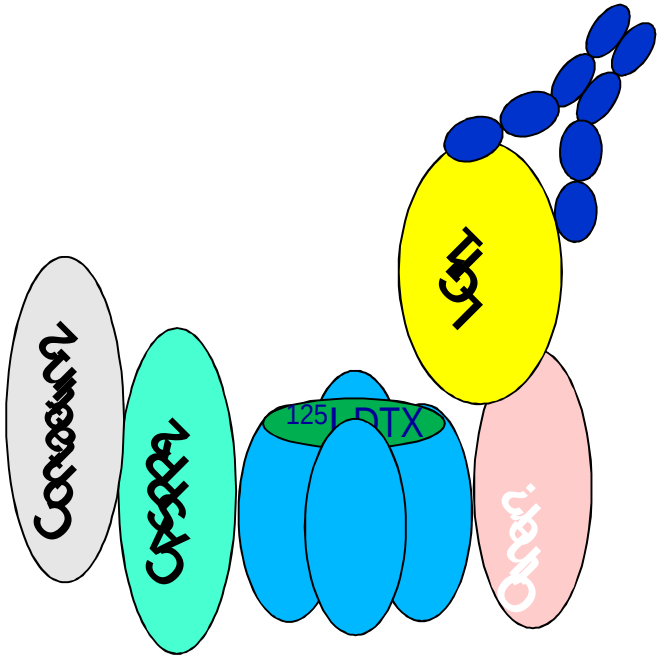
VGKCs are part of a complex

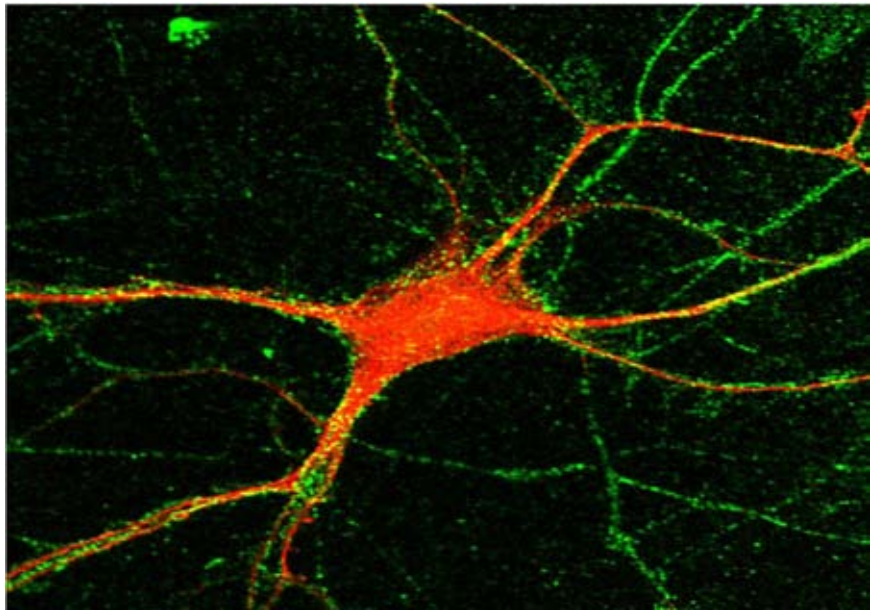
Antibodies to any of these proteins can immunoprecipitate 125I-dendrotoxin-VGKCs



Irani, Alexander, Waters, Kleopa et al Brain 2010

Most VGKC-complex antibodies in limbic encephalitis are against LGI1,
Antibodies to LGI1 bind to live hippocampal neurons in culture

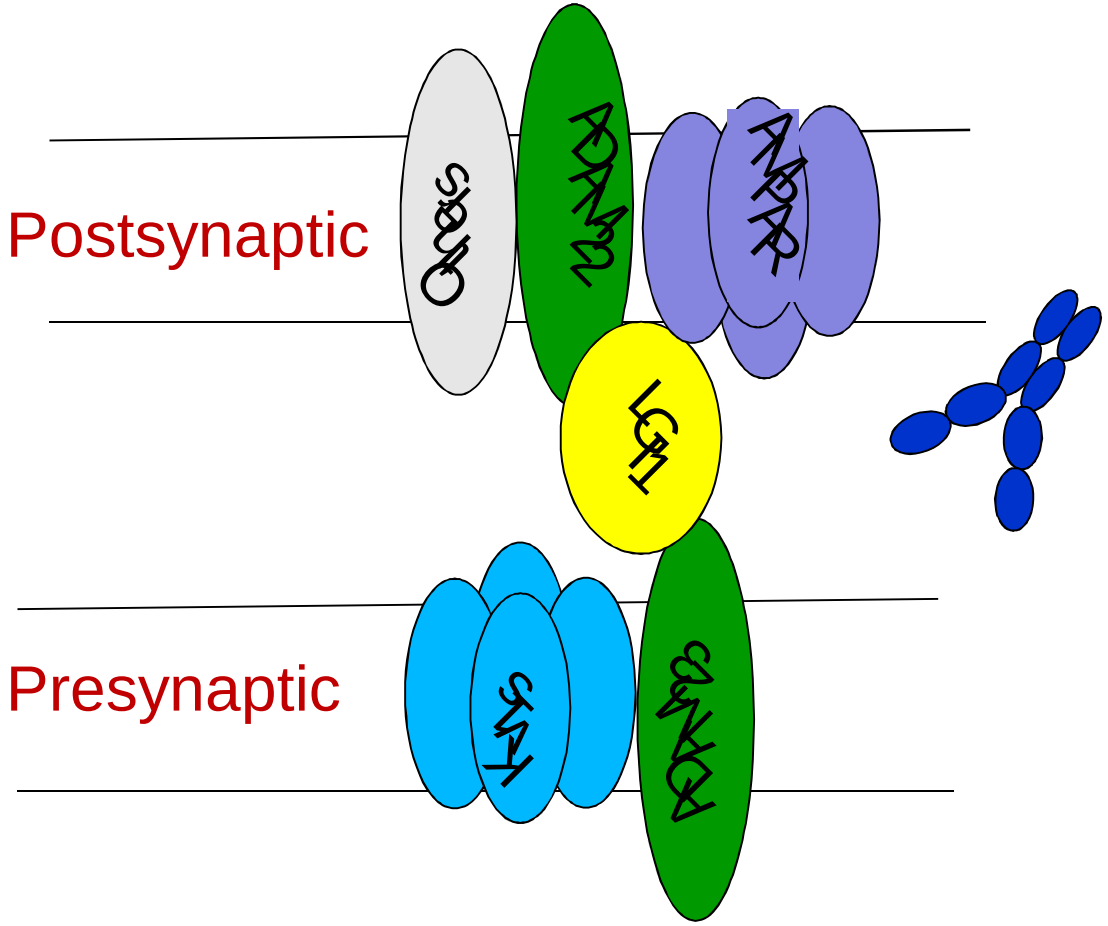




Irani, Alexander, Waters, Kleopa et al Brain 2010
Lai et al Lancet Neurology 2010

Mutations in Lgi1 cause autosomal dominant lateral temporal lobe epilepsy with auditory hallucinations

LGI1 is highly expressed in synapses and may form a bridge between pre and postsynaptic membranes



LGI1 mutations in heterozygous transgenic mice cause seizure susceptibility.
Fukata et al PNAS 2010

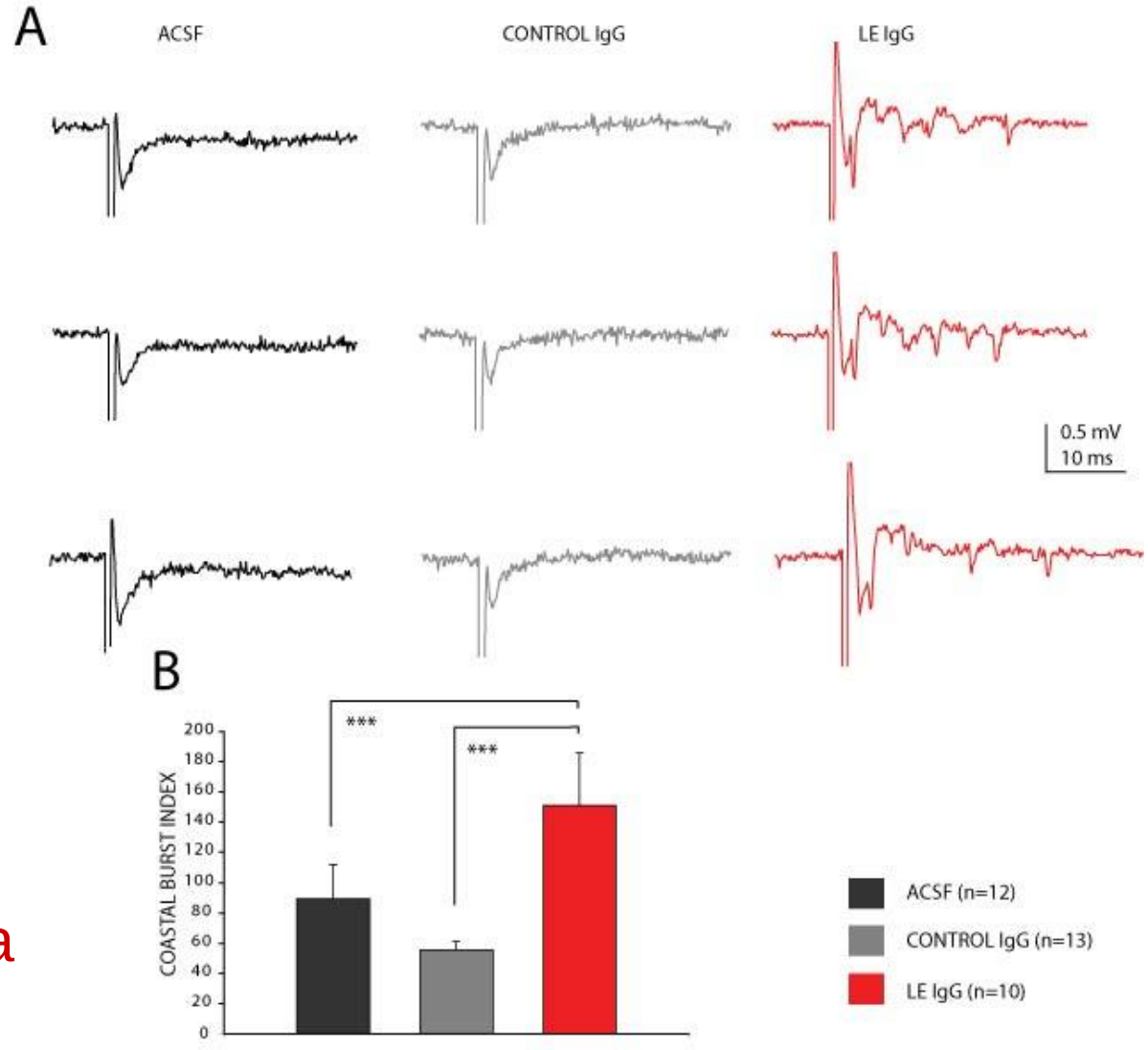
VGKC/LGI1 Ab IgG elicits epileptiform activity in the CA3 area of hippocampus in brain slices

Extracellular potentials recorded in the stratum lucidum of CA3 pyramidal cell layer with extracellular stimulation of mossy fibres

VGKC/Lgi1 IgG increases burst activity in CA3

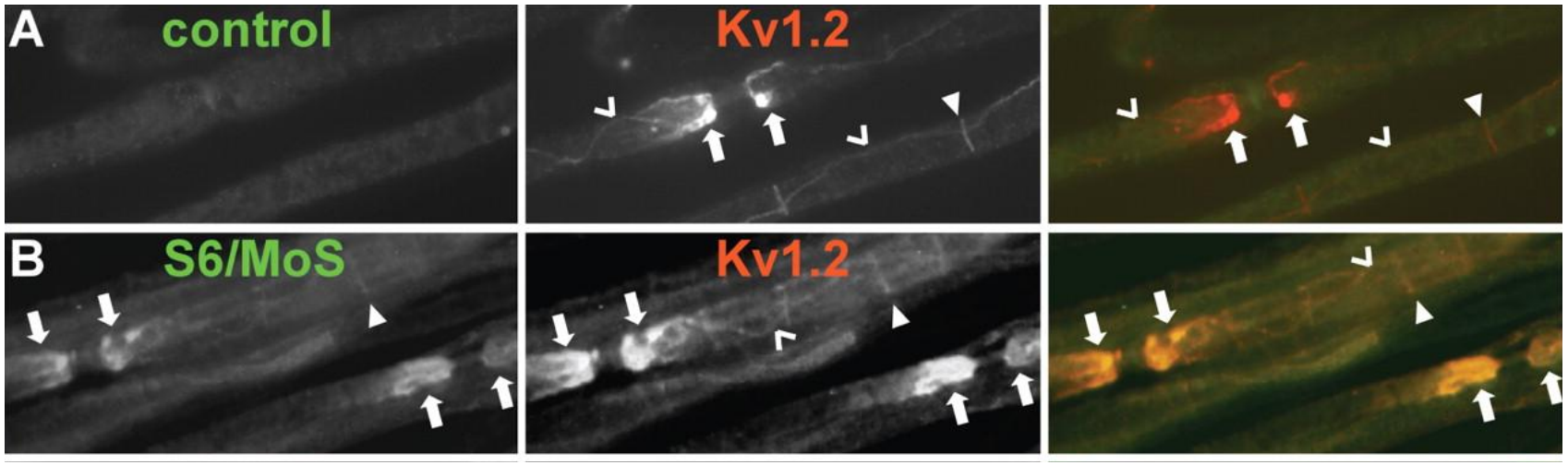
Reduces no of failures to stimulation

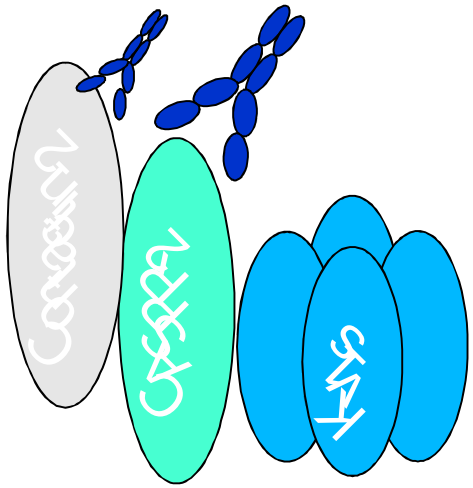
Effects similar to dendrotoxin



Lalic, Pettingill, Vincent and Capogna Epilepsia 2010

CASPR2 antibodies are more often the target in neuromyotonia and Morvans syndrome.: antibodies bind to CASPR2 at juxtaparanodes of myelinated axons co-localising with Kv1 channels



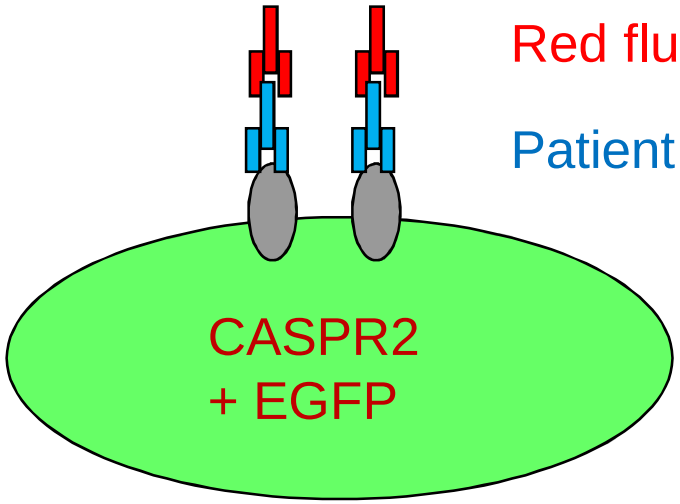


Kleopa K A et al. Brain 2006;129:1570-1584

Irani et al Brain 2010

Mutations in CASPR2 cause cortical myoclonic tremors and epilepsy, other rare familial epilepsies and rare cases of autism

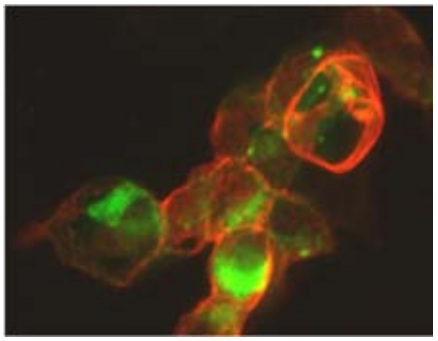
Using the “cell-based assay” approach to measure antibodies to cell-surface neuronal proteins

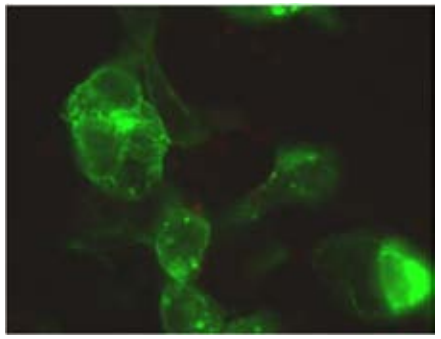


Red fluorescent anti-human IgG

Patient IgG antibody

Patient has specific antibodies Intensity of binding can be scored visually





Patient does not have specific antibodies

Patrick Waters

VGKC-complex antibodies LGI1 and CASPR2

Main components of the VGKC-complex are LGI1 and CASPR2 but others exist

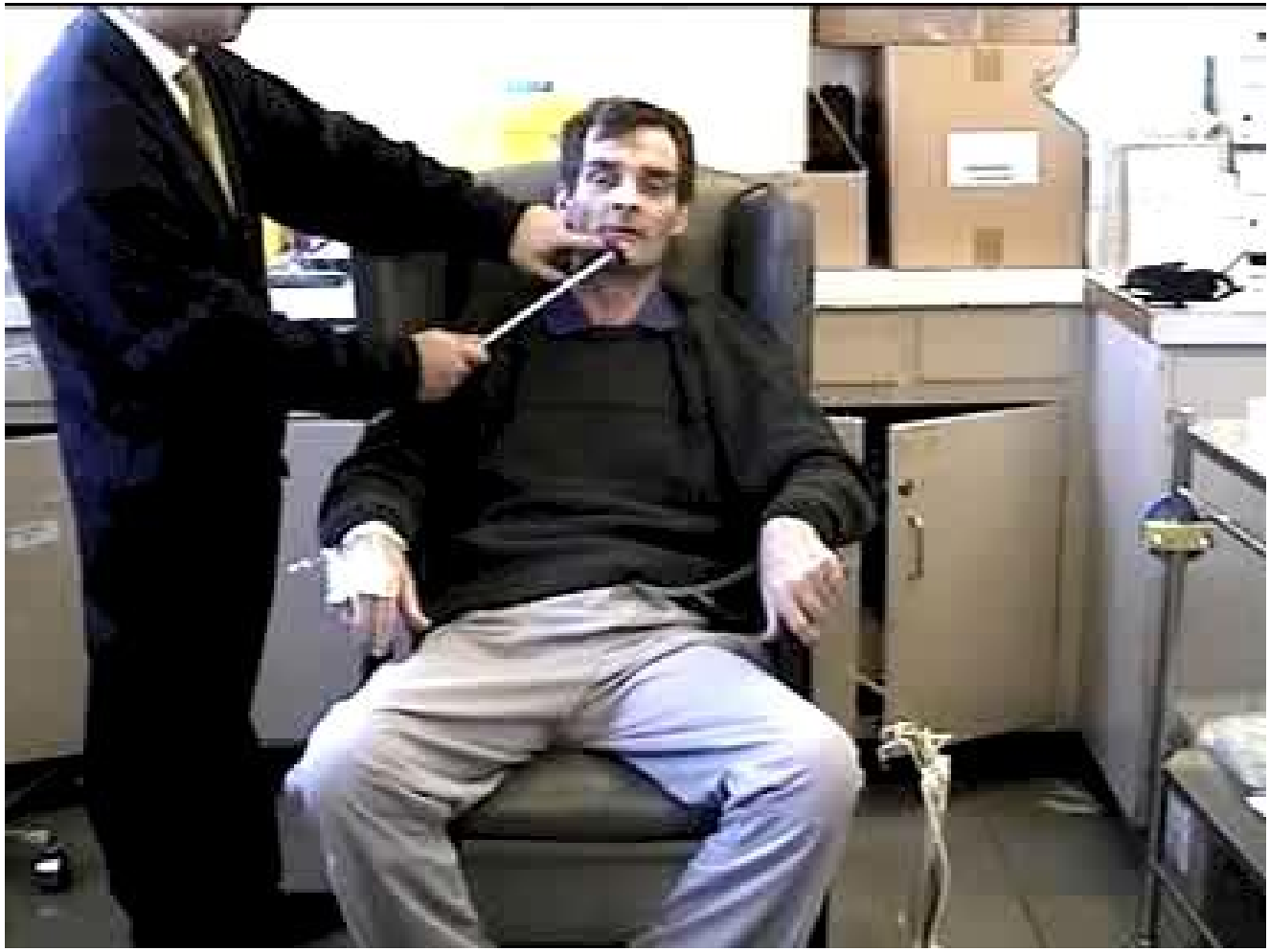
LGI1 mutations cause loss of LGI1 expression in the hippocampus

Mutant mice demonstrate seizure susceptibility

Evidence for epileptogenic effects on rodent slices and in vivo

Lalic et al 2010

54-year old prison officer presenting with whole-body jerks triggered by auditory and tactile stimuli

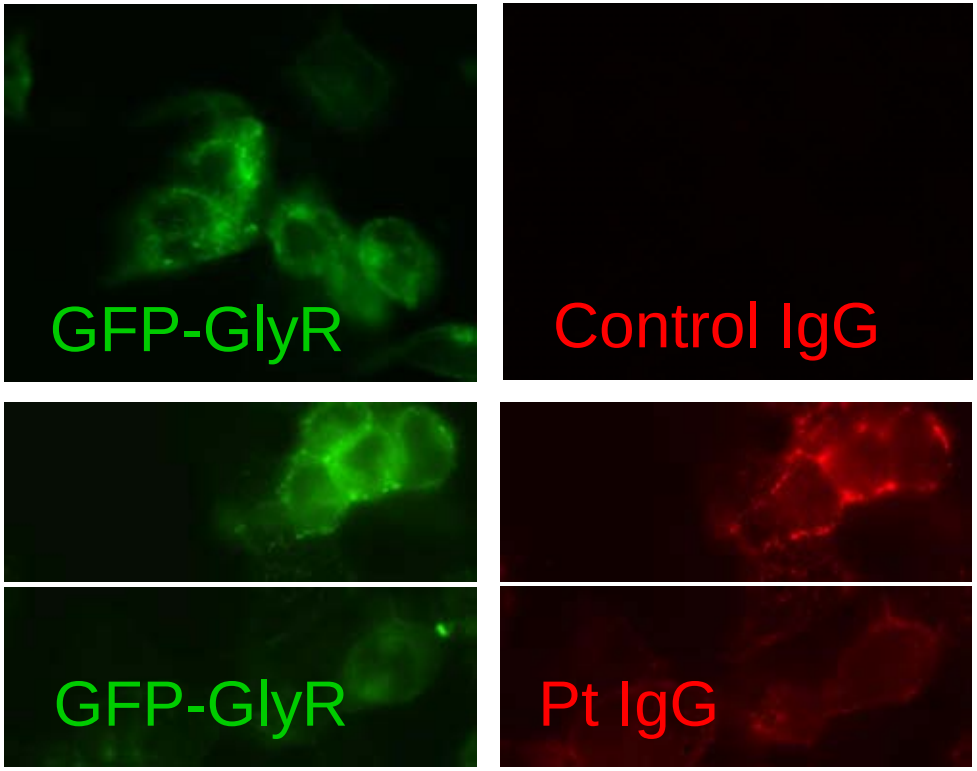


Progressive encephalomyelitis with rigidity and myoclonus

PERM

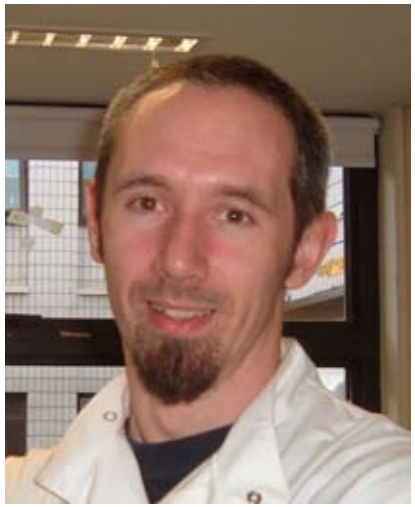
Mutations in the α_1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperekplexia

Rita Shiang[1], Stephen G. Ryan[2], Ya-Zhen Zhu[1], Angelika F. Hahn[4], Peter O'Connell[3] & John Jacob Wasmuth[1]



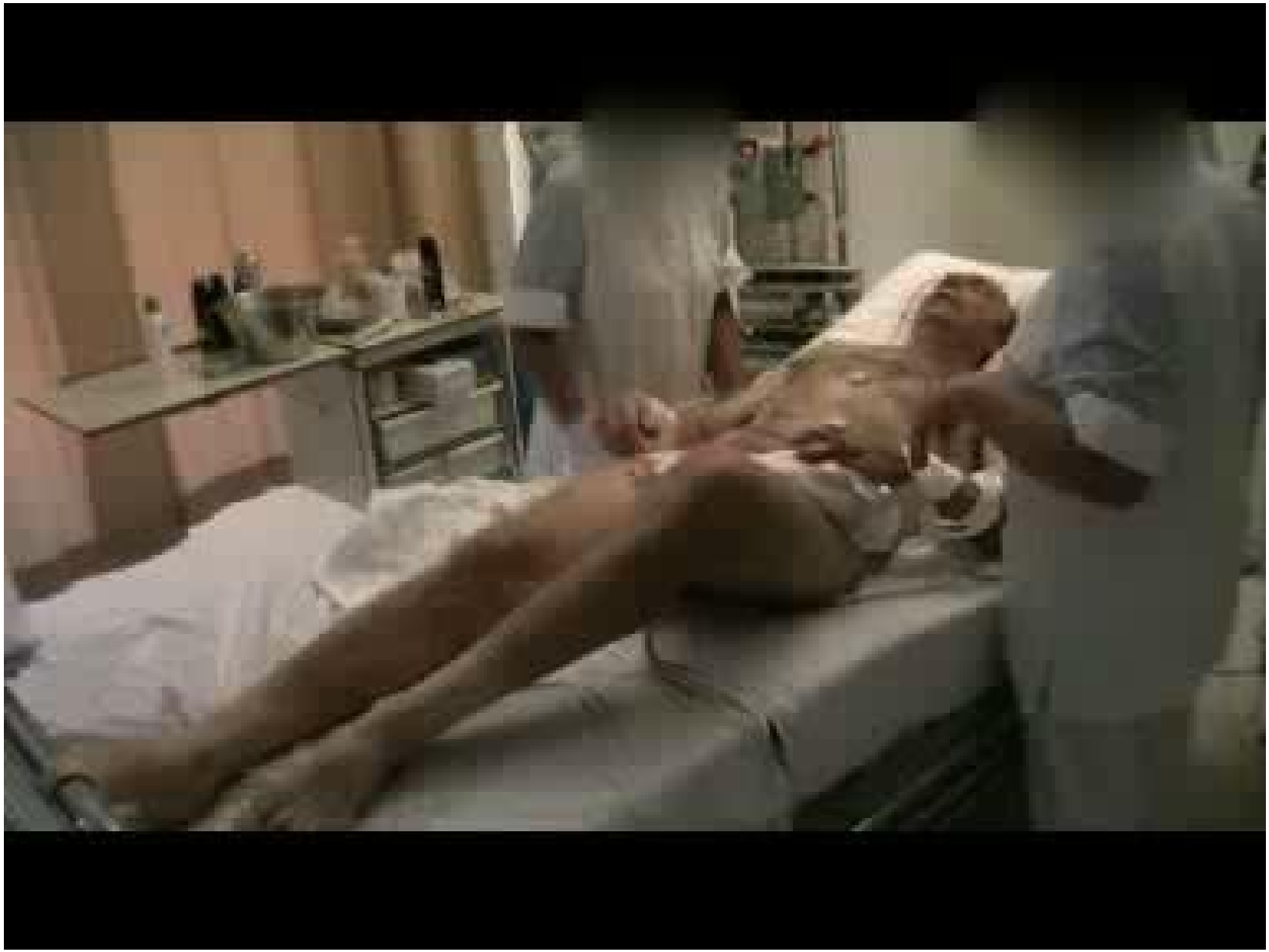
Glycine receptor mutations are found in genetic forms of hyperekplexia in babies and adults

Are there antibodies to GlyR in this patient?



Paddy Waters, Senior postdoc

Hutchinson et al 2008



Clerinx.....Vandenberghe, Neurology 2011

Resolved after thymoma removal and immunosuppression

Clerinx.....Vandenberghe, Neurology 2011

PERM syndromes and GlyR Abs (n=45)

Mainly adults, four children

Brainstem - startle, oculomotor abnormalities

Spinal cord - muscle rigidity and stiffness spasms , very painful

Autonomic – sweating, urinary retention, tachycardia, other

Encephalopathy, limbic encephalitis in some patients

Glycine receptors are the second inhibitory system in the CNS

GlyRs are particularly relevant for the control of excitability in the mammalian spinal cord, brain stem and a few selected brain areas, such as the cerebellum and the retina.

GlyRs regulate important physiological functions, including respiratory rhythms, motor control, muscle tone and sensory as well as pain processing.

In the hippocampus, RNA-edited high affinity extrasynaptic GlyRs may contribute to the pathology of temporal lobe epilepsy.

Anti-NMDAR encephalitis

NMDAR Abs in young females with ovarian teratoma-associated encephalopathies

Dalmau et al Ann Neurol 2007
Dalmau et al Lancet Neurology 2008

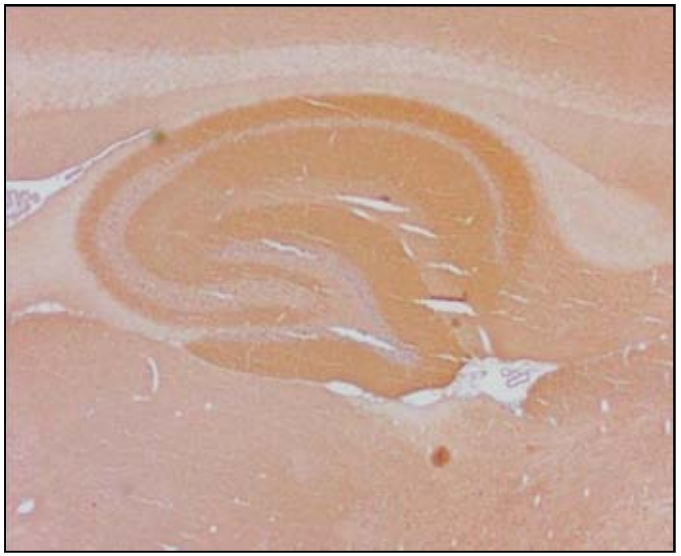
Treatment responses described in detail

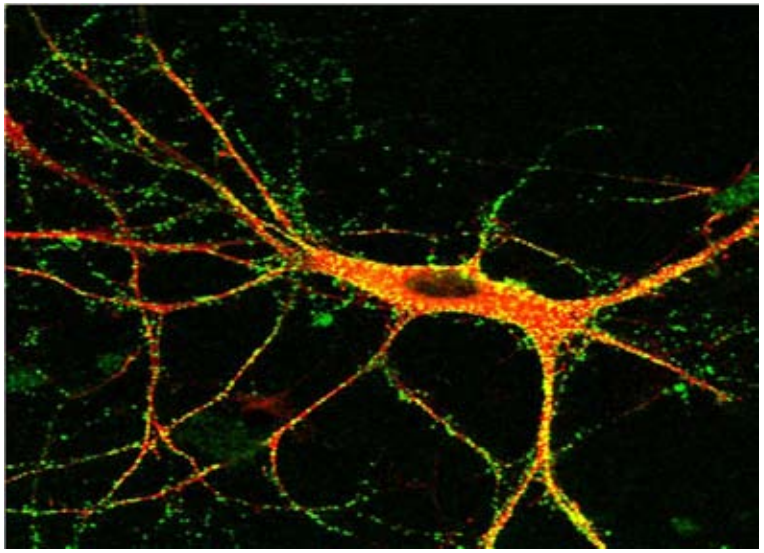
Titulaer et al Lancet Neurology 2013

NMDAR antibodies bind to hippocampus in rodent brain
And to surface of hippocampal neurons in culture

Dalmau et al 2007, 2008
Review Lancet Neurology 2011

Anti-IgG / MAP2 post fix





Dalmau et al 2007, 2008
Review Vincent et al Lancet
Neurology 2011

Neuropsychiatric and movement disorders with NMDAR-Abs

Presented with neuropsychiatric features, amnesia, seizures

Developed facial grimacing and chewing

Choreoathetoid limb movements

Mutism

No tumour found in this patient
Good recovery

Video courtesy of the patient and Dr G Vasello, Manchester

22 month child presented with behavioural changes and sleep disturbance, then general seizures, then movement disorder. Eventually responded to immunotherapies

After treatment

Courtesy Dr Sukhvir Wright and the Consultants at Birmingham Children's Hospital

Autoimmunity and infection

Preceding infections fairly common in patients with VGKC- and NMDAR-antibodies particularly children

Patients with NMDAR- or VGKC-antibodies may be positive for HSV, CMV and other infections, particularly children

Irani et al 2010, Hacohen et al 2012 and others

N-methyl-D-aspartate receptor (NMDAR) Antibodies in Post Herpes Simplex Virus Encephalitis (HSVE) Neurological Relapse

Armangue et al J Ped 2013

Hacohen, et al, Movement Disorders 2013

Conclusions

Antibodies to ion channels, receptors and associated proteins can cause central as well as peripheral diseases

There are strong (but not complete) analogies with the genetic disorders that affect the same proteins

The clinical syndromes involved most aspects of the central nervous system

The autoimmune conditions are immunotherapy-responsive

There are sometimes coexisting or preceding infections

The neurologist needs to be aware of the possibility of immunotherapy-responsive, antibody-mediated CNS disorders

Questions

What antibodies should we measure and how many more antibodies will need to be identified?

How can we diagnose these patients quickly and effectively?

How frequent are these antibodies in more common diseases – epilepsy, dementia, psychosis?

Why do these antibodies appear?

Can they sometimes be secondary to other pathology?
Angus-Lepan et al JAMA Neurol 2013

Muscular Dystrophy Campaign

MRC Medical Research Council

MG Myasthenia Gravis Association

action medical research
the forward thinking charity

AFM

wellcome trust

THE DANA FOUNDATION

NHS
National Institute for Health Research

PNEURONET
Concerted Action on Paraneoplastic Neurological Syndromes

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Leslie Jacobson
Sukhe Wright
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The late John Newsom-Davis and
many neurologists
in UK and elsewhere