New Discoveries in Epilepsy through Related Disorders

Professor Mark Rees

Director of the Wales Epilepsy Research Network (WERN)

Chair of the Scientific Advisory Committee for ERUK

College of Medicine

Swansea University
What is Epilepsy

- Epilepsy incidence 1-1.5% of the UK population with 3% lifetime prevalence
- Most common chronic neurological disorder (ABN) - 700m global (ILAE); 600k UK
- Caused by localised, regional or whole brain dysregulation of neuronal activity
- Belongs to a broad morbidity scale (epilepsies) transcending medical specialities
- SUDEP counselling is difficult, anti-seizure drug complications in pregnancy
- 70% have adequate seizure control with anti-epilepsy drugs (side-effect issues)
- 20-30% misdiagnosis rate with cardiac syncope & TLOC presentation
- Significant co-morbidity with LD, depression, psychosis & degenerative disorders
- Idiopathic and syndromic epilepsy have genetic backgrounds
- Genetic discoveries have given remarkable insight into causality e.g. channels
- Despite progress, most population-based epilepsy has no genetic explanation
Linking health and social data
Diagnosis of Epilepsy

**Phenotyping**

**EEG**

**ECG**

**MRI and CT**

**Causes of Epilepsy**
- 66% Idiopathic
- 11% Vascular
- 5% Congenital
- 4% Trauma
- 3% Tumours
- 3% Degeneration
- 3% Infections

**Types of Epilepsy**
- 36% Complex Partial
- 23% Generalised Tonic-Clonic
- 14% Simple Partial
- 10% Other Generalised
- 8% Absence
- 7% Myoclonic
- 7% Unclassified

**Frontal Lobe**
- Jacksonian seizure (tingling in hand or arm)
- Adverse seizures (eyes or head turn to one side)

**Temporal Lobe**
- Strange smells or tastes
- Altered behaviour
- Deja vu
- Lip smacking or chewing movements

**Parietal Lobe**
- Tingling in or jerking of:
  - leg
  - arm
  - face

**Occipital Lobe**
- Flashing lights or spots
The Paediatric Epilepsies

Epilepsy

Idiopathic Epilepsy
65%

Idiopathic Paediatric Epilepsy
80%

Encephalopathies and Spams

Febrile Seizures (FS, GEFS+)

Childhood Absence Epilepsy (CAE)

Juvenile Myoclonic Epilepsy (JME)

Rolandic Epilepsy
WERN Infrastructure Projects
e-BioBank

WERN Database Hubs

Tertiary Services / Primary care

Patient Blood / Saliva Samples with Idiopathic, Acquired, and Syndromic Epilepsy

Porton Down ECACC Facility

DNA Bank

PBL’s

Plasma

Cell Line – Optional

Serum
Investigation of the GABAergic System in IGE

- Major inhibitory influence in human brain (GABA and glycine)
- GABA prevents over-excitation of neural networks
- Convergent evidence implicates GABA system with IGE - from rodent models, surgical resection tissue, imaging studies and GABAA receptor mutations in rare families
- Genetic hierarchy of other neurotransmitter systems
Genetic Hierarchy in Related Disorders Provides Evidence

Evidence for re-estarle disease the $\alpha_1$ subunit

Mark I. Rees, Martin Andrew, Deparments of Psychological Medicine

Mutations in the presynaptic compartment

Mark I. Rees, Kirsten Harvey, Sarah Beatty, Gail E. Graham, John B. P. Stephenson, Michael J. Trevor, G. Smart, Stéphane Supp

Presynaptic terminal

serine

SHMT

glycine

VIAAT/VGAT

ULIP6

GlyT1

GlyT2

Syntenin-1

Glial cell

GlyR $\alpha_1\beta$

Gephyrin

Collybistin?

Other RhoGEFs?

Postsynaptic neurone

heterozygote hibitory

Paul Govaert

and Recessive

on, Janina Hantke, W. Amira Masri, Frederick Badner, to
Study Structure

Mutation screening of GABAergic genes in 700 IGE samples from Wales, UK, Australia (Melbourne) and New Zealand (Auckland) using Light-Scanner analysis and Sanger sequencing.

IGE phenotypes confirmed by consultant epileptologists.

GABA Transporters

GABA Biosynthesis
21 Mutations Found in 46 CAE cases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amino acid change</th>
<th>No of Cases</th>
<th>Epilepsy Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAT1</td>
<td>L415I</td>
<td>5</td>
<td>CAE and JAE</td>
</tr>
<tr>
<td></td>
<td>M555V</td>
<td>1</td>
<td>CAE and LD</td>
</tr>
<tr>
<td>GAT3</td>
<td>H142Y</td>
<td>1</td>
<td>CAE history, now JME</td>
</tr>
<tr>
<td></td>
<td>N160K</td>
<td>1</td>
<td>CAE history, now TLE</td>
</tr>
<tr>
<td></td>
<td>D295N</td>
<td>1</td>
<td>MAE with absence, atonic, myoclonic features</td>
</tr>
<tr>
<td></td>
<td>V256L</td>
<td>1</td>
<td>JAE</td>
</tr>
<tr>
<td></td>
<td>R597W</td>
<td>1</td>
<td>CAE and JME</td>
</tr>
<tr>
<td>GAD65</td>
<td>C45F</td>
<td>1</td>
<td>CAE</td>
</tr>
<tr>
<td></td>
<td>P153Q</td>
<td>5</td>
<td>CAE; CAE with JME</td>
</tr>
<tr>
<td></td>
<td>I575T</td>
<td>1</td>
<td>CAE</td>
</tr>
<tr>
<td>GAD67</td>
<td>R89W</td>
<td>1</td>
<td>GEFS+ and CAE</td>
</tr>
<tr>
<td></td>
<td>Y127F</td>
<td>1</td>
<td>CAE and LD</td>
</tr>
</tbody>
</table>

**Diagram:**

- **M555V**
  - Homo sapiens: VLIPGYMAYMFLTLKSLK
  - Pan troglodytes: VLIPGYMAYMFLTLKSLK
  - Canis familiaris: VLIPGYMAYMFLTLKSLK
  - Bos taurus: VLIPGYMAYMFLTLKSLK
  - Mus musculus: VLIPGYMAYMFLTLKSLK
  - Rattus norvegicus: VLIPGYMAYMFLTLKSLK
  - Gallus gallus: VLIPGYMAYMFLTLKSLK
  - Danio rerio: VLIPGYMGYFLTLKSYK
Childhood Absence Seizures

The seizures of childhood absence epilepsy usually start between the ages of four to nine years of age and can happen many times a day, from 20 up to several hundreds. A typical absence seizure consists of a sudden loss of awareness. The child will suddenly stop their activities and stare blankly into space. They will be unresponsive to voice. The seizure is sometimes associated with repetitive, purposeless movements of the mouth or eyes (automatisms). This can include eyelid fluttering and lip smacking.
CAE, Consciousness, Sleep and the Superhighway Connectome

Absence seizure

- Neocortex deactivation

Thalamus

- Limbic system
- Basal ganglia

ARAS
Searching for Further Validation

- Mutation Constructs prepared for cellular studies
- Family studies in UK, Australia & New Zealand
- *In Vitro* studies in progress in:
  - Swansea University – cellular assays and ELISA assays
  - Cardiff University - electrophysiology
  - UCL – radiolabelled transporter uptake assays
- *In Vivo* studies planned with Stanford University
Future Impact of this Study

- Pathophysiological mechanisms underlying IGE
- Targeted use of next-generation sequencing for gene-discovery
- Model systems for pre-clinical testing of new and old AED drugs
- Advanced clinical imaging investigation
- Highly-qualitative clinical/health trials using the genetic hierarchy
Conclusions and Acknowledgements

Ø IGE phenotypes are genetically heterogeneous
Ø We have identified a GABAergic subclass of CAE
Ø This may become a diagnostic opportunity for UKGTN

Further insights into epileptogenenic mechanisms

Collaborations:
Rob Harvey, UCL; Vincenzo Crunelli, CU; Sam Berkovic, Melbourne; Peter Bergin, Auckland; Kate Everret, St Georges; John Hugenard, Stanford.

Funders: Medical Research Council

Patients and Families