Gene testing in the epilepsies
- SCN1A, PCDH19 & SLC2A1

Sameer Zuberi
Paediatric Neurologist
Honorary Clinical Associate Professor
Royal Hospital for Sick Children
Glasgow
Genetics of Epilepsy

- Genetic diseases associated with epilepsy
  - Several hundred neurological disorders
  - > 200 with Mendelian inheritance

- The genetics of “idiopathic” epilepsy syndromes
  - 60% of childhood epilepsy
  - *ion channels and beyond*

*New ILAE organisation of the epilepsies— genetic rather than idiopathic*
Major clinical group

- Marked phenotypic heterogeneity
- Predominantly a condition of the first decade
- Recognized because of remarkable dominant pedigrees with 50-60% penetrance
- Generalized spike-wave discharges

Genetic (idiopathic) generalised epilepsies

FS/FS$^+$ and Absences
FS/FS$^+$ and Myoclonic Seizures
FS/FS$^+$ and Atonic Seizures
FS/FS$^+$ and Partial Epilepsy
Myoclonic-Astatic Epilepsy
Severe Myoclonic Epilepsy of Infancy


Courtesy Ingrid Scheffer
Cartoon of voltage gated sodium channel


Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy)  
Charlotte Dravet 1978

- Onset in the first year of life with febrile seizures
- Prolonged unilateral or generalized clonic seizures
- Other seizure types evolve by 1-4 years
  - Myoclonus
  - partial seizures
  - atonic seizures
  - atypical absences
- Hyperthermia often precipitant (bathing, fever)
Dravet Syndrome
Severe Myoclonic Epilepsy in Infancy

• Normal early development

• Psychomotor slowing > 1 year

• Ataxia and pyramidal signs evolve

• Intellectual outcome poor, seizures typically refractory

• Up to 50% have family history of seizures
  – Febrile Seizures
  – Epilepsy
  – Genetic Epilepsy with Febrile Seizures+ spectrum (Singh et al, 2001)
Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome

A. Brunklaus, R. Ellis, E. Reavey, G.H. Forbes and S.M. Zuberi

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2 School of Medicine, University of Glasgow, Wolfson Medical School Building, Glasgow G12 8QQ, UK
3 Duncan Guthrie Institute of Medical Genetics, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ, UK

How Dravet syndrome became a model for studying childhood genetic epilepsies

Charlotte Dravet
Honorary consultant, Childhood Neuropsychiatric Unit, Catholic University, Roma, Italy
Epidemiology

- Hurst et al. 1990: incidence of < 1 in 40,000 in USA
- Yakoub et al.: 1 in 20-30,000 in France

- Brunklaus et al. (Brain 2012)
  - UK Birth cohort 2003-7, 88 SCN1A positive Dravet syndrome cases
  - Incidence at least 1 in 40,900 for SCN1A positive
  - In the cohort now aged 3-7 years there have been 5 deaths (6%) at median age 5 years. 3 SUDEP and 2 status related
<table>
<thead>
<tr>
<th>Feature</th>
<th>Age at onset in months (median ± semi-IQR)</th>
<th>Occurrence number/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First seizure</td>
<td>6.0 ± 1.5</td>
<td>241/241 (100)</td>
</tr>
<tr>
<td>Prolonged febrile seizure (&gt;10 min)</td>
<td>7.0 ± 2.0</td>
<td>168/232 (72)</td>
</tr>
<tr>
<td>Hemidonic seizure</td>
<td>7.0 ± 3.5</td>
<td>161/225 (72)</td>
</tr>
<tr>
<td>Generalized tonic-clonic/clonic seizures</td>
<td>8.0 ± 3.0</td>
<td>216/231 (94)</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>9.0 ± 3.5</td>
<td>188/235 (80)</td>
</tr>
<tr>
<td>Focal seizure with impairment of awareness</td>
<td>10.0 ± 5.8</td>
<td>122/200 (61)</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>14.0 ± 7.5</td>
<td>161/232 (69)</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>21.0 ± 7.5</td>
<td>112/218 (51)</td>
</tr>
<tr>
<td>Age at which development noted to be abnormal</td>
<td>18.0 ± 6.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

First seizure precipitated by:
- Fever/illness: 134/230 (58)
- No precipitant: 75/230 (33)
- Vaccination: 17/230 (7)
- Bath: 4/230 (2)
- Abnormal interictal EEG in first 6 months: 8/47 (17)
- Abnormal interictal EEG in months 7–12: 45/90 (50)
- Abnormal interictal EEG in months 13–24: 34/55 (62)
- Abnormal interictal EEG in months 25–36: 30/38 (79)
- Photosensitivity: 34/211 (16)
- Autistic features: 69/208 (33)
- Behaviour problems: 98/213 (46)
- Motor disorder: 77/214 (36)
  - Hypotonia: 6/214 (3)
  - Ataxia: 56/214 (26)
  - Spasticity: 15/214 (7)
  - Dyskinesia: 6/214 (3)
- MRI abnormalities: 22/200 (11)

IQR = Interquartile range; N/A = not applicable.
Table 3. Ordinal univariate logistic regression analysis for variables predicting worse developmental outcome (n = 157; adjusted for age at assessment)

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>B</th>
<th>Wald test χ²</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor disorder (yes/no)</td>
<td>1.19</td>
<td>12.31</td>
<td>3.28 (1.69–6.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EEG abnormalities in Year 1 (yes/no)</td>
<td>1.74</td>
<td>9.93</td>
<td>5.70 (1.93–16.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Status epileptic (yes/no)</td>
<td>1.12</td>
<td>9.09</td>
<td>3.07 (1.48–6.35)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age at onset of delay (months)</td>
<td>−0.04</td>
<td>6.81</td>
<td>0.96 (0.94–0.99)</td>
<td>0.009</td>
</tr>
<tr>
<td>Early focal seizures with impairment of awareness ≤24 months (yes/no)</td>
<td>1.19</td>
<td>4.24</td>
<td>3.30 (1.06–10.28)</td>
<td>0.039</td>
</tr>
<tr>
<td>Age at onset of myoclonic seizures (months)</td>
<td>−0.03</td>
<td>3.65</td>
<td>0.97 (0.94–1.00)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.

Table 2. Medication response in SCN1A mutation positive Dravet Syndrome (n = 241)

<table>
<thead>
<tr>
<th>Medications reported to have reduced seizure frequency (five most common)</th>
<th>Number/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>81/160 (51)</td>
</tr>
<tr>
<td>Clobazam/clonazepam</td>
<td>55/160 (34)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>45/160 (28)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>21/160 (13)</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>20/160 (13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications reported to have increased seizure frequency (three most common)</th>
<th>Number/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>36/60 (60)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>26/60 (43)</td>
</tr>
<tr>
<td>Valproate</td>
<td>4/60 (7)</td>
</tr>
</tbody>
</table>

Table 1. Age at seizure onset in months according to mutation type

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Truncating</th>
<th>Missense</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/median age at onset (semi-IQR)</td>
<td>No.</td>
</tr>
<tr>
<td>First seizure</td>
<td>6.0/6.0 (1.5)</td>
<td>125</td>
</tr>
<tr>
<td>Prolonged seizure</td>
<td>7.4/6.0 (2.0)</td>
<td>69</td>
</tr>
<tr>
<td>Hemiclonic seizure</td>
<td>9.5/7.0 (3.5)</td>
<td>71</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>13.0/7.0 (3.5)</td>
<td>52</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>16.4/12.0 (5.0)</td>
<td>71</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>19.1/15.0 (6.0)</td>
<td>46</td>
</tr>
</tbody>
</table>

Abbreviation: IQR = interquartile range.

* p Value derived using Mann-Whitney U test.

b Significant.
Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology

Claudia B. Catarino,1,2 Joan Y.W. Liu,1 Ioannis Liagkouras,3 Vaneesha S. Gibbons,4 Robyn W. Labrum,4 Rachael Ellis,5,6 Cathy Woodward,4 Mary B. Davis,4 Shelagh J. Smith,1,2 J. Helen Cross,1,8,9 Richard E. Appleton,10 Simone C. Yendle,11 Jacinta M. McMahon,11 Susannah T. Bellows,11 Thomas S. Jacques,7,8 Sameer M. Zuberi,9 Matthias J. Koepp,1,2 Lillian Martinian,9 Ingrid E. Scheffer,11,12 Maria Thom1 and Sanjay M. Sisodiya1,9

Figure 1 Cross-sectional analysis of acquired autistic features, behavioural problems and motor disorder over time.

Figure 2 Cross-sectional analysis of developmental status over time.
De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study

Samuel F Berkovic, Louise Honkin, Jacinto M McMahon, James F Perlasco, Sameer M Zubari, Elaine C Mitre, Deepak S Gell, Xenia Ions, John C Mulley, Ingrid F Scheffer

Summary

Background: Vaccination, particularly for pertussis, has been implicated as a direct cause of an encephalopathy with refractory seizures and intellectual impairment. We postulated that cases of so-called vaccine encephalopathy could have mutations in the neuronal sodium channel α1 subunit gene (SCN1A) because of a clinical resemblance to severe myoclonic epilepsy of infancy (SMEI) for which such mutations have been identified.

Methods: We prospectively studied 14 patients with alleged vaccine encephalopathy in whom the first seizure occurred within 72 h of vaccination. We reviewed the relation to vaccination from source records and assessed the specific epilepsy phenotype. Mutations in SCN1A were identified by PCR amplification and denaturing high performance liquid chromatography analysis, with subsequent sequencing. Parental DNA was examined to ascertain whether mutations were de novo.

Findings: SCN1A mutations were identified in 11 of 14 patients with alleged vaccine encephalopathy; a diagnosis of a specific epilepsy syndrome was made in all 14 cases. Five mutations predicted truncation of the protein and six were missense in conserved regions of the molecule. In all nine cases where parental DNA was available the mutations were de novo. Clinical-molecular correlation showed mutations in eight of eight cases with phenotypes of SMEI, in three of four cases with borderline SMEI, and in two cases with Lennox-Gastaut syndrome.

Interpretation: Cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. These findings have important clinical implications for diagnosis and management of encephalopathy and, if confirmed in other cohorts, major societal implications for the general acceptance of vaccination.

Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study

Anne M Mcintosh*, Jacinto McMahon*, Leanne M Dibbins, Xenia Ions, John C Mulley, Ingrid F Scheffer, Samuel F Berkovic
Genotype–phenotype associations in SCN1A-related epilepsies

273 mutations in SCN1A in our series

- 134 (49%) missense

(A) Homologous domains (D1–4): transmembrane segments 1, 2, and 3 (shown in green); segments 4 (yellow) are the voltage sensors and segments 5 to 6 (pink) make up the pore-lining regions; NHis — represents the N-terminal and CO2 — the C-terminal. (B) The entire protein is divided into 14 subunits: N-terminal, S1 (segment 1), S1–S2 (segment 1–2 linker), S2, S2–S3, S3, S3–S4, S4, S4–S5, S5, S5–S6, S6, linker regions (large intracellular loops linking the 4 homologous domains), and the C-terminal. The figure illustrates the frequency of missense mutations per amino acid number in a given subunit; for illustration purposes, the average frequency was defined as 1.
UKGTN testing criteria - SCN1A

• Electroclinical phenotype of Dravet Syndrome or clinical sub-types – several seizure types in one individual with onset in infancy, refractory to medication with generalised spike and wave on EEG  OR

• Infants less than 1 year with 2 or more prolonged hemiclonic febrile seizures in early infancy
• First recognised in 1971.
• X-linked disorder with MALE SPARING, mapped to Xq22 in 1997.
• Mutations in the Protocadherin19 (PCDH19) gene were shown to be the cause of EFMR in 2008.
100 Cadherin-related genes in humans – transmembrane proteins with functions in cell-cell adhesion (adherens junctions) and signalling.

70 Protocadherins – subclass of cadherins, these genes are restricted to vertebrates.
   - *PCDH15* - Usher syndrome type 1F (retinopathy and sensorineural deafness).
   - *PCDH21* - AR cone-rod dystrophy.

*PCDH19* is essential for normal brain development in zebrafish. PCDH19 protein is localised to synapses in specific neuronal cell subtypes.

Neurons express distinct combinations of Protocadherins, which may provide a combinatorial “bar code” uniquely identifying cell subclasses.
Mechanism of male sparing for X-linked disorder

**Cellular interference theory**

Random X-inactivation in females generates tissue mosaicism

*PCDH19* positive and negative cells cannot form functional neural network

Males may be rescued by Y chromosome paralogue *PCDH11Y*

Only known affected male was mosaic for a *PCDH19* deletion
16 pathogenic mutations identified in extracellular cadherin repeats encoded by exon 1

Clusters of brief seizures – tonic or clonic or mixture of both

Clusters last a few days often fever related. Clusters rather than status

May be months between clusters

Seizures often remit in teenage years

Variable degree of learning disability from severe to none
UKGTN testing criteria – PCDH19

- Epilepsy onset 6 months – 3 years
- Seizures in association with fever
- Clusters of seizures
- Mental retardation
- Dravet-like syndrome

4 of 5 required
Glut1DS – glucose transporter 1 deficiency syndrome

- 1952 Widdas proposes glucose transport across the red blood cell membrane
- 1965 Crowe proposes glucose has facilitated diffusion across blood brain barrier
- 1967 Owen shows ketones provide alternative fuel during fasting in humans
- 1985 Mueckler discovers the Glut1 transporter
- 1991 De Vivo et al describe Glut1DS.
GLUT1 deficiency syndrome - early classic case presents with infantile drug-resistant seizures, mild to severe developmental delay, acquired microcephaly in up to 50% of the cases.

Hypotonia, spasticity, ataxia and dystonia are elements of a complex movement disorder.

The index case described by De Vivo et al had low CSF glucose and low CSF lactate.

Most cases have milder phenotypes with great variability. Syndrome may not be the right term. More of a spectrum of symptoms associated with the gene defect.
The GLUT1 protein & SLC2A1 gene

Solute carrier family 2 (facilitated glucose transporter), member 1 (\textit{SLC2A1})

97-98\% identity between the human, rat, mouse and pig sequences

GLUT1 – exclusively responsible for D-glucose transport across the blood-brain barrier
Deficiency leads to inadequate cerebral glucose
Glucose transporter 1 deficiency syndrome

- Consider in any individual with fluctuating motor disorder “ataxic cerebral palsy” with no obvious cause. May have ataxia, paroxymal ataxia / dyskinesia, atypical absences, myoclonus. Any child with paroxysmal movement disorder

- Clues in history
  - Neonatal apnoea
  - Eye movement disorder
  - Better after food
  - Always wanting to snack
  - Fluctuation in symptoms
  - Made worse by caffeine, valproate
  - Expanding phenotype
Glucose transporter 1 deficiency syndrome

• Investigation
  • Fasting (4-6h) LP for CSF glucose. Do blood glucose first
  • CSF / blood glucose <0.45 – not absolute figure – have seen up to 0.59
  • CSF testing reliability being called into question
  • EEG pre and post meals
  • Video pre and post treatment
  • Erythrocyte glucose uptake tests
  • **Analysis of SLC2A1 gene - solute carrier family 2, member 1 gene**
  • Negative gene test does not exclude diagnosis
Glut-1 deficiency syndrome masquerading as idiopathic generalized epilepsy

*Eliane Roulet-Perez, †Diana Ballhausen, †Luisa Bonafé, *Stephanie Cronel-Ohayon, and ‡Malin Maeder-Ingvar


Early-onset absence epilepsy caused by mutations in the glucose transporter Glut 1. (4/34 cases)

Absence epilepsies with widely variable onset are a key feature of familial GLUT1 deficiency

Mullen et al. Neurology. 2010; 75:432-440
UKGTN testing criteria – SLC2A1

- Infantile drug resistant seizures
- Developmental delay
- Acquired microcephaly
- Elements of a complex movement disorder (hypotonia, spasticity, ataxia and dystonia)
- Paroxysmal exercise induced dyskinesia +/- epilepsy
- Lumbar puncture features (low glucose concentration in cerebrospinal fluid in absence of hypoglycaemia)
Clinical presentation of Glut1DS
-symptoms of cerebral brain energy deprivation

• “Ataxic cerebral palsy” – always consider Glut1DS
• Early onset absences
• Genetic generalised epilepsy not responsive to medication
• Exercise induced movement disorder
• Patients may or may not have learning disability
• Variability of neurological symptoms
• Paroxysmal ataxia and migraine
• An expanding phenotype
• A treatable disorder – test early in undiagnosed learning disability + neurological symptoms
Treatment

• The ketogenic diet provides an alternative fuel for the brain
• Modified Atkins may be just as effective and is better tolerated in older children and adults.
• Evidence that treatment helps even as an adult
• Can be dramatic improvement in movement disorder, control of epilepsy and better cognition with diet.
• Important to videotape before and after diet
The clinical utility of an \textit{SCN1A} genetic diagnosis in infantile-onset epilepsy

ANDREAS BRUNKLAUS$^1$ | LIAM DORRIS$^1$ | RACHAEL ELLIS$^2$ | ELEANOR REAVEY$^2$ | ELIZABETH LEE$^1$ | GORDON FORBES$^2$ | RICHARD APPLETON$^2$ | J HELEN CROSS$^4$ | COLIN FERRIE$^5$ | IMELDA HUGHES$^6$ | ALICE JOLLANDS$^2$ | MARY D KING$^8$ | JOHN LIVINGSTON$^9$ | BRYAN LYNCH$^8$ | SUNNY PHILIP$^9$ | INGRID E SCHEFFER$^{10}$ | RUTH WILLIAMS$^{11}$ | SAMEER M ZUBERI$^1$

What this paper adds

- A positive \textit{SCN1A} test result enables early diagnosis and can influence treatment choice.
- Children aged 2 years and younger benefit most from testing positive for a mutation.
- A clear diagnostic label helps access to additional therapies.

February 2013
Diagnostic certainty according to age

Higher proportion of unclassified cases in younger age groups
($X^2 = 18; df = 4; p = 0.001$)

### Parent views on genetic testing

<table>
<thead>
<tr>
<th>Genetic testing</th>
<th>Scn1a</th>
<th>Age</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Helpfulness in giving explanation for epilepsy</td>
<td>87%</td>
<td>19%</td>
<td>97%</td>
</tr>
<tr>
<td>Led to a change in medication</td>
<td>55%</td>
<td>9%</td>
<td>69%</td>
</tr>
<tr>
<td>Change improved seizure control</td>
<td>69%</td>
<td>-</td>
<td>81%</td>
</tr>
<tr>
<td>Led to access of therapies</td>
<td>41%</td>
<td>-</td>
<td>59%</td>
</tr>
</tbody>
</table>

# Physician views on genetic testing

<table>
<thead>
<tr>
<th>Genetic testing</th>
<th>Children who tested positive for a mutation (n=124), % (n)</th>
<th>Children who tested negative for a mutation (n=39), % (n)</th>
<th>$\chi^2$ (df=1)</th>
<th>$p$-value</th>
<th>Children who tested positive for a mutation $\leq$2y (n=36), % (n)</th>
<th>Children who tested positive for a mutation $\geq$5y (n=61), % (n)</th>
<th>$\chi^2$ (df=1)</th>
<th>$p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Confirmed an established clinical diagnosis</td>
<td>45 (54/120)</td>
<td>5 (2/39)</td>
<td>20.5</td>
<td>&lt;0.001</td>
<td>55 (17/31)</td>
<td>45 (27/60)</td>
<td>0.8</td>
<td>0.373</td>
</tr>
<tr>
<td>2. Confirmed a suspected clinical diagnosis</td>
<td>83 (100/121)</td>
<td>8 (3/38)</td>
<td>70.8</td>
<td>&lt;0.001</td>
<td>89 (31/35)</td>
<td>78 (45/58)</td>
<td>1.8</td>
<td>0.184</td>
</tr>
<tr>
<td>3. Allowed a diagnosis to be made earlier than with clinical and EEG data alone</td>
<td>48 (59/123)</td>
<td>5 (2/38)</td>
<td>22.5</td>
<td>&lt;0.001</td>
<td>71 (24/34)</td>
<td>41 (24/58)</td>
<td>7.3</td>
<td>0.007</td>
</tr>
<tr>
<td>4. Prevented misdiagnosis</td>
<td>48 (59/123)</td>
<td>26 (10/38)</td>
<td>5.6</td>
<td>0.030</td>
<td>66 (21/32)</td>
<td>41 (24/59)</td>
<td>5.2</td>
<td>0.023</td>
</tr>
<tr>
<td>5. Saved the child additional investigations</td>
<td>67 (82/122)</td>
<td>8 (3/38)</td>
<td>40.9</td>
<td>&lt;0.001</td>
<td>81 (26/32)</td>
<td>66 (37/56)</td>
<td>2.3</td>
<td>0.129</td>
</tr>
<tr>
<td>6. Altered the treatment approach</td>
<td>69 (83/121)</td>
<td>18 (7/38)</td>
<td>29.6</td>
<td>&lt;0.001</td>
<td>83 (29/35)</td>
<td>65 (37/57)</td>
<td>3.4</td>
<td>0.063</td>
</tr>
<tr>
<td>7. Was helpful in choosing the most appropriate medication</td>
<td>74 (91/123)</td>
<td>18 (7/38)</td>
<td>37.6</td>
<td>&lt;0.001</td>
<td>94 (32/34)</td>
<td>66 (37/56)</td>
<td>9.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

### Physician views on genetic testing

<table>
<thead>
<tr>
<th>Genetic testing</th>
<th>Children who tested positive for a mutation (n=124), % (n)</th>
<th>Children who tested positive for a mutation ≥5y (n=61), % (n)</th>
<th>χ² (df=1)</th>
<th>p-value</th>
<th>χ² (df=1)</th>
<th>p ^a</th>
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<tr>
<td>7. Was helpful in choosing the most appropriate medication</td>
<td>74 (91/123)</td>
<td>66 (37/56)</td>
<td>37.6</td>
<td>&lt;0.001</td>
<td>9.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Parent/Carer views

Positive statements

- Importance of having a definite diagnosis (27 statements)
  - “After 8 years of not knowing what she had, we finally could give it a label and get on with life”
- Access to treatment (16 statements)
  - “Finally got diagnosis which resulted in change of medication and better seizure control”
- Importance of genetic counselling (10 statements)
  - “It really helps us advise our two daughters and reassure them that his condition is not likely to occur in any of their children now we know that we have not also got the SCN1A mutation”

Critical statements

- Concerns in relation to length of time taken to obtain results (15 statements)
  - “The day her result was due back we were advised blood had not been sent away and therefore we would have to wait a further three months for results”
- Concerns in Relation to Insufficient Genetic Counselling (7 statements)
  - “We received the devastating news that our daughter has Dravet syndrome and have been left to research what that meant and how we could help her ourselves”
Physician views

Importance of a definite diagnosis (31 statements)

"Patient has an atypical phenotype, identification of his mutation has guided treatment"

Increased parent/carer understanding and adjustment (23 statements)

"Gives family peace of mind knowing what the problem is"

Avoidance of further investigations (17 statements)

"Avoid unnecessary second line investigation for intractable seizure"

Genetic testing leading to medication change (17 statements)

"Treatment change leading to more seizure control"
• ~75% patients without a genetic diagnosis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Total Reports</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1A</td>
<td>2289</td>
<td>532 (23%)</td>
</tr>
<tr>
<td>PCDH19</td>
<td>211</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>401</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>STXBP1</td>
<td>74</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>CDKL5</td>
<td>54</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>ARX</td>
<td>32</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
A Potential Next Generation Epilepsy+ Gene Panel

<table>
<thead>
<tr>
<th>SCN1A</th>
<th>SCN2A</th>
<th>CSTB</th>
<th>BTD</th>
<th>PRICKLE2</th>
<th>GLRA1</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC2A1</td>
<td>SCN1B</td>
<td>GABRB3</td>
<td>HLCS</td>
<td>SCARB2</td>
<td>GLRB</td>
</tr>
<tr>
<td>STXBP1</td>
<td>PNKP</td>
<td>GABRD</td>
<td>HLCS</td>
<td>TBC1D24</td>
<td>GPHN</td>
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<tr>
<td>CDKL5</td>
<td>PLCB1</td>
<td>GABRA1</td>
<td>COL4A2</td>
<td>ARHGEF9</td>
<td>SLC6A5</td>
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<tr>
<td>ARX</td>
<td>CHRNA4</td>
<td>KCNMA1</td>
<td>MFSD8</td>
<td>NRXN1</td>
<td>CASK</td>
</tr>
<tr>
<td>SLC25A22</td>
<td>CHRNБ2</td>
<td>KCNQ3</td>
<td>TPP1</td>
<td>TCF4</td>
<td>ATRX</td>
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<tr>
<td>CACNA1A</td>
<td>KCNA1</td>
<td>KCNJ10</td>
<td>SMS</td>
<td>EFHC</td>
<td>KCNT1</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>ATP1A2</td>
<td>PRRT2</td>
<td>KCTD7</td>
<td>GAMT</td>
<td>?</td>
</tr>
<tr>
<td>PRRT2</td>
<td>SCN9A</td>
<td>PNPO</td>
<td>CACNB4</td>
<td>AGAT</td>
<td>?</td>
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<tr>
<td>GABRG2</td>
<td>FOXG1</td>
<td>KCNA1</td>
<td>EPM2A</td>
<td>SLC6A8</td>
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<tr>
<td>POLG1</td>
<td>MECP2</td>
<td>MEF2C</td>
<td>GRIN2A</td>
<td>CLN3</td>
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<tr>
<td>MECP2</td>
<td>SPTAN1</td>
<td>LGI1</td>
<td>GRIN2B</td>
<td>CLN5</td>
<td></td>
</tr>
<tr>
<td>UBE3A</td>
<td>ALDH7A1</td>
<td>MOCS1</td>
<td>NHLRC1</td>
<td>CLN6</td>
<td></td>
</tr>
<tr>
<td>KCNQ3</td>
<td>CHRNA2</td>
<td>MOCS2</td>
<td>PRICKLE1</td>
<td>CTSD</td>
<td></td>
</tr>
</tbody>
</table>

- ~450kb data/patient (SCN1A sequencing 0.5kb data)

40% childhood epilepsy presents in first 3y and 40% of these are epileptic encephalopathies
Genetics in the management of the epilepsies

- Genetics can help the individual / family / physician understand the cause of the epilepsy and aid psychological adjustment.
- Genetics help make a syndromic diagnosis earlier than with clinical features alone.
- Genetic testing can save unnecessary investigations.
- Genetics can inform genetic counselling in novel ways.
- Genetic testing can inform treatment choices and improve access to therapies.
- Genetic testing can improve clinical outcomes.