The Role of Genetics in Childhood Epilepsies

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Epilepsy

- Two or more seizures
- Affects 2% population, 50 million people worldwide
- > 30 different epilepsy syndromes
- Genetic epilepsy most often begin in childhood
Quality of Life

In 30% people with epilepsy- medications don’t work

Increased mortality - including SUDEP

Increased morbidity - fractures, burns, bruising
- learning, language difficulties
- aggression, depression, anxiety, intellectual disability, autism
Why study genetics of epilepsy?

- Why does my child have epilepsy?
- Epilepsy often difficult to diagnose & treat
- Future course uncertain

Genetic & genomic technologies to find causes of childhood epilepsies
Genetics of Dravet Syndrome (DS)

- Normal development in first year
- Onset 5-6 months with seizures
- Regression of abilities, poor outcome with cognitive and physical impairment (loss of ability to talk, walk)
- Children can have multiple, hundreds of seizures a day
- Seizures resistant to anti-epileptic drugs
SCN1A mutations in Dravet Syndrome (DS)

Utilized genomic & sequencing technologies

80% children with Dravet Syndrome: SCN1A gene mutation

Now >>1000s mutations in SCN1A (Na+ channel)

Mulley et al Hum Mut 2005
Dravet Syndrome due to SCN1A mutations

Incidence ~ 1/20,000 children, better clinical picture

Treatments: avoid “channel blocker” drugs
ketogenic diet benefits some children

90% of SCN1A mutations are “new” in the affected child

Genetic findings allow for genetic counselling

m SCN1A mutation
+ no SCN1A mutation
Rarely - some children develop epilepsy & developmental delay around time of triple antigen (DTP) vaccination, progresses to epilepsy and cognitive decline

• Triple antigen given 2, 4, 6 months of age
• Febrile seizures may occur

• Epidemiological studies fail to support an association between vacc. & seizures with developmental decline

however

Parents want to know- ‘why did it happen to my child?’
Due to timing - vaccination blamed
Children have an SCN1A mutation & Dravet Syndrome

- Genetically analysed 14 children with vaccine-related seizure onset (within 72 hours) who developed infantile encephalopathy
- 11/14 cases found to have an SCN1A mutation
- Showed a genetic cause for the encephalopathy & not caused by vaccine
- Lack of family history of seizures: *de novo* SCN1A mutations

McIntosh et al Lancet Neurol 2010
Discovery of the first epilepsy gene

CHRNA4 gene
family with focal epilepsy

Genetic linkage
& Sanger sequencing

Nature Genetics  volume 11  october 1995
Modern DNA Sequencing

1994

2016
Onset: seizures begin at 6 – 36 months
Seizures: sometimes cease in teenage years, can be ongoing,
Features: developmental decline often occurs
67% girls have intellectual disability
autism, aggression, obsession can occur
Next generation sequencing of affected girls
Wellcome Trust Sanger Institute, UK

Mutations in PCDH19 gene

Dibbens et al Nat Gen 2008
PCDH19 mutations cause epilepsy female limited

50% mutations are “new” in affected girl
50% mutations are inherited
Gene discoveries in Focal Epilepsies

- account for ~ 60% all epilepsy
- A proportion due to structural lesions
- Not considered to have a genetic basis
Next Generation Sequencing in Focal Epilepsies

DEPDC5, NPRL2 & NPRL3 mutations in common forms of focal epilepsy

Dibbens et al Nat Gen 2013
Ricos et al Ann Neurol 2016

KCNT1 mutations in children with focal epilepsy, intellectual disability and psychiatric features
(new ion channel in epilepsy)

Heron et al Nat Gen 2012
DEPDC5 in epilepsy with/without brain malformations

Scheffer et al. Ann Neurol 2014
mTOR signalling

DEPDC5

Bar Peled et al
Science 2013
Translation to care of patients

• Dravet Syndrome due to SCN1A mutations:
  Precise diagnosis, genetic counselling, pre-natal diagnosis,
  DS support groups, channel-blocker medications avoided

• Epilepsy Female Limited due to PCDH19 mutations:
  Precise diagnosis, genetic counselling, pre-natal diagnosis,
  PCH19-Alliance, guides choice of medications

• Focal epilepsies due to KCNT1 or mTOR pathway mutations:
  Precise diagnosis, genetic counselling, pre-natal diagnosis,
  quinidine and mTOR inhibitors trialled for treatment

• Genetics - greater role in epilepsy than previously thought
• Gene discoveries reveal new biological pathways in epilepsy
  and inform the development of new drugs and treatments
  for children with epilepsy
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Patients and their Families
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Modes of Inheritance – Monogenic Epilepsy

Autosomal Dominant

Autosomal Recessive

X-Linked

de novo