European Science Foundation

Eurocores Project; EuroEpinomics
Kick-off meeting
September 20th 2011; Strasbourg

Genetics of rare epilepsy syndromes
Are these “rare” epilepsy syndromes really rare?

• Individually “rare” but “as a group “common”
Where do these monogenic “rare epilepsy syndromes” hide?

• Families
  - Autosomal dominant
  - Autosomal recessive
  - X-linked

• Isolated, early onset epilepsies
MONOGENIC
Mendelian forms

“Common alleles”
GWAS
CNV

GGGE

Parametric linkage
Locus sequencing
CNV

Epileptic encephalopathies

CNV (aCGH)
Whole exome sequencing
SCN1A channelopathies

Generalized epilepsy with febrile seizures plus (GEFS+)

Families
Dravet Syndrome; SMEI
Isolated patients

Missense mutations: altered kinetics

Loss of function
De novo
Missense mutations
Nonsense mutations
whole gene deletions = CNV
# Early onset absences epilepsy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Current Age</th>
<th>Age of Onset</th>
<th>Examination</th>
<th>Outcome</th>
<th>Family History of Epilepsy</th>
<th>SLC2A1 Mutations</th>
<th>Position in Protein</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absence</td>
<td>GTCS</td>
<td>Myoclonus</td>
<td>Motor</td>
<td>Head Circumference</td>
<td>Paroxysmal Dyskinesia</td>
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<tr>
<td>1</td>
<td>F</td>
<td>28 yr</td>
<td>3 yr</td>
<td>7 yr</td>
<td>—</td>
<td>Normal</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>28 yr</td>
<td>3 yr</td>
<td>8 yr</td>
<td>—</td>
<td>Mild upper limb ataxia</td>
<td>Normal</td>
<td>—</td>
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<tr>
<td>3</td>
<td>F</td>
<td>12 yr</td>
<td>14 mo</td>
<td>—</td>
<td>14 mo</td>
<td>Mild gait ataxia</td>
<td>Normal</td>
<td>Subtle, 5 yr</td>
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<tr>
<td>4</td>
<td>F</td>
<td>7 yr</td>
<td>13 mo</td>
<td>12 mo</td>
<td>—</td>
<td>Normal</td>
<td>Normal</td>
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</table>

DNA mutations were numbered using the reference sequence NM_006516.1.

GTCS = generalized tonic-clonic seizure; VPA = valproic acid; TMD = transmembrane domain; ID = intellectual disability; IQ = intelligence quotient; TPM = topiramate; LTG = lamotrigine; ETX = ethosuximide.
SLC2A1 mutations in IGE

Family A

Family B

* SLC2A1 mutation
wt wild type
Proband
Aims

1. Achieve a molecular genetic diagnosis in rare epilepsy cases
   - Better and easier diagnosis
   - Prognosis
   - Genetic counselling
   - Enable pharmacological studies in homogeneous patient groups...
Broader Aims ... links with other CRPS

• 2. Novel genes and pathways
  - Novel insights in seizures and epileptogenesis
  - Construction of cellular and animal models
  - Identification of novel therapeutic targets
    • Seizures
    • More disease specific
Partners

- Caglayan Hande; Istanbul; Turkey
- Craiu Dana; Bucharest; Romania
- Helbig Ingo; Kiel; Germany
- Hoffman-Zacharska Dorota; Warsaw; Poland
- Lemke Johannes; Bern; Switzerland
- Rosenow Felix; Marburg; Germany
- Selmer Kaja; Oslo; Norway
- Serratosa José; Madrid; Spain
- Talvik Tiina; Tartu; Estonia
- De Jonghe Peter; Antwerpen; Belgium
Associated Partners

• Lerche Holger; Tübingen; Germany
• Mefford Heather; Seattle; USA
• Tommerup Niels; Copenhagen; Denmark,
• Hjalgrim; Copenhagen, Denmark
• Barisic Nina; Zagreb; Croatia
Expertise

• Patient populations
  - Large Index families/ trios
  - Follow up cohorts

• In depth phenotyping
  - Clinical; electrophysiology; imaging (MR)

• Technology platforms
  - Large capacities
  - High throughput
  - Complementary technologies
Positional Cloning

Genome search → chromosome → Gene $\rightarrow$ mutation
<table>
<thead>
<tr>
<th>Designation</th>
<th>Locus</th>
<th>Chromosome</th>
<th>Gene</th>
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<tr>
<td>Benign familial neonatal seizures (BFNS)</td>
<td>EBN1</td>
<td>20q13.3</td>
<td>KCNQ2</td>
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<tr>
<td></td>
<td>EBN2</td>
<td>8q24</td>
<td>KCNQ3</td>
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<td></td>
<td>EBN3</td>
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<td>Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)</td>
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<td>CHRNA4</td>
</tr>
<tr>
<td></td>
<td>EFNL2</td>
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<tr>
<td></td>
<td>EFNL3</td>
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<td>CHRNBE2</td>
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<td>EFNL4</td>
<td>8p21</td>
<td>CHRNA2</td>
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<tr>
<td></td>
<td></td>
<td>3p22-p24</td>
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<td></td>
<td></td>
<td>8q11.2-q21.1</td>
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<tr>
<td>Chromosome</td>
<td>Phenotype/Syndrome</td>
<td>No of families</td>
<td>Model of inheritance*</td>
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<tr>
<td>19q</td>
<td>BFIS</td>
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<td>5</td>
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<td>17q12–q24</td>
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<td>8q24</td>
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<td>5p15</td>
<td>absence seizures</td>
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<td>AR</td>
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<td>8p11</td>
<td>IGE, non JME</td>
<td>91</td>
<td>AR</td>
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<td>9q32–33</td>
<td>IGE (GTCS)</td>
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<td>AR</td>
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<td>10q25–q26</td>
<td>GTCS in JME</td>
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<tr>
<td>10p11</td>
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<tr>
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<td>JME</td>
<td>34</td>
<td>AR</td>
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<td>6p21</td>
<td>JME, IGE</td>
<td>24</td>
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<td>2p11.1–q12.2</td>
<td>BAFME</td>
<td>2</td>
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</tbody>
</table>

* AD = autosomal dominant, AR = autosomal recessive
Questions raised

- Are we really so successful?
- Why is the pace of gene-discovery slowing down?

Potential hurdles:
- Some loci may be false positive
- Mistakes in delineation of linkage intervals
- Loci too big to handle with classical Sanger sequencing
- Unusual mutation mechanisms (CNV, promoter...)
- Difficulties in recruiting large families...
Generalized epilepsy with febrile seizures plus
A genetic disorder with heterogeneous clinical phenotypes

Ingrid E. Scheffer and Samuel F. Berkovic

Fig. 4 Pedigree of the core family showing the heterogeneity of epilepsy phenotypes seen.
Generalized Epilepsy with Febrile Seizures Plus (GEFS+)

Febrile seizures plus (FS+)

MAE
SMEI
TLE
PE
JME
CAE
FS/FS+ absences
FS/FS+ myoclonic
FS/FS+ atone

Febrile seizures (FS)
Human Genome project

- Start: 1990
- Completed: 2003
- Total cost: ~$3 billion
New tools

• Targeted next gen sequencing
  - “Epilepsy panels” e.g. 50 known “Epilepsy genes”

• Whole exome sequencing
  - 20,000 genes

• Whole genome sequencing

• Genome-wide Copy Number Variant (CNV) analysis
Revolution in research and diagnostics

Exome Sequencing Allows for Rapid Gene Identification in a Charcot-Marie-Tooth Family

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

Genetic diagnosis by whole exome capture and massively parallel DNA sequencing

A de novo paradigm for mental retardation
Acknowledgments

• Holger Lerche
  - For pushing the EuroEpinomics project forward

• “Kiel Group”
  - Ingo Helbig; Sarah Von Spiczak; Johanna Albers

• And ...
Kick-off meeting RES CRP

- Antwerpen; Belgium
- 17th-18th November, 2011