Dravet Syndrome: What Warrants Further Testing or SCN1A in the Modern Era and SCN1A-negative Dravet syndrome

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Boston Children’s Hospital
DSF Conference Coral Gables, FL June 25, 2016
Outline

• Dravet syndrome
  • $SCN1A$ predominates
  • Are there really other genes?

• Genetic epilepsy overview
  • Many contexts for $SCN1A$
  • One gene $\rightarrow$ many syndromes
  • One syndrome $\rightarrow$ many genes

• $SCN1A$-negative Dravet syndrome
  • De novo mutations
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  • De novo mutations
Dravet Syndrome

• Severe myoclonic epilepsy of infancy
  – Presentation in infancy
  – Convulsive/hemiconvulsive sz, often with fever
  – Myoclonic sz
  – Developmental and EEG regression with ongoing sz

• Incidence in U.S. ~1/15,700-1/30,000

• Standard of care
  – Symptomatic management of symptoms
    • Seizures
      – Based on observation, typical treatments used, some to avoid
      – Risk of SUDEP—higher with untreated epilepsy
    • Intellectual disability, behavioral issues
    • Gait abnormalities

Wu et al., Pediatrics, 2015; Dravet Syndrome Foundation summary
Range of SCN1A mutations in Dravet Syndrome

R. H. Wallace et al. Neurology 2003;61:765-769

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Dravet Syndrome

- *SCN1A* accounts for the overwhelming majority (~80%) of the syndrome
  - Nonsense mutations in *SCN1A* (mostly *de novo*)
  - Missense and microdeletions in *SCN1A*

- Site of dysfunction—evidence for interneuronopathy

- Window to intervene if diagnosis can be made earlier?
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Genetic Epilepsy Overview

Helbig and Lowenstein, *Curr Opin Neurol*, 2013

> 100 association studies with negative or not-reproducible results
Complex genetic architecture of epilepsy

inherited

de novo

de novo post-zygotic
Complex genetic architecture of epilepsy

- Inherited
- De novo
- De novo post-zygotic
Neuronal Sodium-Channel α1-Subunit Mutations in Generalized Epilepsy with Febrile Seizures Plus

R. H. Wallace,1,2 I. E. Scheffer,4 S. Barnett,1 M. Richards,1 L. Dibbens,1,2 R. R. Desai,5 T. Lerman-Sagie,6 D. Lev,6 A. Mazarib,7 N. Brand,8 B. Ben-Zeev,8 I. Goikhman,9 R. Singh,4 G. Kremmidiotis,1,2 A. Gardner,1 G. R. Sutherland,1,2,3 A. L. George Jr.,5 J. C. Mulley,1,3 and S. F. Berkovic4

A Australian Family

B Ashkenazi Family

- febrile seizures (FS) X D188V
- febrile seizures plus (FS+) Y V1353L
- FS+, extended phenotype Z I1656M
- Unclassified 0 no mutation
- Partial epilepsy
- Juvenile myoclonic epilepsy
A Novel SCN1A Mutation Associated with Generalized Epilepsy with Febrile Seizures Plus—and Prevalence of Variants in Patients with Epilepsy

Andrew Escayg,1,* Armin Heils,2* Bryan T. MacDonald,1 Karsten Haug,3 Thomas Sander,4 and Miriam H. Meisler1

1Department of Human Genetics, University of Michigan, Ann Arbor; 2University Clinic of Epileptology, and 3Department of Human Genetics, University of Bonn, Bonn; and 4Department of Neurology, University Hospital Charité, Campus Virchow Clinic, Humboldt University of Berlin, Berlin

We recently in two fami SCN1A mal febrile conv the sample was identifi disease-caus nucleotide upstream of controls, su GEFS+, by i alleles were epilepsy. Th
Inherited $SCN1A$ pedigree with variable expressivity
Complex genetic architecture of epilepsy

inherited

de novo

de novo post-zygotic
De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy

Lieve Claes, Jurgen Del-Favero, Berten Ceulemans, Lieven Lagae, Christine Van Broeckhoven, and Peter De Jonghe

Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp, and Department of Neurology, University Hospital Antwerp, Antwerp; Epilepsy Center for Children and Youth, Pulderbos, Belgium; and Department of Child Neurology, University Hospital Gasthuisberg, Leuven, Belgium

Severe myoclonic epilepsy of infancy (SMEI) is a rare disorder that occurs in isolated patients. The disease is characterized by generalized tonic, clonic, and tonic-clonic seizures that are initially induced by fever and begin during the first year of life. Later, patients also manifest other seizure types, including absence, myoclonic, and simple and complex partial seizures. Psychomotor development stagnates around the second year of life. Missense mutations in the gene that codes for a neuronal voltage-gated sodium-channel α-subunit (SCN1A) were identified in families with generalized epilepsy with febrile seizures plus (GEFS+). GEFS+ is a mild type of epilepsy associated with febrile and afebrile seizures. Because both GEFS+ and SMEI involve fever-associated seizures, we screened seven unrelated patients with SMEI for mutations in SCN1A. We identified a mutation in each patient: four had frameshift mutations, one had a nonsense mutation, one had a splice-donor mutation, and one had a missense mutation. All mutations are de novo mutations and were not observed in 184 control chromosomes.
De novo Mutations in Cohorts with Early Onset Epilepsies

Epilepsy of infancy with migrating focal seizures
- *de novo*: KCNT1, SCN1A, SCN2A
(also recessive: PLCB1, SLC25A22, TBC1D24, QARS)

Ohtahara syndrome
- KCNQ2 (10/34 in our series), STXBP1, SPTAN1, ARX, SCN2A


Barcia et al., 2012; Carranza Rojo et al., 2011; Frielich et al., 2011; Dhamija et al., 2013; Howell et al., 2015
(Poduri et al., 2012; Poduri et al., 2014; Milh et al., 2013; Zhang et al., 2015)
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### Table 1 | Probability of observing the reported number of *de novo* mutations by chance in genes recurrently mutated in this cohort

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<th>Gene</th>
<th>Chromosome</th>
<th>Average effectively captured length (bp)</th>
<th>Weighted mutation rate</th>
<th>De novo mutation number</th>
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</table>
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Overview of Epilepsy Genetics

Poduri and Lowenstein, *Curr Opin Genet Dev* 2011
Early Onset Epilepsy Genes

Poduri and Lowenstein, *Curr Opin Genet Dev* 2011
Early Onset Epilepsy Genes—2016 Update

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Erin Heinzen, Columbia University
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• Genetic epilepsy overview
  • Many contexts for *SCN1A*
  • One gene → many syndromes
  • One syndrome → many genes

• ‘*SCN1A*-negative’ Dravet syndrome
  • *De novo* mutations
Outline

• Dravet syndrome
  • SCN1A predominates
  • Are there really other genes?

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  • One syndrome → many genes

• ‘SCN1A-negative’ ‘Dravet syndrome’
  • De novo mutations
Dravet Syndrome
Lennox-Gastaut Syndrome
autism
EIMFS
Doose Syndrome
GEFS+
80-90%
SCN1A
Dravet Syndrome
?
Complex genetic architecture of epilepsy

- **Inherited**
- **De novo**
- **De novo post-zygotic**
When does a “de novo” somatic mutation arise?

Poduri et al., *Science*, 2013
When does a “de novo” somatic mutation arise?

Poduri et al., *Science*, 2013
Evidence for post-zygotic mutations in SCN1A

Timing of De Novo Mutagenesis — A Twin Study of Sodium-Channel Mutations


SUMMARY

De novo mutations are a cause of sporadic disease, but little is known about the developmental timing of such mutations. We studied concordant and discordant monozygous twins with de novo mutations in the sodium channel α1 subunit gene (SCN1A) causing Dravet's syndrome, a severe epileptic encephalopathy. On the basis of our findings and the literature on mosaic cases, we conclude that de novo mutations in SCN1A may occur at any time, from the premorula stage of the embryo (causing disease in the subject) to adulthood (with mutations in the germ-line cells of parents causing disease in offspring).
So what accounts for the ‘missing’ 10-20% of Dravet Syndrome cases?

• *De novo* mutations in other genes?
• *De novo* post-zygotic *SCN1A* mutations?
SCN1A

Doose Syndrome

autism

GEFS+

Lennox-Gastaut Syndrome

EIMFS

80-90%
## Missing SCN1A

<table>
<thead>
<tr>
<th>Patient</th>
<th>Negative screening</th>
<th>Positive screening</th>
<th>Reason that the mutation was missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>2</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>3</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>4</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>5</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>6</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>7</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>8</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>9</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Missed by the person performing the mutation analysis (visual inspection of Sanger traces)</td>
</tr>
<tr>
<td>10</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Error in the primer design: The mutation was located in the primer binding site</td>
</tr>
<tr>
<td>11</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Error in the primer design: A polymorphism in the primer led to mono-allelic amplification</td>
</tr>
<tr>
<td>12</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Error in the primer design: A polymorphism in the primer led to mono-allelic amplification</td>
</tr>
<tr>
<td>13</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Error in the primer design: The primer did not cover the whole amplicon (only one direction was sequenced)</td>
</tr>
<tr>
<td>14</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>The patient turned out not to be sequenced</td>
</tr>
<tr>
<td>15</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Possible sample swap not to be sequenced</td>
</tr>
<tr>
<td>16</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Wrong sequencing data assigned to the patient</td>
</tr>
<tr>
<td>17</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>The traces were of bad quality so the Sanger should have been redone</td>
</tr>
<tr>
<td>18</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Not reported in the diagnostic report as the mutation is located eight base pairs in the intron</td>
</tr>
<tr>
<td>19</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>An adjacent intronic polymorphic deletion led to misalignment of the alleles and uninterpretable data</td>
</tr>
<tr>
<td>20</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>The annealing temperature of the primers was too high for the polymerase</td>
</tr>
<tr>
<td>21</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>The mutated peak was too low</td>
</tr>
<tr>
<td>22</td>
<td>NGS: WES</td>
<td>Sanger</td>
<td>The mutation is located in a homopolymer stretch</td>
</tr>
<tr>
<td>23</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
<tr>
<td>24</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
<tr>
<td>25</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
<tr>
<td>26</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
<tr>
<td>27</td>
<td>Sanger</td>
<td>NGS: WES</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
<tr>
<td>28</td>
<td>Sanger</td>
<td>NGS: Gene panel</td>
<td>Unable to retrieve the Sanger traces</td>
</tr>
</tbody>
</table>

Djémié et al., 2016
**ABSTRACT**

**Objective:** To determine the genes underlying Dravet syndrome in patients who do not have an SCN1A mutation on routine testing.

**Methods:** We performed whole-exome sequencing in 13 SCN1A-negative patients with Dravet syndrome and targeted resequencing in 67 additional patients to identify new genes for this disorder.

**Results:** We detected disease-causing mutations in 2 novel genes for Dravet syndrome, with mutations in GABRA1 in 4 cases and STXBP1 in 3. Furthermore, we identified 3 patients with previously undetected SCN1A mutations, suggesting that SCN1A mutations occur in even more than the currently accepted ~75% of cases.

**Conclusions:** We show that GABRA1 and STXBP1 make a significant contribution to Dravet syndrome after SCN1A abnormalities have been excluded. Our results have important implications for diagnostic testing, clinical management, and genetic counseling of patients with this devastating disorder and their families. *Neurology® 2014;82:1245-1253*

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical features of patients with Dravet syndrome who underwent whole-exome sequencing or in whom mutations were identified by targeted resequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age, y/sex</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>T20744</td>
<td>2/F</td>
</tr>
<tr>
<td>T16706</td>
<td>7/F</td>
</tr>
<tr>
<td>T23532</td>
<td>18/M</td>
</tr>
<tr>
<td>Co05</td>
<td>18/M</td>
</tr>
<tr>
<td>T1915</td>
<td>11*/M</td>
</tr>
<tr>
<td>EP1807</td>
<td>21/M</td>
</tr>
<tr>
<td>T21717</td>
<td>6/F</td>
</tr>
</tbody>
</table>
Sporadic Infantile Epileptic Encephalopathy Caused by Mutations in \textit{PCDH19} Resembles Dravet Syndrome but Mainly Affects Females

Christel Depienne\textsuperscript{1,2,3,}* \textsuperscript{1}, Delphine Bouteiller\textsuperscript{2}, Boris Keren\textsuperscript{1}, Emmanuel Cheuret\textsuperscript{4}, Karine Poirier\textsuperscript{5}, Oriane Trouillard\textsuperscript{1}, Baya Benyahia\textsuperscript{1}, Chloé Quelin\textsuperscript{5}, Wassila Carpentier\textsuperscript{6}, Sophie Julia\textsuperscript{4}, Alexandra Afenjar\textsuperscript{1,7}, Agnès Gautier\textsuperscript{8}, François Rivier\textsuperscript{9}, Sophie Meyer\textsuperscript{10}, Patrick Berquin\textsuperscript{11}, Marie Hélias\textsuperscript{12}, Isabelle Py\textsuperscript{13}, Serge Rivera\textsuperscript{14}, Nadia Bahi-Buisson\textsuperscript{15}, Isabelle Gourfinkel-An\textsuperscript{2,15,16}, Cécile Cazeneuve\textsuperscript{1}, Merle Ruberg\textsuperscript{2,3}, Alexis Brice\textsuperscript{1,2,3}, Rima Nabout\textsuperscript{16,17}, Eric LeGuern\textsuperscript{1,2,3}

1 AP-HP, Département de Génétique et Cytogénétique, Fédération de Génétique, Hôpital de la Salpêtrière, Paris, France, 2 INSERM U975 (Ex-U679), Paris, France, 3 Université Pierre et Marie Curie-Paris 6, CNRS, UMR-5675, Paris, France, 4 Service de Neurologie Pédiatrique, Hôpital des Enfants, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, 5 Institut Cochin, Inserm U967, UMR 8104, Université René Descartes, Paris, France, 6 Plate-forme Post-Génomique P3S, UPMC, Faculté de Médecine, Paris, France, 7 Service de Neuropédiatrie, Hôpital Trousseau, Paris, France, 8 Service de Neuropédiatrie, CHU Nantes, Nantes, France, 9 Service de Neuropédiatrie - Hôpital Gui de Chauliac, CHU de Montpellier, Montpellier, France, 10 Service de Neuropédiatrie, Hôpital de Bordeaux, Bordeaux, France, 11 Service de Neuropédiatrie, CHU Hôpital Nord Amiens, Amiens, France, 12 ITEP de Champhymeri et ASPEC, Montagne-au-Perche, France, 13 Service de Pédiatrie, Centre Hospitalier de Cholet, Cholet, France, 14 Service de Pédiatrie, Hôpital de Bayonne, Bayonne, France, 15 Département de Neuropédiatrie, AP-HP, Hôpital Necker-Enfants Malades, Paris-Desdentes, Paris, France, 16 Pôle d’Épileptologie, Hôpital de la Salpêtrière, Paris, France, 17 Centre de Référence Épilepsies Rares, Paris, France

Abstract

Dravet syndrome (DS) is a genetically determined epileptic encephalopathy mainly caused by de novo mutations in the \textit{SCN1A} gene. Since 2003, we have performed molecular analyses in a large series of patients with DS, 27\% of whom were negative for mutations or rearrangements in \textit{SCN1A}. In order to identify new genes responsible for the disorder in the \textit{SCN1A}-negative patients, 41 probands were screened for micro-rearrangements with Illumina high-density SNP microarrays. A hemizygous deletion on chromosome Xq22.1, encompassing the \textit{PCDH19} gene, was found in one male patient. To confirm that \textit{PCDH19} is responsible for a Dravet-like syndrome, we sequenced its coding region in 73 additional \textit{SCN1A}-negative patients. Nine different point mutations (four missense and five truncating mutations) were identified in 11 unrelated female patients. In addition, we demonstrated that the fibroblasts of our male patient were mosaic for the \textit{PCDH19} deletion. Patients with \textit{PCDH19} and \textit{SCN1A} mutations had very similar clinical features including the association of early febrile and afebrile seizures, seizures occurring in clusters, developmental and language delays, behavioural disturbances, and cognitive regression. There were, however, slight but constant differences in the evolution of the patients, including fewer polymorphic seizures (in particular rare myoclonic jerks and atypical absences) in those with \textit{PCDH19} mutations. These results suggest that \textit{PCDH19} plays a major role in epileptic encephalopathies, with a clinical spectrum overlapping that of DS. This disorder mainly affects females. The identification of an affected mosaic male strongly supports the hypothesis that cellular interference is the pathogenic mechanism.
Targeted resequencing in epileptic encephalopathies identifies *de novo* mutations in *CHD2* and *SYNGAP1*

Gemma L Carvill¹, Sinéad B Heavin², Simone C Yendle², Jacinta M McMahon², Brian J O’Roak³, Joseph Cook¹, Adiba Khan¹, Michael O Dorschner⁴,⁵, Molly Weaver⁴,⁵, Sophie Calvert⁶, Stephen Malone⁶, Geoffrey Wallace⁶, Thorsten Stanley⁷, Ann M E Bye⁸, Andrew Bleasell⁹, Katherine B Howell¹⁰, Sara Kivity¹¹, Mark T Mackay¹⁰,¹²,¹³, Victoria Rodriguez-Casero¹⁴, Richard Webster¹⁵, Amos Korczyn¹⁶, Zaid Afawi¹⁷, Nathanel Zelnick¹⁸, Tally Lerman-Sagie¹⁹,²⁰, Dorit Lev¹⁹, Rikke S Møller²⁰, Deepak Gill¹⁵, Danielle M Andrade²¹, Jeremy L Freeman¹⁰,¹², Lynette G Sadleir⁷, Jay Shendure³, Samuel F Berkovic², Ingrid E Scheffer²,¹⁰,¹³,²² & Heather C Mefford¹

<table>
<thead>
<tr>
<th>Proband</th>
<th>Sex, study age (years)</th>
<th>Gene</th>
<th>Protein change (Polyphen, SIFT)ᵃ</th>
<th>Diagnosis</th>
<th>Seizuresᵇ (age of onset)</th>
<th>EEG</th>
<th>Development before seizure onset</th>
<th>Cognitive outcome (regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T38</td>
<td>M, 17</td>
<td>CHD2</td>
<td>p.Glu1412Glyfs*64</td>
<td>MAE</td>
<td>A (1 year) FS, absence, MJ-A, MJ, T</td>
<td>3.8-Hz GSW</td>
<td>Mild delay, behavioral problems</td>
<td>Moderate intellectual disability, ASD (no)</td>
</tr>
<tr>
<td>T18697</td>
<td>F, 12</td>
<td>CHD2</td>
<td>p.Arg121*</td>
<td>EE</td>
<td>MJ (1 year) NCS, T, TC, MA</td>
<td>GPSW, MFD, GPFA, SSW</td>
<td>Normal</td>
<td>Severe intellectual disability (yes)</td>
</tr>
<tr>
<td>T20240</td>
<td>M, 12</td>
<td>CHD2</td>
<td>p.Arg1644Lysfs*22</td>
<td>MAE</td>
<td>A (2 years) MJ, SE, T, TC</td>
<td>DS, GPSW, 2.5-Hz GSW</td>
<td>Normal</td>
<td>Severe intellectual disability (yes)</td>
</tr>
<tr>
<td>T17756</td>
<td>M, 15</td>
<td>CHD2</td>
<td>p.Trp548Arg (1, 0)</td>
<td>EE</td>
<td>TC (3 years) FDS, H, MJ</td>
<td>GSW, MFD, DS</td>
<td>Delayed</td>
<td>Moderate intellectual disability (yes)</td>
</tr>
<tr>
<td>T18431</td>
<td>M, 2.5</td>
<td>CHD2</td>
<td>p.Leu823Pro (0.999, 0)</td>
<td>EE</td>
<td>FDS, MJ (2.5 years) MA, T</td>
<td>GSW, GPSW, MFD</td>
<td>Delayed</td>
<td>Severe intellectual disability, ASD (yes)</td>
</tr>
</tbody>
</table>
De novo mutations in HCN1 cause early infantile epileptic encephalopathy

Caroline Nava1,4,25, Carine Dalle1,5,25, Agnès Rastetter1, Pasquale Striano6, Carolien G F de Kovel7, Rima Nabbout8,9, Claude Cancès10, Dorothée Ville11, Eva H Brilstra7, Giuseppe Gobbi12, Emmanuel Raffo13, Delphine Bouteiller14, Yannick Marie14, Oriane Trouillard1,3,4, Angela Robbiano15, Boris Keren16, Dahbia Agher1, Emmanuel Roze1-3, Suzanne Lesage1-3, Aude Nicolas1-3, Alexis Brice1-4, Michel Baulac1-3, Cornelia Vogt17, Nady El Hajj17, Eberhard Schneider17, Arvid Suls18,19, Sarah Weckhuysen18,19, Padhraig Gormley20, Anna-Eлина Lehesjoki21,22, Peter De Jonghe18,19, Ingo Helbig23, Stéphanie Baulac1-3, Federico Zara15, Bobby P C Koelman7, EuroEPINOMICS RES Consortium24, Thomas Haaf17, Eric LeGuern1-4 & Christel Depienne1,3,17

Table 1 Genetic and clinical characteristics of the individuals with HCN1 mutations identified in this study

<table>
<thead>
<tr>
<th>Family number</th>
<th>6</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>4</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td>Subject origin</td>
<td>France</td>
<td>Italy</td>
<td>France</td>
<td>The Netherlands</td>
<td>France</td>
<td>France</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Base change</td>
<td>c.140G&gt;T</td>
<td>c.299C&gt;T</td>
<td>c.814T&gt;C</td>
<td>c.835C&gt;T</td>
<td>c.890G&gt;C</td>
<td>c.1201G&gt;C</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Unknown</td>
<td>De novo</td>
<td>De novo</td>
<td>De novo</td>
<td>De novo</td>
<td>De novo</td>
</tr>
<tr>
<td>Age at time of analysis (years)</td>
<td>13</td>
<td>6</td>
<td>16</td>
<td>12</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Age at seizure onset (months)</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>13</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Seizure types</td>
<td>FS, TCS, absence, focal, myoclonic</td>
<td>FS, TCS, CS, absences, focal, myoclonic</td>
<td>FS, CS, focal, absence</td>
<td>FS (atypical), CS, TCS, absence, myoclonic</td>
<td>FS, focal, absence</td>
<td>FS, TCS, absence, focal, myoclonic</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>Moderate to severe</td>
<td>Severe</td>
<td>Mild</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
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<tr>
<td>MRI</td>
<td>NA</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pharmacoresistance</td>
<td>Absence of language</td>
<td>Autistic features</td>
<td>Behavioral disturbances, autistic features</td>
<td>ADHD</td>
<td>Behavioral disturbances, autistic features</td>
<td>Behavioral disturbances, autistic features</td>
</tr>
<tr>
<td>Behavior and language</td>
<td>None</td>
<td>Motor delay</td>
<td>Truncal ataxia</td>
<td>None</td>
<td>None</td>
<td>Polyphagia</td>
</tr>
</tbody>
</table>

FS, febrile seizure; TCS, tonic-clonic seizure; CS, clonic seizure; MRI, magnetic resonance imaging; ADHD, attention deficit hyperactivity disorder; NA, unavailable.
SCN1A

Doose Syndrome

autism

GEFS+

Lennox-Gastaut Syndrome

EIMFS

80-90%

Dravet Syndrome

?
SCN1A

Doose Syndrome

Lennox-Gastaut Syndrome

autism

GEFS+

EIMFS

80-90%

PCDH19

GABRA1

CHD2

SCN1B

HCN1

STXBP1

Dravet Syndrome
Conclusions

- Dravet syndrome genetics is as complex as the genetics of epilepsy.
  - Includes inherited, *de novo*, even post-zygotic mutations
  - If the phenotype is truly Dravet syndrome, check twice for *SCN1A*
    - Sequencing
    - Deletion/duplication testing
    - Evaluate for post-zygotic mutations (mostly research labs)
  - Majority of cases are due to *SCN1A* mutations, but a growing list of other genes is also implicated.
Question for the future as precision medicine efforts build

• Should we consider new drug trials based on clinical syndromes vs. genetic diagnoses?
Thank you

“Hope is acknowledging that life’s challenges will one day be life’s victories”.
—Spirit of Hope Honoree Bert Bubela

- Patients and families enrolled in epilepsy genetics research
- Numerous colleagues and collaborators

Epilepsy Genetics Research Team
Mark LaCoursiere  Beth Sheidley
Alan Taylor  Heather Olson
Lacey Smith  Gessica Truglio
McKenna Kelly  Jeremy Ullmann
Christelle Achkar  Christopher Yuskaitis
(honorary members: Brian Reidy, Ingrid Scheffer)

NINDS (K23, EPGP, Epi4K, Epilepsy Genetics Initiative)
Bon Anniversaire, Dr. Dravet!