Genetics of Dravet Syndrome

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• History of Dravet syndrome genetics

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Pre-molecular era

**Peculiar features of patients with Dravet syndrome**

- Always isolated in family

- More frequent epilepsy in first-degree relatives
  - Genetic
  - Multi-genetic cause

- Coincidence of post-vaccination epileptic complications
  - Environmental
  - Acquired etiology

Jonghe PD, 2011
Generalized epilepsy with febrile seizures plus
A genetic disorder with heterogeneous clinical phenotypes

Ingrid E. Scheffer and Samuel F. Berkovic

Scheffer IE and Berkovic SF, 1997
**GEFS+**

*Fig. 5* The GEFS+ (generalized epilepsy with febrile seizures plus) spectrum. A schematic representation of the range of epilepsy phenotypes deriving from a single genetic epilepsy syndrome.

*Fig. 4* Pedigree of the core family showing the heterogeneity of epilepsy phenotypes seen.

Scheffer IE and Berkovic SF, 1997
Mutations of \textit{SCN1A}, encoding a neuronal sodium channel, in two families with GEFS+2

Generalized epilepsy with febrile seizures plus type 2 (GEFS+2, MIM 604233) is an autosomal dominant disorder characterized by febrile seizures in children and afebrile seizures in adults. We describe here two mutations of the gene encoding the neuronal voltage-gated sodium channel (SCN1A), Thr875Met and Arg1648His, that co-segregate with the disorder in two families with GEFS+ linked to chromosome 2q. These mutations identify a new disease gene for human inherited epilepsy.

Patients with GEFS+ express a variable phenotype combining febrile seizures, afebrile generalized seizures (tonic-clonic, absence, myoclonic or atonic) and partial seizures\textsuperscript{1}. GEFS+ type 1 (MIM 600235) was associated with a mutation in \textit{SCN1B}, encoding the \(\beta1\)-subunit of the voltage-gated sodium channel\textsuperscript{2}. GEFS+2 was recently mapped to a 20-cM region of chromosome 2q24–q33 in two French families\textsuperscript{3,4}. The sodium channel \(\alpha\)-subunit gene cluster\textsuperscript{5} on chromosome 2q24 contains three neuronal genes (\textit{SCN1A}, \textit{SCN2A} and \textit{SCN3A}), encoding proteins

Escayg A, et al., 2000
Fig. 1 Sequencing, exon organization and evolutionary conservation of SCN1A. a, Amino acid sequence and intron/exon organization. The transmembrane segments (S; underlined), the intron locations (triangles) and the mutant residues Thr875 and Arg1648 (asterisks) are indicated. b, The mutations Thr875Met and Arg1648His are located in D254 and D454 (arrows). c, Evolutionary conservation of the residues Thr875 and Arg1648 (boxed). GenBank accession numbers from the top are as follows: M22253, M94055, Y00766, M81758, M77235, AB027567.1, X82835, AF117907.1, AF188679, D37977, L19979, M22252, M32078.

Escayg A, et al., 2000
GEFS+ and *SCN1A*

- 53 unrelated probands with GEFS+
- Sequencing of SCN1A genomic clones
- Point mutations in SCN1A in three patients
- No mutations in 17 sporadic cases of GEFS+
- Several single-nucleotide polymorphisms

<table>
<thead>
<tr>
<th>Sequence Variants of SCN1A Detected in 53 GEFS+ Samples and in 60 Normal Samples</th>
<th>FREQUENCY</th>
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<tbody>
<tr>
<td></td>
<td>( % )</td>
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<tr>
<td><strong>SCN1A POLYMORPHISM</strong></td>
<td><strong>GEFS+</strong></td>
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<td>Intron 13 IVS13–37C→A</td>
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<td>Exon 14 c.2522C→G</td>
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<td>Exon 26 c.5782C→G</td>
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</table>

Wallace RH, et al., 2001
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

1Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp, and 2Department of Neurology, University Hospital Antwerp, Antwerp; 3Epilepsy Center for Children and Youth, Pulderbos, Belgium; and 4Department of Child Neurology, University Hospital Gasthuisberg, Leuven, Belgium


Discovery of $SCN1A$ association
Discovery of *SCN1A* association

- Seven patients with Dravet syndrome, their unaffected parents, and 92 healthy control
- Heterozygous de novo SCN1A mutation in all pts.

Figure 1  Organization of SCN1A. The neuronal voltage-gated sodium-channel α-subunit SCN1A is a monomer and consists of four homologous domains (DI-DIV). Each domain has six transmembrane segments (S1–S6). S4 has several positively charged amino acids and represents the voltage sensor. P = the pore loop, which delineates the pore of the channel. Mutations identified in this study (described in table 2) were denoted as follows: asterisks (*) = deletion, insertion and nonsense mutations; diamond (♦) = missense mutation; circles (●) = GEFS+ missense mutations reported by Escayg et al. (2000, 2001); and squares (■) = GEFS+ missense mutations reported by Wallace et al (2001).

Claes L, 2001
SCN1A mutation in Dravet syndrome

- About 70% of patients have SCN1A mutation.
  - Missense mutations: mostly located in the transmembrane spanning segments and the proximal part of the carboxyl terminal domains
  - Inframe deletions
  - Truncation mutations

- Approximately 25% of female SCN1A negative patients → PCDH19 mutation

- Others
  - GABRG2 mutation (Harkin LA, 2002)
  - Homozygous SCN1B mutation (Patino GA, 2009)
  - Modifying effect of SCN9A mutations, mostly in combination with SCN1A mutations (Singh NA, 2009)
SCN1A mutation in Dravet syndrome

ICEGTC: idiopathic childhood epilepsy with GTC seizures
SIGEI: severe idiopathic generalized epilepsy of infancy

Kearney and Meisler, 2008
Brain sodium channel

- Voltage-gated Na\(^+\) channels in brain
  - **Alpha** subunit: 260kDa
    - Voltage sensors
    - **Ion-conducting pore** in four internally repeated domains (I-IV)
    - Ion-conducting pore: consists of *six alpha helical trans-membrane segments* (S1-S6)
    - Pore loop: connecting S5 and S6
  - **Beta-1** subunit: 36 kDa
  - **Beta-2** subunit: 33 kDa

Catterall WA, 2000
Brain sodium channel

Catterall WA, 2000
Brain sodium channel

Catterall WA, 2000
Brain sodium channel

- **Mammalian genome**: 9 functional voltage gated sodium channel alpha subunits
  - In CNS: $\text{Na}_v1.1$ (*SCN1A*), $\text{Na}_v1.2$ (*SCN2A*), $\text{Na}_v1.3$ (*SCN3A*), $\text{Na}_v1.6$ (*SCN8A*)

<table>
<thead>
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<th>Channel</th>
<th>Gene</th>
<th>Localization</th>
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<td>SCN2A</td>
<td>Unmyelinated or pre-myelinated exons and dendrites</td>
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<td>Cell body</td>
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<td>$\text{Na}_v1.6$</td>
<td>SCN8A</td>
<td>Myelinated exons and dendrites</td>
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</tbody>
</table>
Puzzle 1

- Sodium channel: major excitatory channel in CNS
  
  Loss of function in sodium channel

  Lead to hyperexcitability in Dravet syndrome
Pathomechanism of Dravet syndrome

Premature deaths of Na\textsubscript{v}1.1 mutant mice

Yu FH, 2006
GAD: glutamic acid decarboxylase, critical enzyme in the synthesis of GABA
Bipolar cell: anti-GAD (+) → GABAergic inhibitory interneuron
Currents of heterozygous and homozygous bipolar neurons were significantly smaller than those of wild-type neurons (f, \( P < 0.05 \))

Yu FH, 2006
Pathomechanism of Dravet syndrome

Depolarization-evoked firing activity of hippocampal interneurons from Na\textsubscript{\textgamma}1.1 mutant mice

Yu FH, 2006
Pathomechanism of Dravet syndrome

Loss of function in sodium channel

Decreased excitability of GABAergic interneuron

Hyperexcitability in Dravet syndrome
Puzzle 2

- Familial recurrence of Dravet syndrome from asymptomatic parents
- Increased prevalence of epilepsy in first-degree relatives
- Discordant monozygotic twins
Parental mosaicism

Germline mosaicism was observed in 7% of the parent pairs.

Depienne C, 2006, 2009
Figure 2. Timing of Mutations in Dravet's Syndrome.

Vadlamudi, 2010
PCDH19 gene mutation

- Protocadherins (pcdhs)
  - Transmembrane protein: calcium dependent adhesion
  - Clustered: ~58 genes, Pcdhα, β, γ
  - Nonclustered: ~13 genes, Pcdhδ and other Pcdhs
  - Predominantly expressed in the brain
  - Significant role in neurodevelopment- neuronal migration and synaptic plasticity
PCDH19 gene mutation

- **PCDH19 (MIM# 300460)**
  - Located on chromosome Xq22.3
  - Belongs to δ2-subclass of nonclustered pcdhs
  - Six coding exons
  - PCDH19 expression is *spatially and temporally regulated during development in the CNS.*
  - Highly expressed in subventricular zone, intermediated zone, subplate, layers II, IV, V, VI

Vadlamudi, 2010
PCDH19 gene mutation

- Function of protocadherin 19
  - δ2-pcdhs: mediate calcium dependent cell-cell adhesion in vitro and cell sorting in vivo
  - Regulate the establishment of neuronal connections during brain development and remodeling of selective synaptic connections

- PCDH19 gene mutation
  - More than 60 different mutations

Vadlamudi, 2010
Pathophysiology

A Normal individual (male or female)
PCDH19-positive cells only
Asymptomatic

B Mutated males
PCDH19-negative cells only
Asymptomatic

C Mutated females and mosaic mutated males
PCDH19-negative and PCDH19-positive cells coexist
Epilepsy and mental retardation

Depienne C, 2009
Pathophysiology

● Mutations in PCDH19: loss of function at the cellular level

● Cellular interference: gain of function at the tissue level
  ▪ Random X inactivation in mutated females
    → leads to tissue mosaicism: normal cell + PCDH19 mutated cell
    → Abnormal interaction between “mutated” and “normal” cells
    → Results in gain of function (hyper-excitability and abnormal function of CNS)

Depienne C, 2009
Clinical phenotype
Female patients with heterozygous PCDH19 mutations

- Seizure
  - Begins in infancy or early childhood (mean 12.9 months)
  - Highly sensitive to fever
  - Febrile seizure: initial manifestation in 50%
  - Frequent seizure types: GT, GC, GTC, focal sz
  - Infrequent seizure types: atypical absence, atonic seizures, myoclonic seizures
  - Brief seizure clusters rather than status epilepticus
  - Intractable, decrease with age

Depienne et al., 2009, 2011; Marini et al., 2011; Scheffer et al., 2008; Specchio et al., 2011
Clinical phenotype
Female patients with heterozygous PCDH19 mutations

- Frequent behavioral disturbance
  - Autistic, obsessive, aggressive

- Cognitive outcome
  - Normal (27.7%), Mild (36.1%), Moderate (21.7%), severe (14.5%) cognitive impairment

Depienne et al., 2009, 2011; Marini et al., 2011; Scheffer et al., 2008; Specchio et al., 2011
Korean patients with Dravet syndrome

SCN1A mutational analysis in Korean patients with Dravet syndrome

Byung Chan Lim\textsuperscript{a,b}, Hee Hwang\textsuperscript{a}, Jong Hee Chae\textsuperscript{a,b}, Ji-Eun Choi\textsuperscript{a}, Yong Seung Hwang\textsuperscript{a,b}, Seong-Ho Kang\textsuperscript{c}, Chang-Seok Ki\textsuperscript{d}, Ki Joong Kim\textsuperscript{a,b,*}

\textsuperscript{a}Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea
\textsuperscript{b}Pediatric Clinical Neuroscience Center, Seoul National University Children’s Hospital, Seoul, Republic of Korea
\textsuperscript{c}Greencross Reference Laboratory, Yongin, Republic of Korea
\textsuperscript{d}Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
19/29 (66%) pathogenic mutations, 15 novel mutations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Phenotype</th>
<th>cDNA</th>
<th>Protein</th>
<th>Subunit location</th>
<th>Family study</th>
<th>Previous report</th>
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Lim BC, 2011
## Genotype-Phenotype correlations

### Table 2
Clinical features and genotype-phenotype correlations of 29 patients.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Phenotype</th>
<th>SCN1A mutation</th>
<th>Onset (months)</th>
<th>Last follow-up (years)</th>
<th>Myoclonic/atypical absence seizure</th>
<th>Video EEG monitoring</th>
<th>Family history</th>
<th>Rufinamide</th>
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<td>Truncation</td>
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GTC, generalized tonic–clonic seizure; SPS, simple partial seizure; CPS, complex partial seizure; IGE, idiopathic generalized epilepsy; FS, febrile seizure; and CAE, childhood absence epilepsy.

Lim BC, 2011
Summary

- About 70% of the patients with Dravet syndrome have mutations in SCN1A gene.

- The pathomechanism of mutated SCN1A gene is that the loss of function caused the decreased excitability of GABAergic inhibitory interneuron, which leads to hyperexcitability of Dravet syndrome.

- Germline or somatic mosaicism can explain the familial recurrence of Dravet syndrome and increased prevalence of epilepsy in first-degree relatives.

- Approximately 25% of female SCN1A negative patients have PCDH19 mutation, which shared some clinical characteristics with Dravet syndrome with SCN1A mutation.
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