Genotype-phenotype correlation studies and tailored treatment for the most common monogenic epilepsies:

**SCN1A**

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Declaration of Interest

- I have received honoraria for speaking at educational symposia and attending advisory boards from Biocodex, Zogenix, GW Pharma, Nutricia and Encoded Therapeutics.

- My institution has received funding from GW Pharma and Zogenix for undertaking research trials.
SCN1A associated phenotypes

Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+
A Escayg, B T MacDonald, M H Meisler, S Baulac, G Huberfeld, I An-Gourfinkel, A Brice, E LeGuern, B Moulard, D Chaigne, C Buresi, A Malafosse

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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

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Not all SCN1A epileptic encephalopathies are Dravet syndrome
Early profound Thr226Met phenotype
Lynette G. Sadleir,

University of Glasgow

Dravet Syndrome

► Onset in first year of life with febrile seizures
► Prolonged unilateral or generalized clonic seizures
► Other seizure types evolve by 1-4 years
► Presumed normal early development
► Psychomotor slowing > 1 year
► Developmental & epileptic encephalopathy
Spectrum of \textit{SCN1A} related epilepsies

\begin{itemize}
  \item \underline{Mild} \quad \text{GEFS+} \quad \text{FS+}
  \item \underline{Severe} \quad \text{Dravet syndrome}
\end{itemize}
241 individuals (1 to 42 years)

Analysis of UK birth cohort from 2003 – 2007 (n=88)

Incidence of Dravet syndrome at least 1 per 40,900
– now 1 per 15,000

Incidence of SCN1A related epilepsy at least 1 per 12,200
Sodium channel alpha 1 subunit (SCN1A)

- Voltage-gated sodium channel
- Widespread expression in CNS
- $\text{Na}_V1.1$ channels are primarily localized in cell bodies
- Role in the generation of action potentials
- $\text{Na}_V1.1$ expression is first detectable postnatally and increases thereafter
Sodium channel alpha 1 subunit (SCN1A)
Dravet syndrome – a channelopathy

Nabbout et al. (2013) Orphanet J Rare Dis.13;8:176
Dravet syndrome – a channelopathy

Nabbout et al. (2013) Orphanet J Rare Dis.13;8:176
Dravet syndrome – a channelopathy

Ogiwara et al. (2007) J Neurosci;27:5903-14

Nabbout et al. (2013) Orphanet J Rare Dis.13;8:176
Dravet syndrome – a channelopathy

Han et al. (2012) Nature; 489:385-90
Nabbout et al. (2013) Orphanet J Rare Dis. 13:8:176
Variant classes

- Missense (49%)
  - ? altered protein function
  - ? phenotype

- Nonsense (17%)
- Frame-shift (18%)
- Splicesite (9%)
- Insert/Deletion (2%)
- Rearrangements (5%)

- Truncating (51%)
  - Loss of protein function
  - Severe phenotype

Phenotypical differences between truncating and missense variants

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age at seizure onset in months according to mutation type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Truncating</td>
</tr>
<tr>
<td></td>
<td>Mean/median age at onset (semi-IQR) No.</td>
</tr>
<tr>
<td>Seizure type</td>
<td>6.0/6.0 (1.5) 125</td>
</tr>
<tr>
<td>First seizure</td>
<td>7.4/6.0 (2.0) 69</td>
</tr>
<tr>
<td>Prolonged seizure</td>
<td>9.5/7.0 (3.5) 71</td>
</tr>
<tr>
<td>Hemiclonic seizure</td>
<td>13.0/7.0 (3.5) 52</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>16.4/12.0 (5.0) 71</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>19.1/15.0 (6.0) 46</td>
</tr>
</tbody>
</table>

Abbreviation: IQR = interquartile range.
<sup>a</sup><sup>b</sup> P Value derived using Mann-Whitney U test.
<sup>b</sup> Significant.
Impact on rate of cognitive decline
How do missense variants from the general population differ from those found in patients?

gnomAD vs pathogenic missense burden (variants from the general population)

Grey Polymorphisms

Courtesy of Perez-Palma & Lal
How do missense variants from the general population differ from those found in patients?

gnomAD vs pathogenic missense burden (variants from the general population)

Grey Polymorphisms
Blue Disease causing variants

Courtesy of Perez-Palma & Lal
Identification of pathogenic variant enriched regions across genes and gene families

Eduardo Pérez-Palma, 1,2 Patrick May, 3 Sumaiya Iqbal, 4,5 Lisa-Marie Nistroj, 1 Juanjiangmeng Du, 1 Henrique O. Heyne, 4,5,6 Jessica A. Castrillon, 1 Anne O’Donnell-Luria, 4 Peter Nürnberg, 1 Aarno Palotie, 4,5,6 Mark Daly, 4,5,6 and Dennis Lal 1,2,4,5,7


A Missense burden analysis: Voltage-Gated Sodium Channel Family:
Conventional pathogenicity modelling
SCN1A variants from bench to bedside—improved clinical prediction from functional characterization

Andreas Brunklaus\textsuperscript{1,2,*}  |  Stephanie Schorge\textsuperscript{3,4,*}  |  Alexander D. Smith\textsuperscript{5}  |
Ismail Ghanty\textsuperscript{1,2}  |  Kirsty Stewart\textsuperscript{6}  |  Sarah Gardiner\textsuperscript{5}  |  Juanjiangmeng Du\textsuperscript{7}  |
Eduardo Pérez-Palma\textsuperscript{7}  |  Joseph D. Symonds\textsuperscript{1,2}  |  Abby C. Collier\textsuperscript{5}  |  Dennis Lal\textsuperscript{7,8,9,10,11}  |
Sameer M. Zuberi\textsuperscript{1,2}  

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**Voltage sensor**

- Dravet syndrome (DS)
- DS/GEFS+/FS+
- Familial Hemiplegic Migraine (FHM)
- Early Epileptic Encephalopathy

**Out**

1234

**In**

6

**D1**

- T226M
- L263V
- I227S
- M145T
- G177A
- G177E
- Y426N
- S259R
- R865G
- R859H
- R859C
- H939Q
- M956T
- C959R
- G979R
- T808S
- T875M
- V983A
- N1011I
- W1204R
- V1353L
- T1624P
- P1632S
- R1648C
- R1648H
- A1685V
- A1685D
- M1664K
- M1664K
- I1656M
- R1657C
- L1673W
- T1909I
- Q1923R

**D2**

- R393H
- Y790C
- R859C
- F902C
- C959R
- G979R
- H939Q
- M956T
- T908S
- R946H
- R946C
- L986F
- A1273V
- M1267I
- V1366I
- Q1489K
- L1649Q
- F1661S
- L1673W
- T1909I
- Q1923R

**D3**

- Out

1234

**In**

6

**D4**

- CO\textsubscript{2}\textsuperscript{−}

- G1749E
- F1765L
- G1674R
- F1808L
- M1852T
- D1866Y

\[ \alpha \]
Whole-cell current as a marker of function for missense variants

χ² = 5.071, df = 1, p = 0.024

Clinical Phenotype
GENETIC DISEASE

Predicting functional effects of missense variants in voltage-gated sodium and calcium channels

Henrike O. Heyne¹,²,³,⁴*, David Baez-Nieto³†, Sumaiya Iqbal¹,²,³,⁵†, Duncan S. Palmer¹,²,³†, Andreas Brunklaus⁶,⁷, Patrick May⁸, Epi25 Collaborative, Katrine M. Johannesen⁹,¹⁰, Stephan Lauermann¹¹, Johannes R. Lemke¹², Rikke S. Møller⁹,¹⁰, Eduardo Pérez-Palma¹³,¹⁴, Ute I. Scholl¹⁵,¹⁶, Steffen Syrbe¹⁷, Holger Lerche¹¹, Dennis Lal¹,²,³,¹³,¹⁴,¹⁸, Arthur J. Campbell³,⁵, Hao-Ran Wang³, Jen Pan³, Mark J. Daly¹,²,³,⁴*

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Evolution of voltage-gated ion channels

Model of sodium channel disorders

Early-onset seizures
(a) Less inhibition
(b) More excitation

Late-onset seizures and NDDs
(c) Less excitation

Inhibitory n.
Excitatory n.
Corticospinal n.

Brunklaus and Lal, DMCN 2020
Variant location as surrogate for function

Mosaicism of de novo pathogenic SCN1A variants in epilepsy is a frequent phenomenon that correlates with variable phenotypes

Iris M. de Lange¹ | Marco J. Koudijs¹ | Ruben van ’t Slot¹ | Boudewijn Gunning²

Key Points

- Mosaicism is present in 7.5% of symptomatic patients with de novo pathogenic SCN1A variants
- Patients with mosaicism of truncating variants have on average milder phenotypes than patients with heterozygous truncating variants, which makes mosaicism an important modifier in SCN1A-related phenotypes
- Detection of mosaicism has important implications for genetic counseling and can be achieved by deep sequencing of unique reads

Appropriate treatment is important

- Early contraindicated medication use has negative impact on cognitive outcome in Dravet syndrome

Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group
C Chiron, M C Marchand, A Tran, E Rey, P d

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome
Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D.,

Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial
Lieven Lagae, Joseph Sullivan, Kelly Knupp, Linda Laux, Tilman Polster

First line
Diagnosis clear and continuing seizures

Second line
(evidence based RCT)

Alternatives for second line

Broad spectrum ASM: Valproate
Valproate + stiripentol +/- clobazam
Or add-on Cannabidiol
Or add-on Fenfluramine (approval conditional)

Ketogenic diet
Clobazam
Topiramate
Bromide
Vagal nerve stimulation

Genotype-phenotype Treatment Considerations

A single-center, retrospective analysis of genotype-phenotype correlations in children with Dravet syndrome

Tracy S Gertler¹, Jeffrey Calhoun², Linda Laux³

► 137 Dravet syndrome patients with pathogenic SCN1A variants subdivided by missense or truncating variant

► Response to antiepileptic therapies did not differ by genotype with regard to medication class.

► Need for prospective natural history data to evaluate treatment effects on seizure burden and development
Future opportunities for precision treatment

1. Viral-delivery: non-AAV
2. Viral-delivery: Two AAV
3. AntagoNAT
4. Antisense oligonucleotide

Ana Mingorance, Dracaena consulting
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University College London, UK
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