Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications

SCN8A unraveled

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Before we begin

Nav1.6 sodium channels
Before we begin

N. Jacob. Drug targets: ligand and voltage gated ion channels
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Before we begin

Patch-Clamp Electrophysiology Assay

1. Prepare bath solution for patching
2. Add neuron cells in bath solution
3. Set up the perfusion system
4. Patch a cell
5. Signal acquisition
6. Data analysis

Loss of function    Gain of function

Created with BioRender.com
Aim of the study

- We know that both gain of function (GOF) and loss of function (LOF) of the SCN8A channel exists
- Thus, we wanted to investigate if there are clinical differences in patient with GOF vs. LOF variants
- This is important for treatment options currently available, such as sodium channel blockers
- This will also be important when drugs specifically for either GOF or LOF variants hits the market, as functional studies are not readily available for all patients
- Clinical markers can then be used to make a qualified guess as to whether a variant is GOF or LOF
Methods

- Descriptive study using data from individuals worldwide. Mainly Europe, US and Australia
- Collaborators from epilepsy centers, pediatricians and geneticists.
- Potential bias towards individuals with epilepsy
- Data from all previously published individuals (PubMed search, only papers in English included)
- In total 392 individuals (91 unpublished)
Methods

Seizure types

Focal seizure types and EEG
- Normal cognition
  - BFIE
    - Normal cognition / mild ID with treatment refractory seizures or moderate ID with treatable seizures
- Cognitive disability
  - Intermediate epilepsy
  - DEE

Generalized seizure types and EEG
- Generalized epilepsy
- Moderate to severe ID + treatment refractory seizures
  - DEE

Both focal and generalized seizure types and EEG or insufficient data
- Unclassifiable epilepsy
Methods
Results

A. Total (n = 392)

B. LOF (n = 34)

C. GOF (n = 136)

- Focal epilepsy (FE):
  - BFIE
  - Intermediate epilepsy (IE)
  - DEE

- Generalized epilepsy (GE)
- Unclassifiable epilepsy (UE)
- NDD without epilepsy
# Results

<table>
<thead>
<tr>
<th></th>
<th>BFIE</th>
<th>Intermediate epilepsy</th>
<th>DEE</th>
<th>Generalized epilepsy</th>
<th>Neurodevelopmental disorder without epilepsy</th>
<th>LOF</th>
<th>GOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>15</td>
<td>33</td>
<td>177</td>
<td>20</td>
<td>20</td>
<td>34</td>
<td>136</td>
</tr>
<tr>
<td>Percentage with epilepsy</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>Median age at seizure onset</td>
<td>6 months</td>
<td>5 months</td>
<td>3 months</td>
<td>42 months</td>
<td>-</td>
<td>24 months</td>
<td>4 months</td>
</tr>
<tr>
<td>Most common seizure types</td>
<td>Focal, focal to bilateral TC and bilateral TC</td>
<td>Focal, bilateral TC and tonic</td>
<td>Bilateral TC, focal and tonic</td>
<td>Absences, bilateral TC and febrile seizures</td>
<td>-</td>
<td>Absence seizures, bilateral TC and myoclonic seizures</td>
<td>Bilateral TCs, tonic and focal</td>
</tr>
<tr>
<td>Phenotype subgroups</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GE 41%</td>
<td>NDDwoE 32%</td>
</tr>
<tr>
<td>Cognition</td>
<td>Normal 100%</td>
<td>Normal 33%</td>
<td>Mild ID 52%</td>
<td>Moderate ID 15%</td>
<td>Moderate ID 22%</td>
<td>Severe ID 73 %</td>
<td>Unknown 5 %</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Paroxysmal kinesigenic dyskinesia</td>
<td>Language delay, behavioral issues</td>
<td>Hypotonia, CVI, ataxia</td>
<td>Language delay, behavioral issues</td>
<td>Behavioral disorders (ASD, ADHD), delayed speech, microcephaly</td>
<td>Language delay, autism, behavioral issues, ataxia</td>
<td>Hypotonia, CVI, dyskinesia, ataxia</td>
</tr>
<tr>
<td>Mortality</td>
<td>0%</td>
<td>0%</td>
<td>10.2%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Precision medicine</td>
<td>Sodium-channel blockers</td>
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<td>Sodium-channel blockers</td>
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</tr>
</tbody>
</table>

![Syddanskuniversitet.dk](https://filadelfia.com/Syddanskuniversitet.dk)
Results

BFIE + Intermediate + DEE vs GE
Median age of seizure onset: 4m vs 42m

GOF vs LOF
Median age of onset: 4m vs 24m
Results
Thank you and questions

See you next year in Denmark?