GABAAR

Sebastian Ortiz MD

Pediatric Neurologist – Pediatric Epileptologist

No conflicts of interest to declare in this presentation

GABA A

ALLIANCE

AGENDA

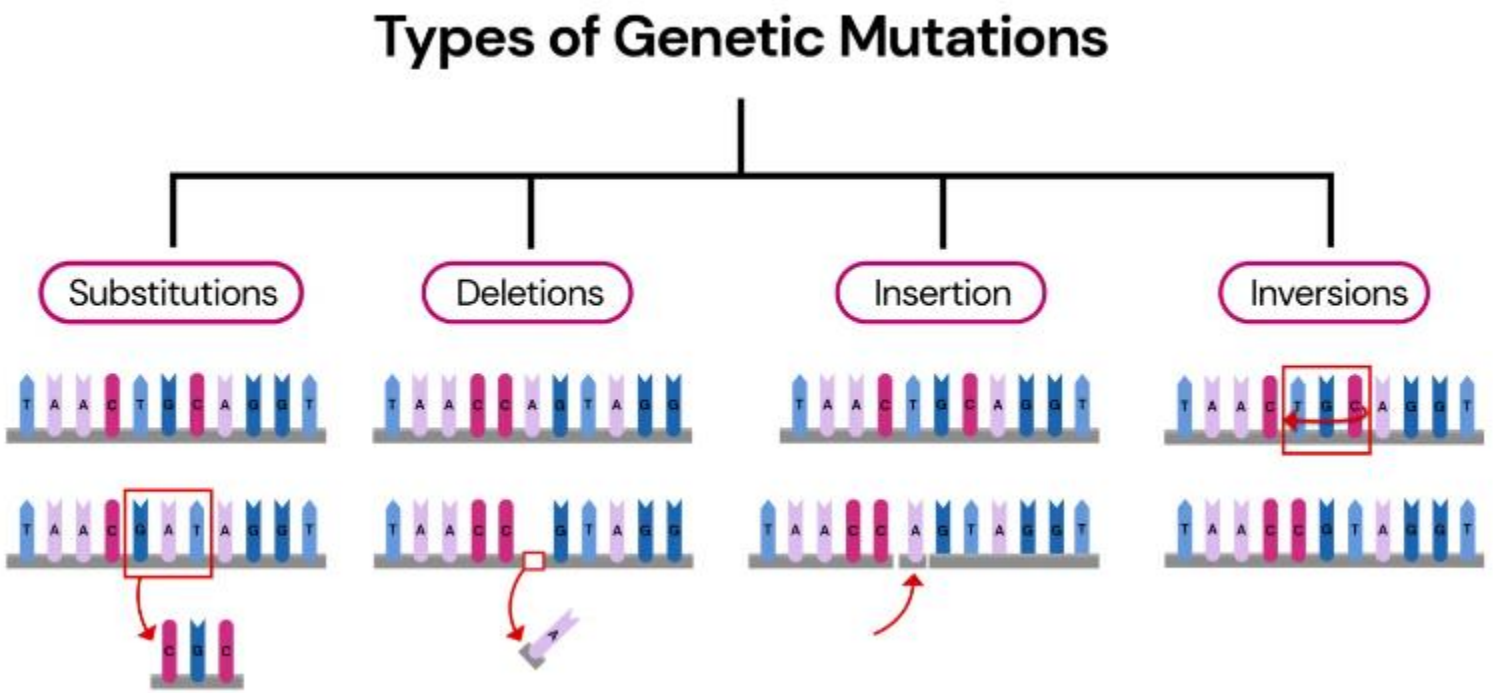
- Overview of GABA receptors and their physiological properties
- What is a variant
- What variants are there
- Clinical overview of patients with GABAAR variants
- What is the functional testing of the variant?
- Research projects
- Questions

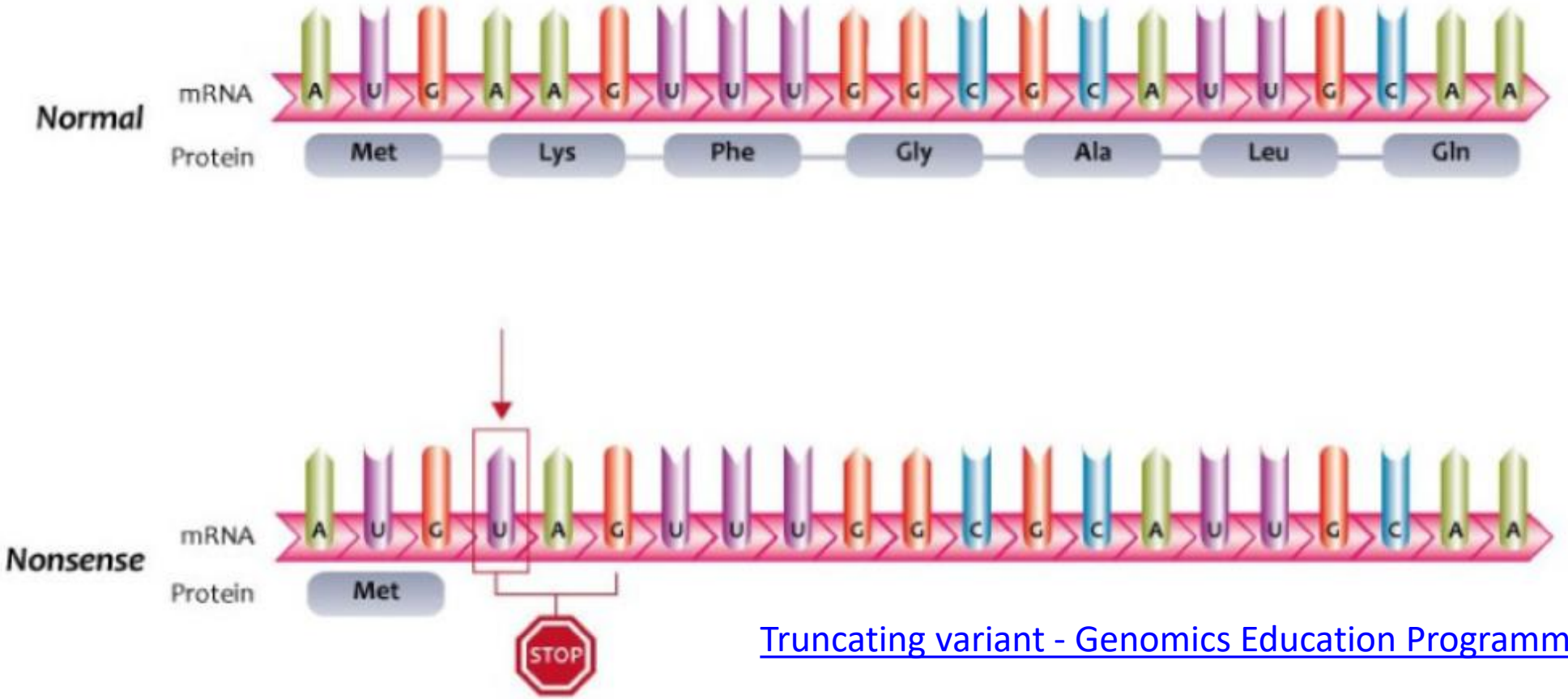
OVERVIEW OF GABA-AR AND GABA

- There are two kinds of inhibition via GABA receptors:
  - Ligand gated Ionotropic channel that mantains Excitatory/Inhibitory balance through synaptic inhibition (***Phasic*** inhibition)
  - Extra-synaptic ***tonic*** inhibition.

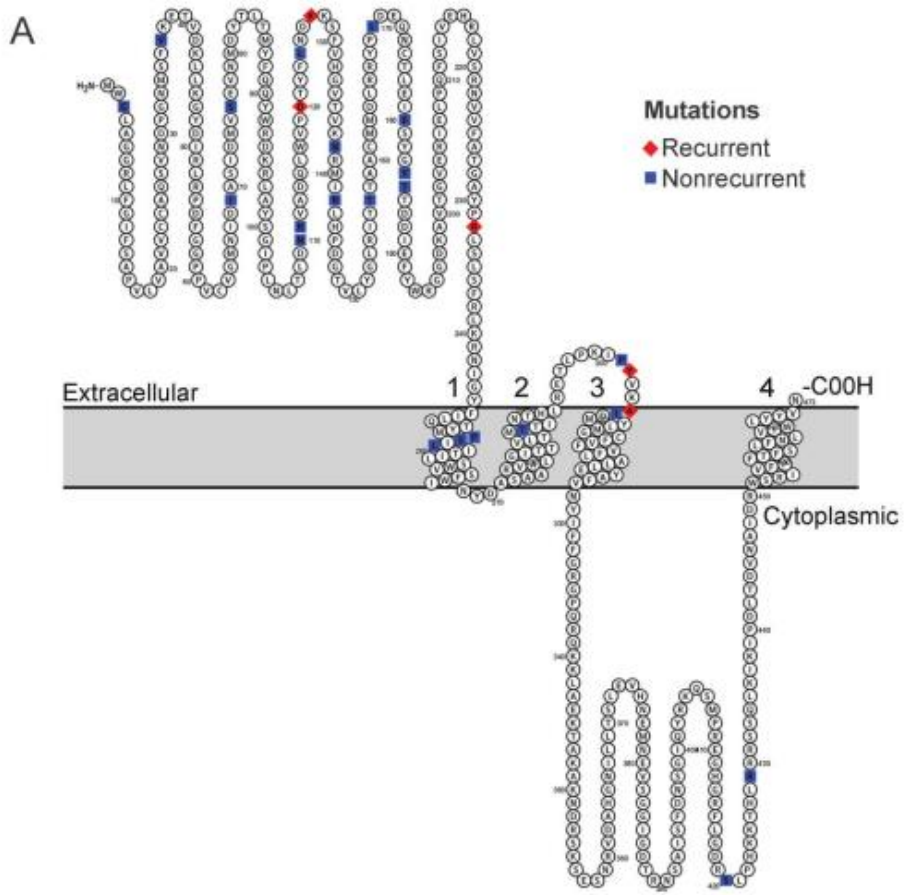
- GABA neurotransmitter
  - Produced via L-Glutamate descarboxylase expressed and produced in GABAergic inhibitory interneurons and astrocytes

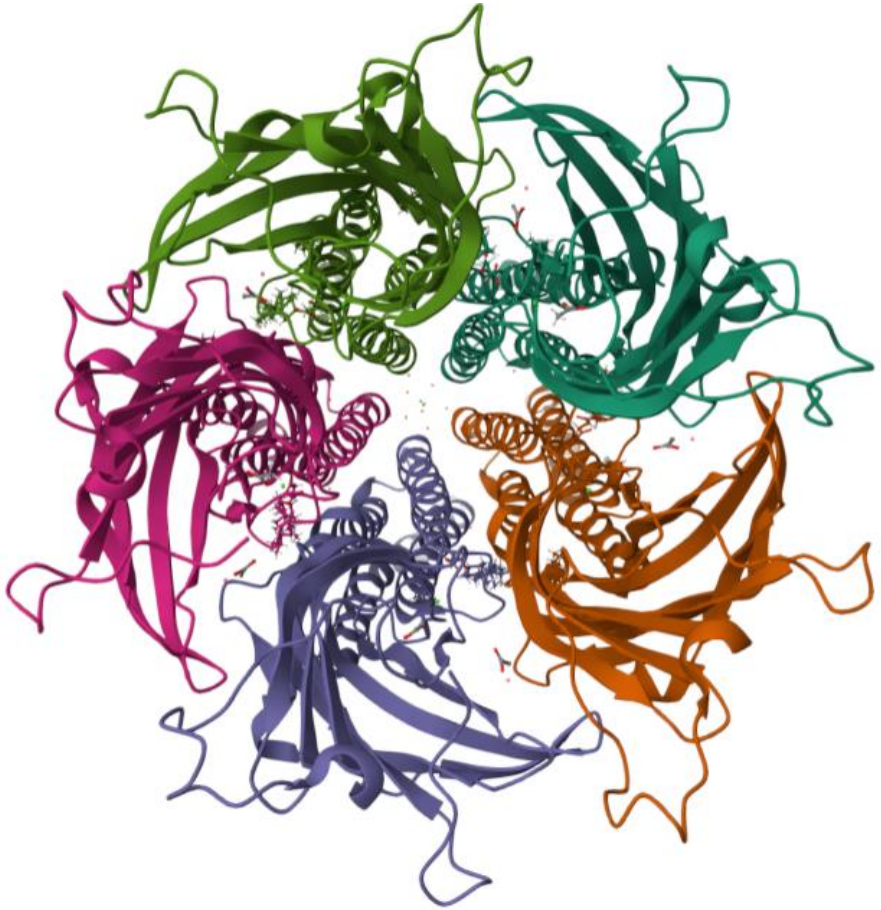
What Is The Ultimate Source Of Genetic Variation? (xcode.life)





[Truncating variant - Genomics Education Programme (hee.nhs.uk)]





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ARTICLE

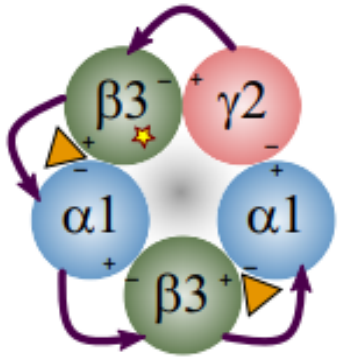
https://doi.org/10.1038/s41467-022-29280-x OPEN

Gain-of-function and loss-of-function *GABRB3* variants lead to distinct clinical phenotypes in patients with developmental and epileptic encephalopathies

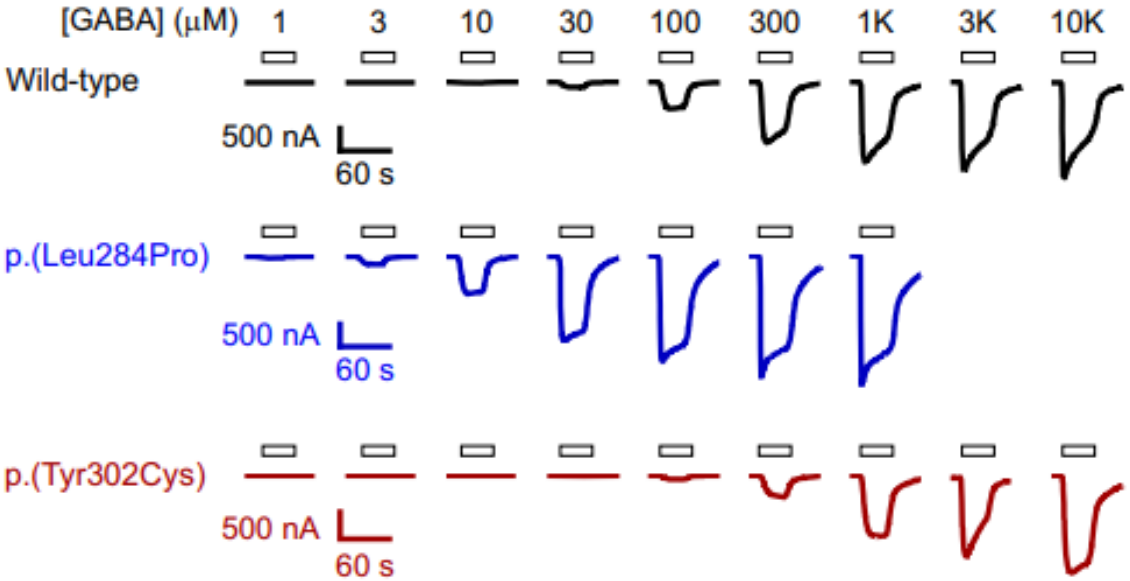
Nathan L. Absalom[1,17,18], Vivian W. Y. Liao[1,18], Katrine M. H. Johannesen[2,3], Elena Gardella[2,3], Julia Jacobs[4,5,6], Gaetan Lesca[7,8], Zeynep Gokce-Samar[9], Alexis Arzimanoglou[9], Shimriet Zeidler[10], Pasquale Striano[11,12], Pierre Meyer[13], Ira Benkel-Herrenbrueck[14], Inger-Lise Mero[15], Jutta Rummel[16], Mary Chebib[1], Rikke S. Møller[2,3]✉ & Philip K. Ahring[1]✉

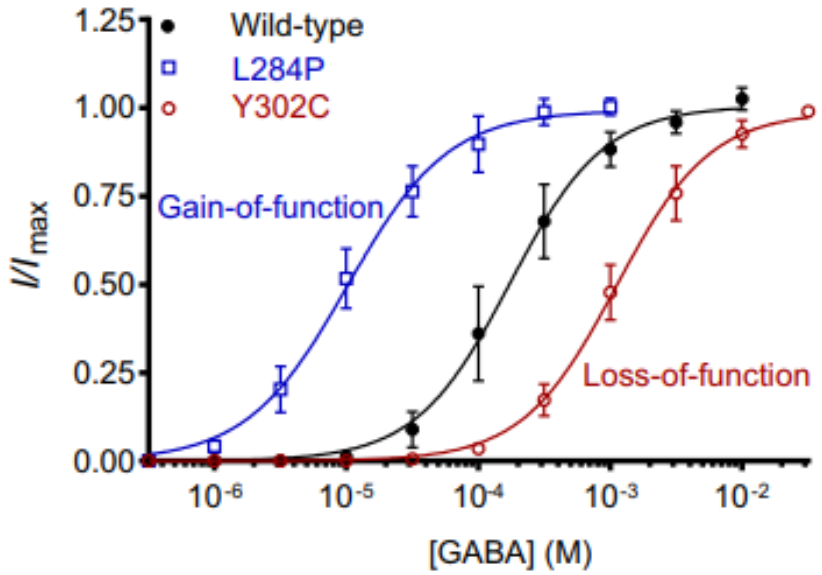
a Concatenated receptor design

cDNA construct where four linkers (L) connect the five subunits in a $\alpha1\beta3\gamma2$ pentamer
Variant β3 subunits are introduced in the second position (heterozygous receptors)



b Electrophysiological recordings of representative *GABRB3* variants





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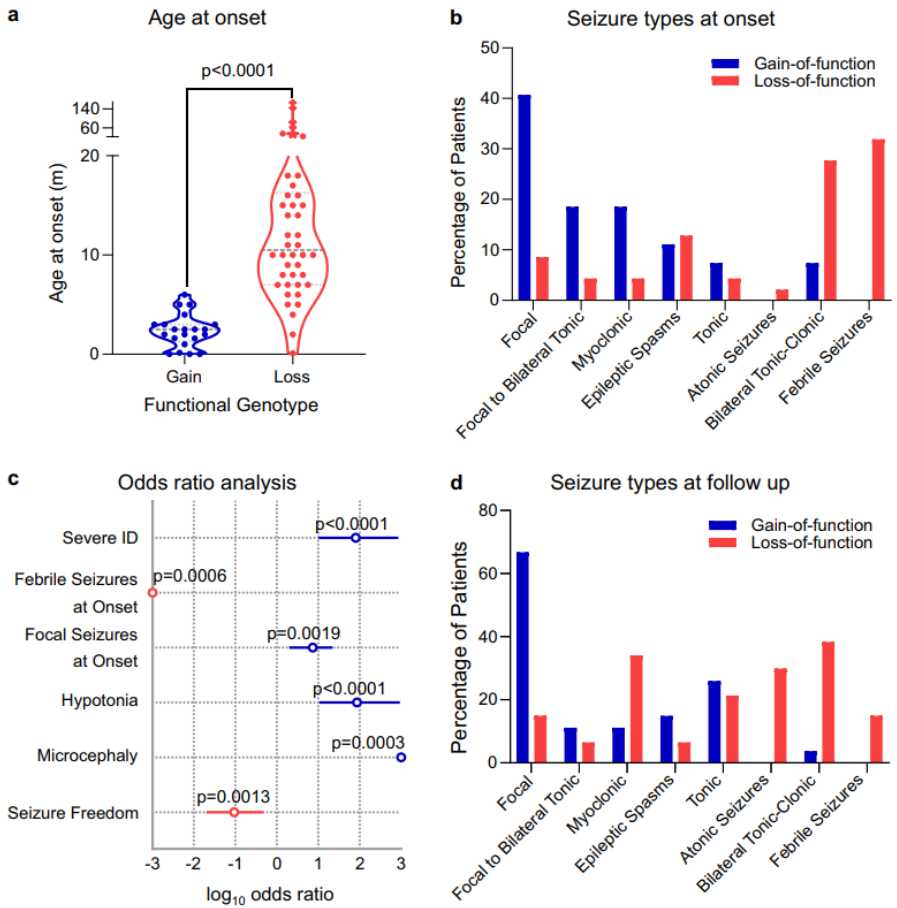
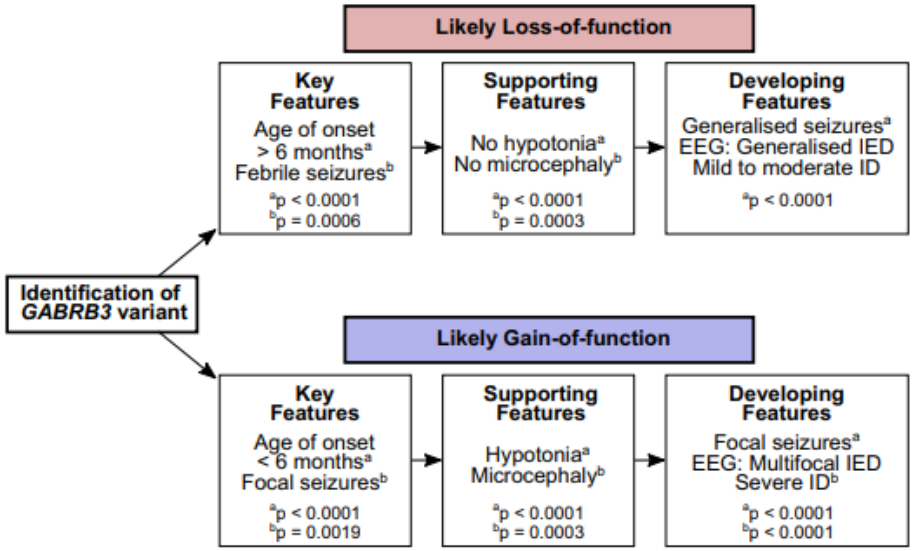


Clinical indicators for predicting gain- and loss-of-function *GABRB3* variants



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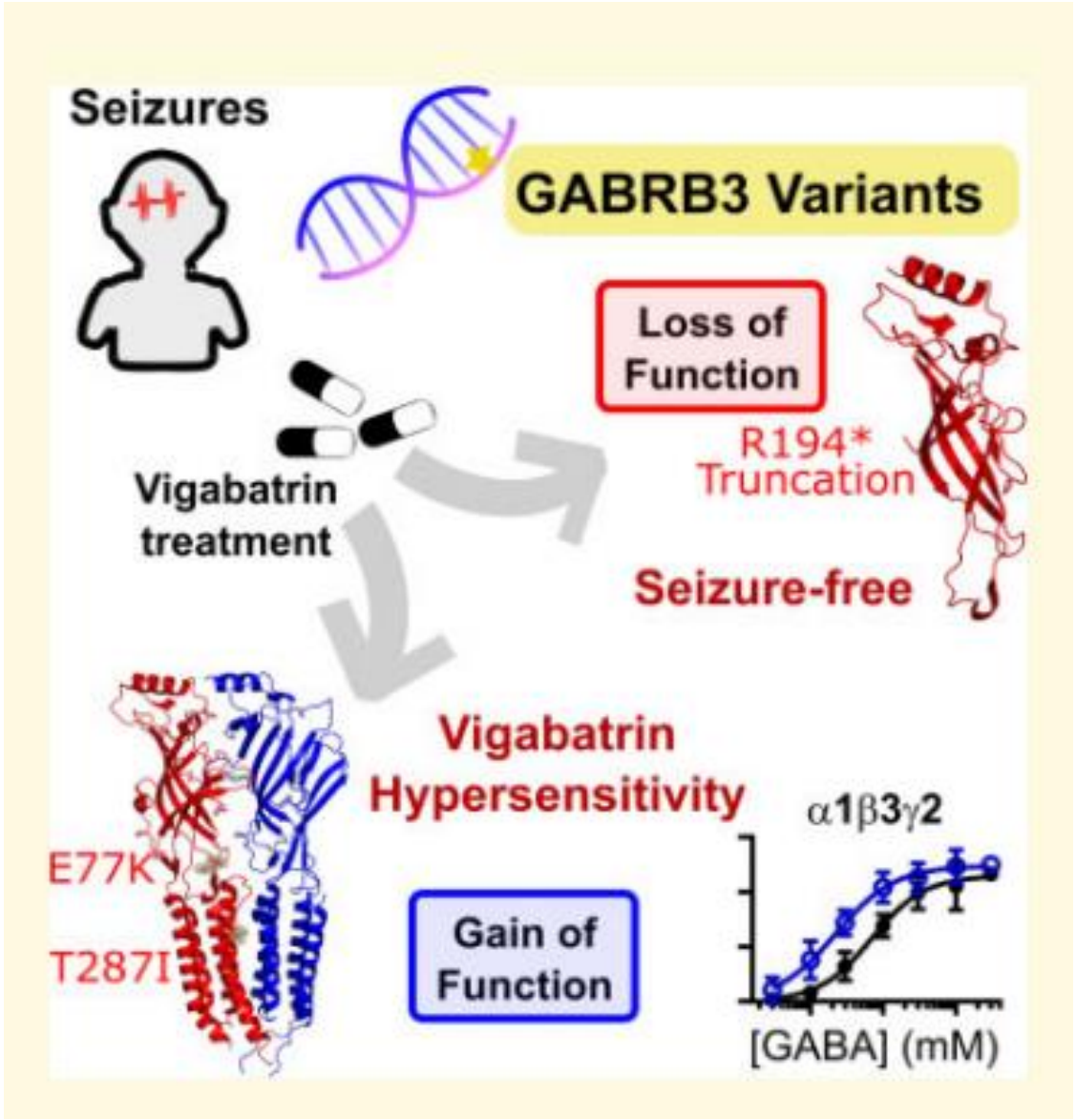
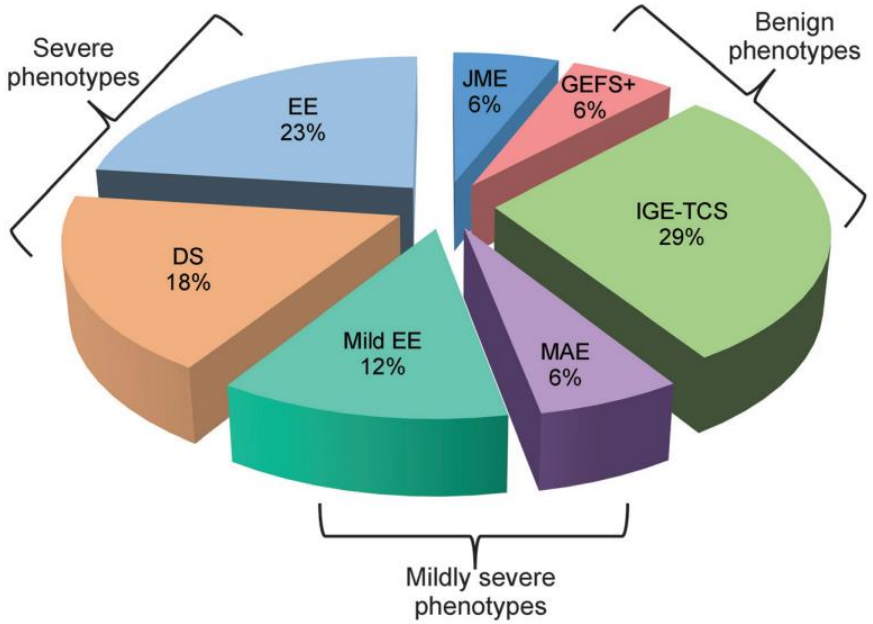
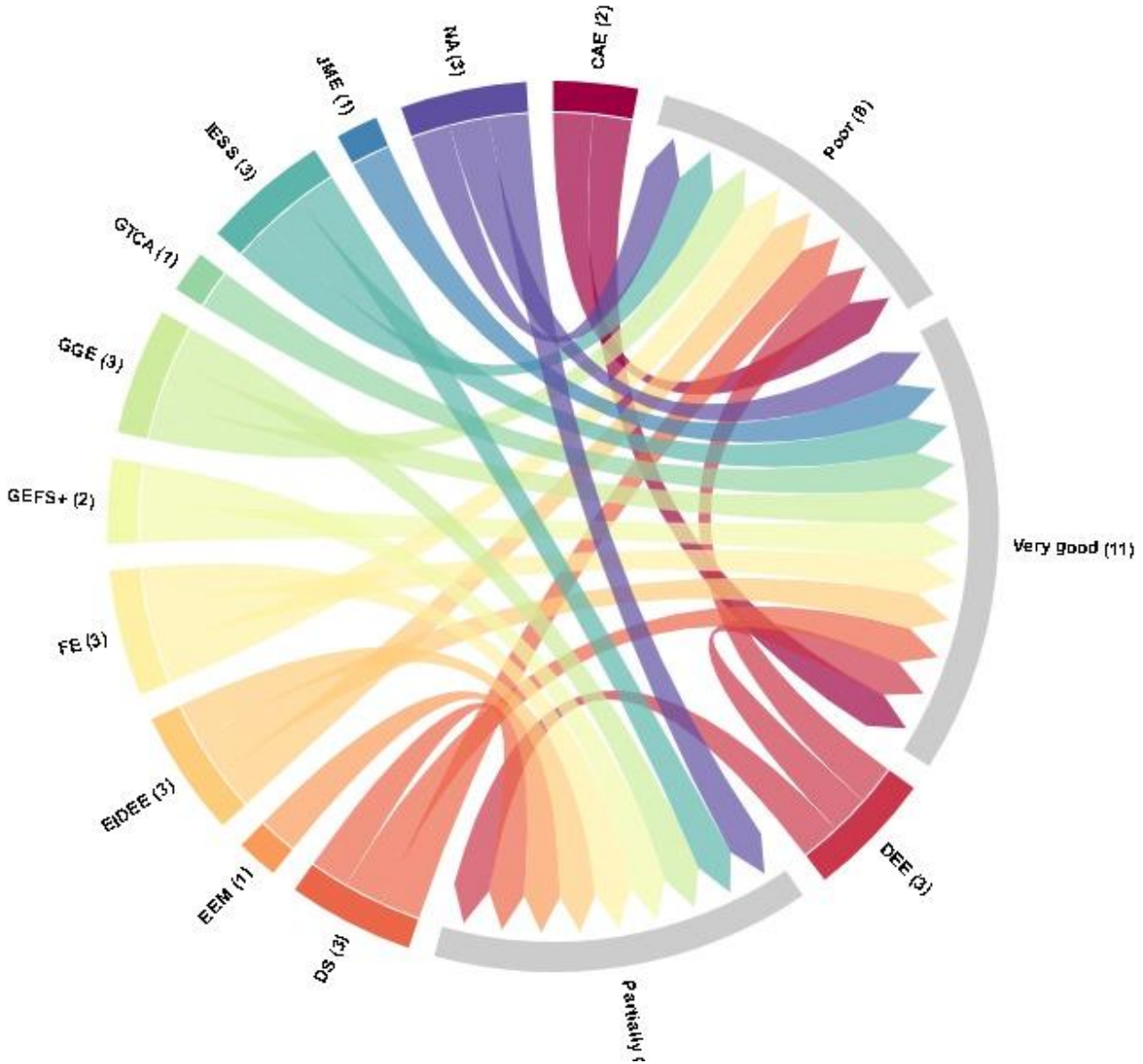

Seizures
GABRB3 Variants
Loss of Function
R194* Truncation
Seizure-free
Vigabatrin treatment
Vigabatrin Hypersensitivity
E77K
T287I
Gain of Function
α1β3γ2
[GABA] (mM)

Phenotypic spectrum of *GABRA1*

From generalized epilepsies to severe epileptic encephalopathies





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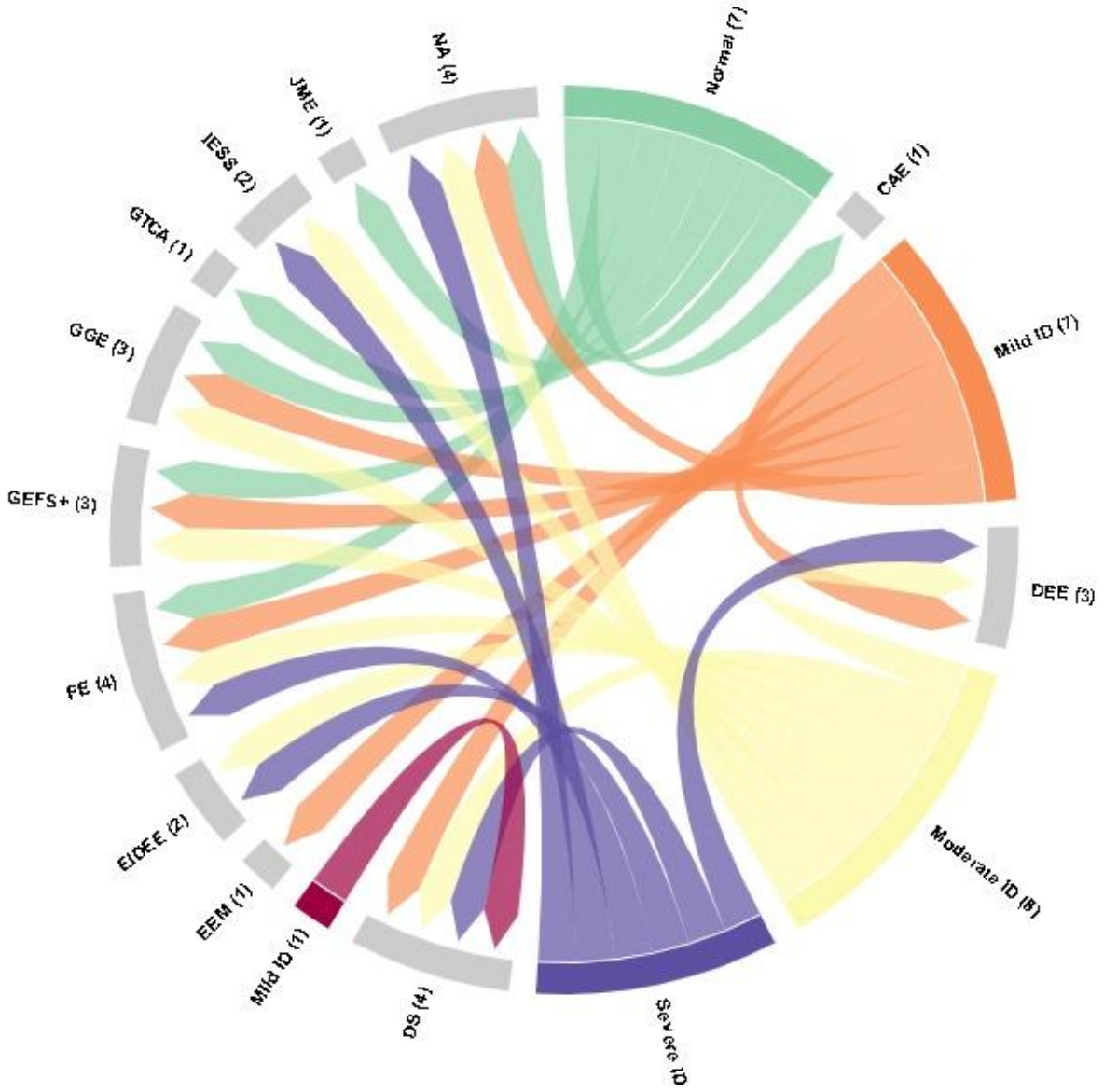
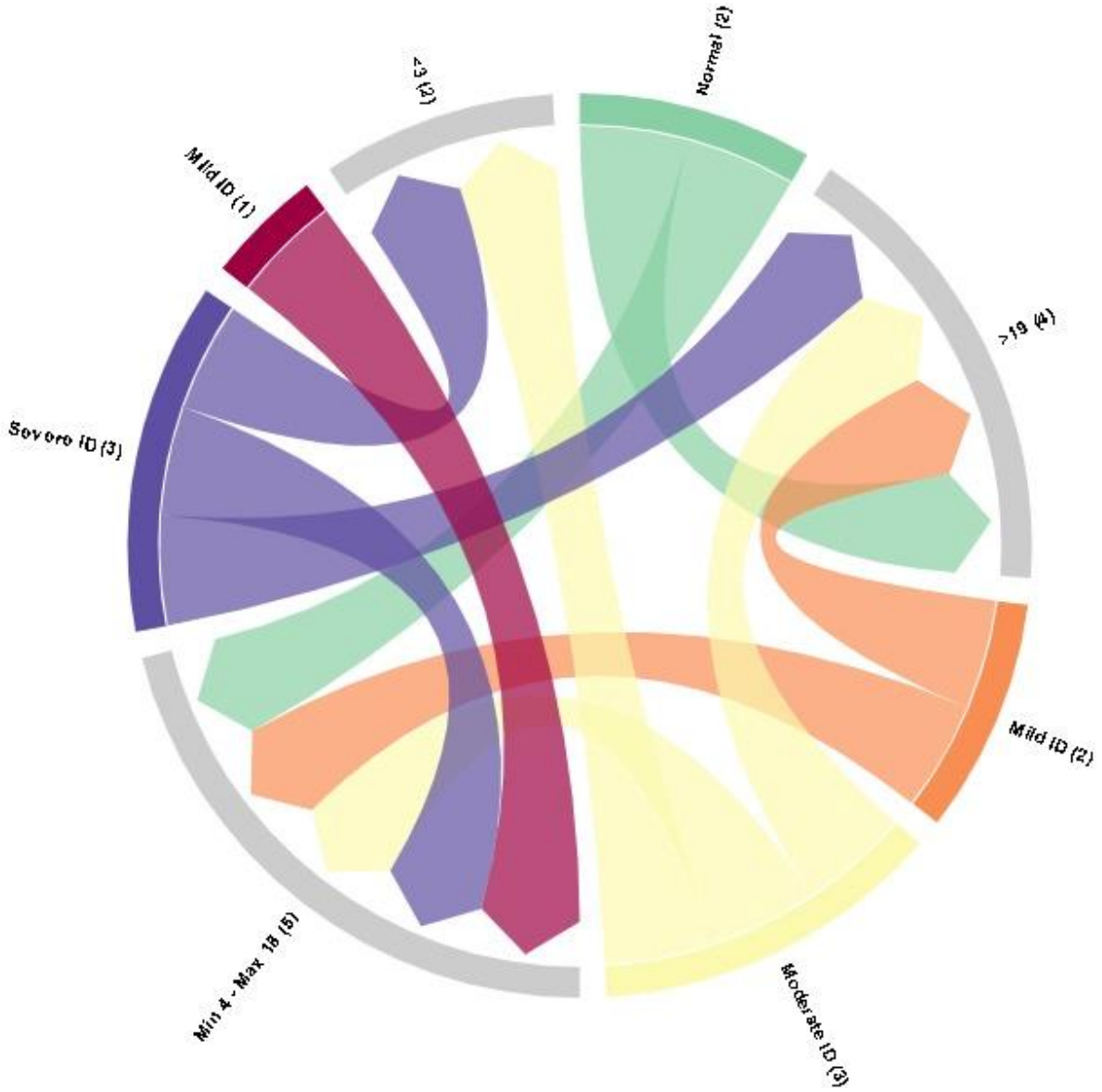
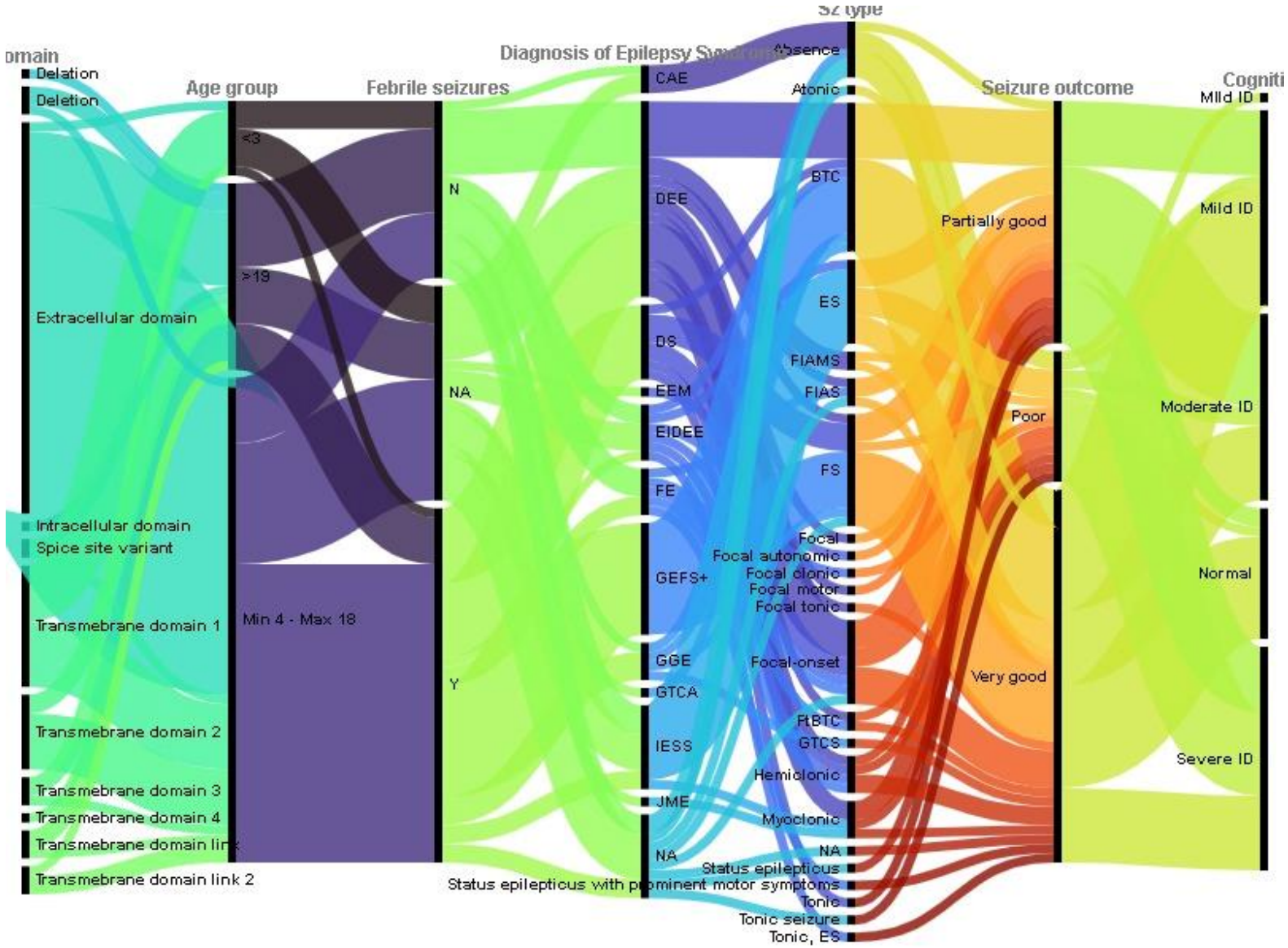

Normal (7)
CAE (1)
Mild ID (7)
DEE (3)
Moderate ID (8)
Severe ID
DS (4)
Mild ID (1)
EEM (1)
EIDEE (2)
FE (4)
GEFS+ (3)
GGE (3)
GTCA (1)
IESS (2)
JME (1)
NA (4)


Normal (2)
<3 (2)
Mild ID (1)
>19 (4)
Severe ID (3)
Mild ID (2)
Min 4 - Max 18 (5)
Moderate ID (3)



QUESTIONS/DISCUSSION

seor@filadelfia.dk

@sebasortizdelar

Ongoing research projects

- To develop animal models to test possible treatments.
- Study disease networks in organoids
- Perform functional testing for all diagnosed variants.
- Establish the movement disorders spectrum.
- Determine the incidence/prevalence of sleep-related problems.
- Explore EEG fingerprints
- Describe the best treatments in the known population
- Suggestions?

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Aledo-Serrano, *et al.* Neurotherapeutics, 2022

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