Rigshospitalet
Afdeling for Genetik

$GABA_A$-related disorders
Including *GABRB3*

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A bit about me

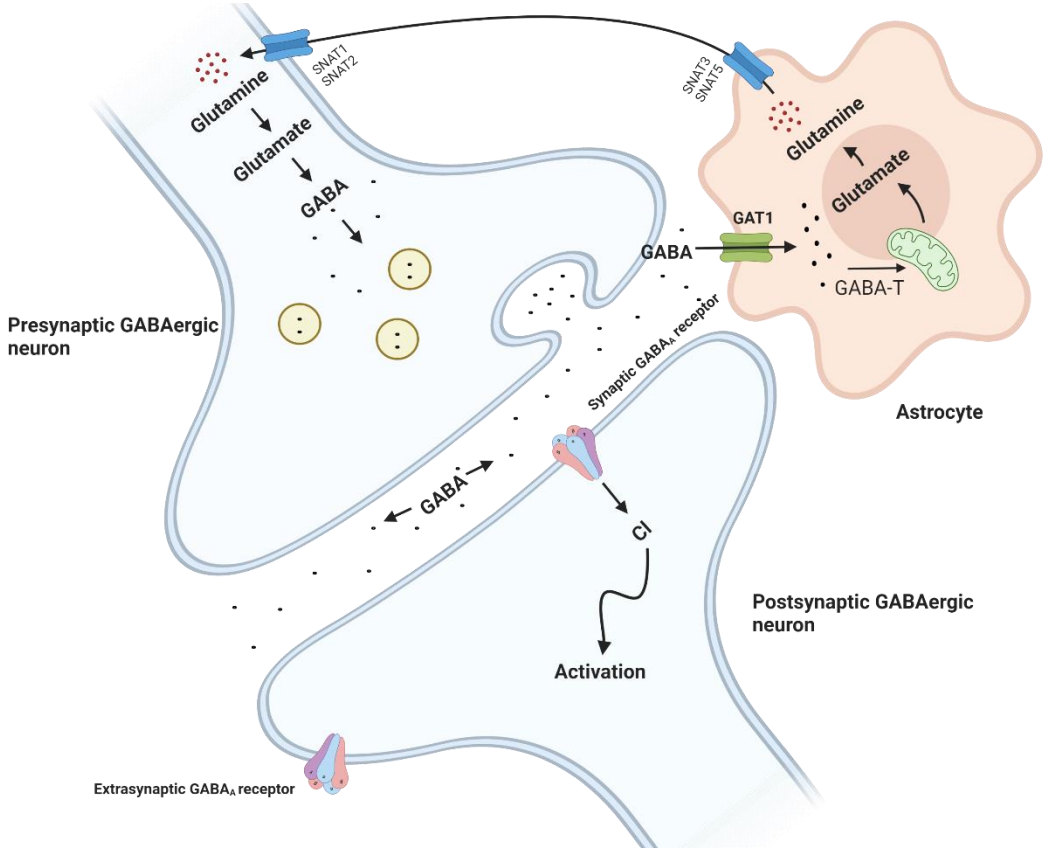
- MD, PhD
- PhD in epilepsy genetics from the Danish Epilepsy Centre
- Current research focus: GABA-related disorders, including *GABRB3, GABRA1, GABRA3, GABRA5, GABRB2, GABRG2, GABRA2* etc.
- Working to become a clinical geneticist at the University Hospital of Copenhagen

LUNDBECKFONDEN

Vocabulary

- **Phenotype**: the clinical presentation of a patient. The seizure types, cognitive skills, motor development etc.
- **Genotype**: the genetics of a patient. Variant type (missense, nonsense or others), the inheritance of the variant (*de novo*, maternal, paternal) and the exact variant: c.123A<G, p.(Arg346Cys), *de novo*
- **Variant:** Genetic mutation / spelling error in a gene
    - *Please ask if unclear!*

GABA in the human brain

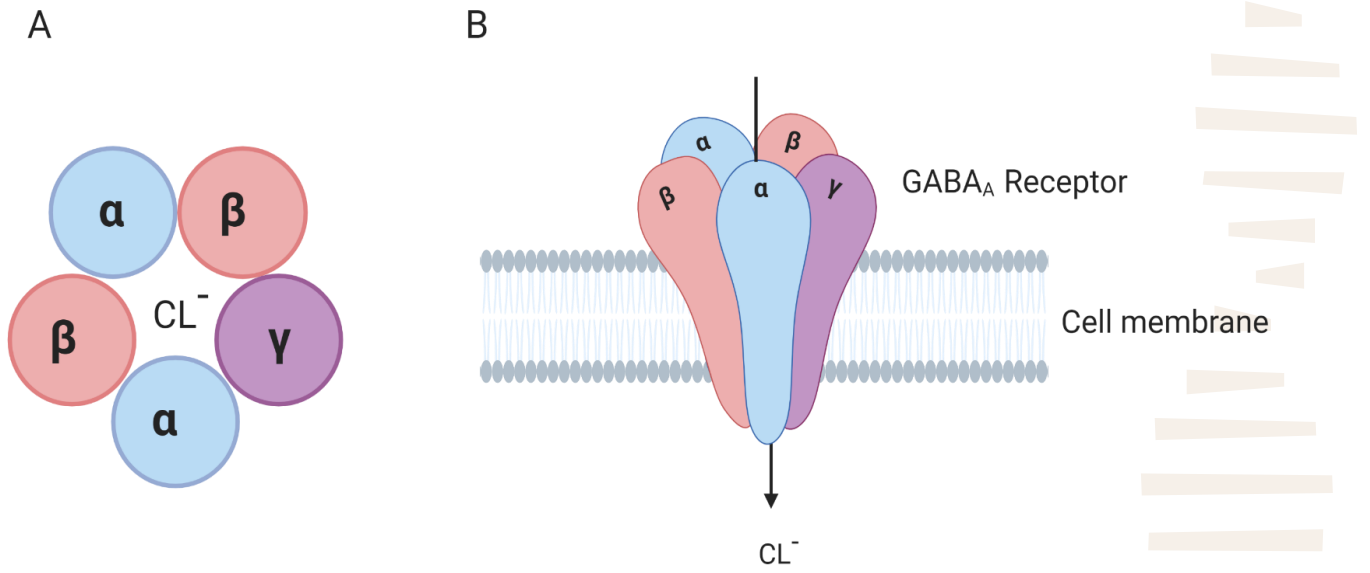


Created with BioRender.com

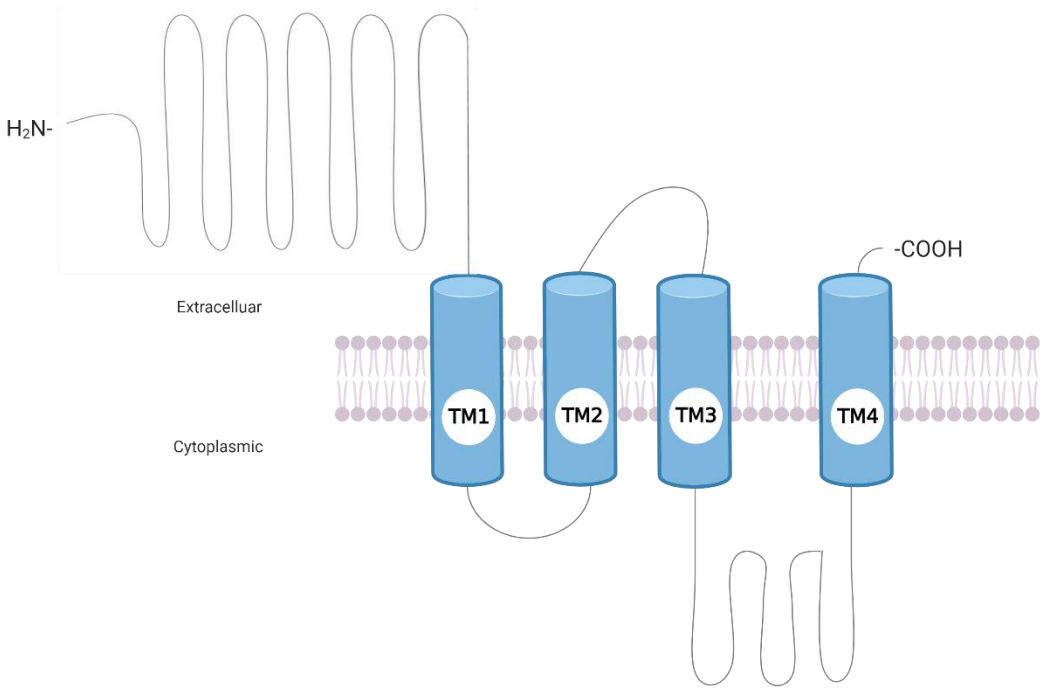
- GABA is the most important inhibitoric neurotransmitter in the brain. Used in 1/3 of all neuronal synapses.
- $GABA_A$ receptors forward these inhibitory signals.

$GABA_A$ receptors

- Pentameric receptors
- More than 19 different subunits, some more common than others
- Subunit composition differs dependent on receptor localization



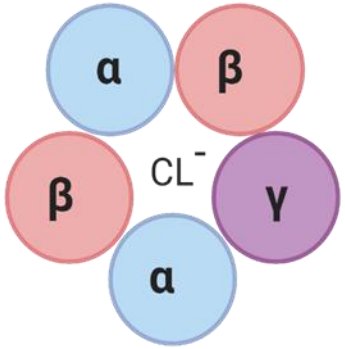
$GABA_A$ receptor genes



Paraloge genes.

Four transmembrane domains.

TM2 and TM3 constitute ”the inside” of the channel.



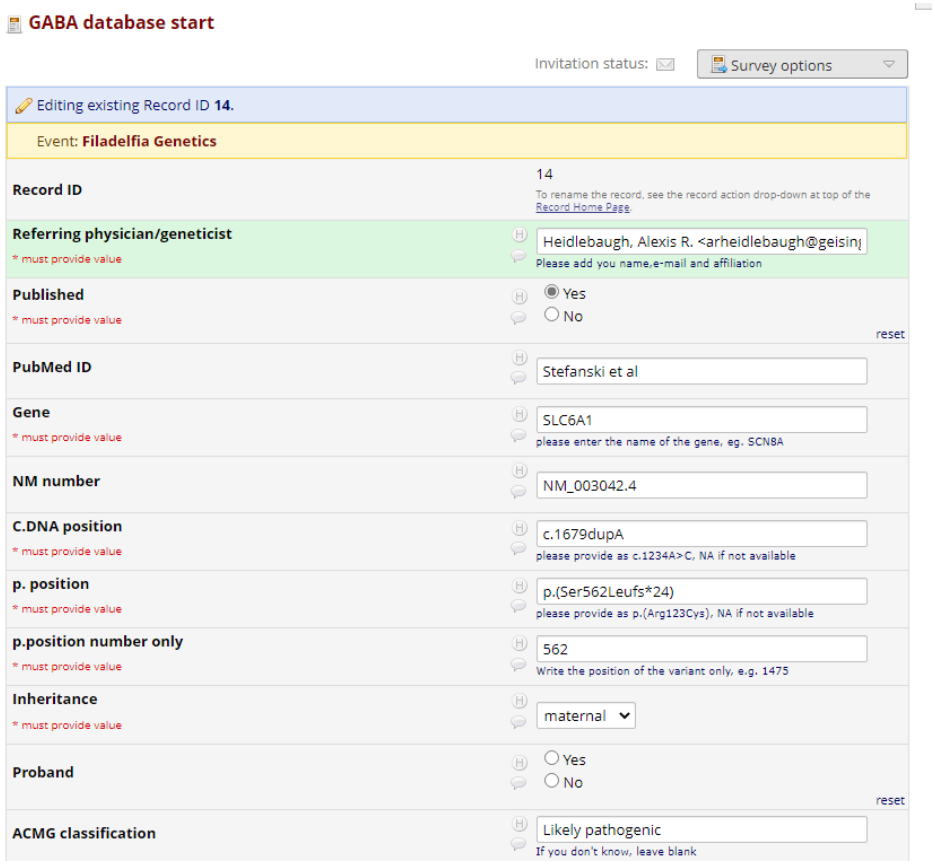
GABRB3 – a case presentation

- 3-year-old boy with developmental and epileptic encephalopathy (DEE)
- Hypotonia and severe developmental delay
- Seizures began at three months of age
- Refractory epilepsy with 10-20 seizures daily, several different seizure types, such as focal, myoclonic and atonic seizures
- Treatment tried: levetiracetam, ketogenic diet, vigabatrin (which caused severe hypotonia, somnolence, respiratoric distress)
- EEG showed a multifocal pattern
- *De novo* variant in *GABRB3*

GABRB3 – a case presentation

- 12-year old girl with genetic generalized epilepsy (GGE)
- Normal development
- Seizures began at 12 months
- Seizures were febrile seizures and later also atonic and myoclonic-atonic seizures
- EEG showed generalized spike and slow waves
- Treated with a valproate, seizure free since 18 months
- Has learning difficulties
- *De novo* variant in *GABRB3*

Metods - Patients


GABA database start

Invitation status: Survey options

Editing existing Record ID 14.

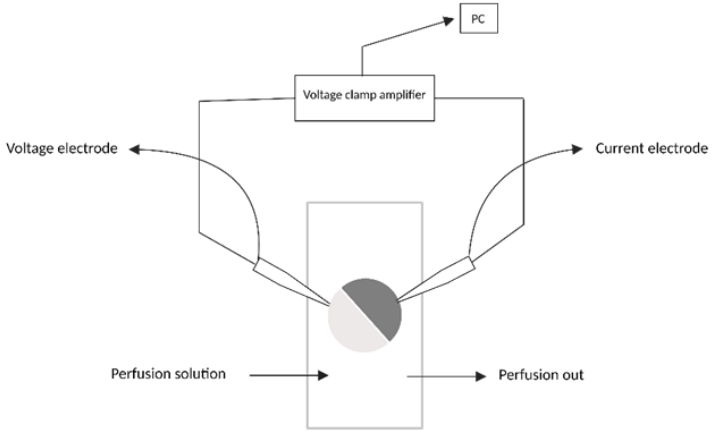
Event: Filadelfia Genetics

Record ID	14 To rename the record, see the record action drop-down at top of the Record Home Page.
Referring physician/geneticist * must provide value	Heidlebaugh, Alexis R. <arheidlebaugh@geisin Please add you name,e-mail and affiliation
Published * must provide value	Yes No reset
PubMed ID	Stefanski et al
Gene * must provide value	SLC6A1 please enter the name of the gene, eg. SCN8A
NM number	NM_003042.4
C.DNA position * must provide value	c.1679dupA please provide as c.1234A>C, NA if not available
p. position * must provide value	p.(Ser562Leufs*24) please provide as p.(Arg123Cys), NA if not available
p.position number only * must provide value	562 Write the position of the variant only, e.g. 1475
Inheritance * must provide value	maternal
Proband	Yes No reset
ACMG classification	Likely pathogenic If you don't know, leave blank

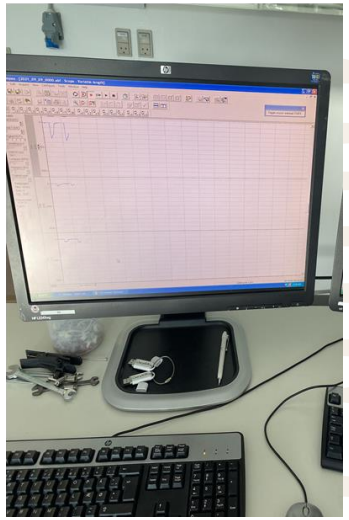
- Patient data collected internationally through:
  - Existing clinical network
  - GeneMatcher
  - Patient organizations / facebook

Metods – functional analysis

- GABA sensitivity in missense variants
- Using frog eggs!
- Done at our collaborating lab in Sydney

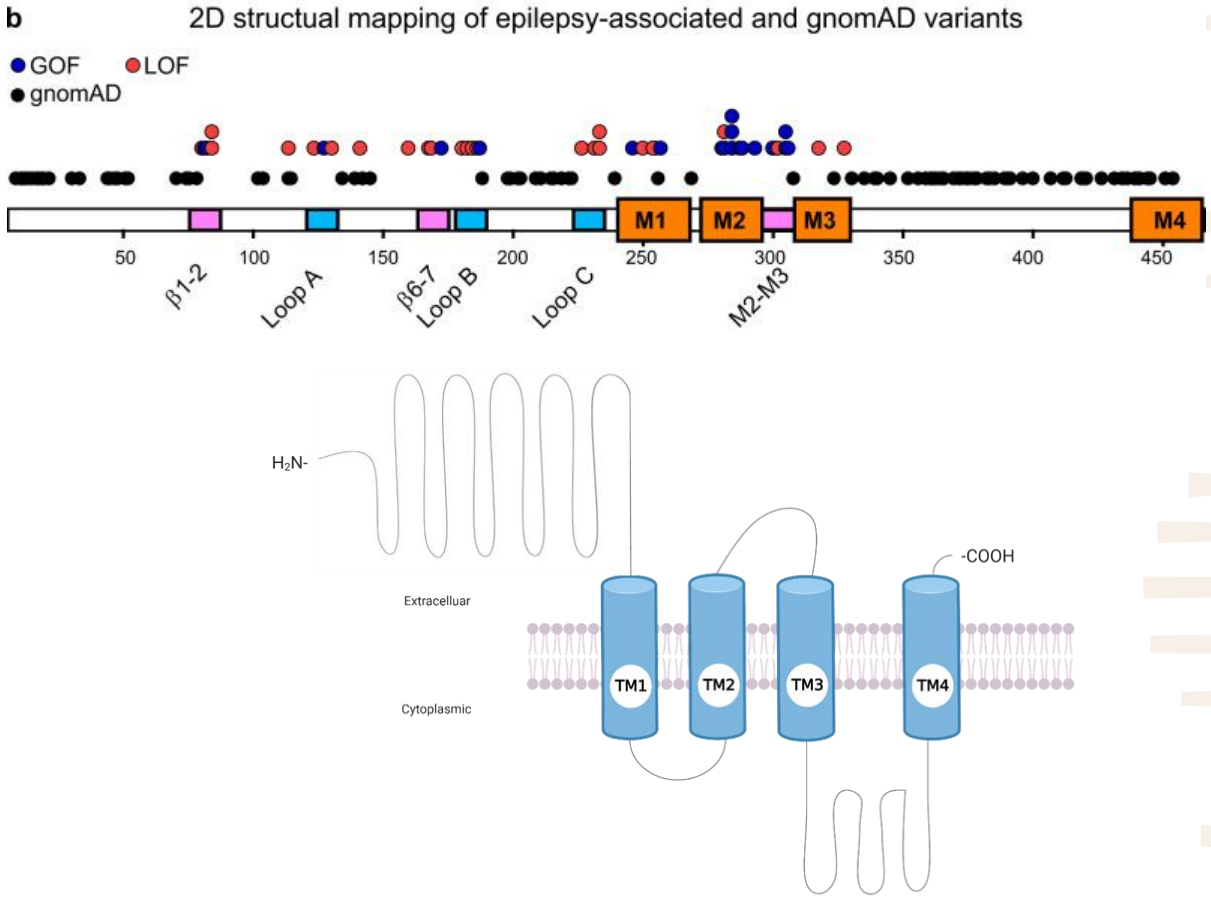


Schematic illustration of two electrode voltage clamp. The Figure is created with Biorender.com



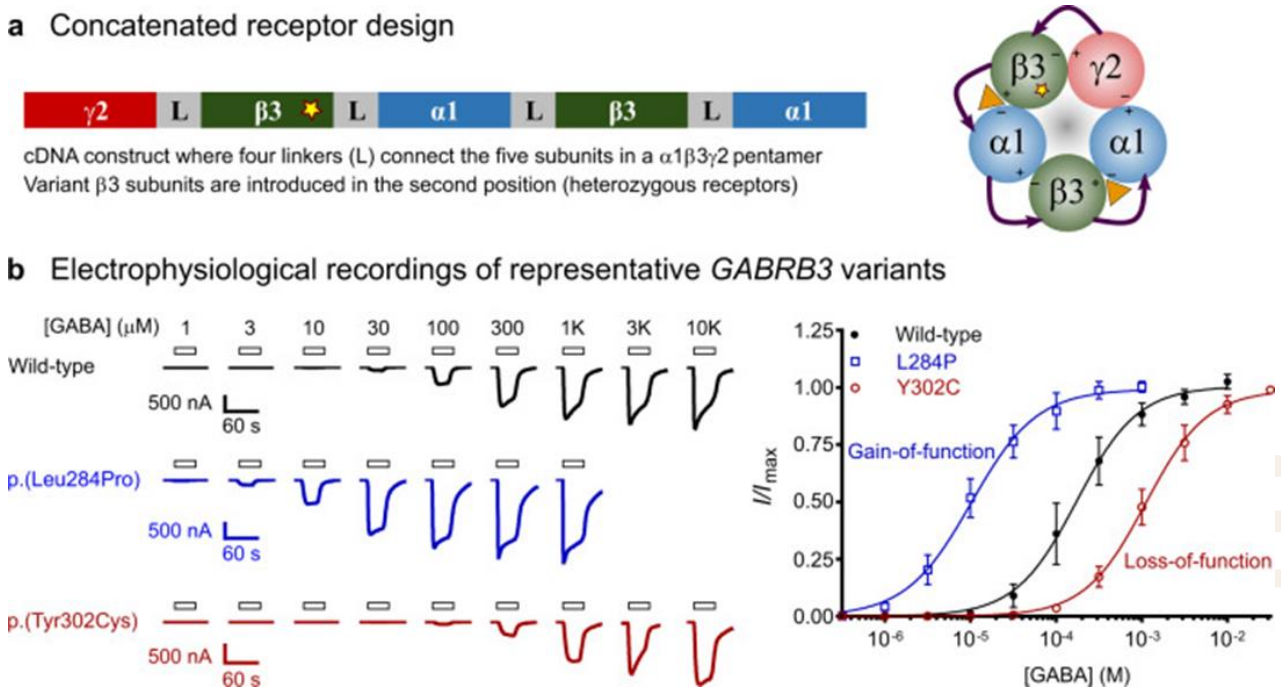
GABRB3 project

- Dominant disorder
- 85 patients in the project (current number 138)
  - = 54 different genetic variants
- Both *de novo* and inherited variants
- Large spread in phenotype
  - Seizure onset ranged from 0 to 14 years!
  - Seizure types were diverse



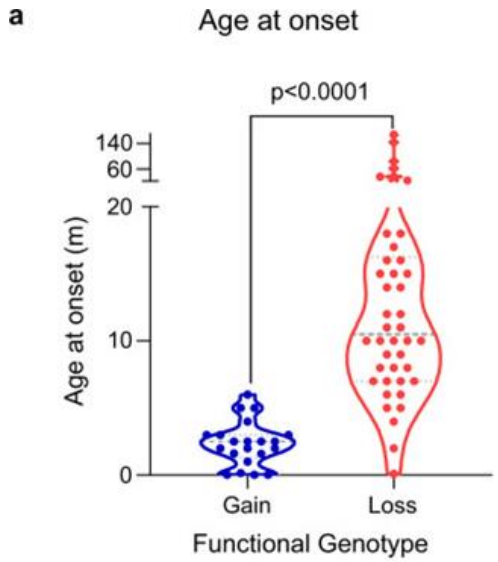
GABRB3 project

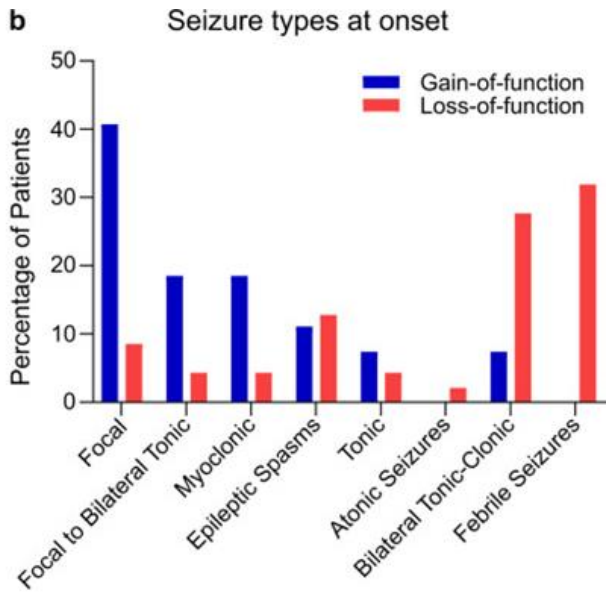
- Functional studies in missense variants showed:
  - gain of function = increased activity of the receptor
  - loss of function = decreased activity of the receptor
  - no change = similar to wildtype receptors

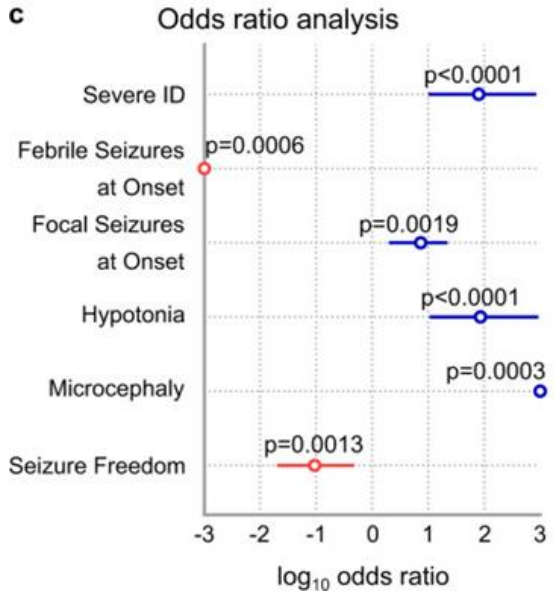


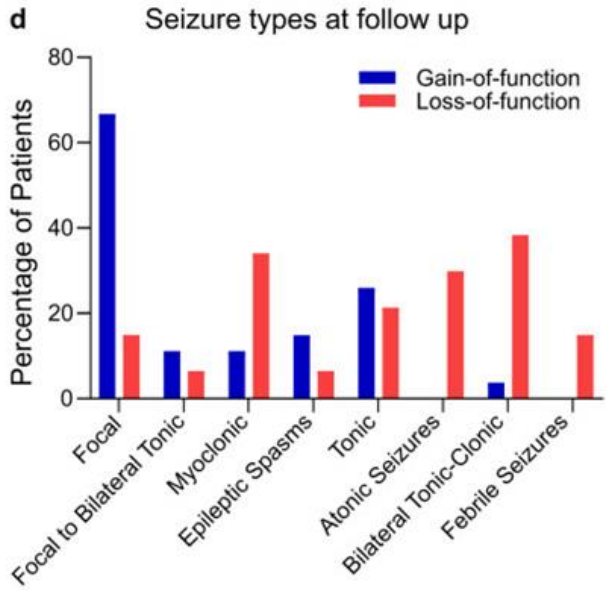
GABRB3 project

- Correlation between functional outcome and phenotype









GABRB3 project

Patients with gain of function variants:

- First seizure at 2.5 months of age
- Seizure types: focal seizures, focal to bilateral tonic-clonic seizures, myoclonic seizures, tonic seizures and epileptic spasms
- Seizure outcome: Refractory epilepsy. Adverse effects to GABA enhancers
- EEG: Severely disorganized background with rapid activity and multifocal epileptiform abnormalities
- Intellectual disability: Severe
- Other characteristics: Hypotonia, microcephaly (only GOF)

Variant GOF
Glu77Lys
Val78Phe
Leu124Phe
Leu170Arg
Thr185Ile
Tyr245His
Ser254Phe
Leu256Gln
Ile280Phe
Thr281Ala
Leu284Met/Arg/Pro
Thr287Ile
Thr288Asn
Leu293His
Ile300Thr
Ala305Thr/Val
Ile306Thr

GABRB3 project

Patients with loss of function variants:

- First seizure at 10.5 months
- Seizure types: Febrile seizure (LOF only), bilateral tonic-clonic seizures, epileptic spasms, myoclonic, atonic and tonic seizures
- Seizure outcome: Treatment responsive (VPA, GABA enhancers). Adverse effects with sodium channel blockers.
- EEG: Normal or mild slowed background and generalized spike and slow waves
- Intellectual disability: mild to severe
- Other characteristics: ADHD and autism

Variant LOF
Ser76Cys
Met80Lys/Thr
Asn110Asp
Asp120Asn
Lys127Arg
Thr157Met
Leu165Gln
Arg166Ser
Glu178Gly
Glu180Gly
Tyr182Phe
Tyr184His
Phe225Cys
Tyr230His
Arg232Gln
Gln249Lys
Thr281Ile
Pro301Leu
Tyr302Cys
Phe318Ser
Asn328Asp

GABRB3 project

Implications:

- Genetic counselling
- Treatment

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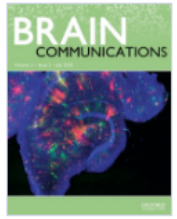

Volume 2, Issue 2
2020

Article Contents

JOURNAL ARTICLE

Gain-of-function *GABRB3* variants identified in vigabatrin-hypersensitive epileptic encephalopathies

Nathan L Absalom ✉, Vivian W Y Liao, Kavitha Kothur, Dinesh C Indurthi ✉, Bruce Bennetts, Christopher Troedson, Shekeeb S Mohammad, Sachin Gupta, Iain S McGregor, Michael T Bowen ... Show more

Brain Communications, Volume 2, Issue 2, 2020, fcaa162,
https://doi.org/10.1093/braincomms/fcaa162
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Article | Open Access | Published: 05 April 2022

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

Nathan L. Absalom, Vivi

Annals of Neurology <onbehalfof@manuscriptcentral.com>
to 08-12-2022, 22:17
elisa.musto86@gmail.com; vivian.liao@sydney.edu.au; Katrine Marie Harries Johannesen; Christina Dühri

Forsigtig: Ekstern mail

08-Dec-2022

Dear Dr Musto:

Your manuscript entitled "GABRA1-related disorders: from genetic to functional pathways" has
staff would like you to know that we strive for rapid turnaround time for our authors, and that

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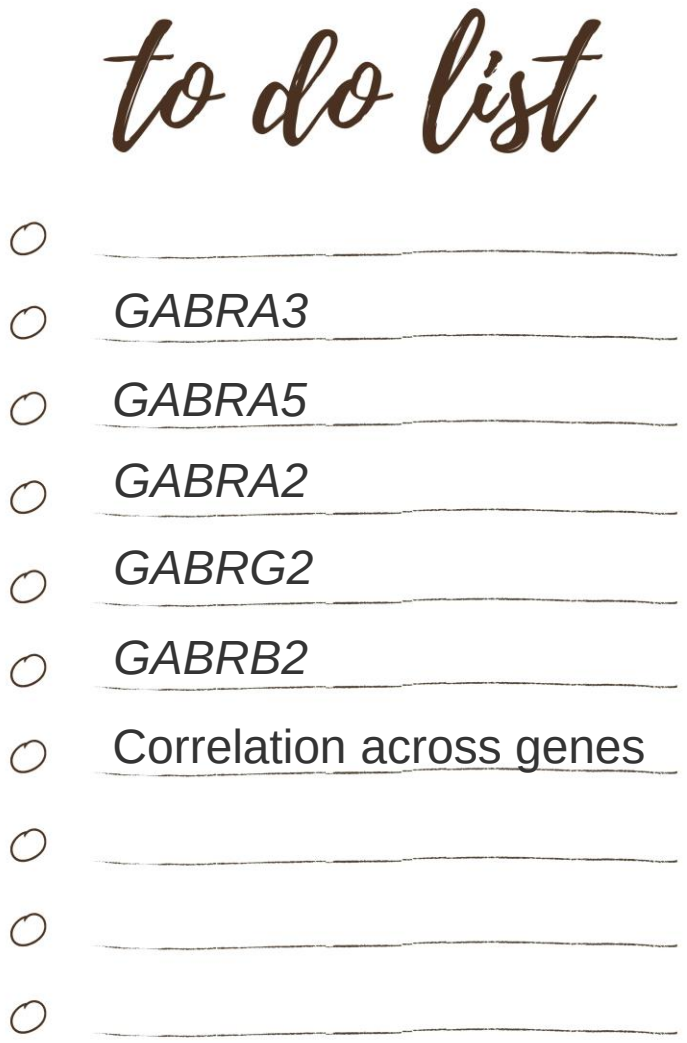
https://doi.org/10.1093/brain/awab391 BRAIN 2022: 145; 1299–1309 | 1299

BRAIN
ORIGINAL ARTICLE

Gain-of-function variants in *GABRD* reveal a novel pathway for neurodevelopmental disorders and epilepsy

Philip K. Ahring,[1] Vivian W. Y. Liao,[1] Elena Gardella,[2,3] Katrine M. Johannesen,[2,3] Ilona Krey,[4] Kaja K. Selmer,[5,6] Barbro F. Stadheim,[6] Hannah Davis,[7] Charlotte Peinhardt,[7] Mahmoud Koko,[8] Rohini K. Coorg,[9] Steffen Syrbe,[10] Astrid Bertsche,[11,12] Teresa Santiago-Sim,[13] Tue Diemer,[14] Christina D. Fenger,[2,3] Konrad Platzer,[4] Evan E. Eichler,[15,16] Holger Lerche,[8] Johannes R. Lemke,[4] Mary Chebib[1] and Rikke S. Møller[2,3]

Future projects



N-of-1 trials

Received: 26 September 2019 | Revised: 25 October 2019 | Accepted: 28 October 2019
DOI: 10.1111/epi.16394

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Personalized medicine: Vinpocetine to reverse effects of *GABRB3* mutation

Santoshi Billakota[1] | J. Michael Andresen[2] | Bryant C. Gay[2] | Gregory R. Stewart[2] | Nikolai B. Fedorov[3] | Aaron C. Gerlach[4] | Orrin Devinsky[5,6]

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[2]Pairnomix, Plymouth, Minnesota
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[6]Saint Barnabas Institute of Neurology and Neurosurgery, Livingston, New Jersey

Correspondence
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Email: santoshi.billakota@nyumc.org

Abstract

Objective: To screen a library of potential therapeutic compounds for a woman with Lennox-Gastaut syndrome due to a Y302C *GABRB3* (c.905A>G) mutation.

Methods: We compared the electrophysiological properties of cells with wild-type or the pathogenic *GABRB3* mutation.

Results: Among 1320 compounds, multiple candidates enhanced *GABRB3* channel conductance in cell models. Vinpocetine, an alkaloid derived from the periwinkle plant with anti-inflammatory properties and the ability to modulate sodium and channel channels, was the lead candidate based on efficacy and safety profile. Vinpocetine was administered as a dietary supplement over 6 months, reaching a dosage of 20 mg three times per day, and resulted in a sustained, dose-dependent reduction in spike-wave discharge frequency on electroencephalograms. Improved language and behavior were reported by family, and improvements in global impression of change surveys were observed by therapists blinded to intervention.

Significance: Vinpocetine has potential efficacy in treating patients with this mutation and possibly other *GABRB3* mutations or other forms of epilepsy. Additional studies on pharmacokinetics, potential drug interactions, and safety are needed.

KEYWORDS
epilepsy, Lennox-Gastaut, precision medicine, refractory, vinpocetine

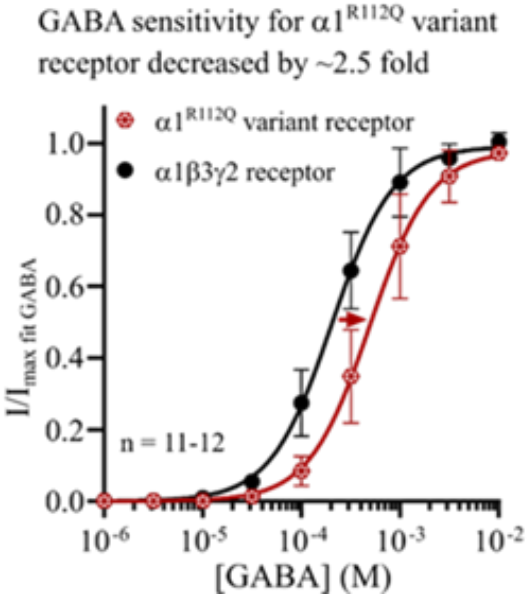
Introduction of VNP 60mg/day

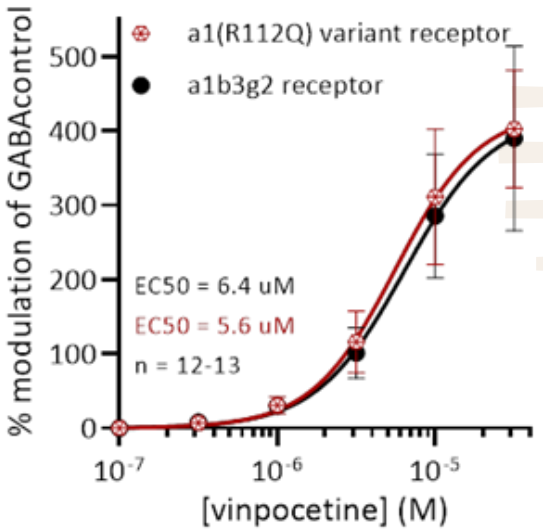
Seizure free for 16 months

Remarkable improvement on OCD, anxiety and depression

Better scores on neuropsychological tests

Periwinkle plant





Future project– GABA portal