CACNA1E–related Developmental & Epileptic Encephalopathy (DEE): Background, mechanisms and therapeutic perspective

Robert Lauerer-Braun
Holger Lerche
Abteilung Neurologie mit Schwerpunkt Epileptologie
Hertie Institut für Klinische Hirnforschung
Universität Tübingen, D

Henning Steinhagen
Tom Otis
Lario Therapeutics LTD
Edinburgh, UK

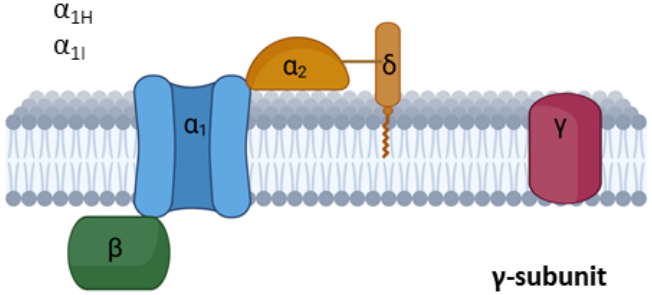
CACNA1E International
Munich
May 18, 2024

Common molecular pathways: Voltage-gated Ca^{2+} channels (VGCC) in genetic diseases

	α-subunit		
L-Type	*CACNA1S*	$Ca_V1.1$	α_{1S}
	CACNA1C	$Ca_V1.2$	α_{1C}
	CACNA1D	$Ca_V1.3$	α_{1D}
	CACNA1F	$Ca_V1.4$	α_{1F}
P/Q-Type	*CACNA1A*	$Ca_V2.1$	α_{1A}
N-Type	*CACNA1B*	$Ca_V2.2$	α_{1B}
R-Type	*CACNA1E*	$Ca_V2.3$	α_{1E}
T-Type	*CACNA1G*	$Ca_V3.1$	α_{1G}
	CACNA1H	$Ca_V3.2$	α_{1H}
	CACNA1I	$Ca_V3.3$	α_{1I}

R-type ($Ca_V2.3$): ‚***R***emaining current'

$\alpha_2\delta$-subunit	
CACNA2D1	$\alpha_2\delta_1$
CACNA2D2	$\alpha_2\delta_2$
CACNA2D3	$\alpha_2\delta_3$
CACNA2D4	$\alpha_2\delta_4$



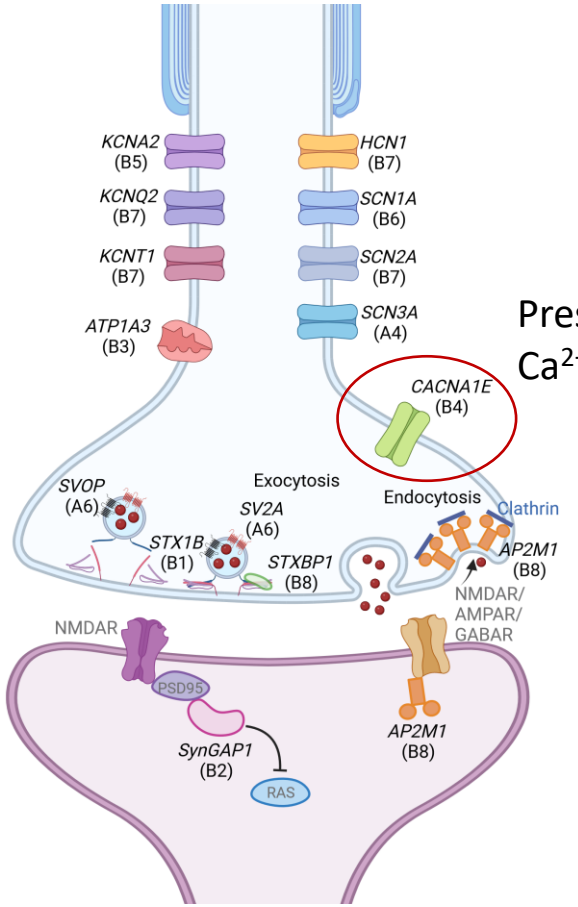
β-subunit	
CACNB1	β_1
CACNB2	β_2
CACNB3	β_3
CACNB4	β_4

γ-subunit	
CACNG1	γ_1
CACNG2	γ_2
CACNG3	γ_3
CACNG4	γ_4
CACNG5	γ_5
CACNG6	γ_6
CACNG7	γ_7
CACNG8	γ_8

Gene	Protein	Phenotype
CACNA1C	$Ca_V1.2$	**GOF:** Timothy syndrome (OMIM# 601005) **GOF & LOF:**Neurodevelopmental disorder with hypotonia, language delay, and skeletal defects with or without seizures (OMIM# 620029)
CACNA1D	$Ca_V1.3$	**GOF:** Primary aldosteronism, seizures, and neurologic abnormalities (OMIM# 615474) **LOF:** Sinoatrial node dysfunction and deafness(OMIM#614896)
CACNA1A	$Ca_V2.1$	**GOF:** Migraine, familial hemiplegic, 1 (OMIM# 141500), Alternating hemiplegia of childhood, DEE42 (OMIM #617106) **LOF**: Episodic ataxia Type 2 (OMIM# 108500), DEE42 with absence seizures (OMIM #617106) CAG-Expansion: Spinocerebellar ataxia type 6 (OMIM #183086)
CACNA1B	$Ca_V2.2$	**Bi-allelic LOF:** Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements (OMIM# 618497)
CACNA1E	$Ca_V2.3$	**GOF**: DEE 69 (OMIM#618285), Developmental delay and regression without epilepsy (Royer-Bertrand et al. 2021) **LOF:** DEE 69 (OMIM#618285)
CACNA1G	$Ca_V3.1$	**GOF & mixed:** Epilepsy, developmental delay, cerebellar atrophy **LOF & Mixed**: SCA42 (OMIM# 616795 /618087)
CACNA1I	$Ca_V3.3$	**GOF:** Neurodevelopmental disorder with speech impairment and with or without seizures (OMIM #620114) Mixed effects: Familial hemiplegic migraine **LOF:** Schizophrenia
CACNA2D1	$\alpha_2\delta_1$	**Bi-allelic LOF/ Monoallelic LOF (debated):** Developmental and epileptic encephalopathy 110 (OMIM#620149)
CACNA2D2	$\alpha_2\delta_2$	**Bi-allelic LOF:** Cerebellar atrophy with seizures and variable developmental delay (OMIM# 618501)

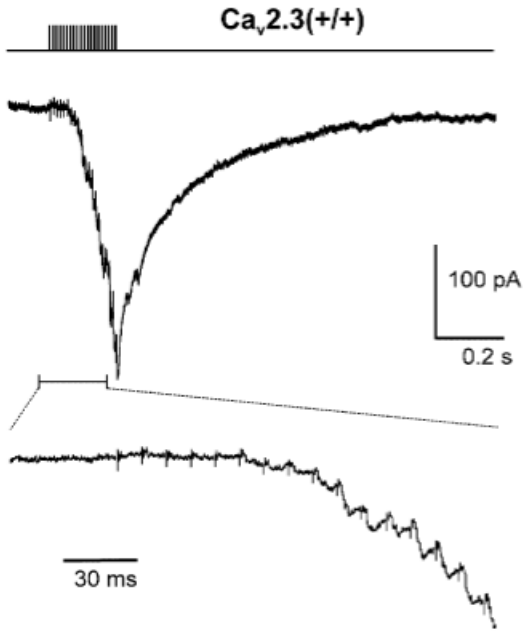
Function of R-type $Ca_V2.3$ channels (encoded by *CACNA1E)*

Important genes involved in different types of DEE

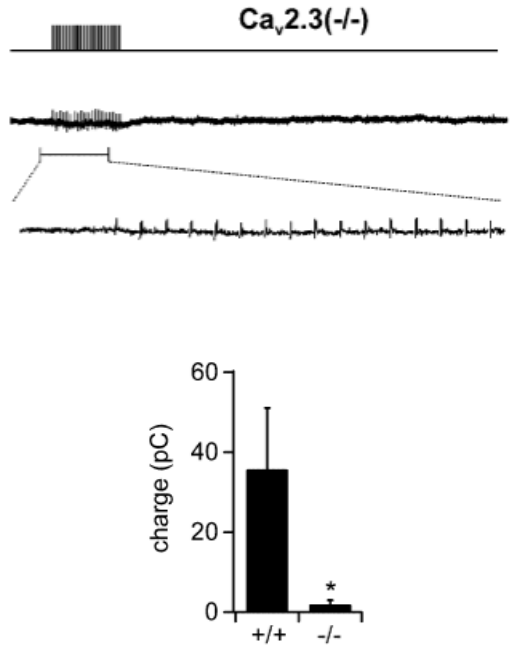


Suppression of postsynaptic currents only upon tetanic stimulation (upon block of P/Q- and N-type Ca^{2+} channels) in $Ca_V2.3$ ko mice

Wild type



$Ca_V2.3$ ko



Dietrich et al., Neuron 2003

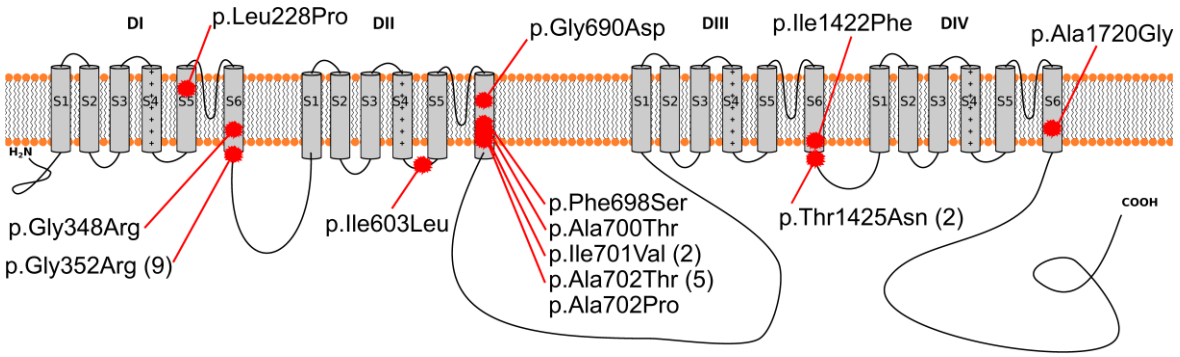
CACNA1E-related DEE

ARTICLE

De Novo Pathogenic Variants in *CACNA1E* Cause Developmental and Epileptic Encephalopathy with Contractures, Macrocephaly, and Dyskinesias

Helbig KL, Lauerer RJ, Bahr JC, Souza IA, Myers CT, Uysal B, Schwarz N, …; Deciphering Developmental Disorders Study; Hedrich UBS, Scheffer IE, Helbig I, Zamponi GW, Lerche H, Mefford HC.

Am J Hum Genet 2018



Mutational hotspots in S6 segments of $Ca_V2.3$ channels

30 patients, age 10 months – 25 years
14 *de novo* missense variants

- Intellectual disability (30/30)
- Developmental regression (9/30)
- Mostly pharmacoresistant epilepsy (26/30)
- Spasms, focal tonic seizures, focal impaired awareness seizures, GTCS
- Hyperkinetic movement disorder / Dystonia (18/30)
- Postpartal Hypotonia (30/30)
- Congenital contractures (13/30)
- Spastic tetraplegia (16/30)
- Early death (7/30)

3 patients with truncating variants

- Intellectual disability (3/3)
- Epilepsy (2/3)
- Hyperkinetic movement disorder (1/3)

CACNA1E-related D(E)E: Broadening the phenotype

Royer-Bertrand *et al. Molecular Autism* (2021) 12:69
https://doi.org/10.1186/s13229-021-00473-3

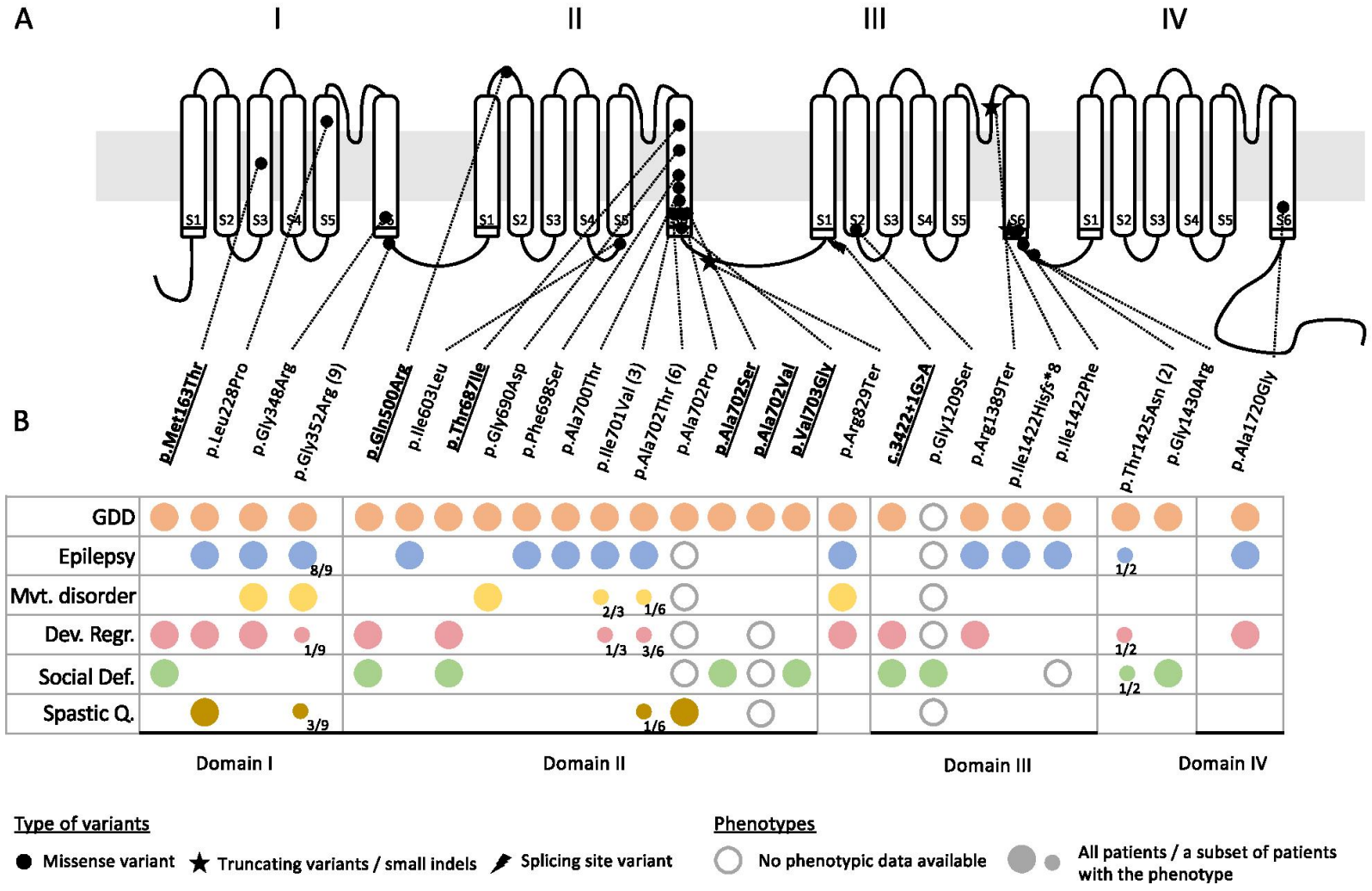
Molecular Autism

RESEARCH Open Access

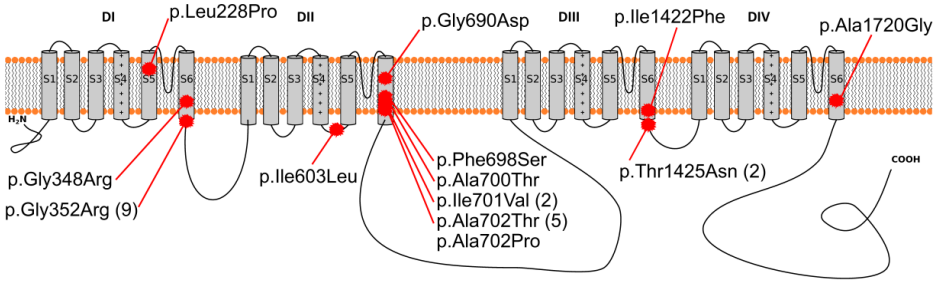
De novo variants in *CACNA1E* found in patients with intellectual disability, developmental regression and social cognition deficit but no seizures

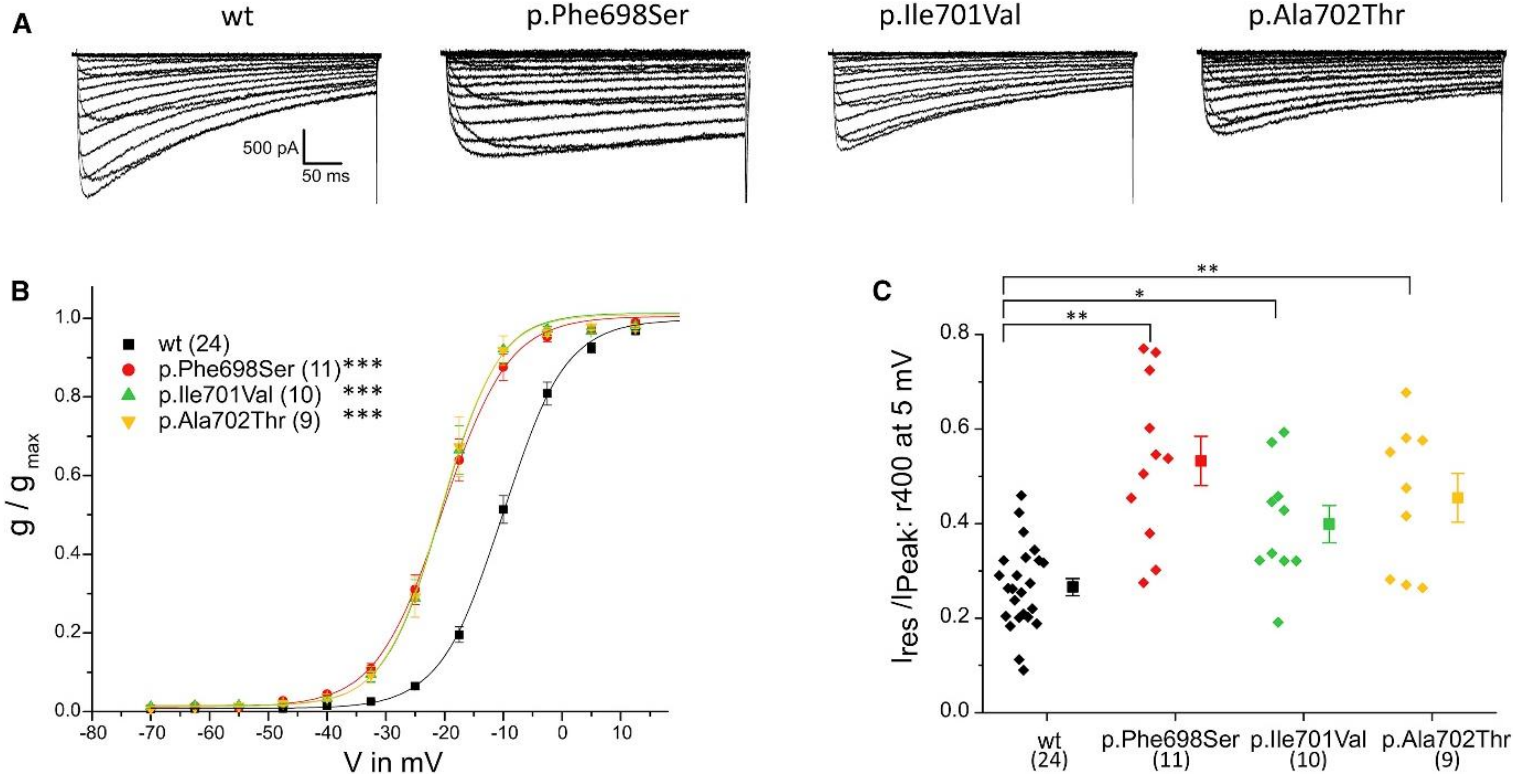
Beryl Royer-Bertrand[1*†], Marine Jequier Gygax[2†], Katarina Cisarova[1†], Jill A. Rosenfeld[3], Jennifer A. Bassetti[4], Oana Moldovan[5], Emily O'Heir[6], Lindsay C. Burrage[3], Jake Allen[7], Lisa T. Emrick[3,8,9], Emma Eastman[10], Camille Kumps[1], Safdar Abbas[11], Geraldine Van Winckel[1], Undiagnosed Diseases Network, Nadia Chabane[2], Elaine H. Zackai[12,13], Sebastien Lebon[14], Beth Keena[12], Elizabeth J. Bhoj[13,15], Muhammad Umair[16,17], Dong Li[15], Kirsten A. Donald[18,19] and Andrea Superti-Furga[1]

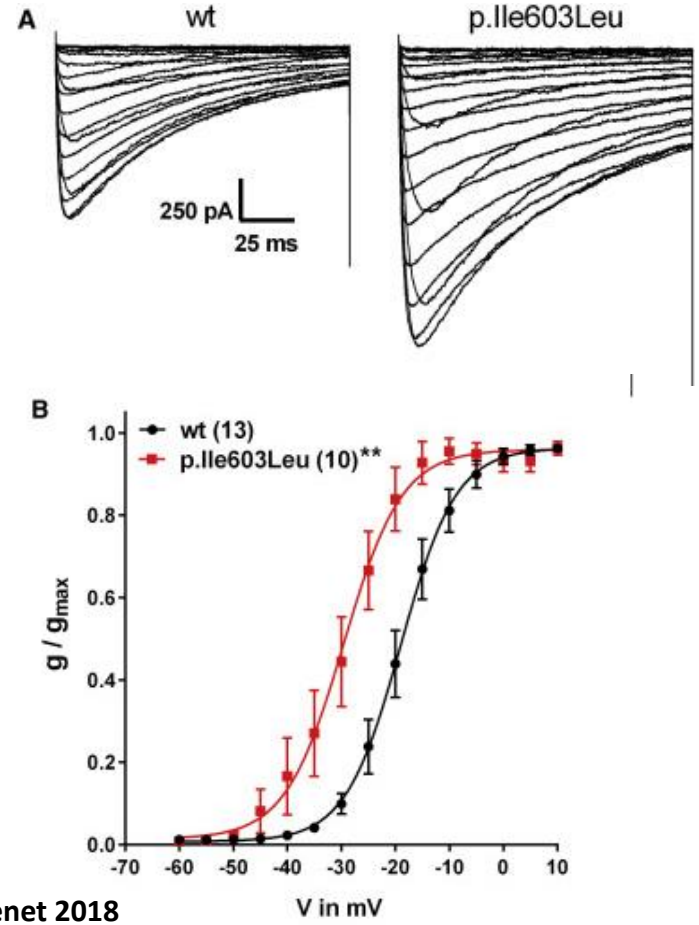
GeneMatcher screen for *CACNA1E* variants with neurodevelopmental phenotypes without epilepsy:
7 unrelated patients



CACNA1E-related DEE: Gain of function of $Ca_V2.3$







Hertie-Institut
für klinische Hirnforschung

Helbig KL, Lauerer RJ, Bahr JC, Souza IA, …, Zamponi GW, Lerche H, Mefford HC: **Am J Hum Genet 2018**

Natural History Study 'DECADE': Deciphering *CACNA1E*-related DEE

- Longitudinal natural history study
- Online eCRF (RedCAP) filled by caregiver and physician
- Yearly intervals ~15-30 min
- Optional yearly video assessments

- Main objective: To assess the **natural course of disease** in *CACNA1E*-related DEE
- Secondary objectives:
  - ➢Genotype-phenotype correlations ?
  - ➢Phenotypic subgroups ?
  - ➢Treatment options ?
  - ➢To build a knowledge base for future pharmacological trials

DECADE: Inclusion/Exclusion Criteria

Inclusion criteria

- Pathogenic or likely pathogenic mutation in *CACNA1E* according to ACMG criteria and neurodevelopmental disorder with
  - ➢ epilepsy
    or
  - ➢ developmental delay
    or
  - ➢ developmental regression
    or
  - ➢ extrapyramidal movement disorder

Exclusion criteria

- Coexistent likely pathogenic mutation in a different gene associated with neurologic and/or developmental symptoms and/or epilepsy
- Acquired brain tissue damage (tumor, stroke, meningitis …)
- Adequate clinical information / medical records cannot be obtained

DECADE: Data to be included

1. Genetic diagnosis
2. Clinical syndrome diagnosis
3. First occurence of *CACNA1E DEE* symptoms
4. General data
   - Sex, age, weight, height, head circumference
5. Gestational history
6. Timepoint of death
7. Neuroimaging

Possible endpoints for treatment study

8. Epilepsy
   - Seizure types
   - Seizure frequency in 28 days
   - Used ASMs, side effects
9. Motor development including movement disorder
10. GMFCS
11. Video assessment of motor developement
12. Speech and cognitive development
13. Social development
14. Global caregiver& physician impression of change

How far are we?

- ✓Study design
- ✓RedCAP form ready
- ✓First approval by ethics committee
- ✓Application for 2nd ethical approval

decade@med.uni-tuebingen.de

Hertie-Institut
für klinische Hirnforschung

Import a new instrument from the official REDCap Instrument Library
Upload instrument ZIP file from another project/user or external libraries

Instrument name	Fields	View PDF	Instrument actions
Pseudonym	2		Choose action
Genetic diagnosis	8		Choose action
Clinical diagnosis	5		Choose action
General	8		Choose action
Special events	5		Choose action
Death	4		Choose action
General retrospective	15		Choose action
Motor skills lower extremities retrospective	58		Choose action
Current motor skills lower extremities	3		Choose action
GMFCS	7		Choose action
Motor skills upper extremities retrospective	18		Choose action
Current motor skills upper extremities	2		Choose action
Movement disorder	41		Choose action
Comorbidities	26		Choose action
Nonmotor development	25		Choose action
Social	5		Choose action
Epilepsy	166		Choose action
EEG	25		Choose action
Neuroimaging	39		Choose action
Treatment	980		Choose action
Non-drug treatment	63		Choose action
Current treatment	52		Choose action
CGI-S clinician	1		Choose action
CGI-I clinician	4		Choose action
CGI-S caregiver	1		Choose action
CGI-I caregiver	4		Choose action
Video Upload	1		Choose action
Free Questions	3		Choose action

Thanks to

Neurology/Epileptology Tübingen
Jacqueline Bahr
Patrizia Cseh
Ulrike Hedrich
Robert Lauerer-Braun
Stephan Lauxmann
Yuanyuan Liu
Peter Müller

Animal Core Facility Tübingen
Thomas Ott

Neuropediatrics Tübingen
Michael Alber

CHOP, Philadelphia
Katherine Helbig
Ingo Helbig

St Jude, Memphis
Heather Mefford

Calgary
Ivana Souza
Gerald Zamponi

Other *CACNA1E* collaborators

all patients; DFG, BMBF, Hertie Foundation, Lario Tx, *CACNA1E* international

LARIO – ACKNOWLEDGEMENTS

Lario Team

Henning Steinhagen, PhD, MBA – CEO

Prof. Tom Otis, PhD – CSO

Paolo Pevarello, PhD – Head of Chemistry

Daniel Gill, MsC – Head of Project Management

Prof. Heidrun Potschka, PhD – Head of Epilepsy Pharmacology

Tim Schulz-Utermoehl, PhD – Head of DMPK

Tim Hammond, PhD – Head of Safety

Academic Collaborator Labs

Prof. Holger Lerche, MD – Univ. Tübingen, Germany

Prof. Birgit Liss, PhD – Univ. Ulm, Germany

Dr. Sila Ultanir, PhD – Francis Crick Institute, London

Prof. Terry O'Brien, MD, PhD – Monash Univ., Australia

Prof. Jörg Striessnig, PhD – Univ. Graz, Austria

Seed funding from

EPIDAREX exeed

AXXAM

GOLGI NEUROSCIENCES

Support & Encouragement from

loulou FOUNDATION

Tackling CDKL5 Deficiency

LARIO

Thank you for your attention!