Precision Medicine and Epilepsy Genetics

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ICNA, 2021

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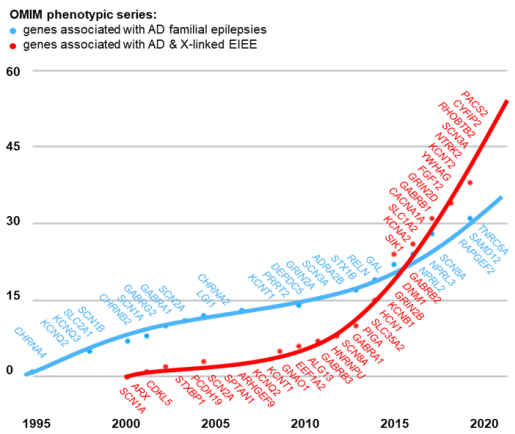
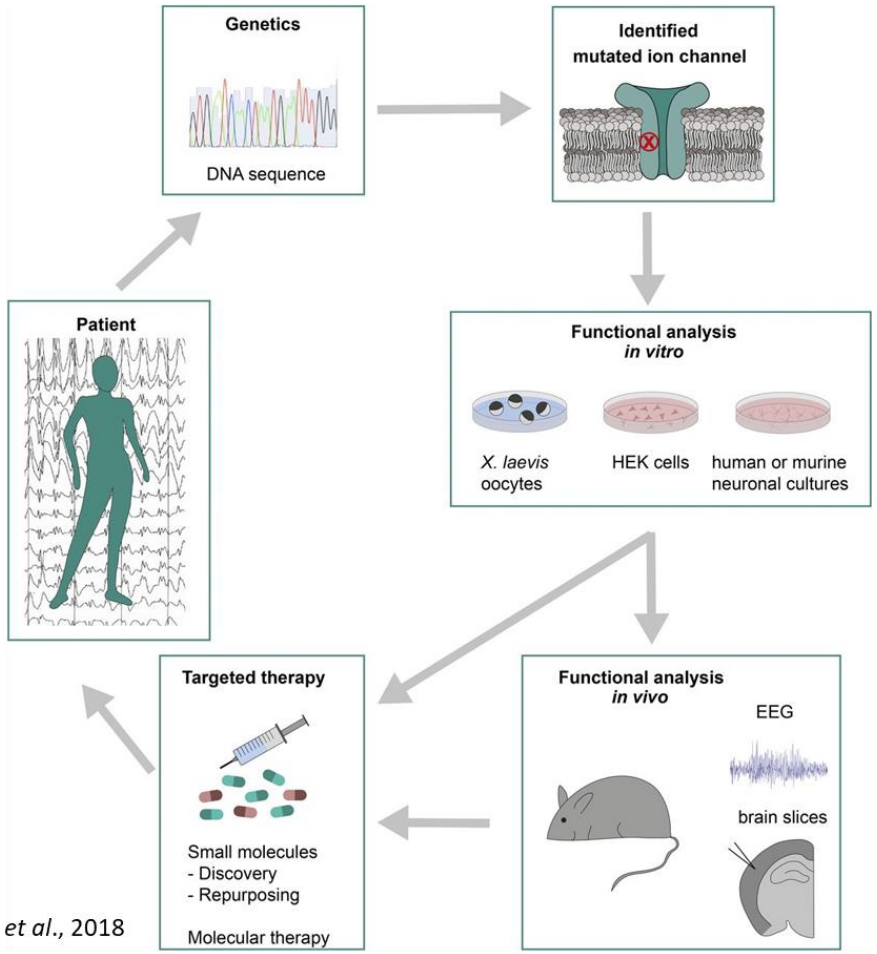
FILADELFIA

Precision medicine in genetic epilepsies

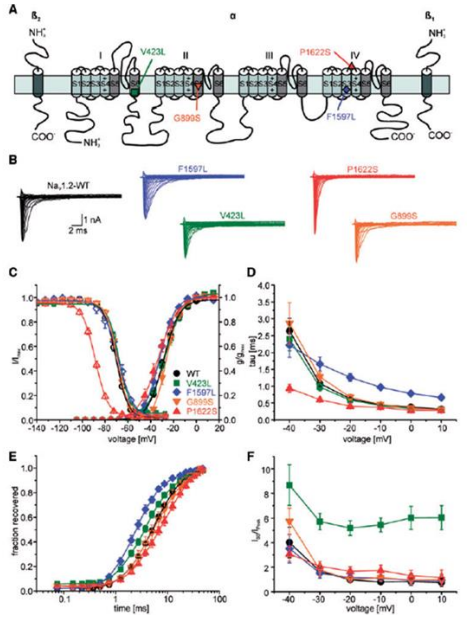
"a treatment approach in which disease treatment and prevention is tailored to individual variability in genes, environment, and lifestyle for each person"



Møller *et al.*, 2019



Oyrer *et al.*, 2018



Wolff *et al.*, 2017

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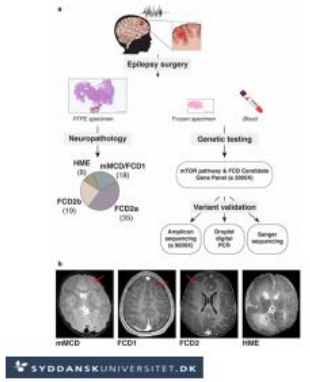
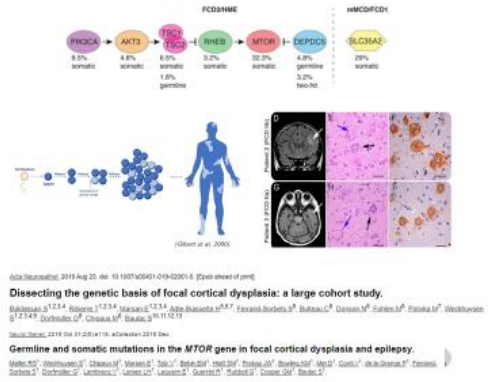
Genetic testing should be considered in:

- Early-onset epilepsies
- Epilepsy with intellectual disability, autism, and/or other comorbidities
- Progressive myoclonus epilepsies
- Non-lesional focal epilepsies in specific familial syndromes
- Non-lesional focal, therapy-resistant epilepsies in presurgical work-up
- Epilepsy in the setting of focal malformations of cortical development

https://www.cureepilepsy.org/egi/index.html





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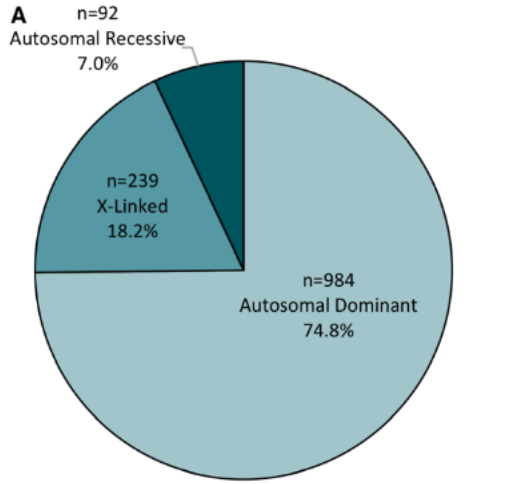
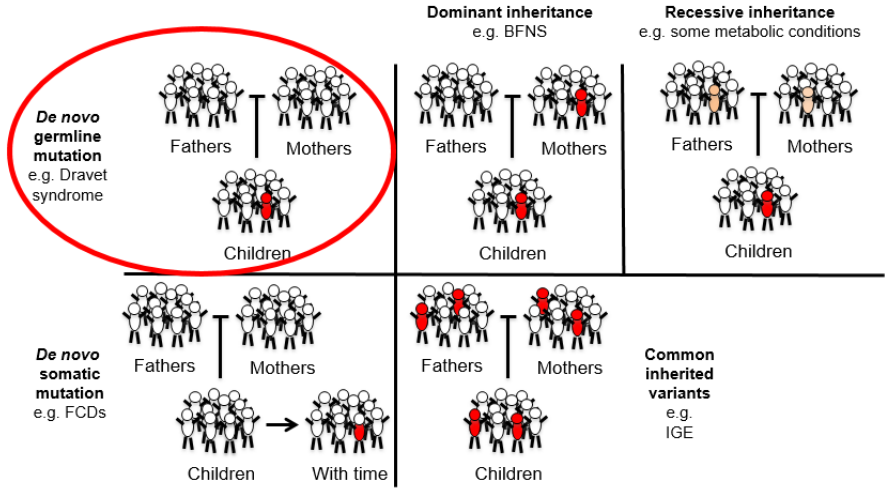
Genetic testing – what can you achieve?

- The type of genetic testing undertaken depends on the clinical situation
- NGS strategies are currently recommended as the first line of testing
- Targeted gene panels/WES: ~ 20-40%
  - Neonatal onset epilepsies: ~ 60%
  - Onset 2m - 2y: 25-30%
  - Onset 2 - 9y: 10-15%
  - Onset >10 y: 1%
- Somatic mutations: ~30% of mMCD/FCD1 patients and ~60% of FCD2/HME patients
- Genetic re-evaluation in unsolved cases





Mol Syndromol. 2016 Sep;7(4):210-219. Epub 2016 Aug 20.

Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies.

Møller RS[1], Larsen LH[2], Johannesen KM[1], Talvik I[3], Talvik T[4], Vaher U[4], Miranda MJ[5], Farooq M[6], Nielsen JE[7], Svendsen LL[8], Kjeldgaard DB[9], Linnet KM[10], Hao Q[2], Uldall P[9], Frangu M[11], Tommerup N[12], Balg SM[13], Abdullah U[6], Born AP[14], Gellert P[9], Nikanorova M[1], Olofsson K[9], Jepsen B[9], Marjanovic D[9], Al-Zehhawi L[15], Peñalva SJ[16], Krag-Olsen B[10], Brusgaard K[2], Hjalgrim H[1], Rubboli G[17], Pal DK[18], Dahl HA[2].

Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with **epilepsy** and neurodevelopmental disorders.

Lindy AS, Stosser MB, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, Brandt T, Richard G, McKnight DA.

Epilepsia. 2018 May;59(5):1062-1071. doi: 10.1111/epi.14074. Epub 2018 Apr 14.

PMID: 29655203

Channelopathies

Loss-of-function: reduced neuronal activity

Gain-of-function: impaired channel inactivation and elevated neuronal activity

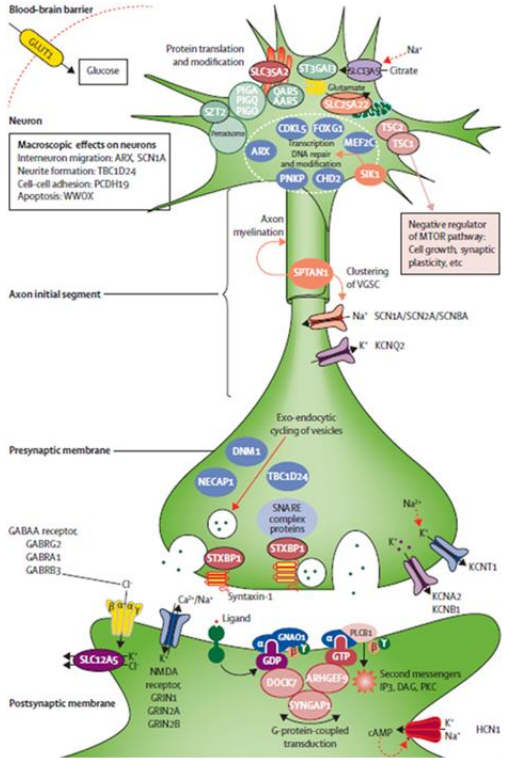
TABLE 1
Ion channel genes mutated in epilepsy, functional impact, and available mouse models

Gene	Protein	Phenotype	OMIM Nr	Functional Impact	Human Mutation-Based Mouse Models
Voltage-Gated					
SCN1A	Na_V 1.1	Dravet syndrome; GEFS+	182389	LOF	R1407X (Yu et al., 2006); R1648H (Martin et al., 2010)
SCN1B	$Na_V\beta1$	GEFS+, temporal lobe epilepsy, an early infantile epileptic encephalopathy	600235	LOF	C121W (Wimmer et al., 2010)
SCN2A	$Na_V1.2$	BFNIE, early-onset epileptic encephalopathies, neurodevelopmental disorders	182390	GOF LOF	A263V (Schattling et al., 2016)
SCN8A	$Na_V1.6$	BFIE, epileptic encephalopathy	600702	GOF	N1768D (Lopez- Santiago et al., 2017)
KCNA1	$K_V1.1$	Partial epilepsy and episodic ataxia	176260	LOF	V408A (Herson et al., 2003)
KCNA2	$K_V1.2$	Epileptic encephalopathy	176262	GOF LOF	
KCNB1	$K_V2.1$	Epileptic encephalopathy	600397	LOF	
KCNC1	$K_V3.1$	Progressive myoclonus epilepsy	176258	LOF	
KCNMA1	$K_{Ca}1.1$	Epilepsy and paroxysmal dyskinesia	600150	LOF	
KCNQ2	$K_V7.2$	BFNE, epileptic encephalopathy	602235	GOF LOF	A306T (Singh et al., 2008)
KCNQ3	$K_V7.3$	BFNE	602232	GOF LOF	G311V (Singh et al., 2008)
KCNT1	$K_{Na}1.1$	ADNFLE, EIMFS	608167	GOF	
KCTD7	KCTD7	Progressive myoclonus epilepsy	611725	LOF	
HCN1	HCN1	*IGE*	602780	GOF LOF	
CACNA1A	$Ca_V2.1$	Epilepsy, episodic ataxia, epileptic encephalopathy	601011	LOF	
CACNA1H	$Ca_V3.2$	GGE	607904	GOF	
Ligand-Gated					
GRIN1	GluN1	Epileptic encephalopathy	138249	LOF	
GRIN2A	GluN2A	Epileptic encephalopathy	138253	GOF LOF	
GRIN2B	GluN2B	Epileptic encephalopathy	138252	GOF LOF	
GRIN2D	GluN2D	Epileptic encephalopathy	602717	GOF	
GABRA1	GABRA1	GGE, epileptic encephalopathy	137160	LOF	A322D (Arain et al., 2015)
GABRB3	GABRB3	CAE, epileptic encephalopathy	137192	LOF	
GABRG2	GABRG2	FS/GEFS+, epileptic encephalopathy	137164	LOF	R43Q (Tan et al., 2007); Q390X (Kang et al., 2015)
CHRNA2	CHRNA2	ADNFLE	118502		
CHRNA4	CHRNA4	ADNFLE	118504	GOF	S252F (Klaassen et al., 2006); +L264 (Klaassen et al., 2006)
CHRNB2	CHRNB2	ADNFLE	605375	GOF	

BFIE, benign familial infantile epilepsy; BFNIE, benign familial neonatal-infantile epilepsy; EIMFS, epilepsy of infancy with migrating focal seizures; FS, febrile seizures GOF, gain-of-function; LOF, loss-of-function; OMIM, Online Mendelian Inheritance in Man.

Oyrer *et al.*, 2018

SCN3A
KCNT2
CACNA1E
GABRA3
GABRA5
GABRB2
GABRD



McTague et al, 2016

- Potential precision medicine approaches in ~25%
- Enormous utility of genetic testing for therapeutic decision-making

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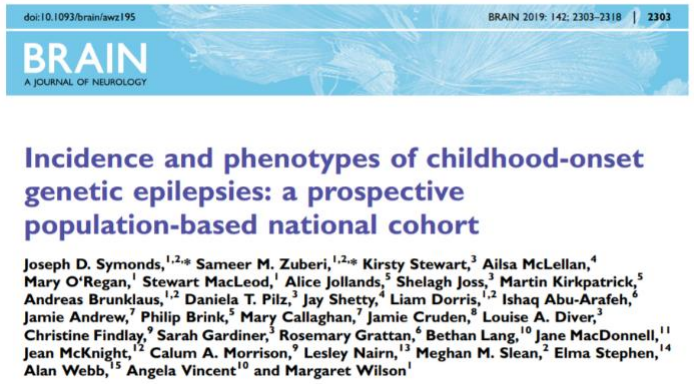
Early-onset genetic epilepsies reaching adult clinics

- The incidence of monogenic epilepsies: 1 per 2120 live births
- Children grow into adults and with advances in paediatric care it is becoming increasingly common for children with even severe DEEs to reach transition
- At least 10–50/100 000 individuals will require the care of an adult neurologist because of a early-onset genetic epilepsy
- The majority have not benefited from recent genetic diagnostic discoveries


doi:10.1093/brain/awz195 BRAIN 2019: 142: 2303–2318 | 2303
BRAIN
A JOURNAL OF NEUROLOGY

Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort

Joseph D. Symonds,[1,2,*] Sameer M. Zuberi,[1,2,*] Kirsty Stewart,[3] Ailsa McLellan,[4] Mary O'Regan,[1] Stewart MacLeod,[1] Alice Jollands,[5] Shelagh Joss,[3] Martin Kirkpatrick,[5] Andreas Brunklaus,[1,2] Daniela T. Pilz,[3] Jay Shetty,[4] Liam Dorris,[1,2] Ishaq Abu-Arafeh,[6] Jamie Andrew,[7] Philip Brink,[5] Mary Callaghan,[7] Jamie Cruden,[8] Louise A. Diver,[3] Christine Findlay,[9] Sarah Gardiner,[3] Rosemary Grattan,[6] Bethan Lang,[10] Jane MacDonnell,[11] Jean McKnight,[12] Calum A. Morrison,[9] Lesley Nairn,[13] Meghan M. Slean,[2] Elma Stephen,[14] Alan Webb,[15] Angela Vincent[10] and Margaret Wilson[1]


doi:10.1093/brain/awaa029 BRAIN 2020: 143: 1–6 | e19
BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Early-onset genetic epilepsies reaching adult clinics

David Lewis-Smith,[1,2] Colin A. Ellis,[3,4] Ingo Helbig,[3,4,5,6] and Rhys H. Thomas[1,2]

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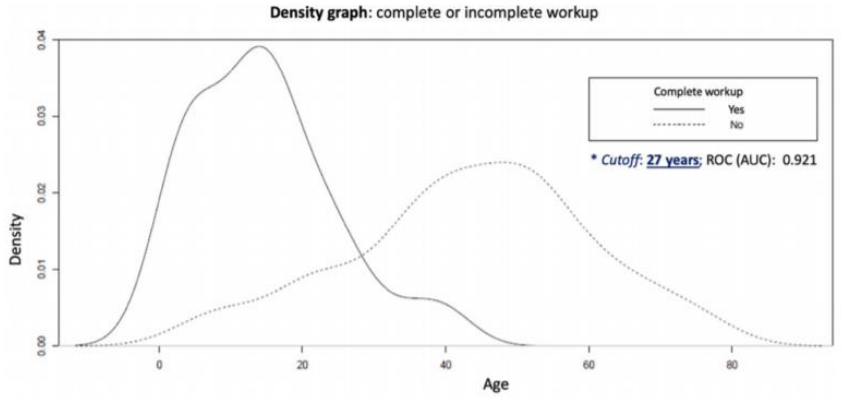
Genetic testing in adults with epilepsy and ID

- 200 adults - epilepsy and ID
- A genetic diagnosis was found in 23%. *SCN1A, KCNT1*, and *STXBP1* (48%).
- Gene-specific treatment changes were initiated in 17% (1 *SLC2A1*, 10 *SCN1A*)
- 10 improved, with seizure reduction and/or increased alertness and general well-being
- Useful for therapeutic decision-making: better seizure control, ultimately improved quality of life.
- Older age and seizure freedom seem to be associated with the highest diagnostic gap.




Received: 12 December 2018 | Revised: 28 May 2019 | Accepted: 7 June 2019
DOI: 10.1111/epi.16273

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability

Felippe Borlot[1,2] | Bruno Ivo de Almeida[1,3] | Shari L. Combe[1] | Danielle M. Andrade[2,4,5] | Francis M. Filloux[1] | Kenneth A. Myers[6,7]

Received: 27 November 2019 | Revised: 18 April 2020 | Accepted: 21 April 2020
DOI: 10.1111/epi.16533

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Utility of genetic testing for therapeutic decision-making in adults with epilepsy

Katrine M. Johannesen[1,2] | Natalya Nikanorova[1] | Dragan Marjanovic[3] | Agnieszka Pavbro[3] | Line H. G. Larsen[4] | Guido Rubboli[1,5] | Rikke S. Møller[1,2]

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

ELSEVIER

Brief Communication

Diagnostic gap in genetic epilepsies: A matter of age

Angel Aledo-Serrano [a,*], Irene García-Morales [a,b], Rafael Toledano [a,c], Adolfo Jiménez-Huete [a], Beatriz Parejo [b], Carla Anciones [a], Ana Mingorance [d], Primitivo Ramos [e], Antonio Gil-Nagel [a]

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Why should genetic investigations be performed?

- to obtain a definitive diagnosis and avoid further (costly and laborious) diagnostic procedures
- to better estimate the prognosis
- to obtain a solid basis for genetic counselling
- to improve therapy
- to join disease-specific support groups

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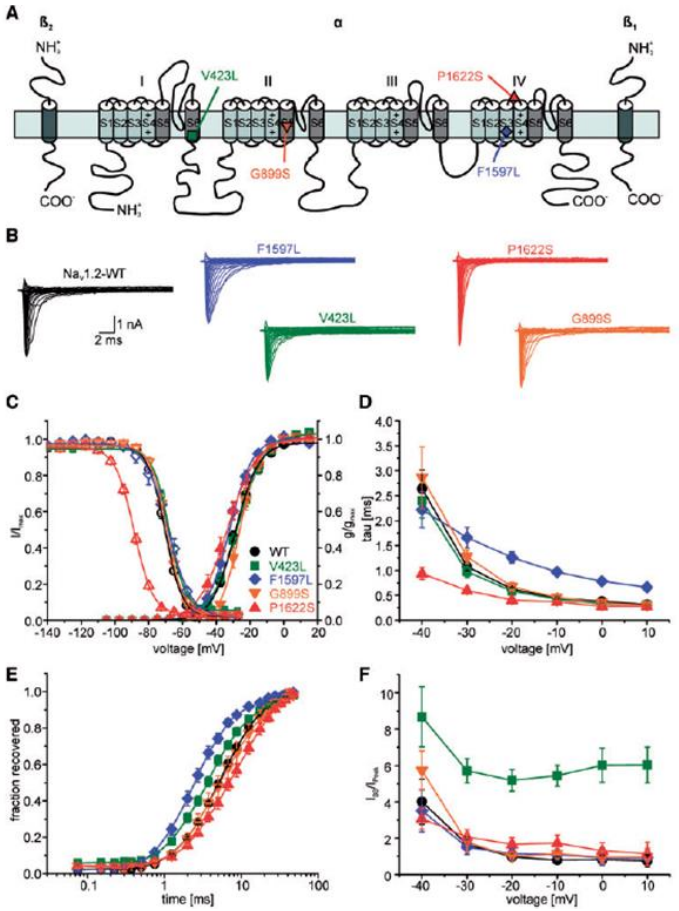
Precision medicine in genetic epilepsies

- ***SCN1A*** (LOF and GOF): LOF Drugs of choice: STP, VPA, BDZ: Proof of concept: Fenfluamine, ASO; LOF Avoid: SCBs
- ***SCN2A*** (LOF and GOF): GOF Drugs of choice: SCBs; LOF Avoid: SCBs
- ***SCN8A*** (LOF and GOF): GOF Drugs of choice: SCBs; GOF Avoid: LEV
- ***SLC2A1*** (LOF): Treament of choice: Ketogenic diet
- ***KCNQ2*** (LOF, DNE and GOF): LOF/DNE Drug of choice: SCBs, LOF/DNE Proof of concept: Retigabine
- ***KCNT1*** (GOF) Proof of concept: Quinidine – mixed results
- ***KCNA2*** (LOF and GOF): GOF Proof of concept: 4-amino-pyridine
- ***GABRB3*** (LOF and GOF): GOF Avoid: Vigabatrin
- ***GRIN2A, GRIN2B*** (LOF and GOF): Proof of concept: Memantine, L-Serine, dextromethorphan
- ***MEF2C*** Drug of choice: Valproic acid
- ***PNPO* and *ALDH7A1*** Drug of choice: Pyridoxal 5'-phosphate or Pyridoxine
- ***CLN2*** Treatment of choice: Enzyme replacement therapy
- ***PRRT2*** Drug of choice: Carbmazepine
- ***PLCB1*** Drug of choice: Inositol
- ***CAD*** Drug of choice: urdine
- ***PCDH19*** Drug of choice: clobazam Trial: ganaxolone
- ***TSC, DEPDC5, NPRL2, NPRL3, mTOR*** Proof of concept: mTOR inhibitors (Everolimus)



Wolff et al., 2017

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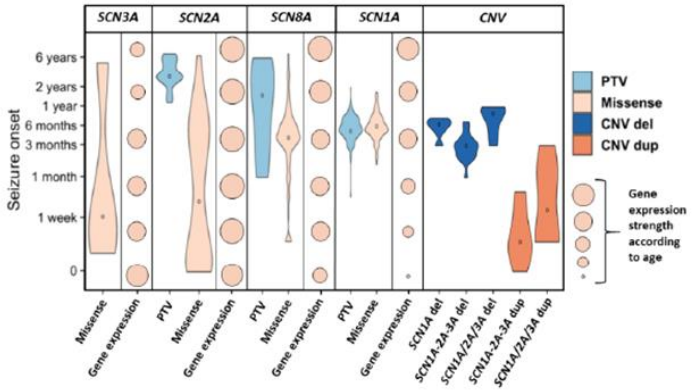
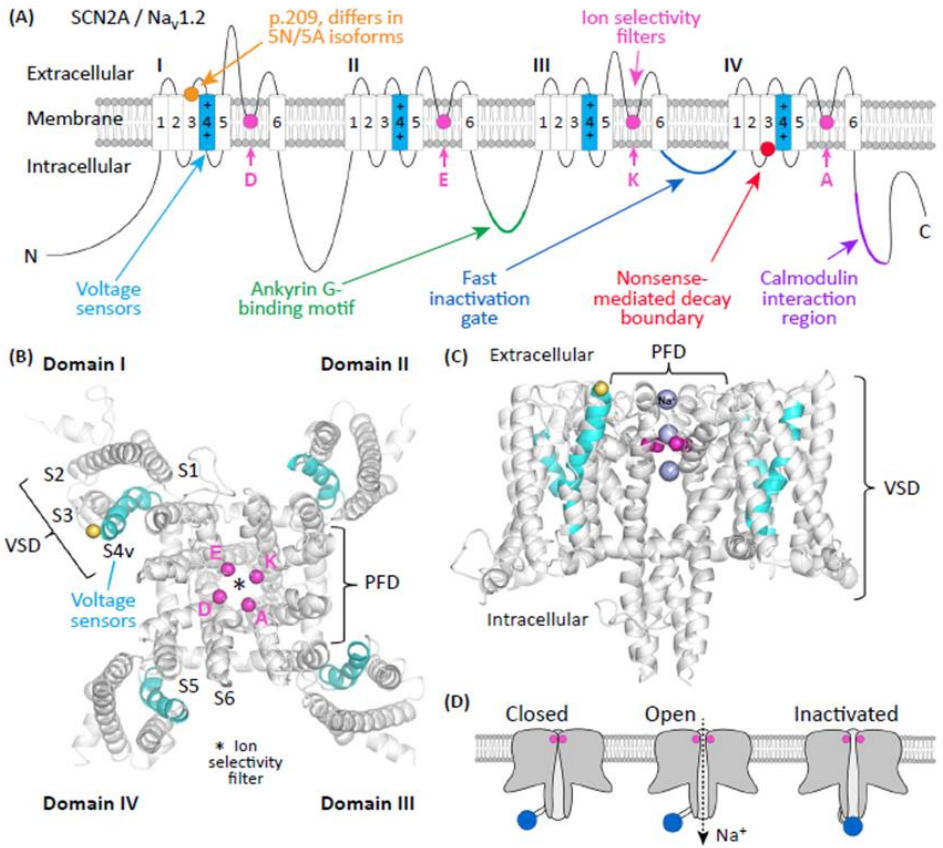
Voltage gated sodium channels

- Large transmembrane proteins
- Initiation and propagation of action potentials
- *SCN2A* and *SCN3A* are starting prenatally, followed by *SCN1A* and *SCN8A* neonatally



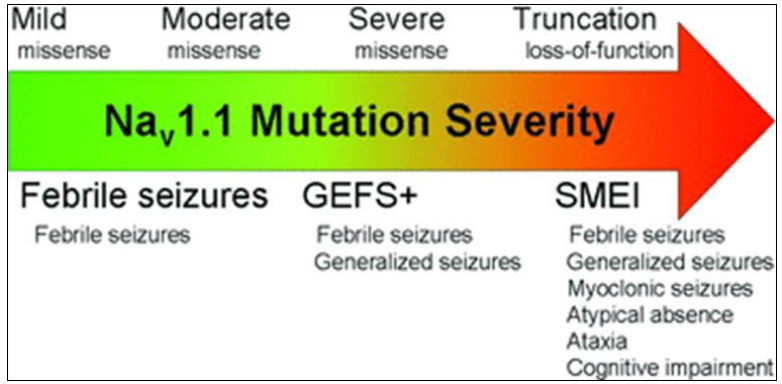


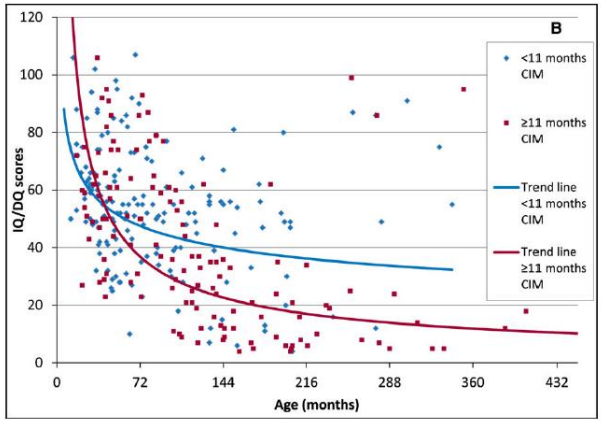
Progress in Understanding and Treating **SCN2A**-Mediated Disorders.
Sanders SJ, Campbell AJ, Cottrell JR, Moller RS, Wagner FF, Auldridge AL, Bernier RA, Catterall WA, Chung WK, Empfield JR, George AL Jr, Hipp JF, Khwaja O, Kiskinis E, Lal D, Malhotra D, Millichap JJ, Otis TS, Petrou S, Pitt G, Schust LF, Taylor CM, Tjernagel J, Spiro JE, Bender KJ.
Trends Neurosci. 2018 Jul;41(7):442-456. doi: 10.1016/j.tins.2018.03.011. Epub 2018 Apr 23.

Biological concepts in human sodium channel epilepsies and their relevance in clinical practice.
Brunklaus A, Du J, Steckler F, Ghanty II, Johannesen KM, Fenger CD, Schorge S, Baez-Nieto D, Wang HR, Allen A, Pan JQ, Lerche H, Heyne H, Symonds JD, Zuberi SM, Sanders S, Sheidley BR, Craiu D, Olson HE, Weckhuysen S, DeJonge P, Helbig I, Van Esch H, Busa T, Milh M, Isidor B, Depienne C, Poduri A, Campbell AJ, Dimidschstein J, Møller RS, Lal D.
Epilepsia. 2020 Mar;61(3):387-399. doi: 10.1111/epi.16438. Epub 2020 Feb 23.

SCN1A-related epilepsies

- Archetype of *SCN1A*-related epilepsy: Dravet syndrome (1:15.700)
- Onset in the first year of life with prolonged, febrile and afebrile, generalised clonic or hemiclonic seizures. The epilepsy is usually resistant and affected individuals develop cognitive, behavioural, and motor impairment
- Inhibitory interneurons
- Loss-of-function variants
- First line drugs: Stiripentol, VPA, CLB: Proof of concept: Fenfluramine
- Avoid: Sodium channel blockers
- Longer CIM use in the first 5 years of disease can have negative effects on cognitive outcome





Accepted: 6 April 2018
DOI: 10.1111/epi.14191

FULL-LENGTH ORIGINAL RESEARCH
Epilepsia

Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in *SCN1A*-related seizure phenotypes

Iris M. de Lange[1] | Boudewijn Gunning[2] | Anja C. M. Sonsma[1] | Lisette van Gemert[3] | Marjan van Kempen[1] | Nienke E. Verbeek[1] | Joost Nicolai[3] | Nine V. A. M. Knoers[1] | Bobby P. C. Koeleman[1] | Eva H. Brilstra[1]

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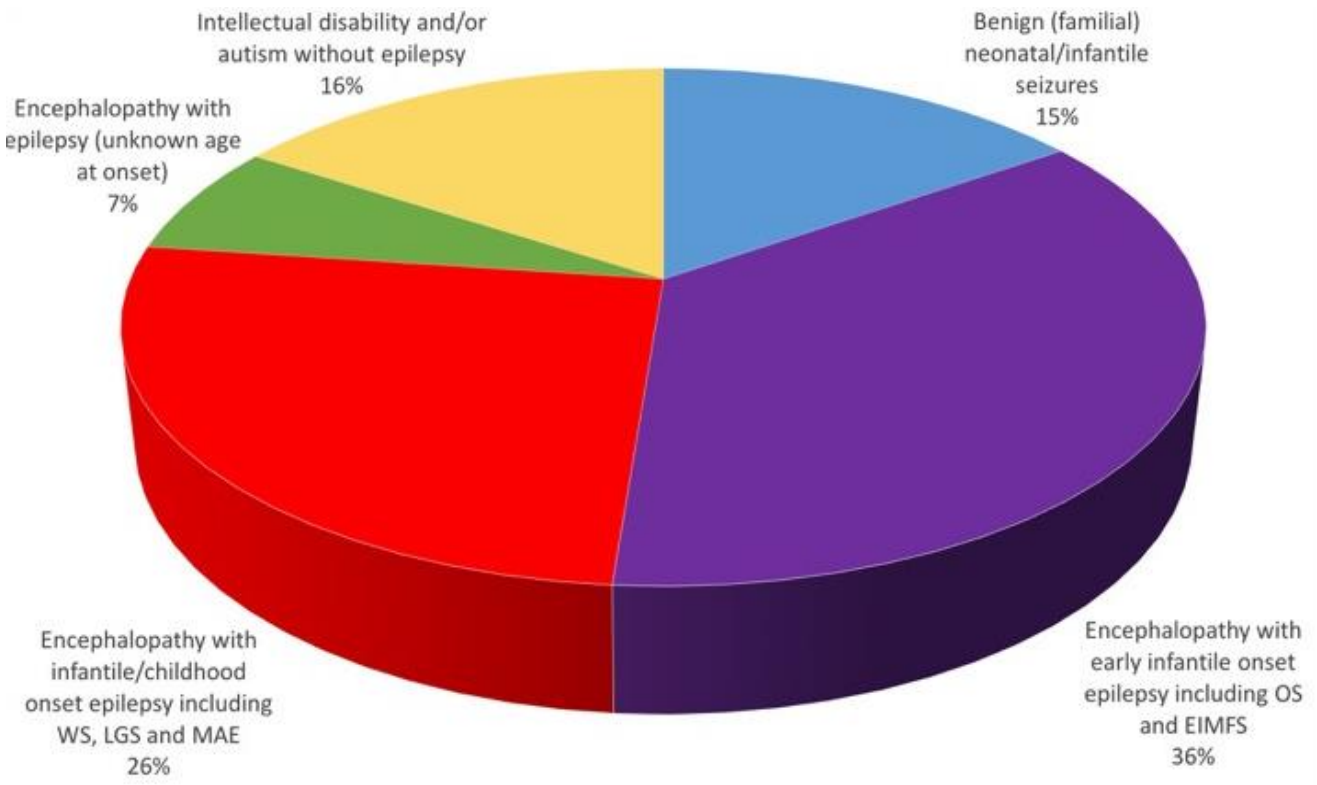
SCN2A/NaV1.2- related disorders

SCN2A related disorders: 1: 78.000 (Wolff et al., 2017)



Brain. 2017 May 1;140(5):1316-1336. doi: 10.1093/brain/awx054.

Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders.

Wolff M[1], Johannesen KM[2,3], Hedrich UBS[4], Masnada S[5], Rubboli G[2,6], Gardella E[2,3], Lesca G[7,8,9], Ville D[10], Milh M[11,12], Villard L[12], Afenjar A[13], Chantot-Bastaraud S[13], Mignot C[14], Lardennois C[15], Nava C[16,17], Schwarz N[4], Gérard M[18], Perrin L[19], Doummar D[20], Auvin S[21,22], Miranda MJ[23], Hempel M[24], Brilstra E[25], Knoers N[25], Verbeek N[25], van Kempen M[25], Braun KP[26], Mancini G[27], Biskup S[28], Hörtnagel K[28], Döcker M[28], Bast T[29], Loddenkemper T[30], Wong-Kisiel L[31], Baumeister FM[32], Fazeli W[33], Striano P[34], Dilena R[35], Fontana E[36], Zara F[37], Kurlemann G[38], Klepper J[39], Thoene JG[40], Arndt DH[41], Deconinck N[42], Schmitt-Mechelke T[43], Maier O[44], Muhle H[45], Wical B[46], Finetti C[47], Brückner R[48], Pietz J[49], Golla G[50], Jillella D[51], Linnet KM[52], Charles P[53], Moog U[54], Õiglane-Shlik E[55], Mantovani JF[56], Park K[57], Deprez M[58], Lederer D[58], Mary S[58], Scalais E[59], Selim L[60], Van Coster R[61], Lagae L[62], Nikanorova M[2], Hjalgrim H[2,3], Korenke GC[63], Trivisano M[64], Specchio N[64], Ceulemans B[65], Dorn T[66], Helbig KL[67], Hardies K[68,69], Stamberger H[68,69,70], de Jonghe P[68,69,70], Weckhuysen S[68,69,70], Lemke JR[71], Krägeloh-Mann I[1], Helbig I[45,72], Kluger G[73,74], Lerche H[4], Møller RS[2,3].

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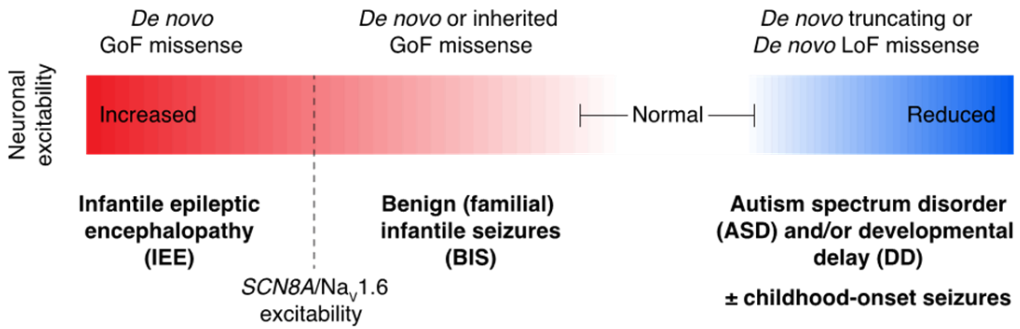
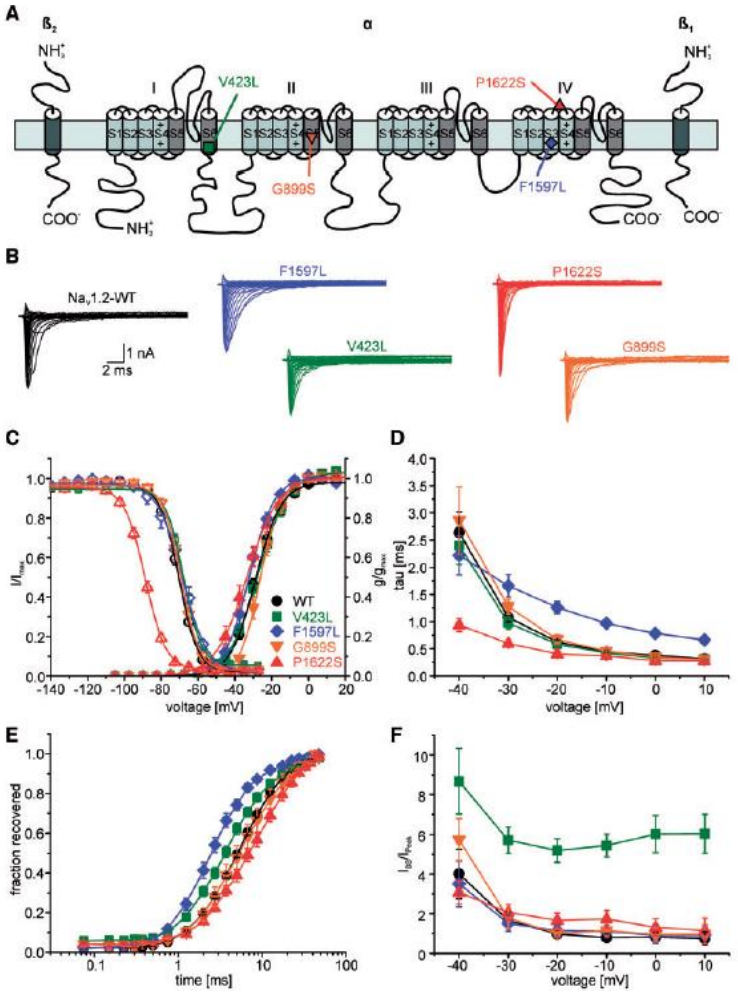
SCN2A related disorders

- Neonatal onset *SCN2A* related epilepsies (< 3 months) – BFNS, OS, EIMFS, EEs
  - **GOF** mutations
- Infantile and childhood onset epilepsies (> 3 months) – WS, MAE, LGS, EEs, unclassified
  - **LOF** mutations
- ASD/ID without epilepsy
  - **LOF** mutations





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Brain. 2017 May 1;140(5):1316-1336. doi: 10.1093/brain/awx054.
Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders.
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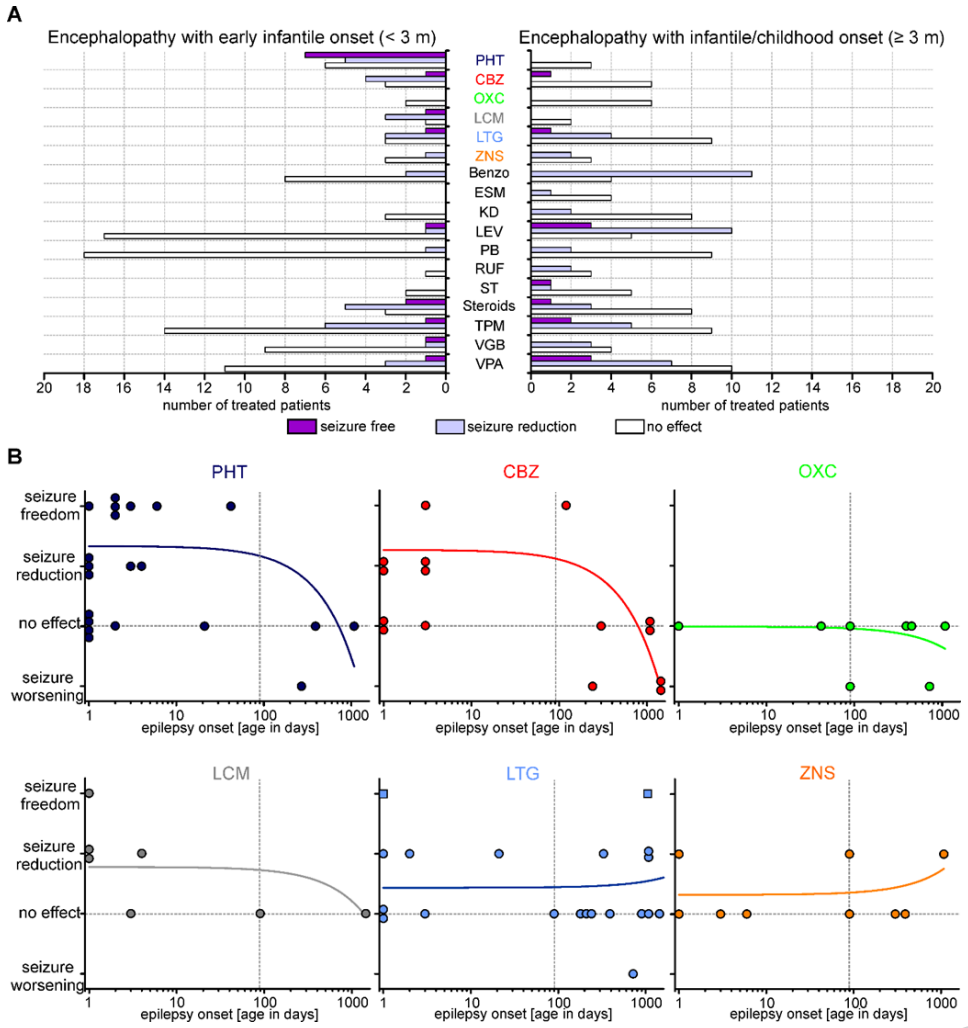
Treatment response

- Neonatal onset *SCN2A* related epilepsies (< 3 months) – BFNS, OS, EIMFS, EEs
  - Due to GOF mutations
  - Benefit from SCB – phenytoin, carbamazepine
  - Good chances of getting seizure free within first years of life

- Infantile and childhood onset epilepsies (> 3 months) – WS, MAE, LGS, EEs, unclassified
  - LOF mutations
  - No effect or seizure aggrevation on SCB
  - Often more intractable levetiracetam, benzodiazepines valproate
  - ID +/- autism



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Cognitive outcome depends on the underlying pathophysiology

- Ohthara syndrome
- *SCN2A* GOF variant
- Seizure free on PHT in the first week of life
- Neurological examination 2y 3m:
  - marked developmental delay
  - strabismus
  - hypotonia
  - clumsiness
  - ataxic gait requiring bilateral support
  - hand stereotypies

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Brain & Development 39 (2017) 345–348

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BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Efficacy of sodium channel blockers in *SCN2A* early infantile epileptic encephalopathy

Robertino Dilena [a,*], Pasquale Striano [b], Elena Gennaro [c], Laura Bassi [d], Sara Olivotto [e], Laura Tadini [a], Fabio Mosca [d], Sergio Barbieri [a], Federico Zara [f], Monica Fumagalli [d]

[a] *Service of Pediatric Epileptology – Unit of Clinical Neurophysiology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy*
[b] *Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophtalmology, Genetics, Maternal and Child Health, Institute "G. Gaslini" University of Genova, Genoa, Italy*
[c] *Laboratory of Genetics, E.O. Ospedali Galliera, Genova, Italy*
[d] *NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Università degli Studi di Milano, Milan, Italy*
[e] *Child and Adolescent Neuropsychiatric Service (UONPIA), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[f] *Pediatric Neurology and Muscular Diseases Unit, Laboratory of Neurogenetics, Institute "G. Gaslini", Genoa, Italy*

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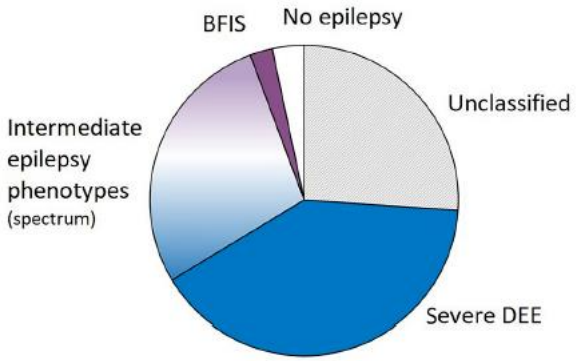
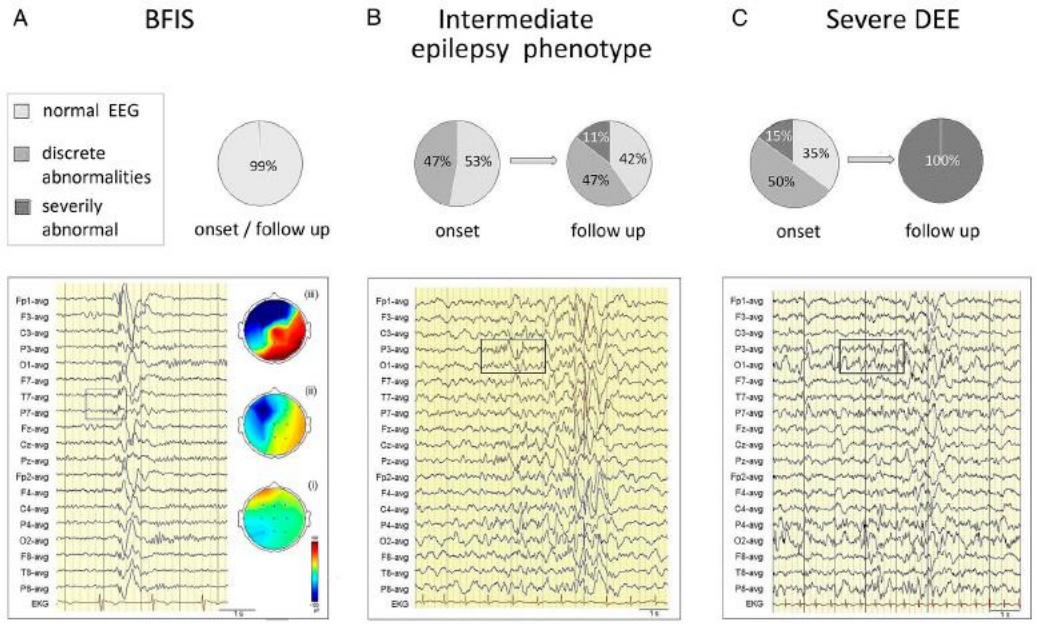
SCN8A/NaV1.6: Phenotypic spectrum

SCN8A related disorders: 1: 56.000



	No epilepsy	7	3.3%
	BFIS	5	2.4%
DEE	Intermediate	59	28%
DEE	Severe	85	40.3%
DEE	Unclassified	55	26%



	BFIS	Intermediate	Severe DEE
Age at onset	4-13 mo	14 mo (1.5 mo - 7 y)	4 mo (1 d - 3 y)
Sz Type	F (apnea) -> bilat TCS	TCS, M, F, Abs, T, AT, Sp	F (apnea) -> bilat TCS, T, Sp, M
Cognition / behavior	19 normal / 1 mild ID	Mild/moderate ID +/- autistic features	Severe / profound ID (+/- regression)
Outcome	All sz free	Ca. 50% sz free	Rare / short periods sz freedom
Neurological symptoms	Paroxysmal Kinesigenic Dykinesia	Ataxia, hypotonia, fine motor imp, speech delay, autistic features	No speech / eye contact, hypotonia tetraparesis, dyskinesia

Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes.

Gardella E, Møller RS.

Epilepsia. 2019 Dec;60 Suppl 3:S77-S85. doi: 10.1111/epi.16319.

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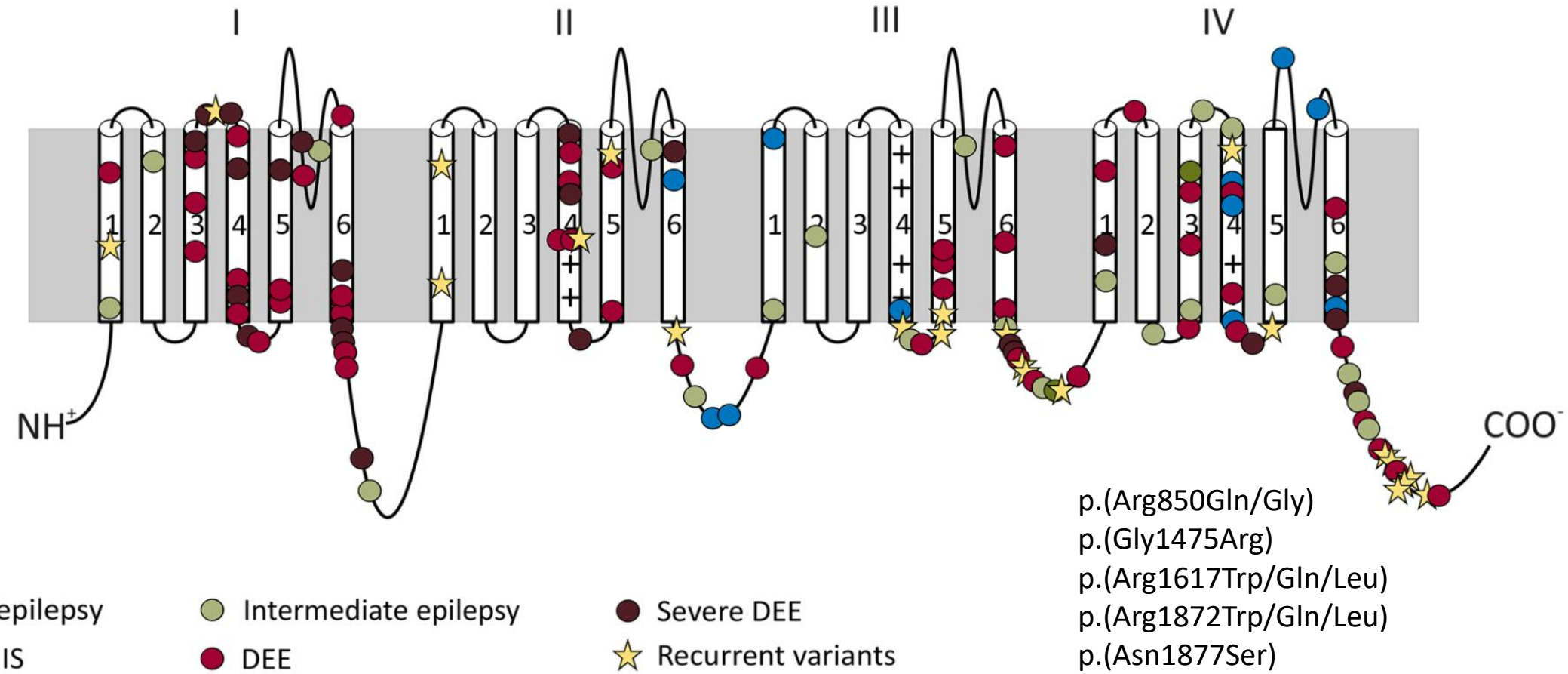
Genetic landscape

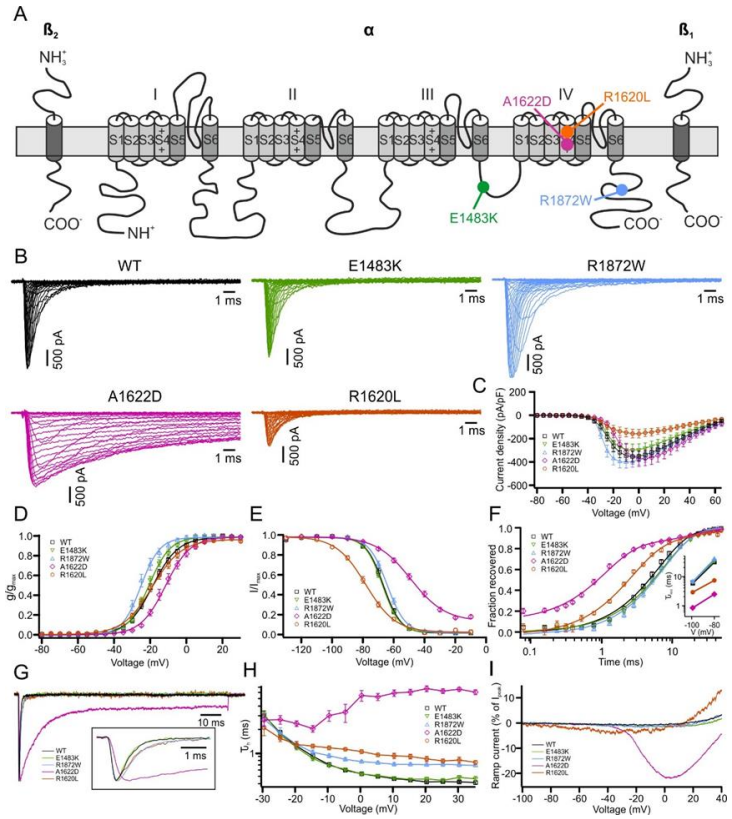


p.(Arg850Gln/Gly)
p.(Gly1475Arg)
p.(Arg1617Trp/Gln/Leu)
p.(Arg1872Trp/Gln/Leu)
p.(Asn1877Ser)

Functional effects

- Variants with clear **GOF**
  - Increased firing
  - BFIS, treatable epilepsy + ID, DEE
  - Beneficial effect of SCBs
- Variants with clear **LOF**
  - Decreased firing
  - DD, ID, movement disorders, or autism without epilepsy
- Selected variants with partial or complete **LOF**
  - Later onset generalized epilepsy with absence seizures
  - CIM SCBs

Functional studies of *SCN8A* mutants in ND7/23 cells

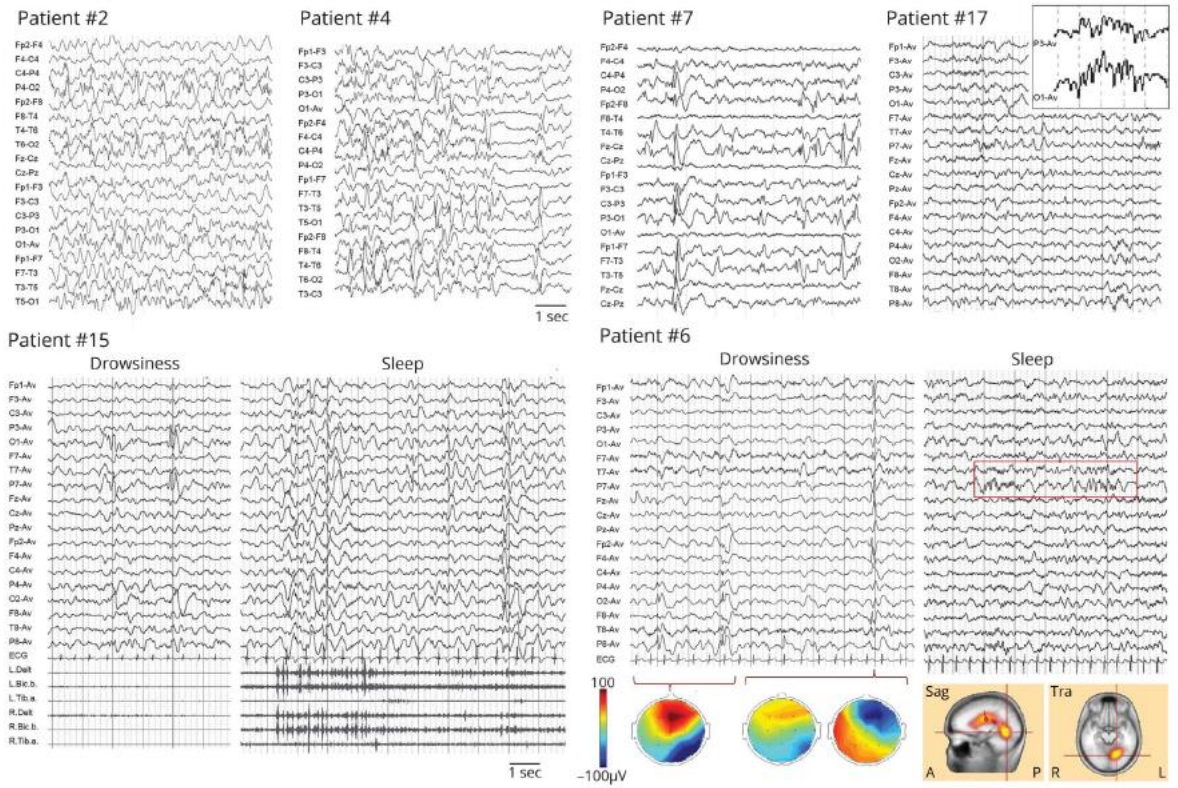


(Liu *et al.,* Brain 2019)

(Barker et al., 2016; Blanchard et al., 2015; Estacion et al., 2014; Veeramah et al., 2012; Wagnon et al., 2016; Trudeau et al., 2006; Wagnon et al., 2017; Liu et al., 2019; de Kovel et al., 2014; Møller et al., 2016, unpublished data)

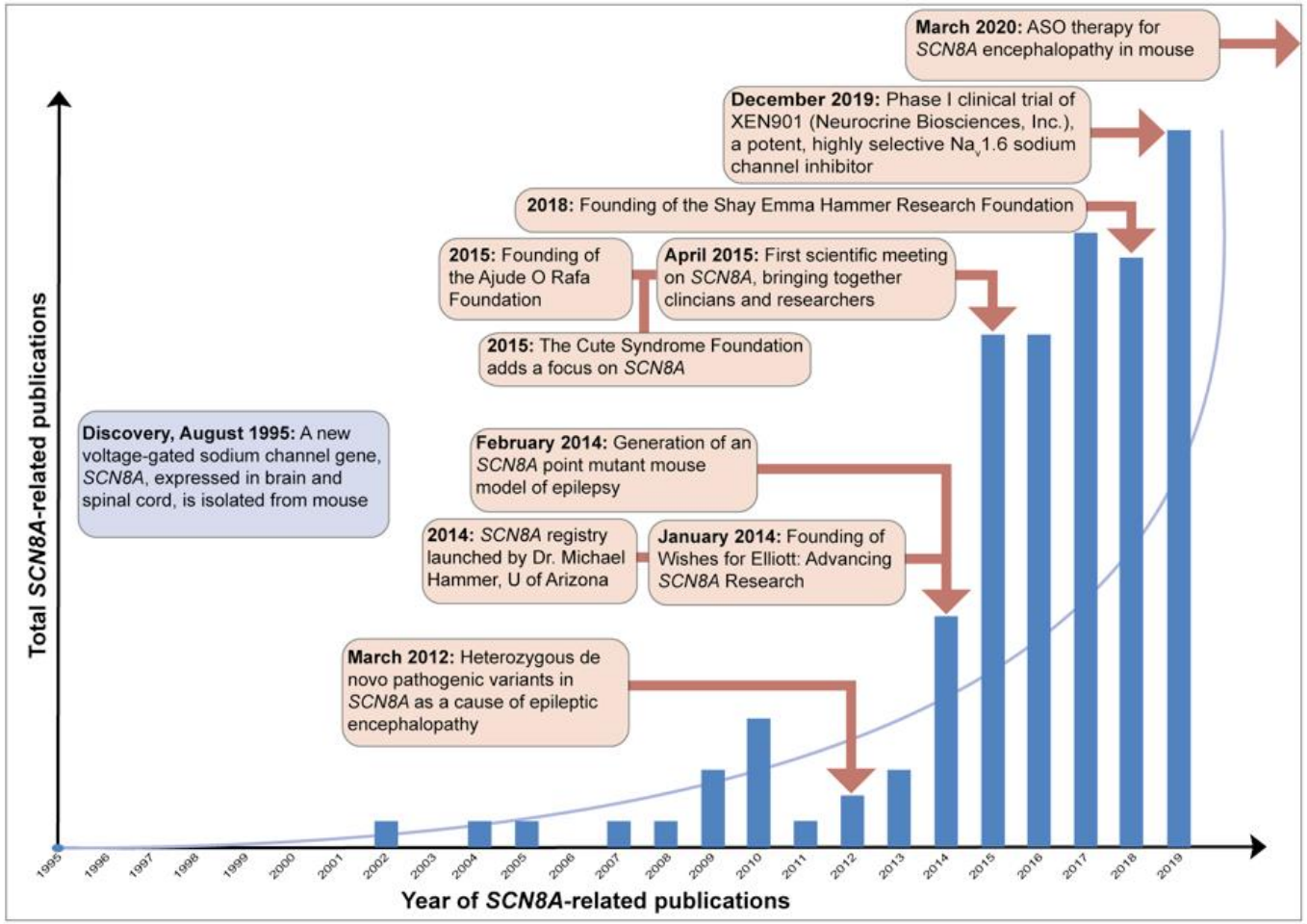
SCN8A developmental and epileptic encephalopathy

- GOF variants
- Median age of seizure onset: 4 months
- Developmental slowing, pyramidal/extrapyramidal signs, movement disorders, cortical blindness and severe gastrointestinal symptoms
- Focal seizures, spasm-like episodes, cortical myoclonus, nonconvulsive
- EEG: background deterioration, epileptiform abnormalities with a temporo-occipital predominance, and posterior delta/beta activity correlating with visual impairment
- MRI: progressive parenchymal atrophy and restriction of the optic radiations
- AEDs: oxcarbazepine, carbamazepine, phenytoin, and benzodiazepines
- Remain intractable



The phenotype of **SCN8A** developmental and epileptic encephalopathy.
Gardella E, Marini C, Trivisano M, Fitzgerald MP, Alber M, Howell KB, Darra F, Siliquini S, Bölsterli BK, Masnada S, Pichiecchio A, Johannesen KM, Jepsen B, Fontana E, Anibaldi G, Russo S, Cogliati F, Montomoli M, Specchio N, Rubboli G, Veggiotti P, Beniczky S, Wolff M, Helbig I, Vigevano F, Scheffer IE, Guerrini R, **Møller RS.**
Neurology. 2018 Sep 18;91(12):e1112-e1124. doi: 10.1212/WNL.0000000000006199. Epub 2018 Aug 31.

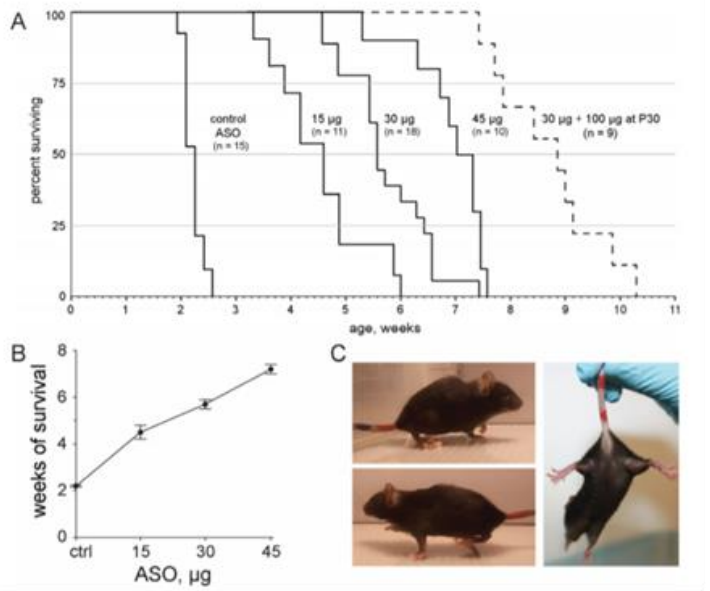
New treatments in the horizon



Borrowed from Ingo Helbig

Antisense oligonucleotides (ASO)

- ASOs offer the potential to correct or compensate for GOF/LOF variants
- ASOs can reduce the expression of an affected gene in a dose-dependent manner
- Demonstrated to reduce premature death and seizures in knock-in mouse models carrying *SCN2A* or *SCN8A* GOF mutations
- Application of *SCN8A* ASO was also effective in a mouse model of Dravet syndrome
- *SCN8A* suppression reduces neuronal network hyperexcitability
- ASOs can also be used to enhance gene expression by modulating nonproductive splicing events
- One of these approaches was shown to reduce seizures and mortality in a Dravet mouse model
- Some of these promising approaches are entering clinical trials

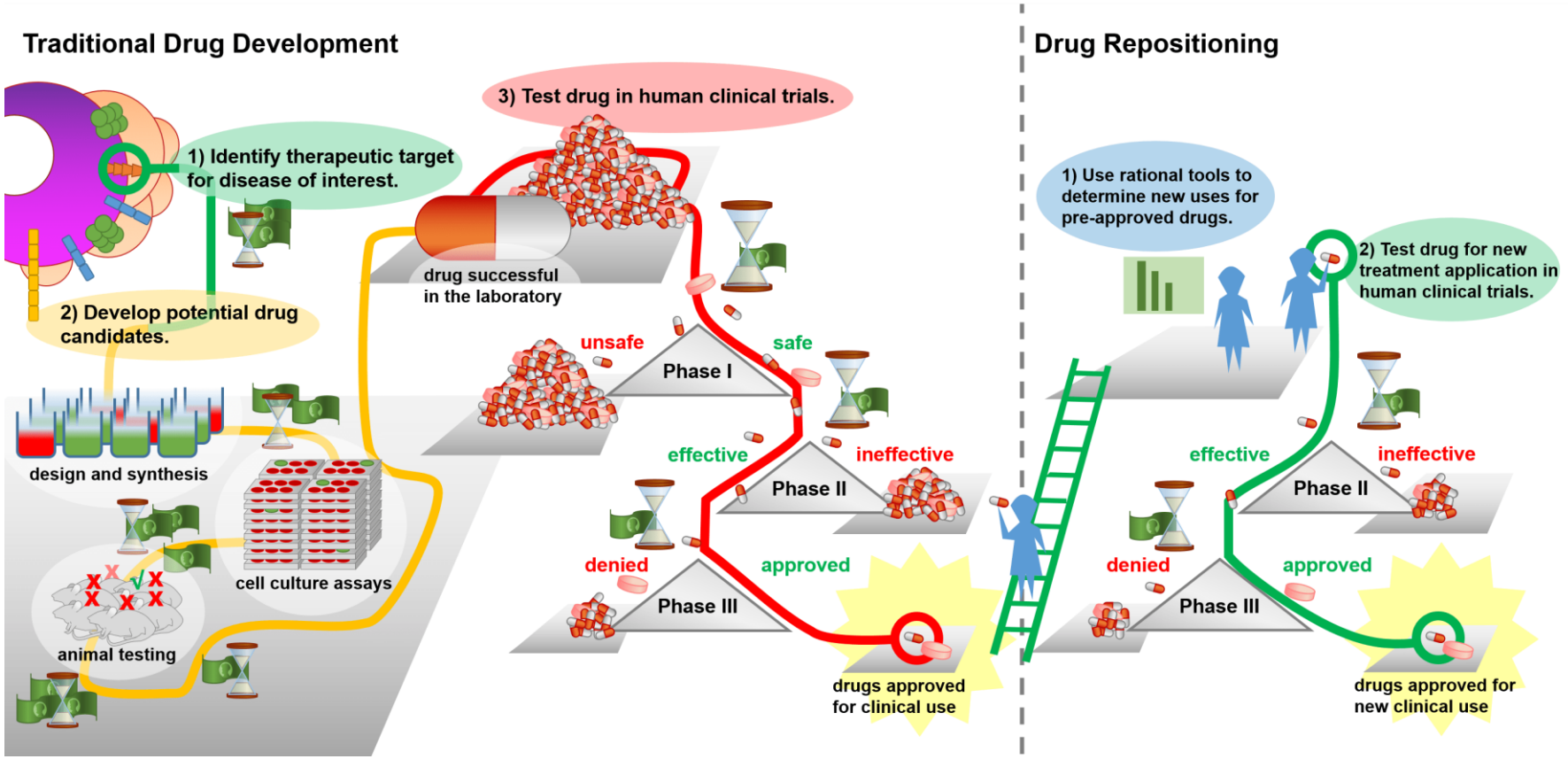


Scn8a Antisense Oligonucleotide Is Protective in Mouse Models of SCN8A Encephalopathy and Dravet Syndrome.
Lenk GM, Jafar-Nejad P, Hill SF, Huffman LD, Smolen CE, Wagnon JL, Petit H, Yu W, Ziobro J, Bhatia K, Parent J, Giger RJ, Rigo F, **Meisler MH.**
Ann Neurol. 2020 Mar;87(3):339-346. doi: 10.1002/ana.25676. Epub 2020 Feb 6.

Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of **Dravet** syndrome.
Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, Liu C, Leiser SC, Meena, Aznarez I, Liau G, Isom LL.
Sci Transl Med. 2020 Aug 26;12(558):eaaz6100. doi: 10.1126/scitranslmed.aaz6100.

Drug repurposing

- Drugs that are already approved for clinical use, and known to target a pathway that is also disrupted in epilepsy, can be considered as candidates for drug repositioning



http://sitn.hms.harvard.edu/flash/2016/re-engineering-cures-big-data-age-precision-medicine-computational-drug-repositioning/

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Drug repurposing in genetic epilepsies

- **Fenfluramine:**
  - From an anorexigen to an AED
  - Dravet syndrome (LOF)
  - Increases the levels of serotonin in the brain (inducing its release and by inhibiting its reuptake)
  - Phase III trial: >50% reduction was seen in 70%, and >75% reduction was seen in 45%

- **Quinidine:**
  - From antiarrhythmic drug to potential AED
  - *KCNT1* encephalopathy (GOF)
  - Potassium channel blocker
  - Case studies: variable effect

- **Memantine:**
  - From Alzheimer medication to potential AED
  - GRIN mutations (GOF)
  - NMDA-receptor antagonist
  - Case studies: variable effect

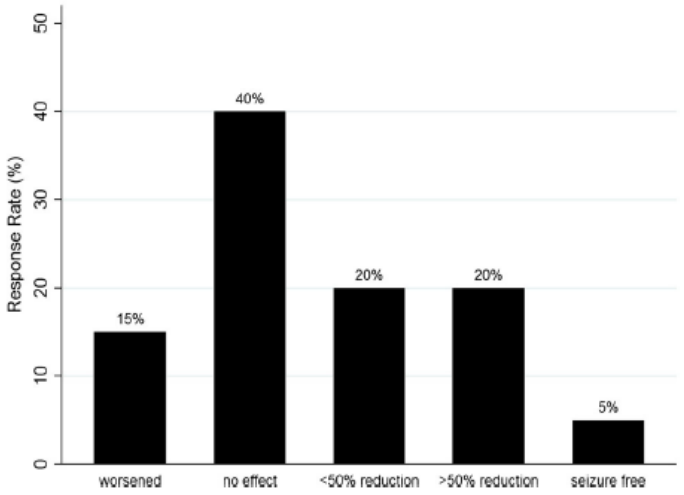
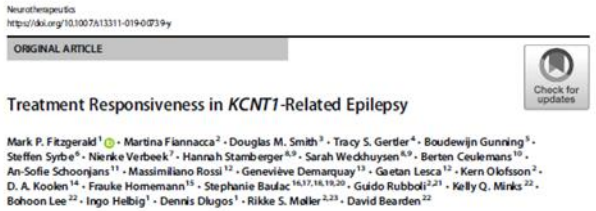


Fig. 1 Sustained efficacy of quinidine in KCNT1-related epilepsy. Response to quinidine was considered sustained if it lasted at least 3 months

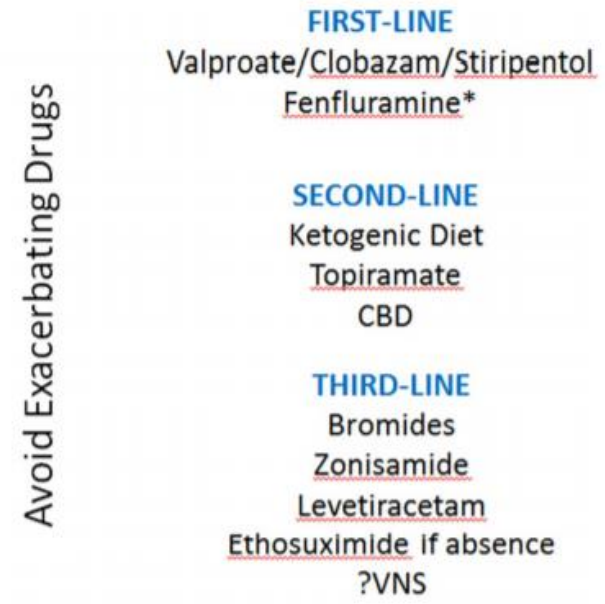

Neurotherapeutics
https://doi.org/10.1007/s13311-019-00739-y

ORIGINAL ARTICLE

Check for updates

Treatment Responsiveness in *KCNT1*-Related Epilepsy

Mark P. Fitzgerald[1] · Martina Fiannacca[2] · Douglas M. Smith[3] · Tracy S. Gertler[4] · Boudewijn Gunning[5] · Steffen Syrbe[6] · Nienke Verbeek[7] · Hannah Stamberger[8,9] · Sarah Weckhuysen[8,9] · Berten Ceulemans[10] · An-Sofie Schoonjans[11] · Massimiliano Rossi[12] · Geneviève Demarquay[13] · Gaetan Lesca[12] · Kern Olofsson[2] · D. A. Koolen[14] · Frauke Horemann[15] · Stephanie Baulac[16,17,18,19,20] · Guido Rubboli[2,21] · Kelly Q. Minks[22] · Bohoon Lee[22] · Ingo Helbig[1] · Dennis Dlugos[1] · Rikke S. Møller[2,23] · David Bearden[22]



Wirrell and Nabbout, 2019

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KCNA2: from gene discovery to potential treatment

Nat Genet. 2015 Apr;47(4):393-399. doi: 10.1038/ng.3239. Epub 2015 Mar 9.

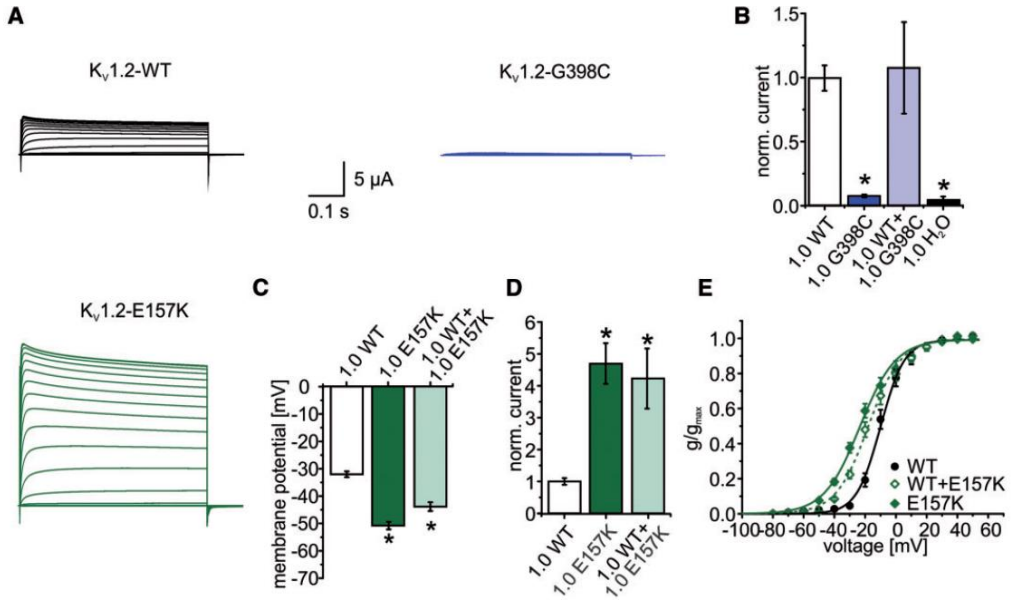
De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy.

Syrbe S[#1], Hedrich UBS[#2], Riesch E[#3,4,5], Djémié T[#6,7], Müller S[2], Møller RS[8,9], Maher B[10,11], Hernandez-Hernandez L[10,11], Synofzik M[12,13], Caglayan HS[14], Arslan M[15], Serratosa JM[16,17], Nothnagel M[18], May P[19], Krause R[19], Löffler H[2], Detert K[2], Dorn T[5], Vogt H[5], Krämer G[5], Schöls L[12,13], Mullis PE[20], Linnankivi T[21], Lehesjoki AE[22,23,24], Sterbova K[25], Craiu DC[26,27], Hoffman-Zacharska D[28], Korff CM[29], Weber YG[2], Steinlin M[30], Gallati S[4], Bertsche A[1], Bernhard MK[1], Merkenschlager A[1], Kiess W[1]; EuroEPINOMICS RES consortium, Gonzalez M[31], Züchner S[31], Palotie A[32,33,34], Suls A[6,7], De Jonghe P[6,7,35], Helbig I[36,37], Biskup S[3], Wolff M[38], Maljevic S[2], Schüle R[12,13,30], Sisodiya SM[10,11], Weckhuysen S[6,7], Lerche H[2], Lemke JR[1,4,39].

Brain. 2017 Sep 1;140(9):2337-2354. doi: 10.1093/brain/awx184.

Clinical spectrum and genotype-phenotype associations of KCNA2-related encephalopathies.

Masnada S[1,2,3], Hedrich UBS[4], Gardella E[5,6], Schubert J[4], Kaiwar C[7], Klee EW[8], Lanpher BC[9], Gavrilova RH[10], Synofzik M[11,12], Bast T[13], Gorman K[14,15], King MD[14,15], Allen NM[14,15], Conroy J[15], Ben Zeev B[16], Tzadok M[17], Korff C[18], Dubois F[19], Ramsey K[20,21], Narayanan V[20,21], Serratosa JM[22,23], Giraldez BG[22,23], Helbig I[24,25], Marsh E[24], O'Brien M[24], Berggvist CA[24], Binelli A[26,27], Porter B[28], Zaeyen E[29], Horovitz DD[30], Wolff M[31], Marjanovic D[3], Caglayan HS[32], Arslan M[33], Pena SDJ[34], Sisodiya SM[35], Balestrini S[35], Syrbe S[36,37], Veggiotti P[1,2], Lemke JR[38], Møller RS[3,6], Lerche H[4], Rubboli G[3,39].



- *KCNA2*, encoding the potassium channel $K_V1.2$
- **Loss of function** with a dominant-negative effect: febrile/afebrile, often focal seizure types, mild/moderate intellectual disability, ESES, favorable seizure outcome
- **Gain-of-function** effect leading to permanently open channels: more severe EE phenotype. Severe ID, intractable epilepsy, ataxia, and atrophy of the cerebellum

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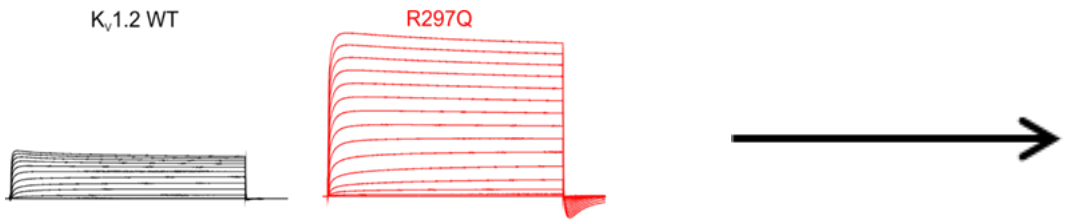
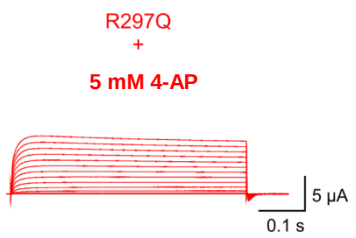
Targeted treatment – *KCNA2* gain-of-function encephalopathy

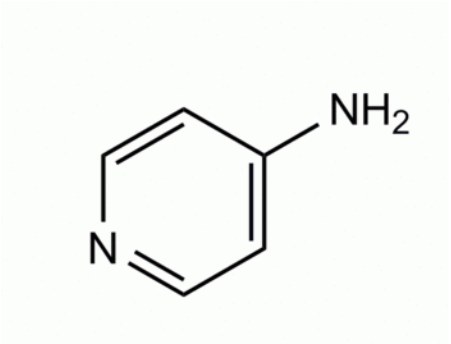
- Looking for potasium channel blockers
- 4-aminopyridine (4-AP): symptomatic treatment of decreased walking capacity in patients with multiple sclerosis
- Selective blocker of members of Kv1 (Shaker, KCNA) family of voltage-activated K+ channels)



gain of function



blocked by 4-AP



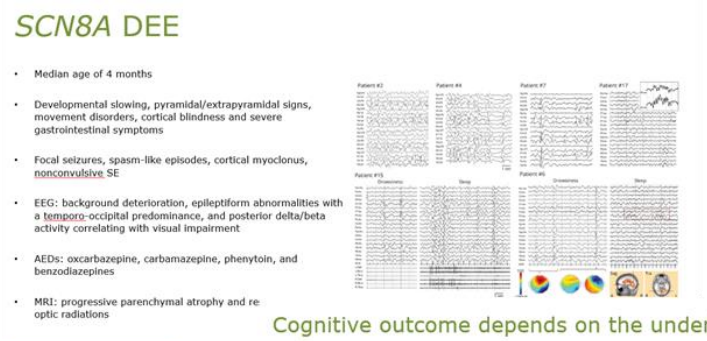
Case: 4-AP

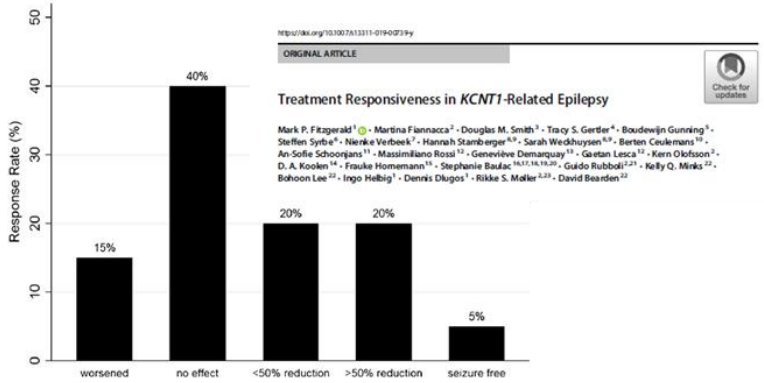
- June: spikes every 10-20 sec., 100 absence seizures pr day, rare GTCS, LTG, LCM, bromide
- September: 4-AP: 2 spikes in 20 min., seizure-free

Borrowed from Holger Lerche

Challenges towards precision medicine

- Largely so far unassociated with good quality data
- Anecdotal case reports, case series
- Lack of RCT
- Lack of standardized protocols in small clinical studies that would allow for clinical data to be meaningfully pooled and jointly analyzed
- Lack of functional data





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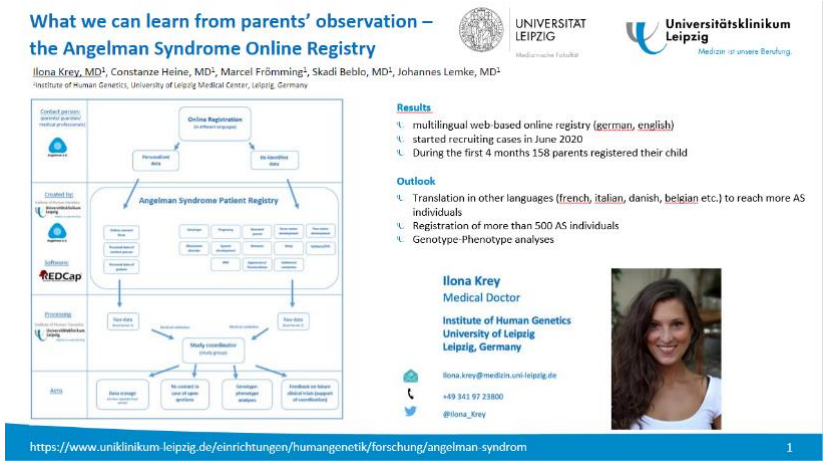
Phenotyping bottleneck

- Genome-first approaches, identifying novel genes first and then working backwards to understand the associated phenotypes
- "phenotyping bottleneck" : indicating the discrepancy between the genetic data that can be generated at an industrial scale and the clinical data that often still requires manual phenotyping
- Patient registries and natural history studies
- Develop protocols to systematically collect and analyze large-scale clinical data, including standardized outcomes and natural history data
- Patient advocacy groups



Borrowed from Ilona Krey

SLC6A1 Connect
SLC6A1 Research & Support

GRIN2B EUROPE

KCNT1 EPILEPSY
HOPE IS ON THE HORIZON

SCN8A EPILEPSY
The Cute Syndrome FOUNDATION
www.TheCuteSyndrome.com

KCNQ2 Cure ORG

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Take home messages

- First step towards precision medicine is precision diagnosis

- Genetic testing:
  - Early-onset epilepsies
  - Epilepsy with intellectual disability, autism, and/or other comorbidities
  - Progressive myoclonus epilepsies
  - Non-lesional focal epilepsies in specific familial syndromes
  - Non-lesional focal, therapy-resistant epilepsies in presurgical work-up
  - Epilepsy in the setting of focal malformations of cortical development

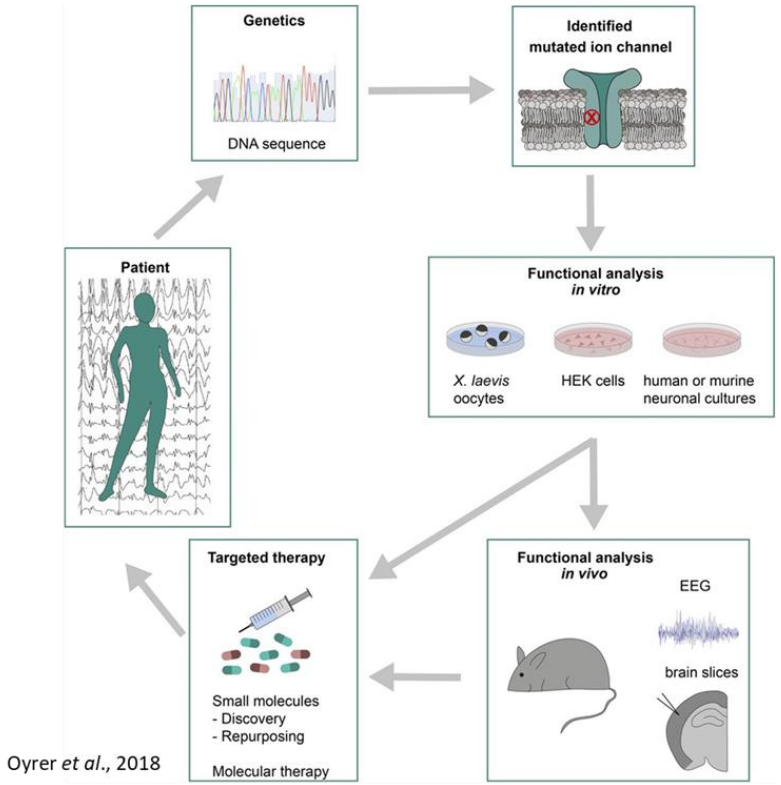
- Diagnostic testing is highly relevant in adults with epilepsy and ID

- Patient registries and natural history studies are needed

- Many precision medicine approaches – not always straightforward

- Complexities need to be acknowledged and addressed

- Entering an era of novel disease-modifying therapies targeting the cause of seizures, rather than seizures themselves



Oyrer *et al.*, 2018

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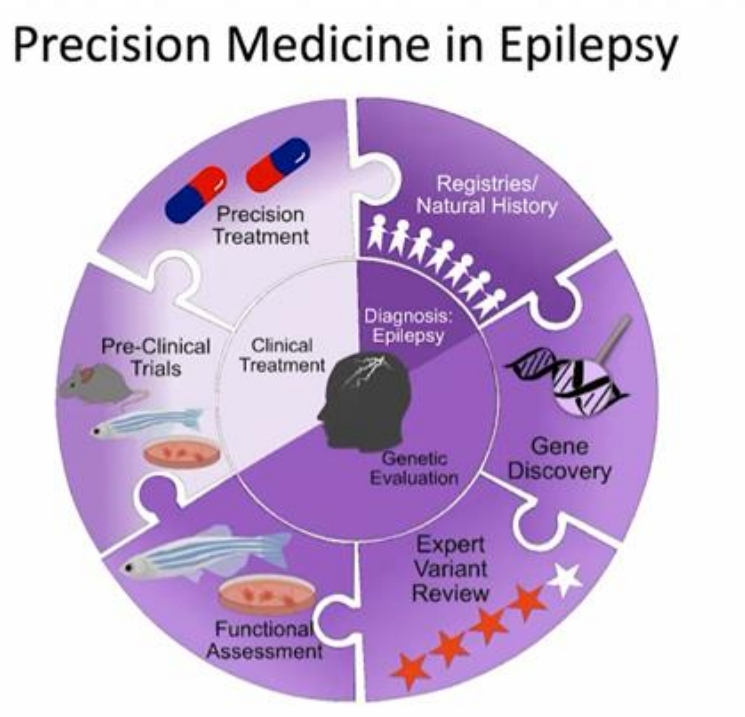
Whats next?

- Promising therapies are in the horizon: repurposed drugs, ASOs, small molecules
- Careful assessment and strategic application of novel functional tools
- Infrastructure and common standards for epilepsy precision trials
- From experimental models to N-of-1 trials and to randomized clinical trials
- Establish a framework to assess treatment responses, non-seizure outcomes, and develop protocols to systematically collect and analyze large-scale clinical data
- Registry of N-of-1 trials, that also records unsuccessful results
- Clinicians, geneticists, basic scientists, patient advocacy groups and industrial partners
- Will allow us to make significant progress in epilepsy precision medicine.



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