Genetics in epilepsy

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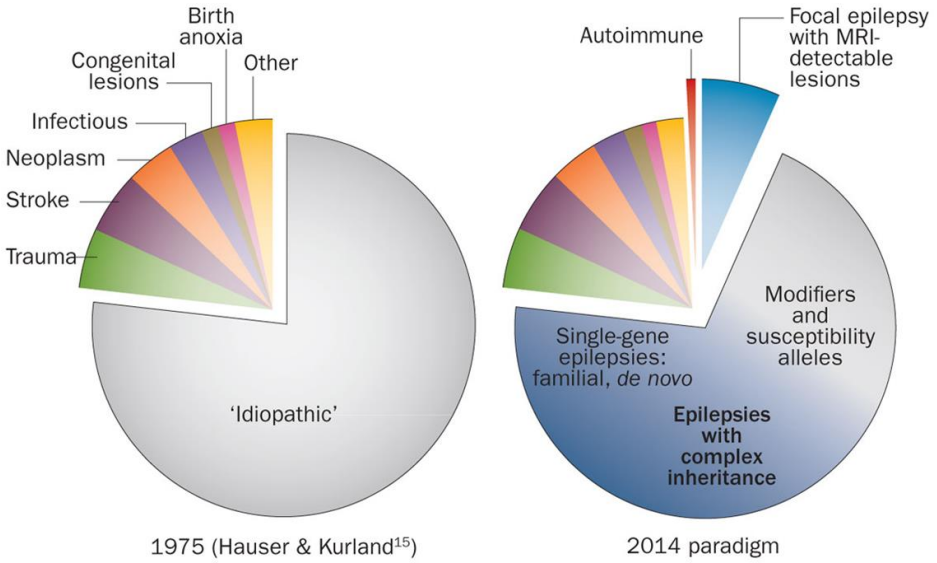
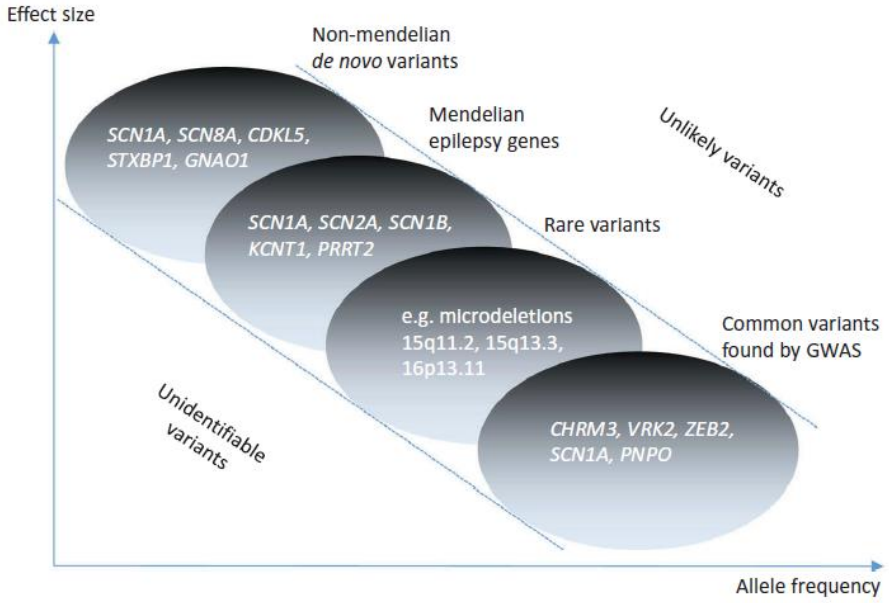
Background

- Spectrum disorder having different causative factors and phenotypes with individual prognosis and severity *(Brodie et al., 2009; Jensen, 2011)*
- Genetically heterogeneous
- The genetic contribution ranges from monogenic disorders involving genes with large effect size to complex disorders with many genes involved



Thomas and Berkovic, 2014



Møller et al, 2016

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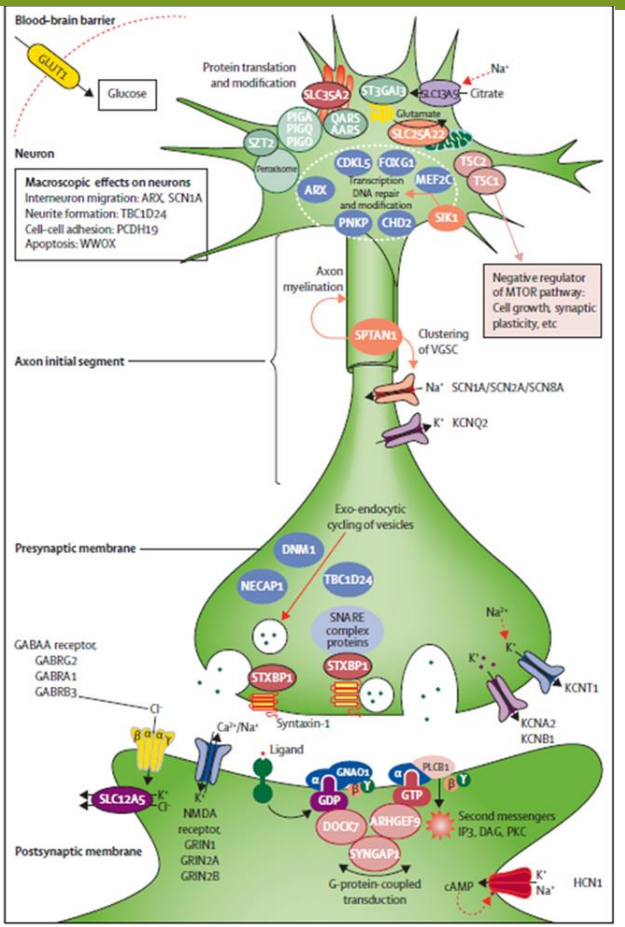

Figure 2: Disease mechanisms in childhood epileptic encephalopathies

McTague et al, 2015

Next Generation Sequencing Era: gene panels, exomes, genomes

Microdeletions

15q13.3
16p13.11
15q11.2

STX1B
SLC6A1
GABRA1
GABRB3
SIK1
KCNA2
ALG13
GRIN2B
PURA
KCNB1
KCNC1
DNM1
HCN1
CHD2
SCN8A
SCN2A
GRIN2A
DEPDC5
KCNT1
PRRT2
TBC1D24
STXBP1
PCDH19

Channelopathy Era

CHRNA4
SCN1B
KCNQ2
KCNQ3
SLC2A1
SCN1A
GABRG2
GABRA1
LGI1
CACNA1H
ARX
CDKL5

1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

Epileptic encephalopathies and familial focal epilepsies

Helbig et al, 2016

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Epileptic encephalopathies

- 40% of epilepsies with onset in infancy
- Genetic cause can be found in ~ 40%

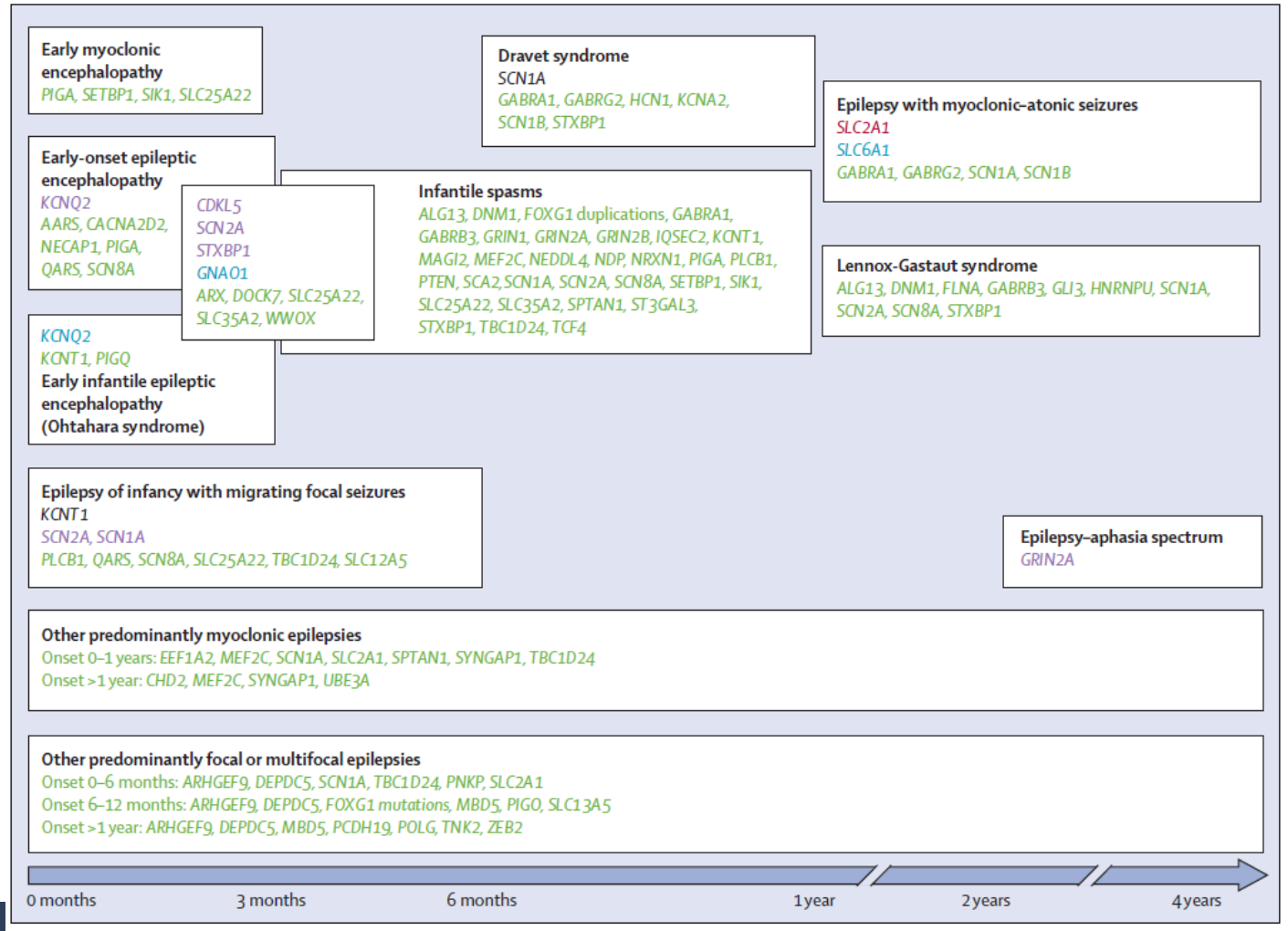

Figure 1: Genetic causes of epilepsy syndromes

McTague et al, 2015

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Familial focal epilepsies

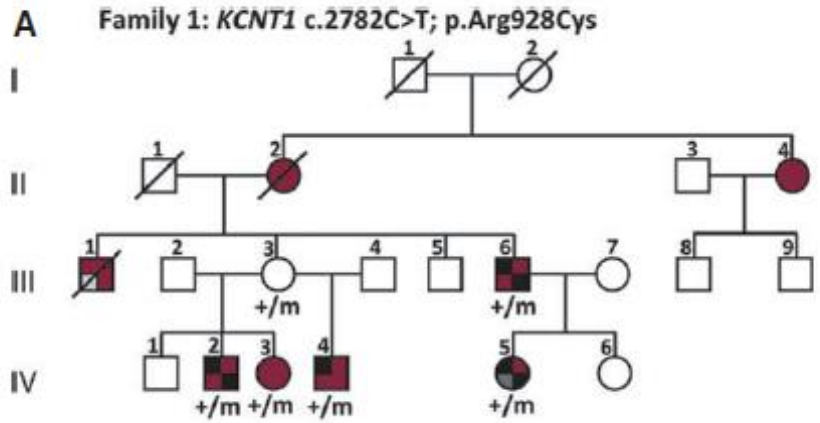
- Genetically heterogeneous group of epilepsy syndromes:
    - Benign familial neonatal seizures
    - Benign familial infantile seizures
    - Autosomal dominant nocturnal frontal lobe epilepsy
    - Familial autosomal dominant lateral temporal lobe epilepsy
    - Familial focal epilepsy with variable foci
    - Familial mesial temporal lobe epilepsy

- Ion channels (*SCN2A*, *SCN8A*, *KCNT1, KCNQ2, KCNQ3*)
- Acetylcholine nicotinic receptors (*CHRNA4*, *CHRNB2*, and *CHRNA2*)
- Glutamate receptors (*GRIN2A*)
- Repressors of mTORC1 (*DEPDC5*, *NPRL3*, *NPRL2*)
- Other proteins (*LGI1*, *RELN, PCDH19, PRRT2*)

- Mutations in repressors of the mTORC1 pathway, *DEPDC5*, *NPRL3*, and *NPRL2* have been found in 11%

- Age at onset varies markedly (range months to 43 years)

- Incomplete penetrance is frequently observed



McTague et al, 2015

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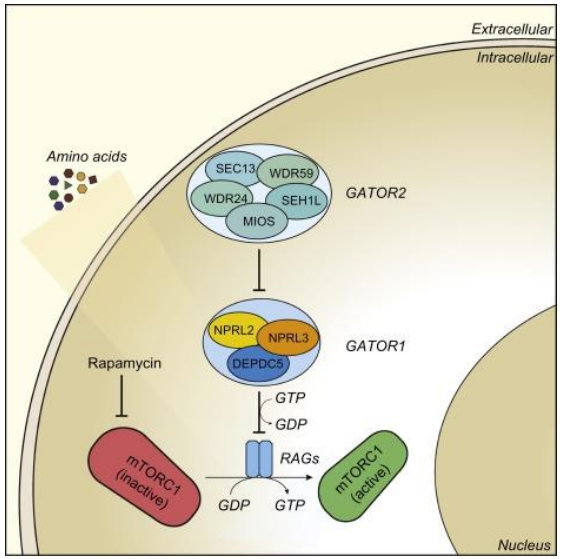
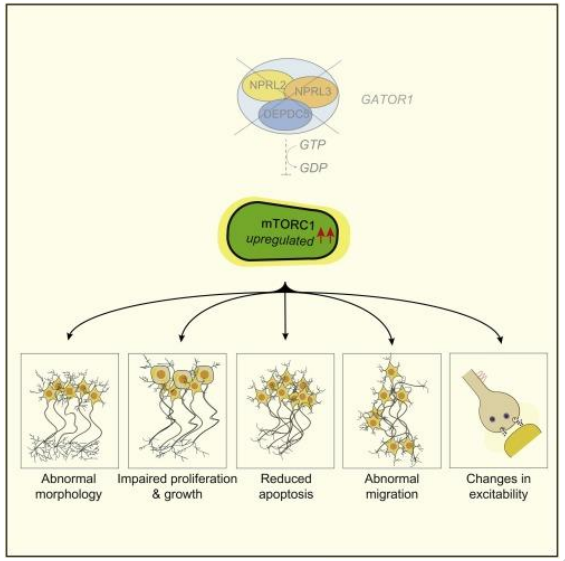
Case - *NPRL3*

- 8 year old normally developed girl
- Onset of seizures with headdrop and balance problems 1 year old
- Seizure free on VPA
- 5 years of age: Relapse of focal seizures with a tickling sensation behind her right ear. She is laughing, flexing her right arm and has balance problems – 2-12 pr day (10-15 sec)
- MRI normal
- Ictal EEG: focus in the left temporal lobe
- Currently seizure free on VPA and LTG
- *NPRL3:* (maternally)
- Mother and paternal halfsister of the mother with same symptoms





(Baulac S, 2016)

Genet Med. 2018 Aug 10. doi: 10.1038/s41436-018-0060-2. [Epub ahead of print]

The landscape of epilepsy-related GATOR1 variants.

Baldassari S[1,2,3,4,5], Picard F[6], Verbeek NE[7], van Kempen M[7], Brilstra EH[7], Lesca G[8], Conti V[9], Guerrini R[9], Bisulli F[10], Licchetta L[10], Pippucci T[11], Tinuper P[10], Hirsch E[12], de Saint Martin A[13], Chelly J[14], Rudolf G[14], Chipaux M[15], Ferrand-Sorbets S[15], Dorfmüller G[15], Sisodiya S[16], Balestrini S[16], Schoeler N[16], Hernandez-Hernandez L[16], Krithika S[16], Oegema R[7], Hagebeuk E[17], Gunning B[17], Deckers C[17], Berghuis B[17], Weqner I[17], Niks E[18], Jansen FE[19], Braun K[19], de Jong D[20], Rubboli G[21], Talvik I[22], Sander V[22], Uldall P[23], Jacquemont ML[24], Nava C[1,2,3,4,5], Lequern E[1,2,3,4,5], Julia S[25], Gambardella A[26], d'Orsi G[27], Crichiutti G[28], Faivre L[29], Darmency V[30], Benova B[31], Krsek P[31], Biraben A[32], Lebre AS[33], Jennesson M[34], Sattar S[35], Marchal C[36], Nordli DR Jr[37], Lindstrom K[38], Striano P[39], Lomax LB[40,41], Kiss C[41], Bartolomei F[42], Lepine AF[42], Schoonjans AS[43], Stouffs K[44], Jansen A[44], Panagiotakaki E[45], Ricard-Mousnier B[46], Thevenon J[47], de Bellescize J[45], Catenoix H[45], Dorn T[48], Zenker M[49], Müller-Schlüter K[50], Brandt C[51], Krey I[52], Polster T[51], Wolff M[53], Balci M[54], Rostasy K[54], Achaz G[55], Zacher P[56], Becher T[57], Cloppenborg T[51], Yuskaitis CJ[58,59,60], Weckhuysen S[61], Poduri A[58,59,60], Lemke JR[52], Møller RS[62], Baulac S[63,64,65,66,67].

Genetics of IGE

- One third of all epilepsies

- Include several distinct epilepsy syndromes:
  - Juvenile myoclonic epilepsy
  - Childhood absence epilepsy
  - Juvenile Absence Epilepsy
  - Epilepsy with generalized tonic–clonic seizures

Genetics of IGE
Monogenic
GABRG2, GABRA1, SLC2A1 (GLUT1-DS)
Rare genetic risk factors
Microdeletions e.g. 15q13.3, 16p13.11, 15q11.2
Common genetic risk factors
CHRM3, VRK2, ZEB2, SCN1A, PNPO

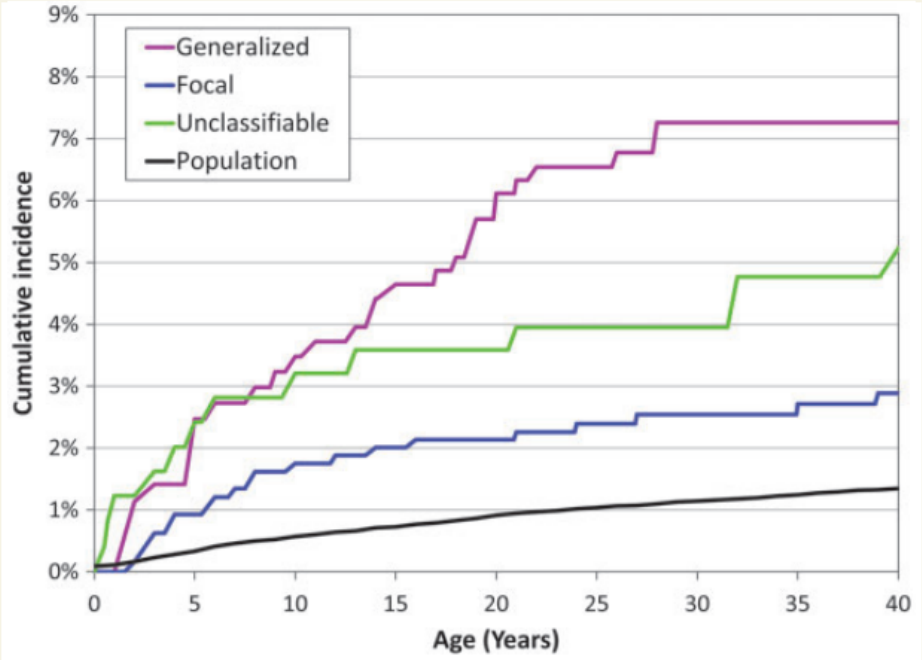


Figure 1 Age-specific cumulative incidence of epilepsy in first-degree relatives of probands with epilepsy, by proband epilepsy type.

(Peljto et al, 2014)

Technologies

- Targeted gene panels
- Whole exome sequencing
- Array CGH

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

Gene panels in epilepsy

- A gene panel is a test that analyzes multiple genes at once
- Offer a middle ground between sequencing just a single gene and sequencing every gene in the genome
- Gene panels of 30–>500 genes: diagnostic yields ranging between 10% and 48.5%

DOI: 10.1111/epi.14074

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

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

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Summary

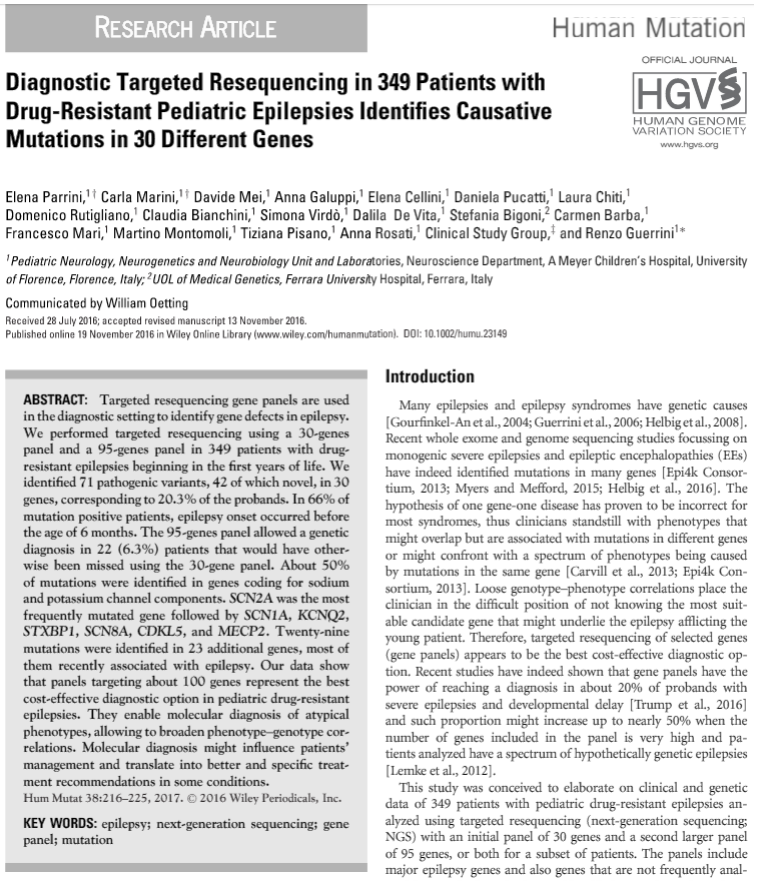
Objective: We evaluated >8500 consecutive, unselected patients with epilepsy and neurodevelopmental disorders who underwent multigene panel testing to determine the average age at molecular diagnosis and diagnostic yield of 70 genes.

Methods: We reviewed molecular test results for 70 genes known to cause epilepsy and neurodevelopmental disorders using next generation sequencing (NGS) and exon-level array comparative genomic hybridization (aCGH). A positive result was defined as the presence of 1 or 2 pathogenic or likely pathogenic (P/LP) variants in a single gene, depending on the mode of inheritance of the associated disorder.

Results: Overall, 22 genes were found to have a high yield of positive findings by genetic testing, with *SCN1A* and *KCNQ2* accounting for the greatest number of positive findings. In contrast, there were no positive findings in 16 genes. Most of the P/LP variants were sequence changes identified by NGS (90.9%), whereas ~9% were gross deletions or duplications detected by exon-level aCGH. The mean age of molecular diagnosis for the cohort was 5 years, 8 months (ranging from 1 week to 47 years). Recurrent P/LP variants were observed in 14 distinct genes, most commonly in *MECP2, KCNQ2, SCN1A, SCN2A, STXBP1,* and *PRRT2*. Parental testing was performed in >30% of positive cases. All variants identified in *CDKL5, STXBP1, SCN8A, GABRA1,* and *FOXG1* were de novo, whereas 85.7% of variants in *PRRT2* were inherited.

Significance: Using a combined approach of NGS and exon-level aCGH, testing identified a genetic etiology in 15.4% of patients in this cohort and revealed the age at molecular diagnosis for patients. Our study highlights both high- and low-yield genes associated with epilepsy and neurodevelopmental disorders, indicating which genes may be considered for molecular diagnostic testing.

KEYWORDS
epilepsy, genetic testing, next generation sequencing



RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Diagnostic Targeted Resequencing in 349 Patients with Drug-Resistant Pediatric Epilepsies Identifies Causative Mutations in 30 Different Genes

Elena Parrini,[1†] Carla Marini,[1†] Davide Mei,[1] Anna Galuppi,[1] Elena Cellini,[1] Daniela Pucatti,[1] Laura Chiti,[1] Domenico Rutigliano,[1] Claudia Bianchini,[1] Simona Virdò,[1] Dalila De Vita,[1] Stefania Bigoni,[2] Carmen Barba,[1] Francesco Mari,[1] Martino Montomoli,[1] Tiziana Pisano,[1] Anna Rosati,[1] Clinical Study Group,[‡] and Renzo Guerrini[1*]

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Published online 19 November 2016 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.23149

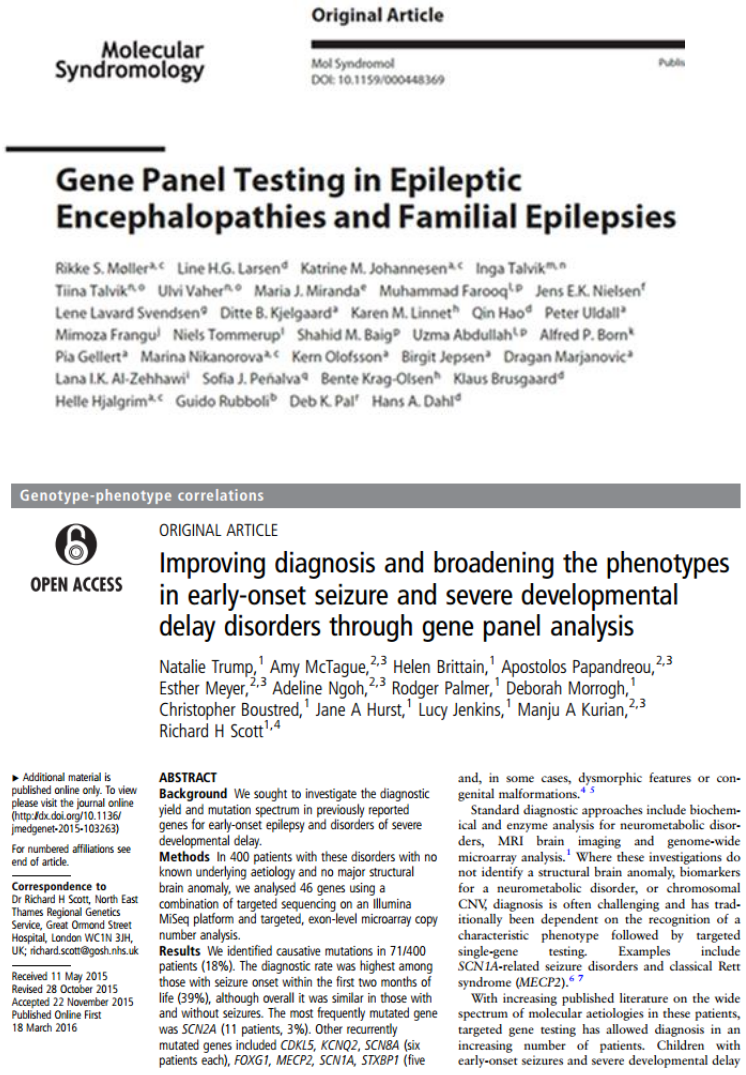
ABSTRACT: Targeted resequencing gene panels are used in the diagnostic setting to identify gene defects in epilepsy. We performed targeted resequencing using a 30-genes panel and a 95-genes panel in 349 patients with drug-resistant epilepsies beginning in the first years of life. We identified 71 pathogenic variants, 42 of which novel, in 30 genes, corresponding to 20.3% of the probands. In 66% of mutation positive patients, epilepsy onset occurred before the age of 6 months. The 95-genes panel allowed a genetic diagnosis in 22 (6.3%) patients that would have otherwise been missed using the 30-gene panel. About 50% of mutations were identified in genes coding for sodium and potassium channel components. *SCN2A* was the most frequently mutated gene followed by *SCN1A, KCNQ2, STXBP1, SCN8A, CDKL5,* and *MECP2*. Twenty-nine mutations were identified in 23 additional genes, most of them recently associated with epilepsy. Our data show that panels targeting about 100 genes represent the best cost-effective diagnostic option in pediatric drug-resistant epilepsies. They enable molecular diagnosis of atypical phenotypes, allowing to broaden phenotype–genotype correlations. Molecular diagnosis might influence patients' management and translate into better and specific treatment recommendations in some conditions.
Hum Mutat 38:216–225, 2017. © 2016 Wiley Periodicals, Inc.

KEY WORDS: epilepsy; next-generation sequencing; gene panel; mutation

Introduction

Many epilepsies and epilepsy syndromes have genetic causes [Gourfinkel-An et al., 2004; Guerrini et al., 2006; Helbig et al., 2008]. Recent whole exome and genome sequencing studies focussing on monogenic severe epilepsies and epileptic encephalopathies (EEs) have indeed identified mutations in many genes [Epi4k Consortium, 2013; Myers and Mefford, 2015; Helbig et al., 2016]. The hypothesis of one gene-one disease has proven to be incorrect for most syndromes, thus clinicians standstill with phenotypes that might overlap but are associated with mutations in different genes or might confront with a spectrum of phenotypes being caused by mutations in the same gene [Carvill et al., 2013; Epi4k Consortium, 2013]. Loose genotype–phenotype correlations place the clinician in the difficult position of not knowing the most suitable candidate gene that might underlie the epilepsy afflicting the young patient. Therefore, targeted resequencing of selected genes (gene panels) appears to be the best cost-effective diagnostic option. Recent studies have indeed shown that gene panels have the power of reaching a diagnosis in about 20% of probands with severe epilepsies and developmental delay [Trump et al., 2016] and such proportion might increase up to nearly 50% when the number of genes included in the panel is very high and patients analyzed have a spectrum of hypothetically genetic epilepsies [Lemke et al., 2012].

This study was conceived to elaborate on clinical and genetic data of 349 patients with pediatric drug-resistant epilepsies analyzed using targeted resequencing (next-generation sequencing; NGS) with an initial panel of 30 genes and a second larger panel of 95 genes, or both for a subset of patients. The panels include major epilepsy genes and also genes that are not frequently anal-



Original Article

Molecular Syndromology

Mol Syndromol
DOI: 10.1159/000448369

Gene Panel Testing in Epileptic Encephalopathies and Familial Epilepsies

Rikke S. Møller[a,c] Line H.G. Larsen[d] Katrine M. Johannesen[a,c] Inga Talvik[m,n] Tiina Talvik[n,o] Ulvi Vaher[n,o] Maria J. Miranda[e] Muhammad Farooq[i,p] Jens E.K. Nielsen[f] Lene Lavard Svendsen[g] Ditte B. Kjelgaard[a] Karen M. Linnet[h] Qin Hao[d] Peter Uldall[a] Mimoza Frangu[j] Niels Tommerup[j] Shahid M. Baig[p] Uzma Abdullah[i,p] Alfred P. Born[k] Pia Gellert[a] Marina Nikanorova[a,c] Kern Olofsson[a] Birgit Jepsen[a] Dragan Marjanovic[a] Lana I.K. Al-Zehhawi[l] Sofia J. Peñalva[q] Bente Krag-Olsen[h] Klaus Brusgaard[d] Helle Hjalgrim[a,c] Guido Rubboli[b] Deb K. Pal[r] Hans A. Dahl[d]

Genotype-phenotype correlations

OPEN ACCESS

ORIGINAL ARTICLE

Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis

Natalie Trump,[1] Amy McTague,[2,3] Helen Brittain,[1] Apostolos Papandreou,[2,3] Esther Meyer,[2,3] Adeline Ngoh,[2,3] Rodger Palmer,[1] Deborah Morrogh,[1] Christopher Boustred,[1] Jane A Hurst,[1] Lucy Jenkins,[1] Manju A Kurian,[2,3] Richard H Scott[1,4]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2015-103263)

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ABSTRACT

Background We sought to investigate the diagnostic yield and mutation spectrum in previously reported genes for early-onset epilepsy and disorders of severe developmental delay.

Methods In 400 patients with these disorders with no known underlying aetiology and no major structural brain anomaly, we analysed 46 genes using a combination of targeted sequencing on an Illumina MiSeq platform and targeted, exon-level microarray copy number analysis.

Results We identified causative mutations in 71/400 patients (18%). The diagnostic rate was highest among those with seizure onset within the first two months of life (39%), although overall it was similar in those with and without seizures. The most frequently mutated gene was *SCN2A* (11 patients, 3%). Other recurrently mutated genes included *CDKL5, KCNQ2, SCN8A* (six patients each), *FOXG1, MECP2, SCN1A, STXBP1* (five and, in some cases, dysmorphic features or congenital malformations.[4 5]

Standard diagnostic approaches include biochemical and enzyme analysis for neurometabolic disorders, MRI brain imaging and genome-wide microarray analysis.[1] Where these investigations do not identify a structural brain anomaly, biomarkers for a neurometabolic disorder, or chromosomal CNV, diagnosis is often challenging and has traditionally been dependent on the recognition of a characteristic phenotype followed by targeted single-gene testing. Examples include *SCN1A*-related seizure disorders and classical Rett syndrome (*MECP2*).[6 7]

With increasing published literature on the wide spectrum of molecular aetiologies in these patients, targeted gene testing has allowed diagnosis in an increasing number of patients. Children with early-onset seizures and severe developmental delay

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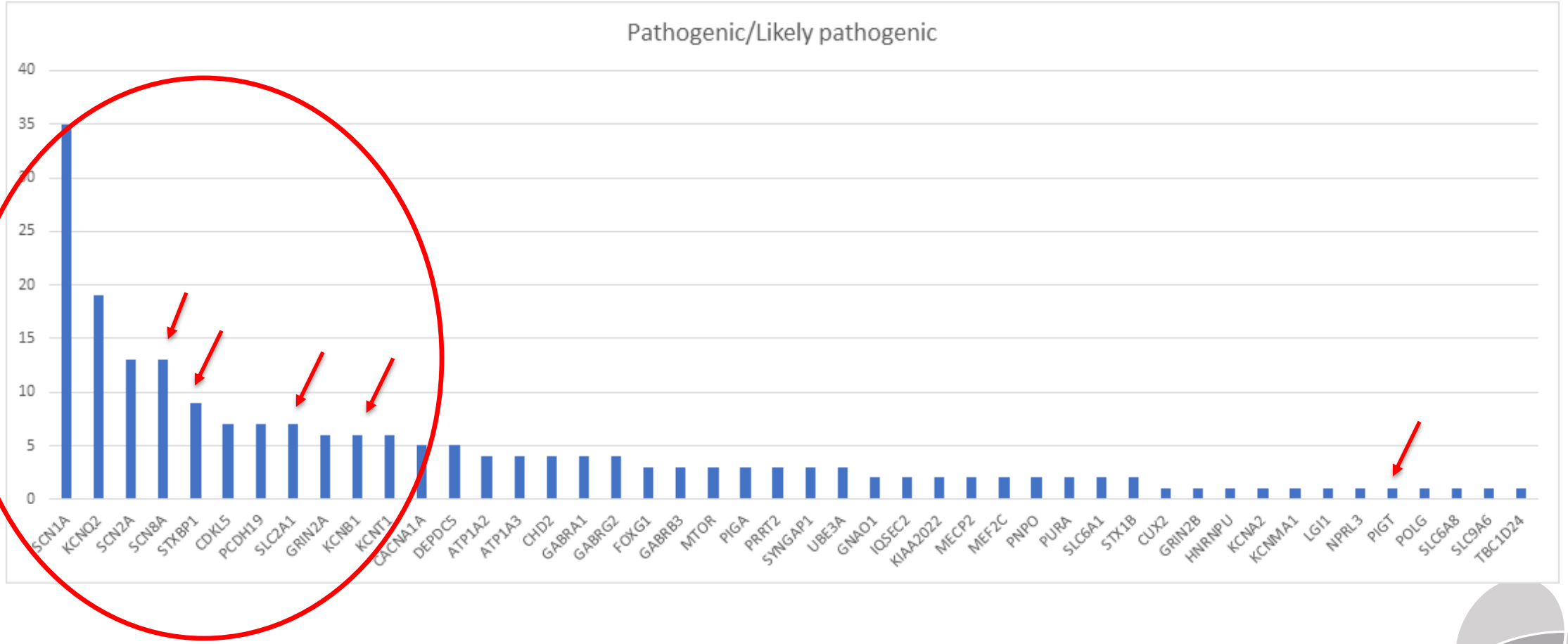
Gene panel testing

- Pathogenic/likely pathogenic: 209/1041 (20.1%) in 46 different genes

- Mainly early onset EEs or intractable focal/multifocal epilepsies, but also milder phenotypes



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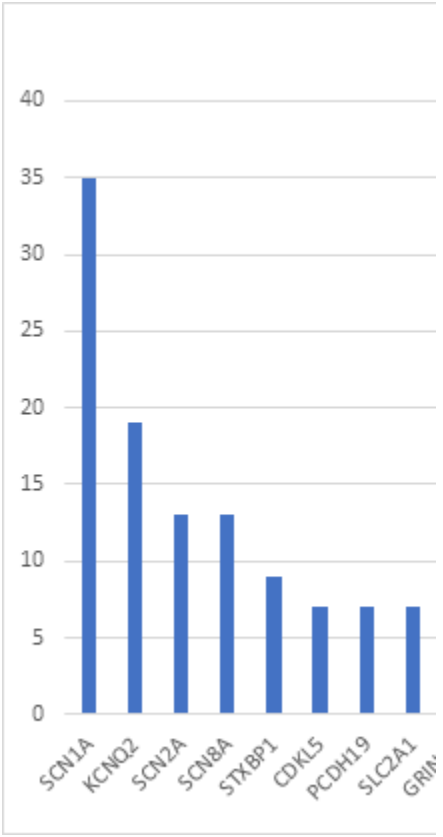
Incidence in the Danish population

- Birth cohort from 2008-2014

- Incidence of common epilepsy genes
  - *SCN1A* related DS: 1: 22.000 *(Bayat et al., 2015)*
  - *CDKL5* EE 1: 50.000
  - *SCN8A* related disorders: 1: 61.000
  - *SCN2A* related disorders: 1: 78.000 *(Wolff et al., 2017)*
  - *STXBP1* EE: 1: 80.000
  - GLUT1 deficiency: 1: 83.000 *(Larsen et al., 2015)*



NHS SCOTLAND

The Genetic and Autoimmune Childhood Epilepsy **(GACE)** Study

Scottish whole population prospective screening for genetic and autoimmune etiologies in epilepsy and complex febrile seizures for children < 3 years: diagnostic and clinical utility

University of Glasgow

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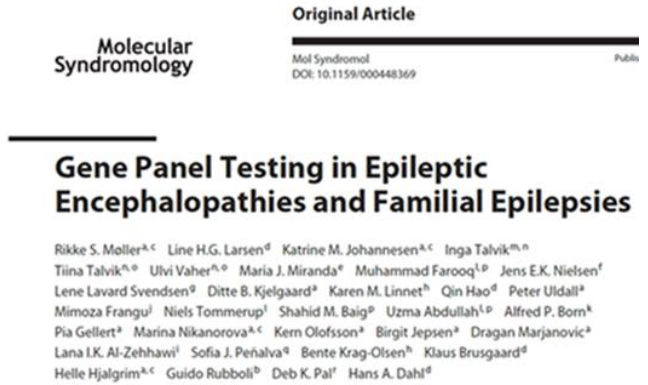
NGS gene panel – yield versus age of onset

- Neonatal-onset epilepsies: 57%
- Onset between 2 mo and 2y: 26%
- Onset between 2 and 9y: 14%
- Onset between 10 and 28y: 0



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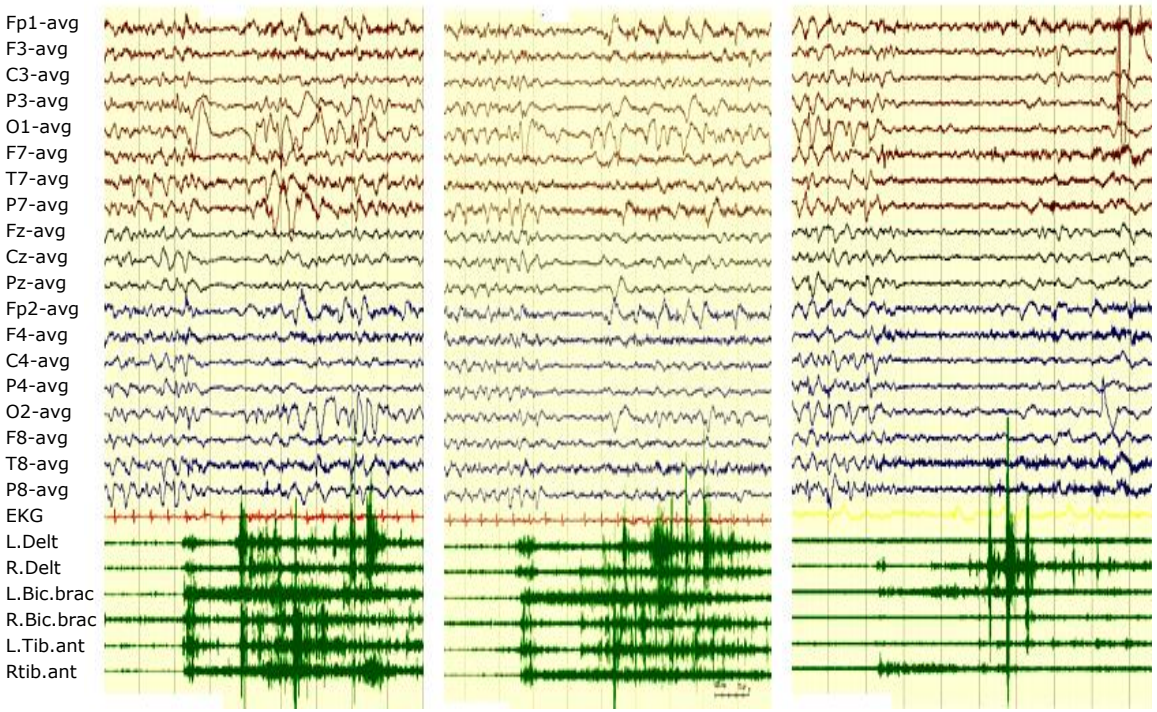
Helle Hjalgrim[a,c] Guido Rubboli[b] Deb K. Pal[r] Hans A. Dahl[d]

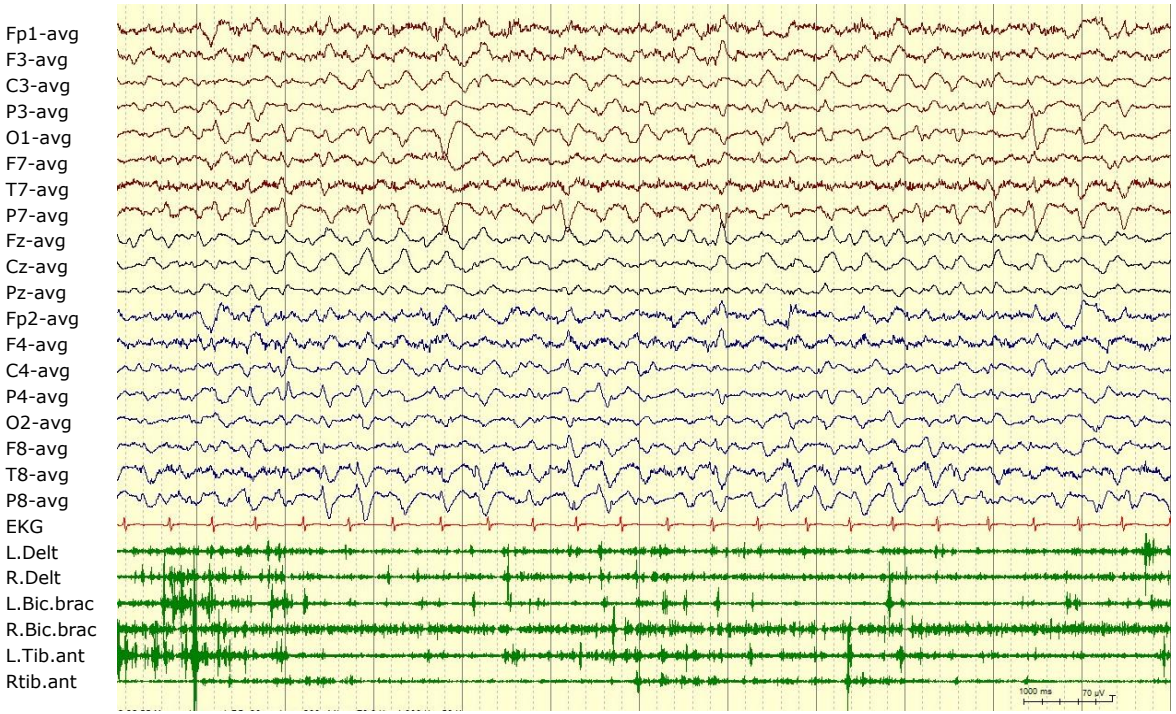
Case – *SCN8A*

- 11 year old girl with profound ID, intractable epilepsy
- Normal early development
- Onset 2.5 months: focal clonic seizures and tonic seizures
- EEG: normal
- Seizure free for a few weeks
- Multiple seizure types: spasms, focal, clonic, tonic, myoclonus, SE
- Intractable epilepsy: daily seizures in clusters

Spasm-like episode



Myoclonus


Fp1-avg
F3-avg
C3-avg
P3-avg
O1-avg
F7-avg
T7-avg
P7-avg
Fz-avg
Cz-avg
Pz-avg
Fp2-avg
F4-avg
C4-avg
P4-avg
O2-avg
F8-avg
T8-avg
P8-avg
EKG
L.Delt
R.Delt
L.Bic.brac
R.Bic.brac
L.Tib.ant
Rtib.ant
1000 ms
70 µV

Follow up

- Stagnation after seizure onset
- 20 m: developmental regression and worsening of pyramidal/extra-pyramidal signs
- EEG: 20 m: bilateral temporo-occipito-parietal delta activity and spike-and-slow wave with superimposed beta activity
- Gradually lost eye contact – cortical visual impairment
- Profound neurological deterioration – hypertonia, hyperreflexia
- Gastrointestinal disorder: severe gastro-esophageal reflux, constipation, PEG feeding tube
- Slight improvement from 8y
- Treatment: OXC, TPM

Neurology. 2018 Aug 31. pii: 10.1212/WNL.0000000000006199. doi: 10.1212/WNL.0000000000006199. [Epub ahead of print]

The phenotype of *SCN8A* developmental and epileptic encephalopathy.

Gardella E[1], Marini C[2], Trivisano M[2], Fitzgerald MP[2], Alber M[2], Howell KB[2], Darra F[2], Siliquini S[2], Bölsterli BK[2], Masnada S[2], Pichiecchio A[2], Johannesen KM[2], Jepsen B[2], Fontana E[2], Anibaldi G[2], Russo S[2], Cogliati F[2], Montomoli M[2], Specchio N[2], Rubboli G[2], Veggiotti P[2], Beniczky S[2], Wolff M[2], Helbig I[2], Vigevano F[2], Scheffer IE[2], Guerrini R[2], Møller RS[2].

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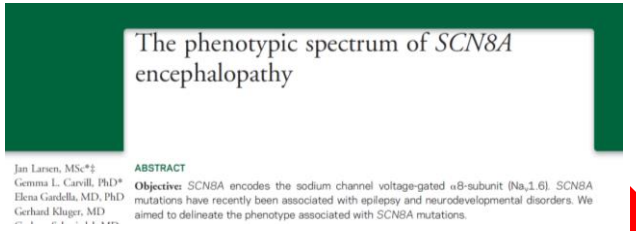
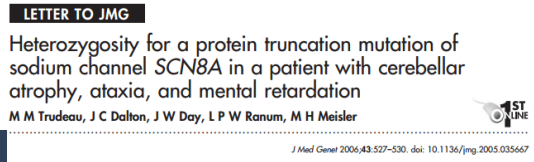
Phenotypic spectrum



BFIS → **Treatable epilepsy** → **Severe DEE**

Movement disorders

ID/ASD +/- movement disorder



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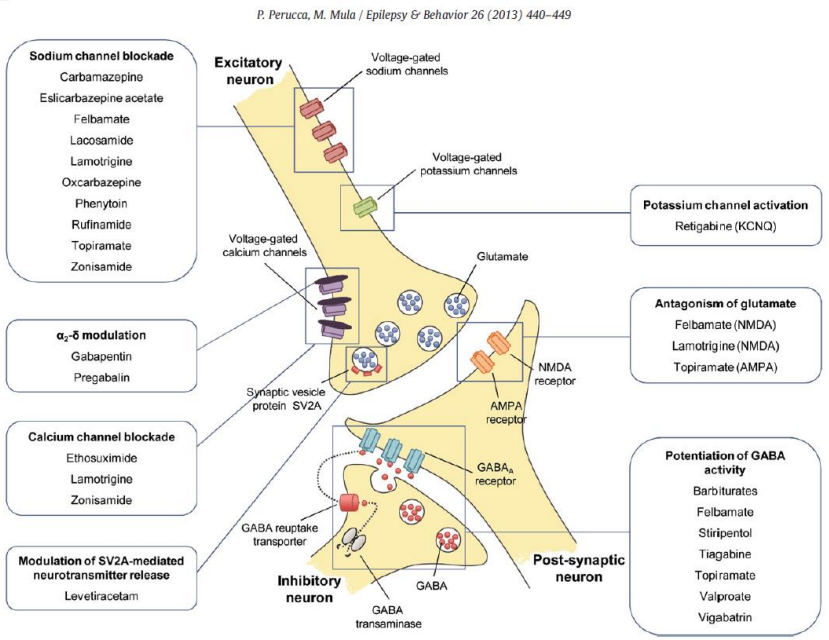
Drug development

SCN8A associated seizure disorders are often caused by gain of function mutations

Sodium channels exist in 3 main conformations: the resting state, the open state, and the inactive state

Phenytoin binds preferentially to the inactive form. Carbamazepine is thought to have a similar working mechanism. The affinity of CBZ is around 3 times lower than that of PHT



Epilepsia. 2018 Jun;59(6):1166-1176. doi: 10.1111/epi.14196. Epub 2018 May 21.

The novel sodium channel modulator GS-458967 (GS967) is an effective treatment in a mouse model of SCN8A encephalopathy.

Baker EM[1], Thompson CH[1], Hawkins NA[1], Wagnon JL[2], Wengert ER[3], Patel MK[3], George AL Jr[1], Meisler MH[2], Kearney JA[1].

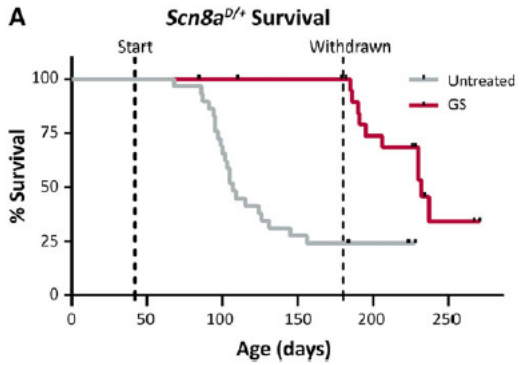


TABLE 1 Extended spontaneous seizure monitoring in *Scn8a*$^{D/+}$ and WT mice treated chronically with 1.5 mg/kg/d GS967 and untreated controls

Treatment	Genotype	n	Total hours monitored	Average hours monitored per animal ± SEM (range)	Total seizures, n	Seizures with multiple transitions, %	Average seizure frequency[a]	Fraction of mice with observed seizures
GS967	*Scn8a*$^{D/+}$	7	1699	243 ± 52 (62-361)	9	0	0.3 ± 0.2	2/7
Untreated	*Scn8a*$^{D/+}$	7	2189	313 ± 94 (60-614)	137	46	1.6 ± 0.4	7/7
GS967	WT	3	628	209 ± 172 (102-408)	0	0	0 ± 0.0	0/3
Untreated	WT	2	96	48 ± 24 (24-72)	0	0	0 ± 0.0	0/2

SEM, standard error of the mean; WT, wild-type.

[a]Seizures per 24 hours ± SEM, calculated by averaging individual seizure frequencies within each group.

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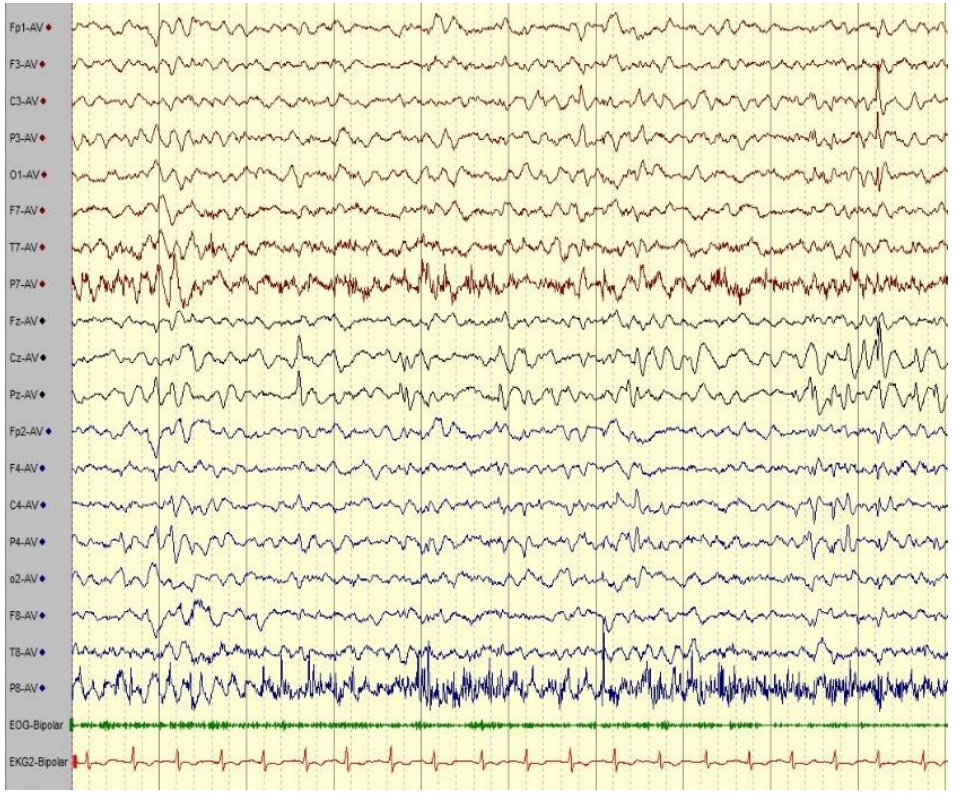
Case - *KCNB1*

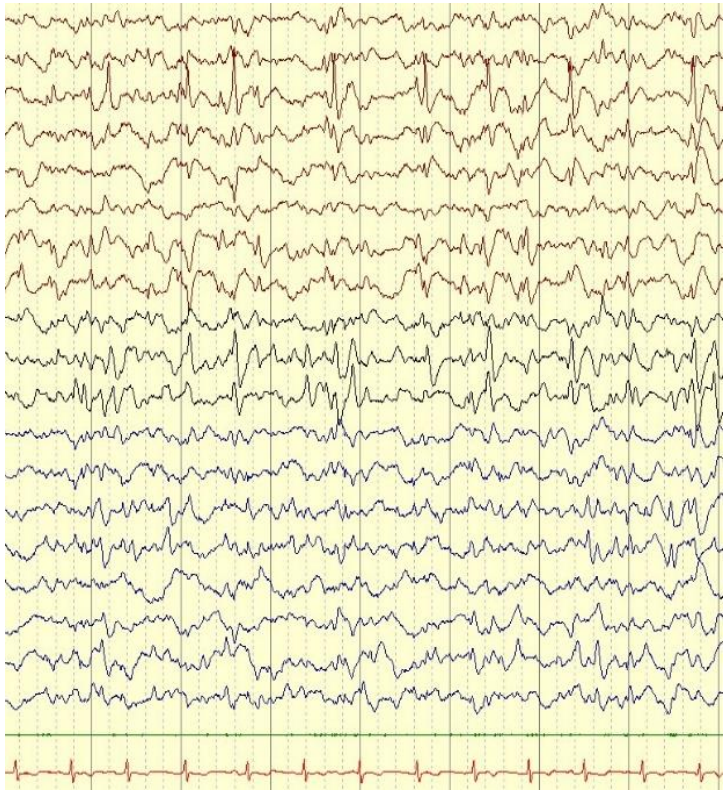
- 3½-year-old male
- Normal pregnancy and birth. Born at term with normal birth parameters.
- Global cognitive development is moderately delayed.
- No speech
- Was able to sit at 12 months of age and walk at 2 years of age.
- Has an unstable gait
- Seizure onset 14 months of age. Focal seizures: becomes distant and pale, sometimes with cyanosis of the lips, eye rolling and lip smacking. Rhythmic myoclonic jerks. Duration: 20s to 2min
- MRI at 2½ years of age showed delayed myelination of the anterior part of the temporal lobes.
- Daily seizures on VPA+LGT
- Seizure free on VPA+LEV

Case – *KCNB1*

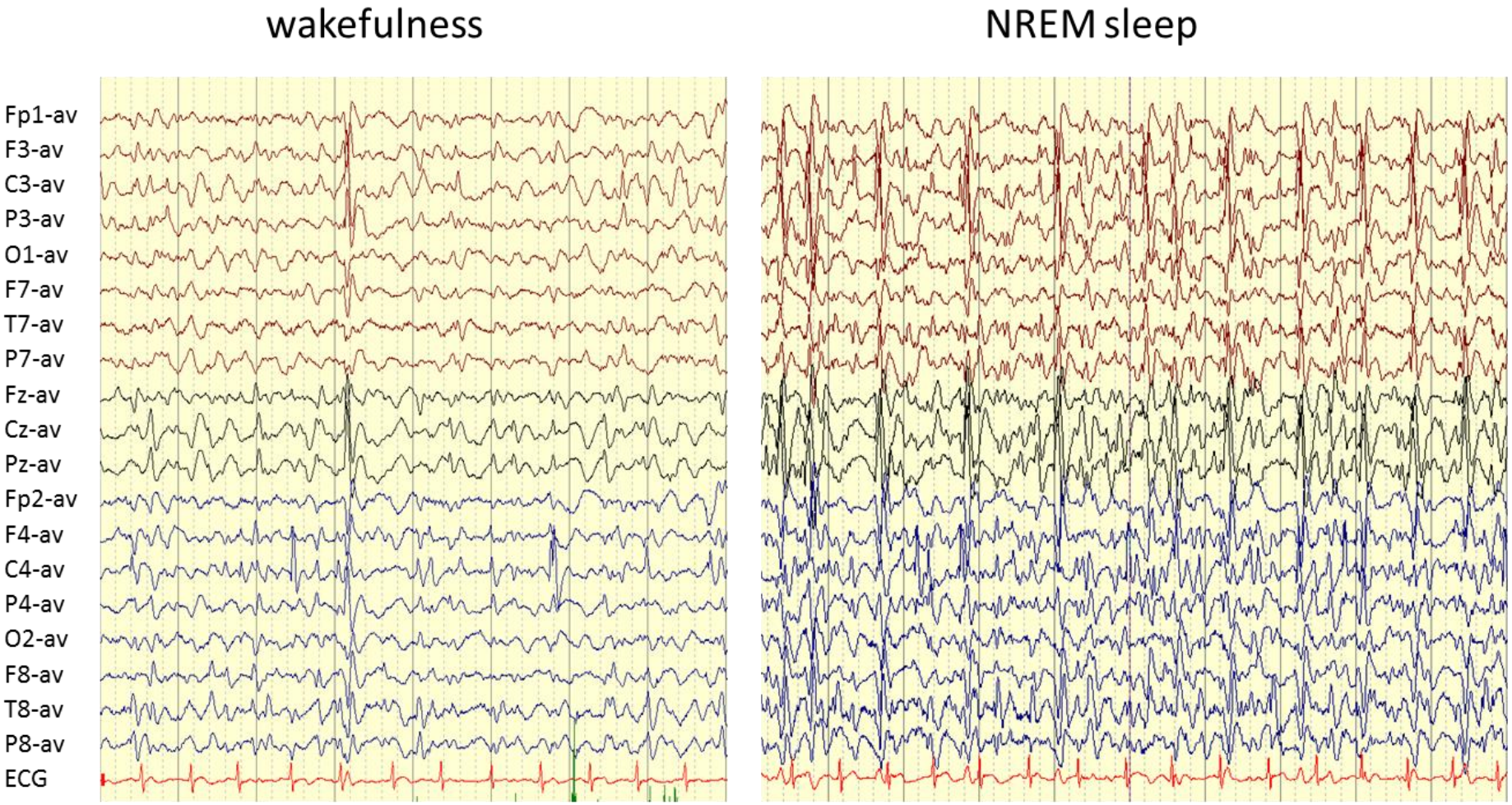
Standard EEG: Sharp waves and sharp low waves in left fronto-temporo-central region. Accentuation during sleep



sleep



Case – *KCNB1*

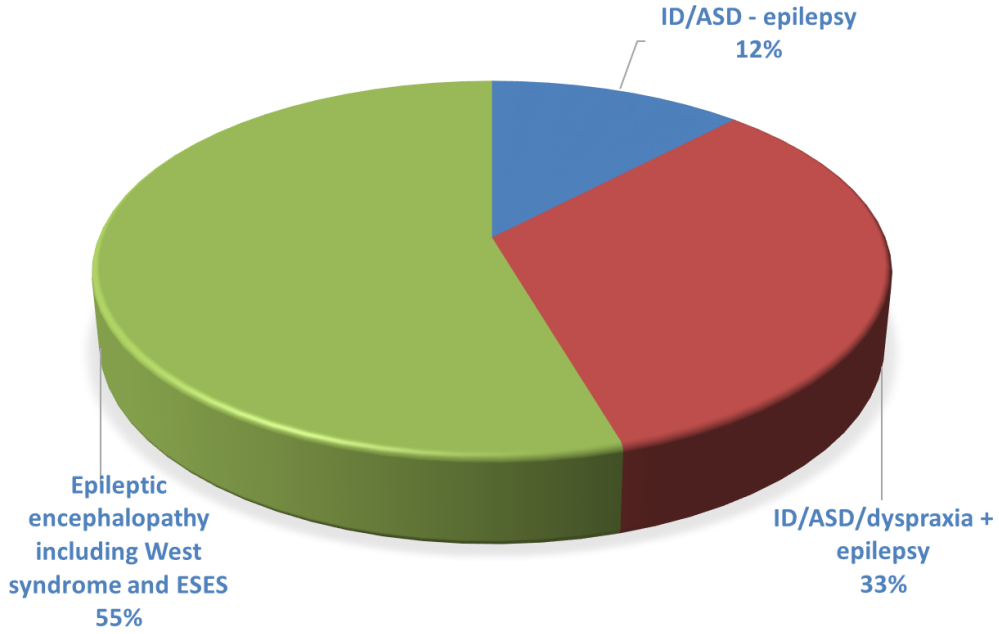


Male_ 3 yrs, 1 mo_ therapy LEV 750 mg/die

24 h- EEG: SWI – NREM sleep: 98%

KCNB1 phenotype

- Voltage-gated delayed rectifier potassium channel
- Developmental delay, preceding onset of epilepsy
- Mild to severe ID
- Most are nonverbal
- Difficult to treat epilepsy (median onset: 11 months): spasms, tonic, focal-clonic, myoclonic, atypical absences, eyelid myoclonia
- 25% develops ESES
- ASD, ADHD and movement disorders are frequent



Research

JAMA Neurology | Original Investigation

Neurodevelopmental Disorders Caused by De Novo Variants in *KCNB1* Genotypes and Phenotypes

Carolien G. F. de Kovel, PhD; Steffen Syrbe, MD, PhD; Eva H. Brilstra, MD, PhD; Nienke Verbeek, MD, PhD; Bronwyn Kerr, PhD; Holly Dubbs, MD; Allan Bayat, MD, PhD; Sonal Desai, MGC, CGC; Sakkubai Naidu, MD; Siddharth Srivastava, MD; Hande Cagaylan, MD; Uluc Yis, MD, PhD; Carol Saunders, PhD; Martin Rook, PhD; Susanna Plugge, MSc; Hiltrud Muhle, MD; Zaid Afawi, MD, PhD; Karl-Martin Klein, MD, PhD; Vijayakumar Jayaraman, MSc; Ramakrishnan Rajagopalan, PhD; Ethan Goldberg, MD, PhD; Eric Marsh, MD, PhD; Sudha Kessler, MD, MSCE; Christina Bergqvist, MD; Laura K. Conlin, PhD; Bryan L. Krok, PhD; Isabelle Thiffault, PhD; Manuela Pendziwiat, MSc; Ingo Helbig, MD; Tilman Polster, MD, PhD; Ingo Borggraefe, MD, PhD; Johannes R. Lemke, MD, PhD; Marie-José van den Boogaardt, MD, PhD; Rikke S. Møller, MSc, PhD; Bobby P. C. Koeleman, PhD

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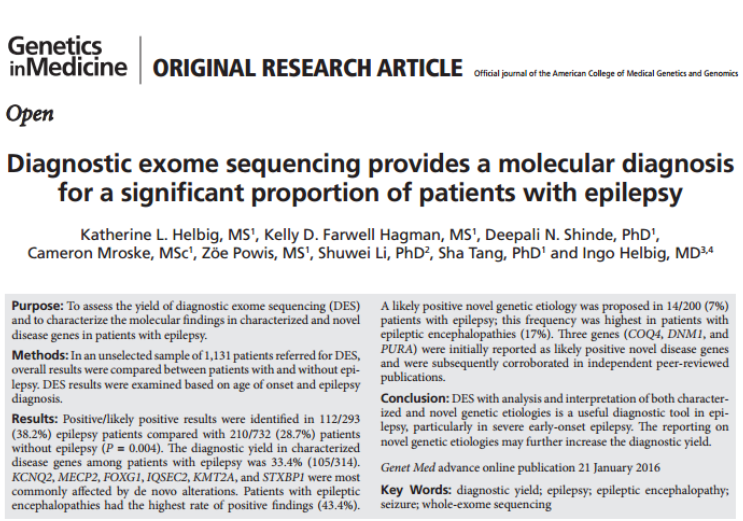
WES

- Overall diagnostic yield ranges from 25 to 37%
- Positive results were identified in 38.2% epilepsy patients compared with 28.7% patients without epilepsy.
- Patients with EEs had the highest rate of positive findings: 43.4%. Neonatal EEs 58.3%



Genetics inMedicine | ORIGINAL RESEARCH ARTICLE Official journal of the American College of Medical Genetics and Genomics

Open

Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy

Katherine L. Helbig, MS[1], Kelly D. Farwell Hagman, MS[1], Deepali N. Shinde, PhD[1], Cameron Mroske, MSc[1], Zöe Powis, MS[1], Shuwei Li, PhD[2], Sha Tang, PhD[1] and Ingo Helbig, MD[3,4]

Purpose: To assess the yield of diagnostic exome sequencing (DES) and to characterize the molecular findings in characterized and novel disease genes in patients with epilepsy.

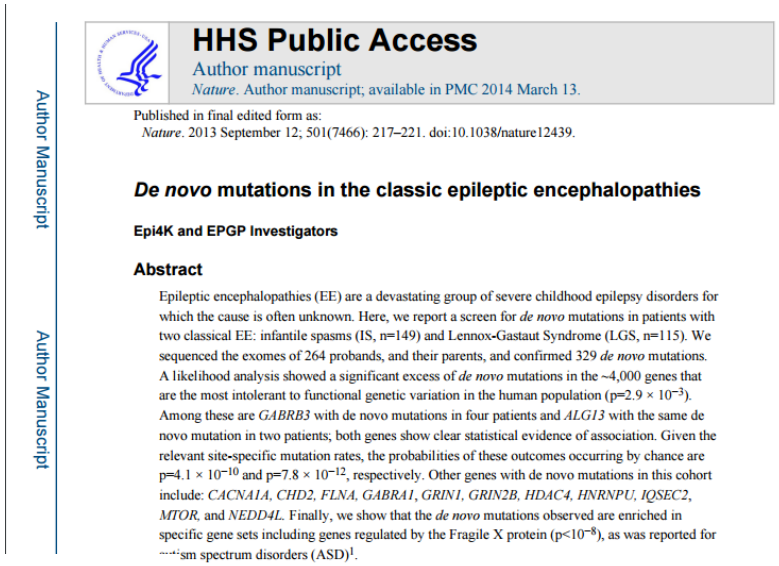
Methods: In an unselected sample of 1,131 patients referred for DES, overall results were compared between patients with and without epilepsy. DES results were examined based on age of onset and epilepsy diagnosis.

Results: Positive/likely positive results were identified in 112/293 (38.2%) epilepsy patients compared with 210/732 (28.7%) patients without epilepsy ($P = 0.004$). The diagnostic yield in characterized disease genes among patients with epilepsy was 33.4% (105/314). *KCNQ2*, *MECP2*, *FOXG1*, *IQSEC2*, *KMT2A*, and *STXBP1* were most commonly affected by de novo alterations. Patients with epileptic encephalopathies had the highest rate of positive findings (43.4%). A likely positive novel genetic etiology was proposed in 14/200 (7%) patients with epilepsy; this frequency was highest in patients with epileptic encephalopathies (17%). Three genes (*COQ4*, *DNM1*, and *PURA*) were initially reported as likely positive novel disease genes and were subsequently corroborated in independent peer-reviewed publications.

Conclusion: DES with analysis and interpretation of both characterized and novel genetic etiologies is a useful diagnostic tool in epilepsy, particularly in severe early-onset epilepsy. The reporting on novel genetic etiologies may further increase the diagnostic yield.

Genet Med advance online publication 21 January 2016

Key Words: diagnostic yield; epilepsy; epileptic encephalopathy; seizure; whole-exome sequencing



Published in final edited form as:

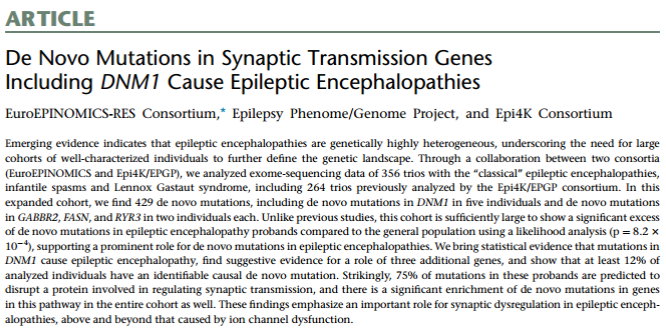
Nature. 2013 September 12; 501(7466): 217–221. doi:10.1038/nature12439.

De novo mutations in the classic epileptic encephalopathies

Epi4K and EPGP Investigators

Abstract

Epileptic encephalopathies (EE) are a devastating group of severe childhood epilepsy disorders for which the cause is often unknown. Here, we report a screen for *de novo* mutations in patients with two classical EE: infantile spasms (IS, n=149) and Lennox-Gastaut Syndrome (LGS, n=115). We sequenced the exomes of 264 probands, and their parents, and confirmed 329 *de novo* mutations. A likelihood analysis showed a significant excess of *de novo* mutations in the ~4,000 genes that are the most intolerant to functional genetic variation in the human population ($p=2.9 \times 10^{-3}$). Among these are *GABRB3* with de novo mutations in four patients and *ALG13* with the same de novo mutation in two patients; both genes show clear statistical evidence of association. Given the relevant site-specific mutation rates, the probabilities of these outcomes occurring by chance are $p=4.1 \times 10^{-10}$ and $p=7.8 \times 10^{-12}$, respectively. Other genes with de novo mutations in this cohort include: *CACNA1A*, *CHD2*, *FLNA*, *GABRA1*, *GRIN1*, *GRIN2B*, *HDAC4*, *HNRNPU*, *IQSEC2*, *MTOR*, and *NEDD4L*. Finally, we show that the *de novo* mutations observed are enriched in specific gene sets including genes regulated by the Fragile X protein ($p<10^{-8}$), as was reported for ~~~~ism spectrum disorders (ASD)[1].



ARTICLE

De Novo Mutations in Synaptic Transmission Genes Including *DNM1* Cause Epileptic Encephalopathies

EuroEPINOMICS-RES Consortium,* Epilepsy Phenome/Genome Project, and Epi4K Consortium

Emerging evidence indicates that epileptic encephalopathies are genetically highly heterogeneous, underscoring the need for large cohorts of well-characterized individuals to further define the genetic landscape. Through a collaboration between two consortia (EuroEPINOMICS and Epi4K/EPGP), we analyzed exome-sequencing data of 356 trios with the "classical" epileptic encephalopathies, infantile spasms and Lennox Gastaut syndrome, including 264 trios previously analyzed by the Epi4K/EPGP consortium. In this expanded cohort, we find 429 de novo mutations, including de novo mutations in *DNM1* in five individuals and de novo mutations in *GABBR2*, *FASN*, and *RYR3* in two individuals each. Unlike previous studies, this cohort is sufficiently large to show a significant excess of de novo mutations in epileptic encephalopathy probands compared to the general population using a likelihood analysis ($p = 8.2 \times 10^{-4}$), supporting a prominent role for de novo mutations in epileptic encephalopathies. We bring statistical evidence that mutations in *DNM1* cause epileptic encephalopathy, find suggestive evidence for a role of three additional genes, and show that at least 12% of analyzed individuals have an identifiable causal de novo mutation. Strikingly, 75% of mutations in these probands are predicted to disrupt a protein involved in regulating synaptic transmission, and there is a significant enrichment of de novo mutations in genes in this pathway in the entire cohort as well. These findings emphasize an important role for synaptic dysregulation in epileptic encephalopathies, above and beyond that caused by ion channel dysfunction.

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WES - case

- 8 year old girl with profound ID and intractable epilepsy
- Neonatal: severe hypotonia. Seizure onset day one. Tonic seizures, myoclonus, apnea. Feeding problems
- Daily seizures from day 1 to 1.5 yoa.
- Seizure free on AED from 1.5 to 3 yoa.
- Weekly tonic seizures, myoclonus + GTCS
- Severe hypotonia, wheelchairbound, no purposeful movements, profound ID, poor eyecontact, PEG fed.
- MRI cerebrum: hypomyelination, white matter atrophy. Hypoplasia of corpus callosum.
- EEG: Background activity with diffuse slowing. Epileptiform activity frontally.

WES - case

- Neonatal: severe hypotonia. Seizure onset day one. Feeding problems
- Intractable epilepsy. Daily seizures. Myoclonic, tonic and GTCS
- Development: Severe hypotonia, severe ID, no eyecontact, PEG fed.
- MRI (2 weeks old): hypomyelination, hypoplastic corpus callosum
- EEG: Background activity with diffuse slowing. Multifocal epileptiform activity.
- Died 11 months old, due to pneumonia
- WES: compound heterozygous variants in *PIGT*
- An autosomal recessive syndromic form of a glycosylphosphatidylinositol biosynthesis defect

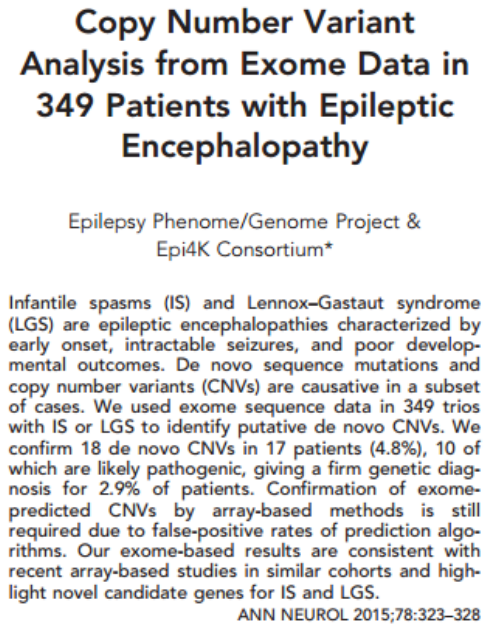
PIGT

- 26 families worldwide

- Epilepsy, severe hypotonia, profound ID/DD, dysmorphic features, cerebral and cerebellar atrophy, congenital malformations (heart, skeletal)

Copy number variants in epilepsy

- Array CGH: larger deletions and duplications
- Diagnostic yield: less than 10% (from 2.9 – 8%)
- Higher yield in patients with dysmorphic features and/or congenital malformations

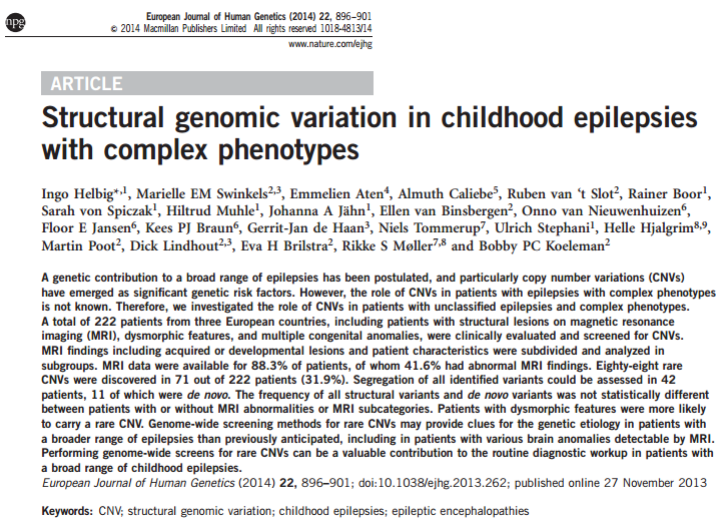


Copy Number Variant Analysis from Exome Data in 349 Patients with Epileptic Encephalopathy

Epilepsy Phenome/Genome Project & Epi4K Consortium*

Infantile spasms (IS) and Lennox–Gastaut syndrome (LGS) are epileptic encephalopathies characterized by early onset, intractable seizures, and poor developmental outcomes. De novo sequence mutations and copy number variants (CNVs) are causative in a subset of cases. We used exome sequence data in 349 trios with IS or LGS to identify putative de novo CNVs. We confirm 18 de novo CNVs in 17 patients (4.8%), 10 of which are likely pathogenic, giving a firm genetic diagnosis for 2.9% of patients. Confirmation of exome-predicted CNVs by array-based methods is still required due to false-positive rates of prediction algorithms. Our exome-based results are consistent with recent array-based studies in similar cohorts and highlight novel candidate genes for IS and LGS.

ANN NEUROL 2015;78:323–328



European Journal of Human Genetics (2014) 22, 896–901

www.nature.com/ejhg

ARTICLE

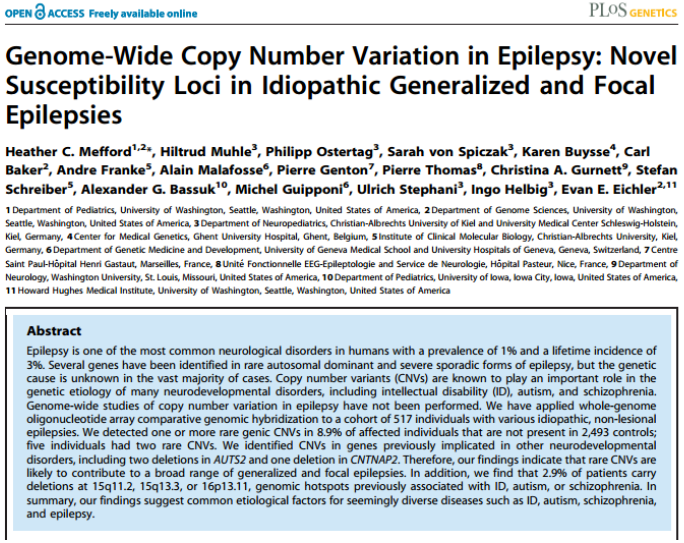
Structural genomic variation in childhood epilepsies with complex phenotypes

Ingo Helbig*[,1], Marielle EM Swinkels[2,3], Emmelien Aten[4], Almuth Caliebe[5], Ruben van 't Slot[2], Rainer Boor[1], Sarah von Spiczak[1], Hiltrud Muhle[1], Johanna A Jähn[1], Ellen van Binsbergen[2], Onno van Nieuwenhuizen[6], Floor E Jansen[6], Kees PJ Braun[6], Gerrit-Jan de Haan[3], Niels Tommerup[7], Ulrich Stephani[1], Helle Hjalgrim[8,9], Martin Poot[2], Dick Lindhout[2,3], Eva H Brilstra[2], Rikke S Møller[7,8] and Bobby PC Koeleman[2]

A genetic contribution to a broad range of epilepsies has been postulated, and particularly copy number variations (CNVs) have emerged as significant genetic risk factors. However, the role of CNVs in patients with epilepsies with complex phenotypes is not known. Therefore, we investigated the role of CNVs in patients with unclassified epilepsies and complex phenotypes. A total of 222 patients from three European countries, including patients with structural lesions on magnetic resonance imaging (MRI), dysmorphic features, and multiple congenital anomalies, were clinically evaluated and screened for CNVs. MRI findings including acquired or developmental lesions and patient characteristics were subdivided and analyzed in subgroups. MRI data were available for 88.3% of patients, of whom 41.6% had abnormal MRI findings. Eighty-eight rare CNVs were discovered in 71 out of 222 patients (31.9%). Segregation of all identified variants could be assessed in 42 patients, 11 of which were *de novo*. The frequency of all structural variants and *de novo* variants was not statistically different between patients with or without MRI abnormalities or MRI subcategories. Patients with dysmorphic features were more likely to carry a rare CNV. Genome-wide screening methods for rare CNVs may provide clues for the genetic etiology in patients with a broader range of epilepsies than previously anticipated, including in patients with various brain anomalies detectable by MRI. Performing genome-wide screens for rare CNVs can be a valuable contribution to the routine diagnostic workup in patients with a broad range of childhood epilepsies.

European Journal of Human Genetics (2014) **22**, 896–901; doi:10.1038/ejhg.2013.262; published online 27 November 2013

Keywords: CNV; structural genomic variation; childhood epilepsies; epileptic encephalopathies



OPEN ACCESS Freely available online PLoS GENETICS

Genome-Wide Copy Number Variation in Epilepsy: Novel Susceptibility Loci in Idiopathic Generalized and Focal Epilepsies

Heather C. Mefford[1,2]*, Hiltrud Muhle[3], Philipp Ostertag[3], Sarah von Spiczak[3], Karen Buysse[4], Carl Baker[2], Andre Franke[5], Alain Malafosse[6], Pierre Genton[7], Pierre Thomas[8], Christina A. Gurnett[9], Stefan Schreiber[5], Alexander G. Bassuk[10], Michel Guipponi[6], Ulrich Stephani[3], Ingo Helbig[3], Evan E. Eichler[2,11]

1 Department of Pediatrics, University of Washington, Seattle, Washington, United States of America, **2** Department of Genome Sciences, University of Washington, Seattle, Washington, United States of America, **3** Department of Neuropediatrics, Christian-Albrechts University of Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany, **4** Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium, **5** Institute of Clinical Molecular Biology, Christian-Albrechts University, Kiel, Germany, **6** Department of Genetic Medicine and Development, University of Geneva Medical School and University Hospitals of Geneva, Geneva, Switzerland, **7** Centre Saint Paul-Hôpital Henri Gastaut, Marseilles, France, **8** Unité Fonctionnelle EEG-Epileptologie and Service de Neurologie, Hôpital Pasteur, Nice, France, **9** Department of Neurology, Washington University, St. Louis, Missouri, United States of America, **10** Department of Pediatrics, University of Iowa, Iowa City, Iowa, United States of America, **11** Howard Hughes Medical Institute, University of Washington, Seattle, Washington, United States of America

Abstract

Epilepsy is one of the most common neurological disorders in humans with a prevalence of 1% and a lifetime incidence of 3%. Several genes have been identified in rare autosomal dominant and severe sporadic forms of epilepsy, but the genetic cause is unknown in the vast majority of cases. Copy number variants (CNVs) are known to play an important role in the genetic etiology of many neurodevelopmental disorders, including intellectual disability (ID), autism, and schizophrenia. Genome-wide studies of copy number variation in epilepsy have not been performed. We have applied whole-genome oligonucleotide array comparative genomic hybridization to a cohort of 517 individuals with various idiopathic, non-lesional epilepsies. We detected one or more rare genic CNVs in 8.9% of affected individuals that are not present in 2,493 controls; five individuals had two rare CNVs. We identified CNVs in genes previously implicated in other neurodevelopmental disorders, including two deletions in *AUTS2* and one deletion in *CNTNAP2*. Therefore, our findings indicate that rare CNVs are likely to contribute to a broad range of generalized and focal epilepsies. In addition, we find that 2.9% of patients carry deletions at 15q11.2, 15q13.3, or 16p13.11, genomic hotspots previously associated with ID, autism, or schizophrenia. In summary, our findings suggest common etiological factors for seemingly diverse diseases such as ID, autism, schizophrenia, and epilepsy.

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Array CGH – case: *STXBP1*

- 8 year old boy with severe ID and intractable epilepsy
- Onset of focal seizures: 2 moa.
- EEG: normal
- Seizure free for 6 weeks
- 4 moa: infantile spasms + hypsarrythmia
- 3 to 9 series of spasms/day. 8 to 60 spasms/serie
- Developmental stagnation
- MRI hypomyelinisation
- Seizure free for 13 months after VNS treatment (4-5 yoa)

Array CGH – case, followup

- 7-40 seizures pr/day
  - Epileptic spasms
  - Tonic seizures
  - Focal seizures
- Dystonia
- Severe ID, no spoken language
- Not able to walk
- CVI
- Hypotonia
- Array CGH: *de novo* 9q34.11 deletion including *STXBP1*

Dev Med Child Neurol. 2013 Aug;55(8):769-72. doi: 10.1111/dmcn.12197. Epub 2013 Jun 13.

Head stereotypies in STXBP1 encephalopathy.

Kim YO[1], Korff CM, Villaluz MM, Suls A, Weckhuysen S, De Jonghe P, Scheffer IE.

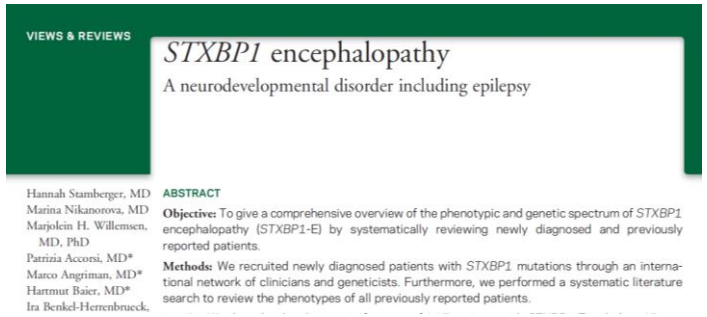
Author information

Abstract

STXBP1 encephalopathy is associated with a range of movement disorders. We observed head stereotypies in three patients. These comprised a slow (<1Hz), high-amplitude, horizontal, 'figure-of-eight' pattern, beginning at age 4-6 years and resulting in neck muscle hypertrophy, in two males; a faster (2-3Hz), side-to-side, 'no' movement, starting at the age of 9 years 6 months was observed in one female. Upper limb and truncal stereotypies and vocalization occurred intermittently with the head movements. The stereotypies increased with excitement but settled with concentration and sleep. Head and upper limb stereotypies are valuable clinical clues to the diagnosis of STXBP1 encephalopathy in patients with profound impairments.

STXBP1 encephalopathy

- Discovered in patients with Ohtahara Syndrome
- One of the most common genetic causes of EE
- Phenotypes ranging from severe neonatal epilepsy to infantile-onset epilepsy such as Dravet Syndrome or West syndrome.
- The epilepsy in can be quite dynamic, starting very abruptly with a highly pathological EEG pattern, sometimes with a dramatic improvement after the age of 6 months that may not necessarily be due to the antiepileptic medication.
- Many patients have non-epileptic movement disorders, including truncal and limb ataxia, generalized tremors, and dystonia.
- Intellectual disability without seizures have also been reported.


VIEWS & REVIEWS

STXBP1 encephalopathy

A neurodevelopmental disorder including epilepsy

Hannah Stamberger, MD
Marina Nikanorova, MD
Marjolein H. Willemsen, MD, PhD
Patrizia Accorsi, MD*
Marco Angriman, MD*
Hartmut Baier, MD*
Ira Benkel-Herrenbrueck,

ABSTRACT

Objective: To give a comprehensive overview of the phenotypic and genetic spectrum of *STXBP1* encephalopathy (*STXBP1*-E) by systematically reviewing newly diagnosed and previously reported patients.

Methods: We recruited newly diagnosed patients with *STXBP1* mutations through an international network of clinicians and geneticists. Furthermore, we performed a systematic literature search to review the phenotypes of all previously reported patients.

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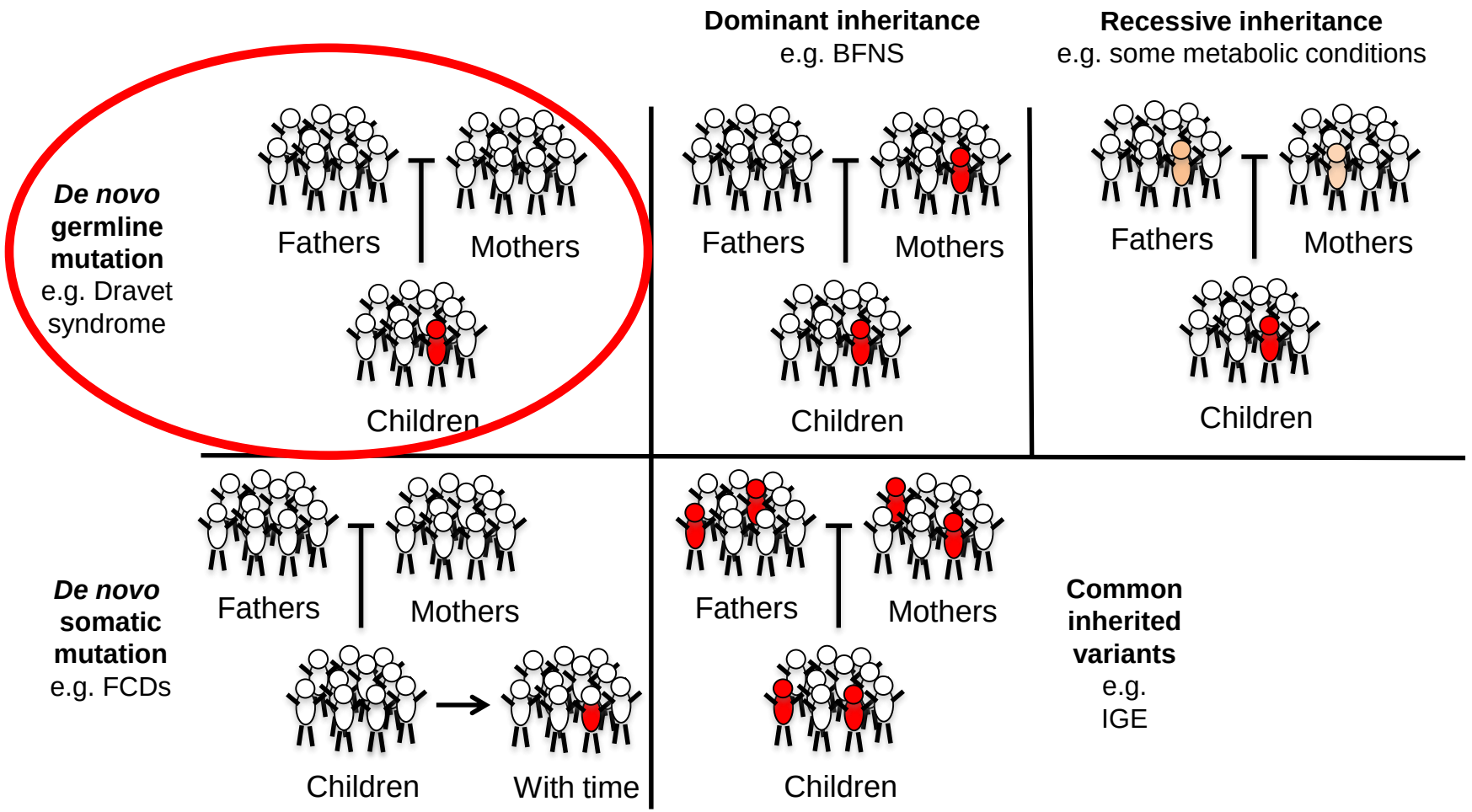
Technologies – diagnostic yield

- Targeted gene panels: around 20%
- Whole exome sequencing: 25 to 37%
- Array CGH: less than 10%

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

Inheritance patterns



Somatic mosaicism

- The estimated overall recurrence risk for alleged *de novo* disorders is approximately 1%
- 46 trios with *de novo* mutations
- *CACNA1A, CDKL5, CHD2, GABRA1, GRIN2B, KCNQ2, PCDH19, SCN1/2/8A, SLC2A1, STXBP1*
- Mean read depth: 6600X (409X-78764X)
- Mosaicism detected: 4/46 **(9%)**
- *SCN8A*: p.Arg1872Gln (father 29% mosaic)
- *SCN1A*: p.Arg1322Glufs*10 (mother 9.6% mosaic)
- *SCN2A*: p.Ser863Phe (father 7.8% mosaic)
- *STXBP1*: p.Glu463* (father 0.8% mosaic)
- The estimated overall recurrence risk for alleged *de novo* disorders remains approximately 1%

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Amplicon Resequencing Identified Parental Mosaicism for Approximately 10% of "*de novo*" *SCN1A* Mutations in Children with Dravet Syndrome

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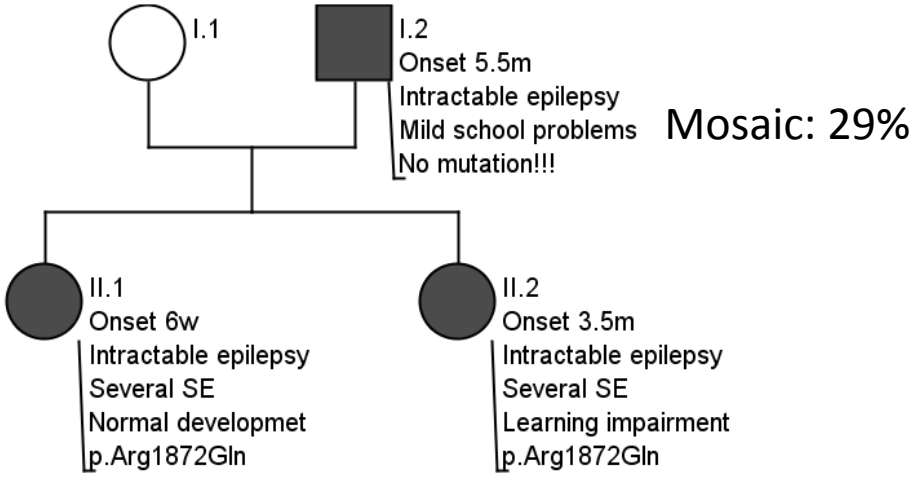
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Parental Mosaicism in "De Novo" Epileptic Encephalopathies



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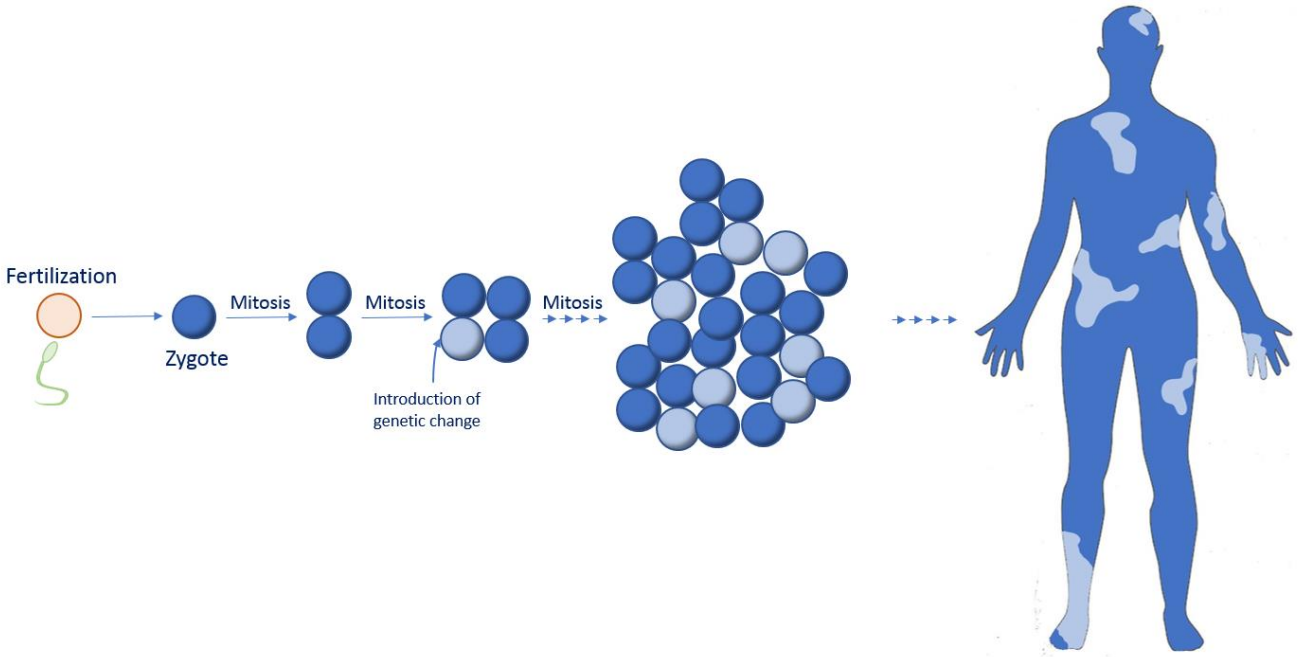
Mosaicism

- Mosaicism means that a person has two or more unique cell populations.
- In case of parental mosaicism, the parent has a cell population without the pathogenic variant and a minor proportion of cells with the pathogenic variant.
- Occurred spontaneously in a single cell, and all subsequent cells that arose from that particular cell contain the variant.
- Mosaic parents are in increased risk of transmitting the disease-associated variant to their offspring
- In case of transmission, the child will carry the pathogenic variant in all its cells.

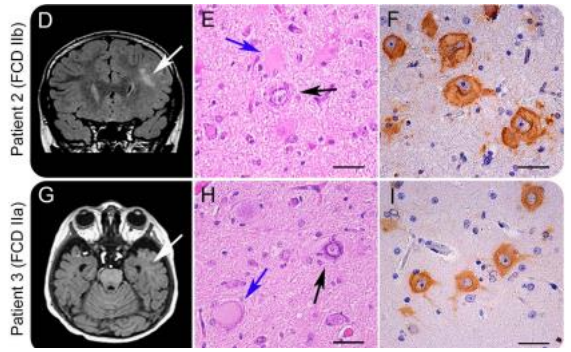


(Gilbert et al, 2000)

Neurol Genet. 2016 Oct 31;2(6):e118. eCollection 2016 Dec.

Germline and somatic mutations in the *MTOR* gene in focal cortical dysplasia and epilepsy.

Møller RS[1], Weckhuysen S[1], Chipaux M[1], Marsan E[1], Taly V[1], Bebin EM[1], Hiatt SM[1], Prokop JW[1], Bowling KM[1], Mei D[1], Conti V[1], de la Grange P[1], Ferrand-Sorbets S[1], Dorfmüller G[1], Lambrecq V[1], Larsen LH[1], Lequern E[1], Guerrini R[1], Rubboli G[1], Cooper GM[1], Baulac S[1].



A new gene and so what? From gene to function (and therapy!)

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

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].

KCNA2, encoding the potassium channel $K_V1.2$

4 individuals: febrile/afebrile, often focal seizure types, mild/moderate intellectual disability, ESES, favourable seizure outcome
Functional studies: almost complete **loss of function** with a dominant-negative effect.

2 individuals: more severe EE phenotype. Severe ID, intractable epilepsy (generalized), ataxia, and atrophy of the cerebellum
Functional studies: drastic **gain-of-function** effect leading to permanently open channels.

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], Bergqvist 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].

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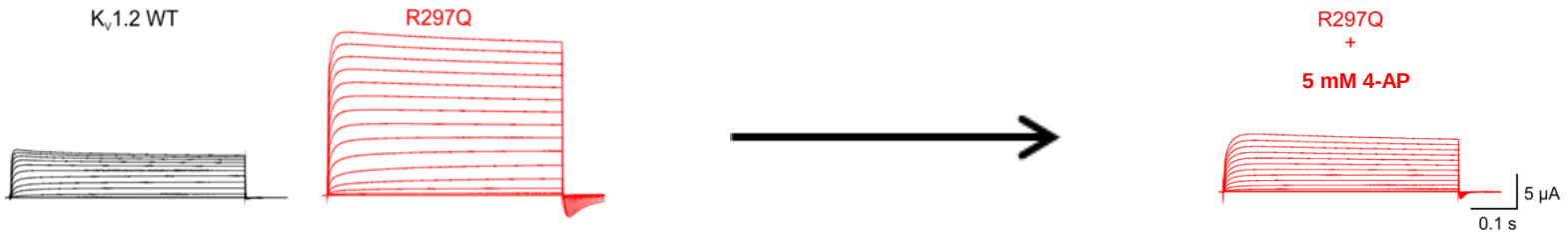
Targeted treatment – *KCNA2* gain of function encephalopathy

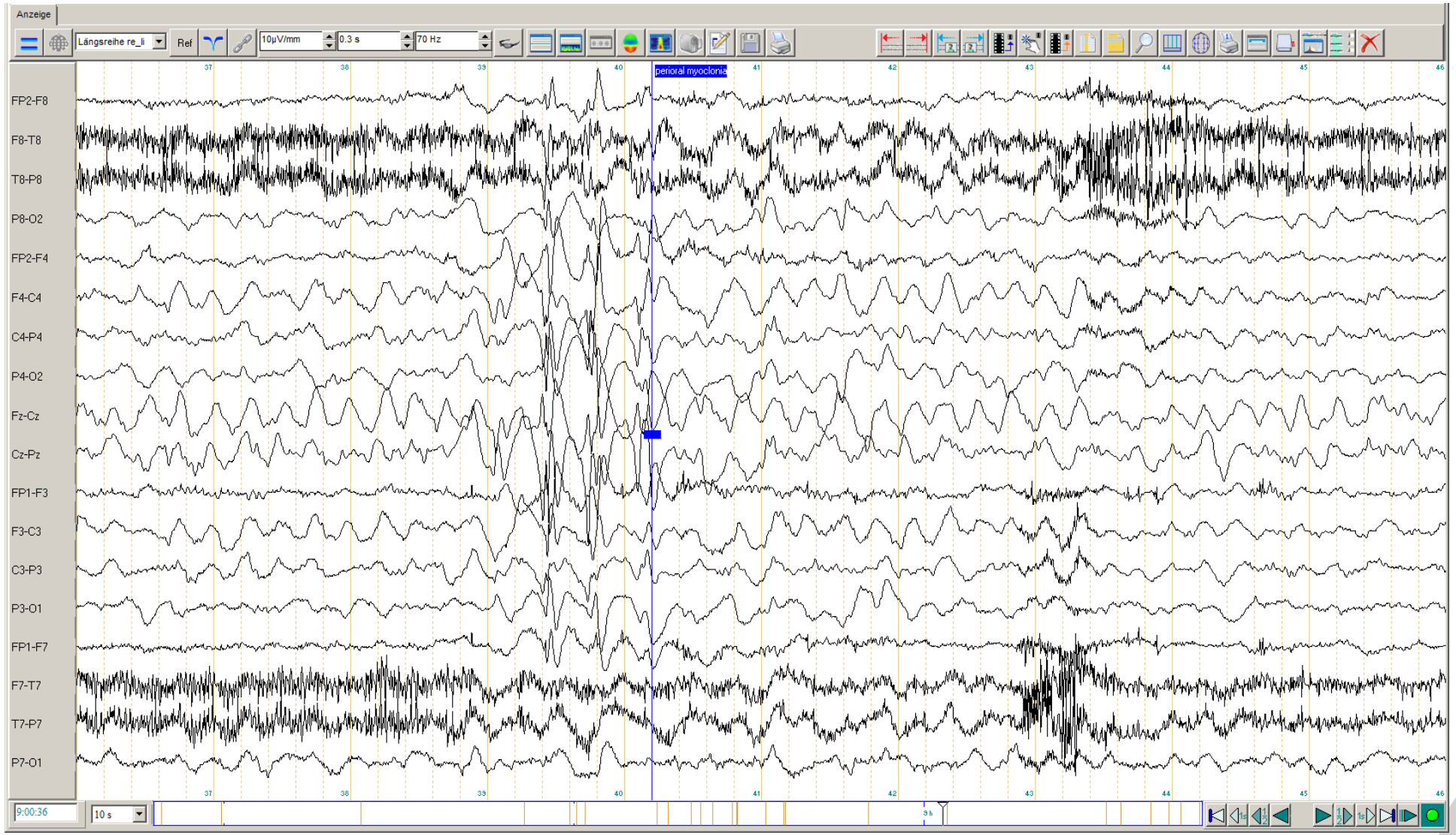
- Aminopyridines are monoamino and diamino derivatives of pyridine whose principal mechanism of action is a dose-dependent blockade of voltage-gated potassium channels.
- 4-aminopyridine (4-AP): symptomatic treatment of decreased walking capacity in patients with multiple sclerosis



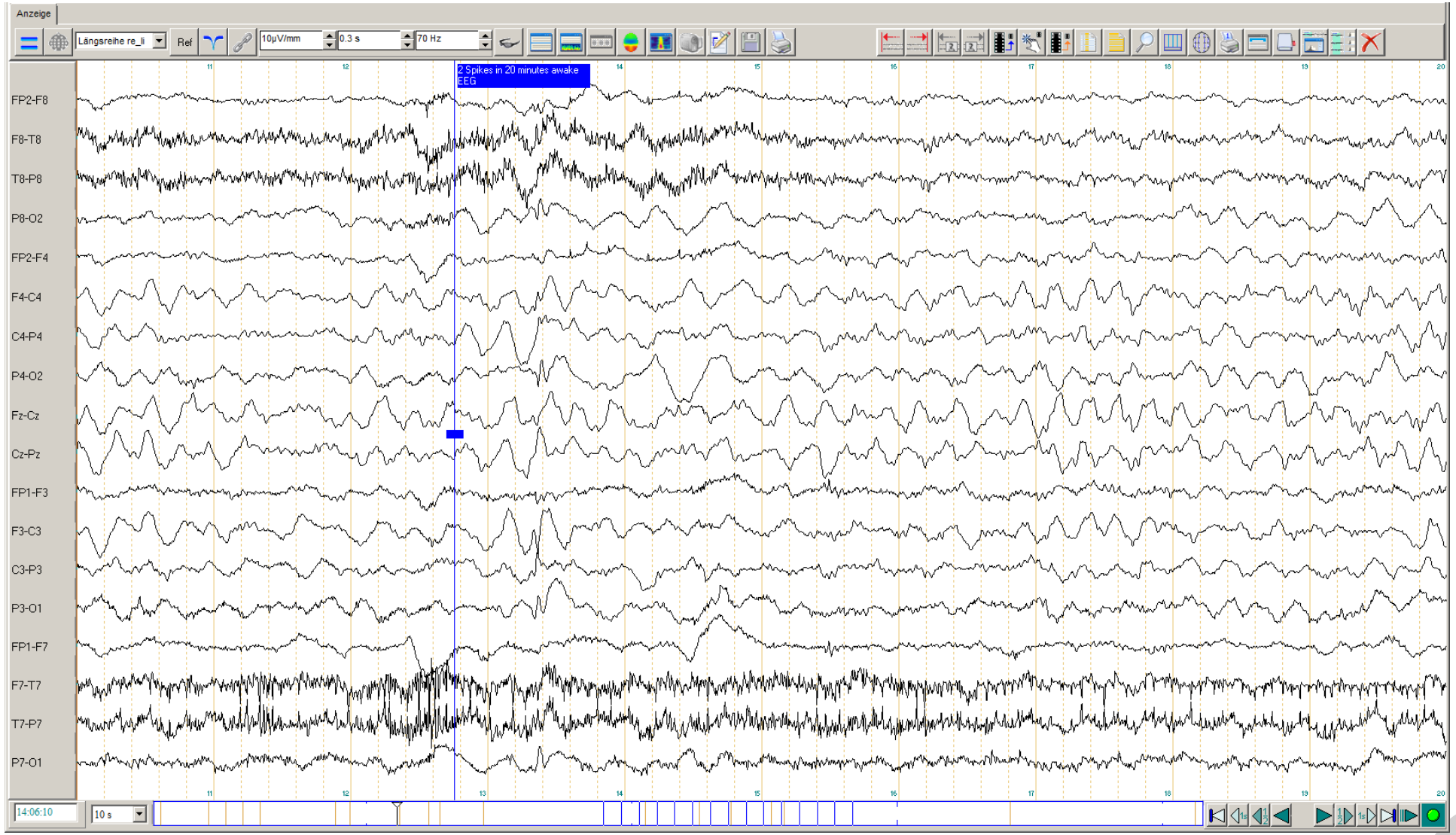
gain of function

blocked by 4-AP

2015-06-18, LTG, LCM, bromide: spikes (GSW) every 10-20 sec., +/- myoclonic seizures in EEG (+ daily absence seizures, rare GTCS)



2015-09-03, 4-aminopyridine 2x15 mg: 2 spikes in 20 min., seizure-free



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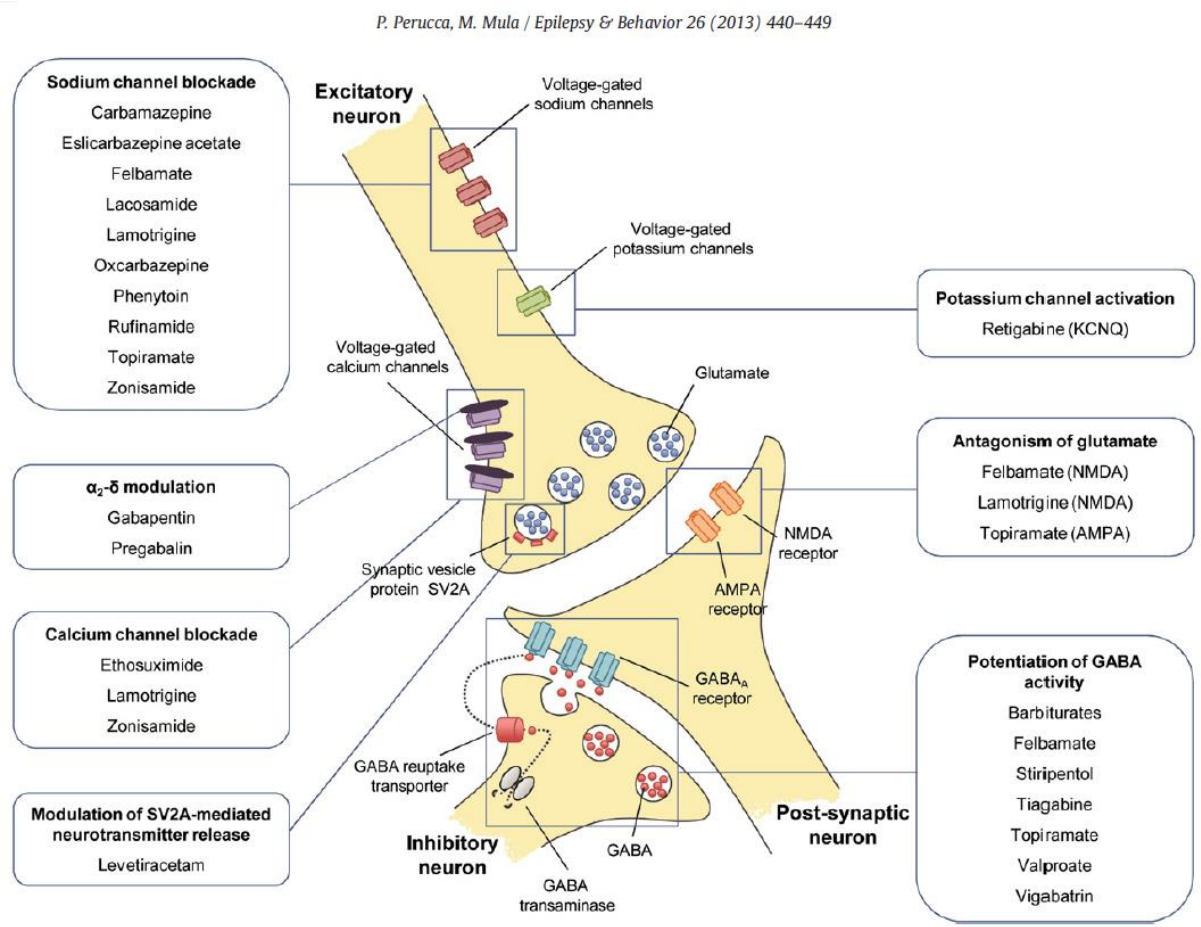
Specific therapeutic consequences (‘personalized therapies’) for defined genetic defects

- *SCN1A*:
  - **Drugs of choice:** Stiripentol, VPA, CLB: **Proof of concept:** Fenfluramine
  - **Avoid:** Sodium channel blockers
- *SCN2A*:
  - **Drugs of choice:** Sodium channel blockers (onset <3 months)
  - **Avoid:** Sodium channel blockers (onset >3 months)
- *SCN8A*:
  - **Drugs of choice:** Sodium channel blockers
  - **Avoid:** Levetiracetam
- *SLC2A1* (GLUT1-DS):
  - **Treatment of choice:** Ketogenic diet
- *KCNQ2*
  - **Drugs of choice:** Sodium channel blockers, **Proof of concept:** Retigabine
- *MEF2C*
  - **Drug of choice:** Valproic acid
- *PNPO and ALDH7A1*
  - **Drug of choice:** Pyridoxal 5'-phosphate or Pyridoxine
- *KCNT1*
  - **Proof of concept:** Quinidine
- *GRIN2A, GRIN2B*
  - **Proof of concept:** Memantine, Serine
- *KCNA2*
  - **Proof of concept:** 4-amino-pyridine
- *TSC1, TSC2, DEPDC5, NPRL2, NPRL3, mTOR*
  - **Proof of concept:** mTOR inhibitors (Everolimus)



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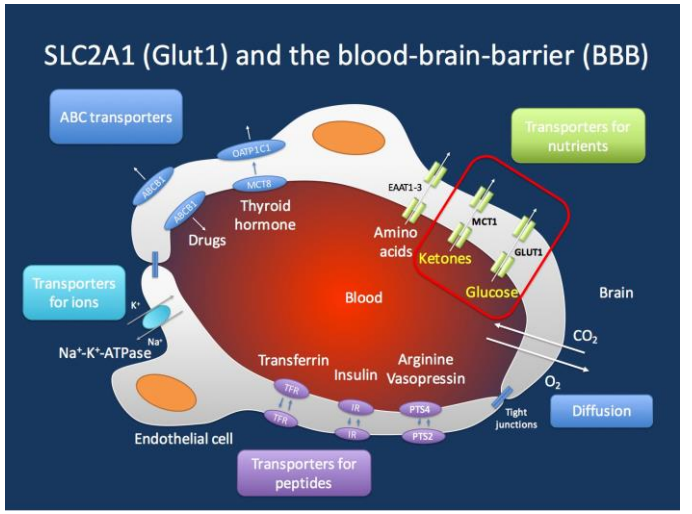
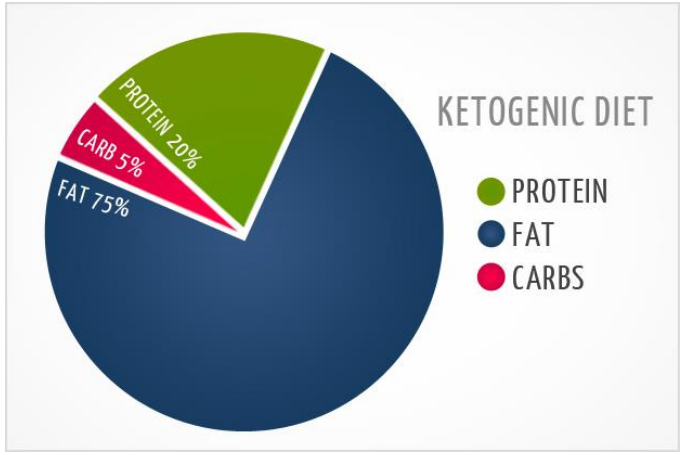
GLUT1 Case – 8 year old girl

- Neonatal period: failure to trive, obstipation
- Seizure onset 10 weeks of age
- EEG normal, MRI: normal
- Weekly seizures (3-5 min)
- 9 mo: sligthly developmental delay
- 18 mo: Status epilepticus lasting 40 minutes
- 18 mo: balance problems, ataxic gait, moderate developmetal delay
- *SLC2A1* mutation (c.641T>C; pLeu214Pro) – Modified Atkins diet was initiated
- 2 years: absences (up to 10 pr day)
- Changed to ketogenic diet
- Seizure free and near to normal development





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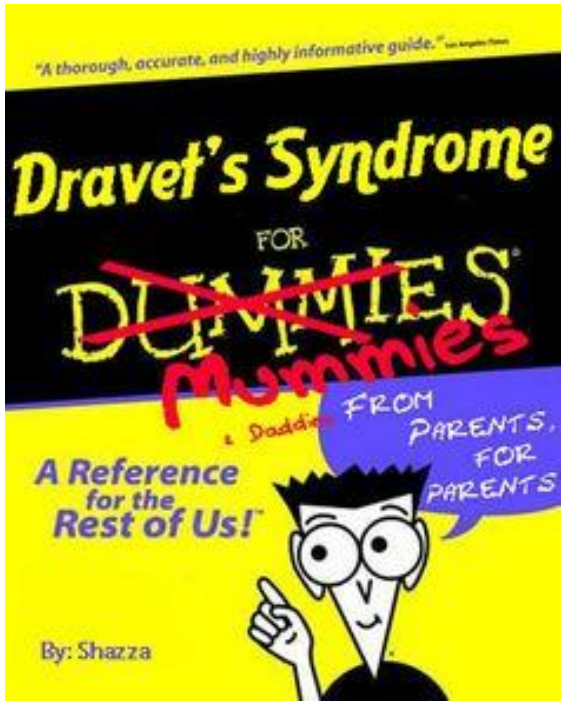
It is never too late

- 51 year old man with an unclassified EE and ID
- Seizure onset 8 moa – prolonged febrile GTCS
- Following seizure types: myoclonic seizures, atypical absences, astatic seizures, status epilepticus
- Daily seizures
- Severe ID – no language
- AED: Valproate, Carbamazapine, Lamotrigine
- Cognitive decline over the last years
- *SCN1A* mutation found 1 year ago
- Tapered off Carbamazapine and Lamotrigine
- The institution reports that he has fewer seizures, is more alert and they haven't seen him so fresh and full of energy for many years



Consider genetic testing

- Neonatal or infantile onset epilepsies
- Epileptic encephalopathies
- Patients with ID/ASD and epilepsy
- Progressive myoclonic epilepsies
- Familial epilepsies – both generalized and focal

Why should genetic investigations be performed?

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