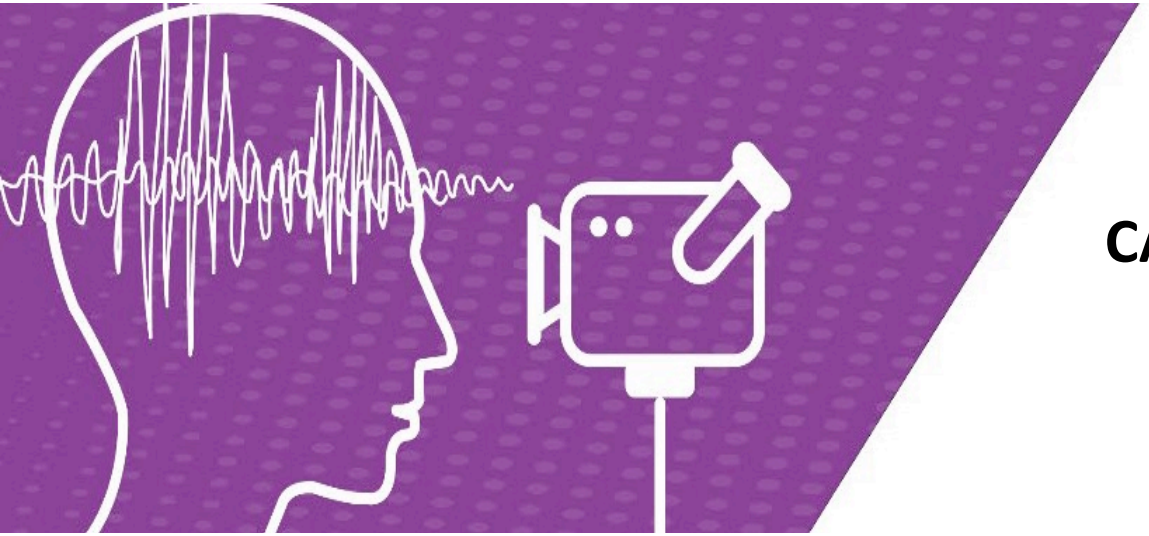

CORSO VIDEO EEG LICE
3° EDIZIONE
CATANIA, 24-27 OTTOBRE 2021

LICE Lega Italiana Contro l'Epilessia

Sleep-related Hypermotor Epilepsy (SHE) e crisi ipermotorie

Francesca Bisulli

Dipartimento di Scienze Biomediche e Neuromotorie. Università di Bologna.
IRCCS Istituto delle Scienze Neurologiche. Ospedale Bellaria. Bologna

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA A.D. 1088

ISNB IRCCS Istituto delle Scienze Neurologiche di Bologna

Who is SHE?

Outlines

- History and nomenclature
- The diagnostic criteria
- Phenotype: clinical and demographic features
- Etiology
- Treatment
- Grey areas

Who is SHE?

Outlines

- History and nomenclature

SHE is forty years old

1981

NPD
Nocturnal
Paroxysmal Dystonia

Lugaresi & Cirignotta, 1981

1990

NFLE
Nocturnal Frontal
Lobe Epilepsy

Tinuper et al., 1990
Scheffer et al., 1994-1995

2014

SHE
Sleep Related Hyper
motor Epilepsy

Tinuper et al., 2016

2021

SHE included in the
ILAE Classification
and Definition of
Epilepsy Syndromes

Riney et al., 2021 (submitted)

Paolo Tinuper, MD
Francesca Bisulli, MD, PhD
J.H. Cross, MD, PhD
Dale Hesdorffer, PhD
Philippe Kahane, MD, PhD
Lino Nobili, MD, PhD
Federica Provini, MD, PhD
Ingrid E. Scheffer, PhD, MBBS
Laura Tassi, MD
Luca Vignatelli, MD, PhD
Claudio Bassetti, MD
Fabio Cirignotta, MD
Christopher Derry, PhD
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Renzo Guerrini, MD
Peter Halasz, MD, PhD
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Mark Mahowald, MD
Raffaele Manni, MD
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Maura Pugliatti, MD, PhD
Philippe Ryvlin, MD, PhD
Federico Vigevano, MD
Marco Zucconi, MD
Samuel Berkovic, MD, FRS*
Ruth Ottman, PhD*

VIEWS & REVIEWS

Definition and diagnostic criteria of sleep-related hypermotor epilepsy

Neurology 86 May 10, 2016

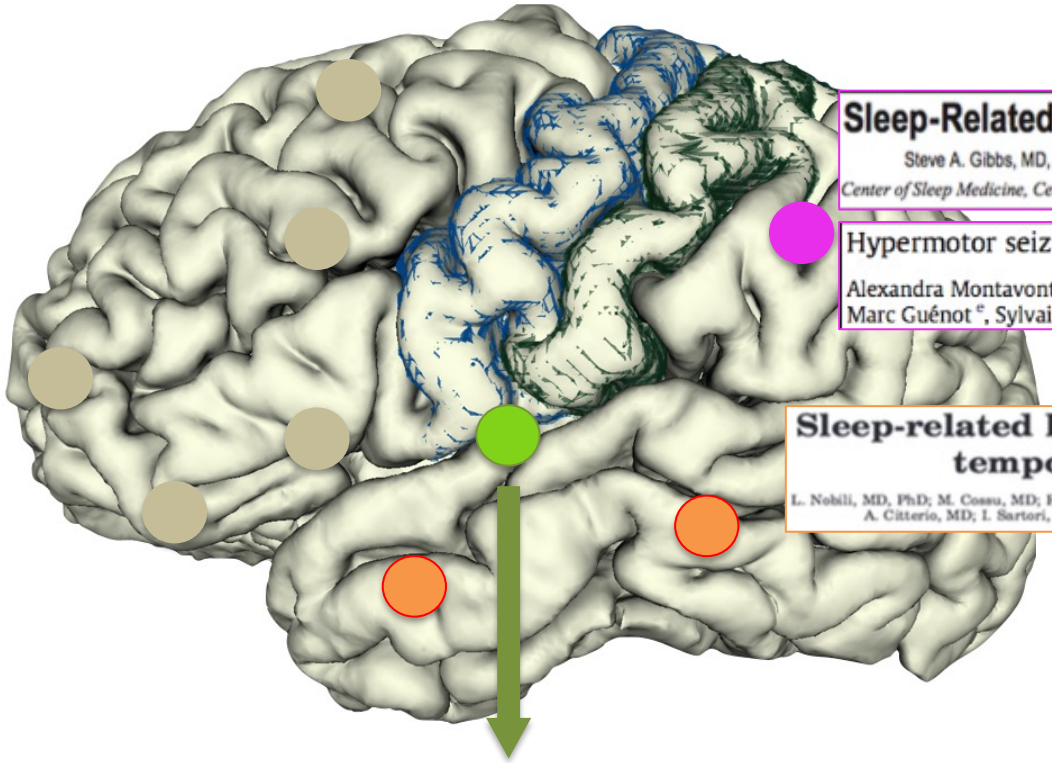
International Consensus conference on NFLE
Progress and challenges in an enigmatic epilepsy syndrome
Bologna, 30th August -1st September 2014

What was wrong with NFLE?

"Nocturnal Frontal Lobe Epilepsy" was misleading because:

- Seizures may arise from extra-frontal regions

Not always FRONTAL: the evidence for extra-frontal origin of NFLE



Sleep-Related Hypermotor Seizures with a Right Parietal Onset

Steve A. Gibbs, MD, PhD; Michela Figorilli, MD; Giuseppe Casaceli, MD; Paola Proserpio, MD; Lino Nobili, MD, PhD

Center of Sleep Medicine, Centre for Epilepsy Surgery "C. Munari," Department of Neurosciences, Hospital Niguarda, Milan, Italy

Hypermotor seizures in lateral and mesial parietal epilepsy

Alexandra Montavont [a,b,c,*], Philippe Kahane [d], Hélène Catenoix [c], Karine Ostrowsky-Coste [a,b], Jean Isnard [c], Marc Guénot [e], Sylvain Rheims [b,c], Philippe Ryvlin [a,b,c]

Sleep-related hyperkinetic seizures of temporal lobe origin

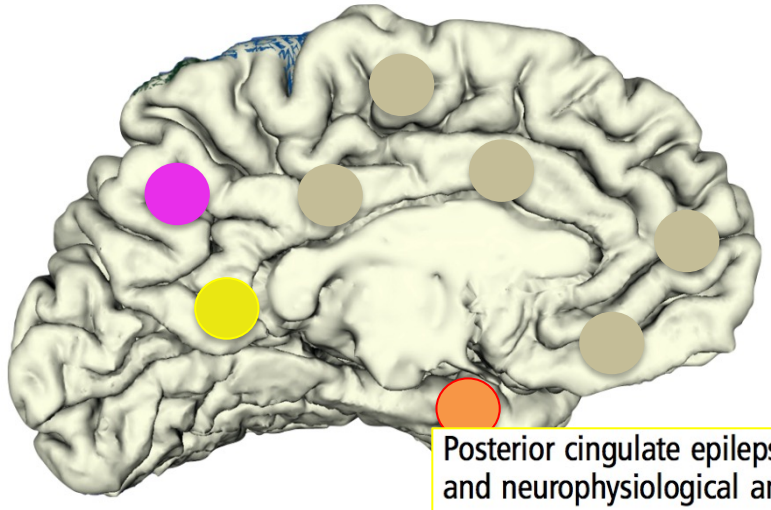
L. Nobili, MD, PhD; M. Cossu, MD; R. Mai, MD; L. Tassi, MD; F. Cardinale, MD; L. Castana, MD; A. Citterio, MD; I. Sartori, MD; G. Lo Russo, MD; and S. Francione, MD, PhD

Insular-opercular seizures manifesting with sleep-related paroxysmal motor behaviors: A stereo-EEG study

*†Paola Proserpio, *Massimo Cossu, *Stefano Francione, *Laura Tassi, *Roberto Mai, ‡Giuseppe Didato, *Laura Castana, *Francesco Cardinale, *Ivana Sartori, *Francesca Gozzo §Alberto Citterio, *Marco Schiariti, *Giorgio Lo Russo, and *†¶Lino Nobili

Nocturnal Hypermotor Seizures, Suggesting Frontal Lobe Epilepsy, Can Originate in the Insula

*Philippe Ryvlin, ‡Lorella Minotti, *Geneviève Demarquay, §Edouard Hirsch, ‖Alexis Arzimanoglou, ‡Dominique Hoffman, †Marc Guénot, ¶Fabienne Picard, *Sylvain Rheims, and ‡Philippe Kahane



Posterior cingulate epilepsy: clinical and neurophysiological analysis

Rei Enatsu,[1,2] Juan Bulacio,[1,3] Dileep R Nair,[1,3] William Bingaman,[1,2] Imad Najm,[1,3] Jorge Gonzalez-Martinez[1,2]

Nobili 2002; Mai 2005; Duffau 2006, Ryvlin 2006, Rheims 2008; Proserpio 2011

Not always FRONTAL: the evidence for extra-frontal origin of NFLE

30% extrafrontal origin

Nobili 2002; Mai 2005; Duffau 2006, Ryvlin 2006, Rheims 2008; Proserpio 2011

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VIEWS & REVIEWS

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What was wrong with NFLE?

"Nocturnal Frontal Lobe Epilepsy" was misleading because:

- Seizures may arise from extra-frontal regions
- The relationship to sleep is crucial, rather than time of day
- Name did not capture typical semiology

SHE: diagnostic criteria

Diagnosis based on clinical history

- Brief (<2 minutes) seizures with **stereotyped motor pattern**, abrupt onset and offset, may cluster

- Most common motor activity is hypermotor: vigorous **hyperkinetic** movements

Epileptic Nocturnal Wandering

Plazzi et al., 1995

SHE: diagnostic criteria

Diagnosis based on clinical history

- Brief (<2 minutes) seizures with **stereotyped motor pattern**, abrupt onset and offset, may cluster

- Most common motor activity is hypermotor: vigorous **hyperkinetic** movements, and/or **tonic or dystonic asymmetric posturing**, with or without impaired awareness

Dystonic asymmetric posturing

SHE: diagnostic criteria

Diagnosis based on clinical history

- Brief (<2 minutes) seizures with **stereotyped motor pattern**, abrupt onset and offset, may cluster

- Most common motor activity is hypermotor: vigorous **hyperkinetic** movements, and/or **asymmetric tonic or dystonic posturing**, with or without impaired awareness

Asymmetric tonic-dystonic

Supplementary motor seizures are an important exception to the rule that consciousness is invariably impaired in patients with seizures in whom all four extremities are involved. Several of our patients were thought to have pseudoseizures because they "broke the rule." Compounding the difficulty in separating supplementary motor seizures from pseudoseizures are the routine EEG findings. Usually there is no disturbance of background rhythms, and interictal sharp waves may be rare or absent; when present they are usually confined to the vertex and may be confused with normal EEG patterns, especially during sleep. Interictal sharp waves are at or near the midline, and that by itself should suggest seizures from the SMA. The ability to simultaneously record EEG and video over a prolonged time period may be most helpful in this clinical circumstance. The presence of clinical or neuroimaging abnormalities should suggest an organic process.

Morris et al., Neurology 1988

SHE: diagnostic criteria

Diagnosis based on clinical history

- Brief (<2 minutes) seizures with **stereotyped motor pattern**, abrupt onset and offset, may cluster

- Most common motor activity is hypermotor: vigorous **hyperkinetic** movements, and/or **asymmetric tonic or dystonic posturing**, with or without impaired awareness

Tinuper et al., Neurology 2016

SHE: diagnostic criteria

Diagnosis based on clinical history

- Brief (<2 minutes) seizures with **stereotyped motor pattern**, abrupt onset and offset, may cluster
- Most common motor activity is hypermotor: vigorous **hyperkinetic** movements, and/or **asymmetric tonic or dystonic posturing**, with or without impaired awareness
- Occurrence predominantly during sleep
- Diagnosis **not excluded** by intellectual disability, neuropsychiatric features, absence of interictal and ictal EEG correlates, extrafrontal origin

Tinuper et al., Neurology 2016

SHE: diagnostic criteria

Three levels of certainty

Witnessed (possible)

- Clinical features provided by **observer**

Video-documented (clinical)

- At least one stereotyped event, confirmed by observer to be typical
- High quality audio-video including the onset and offset with clear visualization of the entire event

COMMENTARY

Can Homemade Video Recording Become More Than a Screening Tool?

A commentary on Derry et al. NREM Arousal Parasomnias and their distinction from nocturnal frontal lobe epilepsy: a video EEG analysis SLEEP 2009;32:1637-1644.

Lino Nobili. MD. PhD

CRISI IPERCINETICHE

COMMENTARY

Can Homemade Video Recording Become More Than a Screening Tool?

A commentary on Derry et al. NREM Arousal Parasomnias and their distinction from nocturnal frontal lobe epilepsy: a video EEG analysis SLEEP 2009;32:1637-1644.

Lino Nobili, MD, PhD

CRISI TONICO ASIMMETRICHE

Smartphones in Epilepsy: The New Age of Aquarius

William O. Tatum, DO, and Emily K. Acton, BS

Mayo Clin Proc.January 2021

HOME-MADE video

- Raccomandare uso ai pz fin dalla prima visita
- Telecamera (infrarossi) accesa tutta la notte per almeno 1 sett
- Dormire senza lenzuolo, accendere luce all'inizio, etc

VANTAGGI

- Setting fisiologico
- Risparmio tempo
- Abbattimento costi VPSG
- Ottima "resa" diagnostica per episodi maggiori
- ↓ misdiagnosis

SHE: diagnostic criteria

Three levels of certainty

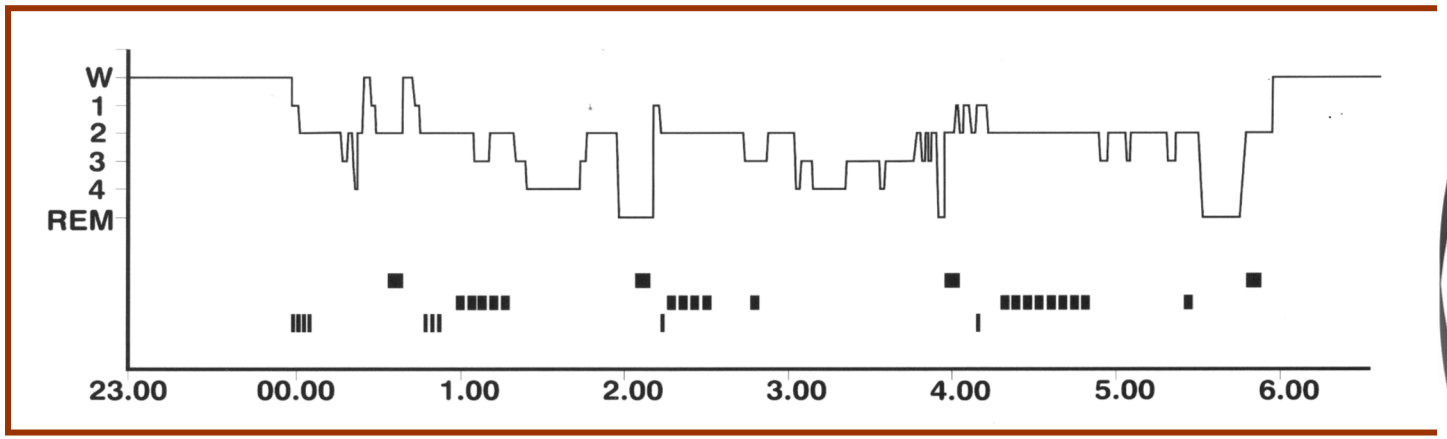
Witnessed (possible)

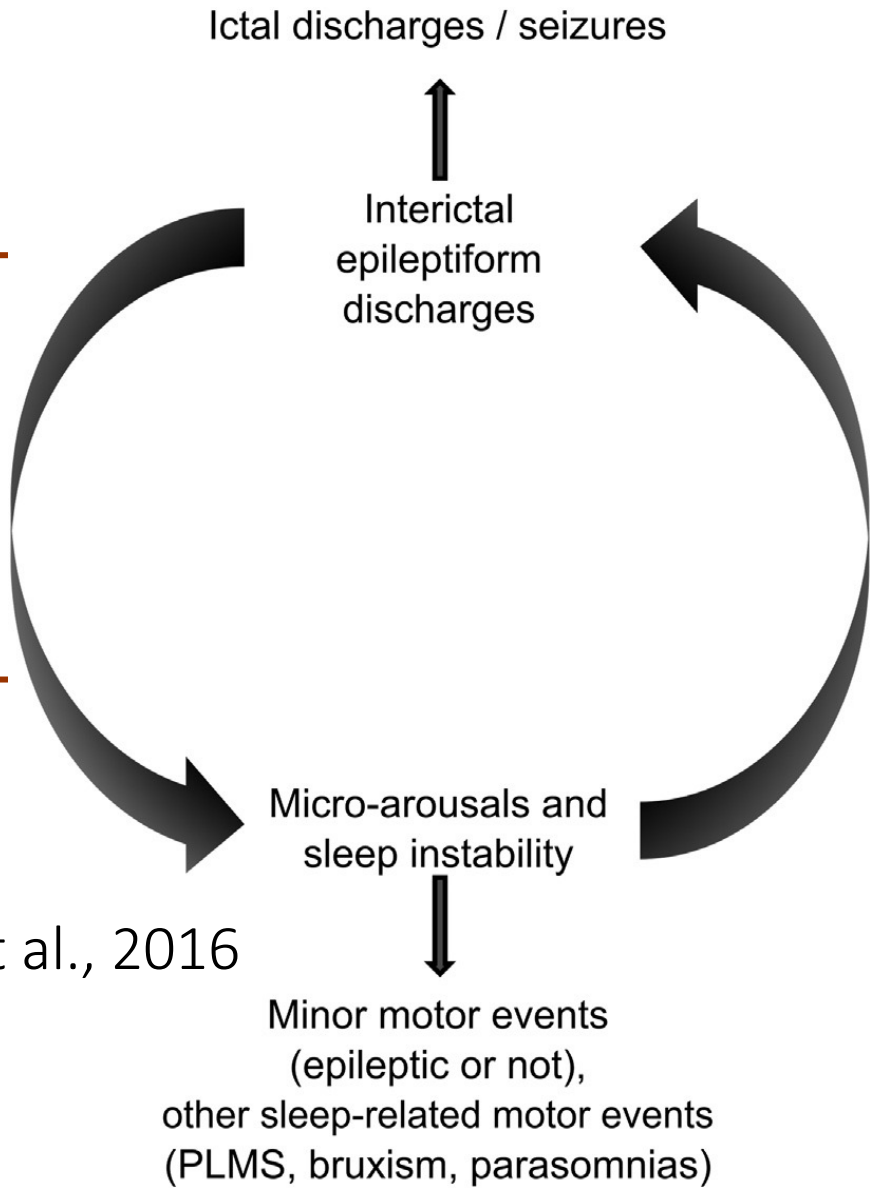
- Clinical features provided by observer

Video-documented (clinical)

- At least one stereotyped event, confirmed by observer to be typical
- High quality audio-video including the onset and offset with clear visualization of the entire event
- **Minor motor events** or **paroxysmal arousals** excluded

Minimal motor events





Gibbs et al., 2016

Paroxysmal Arousals, Montagna 1990; Minimal, Minor and Major motor activity Oldani 1996, Zucconi 1997

SHE: diagnostic criteria

Three levels of certainty

Witnessed (possible)

- Clinical features provided by observer

Video-documented (clinical)

- At least one stereotyped event, confirmed by observer to be typical
- High quality audio-video including the onset and offset with clear visualization of the entire event
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SHE: diagnostic criteria

Three levels of certainty

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- Clinical features provided by observer

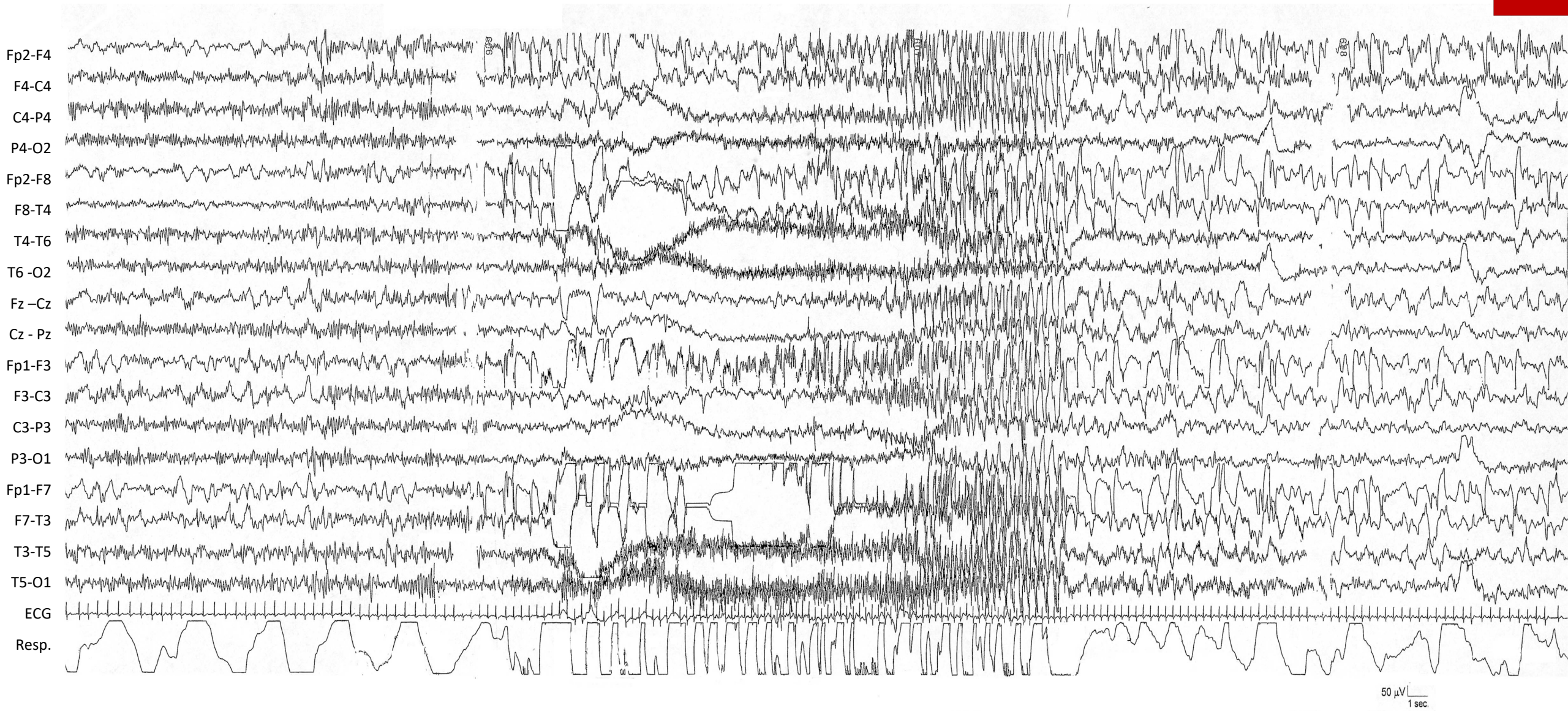
Video-documented (clinical)

- At least one stereotyped event, confirmed by observer to be typical
- High quality audio-video including the onset and offset with clear visualization of the entire event
- Minor motor events or paroxysmal arousals excluded

Video-EEG documented (confirmed)

- At least **one stereotyped** event during daytime sleep recording after sleep deprivation, or during full night sleep recording using ≥19 EEG channels, ECG, oculogram, and chin EMG
- **Definitive ictal epileptic discharge**

Tinuper et al., Neurology 2016



6 yrs, F, Right handed

SHE: diagnostic criteria

Three levels of certainty

Witnessed (possible)

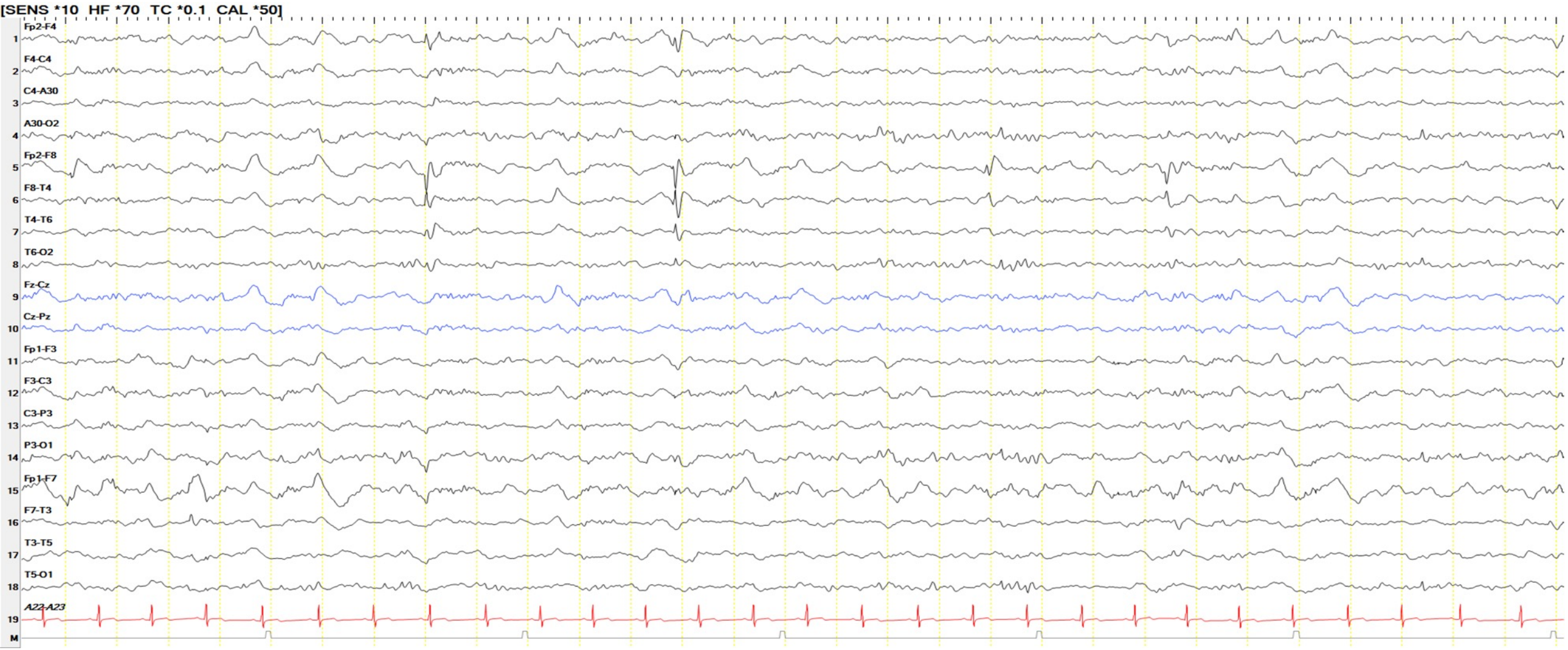
- Clinical features provided by observer

Video-documented (clinical)

- At least one stereotyped event, confirmed by observer to be typical
- High quality audio-video including the onset and offset with clear visualization of the entire event
- Minor motor events or paroxysmal arousals excluded

Video-EEG documented (confirmed)

- At least **one stereotyped** event during daytime sleep recording after sleep deprivation, or during full night sleep recording using ≥19 EEG channels, ECG, oculogram, and chin EMG
- **Definitive ictal epileptic discharge** or interictal epileptiform abnormality


[SENS *10 HF *70 TC *0.1 CAL *50]
1 Fp2-F4
2 F4-C4
3 C4-A30
4 A30-O2
5 Fp2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 Fz-Cz
10 Cz-Pz
11 Fp1-F3
12 F3-C3
13 C3-P3
14 P3-O1
15 Fp1-F7
16 F7-T3
17 T3-T5
18 T5-O1
19 A22-A23
M

Who is SHE?

Outlines

- History and nomenclature
- The diagnostic criteria
- Phenotype: clinical and demographic features
- Etiology
- Treatment
- Grey areas

Who is SHE?

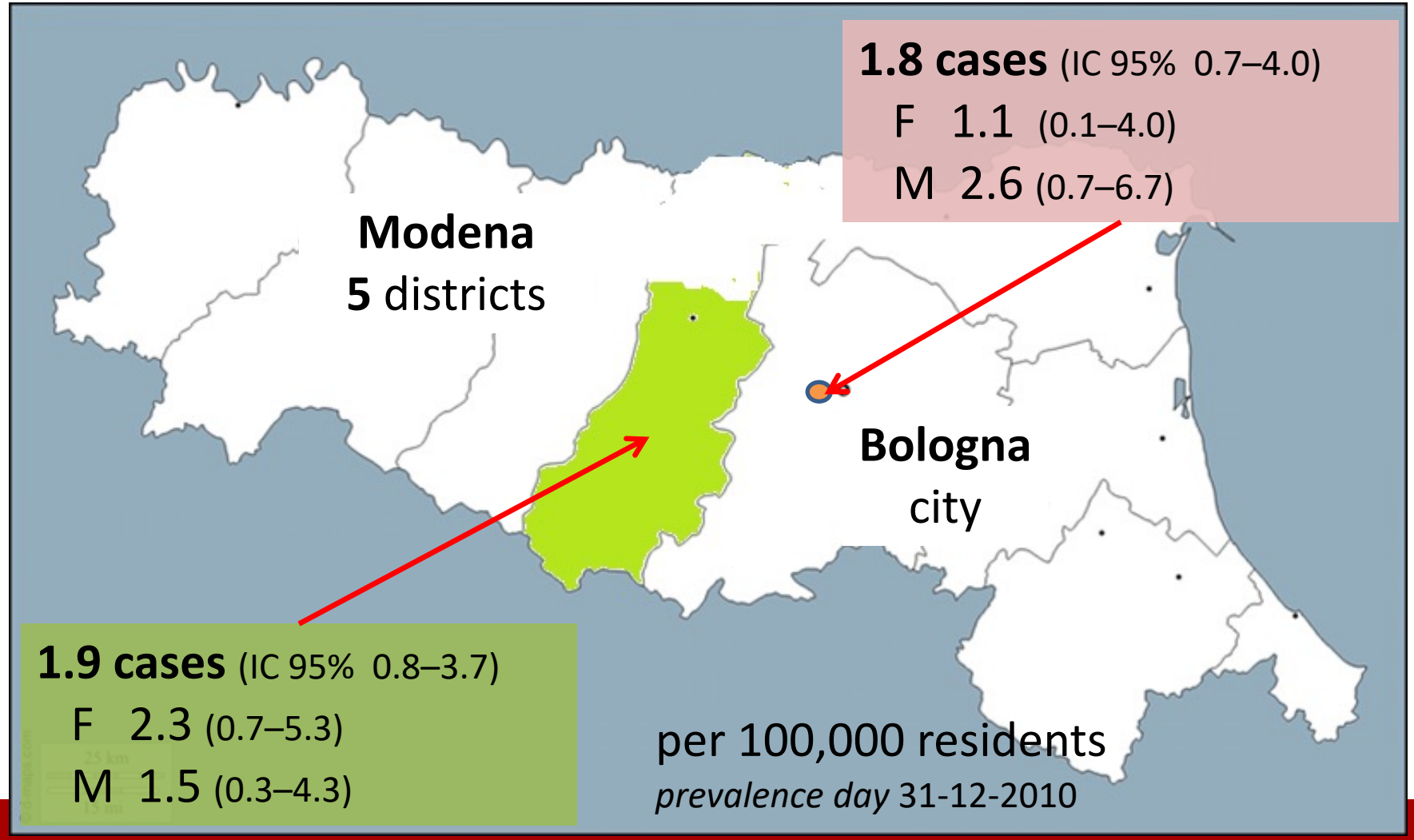
Outlines

- Phenotype: clinical and demographic features

Prevalence of Sleep-Related Hypermotor Epilepsy—Formerly Named Nocturnal Frontal Lobe Epilepsy—in the Adult Population of the Emilia-Romagna Region, Italy

Luca Vignatelli, MD, PhD[1]; Francesca Bisulli, MD, PhD[1,2]; Giada Giovannini, MD[3]; Laura Licchetta, MD[1,2]; Ilaria Naldi, MD, PhD[1]; Barbara Mostacci, MD, PhD[1]; Guido Rubboli, MD[1,4,5]; Federica Provini, MD, PhD[1,2]; Paolo Tinuper, MD[1,2]; Stefano Meletti, MD, PhD[3]

SLEEP, Vol. 40, No. 2, 2017



SHE phenotype

Laura Licchetta, MD
Francesca Bisulli, MD, PhD*
Luca Vignatelli, MD, PhD*
Corrado Zenesini, MSc
Lidia Di Vito, MD
Barbara Mostacci, MD, PhD
Claudia Rinaldi, MD
Irene Trippi, MD
Ilaria Naldi, MD, PhD
Giuseppe Plazzi, MD, PhD
Federica Provini, MD, PhD
Paolo Tinuper, MD

Sleep-related hypermotor epilepsy

Long-term outcome in a large cohort

OPEN

139 cases

Neurology® 2017;88:70-77

- Prevalence 1.8-1.9/100.000 Vignatelli et al., 2017
- M>F (63% M)
- Age at onset mean 13.4 ± 10.2 yrs (range: 1-56 yrs)
- Sporadic 85.6%, Familial 14.4% (ADSHE 5%)
- Parasomnias: familiy history 48.2%; [personal history 30%]
- Normal neurological exam and IQ 89.2%
- Bilateral convulsive tonic-clonic seizures: 33.8%
- EEG negative: 43.8% interictal and 61.15% ictal
- Drug resistance rate: 38.8%

Increased frequency of arousal parasomnias in families with nocturnal frontal lobe epilepsy: A common mechanism?

*Francesca Bisulli, †Luca Vignatelli, *Ilaria Naldi, *Laura Licchetta, *Federica Provini, *Giuseppe Plazzi, *Lidia Di Vito, *Simona Ferioli, *Pasquale Montagna, and *Paolo Tinuper

Family study
Proband vs control relatives

		Probands N = 200		Controls N = 194			
Group	Parasomnia	N	%	N	%	p-value	OR (CI 95%)
Arousal disorders	Confusional arousal	7	3.5	1	0.5	0.068	7.0 (0.9–57.4)
	First criterion	19	9.5	13	6.7	0.359	1.5 (0.7–3.0)
	Sleep walking	16	8.0	5	2.6	0.023	3.3 (1.2–9.2)
	First criterion	31	15.5	19	9.8	0.097	1.7 (0.9–3.1)
	Sleep terrors	4	2.0	–	–	0.123	–
	First criterion	38	19,0	18	9.3	0.006	2.3 (1.3–4.2)
	Total[a]	26	13.0	6	3.1	<0.001	4.7 (2.0–11.6)
	First degree	13	14.4	3	3.1	0.007	5.3 (1.5–19.4)
	Second and third degree	13	11.8	3	3.1	0.034	4.2 (1.1–15.0)
	Total including adult onset[a,b]	34	17.0	9	4.6	<0.001	4.2 (2.0–9.0)
Wake-sleep transition disorders	Rhythmic movement disorder	6	0	4	2.1	0.751	1.5 (0.4–5.3)
	Sleep starts	133	66.5	129	66.5	1.000	1.0 (0.7–1.5)
	Sleep talking	85	42.5	64	33.0	0.061	1.5 (2.0–2.3)
	Nocturnal leg cramps	23	11.5	20	10.4	0.749	1.1 (0.6–2.1)
Parasomnias usually associated with REM sleep	Nightmares	62	31.0	29	14.9	<0.001	2.6 (1.6–4.2)
	First criterion	123	61.5	120	61.9	1.000	2.0 (0.6–1.5)
	Sleep paralysis	8	4.0	2	1.0	0.105	4.0 (0.8–19.0)
	RBD	17	8.5	8	4.1	0.098	2.2 (0.9–5.3)
Other parasomnias	Sleep bruxism	42	21.0	35	18.0	0.526	1.2 (0.7–2.0)
	Sleep enuresis	16	8.0	11	5.7	0.427	1.4 (0.7–3.2)
	Primary snoring	116	58.0	110	51.8	0.225	1.9 (0.8–1.9)

SHE and parasomnias: OVERLAPPING

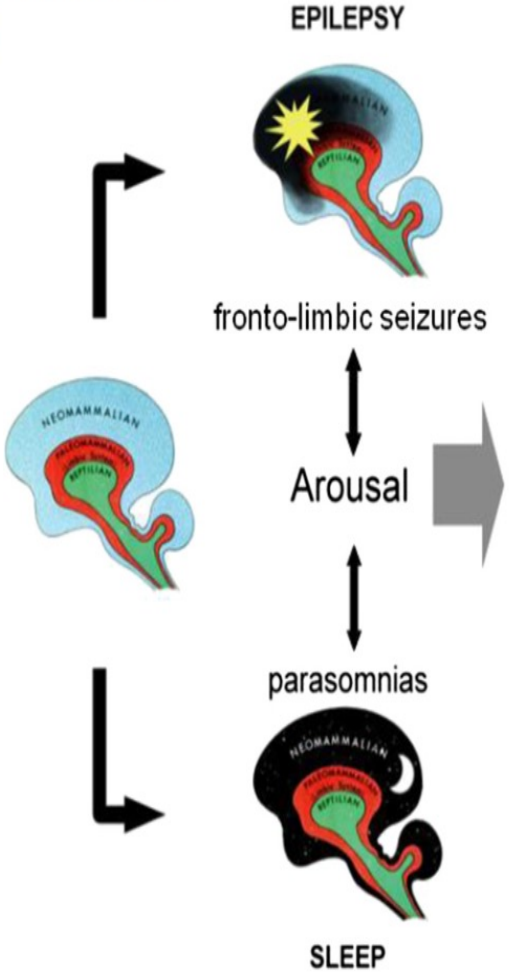
PARASOMNIAS

SHE

SHE and parasomnias: OVERLAPPING

C.A. Tassinari • G. Rubboli • E. Gardella • G. Cantalupo • G. Calandra-Buonaura • M. Vedovello
M. Alessandria • G. Gandini • S. Cinotti • N. Zamponi • S. Meletti

Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach



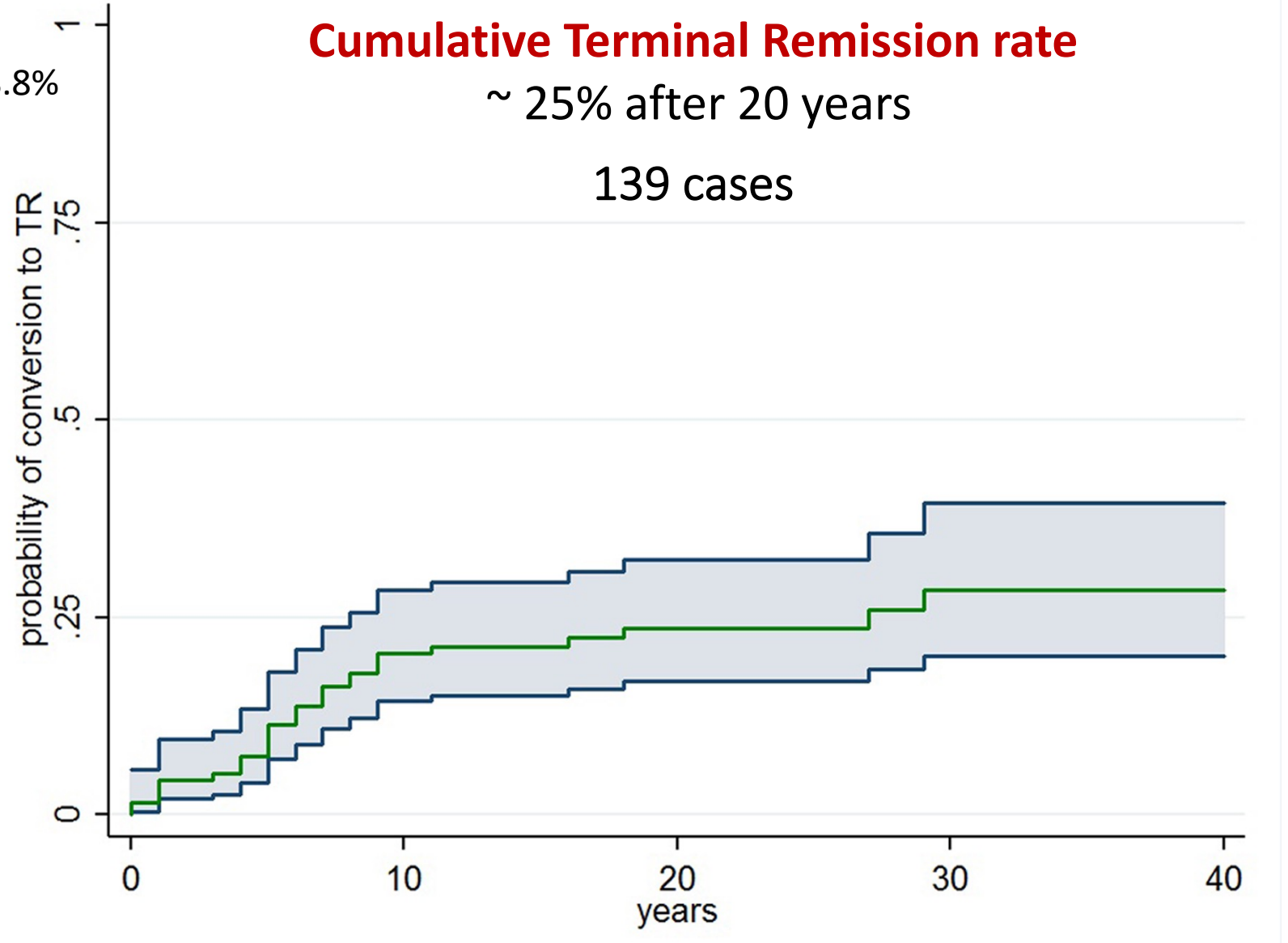
Innate motor behaviors

bruxism - teeth grinding oral automatisms (chewing, swallowing, lip-smacking)	alimentary
biting - flybiting teeth chattering facio-mandibular myoclonus	defensive / predatory
universal facial expression (fear - pavor etc.) and encoded vocalizations	emotional
pedalling (supine), tetrapod progression (prone) fugue - wandering cyclic legs movements bimanual - bipedal activity	locomotory
repetitive pelvic thrusting	mounting/copulatory

Tassinari et al., 2005, 2009, 2012

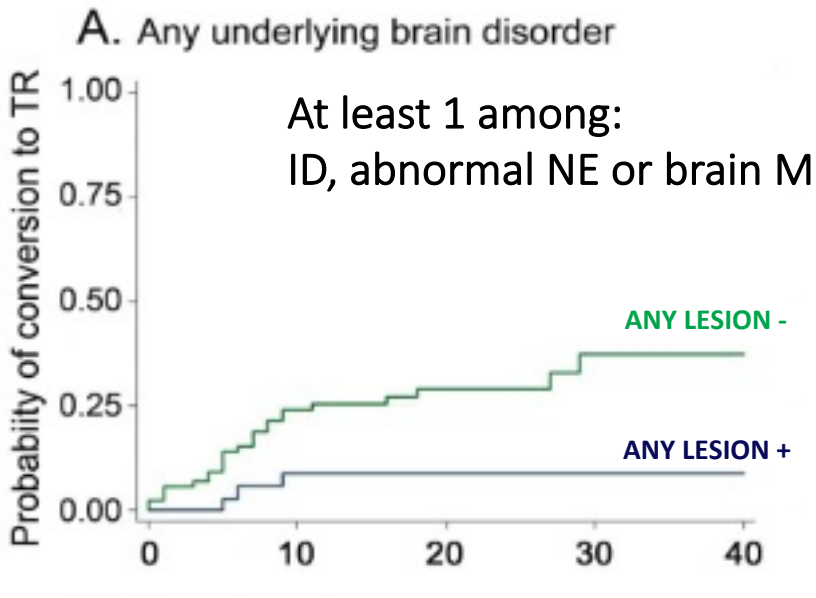
SHE prognosis

Drug resistance rate: 38.8%



Licchetta et al., Neurology 2017

Predictor of Terminal Remission



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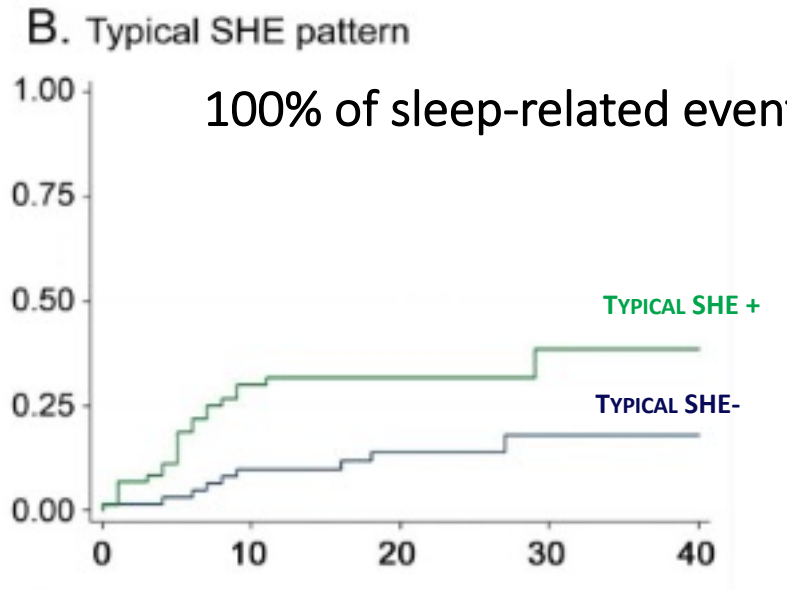

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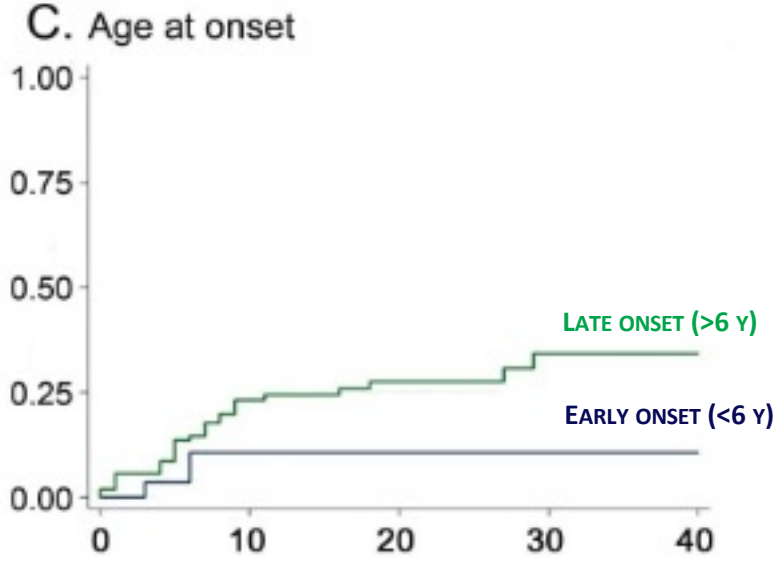


P: 0.076

Negative

Early onset <6 yrs

Atypical SHE (<100% of sleep-related events)

ID, abnormal NE/MRI

SHE etiology

139 cases

Sporadic 85.6%, Familial 14.4% (ADSHE 5%)

- **Unknown 78.3%**
- Structural 13.7%
- Genetic 5%
- Genetic-structural 3%

} **8% genetic etiology**

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)

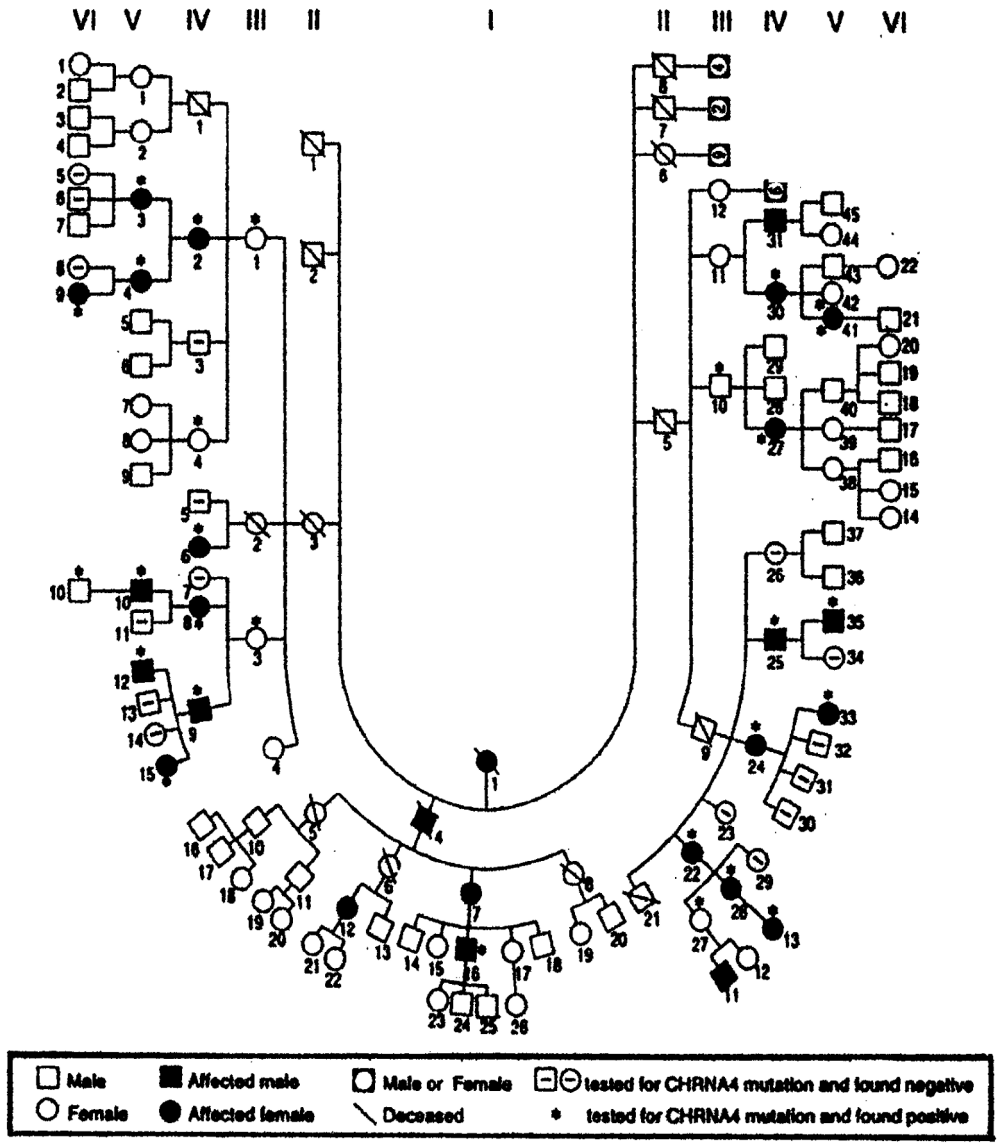
1994-1995

THE LANCET

Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder

Ingrid E Scheffer, Kailash P Bhatia, Iscia Lopes-Cendes, David R Fish, C David Marsden, Frederick Andermann, Eva Andermann, Richard Desbiens, Fernando Cendes, James I Manson, Samuel F Berkovic

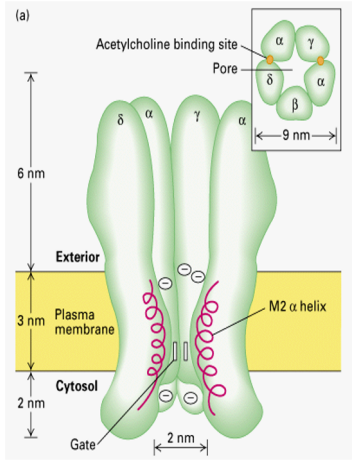
Vol 343 • February 26, 1994



Nat Genet. 1995 May

Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2

H.A. Phillips[1], I.E. Scheffer[2], S.F. Berkovic[2], G.E. Hollway[1,3], G.R. Sutherland[1,3] & J.C. Mulley[1]

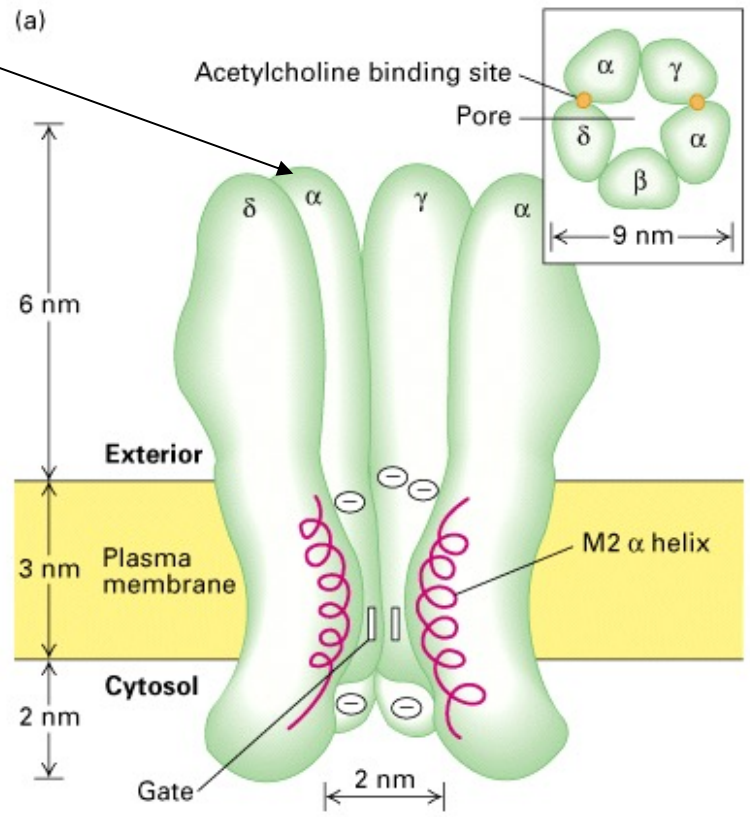


Stenlein et al., 1995

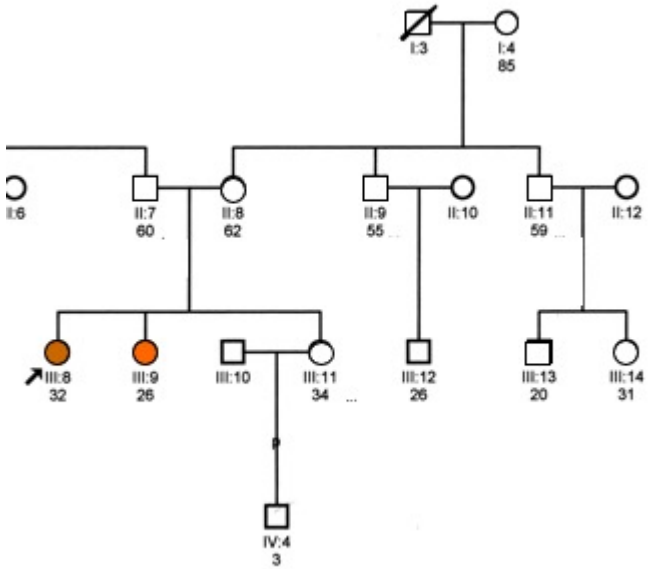
Nature Genetics volume 11 october 1995

Autosomal Dominant SHE (ADSHE)

ENFL1
20q13.2
CHRNA4
α4
Steinelin et al, 1995



Autosomal Dominant SHE (ADSHE)

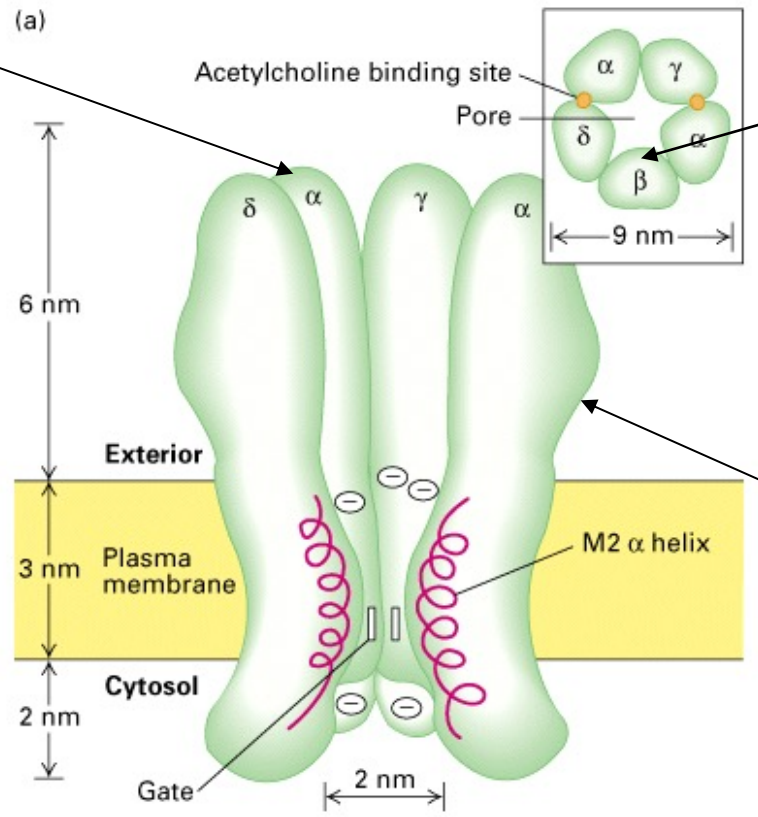


CHRNA4 p.Gly307Val

Autosomal Dominant SHE (ADSHE)

ENFL1
20q13.2
CHRNA4
α4
Steinelin et al, 1995

ENFL2 15q24
Gene ?
Philips et al, 1998



ENFL3
1q21
CHRNB2
β2
De Fusco et al,2000

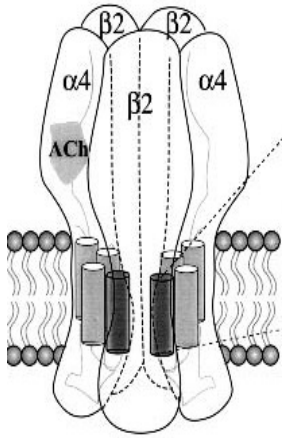
ENFL4
8p12.3
CHRNA2
α2
Aridon et al, 2006

Autosomal Dominant SHE (ADSHE)

From 1995 only nAChr genes

nAChRs genes

~15% ADSHE



Autosomal Dominant SHE (ADSHE)

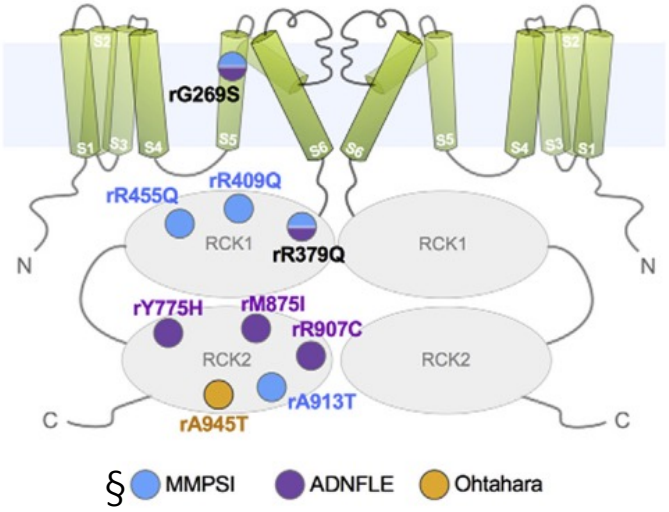
From 2012 to now→Genetic heterogeneity

KCNT1

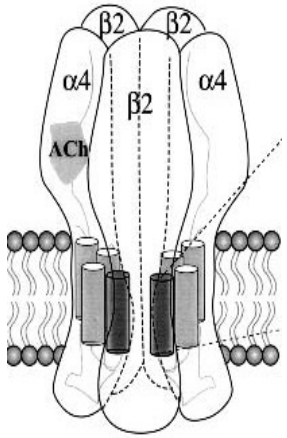
nAChRs genes

SEVERE PHENOTYPE

~15% ADSHE



Heron et al., 2012

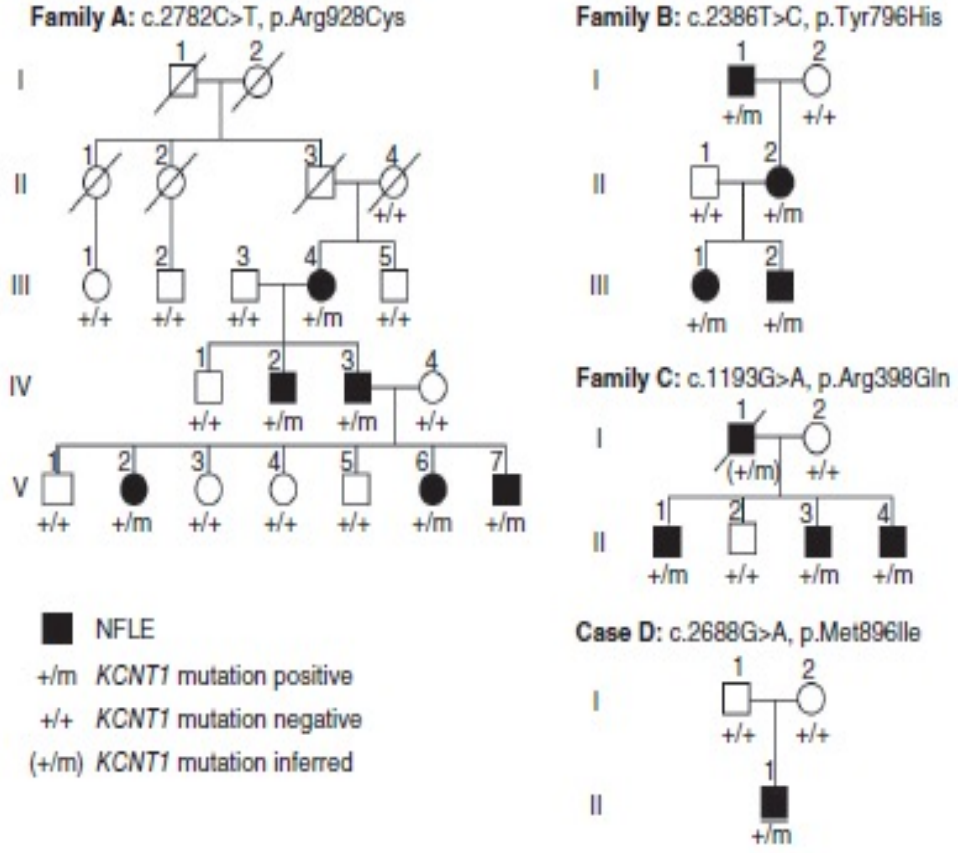


§ Malignant Migrating Focal Seizures of Infancy (MMFSI)

VOLUME 44 | NUMBER 11 | NOVEMBER 2012 NATURE GENETICS

Missense mutations in the sodium-gated potassium channel gene *KCNT1* cause severe autosomal dominant nocturnal frontal lobe epilepsy

Sarah E Heron[1,2], Katherine R Smith[3,4], Melanie Bahlo[3,5], Lino Nobili[6], Esther Kahana[7], Laura Licchetta[8], Karen L Oliver[8], Aziz Mazarib[9], Zaid Afawi[10], Amos Korczyn[11], Giuseppe Plazzi[12], Steven Petrou[13–15], Samuel F Berkovic[8], Ingrid E Scheffer[8,13,16,17] & Leanne M Dibbens[1,2,17]



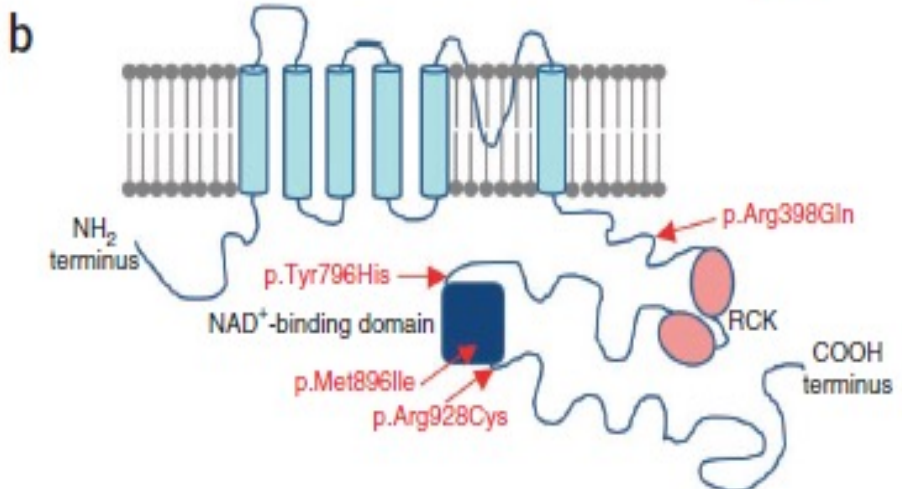
SHE-KCNT1

ADSHE 100% penetrance

Early onset

Drug resistancy

ID/Psychiatric disorders



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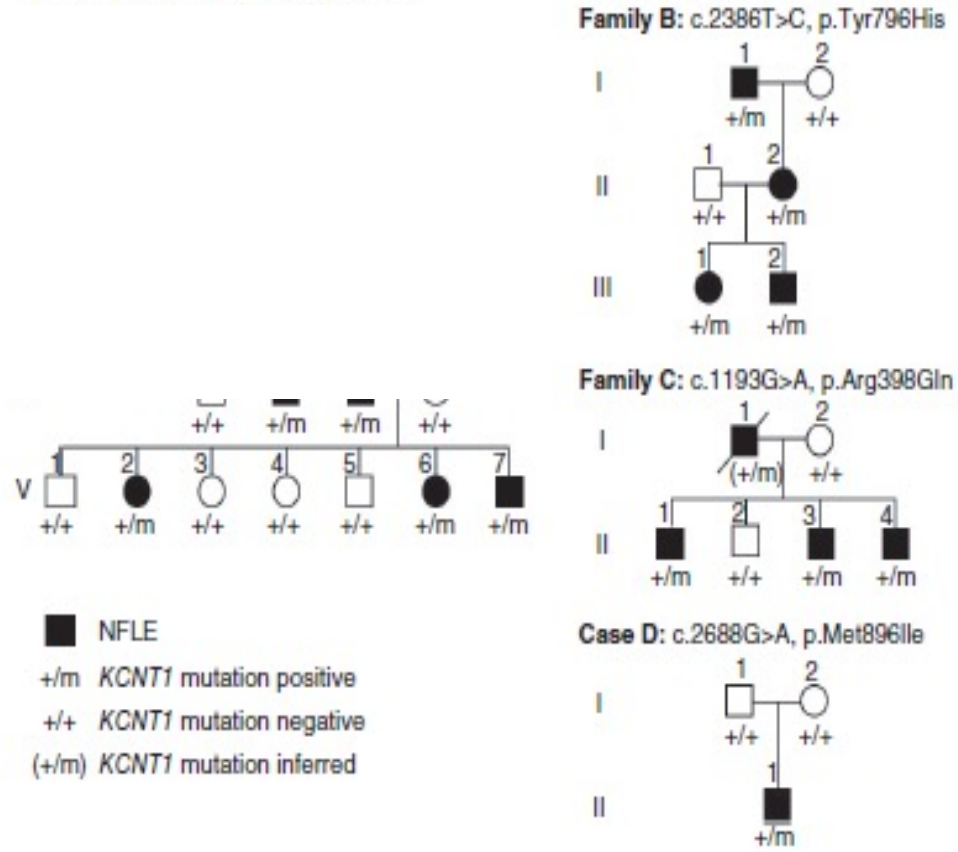
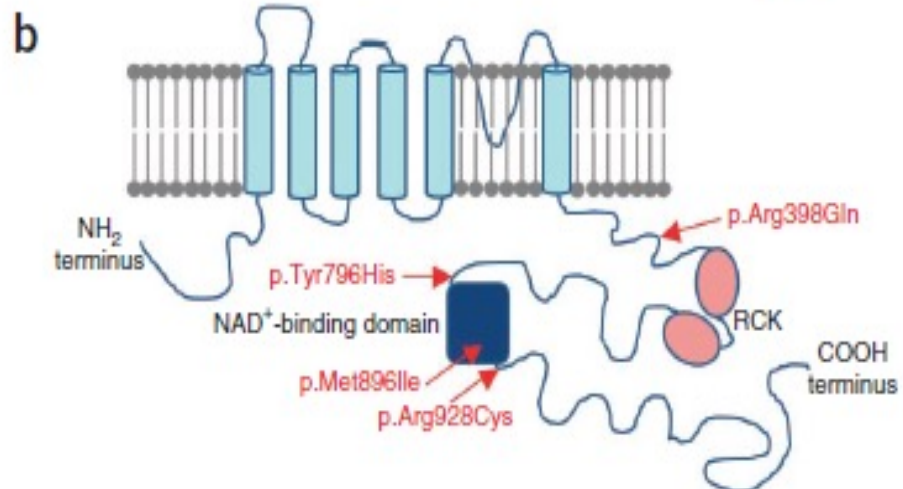




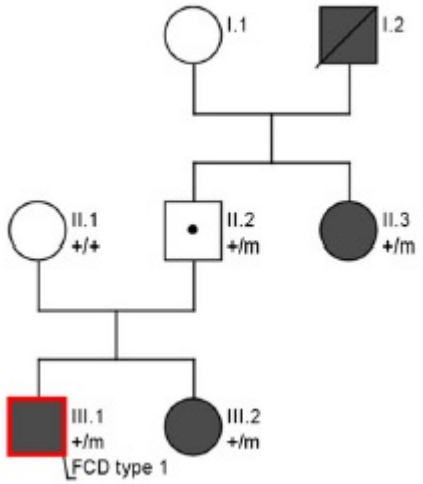
ANNALS of Clinical and Translational Neurology
Open Access
BRIEF COMMUNICATION

Mild malformations of cortical development in sleep-related hypermotor epilepsy due to *KCNT1* mutations

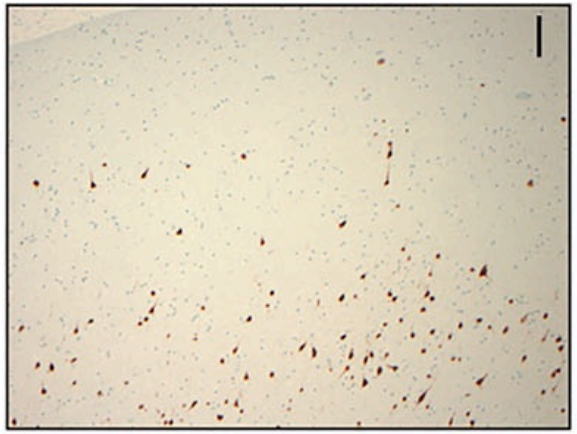
Guido Rubboli[1,2], Giuseppe Plazzi[3,4], Fabienne Picard[5], Lino Nobili[6], Edouard Hirsch[7], Jamel Chelly[8], Richard A. Prayson[9], Jean Boutonnat[10], Manuela Bramerio[11], Philippe Kahane[12], Leanne M. Dibbens[13], Elena Gardella[1,14], Stéphanie Baulac[15,16,17,*] & Rikke S. Møller[1,14,*]

4 MRI negative pts with DR SHE
3 underwent surgery→ mMCD

Family A: c.2849G>A; p.Arg950Gln



A

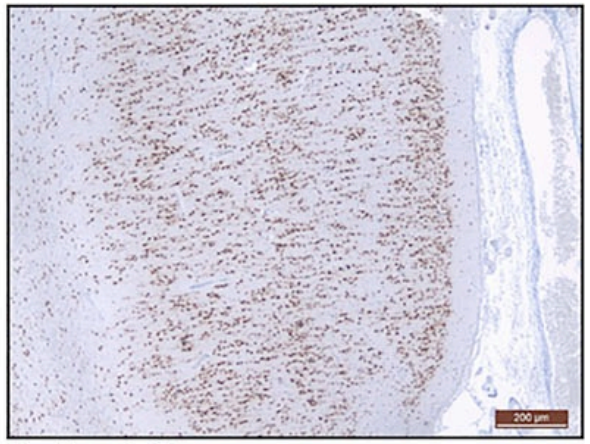


Patient A.III.1

B

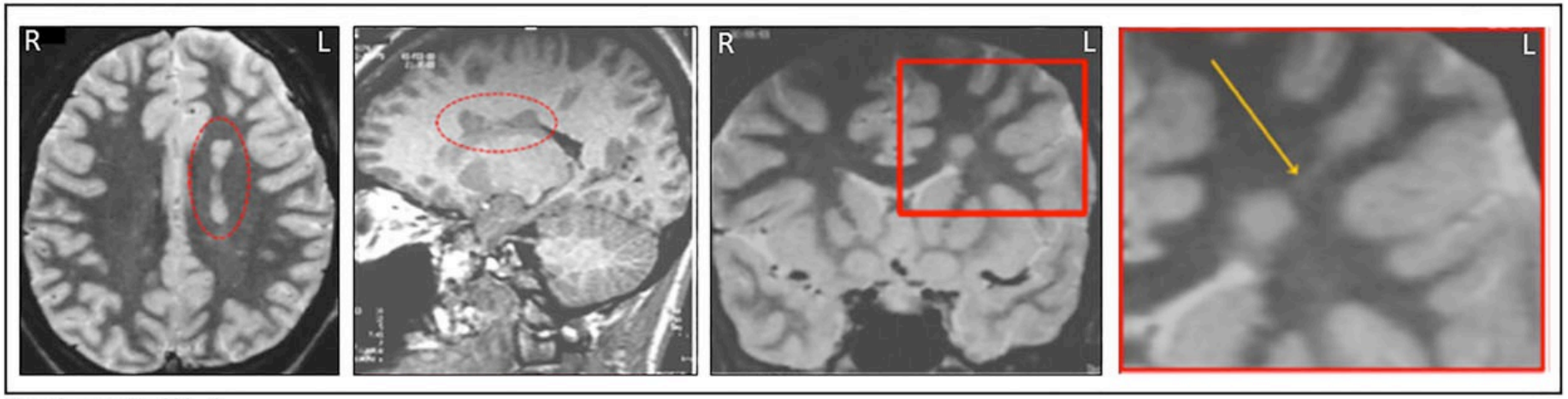
Patient B.III.2

C



Patient C

D



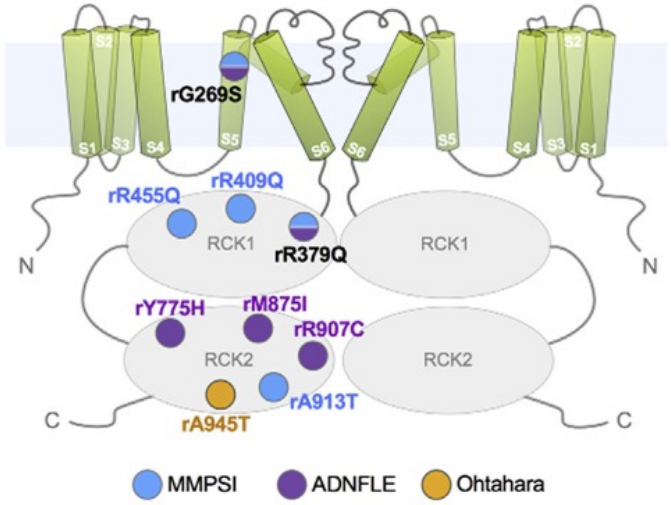
Patient B.III.1

Autosomal Dominant SHE (ADSHE)

From 2012 to now→Genetic heterogeneity

KCNT1

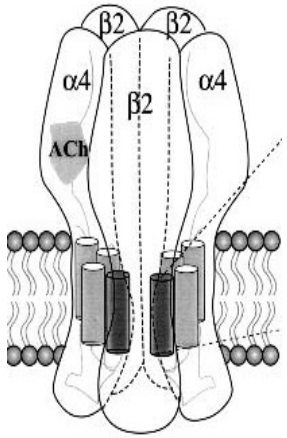
SEVERE PHENOTYPE



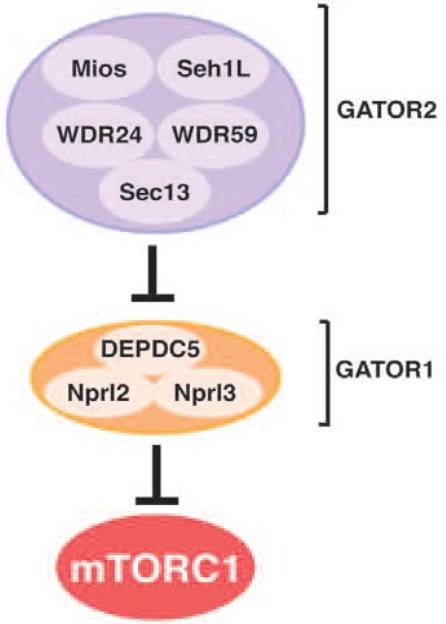
Heron et al., 2012

nAChRs genes

~15% ADSHE



GATOR1 genes



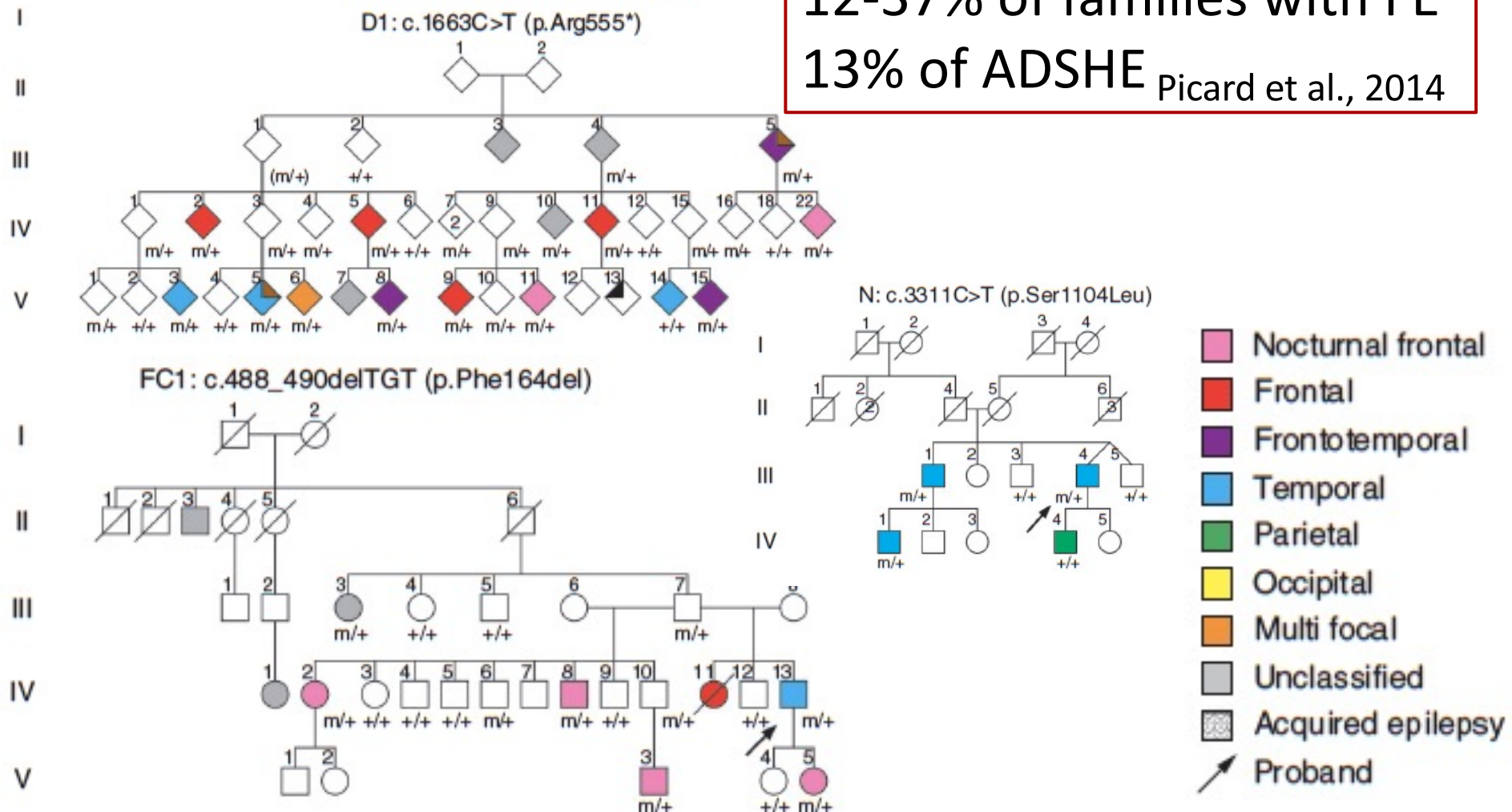
Dibbens et al., 2013
Hishida et al., 2013
Picard et al., 2014

nature genetics
VOLUME 45 | NUMBER 5 | MAY 2013 NATURE GENETICS

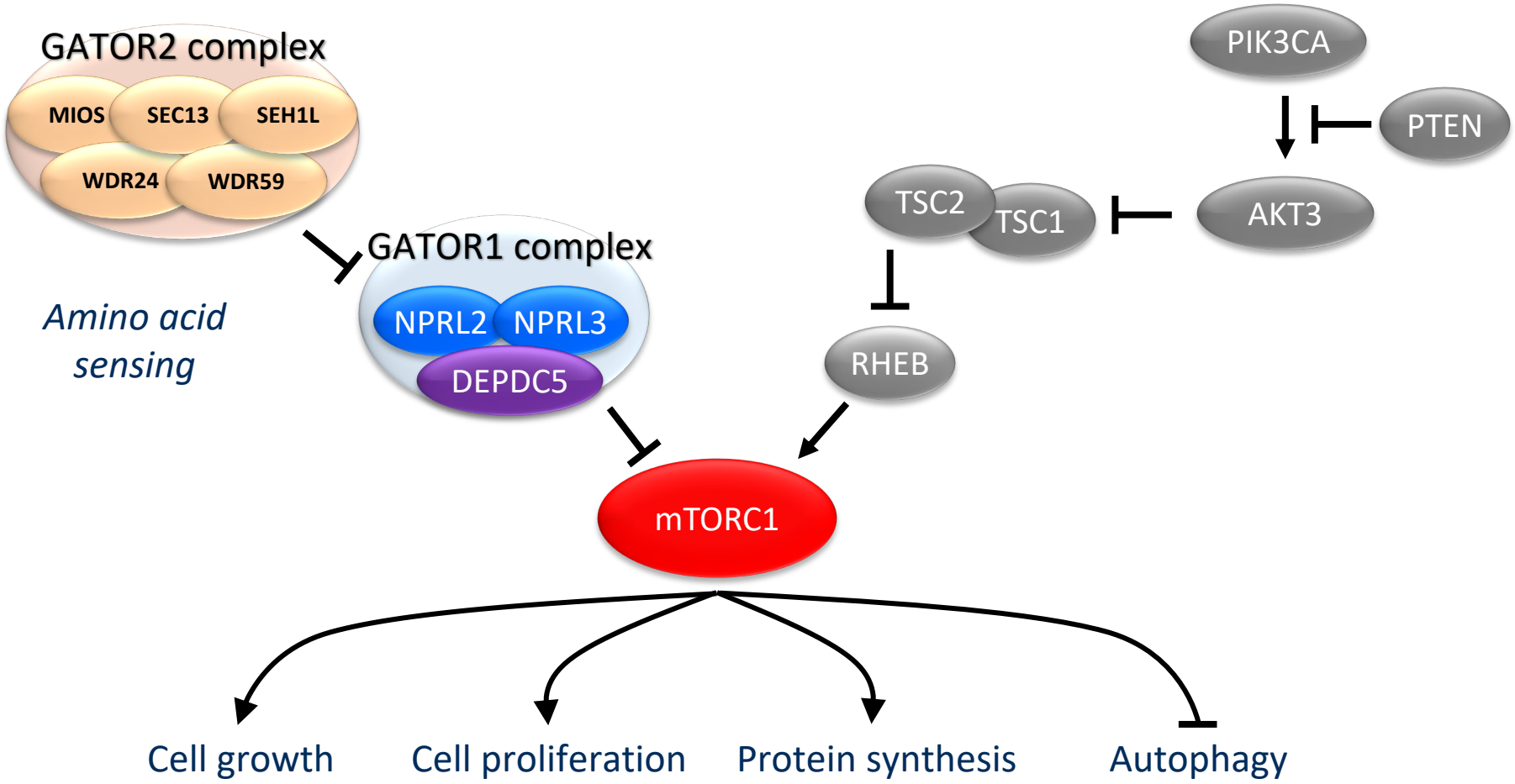
Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

Leanne M Dibbens

12-37% of families with FE
13% of ADSHE Picard et al., 2014



GATOR1 complex is a repressor of mTOR complex 1

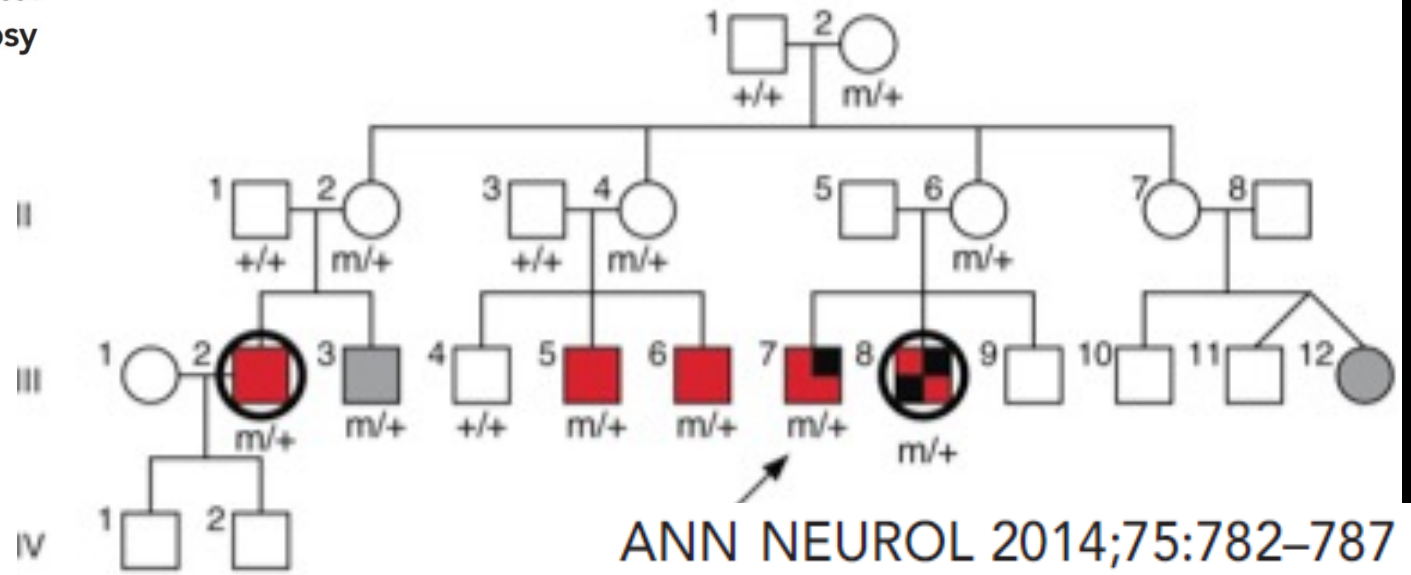


Bar-Peled et al., Science 2013

Mutations in Mammalian Target of Rapamycin Regulator *DEPDC5* Cause Focal Epilepsy with Brain Malformations

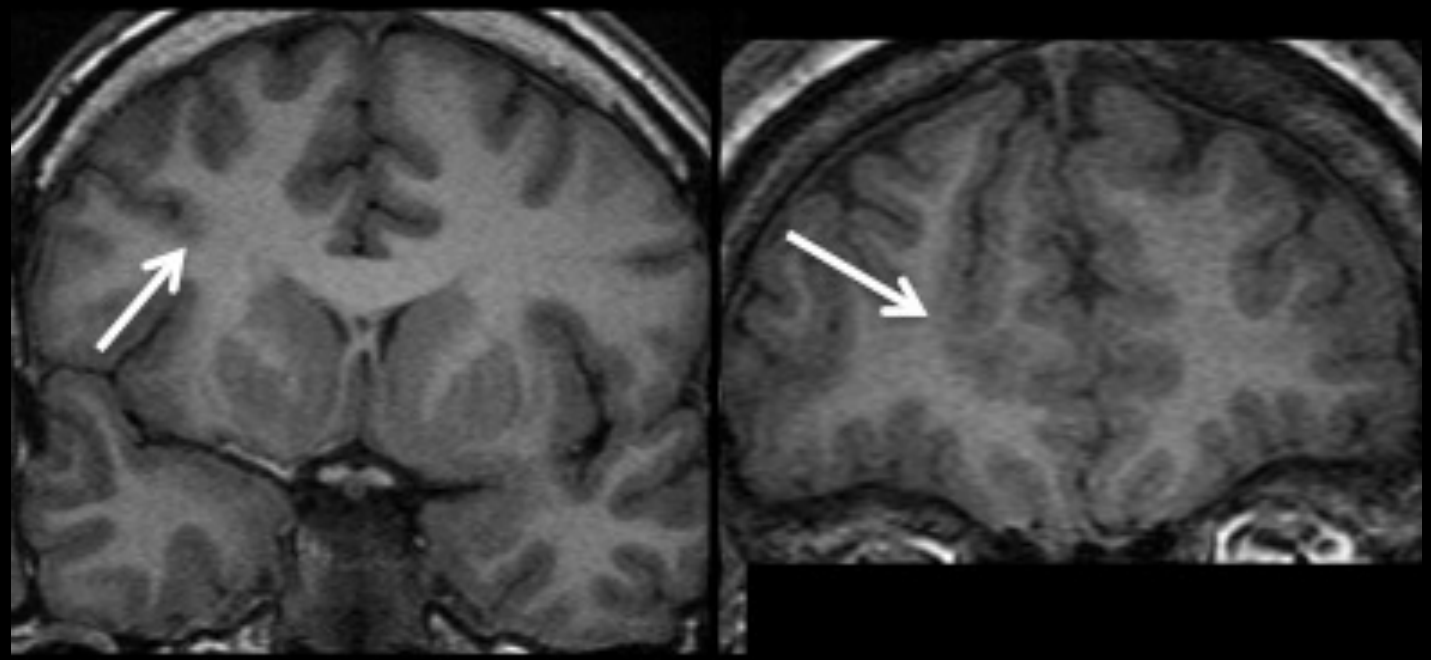
Ingrid E. Scheffer, MB, BS, PhD,[1,2,3]
Sarah E. Heron, BSc, PhD,[4,5]
Brigid M. Regan, BSc,[1]
Simone Mandelstam, MB, ChB,[2,3,6]
Douglas E. Crompton, MBBS, PhD,[7]
Bree L. Hodgson, Dip Biomed Sci,[4,5]
Laura Licchetta, MD,[8]
Federica Provini, MD, PhD,[8,9]
Francesca Bisulli, MD, PhD,[8,9]
Lata Vadlamudi, MB, BS, PhD,[1,10]
Jozef Gecz, PhD,[11]
Alan Connelly, PhD,[2,12]
Paolo Tinuper, MD,[8,9]
Michael G. Ricos, BSc, PhD,[4,5]
Samuel F. Berkovic, MD, FRS,[1] and
Leanne M. Dibbens, BSc, PhD[4,5]

Family B *DEPDC5* c.418C>T (p.Gln140*)

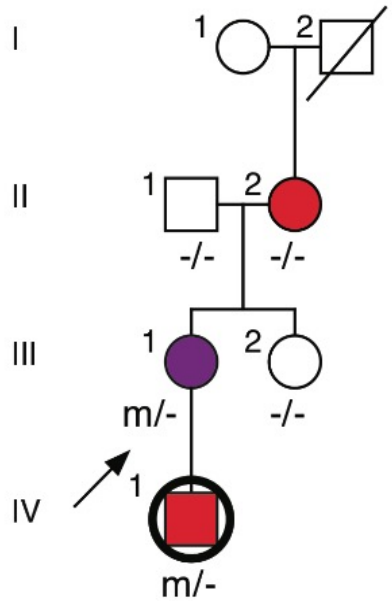


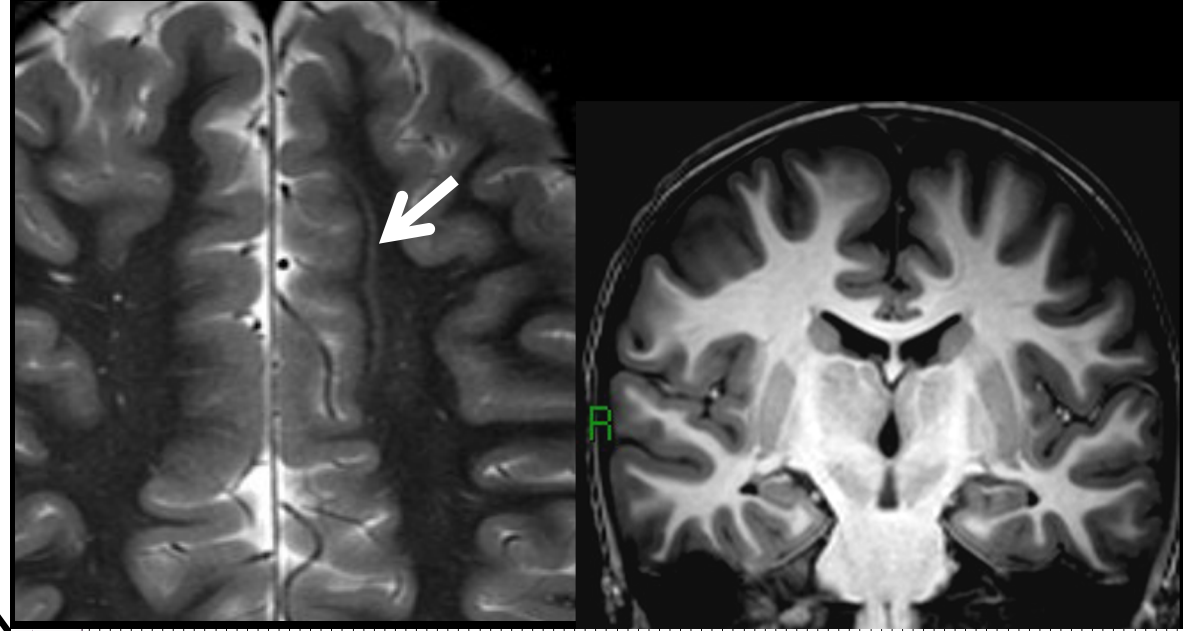
ANN NEUROL 2014;75:782–787

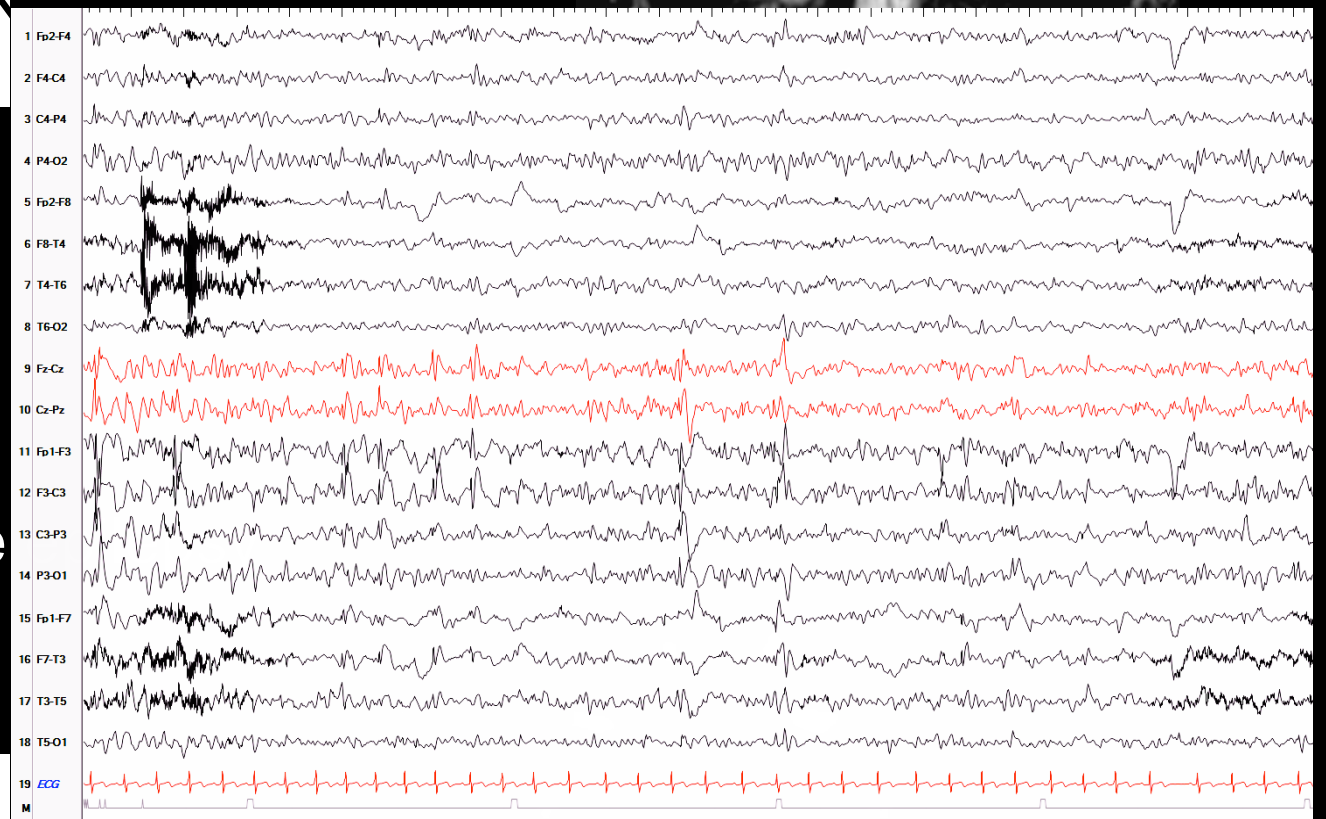
SHE



Family I *DEPDC5* c.279+1 G>A







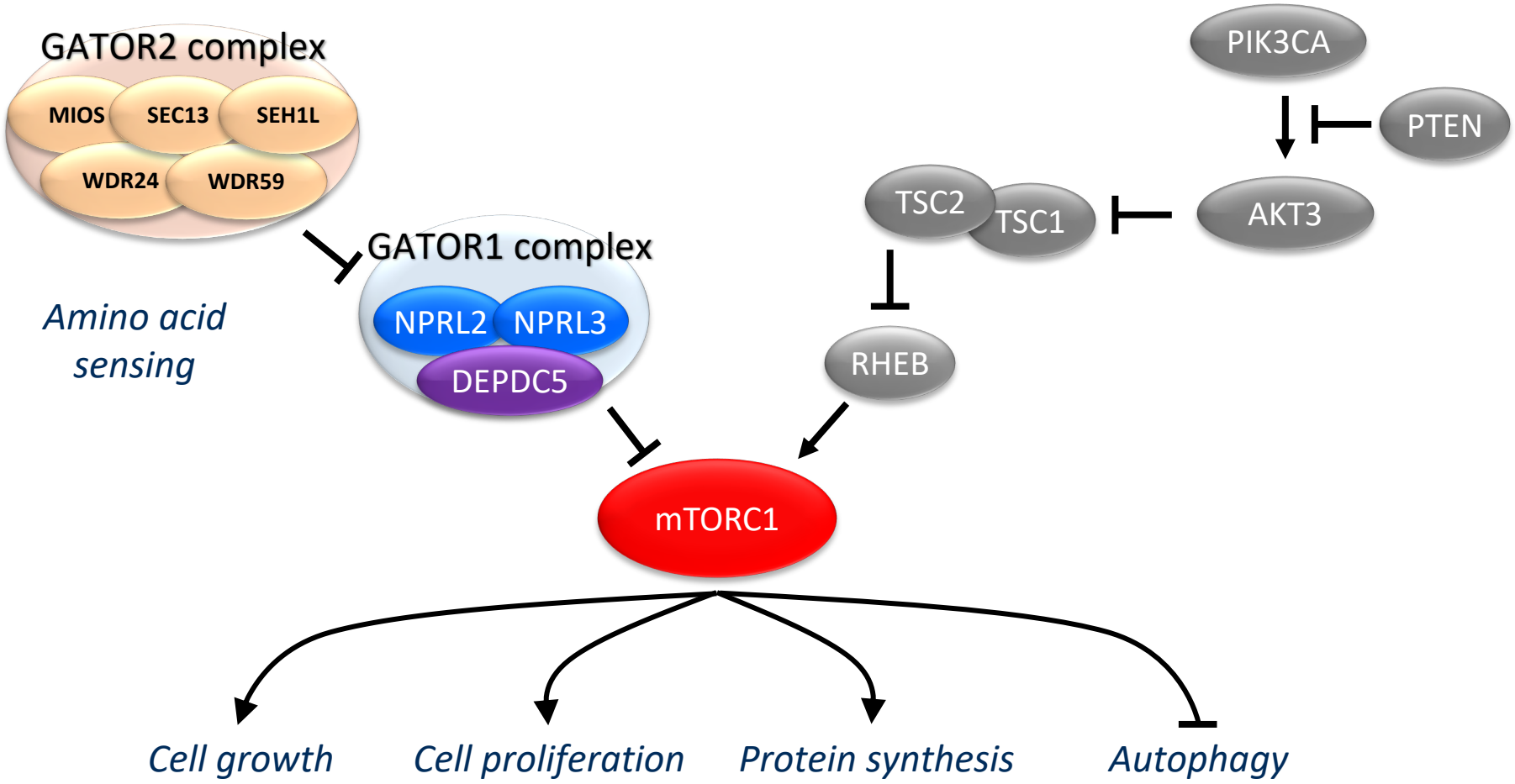
SHE

Fronto-temporal lobe

Abnormal MRI

ANN NEUROL 2014;75:782–787

GATOR1 complex is a repressor of mTOR complex 1



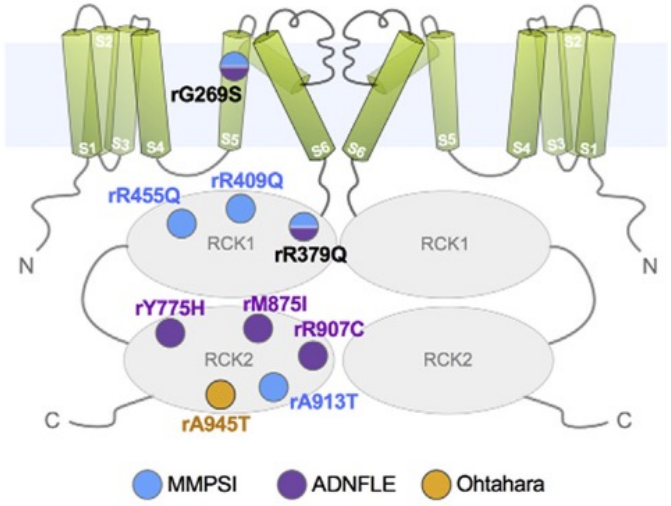
Bar-Peled et al., Science 2013

Autosomal Dominant SHE (ADSHE)

From 2012 to now→Genetic heterogeneity

KCNT1

SEVERE PHENOTYPE



Heron et al., 2012

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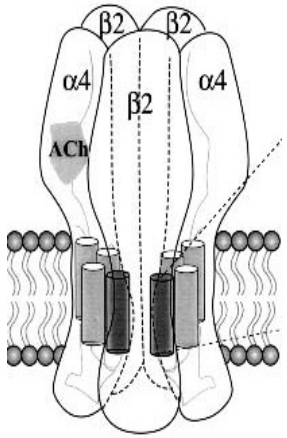
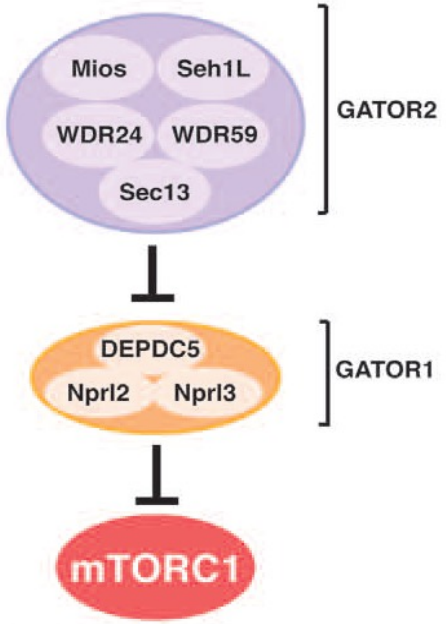


GATOR1 genes



Hishida et al., 2013
Picard et al., 2014

Ricos et al., Ann Neur 2016
Korenke et al., Epilepsia 2016

NPRL2 Nitrogen Permease Regulator-Like 2, 3p21.31

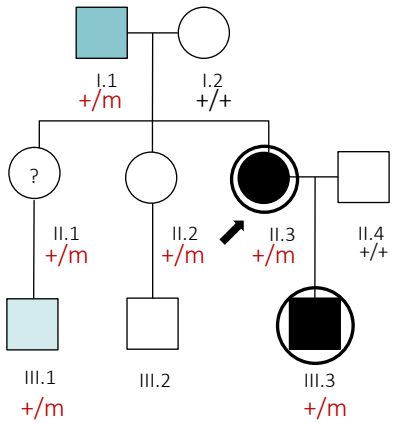
SHE

EPILEPSY, OTHER FOCAL

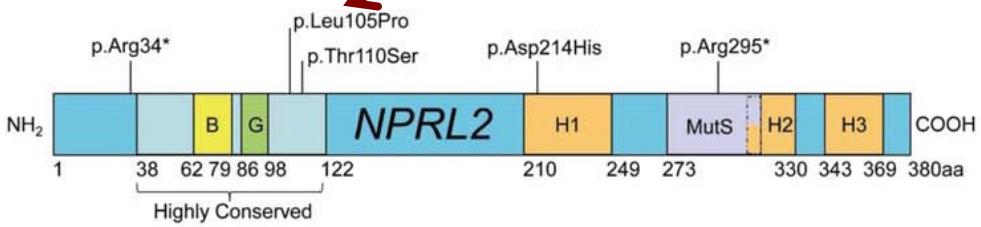
UNDETERMINED (e.g. GTCS)

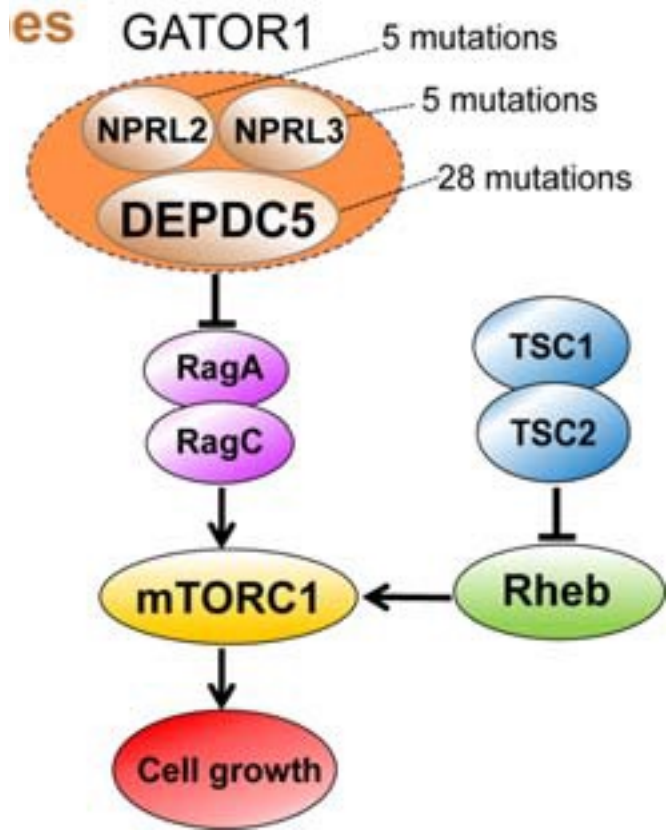
Mutations in the Mammalian Target of Rapamycin Pathway Regulators *NPRL2* and *NPRL3* Cause Focal Epilepsy

Ricos et al: ANN NEUROL 2016;79:120–131



p.L105P





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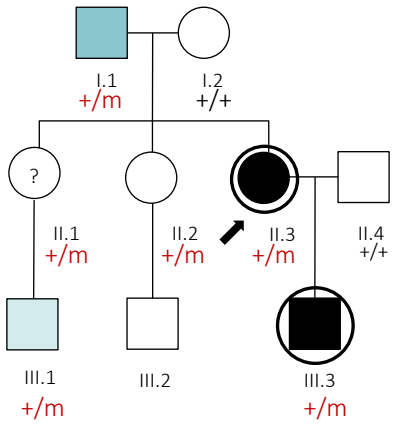
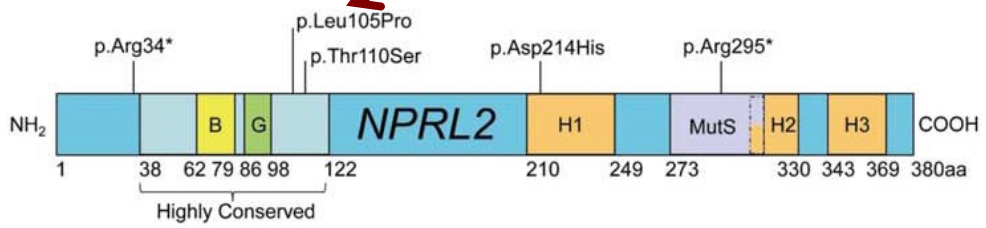


p.L105P



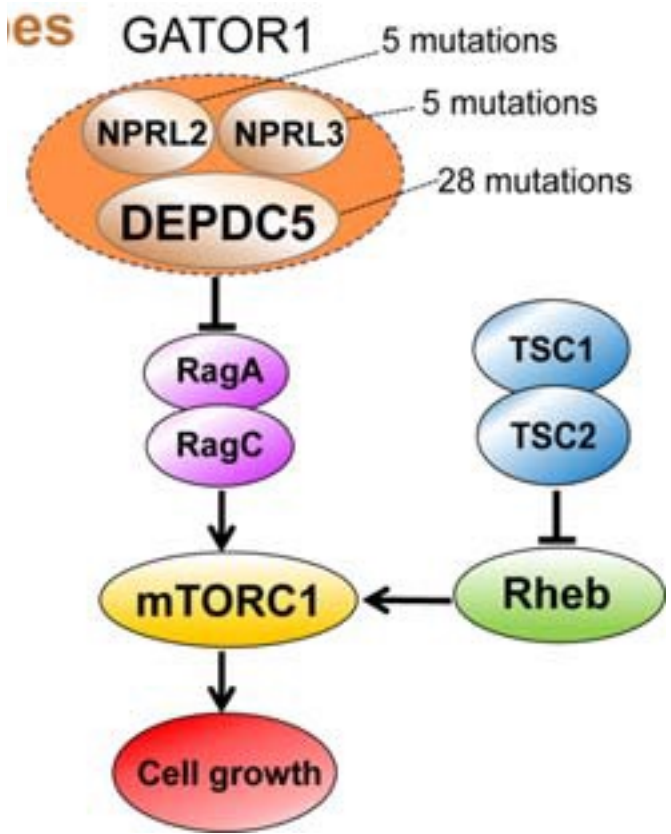
NPRL2 Nitrogen Permease Regulator-Like 2, 3p21.31

Mutations in the Mammalian Target of Rapamycin Pathway Regulators *NPRL2* and *NPRL3* Cause Focal Epilepsy

Ricos et al: ANN NEUROL 2016;79:120–131

NPRL2/NPRL3/DEPDC5 phenotypes

- Penetrance: 67%, but variable
- Familial or *de novo* mutations
- Onset usually childhood/adolescence
- Epilepsy usually mild
- Intellectual disability rare
- Dysplastic lesions in some

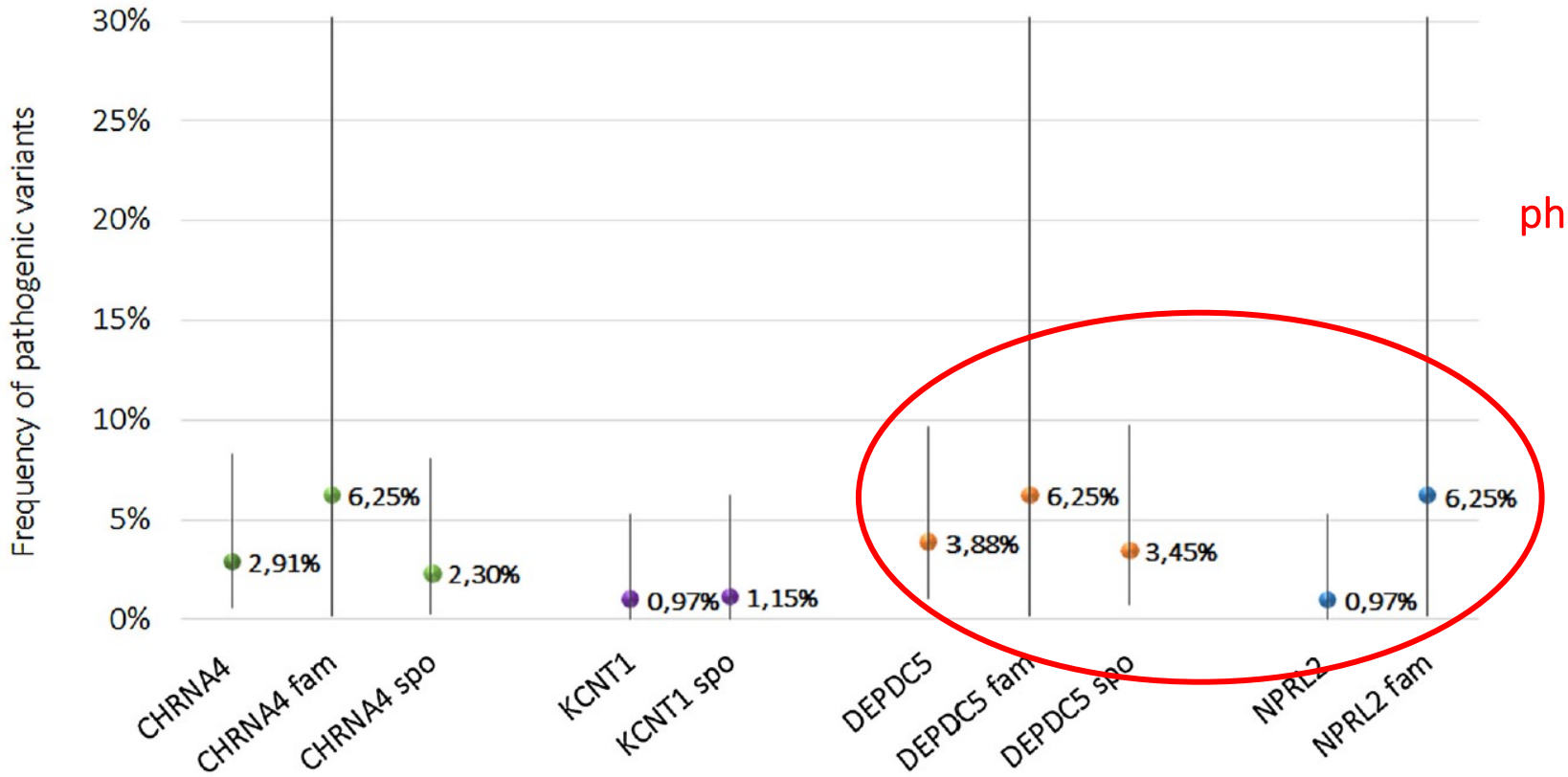


Sleep-related hypermotor epilepsy (SHE): Contribution of known genes in 103 patients

Laura Licchetta[a,b,*,1], Tommaso Pippucci[c,1], Sara Baldassari[d], Raffaella Minardi[a], Federica Provini[a,b], Barbara Mostacci[a], Giuseppe Plazzi[a,b], Paolo Tinuper[a,b], Francesca Bisulli[a,b], On behalf of the Collaborative Group of Italian League Against Epilepsy (LICE) Genetic Study Group on SHE (Amedeo Bianchi[e], Pasquale Striano[f], Antonio Gambardella[g], Lucio Giordano[h], Margherita Santucci[i], Stefano Meletti[j,k], Giovanni Crichiutti[l], Carla Marini[m], Aglaia Vignoli[n,o], Roberto Dilena[p], Eleonora Briatore[q])

Seizure: European Journal of Epilepsy 74 (2020) 60–64

Overall detection rate: 8.7%
familial cases 19%
sporadic cases:7%



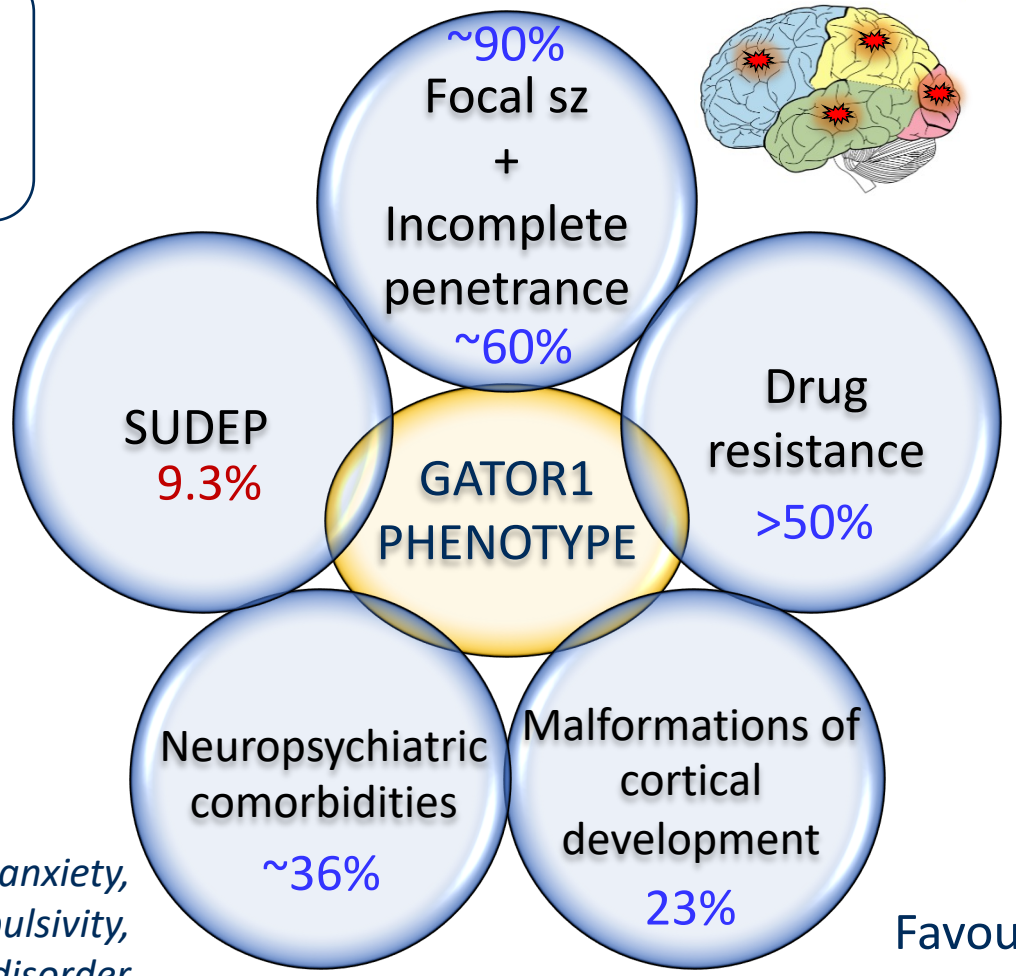
phenotypic spectrum of mTORpathies

(GATOR1-complex)

3/4 pts with DEPDC5 variants had FCD

GATOR1 phenotype

183 probands



mostly sleep-related hypermotor seizures

Early age at onset:
30% of probands <1y

ASD, ADHD, anxiety, depression, impulsivity, obsessive compulsive disorder

Favourable surgery outcome in most patients

Baldassari et al., Genetics in Medicine 2018

SHE & surgery

- 1/3 of SHE pts are drug-resistant
- >70% high seizure frequency (>25 seizures/month)
- SEEG often necessary if MRI is negative

Epilepsy surgery

Excellent outcome in selected cases (>>FCDII)

→Both frontal or extra-frontal

Genetic SHE & surgery ?

Surgical outcome of genetic dysplasia

FCD with *DEPDC5* mutations suggests patients may still benefit from surgical resection→ DEPDC5 mutation means one should look again for FCD!

KCNT1→ Subtle dysplasia (FCD type 1)

Frequency of genetic-structural cases?

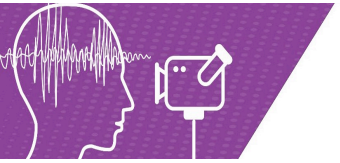
Surgical outcome pts without dysplasia?

Somatic mutations in cases with dysplasia (25% FCDIIb Niguarda Hospital)

Genetic study for cases excluded from surgery?

Outcome following resection

Follow-up, Correlation with pathology



CONCLUSIONS

- ✓ SHE is a rare disorder (possibly underdiagnosed/misdiagnosed parasomnias)
- ✓ Video recording of episodes mandatory for diagnosis
- ✓ Sporadic ≅ Familial cases
- ✓ Etiology largely unknown (<10 % genetic, >15% lesional)
- ✓ **Genetic heterogeneity** → different pathways involved
- ✓ Mutations in **GATOR1** genes play **major role** in genetic cases of SHE**: precision medicine?**
- ✓ A proportion of mutated SHE patients fall into the **mTORopathy spectrum** → have **drug-resistant epilepsy**, possibly associated with **FCD** → **surgery**

EPILEPSY TEAM

PROF. TINUPER

PROVINI

LICCHETTA

MOSTACCI

STIPA

DI VITO

MENGHI

FERRI

MUCCIOLI

PONDRELLI

DI MAURO

LODDO

EEG TECHNICIANS

ALVISI

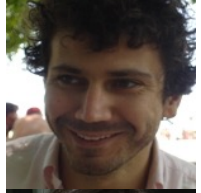
FRANCESCHINI

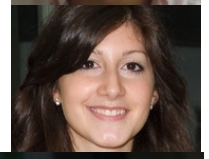
MONFREDA

EPILEPSY NURSE

GAMBERINI

GRAZIE!





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