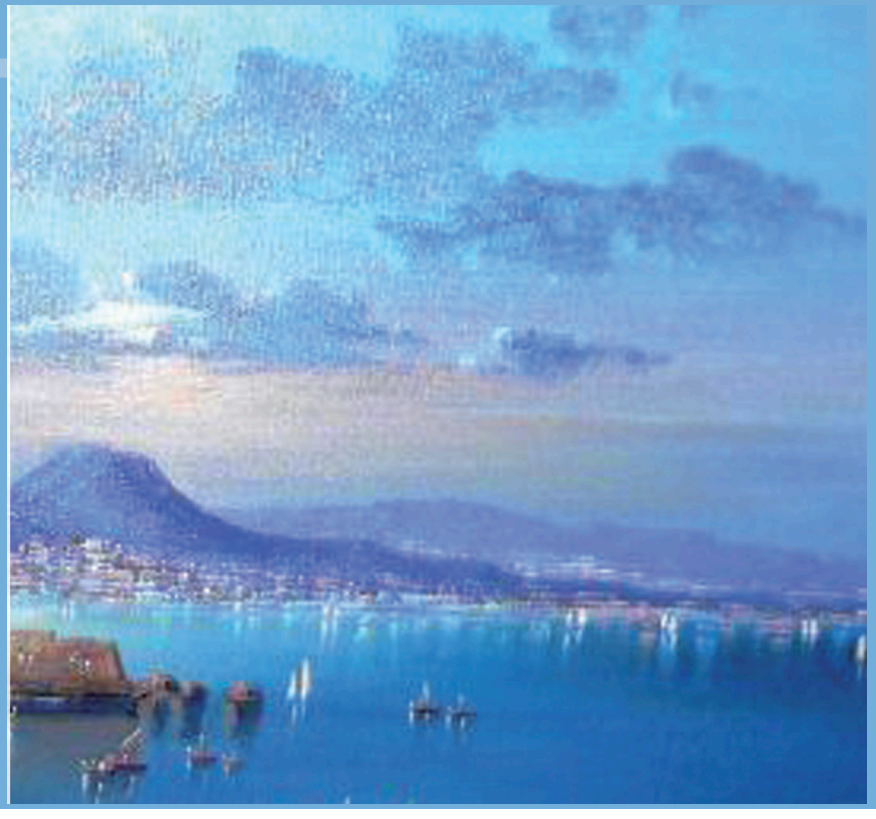


Dipartimento di
Neuroscienze, Scienze
Riproduttive ed
Odontostomatologiche

Università Federico II
di Napoli

Convegno SIN
Campania
Focus su novità
diagnostiche e
terapeutiche

Napoli,
13 Dicembre 2019

Nuove acquisizioni nella genetica delle epilessie

Antonietta Coppola MD PhD
antonietta.coppola1@gmail.com

What's new?

New genes
New pathways

DEPDC5
CDKL5

Novel genetic mechanisms

FAME

Precision/ personalized medicine

KCNT1
KCNQ2

+ *DEPDC5* associated epilepsy

(disheveled Egl-10 and pleckstrin domain containing protein 5)

Firstly described by Dibbens et al (nature 2013) associated **with familial focal epilepsy with variable foci**

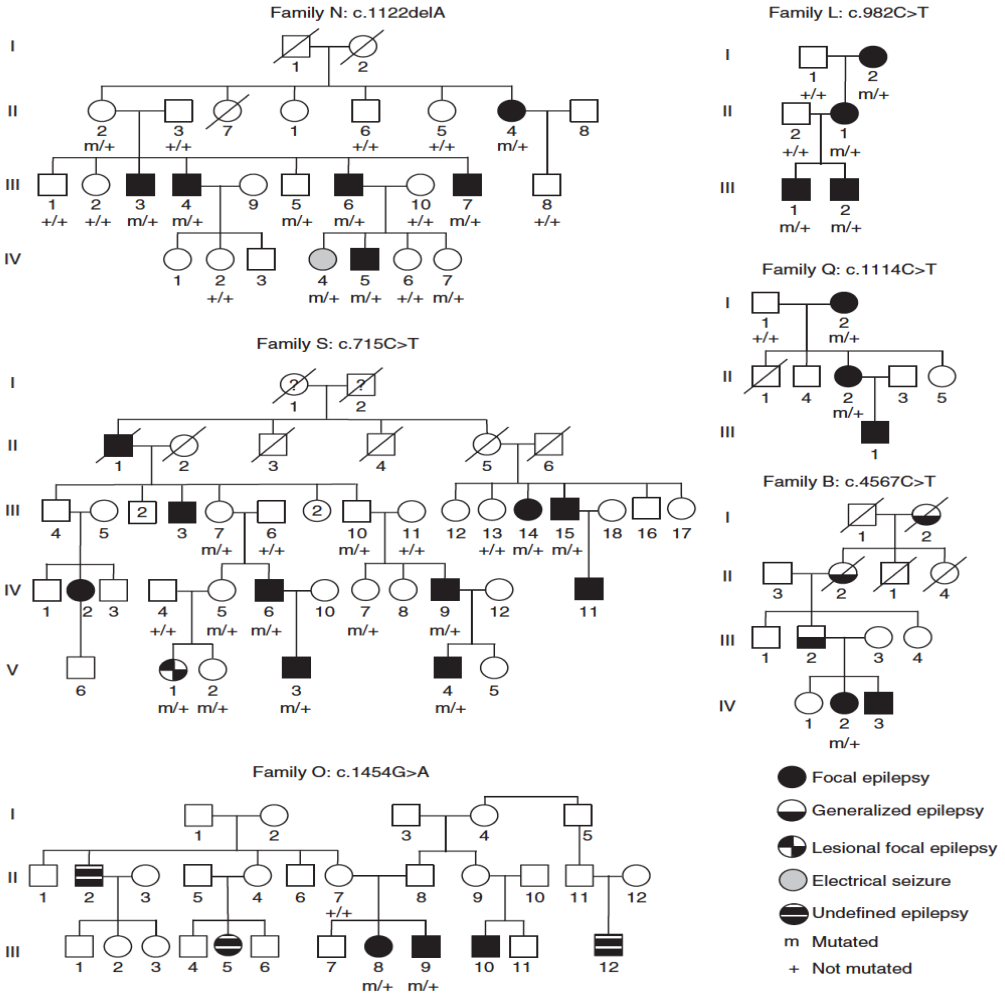
Mutations of *DEPDC5* cause autosomal dominant focal epilepsies

Saeko Ishida[1,2], Fabienne Picard[3], Gabrielle Rudolf[4,5], Eric Noé[1,2], Guillaume Achaz[2,6,7], Pierre Thomas[8], Pierre Genton[9,10], Emeline Mundwiller[11], Markus Wolff[12], Christian Marescaux[4], Richard Miles[1,2], Michel Baulac[1,2,13], Edouard Hirsch[4], Eric Leguern[1,2,14] & Stéphanie Baulac[1,2]

nature genetics

- Different lobes: frontal and **temporal** (both mesial and lateral)
- Variability within the same family
- **NON** lesional focal epilepsies

- Truncating mutations
- Loss of function of *DEPDC5*



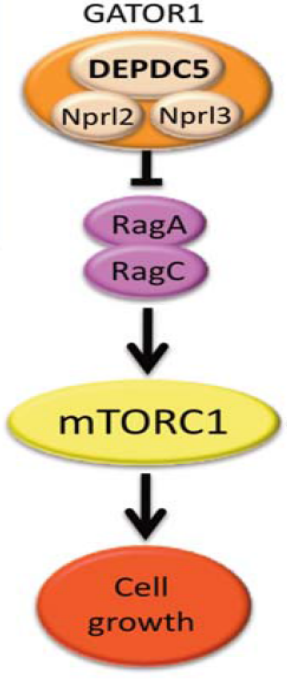
DEPDC5 associated epilepsy… mTORopathies

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

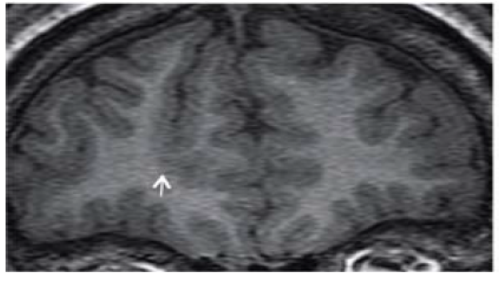
ANNALS *of Neurology*

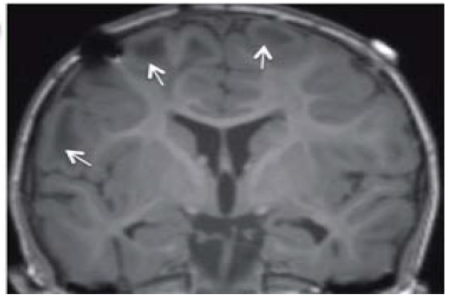
Highly expressed in the developing and adult **human brain**
Highly **conserved** across species
Unknown function, possibly a G-protein
Maybe involved in **oncological processes** (glioblastoma and hepatocellular carcinoma)

DEPDC5 phenotypes
- Focal epilepsy
- Onset usually childhood - adolescence
- Epilepsy usually mild
- Intellectual disability rare
- Autistic spectrum disorders rare
- Familial or *de novo* mutations
- Variable penetrance
- Dysplastic lesions in some



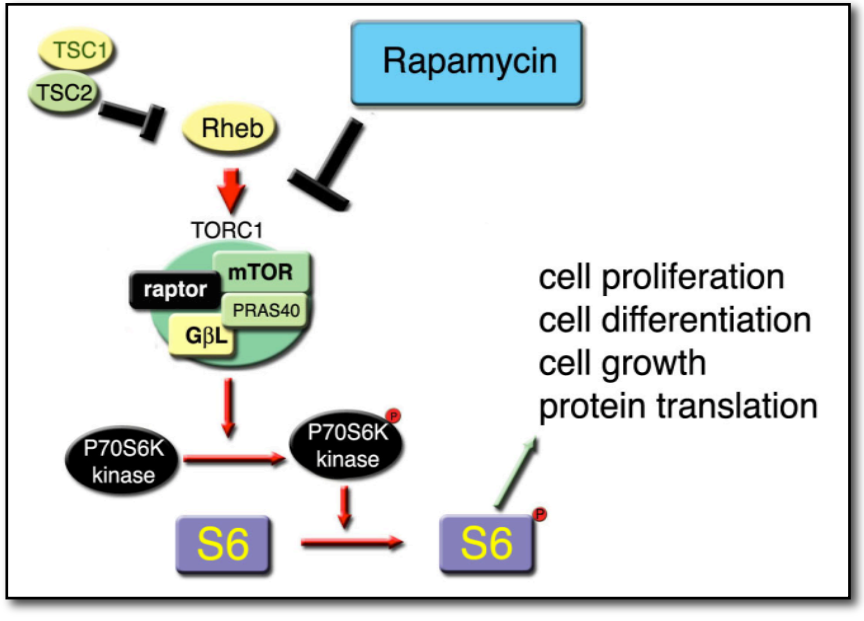
Tuberous Sclerosis
- Focal epilepsy
- Onset usually infancy - childhood
- Epilepsy often severe
- Intellectual disability common
- Autistic spectrum disorders common
- Familial or *de novo* mutations
- Variable penetrance
- Multiple tubers with type IIB dysplasia





mTOR: *TSC1/TSC2*, and *DEPDC5*

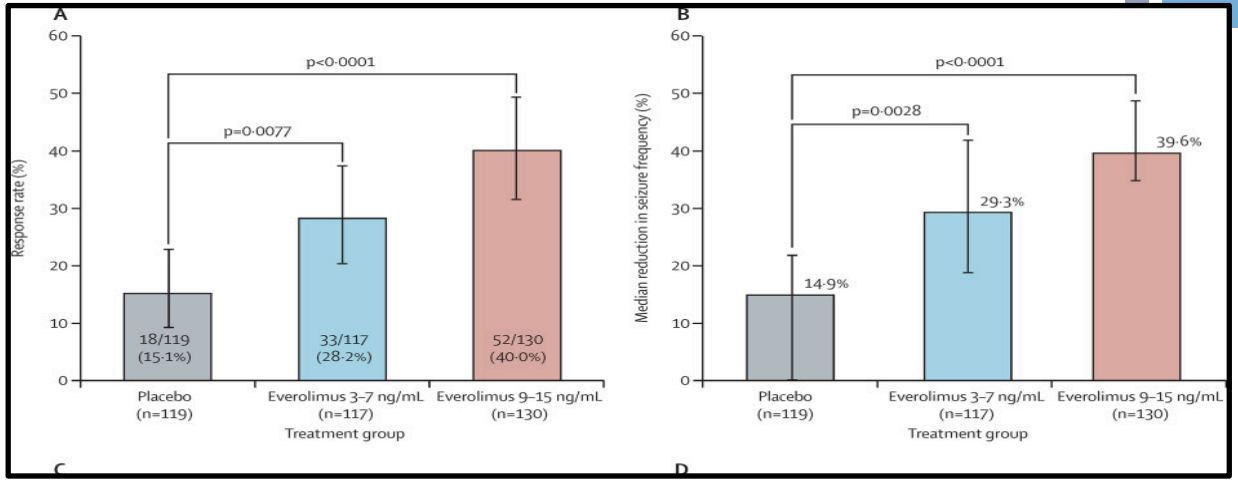
Rapamycin

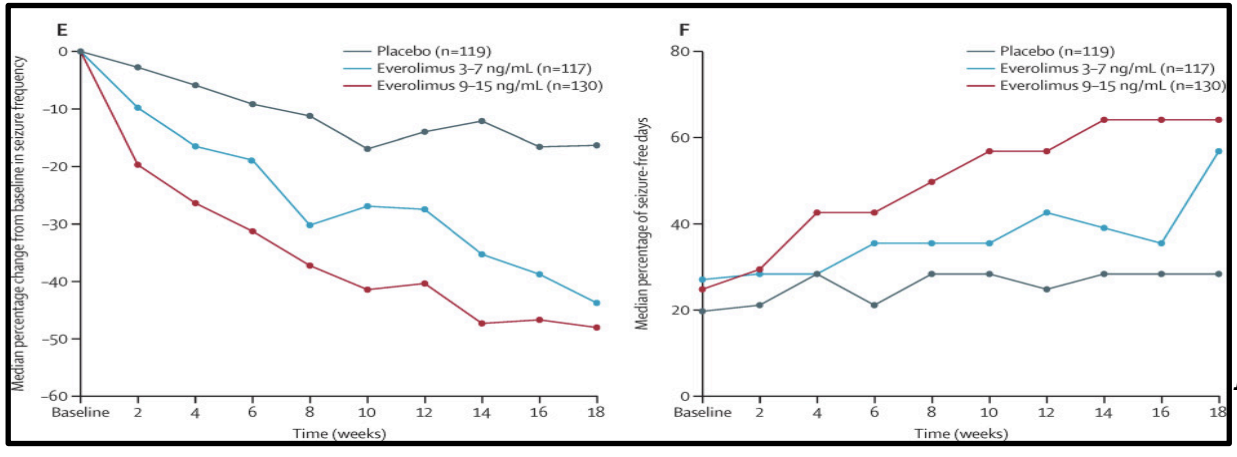


Rapamycin has shown seizures and SUDEP reduction in a TSC mouse model ((Zeng et al, 2008, Meikle et al, 2008)

Everolimus has been licensed for TSC-related epilepsy!

Everolimus





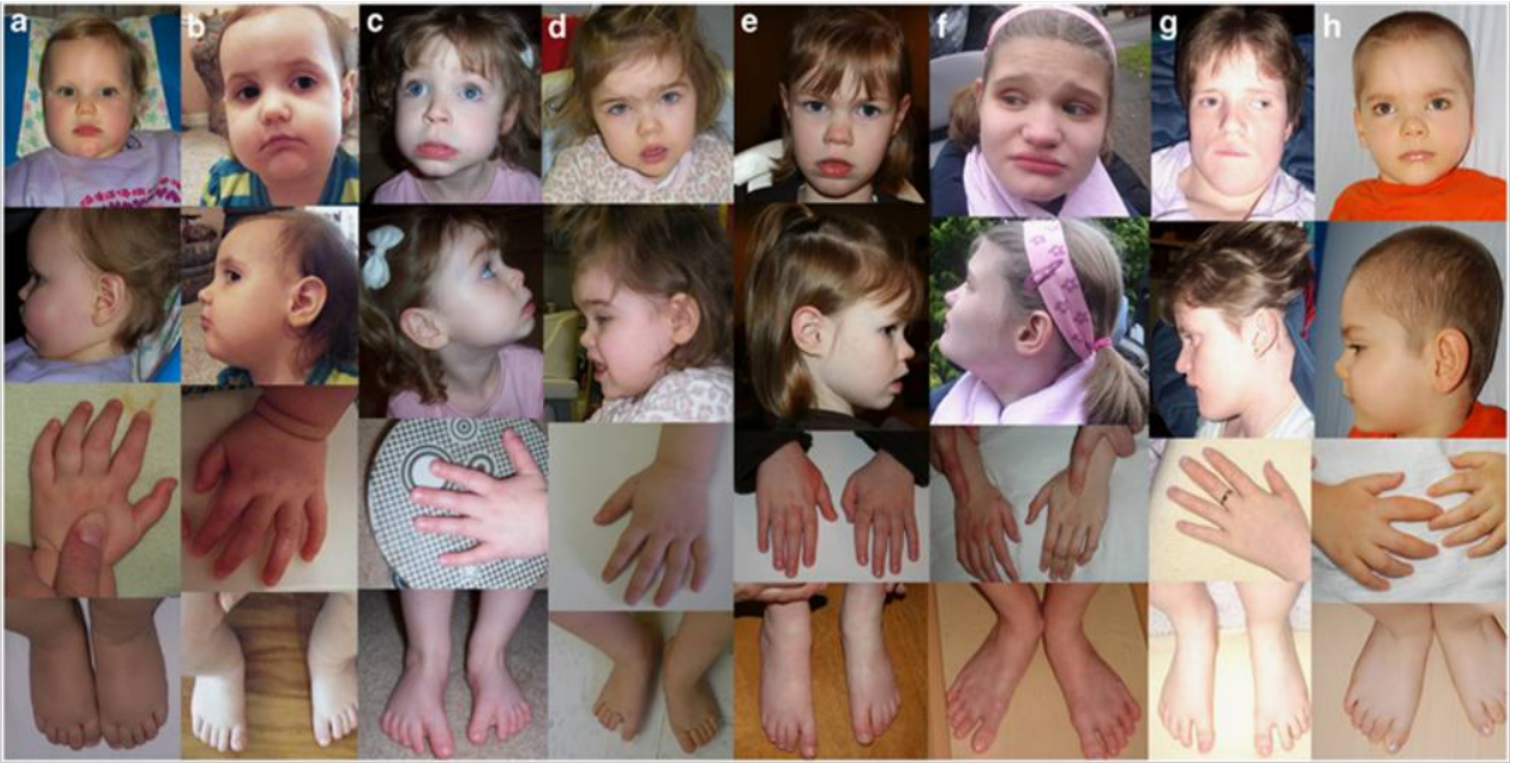
French et al, 2016

CDKL5 Hanefeld variant of Rett syndrome EIEE2

European Journal of Human Genetics (2013) 21, 266–273

The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy

Stephanie Fehr[1], Meredith Wilson[2,3], Jenny Downs[1,4], Simon Williams[5], Alessandra Murgia[6], Stefano Sartori[6],



– **females** (less frequent males);
- encephalopathy with early severe developmental delay (severely impairment **gross motor function**)
– **early onset** epilepsy, by 3 months; (infantile spasms, multifocal, myoclonic GTC)
– **hypotonia**
– **sleep disturbances**
–Dysmorphisms
– negative brain MRI
–**Honeymoon periods**

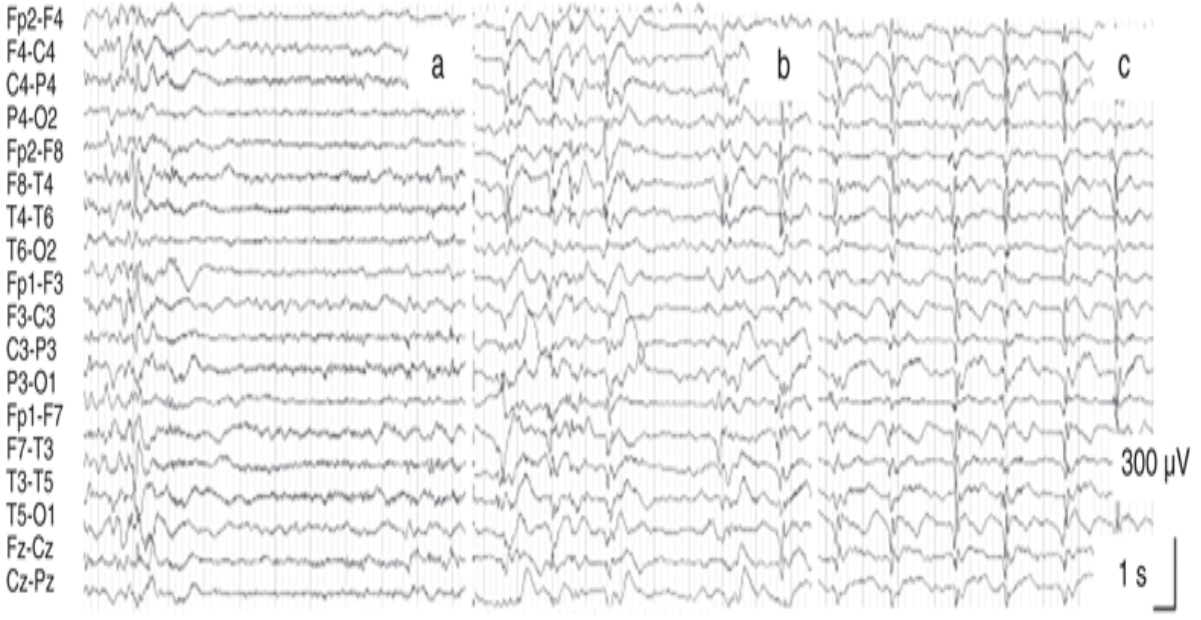
CDKL5-related encephalopathy

CDKL5 gene-related epileptic encephalopathy: electroclinical findings in the first year of life

FEDERICO MELANI[1] | DAVIDE MEI[1] | TIZIANA PISANO[1] | SALVATORE SAVASTA[2] | EMILIO FRANZONI[3] |

CDKL5 gene-related epileptic encephalopathy: electroclinical findings in the first year of life

WILLEM F M ARTS



Typical ictal electroclinical pattern: 'prolonged' generalized tonic–clonic-myoclonic seizures
This seizure type started with a **tonic–tonic/vibratory contraction**, followed by a **clonic** phase, after which a series of **spasms** ensued, gradually translating into rhythmic distal **myoclonic jerks.**
It suggests that the thalamus or the brain stem is their generator

CDKL5: Honeymoon periods

ORIGINAL ARTICLE

CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients

H L Archer*, J Evans*, S Edwards, J Colley, R Newbury-Ecob, F O'Callaghan, M Huyton, M O'Regan, J Tolmie, J Sampson, A Clarke, J Osborne

J Med Genet 2006;43:729–734. doi: 10.1136/jmg.2006.041467

ELSEVIER

Clinical Neurophysiology 117 (2006) 223–227

Myoclonic encephalopathy in the CDKL5 gene mutation

Sabrina Ruoni [a,*] Raffaella Zannolli [a,**] Vito Colamaria [b] Francesca Mazzei [a] Rosanna

Epilepsy in Rett syndrome, and *CDKL5*- and *FOXG1*-gene–related encephalopathies

*†Renzo Guerrini and *Elena Parrini *Epilepsia*, 53(12):2067–2078, 2012

of life. For the remaining eight patients showing responses to the antiepileptic treatment, each showed a "honeymoon period," the duration of which lasted from 1 to 30 months (median 6 months). Follow-up of interictal EEG during this "honeymoon" period was available in five cases. This remained normal or showed a slight slow background activity until the median age of 6 months (range 5–24 months). Then, interictal EEG progressively deteriorated with slowing of the basal rhythm and disappearance of physiological sleep figures. For the remaining three patients (patients 4, 9, and 11), no information on the EEG during this transient seizure-free period was available.

a daily basis. Four patients had a period without seizures in the second year of life, lasting between six weeks and nine months (patients 1, 2, 5, and 7). Honeymoon periods with new drugs were described in all patients but were followed by more severe seizures or by a change in seizure type. All but one had multiple seizure types and experienced one or more major seizures (such as generalised tonic-clonic or complex partial seizures) as well as numerous (up to 200) brief seizures (such as absences, drop fits, myoclonic jerks) every day. Patient 5, who was two years old, had the mildest

Original Article

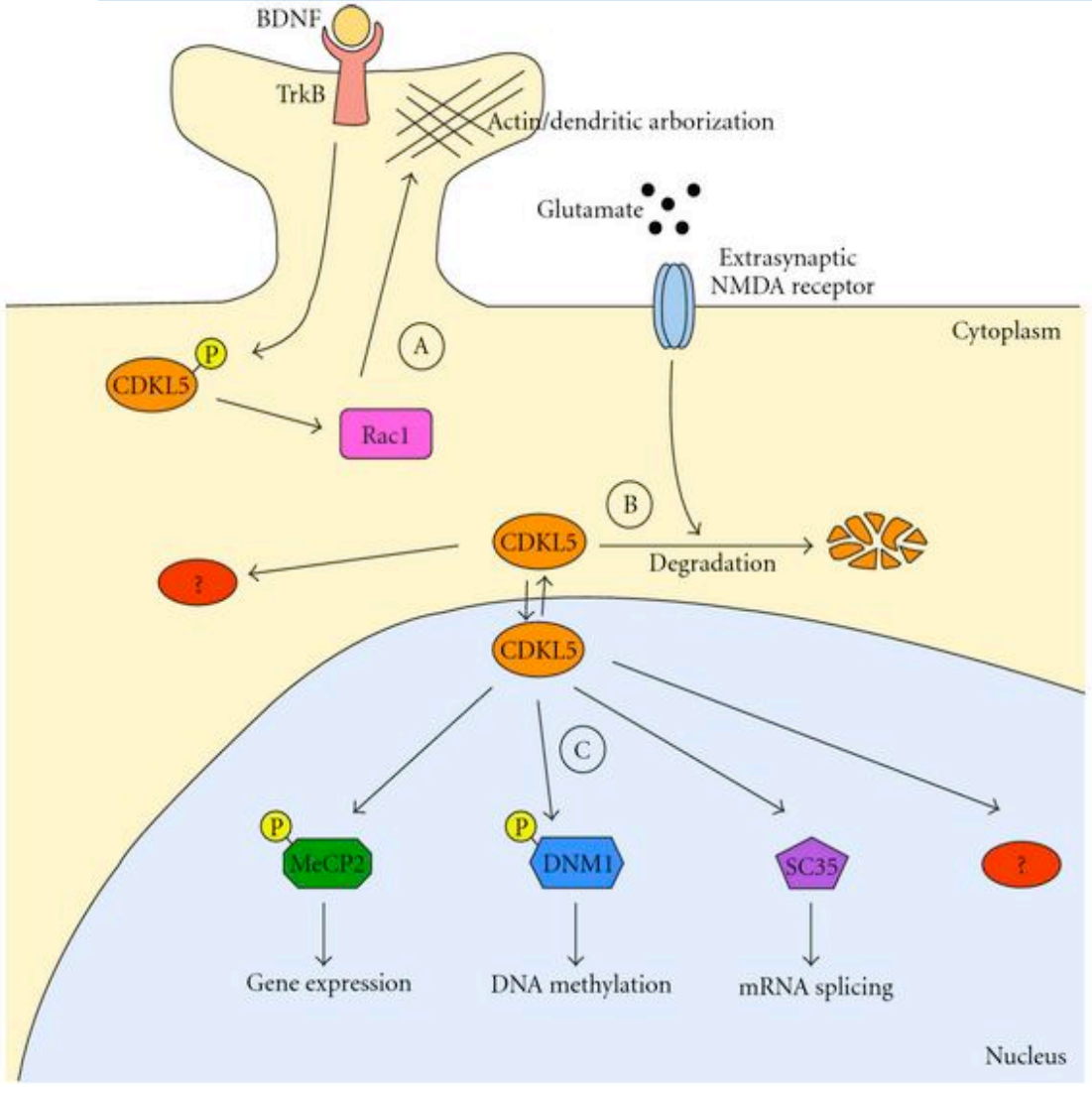
Historic, Clinical, and Prognostic Features of Epileptic Encephalopathies Caused by *CDKL5* Mutations

Brian D. Moseley MD[a,*], Radhika Dhamija MBBS[b], Elaine C. Wirrell MD[b,c], Katherine C. Nickels MD[b,c]

up. Although children with *CDKL5* mutations can experience a "honeymoon" period when seizures become responsive to treatment (previously reported as lasting 1-30 months), their seizures invariably recur [12]. Similar to previous reports, we also documented infantile spasms in our entire cohort. Although 4/6

CDKL5-related encephalopathy

CDKL5 and *MECP2*



- Mutations affecting the N-terminal results in a more severe phenotype
- *De novo*
- Two functions (cytoplasmatic and nuclear)
- Defective CDKL5 protein influence phosphorylation of **MECP2** and the trafficking of itself between the nucleus and the cytoplasm

What's new?

New genes
New pathways

DEPDC5
CDKL5

Novel genetic mechanisms

FAME

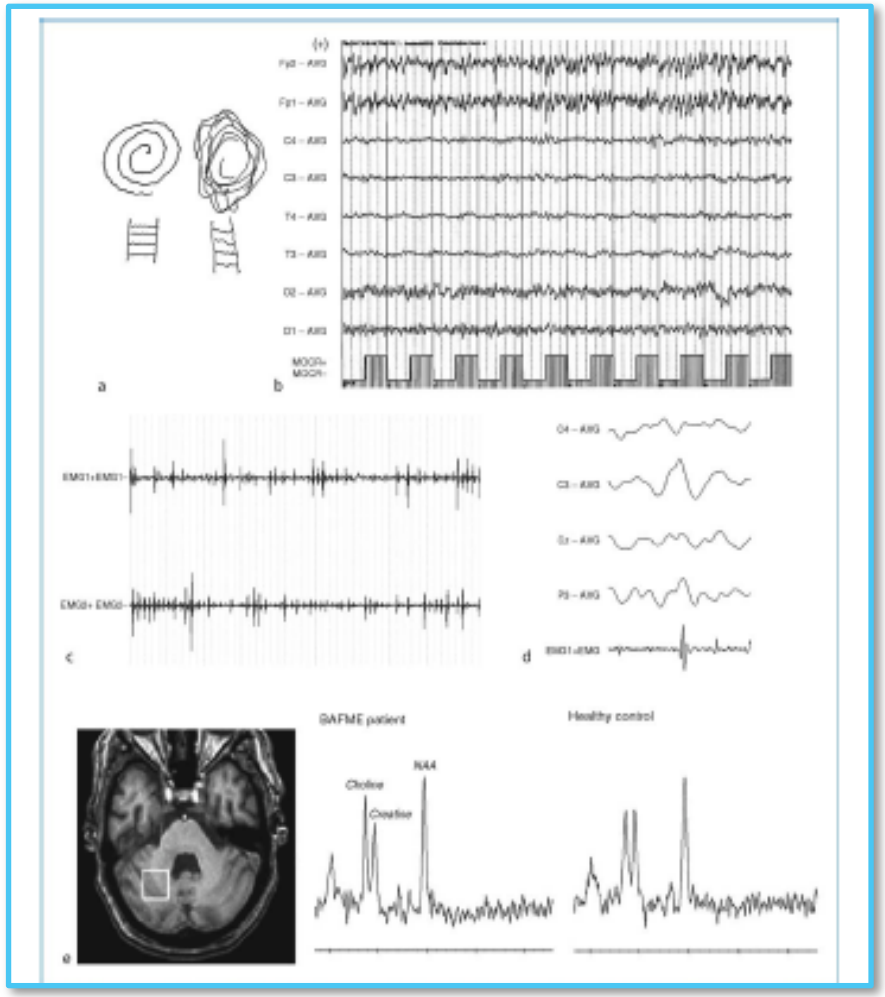
Precision/ personalized medicine

KCNT1
KCNQ2

Familial cortical tremor, myoclonus and epilepsy

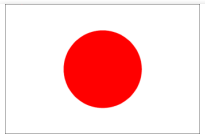
Firstly described by Uyuma in 1985 (**FAME**)
BAFME: Benign Adult Familial Myoclonic Epilepsy (BAFME/**FAME**; OMIM:601068)
ADCME: Autosomal dominant cortical myoclonus, and epilepsy (ADCME/FCTME; OMIM:607876)
Other achronyms **FCMTE, FCTE**

- familial occurrence **(autosomal dominant)**
- postural and action-induced shivering movement of the hands mimicking essential tremor, but showing the electrophysiological findings of **cortical reflex myoclonus** *[Ikeda et al., 1990; Striano et al., 2005, Uyama et al., 2005]*
- **Myoclonus of upper limbs and tonic-clonic seizures**, often precipitated by sleep-deprivation or photic stimulation *[Ikeda et al., 1990; de Falco et al., 2003; Striano et al., 2005*]



Striano & Zara 2010; The Atlas of epilepsies

FAME History: loci



Expedited Publication

FAME1

Genetic localization of the familial adult myoclonic epilepsy (*FAME*) gene to chromosome 8q24

N.M. Plaster; E. Uyama, MD; M. Uchino, MD; T. Ikeda, MD; K.M. Flanigan, MD; I. Kondo, MD; and L.J. Ptáček, MD

Neurology, 1999

FAME3

Familial cortical myoclonic tremor with epilepsy

The third locus (FCMTE3) maps to 5p

Neurology® 2010;74:2000-2003

C. Depienne, PhD*
E. Magnin, MD*
D. Bouteiller, MS
G. Stevanin, PhD
C. Saint-Martin, PhD
M. Vidailhet, MD
E. Apartis, MD
E. Hirsch
E. LeGuern, MD, PhD
P. Labauge, MD, PhD
L. Rumbach, MD, PhD

ABSTRACT

Background: Familial cortical myoclonic tremor with epilepsy (FCMTE) is defined by autosomal dominant adult-onset cortical myoclonus (CM) and seizures in 40% of patients. Two loci, 8q23.3-q24.11 (FAME1/FCMTE1) and 2p11.1-q12.2 (FAME2/FCMTE2), were previously reported without an identified gene. Unlinked families argue for a third mutated gene.

Methods: A genome-wide scan was performed in a large FCMTE family using Linkage-12 microarrays (Illumina). Refinement of the locus on 5p was performed by genotyping 13 polymorphic microsatellite markers in the 45 available family members.

Results: This large French FCMTE family included 16 affected relatives. The first symptoms were CM in 5 patients (31.2%), seizures in 5 patients (31.2%), and both at the same time in 6 patients

FAME2

Brain (2001), **124**, 2459–2475

Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures

A newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2

Renzo Guerrini,[1] Paolo Bonanni,[3] Andrea Patrignani,[4] Peter Brown,[2] Lucio Parmeggiani,[1] Pascal Grosse,[2,6] Paola Brovedani,[3] Francesca Moro,[3] Paolo Aridon,[4] Romeo Carrozzo[4] and Giorgio Casari[4,5]

A newly identified locus for benign adult familial myoclonic epilepsy on chromosome 3q26.32-3q28

FAME4

Patra Yeetong[1,2,3], Surasawadee Ausavarat[2,3], Roongroj Bhidayasiri[4], Krisna Piravej[5], Nath... Tayard Desudchit[6], Chaipat Chunharas[4], Jakrin Loplumlert[4], Chusak Limotai[4], Kanya Su... and Vorasuk Shotelersuk[2,3]

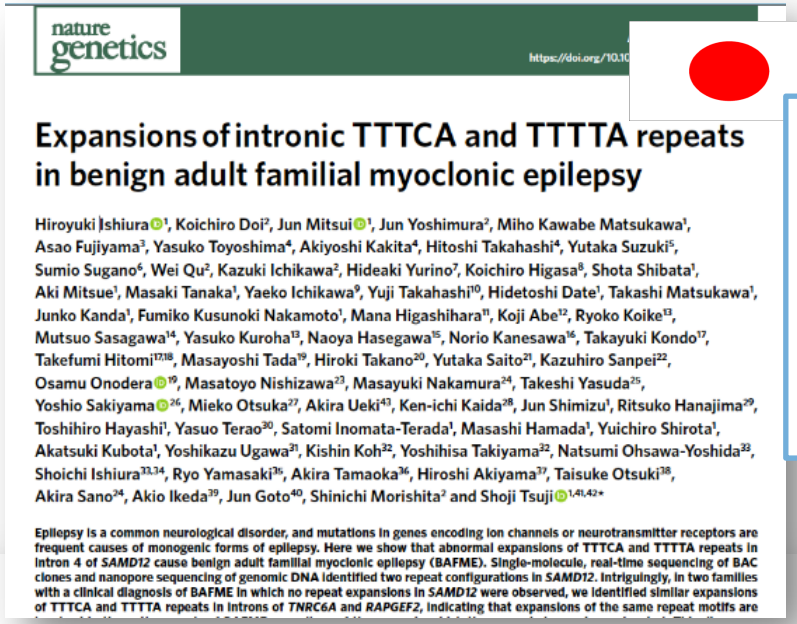
FAME5

BRAIN
A JOURNAL OF NEUROLOGY

Autosomal recessive cortical myoclonic tremor and epilepsy: association with a mutation in the potassium channel associated gene *CNTN2*

Elisabeth Stogmann,[1] Eva Reinthaler,[1] Salwa ElTawil,[2] Mohammed A. El Etribi,[2] Mahmoud Hemeda,[2] Nevine El Nahhas,[2] Ahmed M. Gaber,[2] Amal Fouad,[2] Sherif Edris,[3] Anna Benet-Pages,[4] Sebastian H. Eck,[4] Ekaterina Pataraia,[1] Davide Mei,[5] Alexis Brice,[6,7,8,9] Suzanne Lesage,[6,7,8] Renzo Guerrini,[5] Friedrich Zimprich,[1] Tim M. Strom[4] and Alexander Zimprich[1]

FAME History: gene(s)



nature genetics

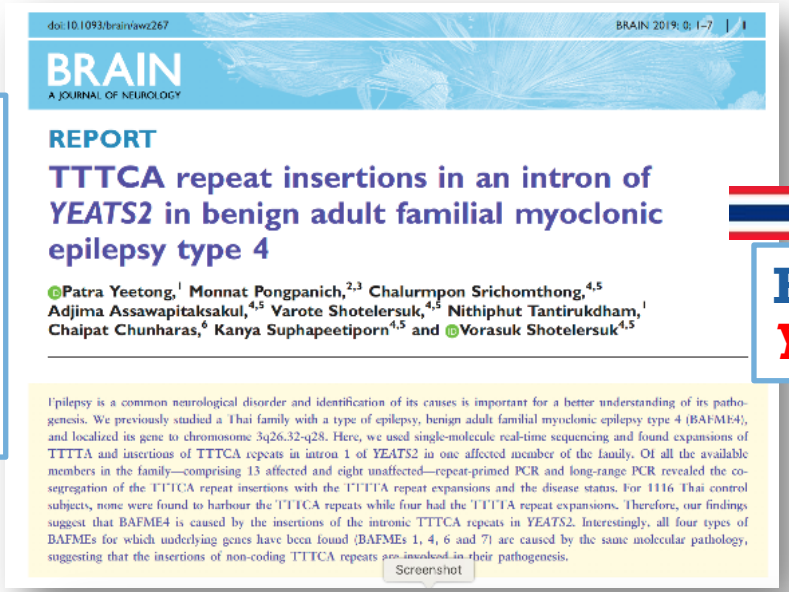
https://doi.org/10.1

Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy

Hiroyuki Ishiura[1], Koichiro Doi[2], Jun Mitsui[1], Jun Yoshimura[2], Miho Kawabe Matsukawa[1], Asao Fujiyama[3], Yasuko Toyoshima[4], Akiyoshi Kakita[4], Hitoshi Takahashi[4], Yutaka Suzuki[5], Sumio Sugano[6], Wei Qu[2], Kazuki Ichikawa[2], Hideaki Yurino[7], Koichiro Higasa[8], Shota Shibata[1], Aki Mitsue[1], Masaki Tanaka[1], Yaeko Ichikawa[9], Yuji Takahashi[10], Hidetoshi Date[1], Takashi Matsukawa[1], Junko Kanda[1], Fumiko Kusunoki Nakamoto[1], Mana Higashihara[11], Koji Abe[12], Ryoko Koike[13], Mutsuo Sasagawa[14], Yasuko Kuroha[13], Naoya Hasegawa[15], Norio Kanesawa[16], Takayuki Kondo[17], Takefumi Hitomi[17,18], Masayoshi Tada[19], Hiroki Takano[20], Yutaka Saito[21], Kazuhiro Sanpei[22], Osamu Onodera[19], Masatoyo Nishizawa[23], Masayuki Nakamura[24], Takeshi Yasuda[25], Yoshio Sakiyama[26], Mieko Otsuka[27], Akira Ueki[43], Ken-ichi Kaida[28], Jun Shimizu[1], Ritsuko Hanajima[29], Toshihiro Hayashi[1], Yasuo Terao[30], Satomi Inomata-Terada[1], Masashi Hamada[1], Yuichiro Shirota[1], Akatsuki Kubota[1], Yoshikazu Ugawa[31], Kishin Koh[32], Yoshihisa Takiyama[32], Natsumi Ohsawa-Yoshida[33], Shoichi Ishiura[33,34], Ryo Yamasaki[35], Akira Tamaoka[36], Hiroshi Akiyama[37], Taisuke Otsuki[38], Akira Sano[24], Akio Ikeda[39], Jun Goto[40], Shinichi Morishita[2] and Shoji Tsuji[1,41,42*]

Epilepsy is a common neurological disorder, and mutations in genes encoding ion channels or neurotransmitter receptors are frequent causes of monogenic forms of epilepsy. Here we show that abnormal expansions of TTTCA and TTTTA repeats in intron 4 of *SAMD12* cause benign adult familial myoclonic epilepsy (BAFME). Single-molecule, real-time sequencing of BAC clones and nanopore sequencing of genomic DNA identified two repeat configurations in *SAMD12*. Intriguingly, in two families with a clinical diagnosis of BAFME in which no repeat expansions in *SAMD12* were observed, we identified similar expansions of TTTCA and TTTTA repeats in introns of *TNRC6A* and *RAPGEF2*, indicating that expansions of the same repeat motifs are

FAME 1: *SAMD12*
FAME 6: *TNRC6A*
FAME 7: *RAPGEF2*



doi:10.1093/brain/awz267 BRAIN 2019: 0; 1–7

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

TTTCA repeat insertions in an intron of *YEATS2* in benign adult familial myoclonic epilepsy type 4

Patra Yeetong,[1] Monnat Pongpanich,[2,3] Chalurmpon Srichomthong,[4,5] Adjima Assawapitaksakul,[4,5] Varote Shotelersuk,[4,5] Nithiphut Tantirukdham,[1] Chaipat Chunharas,[6] Kanya Suphapeetiporn[4,5] and Vorasuk Shotelersuk[4,5]

Epilepsy is a common neurological disorder and identification of its causes is important for a better understanding of its pathogenesis. We previously studied a Thai family with a type of epilepsy, benign adult familial myoclonic epilepsy type 4 (BAFME4), and localized its gene to chromosome 3q26.32-q28. Here, we used single-molecule real-time sequencing and found expansions of TTTTA and insertions of TTTCA repeats in intron 1 of *YEATS2* in one affected member of the family. Of all the available members in the family—comprising 13 affected and eight unaffected—repeat-primed PCR and long-range PCR revealed the co-segregation of the TTTCA repeat insertions with the TTTTA repeat expansions and the disease status. For 1116 Thai control subjects, none were found to harbour the TTTCA repeats while four had the TTTTA repeat expansions. Therefore, our findings suggest that BAFME4 is caused by the insertions of the intronic TTTCA repeats in *YEATS2*. Interestingly, all four types of BAFMEs for which underlying genes have been found (BAFMEs 1, 4, 6 and 7) are caused by the same molecular pathology, suggesting that the insertions of non-coding TTTCA repeats are involved in their pathogenesis.

Screenshot

FAME4: *YEATS2*

https://doi.org/10.1038/s41467-019-12671-y OPEN

Intronic ATTTC repeat expansions in *STARD7* in familial adult myoclonic epilepsy linked to chromosome 2

Mark A. Corbett et al.#

Familial Adult Myoclonic Epilepsy (FAME) is characterised by cortical myoclonic tremor usually from the second decade of life and overt myoclonic or generalised tonic-clonic seizures. Four independent loci have been implicated in FAME on chromosomes (chr) 2, 3, 5 and 8. Using whole genome sequencing and repeat primed PCR, we provide evidence that chr2-linked FAME (FAME2) is caused by an expansion of an ATTTC pentamer within the first intron of *STARD7*. The ATTTC expansions segregate in 158/158 individuals typically affected

FAME2 *STARD7*

ARTICLE

https://doi.org/10.1038/s41467-019-12763-9 OPEN

Unstable TTTTA/TTTCA expansions in *MARCH6* are associated with Familial Adult Myoclonic Epilepsy type 3

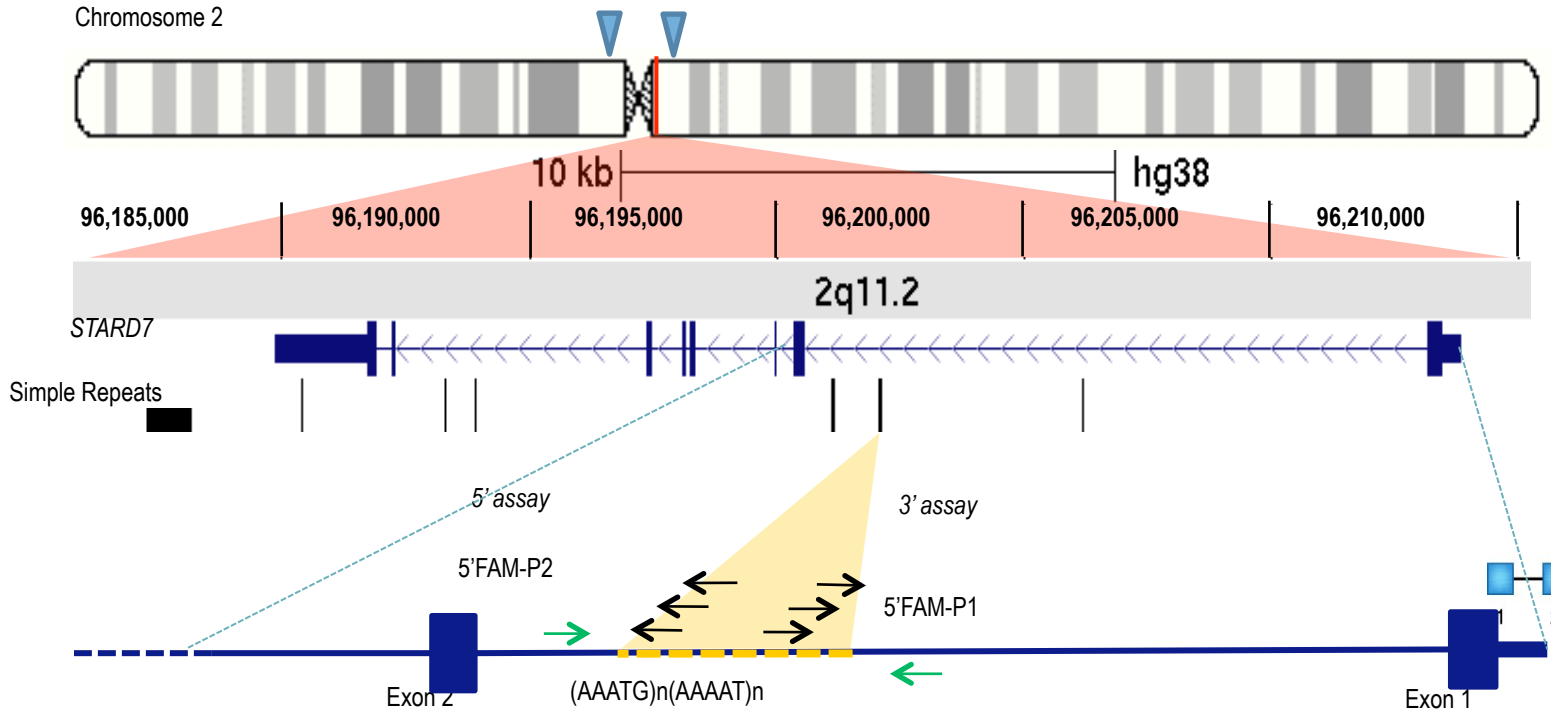
Rahel T. Florian et al.#

Familial Adult Myoclonic Epilepsy (FAME) is a genetically heterogeneous disorder characterized by cortical tremor and seizures. Intronic TTTTA/TTTCA repeat expansions in *SAMD12* (FAME1) are the main cause of FAME in Asia. Using genome sequencing and repeat-primed PCR, we identify another site of this repeat expansion, in *MARCH6* (FAME3) in four European families. Analysis of single DNA molecules with nanopore sequencing and

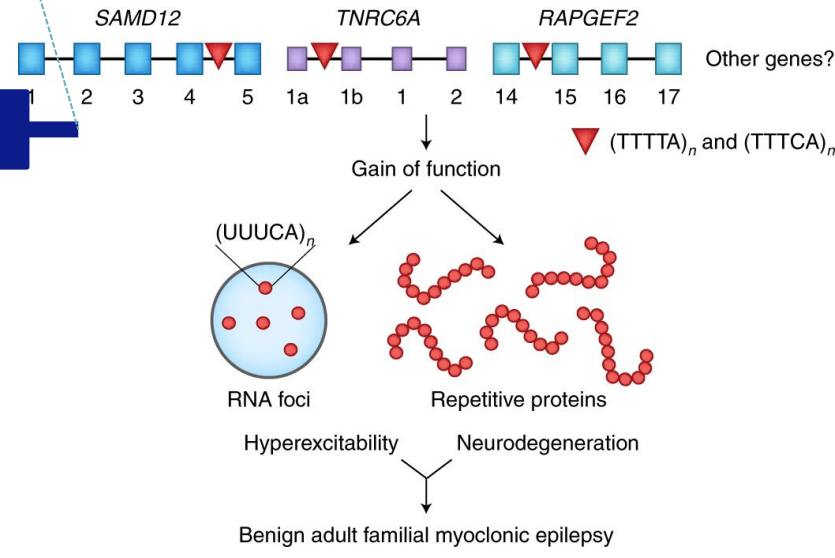
FAME3: *MARCH6*

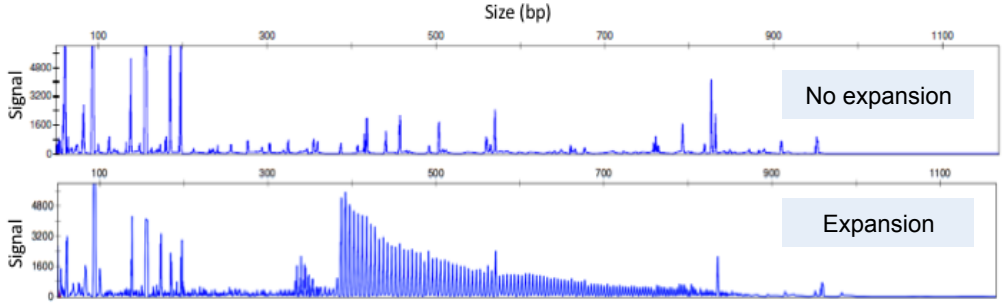
+ FAME 2: *STARD7*

Corbett et al, Nat Comm in press



van Blitterswijk, Nat Genet 2018





Repeated Primer-PCR

What's new?

New genes
New pathways

DEPDC5
CDKL5

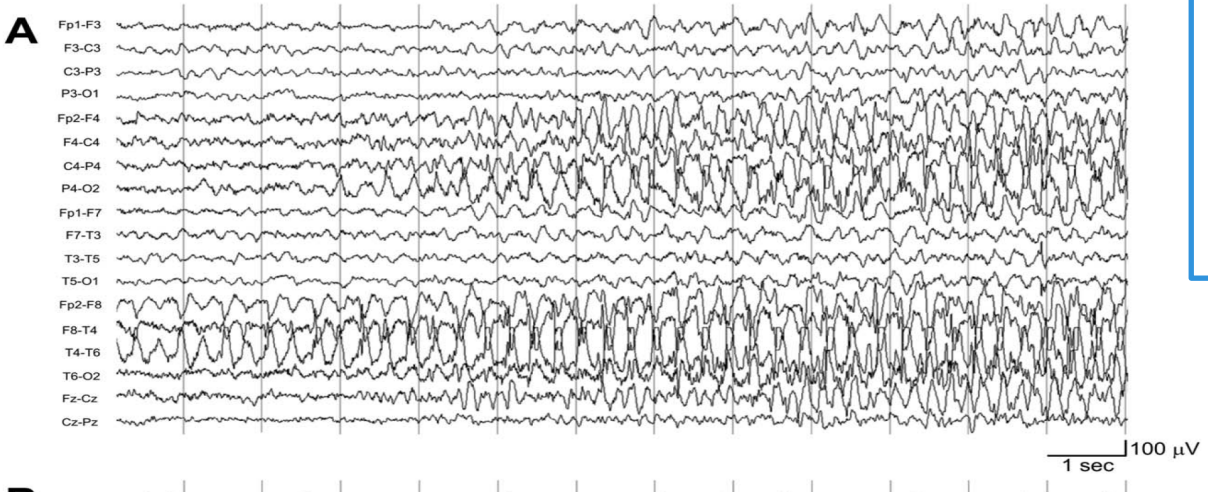
Novel genetic mechanisms

FAME

Precision/ personalized medicine

KCNT1
KCNQ2

KCNT1 mutations: Migrating partial seizures of infancy



Quinidine
antiarrhythmic, partial antagonist of *KCNT1*
previously used to reverse the hyperactivity of the mutant *KCNT1* in Xenopus oocytes

Gain of function!

Targeted Treatment of Migrating Partial Seizures of Infancy with Quinidine

David Bearden, MD,[1]
Alanna Strong, PhD,[2]
Jessica Ehnot, PharmD,[3]
Marissa DiGiovine, MD,[1]
Dennis Dlugos, MD, MSCE,[1] and
Ethan M. Goldberg, MD, PhD[1]

Migrating partial seizures of infancy is an early onset epileptic encephalopathy syndrome that is typically resistant to treatment. The most common cause is a gain of function mutation in the potassium channel *KCNT1*. The antiarrhythmic drug quinidine is a partial antagonist of *KCNT1* and hence may be a candidate drug for treatment of this condition. We report the case of a child with migrating partial seizures of infancy secondary to an activating mutation in *KCNT1* treated with quinidine. Treatment with quinidine was correlated with a marked reduction in seizure frequency and improved psychomotor development.

ANN NEUROL 2014;76:457–461

KCNT1 mutations: "ADNFLE"

Quinidine: antiarrhythmic, partial antagonist of *KCNT1*

Precision therapy for epilepsy due to *KCNT1* mutations

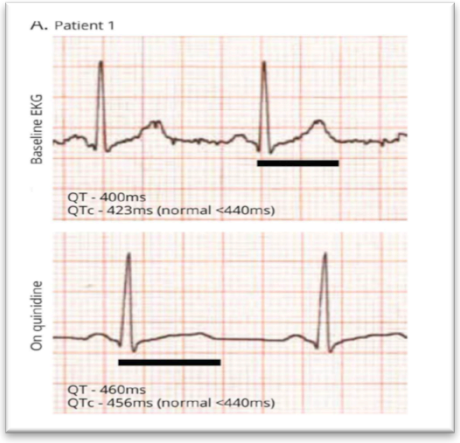
A randomized trial of oral quinidine

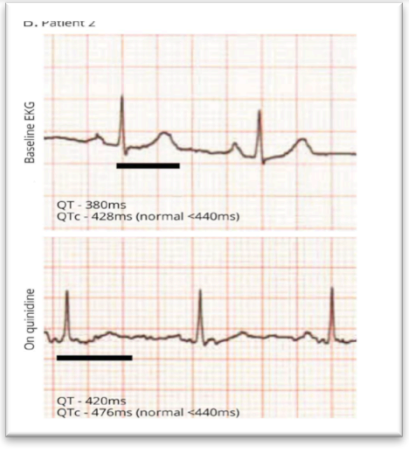
Saul A. Mullen, MBBS, PhD, Patrick W. Carney, MBBS, PhD, Annie Roten, BAppSc, Michael Ching, MPharm, PhD, Paul A. Lightfoot, BSc, Leonid Churilov, PhD, Umesh Nair, BSc, Melody Li, PhD, Samuel F. Berkovic, MBBS, MD, Steven Petrou, PhD, and Ingrid E. Scheffer, MBBS, PhD

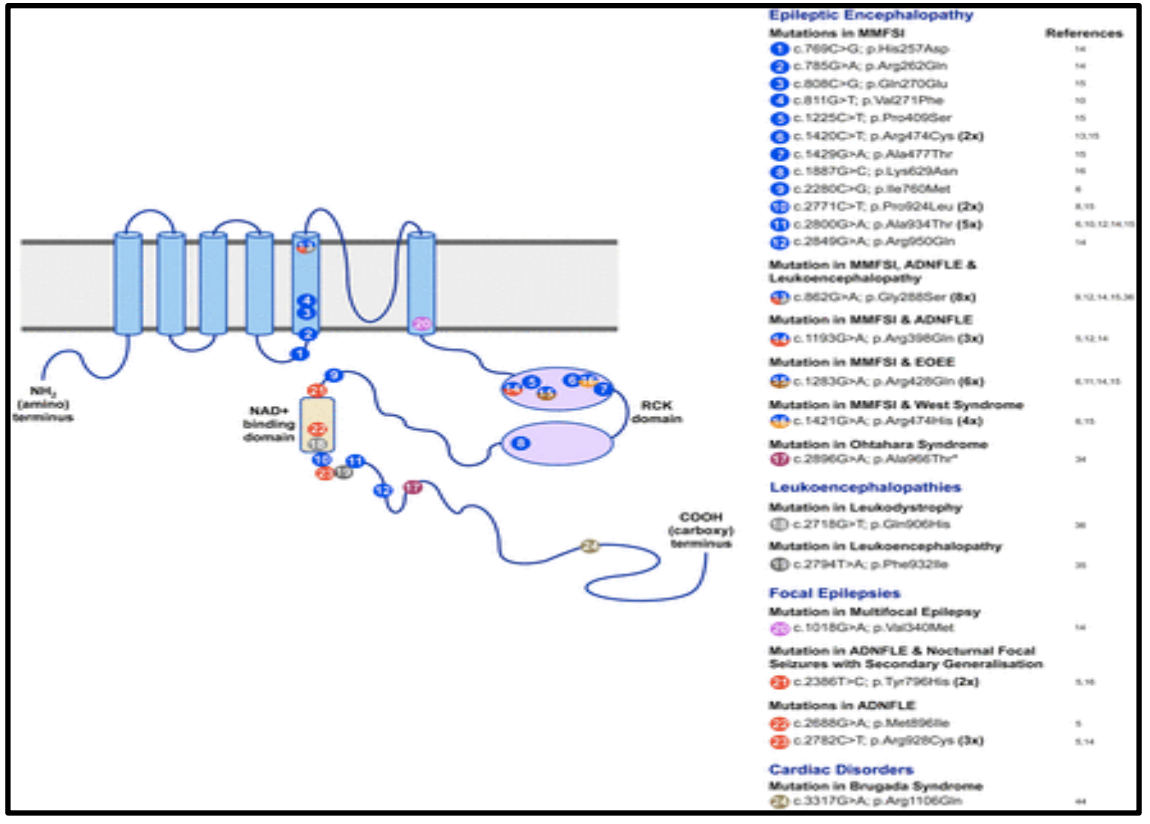
Neurology® 2018;90:e1-6. doi:10.1212/WNL.0000000000004769

Conclusion

Quinidine did not show efficacy in adults and teenagers with ADNFLE. Dose-limiting cardiac side effects were observed even in the presence of low measured serum quinidine levels. Although small, this trial suggests use of quinidine in ADNFLE is likely to be ineffective coupled with considerable cardiac risks.







Lim et al, 2015

KCNQ2: Early-onset epileptic encephalopathy

KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,[1,2,3] Simone Mandelstam, MB ChB,[4,5] Arvid Suls, PhD,[1,2] Dominique Audenaert, PhD,[1,2,6] Tine Deconinck, MSc,[1,2] Lieve R.F. Claes, PhD,[1,2] Liesbet Deprez, PhD,[1,2] Katrien Smets, MD,[1,2,7] Dimitrina Hristova, MD,[8] Iglika Yordanova, MSc,[9] Albena Jordanova, PhD,[1,2] Berten Ceulemans, MD, PhD,[2,10] An Jansen, MD, PhD,[11,12] Danièle Hasaerts, MD,[11] Filip Roelens, MD,[13] Lieven Lagae, MD, PhD,[14] Simone Yendle, BSc (Hons),[15] Thorsten Stanley, MD,[16] Sarah E. Heron, PhD,[17] John C. Mulley, PhD,[18,19] Samuel F. Berkovic, MD, FRS,[15] Ingrid E. Scheffer, MBBS, PhD,[4,15,20] and Peter de Jonghe, MD, PhD[1,2,7]

ANN NEUROL 2012;71:15–25

Children with neonatal and/or infantile convulsions of unknown origin, neuropsychomotor delays, and peculiar neuroradiologic features

Whole Exome Sequencing Identifies *KCNQ2* Mutations in Ohtahara Syndrome

Hirotomo Saitsu, MD, PhD,[1] Mitsuhiro Kato, MD, PhD,[2] Ayaka Koide, MD, PhD,[3] Tomohide Goto, MD, PhD,[3] Takako Fujita, MD,[4] Kiyomi Nishiyama, PhD,[1] Yoshinori Tsurusaki, PhD,[1] Hiroshi Doi, MD, PhD,[1] Noriko Miyake, MD, PhD,[1] Kiyoshi Hayasaka, MD, PhD,[2] and Naomichi Matsumoto, MD, PhD[1]

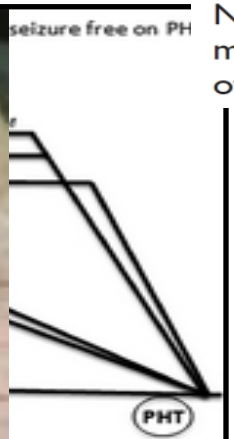
ANNALS *of Neurology*

2012; 72:298-300

Children with Ohtahara Syndrome (or Early Infantile Epileptic Encephalopathy with Suppression-Burst), the most severe and early onset epileptic encephalopathy

+ *KCNQ2:* Early-onset epileptic encephalopathy

Sodium channel blockers **Retigabine** (positive allosteric modulator of KCNQ2-5, partially reversing LOF in vitro)



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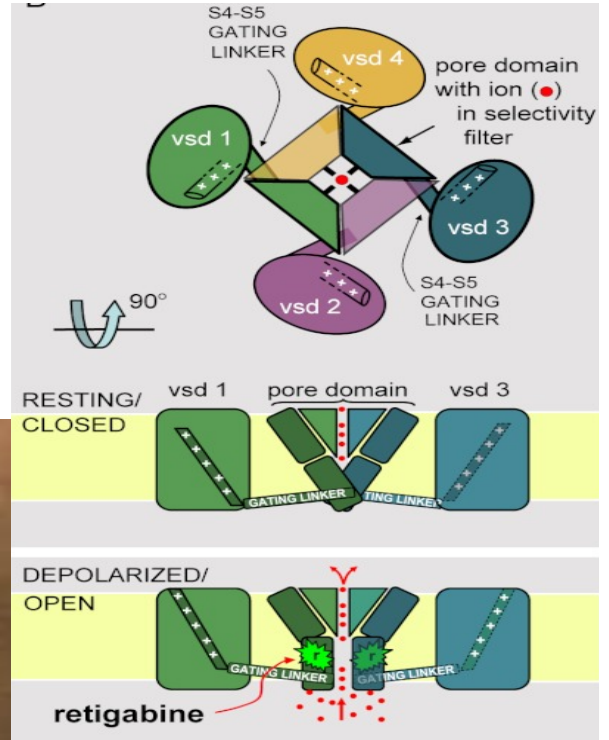
REVIEW

Neuronal potassium channel openers in the management of epilepsy: role and potential of retigabine



Highlights and take home messages

- ✓New genes
- ✓New genetic mechanisms
- ✓Precision medicine is the future
- ✓Counselling

GENETICS

This is how it works

Thanks for your attention!