European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

CACNA1A-related disorders

Clinical presentation and therapeutics options

Elisabetta Indelicato

Center for Rare Movement Disorders Innsbruck

Learning objectives

- When to suspect a (non-polyglutamine) *CACNA1A* disorders
- How to treat *CACNA1A* related disorders

Webinar Outline

- *CACNA1A*: the basics.
- "Classical" *CACNA1A* disorders (FHM1, EA2, SCA6)
- The expanding spectrum of *CACNA1A*: an age dependent –non only motor- phenotype
- Therapy of *CACNA1A* disorders
- Future directions

plus…some questions here and there

Question 1: What is your professional background?

a. Neurologist

b. Neuropediatrician

c. Neurology/ Neuropediatrician in training

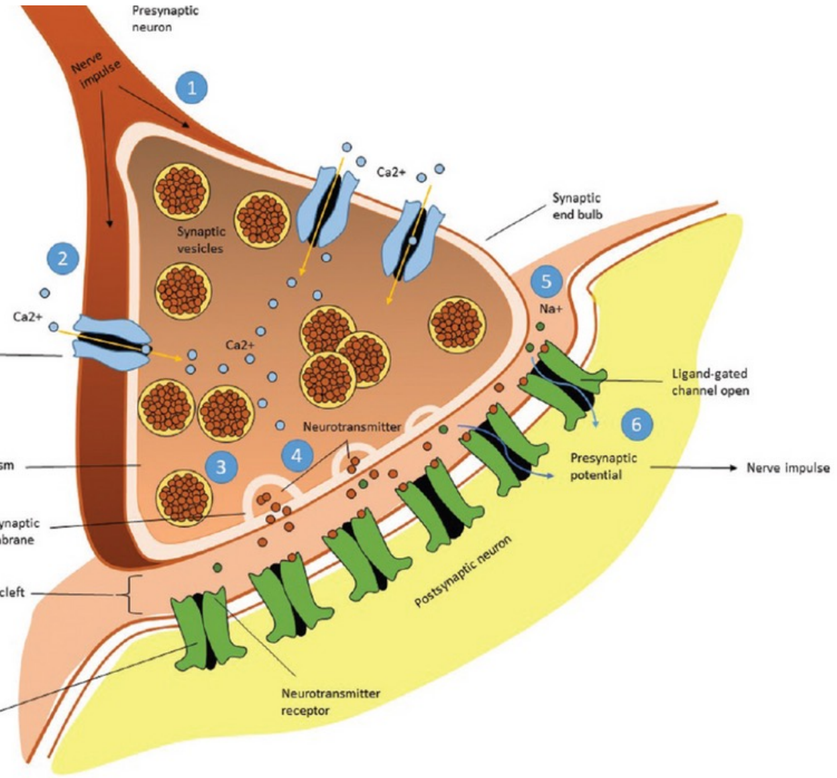
d. Geneticist

e. Nurse

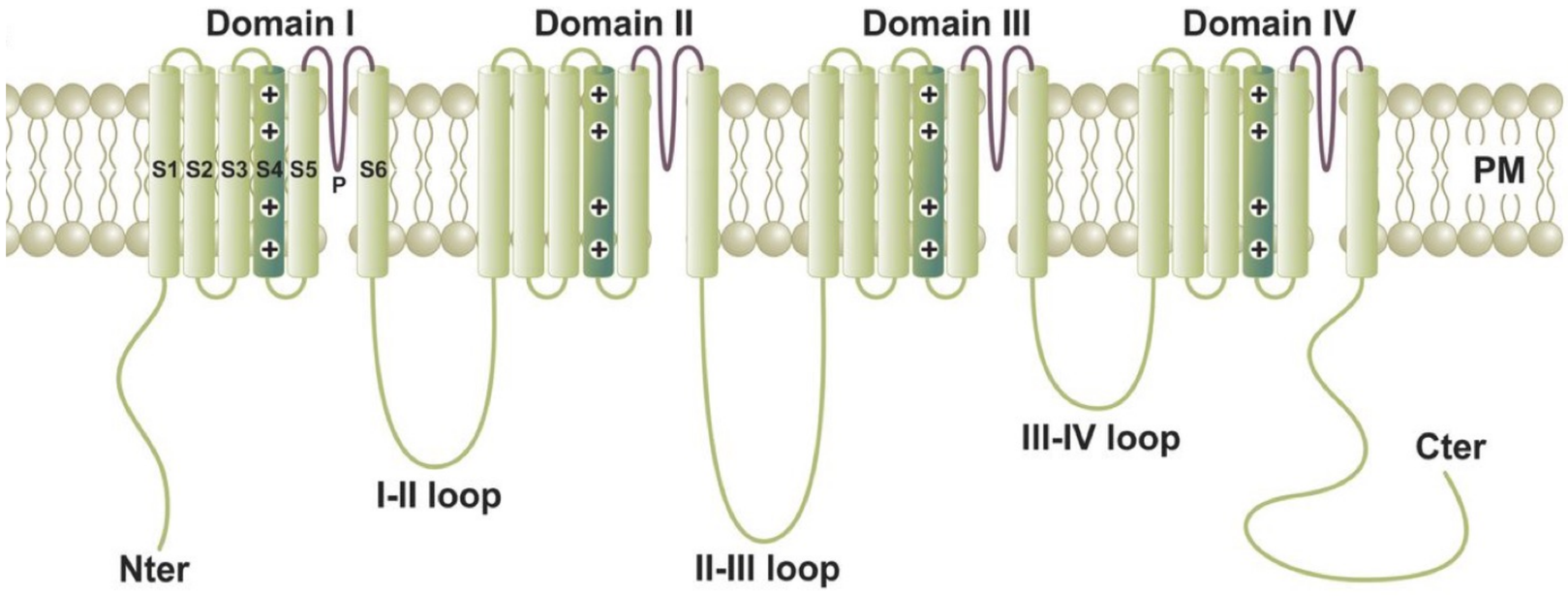
f. Physiotherapist

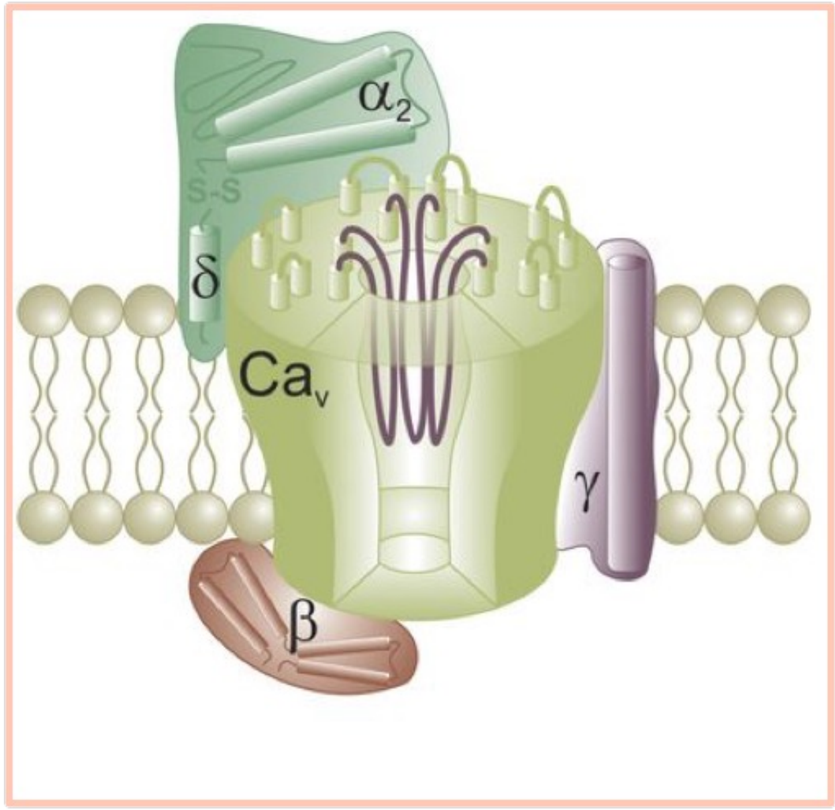
g. Patient or patient representative

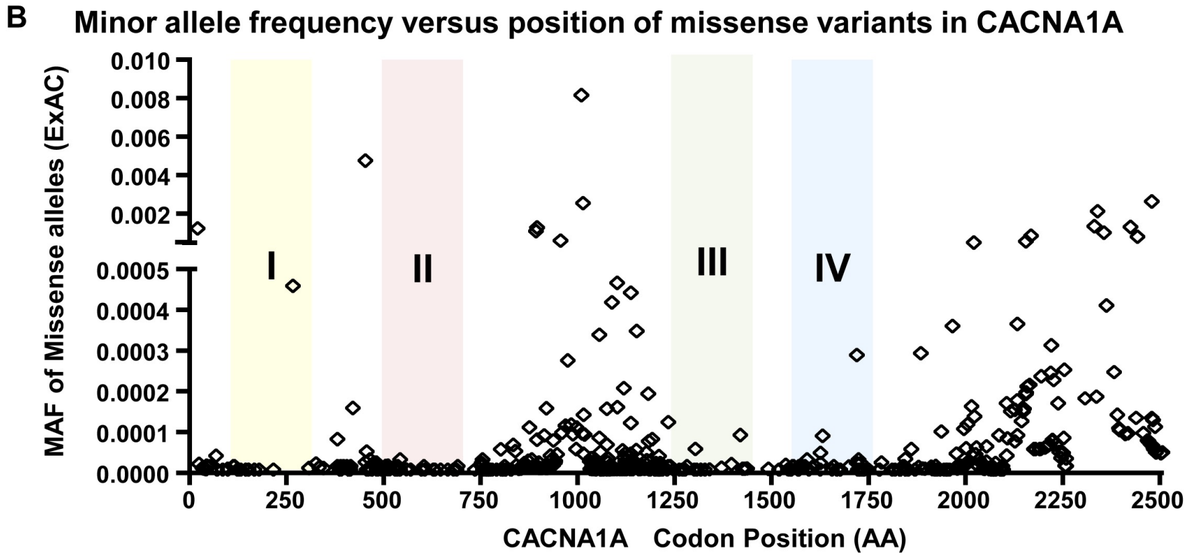
h. Other



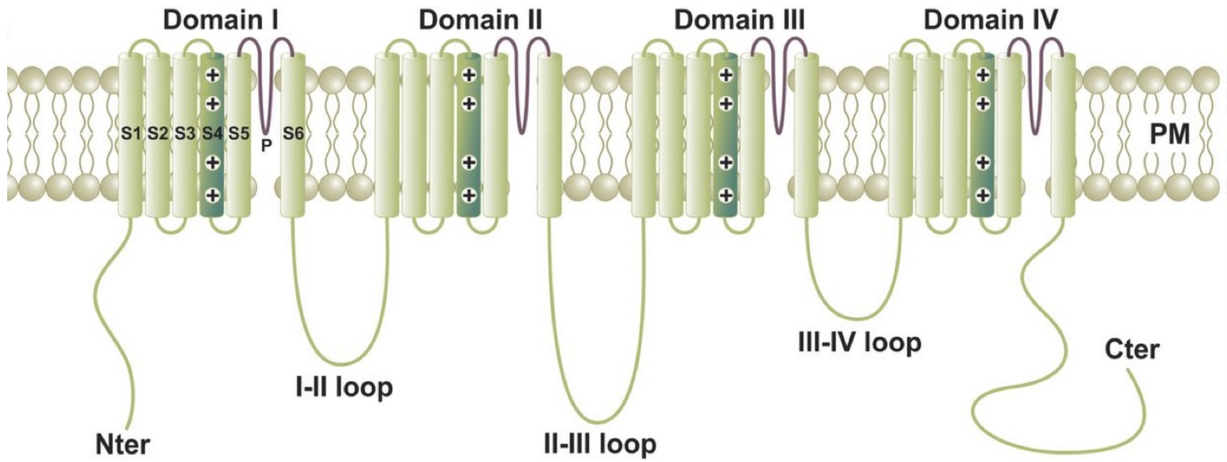
CACNA1A **encodes the α1A-subunit of the voltage-gate calcium channel P/Q and it is ubiquitary express in the CNS, but mostly expressed in the cerebellum**
P/Q channel regulate the synaptic transmission by enabling the calcium influx which trigger neurotransmitter release.

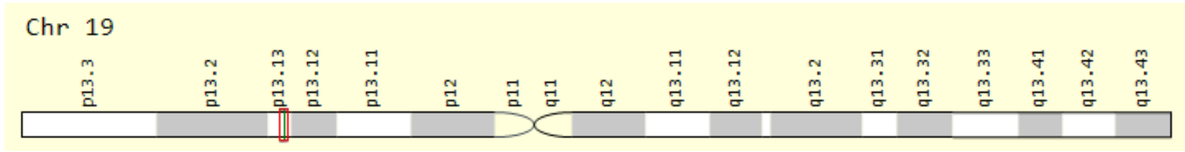






The CACNA1A gene is located on chromosome 19. It contains 47 exons, many of which undergo a canonical alternative splicing that results in myriad isoforms with different functional properties and regional expression patterns.
CACNA1A scores among the 2% most intolerant genes of the human genome. Particularly the transmembrane region shows paucity of variations





1996

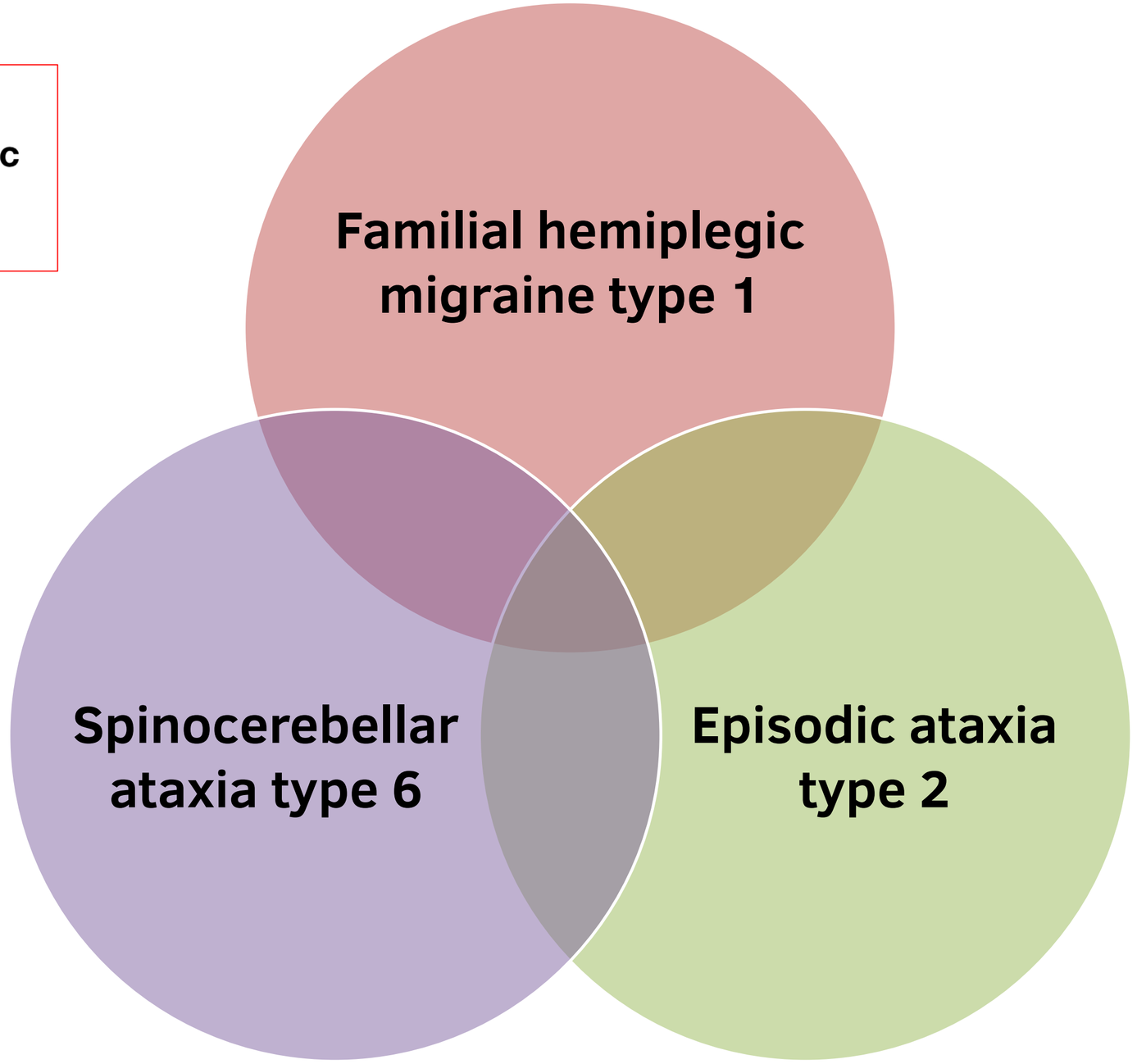
Cell, Vol. 87, 543–552, November 1, 1996, Copyright 1996 by Cell Press

Familial Hemiplegic Migraine and Episodic Ataxia Type-2 Are Caused by Mutations in the Ca^{2+} Channel Gene CACNL1A4

1997

article

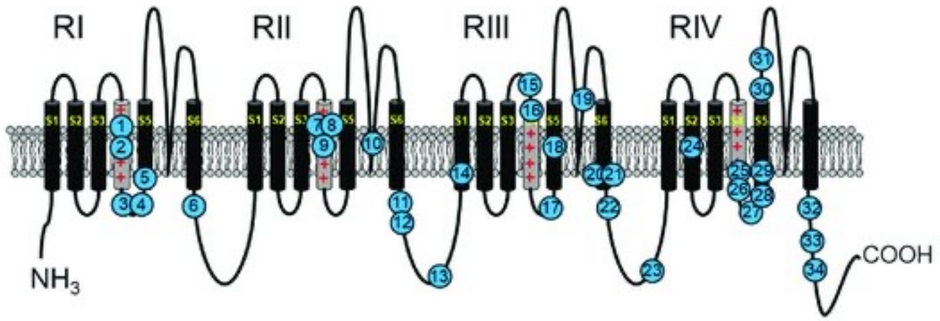
Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the α_{1A}-voltage-dependent calcium channel



- Autosomal dominant transmission
- Cerebellar dysfunction
- Peculiar paroxysmal manifestations

FHM1

- **Monogenic form of Migraine with Aura**
- ***CACNA1A* missense Mutations (Gain-of-function)**



1 R192Q	8 V581L	15 K1336E	22 I1512T	29 V1696I
2 R195K	9 R583Q	16 R1347Q	23 C1535S	30 I1710T
3 S218L	10 T666M	17 C1370Y	24 F1609L	31 D1725N
4 P225H	11 V714A	18 Y1385C	25 R1668W	32 I1811L
5 G230V	12 D715E	19 V1457L	26 K1670R	33 A2006T
6 F363S	13 E1015K	20 F1506S	27 L1682P	34 R2157G
7 V581M	14 Y1245C	21 F1506Y	28 W1684R	

modified from Tyagi 2020, Frontiers in Molecular Science

FAMILIAL HEMIPLEGIC MIGRAINE ASSOCIATED WITH MUTATIONS IN A NEURONAL CALCIUM CHANNEL

THE CLINICAL SPECTRUM OF FAMILIAL HEMIPLEGIC MIGRAINE ASSOCIATED WITH MUTATIONS IN A NEURONAL CALCIUM CHANNEL

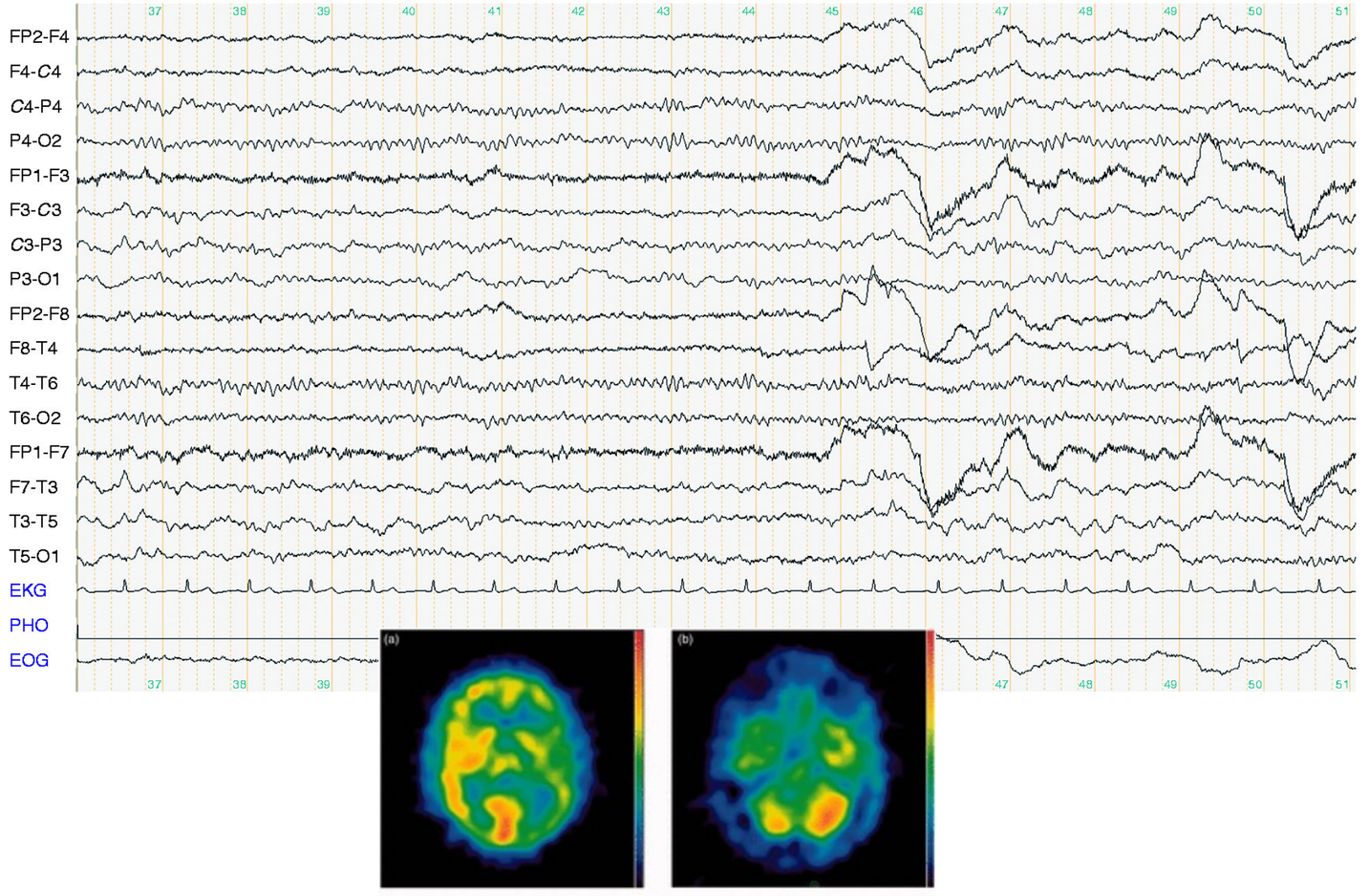
ANNE DUCROS, M.D., PH.D., CHRISTIAN DENIER, M.D., ANNE JOUTEL, M.D., PH.D., MICHAËLLE CECILLON, CHRISTELLE LESCOAT, KATAYOUN VAHEDI, M.D., FRANÇOISE DARCEL, M.D., ERIC VICAUT, M.D., PH.D., MARIE-GERMAINE BOUSSER, M.D., AND ELISABETH TOURNIER-LASSERVE, M.D.

- **Recurrent attacks with hemi/tetraparesis, dysphasia, sensory loss, visual disturbances, dizziness, confusion till coma, etc..**
  - **Frequency: 1-2 in a lifetime to several times per month.**
  - **Trigger: head trauma, physical and emotional stress, cerebral angiography**

plus

- **Cerebellar signs in the interval (in up to 50% of cases)**

FHM1


37 38 39 40 41 42 43 44 45 46 47 48 49 50 51
FP2-F4
F4-C4
C4-P4
P4-O2
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
EKG
PHO
EOG
37 38 39 47 48 49 50 51
(a)
(b)

FHM1

- **The aura manifestations often outlast the burden of the following headache and may last hours or days.**

- **“Severe” Attacks may be accompanied by disorders of consciousness. In “malignant” mutations (*e.g.* S218L), trivial head trauma may trigger severe attacks with disorders of consciousness up to coma and symptomatic seizures (underlying brain edema).**

from Stam et al JNNP 2019

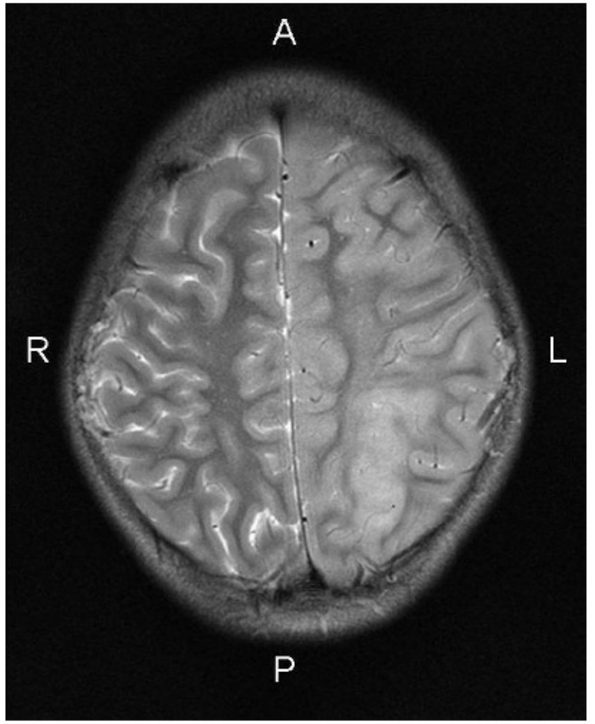
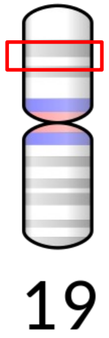


Figure 3 T2 axial brain MRI of patient No 2 showing severe left-sided cortical oedema. MRI was performed during the coma episode at age 15 years with right-sided hemiparesis and generalised seizures. A, anterior; L, left; P, posterior; R, right.

FHM1

1996



CACNA1A
p13.13

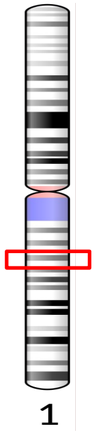
Episodic Ataxia

Spinocerebellar ataxia

Epilepsy

FHM2

2003



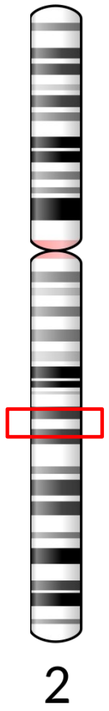
ATP1A2
p13.13

Alternating hemiplegia of childhood

Epilepsy

FHM3

2005



SCN1A
q24.3

Epilepsy

FHM4?

2020-2022

PRRT2
q24.3

Epilepsy

Paroxysmal kinesigenic dyskinesia

FHM1

February 13, 2018; 90 (7) ARTICLE

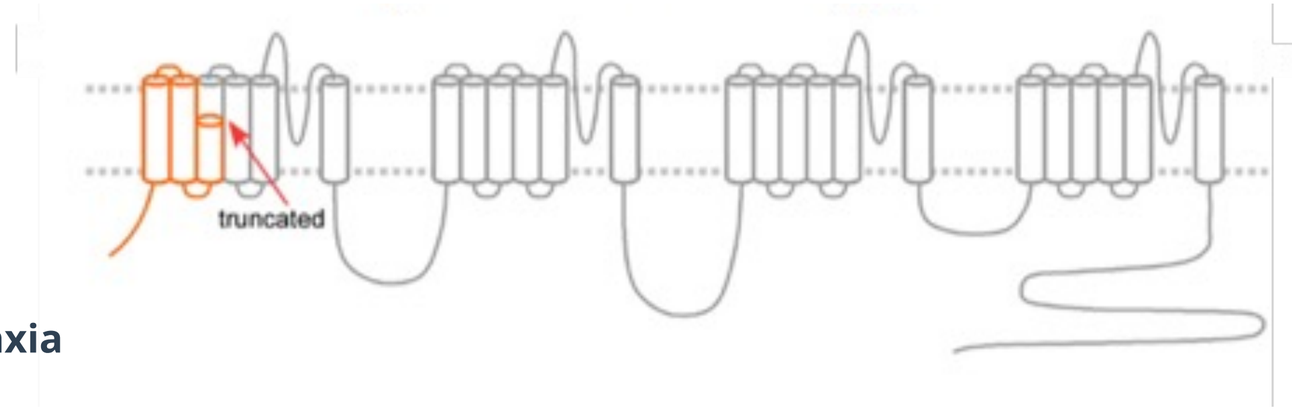
Clinical spectrum of hemiplegic migraine and chances of finding a pathogenic mutation

Nadine Pelzer, Joost Haan, Anine H. Stam, Lisanne S. Vijfhuizen, Stephany C. Koelewijn, Amber Smagge, Boukje de Vries, Michel D. Ferrari, Arn M.J.M. van den Maagdenberg, Gisela M. Terwindt

Patients with mutations in *CACNA1A, ATP1A2*, or *SCN1A* had:

1. a lower age at disease onset
2. larger numbers of affected family members
3. more often attacks (a) triggered by mild head trauma, (b) with extensive motor weakness, and (c) with brainstem features, confusion, and brain edema
4. Mental retardation and progressive ataxia were exclusively found in patients with a mutation.

EA2



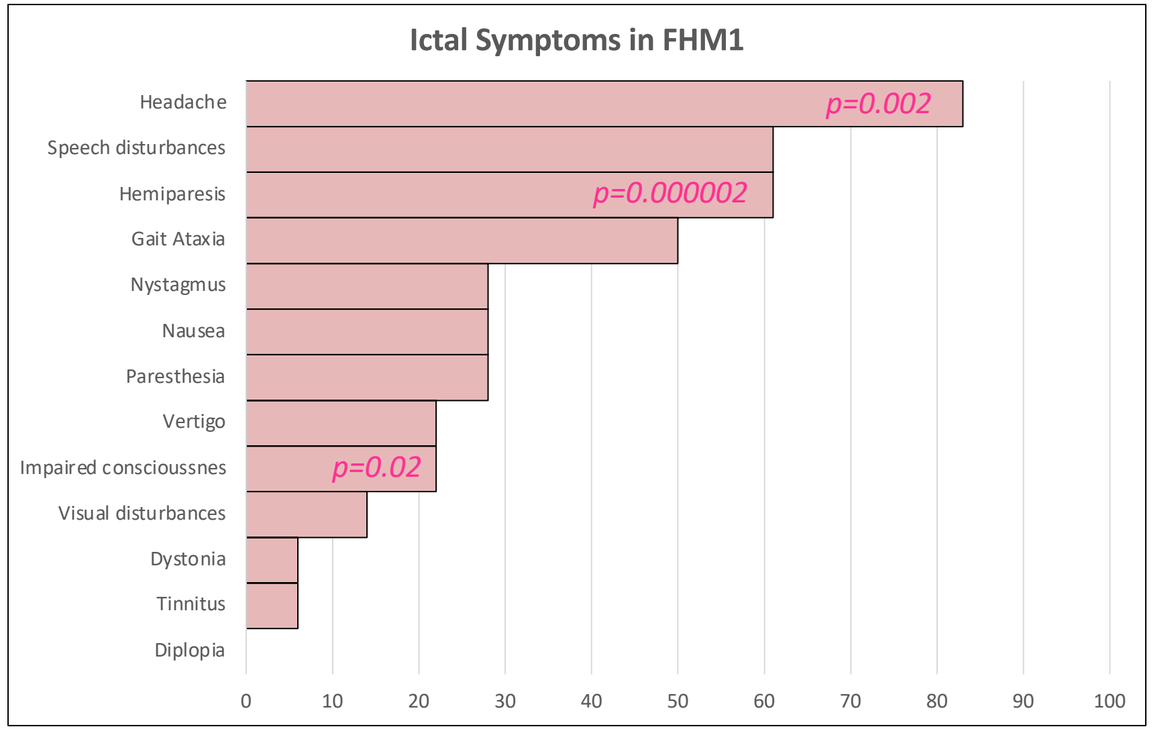
- Most common form of episodic ataxia
- Mostly associated with truncating/frameshift mutation
- Recurrent episodes with acute onset of balance disorder, dysarthria, double vision, nausea/vomiting.
  - Possible additional symptoms: paroxysmal dystonia, hemiplegia, tinnitus, headache.
  - Shorter duration than in FHM1 (few minutes till hours) but more frequent (even daily).
- Triggers: stress, caffeine, alcohol, physical exertion, fever, heat, phenytoin

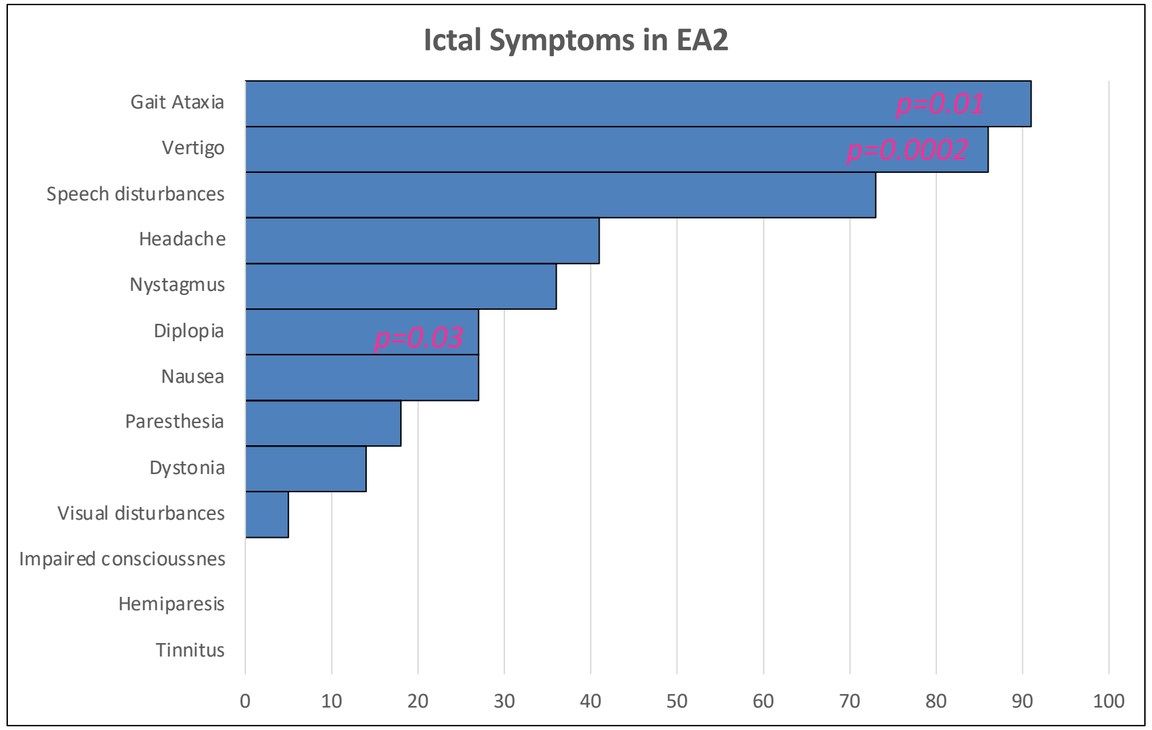
plus

- Permanent cerebellar signs in the intervals in up to 50-75% of patients.

EA2

Innsbruck Cohort, unpublished data

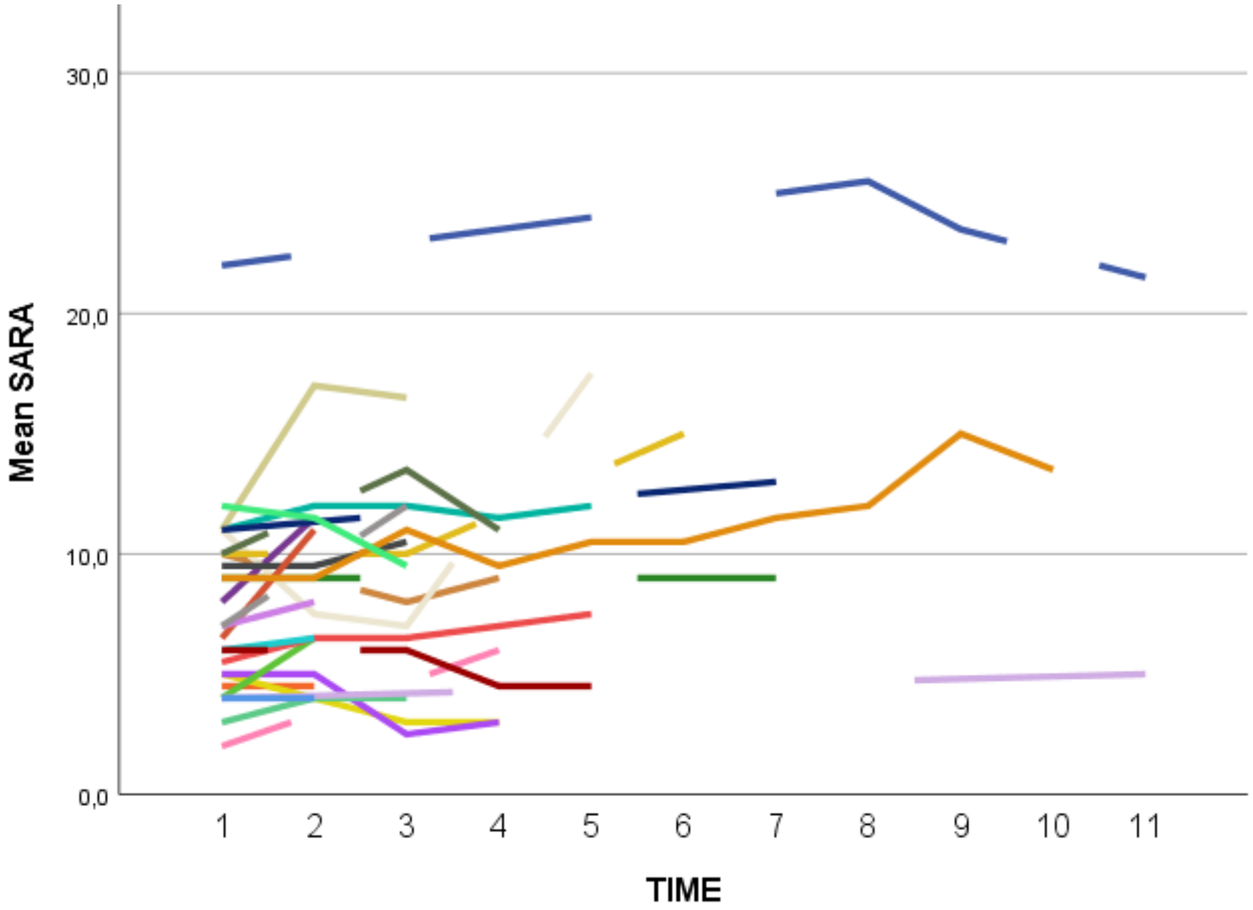


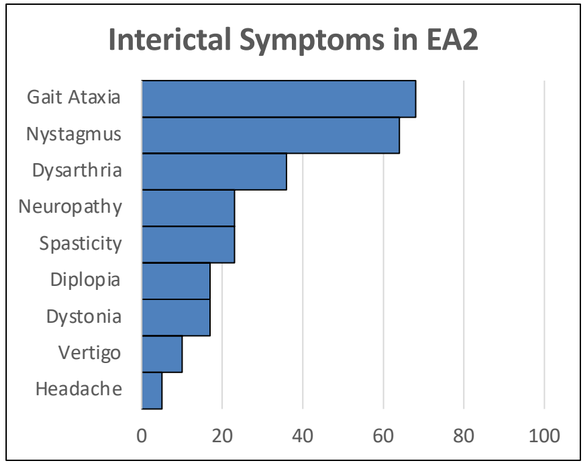


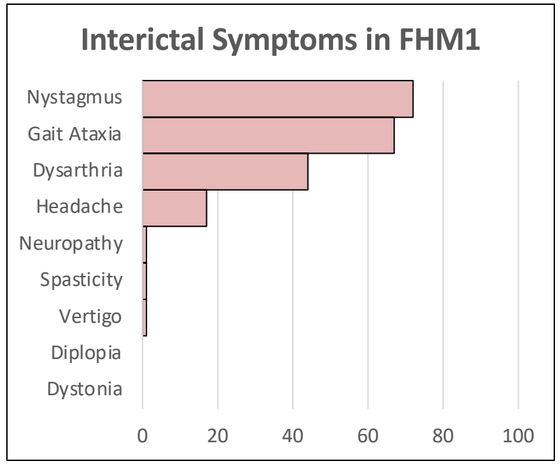
40 genetically confirmed patients

- Paroxysmal manifestations were markedly more frequent in patients with EA2 (Median 108/year (IQR=24;216) versus 6,5/year (IQR=1;12) in FHM1, *p*=0,0003).
- Some adult FHM1 patients (n=4) could recall a two-peak course of paroxysmal manifestations. Patients with EA2 could not recall such a two-peak course. However, in several cases episodic manifestations ceased during the disease course, either spontaneously or upon medical treatment.
- The duration of paroxysmal manifestations was significantly shorter in EA2 (attack duration < 1 hour in 8/21 in EA2 patients and in 0/12 FHM1 patients, *p*=0,03).

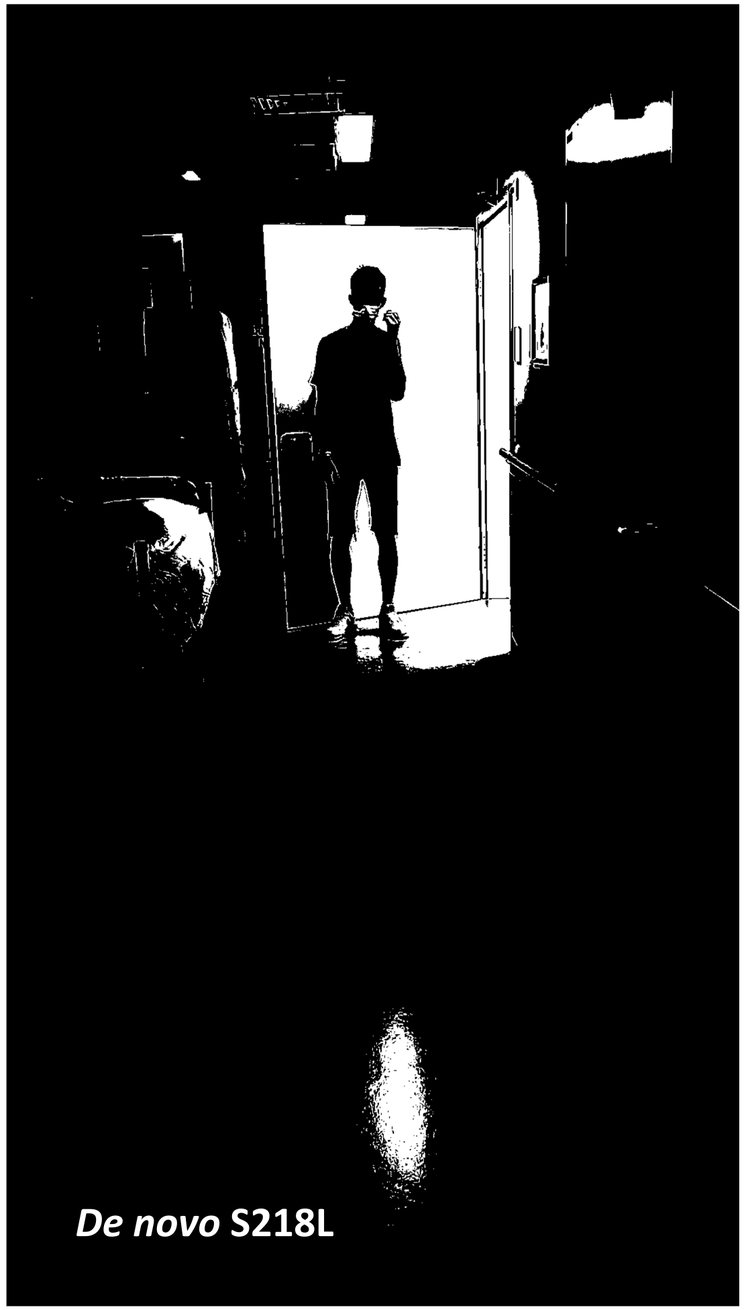
Innsbruck Cohort, unpublished data



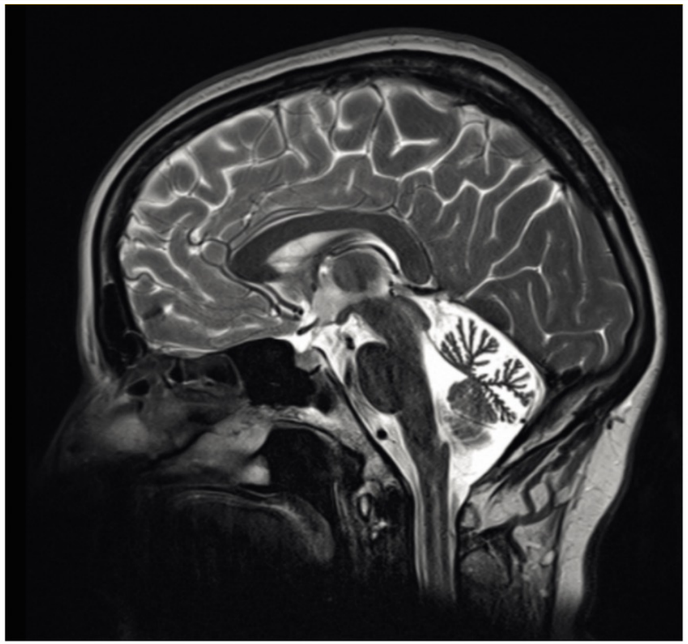




- Patients with chronic gait ataxia were older (age at examination 42±21 years versus 23±18 in those without gait ataxia, *p*=0,02).
- The average SARA score at the first examination was 8±4 and was similar in both phenotypes.


De novo S218L


EA2

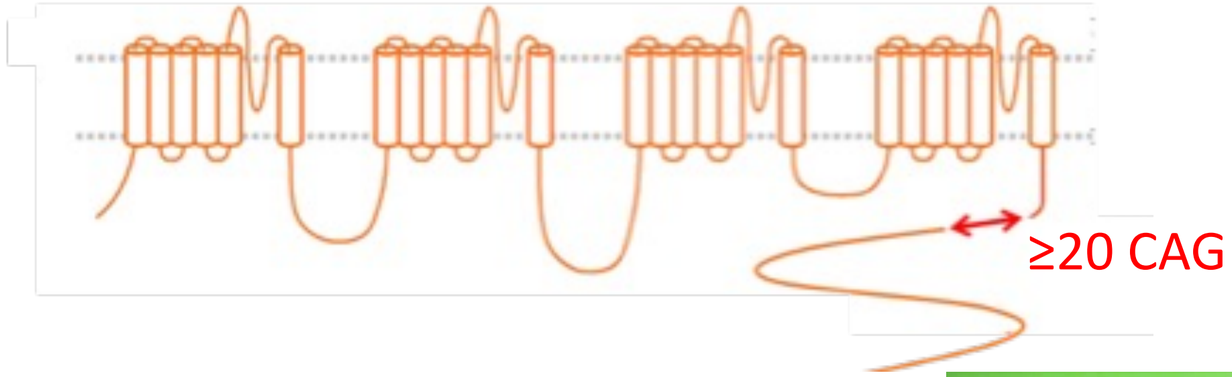


FHM1/EA2: overlapping Manifestations

- Onset in late childhood/young adulthood
- Cooccurrence of paroxysmal vertigo/ataxia and migraine in the same family
- Chronic cerebellar signs and cerebellar atrophy in 50-75% of patients

SCA6

A Poly-Q SCA



- Caused by pathologically expanded CAG repeat within the C-terminus (normal allele ≤18; pathological allele 20-33 repeats)
- Onset typically in the **6. Decade** with an isolated progressive cerebellar ataxia (“pancerebellar syndrome”)
- Pathogenesis: no primary effect of calcium currents. Most likely disturbances in intracellular signal pathway.
- Interestingly, several patients may display episodic vertigo at disease onset, resembling the paroxysmal manifestations of EA2.

1997

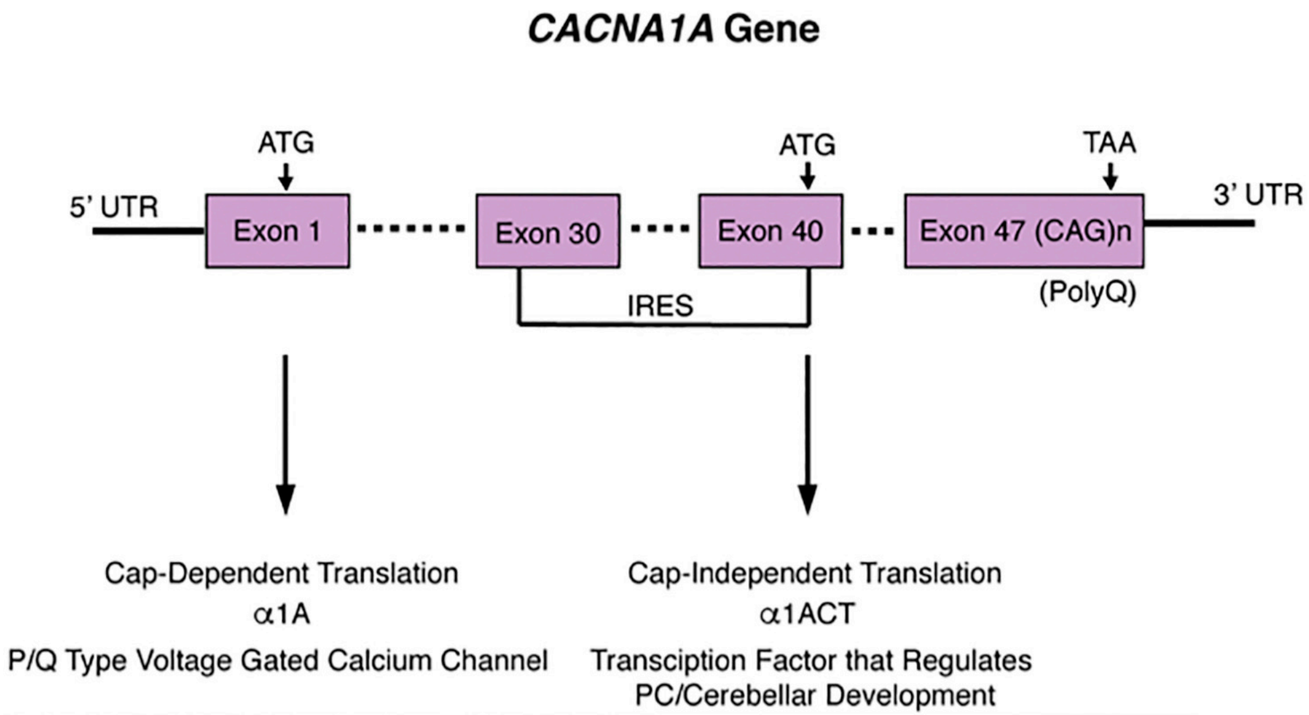
2013

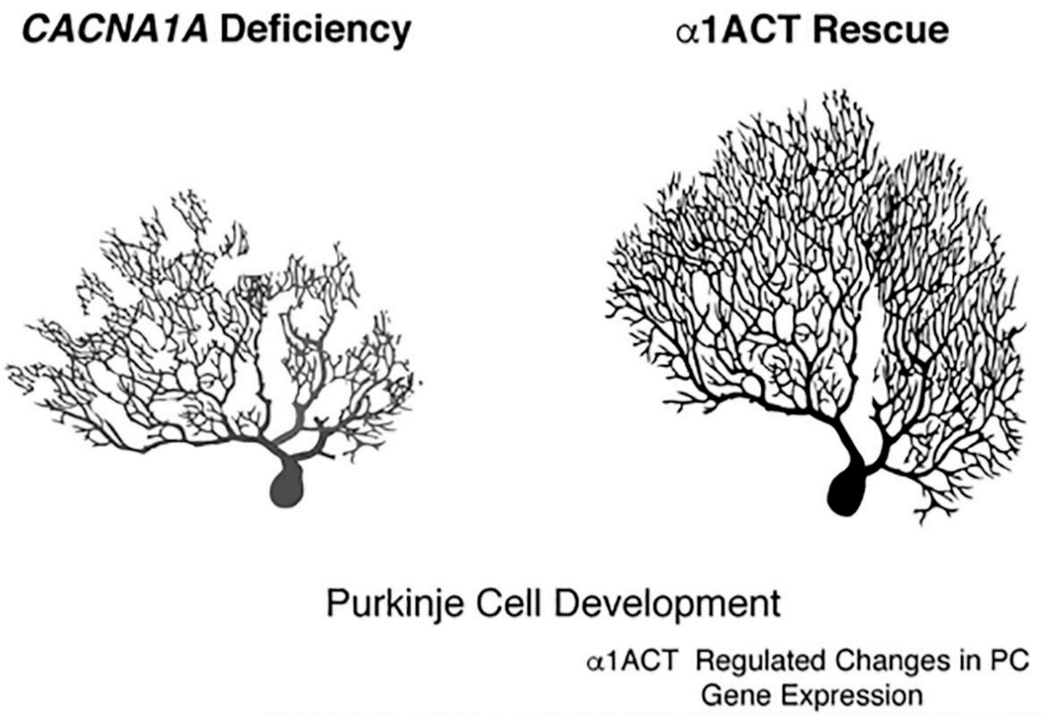
Cell

Second Cistron in *CACNA1A* Gene Encodes a Transcription Factor Mediating Cerebellar Development and SCA6

Xiaofei Du,[1] Jun Wang,[1] Haipeng Zhu,[1] Lorenzo Rinaldo,[2] Kay-Marie Lamar,[1] Ann C. Palmenberg,[3] Christian Hansel,[2] and Christopher M. Gomez[1,*]

Discovery of a IRES (internal ribosomal entry site) within the CACNA1A gene promoting the translation of a second gene product, a1ACT, a transcription factor involved in the cerebellar development





Question 2: Which paroxysmal feature is typical of FHM1?

a. Vertigo

b. Speech disorders

c. Disturbances of Consciousness

d. Headache

e. Nausea and vomiting

Beyond the “classical” phenotype

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

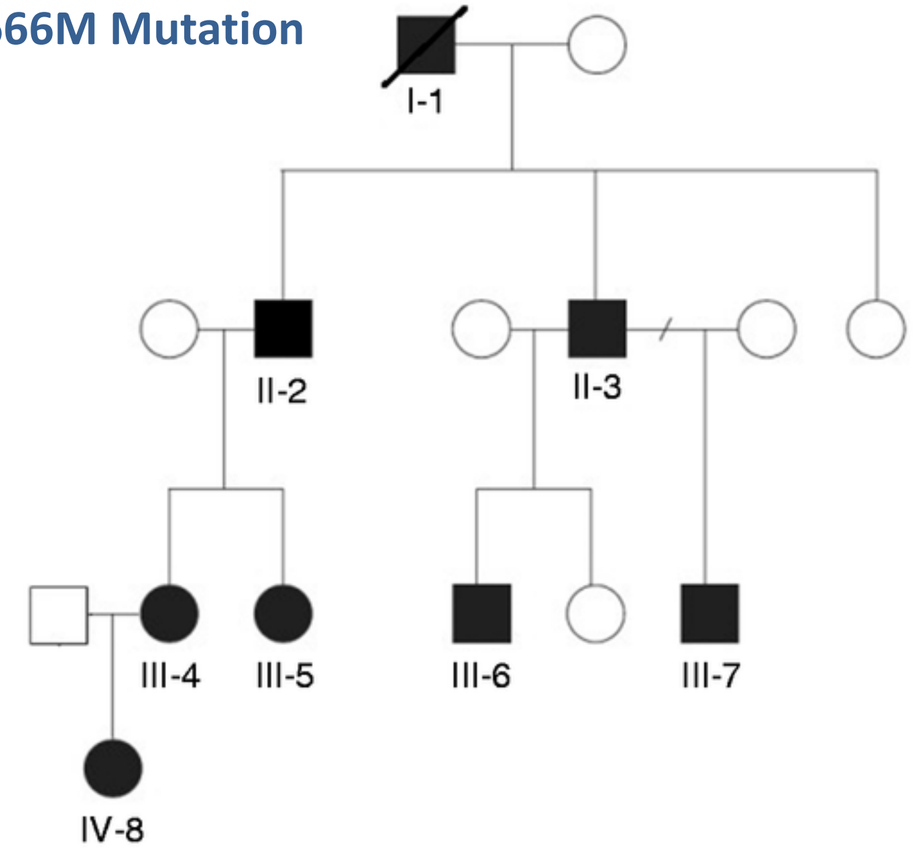
Ten years of follow-up in a large family with familial hemiplegic migraine type 1: Clinical course and implications for treatment

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102417715229
journals.sagepub.com/home/cep
SAGE

European Reference Network | Neurological Diseases (ERN-RND)

T666M Mutation



III-5 delayed motor development (learned to sit by herself at the age of three years, recover after intensive physiotherapy, she was able to walk at about seven years of age). She never suffered from hemiplegic episodes, but had attacks with headache, vertigo and worsening of ataxia.

IV-8 delayed motor development with first walking attempts at 18 months of age. Additionally, episodes of drowsiness with walking difficulties leading to falls and intermittent cervical dystonia Episodes lasted in the range of 1–3 days and were followed by increased sleepiness. General and neurological examination as well as EEG were unremarkable.

Original Article

Cephalalgia
An International Journal of Headache

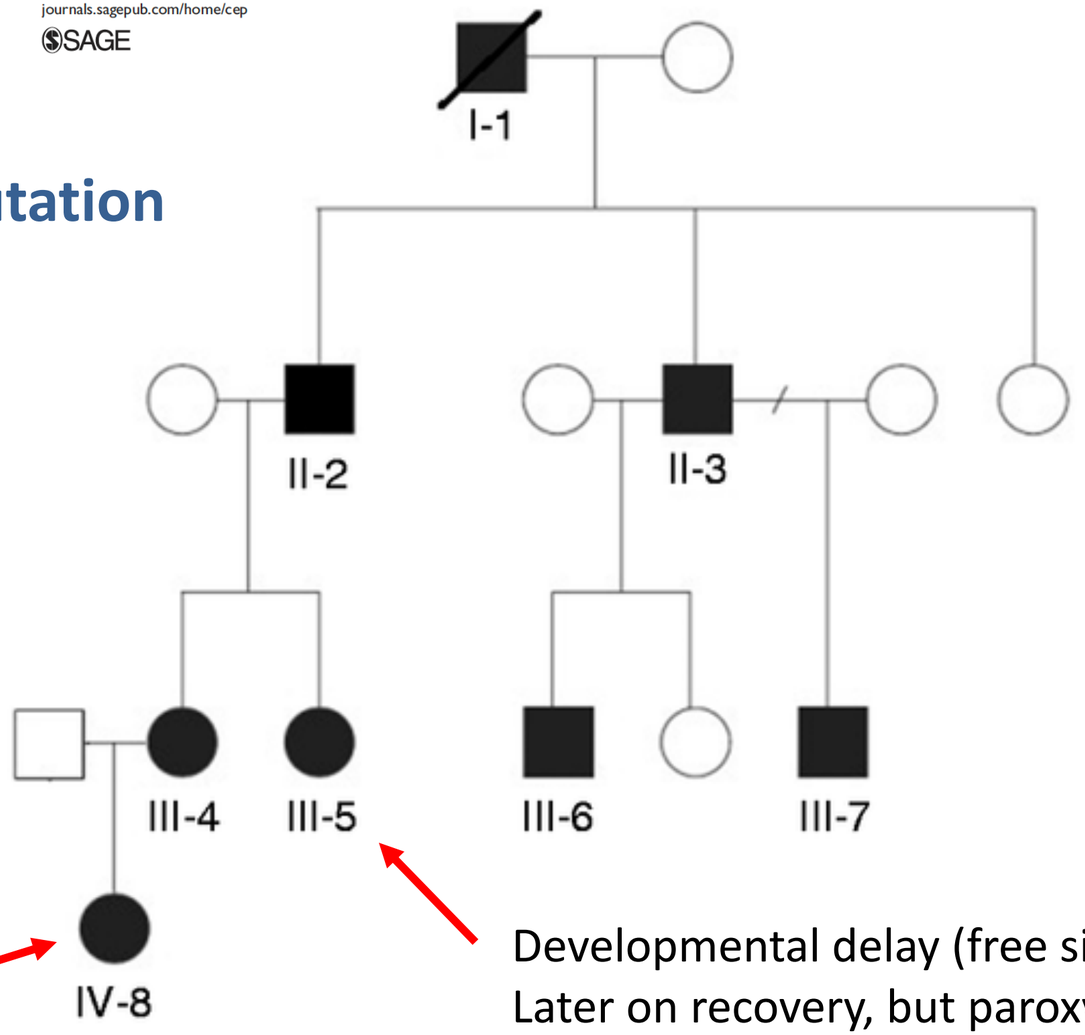
International Headache Society

Ten years of follow-up in a large family with familial hemiplegic migraine type 1: Clinical course and implications for treatment

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102417715229
journals.sagepub.com/home/cep
SAGE

T666M Mutation



Slight developmental delay
(walking with 18 months)
Paroxysmal torticollis

Developmental delay (free sitting at 3 yo)
Later on recovery, but paroxysmal vertigo

Genetically confirmed
T666M Mutation

ORIGINAL STUDY

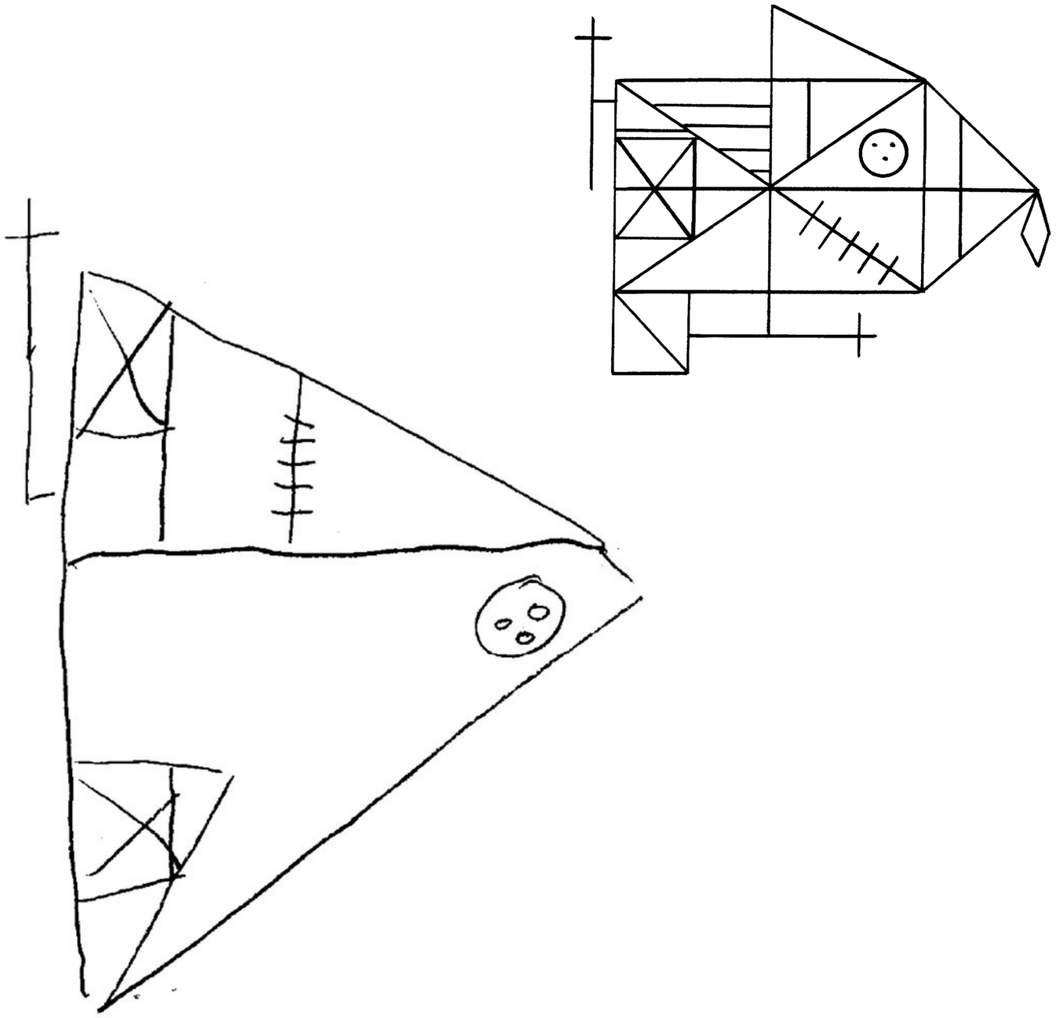
Cognitive Functions, Emotional Behavior, and Quality of Life in Familial Hemiplegic Migraine

Elfriede Karner, MSc, Margarete Delazer, PhD, Thomas Benke, MD, and Sylvia Bösch, MD

ORIGINAL STUDY

Long-term Outcome of Cognitive Functions, Emotional Behavior, and Quality of Life in a Family With Familial Hemiplegic Migraine

Elfriede Karner, MS, Wolfgang Nachbauer, MD, Thomas Bodner, PhD, Thomas Benke, MD, Sylvia Boesch, MD, and Margarete Delazer, PhD

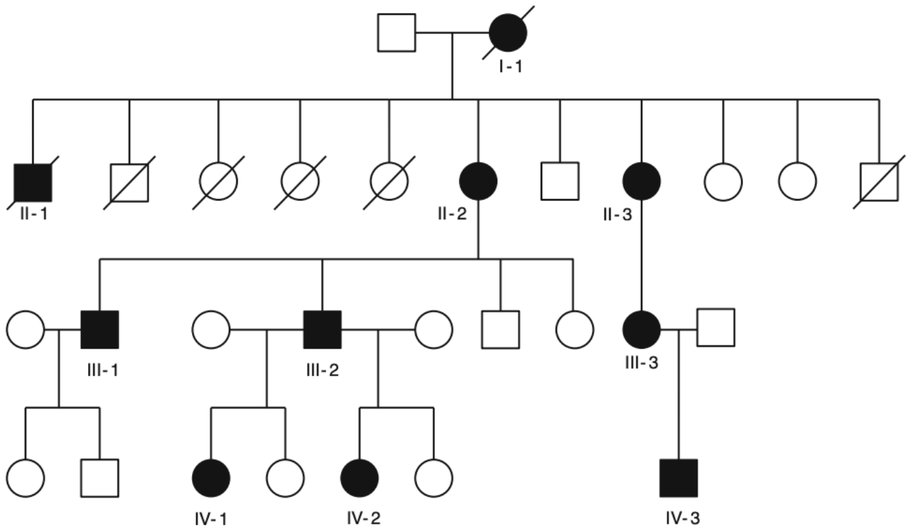


ORIGINAL COMMUNICATION

Episodic ataxia type 2: phenotype characteristics of a novel CACNA1A mutation and review of the literature

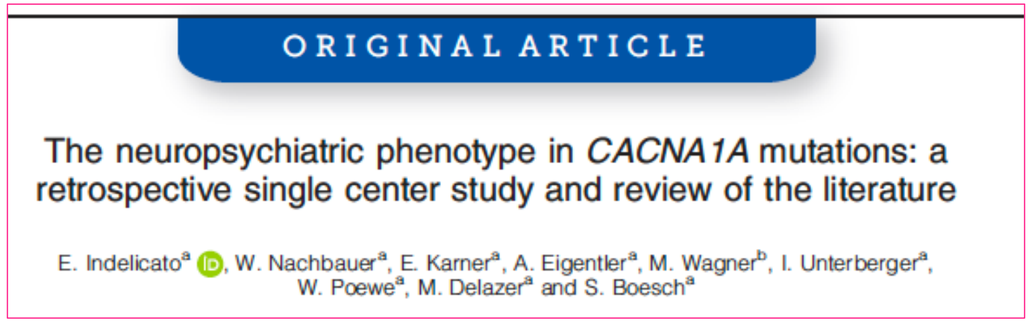
Wolfgang Nachbauer · Michael Nocker · Elfriede Karner · Iva Stankovic · Iris Unterberger · Andreas Eigentler · Rainer Schneider · Werner Poewe · Margarete Delazer · Sylvia Boesch

c.3089+2T>C Mutation



„…Apart from overt neuropsychological deficits, ***patients with severe or frequent attacks appear to exert socio-phobic behavior or anxiety disorder****. Although psychotic symptoms were denied by all our patients, anxiety and* ***bad performance in school, especially when the disease started early in life, was striking.*** *This phenomenon was anticipated in patient III-2 who scored high for anxiety and depression.* ***Moreover, socio-phobic behavior appears to ameliorate gradually after treatment or even disappears (as observed in patient IV-3 after treatment initiation).****“*

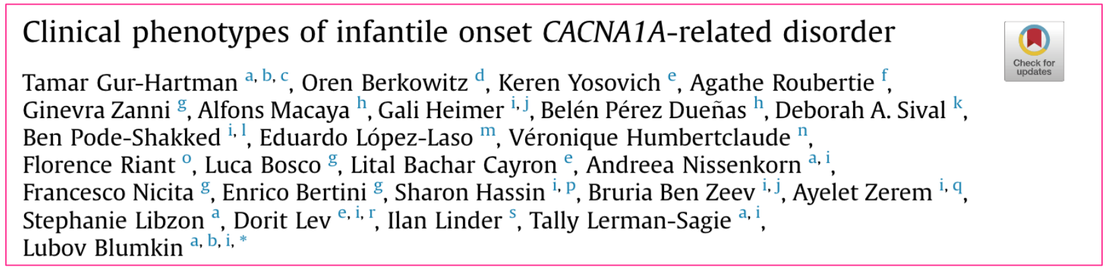
Neuropsychological disturbances and developmental delay



ORIGINAL ARTICLE

The neuropsychiatric phenotype in *CACNA1A* mutations: a retrospective single center study and review of the literature

E. Indelicato[a], W. Nachbauer[a], E. Karner[a], A. Eigentler[a], M. Wagner[b], I. Unterberger[a], W. Poewe[a], M. Delazer[a] and S. Boesch[a]



Clinical phenotypes of infantile onset *CACNA1A*-related disorder

Tamar Gur-Hartman [a, b, c], Oren Berkowitz [d], Keren Yosovich [e], Agathe Roubertie [f], Ginevra Zanni [g], Alfons Macaya [h], Gali Heimer [i, j], Belén Pérez Dueñas [h], Deborah A. Sival [k], Ben Pode-Shakked [i, l], Eduardo López-Laso [m], Véronique Humbertclaude [n], Florence Riant [o], Luca Bosco [g], Lital Bachar Cayron [e], Andreea Nissenkorn [a, i], Francesco Nicita [g], Enrico Bertini [g], Sharon Hassin [i, p], Bruria Ben Zeev [i, j], Ayelet Zerem [i, q], Stephanie Libzon [a], Dorit Lev [e, i, r], Ilan Linder [s], Tally Lerman-Sagie [a, i], Lubov Blumkin [a, b, i, *]

In children of **genetically confirmed** FHM1/EA2 families:

- psychomotor developmental delay
- learning disability
- Behavioral disturbances (ADHD, Autism spectrum disorders)

In adults:

- Partial compensation of earlier severe deficits
- Standardized neuropsychological tests: deficits in attention, memory, visuocontruction abilities
- Rarely dementia

Non epileptic paroxysmal events of the childhood

Benign paroxysmal torticollis of the infancy (BPTI)

intermittent cervical dystonia, accompanied by pallor, irritability, vomiting and ataxia

ICHD-3 counts it under the episodic syndromes which can precede migraine

BPTI can occur isolated or in combination with a developmental delay → hint to an underlying *CACNA1A*-Mutation.

Greene 2021, Pediatric research

Non epileptic paroxysmal events of the childhood

Paroxysmal tonic upward Gaze (PTU)

Intermittent tonic conjugated upward gaze with compensatory nodding; it can be accompanied by coordination disturbances.

It is often associated to structural pathologies and can precede further neurological syndromes with chronic ataxia, epilepsy and intellectual disability.

Lispi 2002, ILAE

CACNA1A and Epilepsy

European Reference Network | Neurological Diseases (ERN-RND)

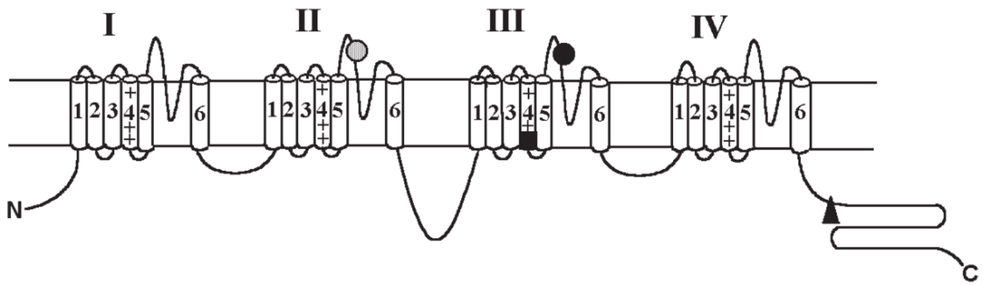
Cell, Vol. 87, 607–617, November 15, 1996, Copyright ©1996 by Cell Press

Absence Epilepsy in Tottering Mutant Mice Is Associated with Calcium Channel Defects

Colin F. Fletcher,* Cathleen M. Lutz,†
T. Norene O'Sullivan,* John D. Shaughnessy, Jr.,*
Richard Hawkes,‡ Wayne N. Frankel,†
Neal G. Copeland,* and Nancy A. Jenkins*
*Mammalian Genetics Laboratory
ABL–Basic Research Program
NCI–Frederick Cancer Research
and Development Center
Frederick, Maryland 21702
†The Jackson Laboratory
Bar Harbor, Maine 04609
‡Department of Anatomy and Neuroscience
Research Group
Faculty of Medicine
University of Calgary
Calgary, Alberta T2N 4N1
Canada

Mutations at the mouse tottering (*tg*) locus cause a delayed-onset, recessive neurological disorder resulting in ataxia, motor seizures, and behavioral absence seizures resembling petit mal epilepsy in humans. A more severe allele, leaner (tg^{la}), also shows a slow, selective degeneration of cerebellar neurons. By positional cloning, we have identified an α_{1A} voltage-sensitive calcium channel gene that is mutated in *tg* and tg^{la} mice. The α_{1A} gene is widely expressed in the central nervous system with prominent, uniform expression in the cerebellum. α_{1A} expression does not mirror the localized pattern of cerebellar degeneration observed in tg^{la} mice, providing evidence for regional differences in biological function of α_{1A} channels. These studies define the first mutations in a mammalian central nervous system–specific voltage-sensitive calcium channel and identify the first gene involved in absence epilepsy.

Spontaneus recessive mutation at tottering locus causing ataxia, paroxysmal dystonia and absence epilepsy in mice



Tottering (Cacna1a ^{tg})
P601L

Rocker (Cacna1a ^{rkr})
T1310K

Leaner (Cacna1a $^{tg\ la}$)
aberrant splicing

Rolling (Cacna1a ^{rol})
R1262G

CACNA1A and Epilepsy

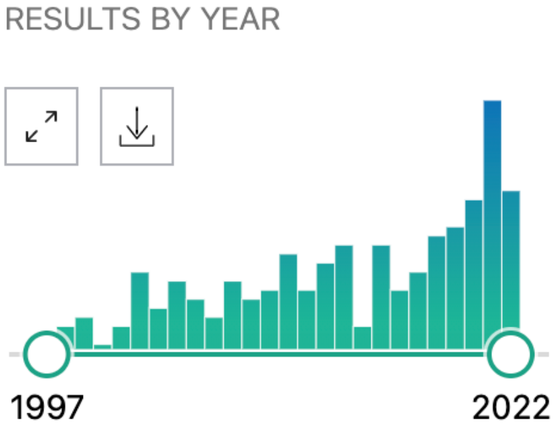
ORIGINAL COMMUNICATION

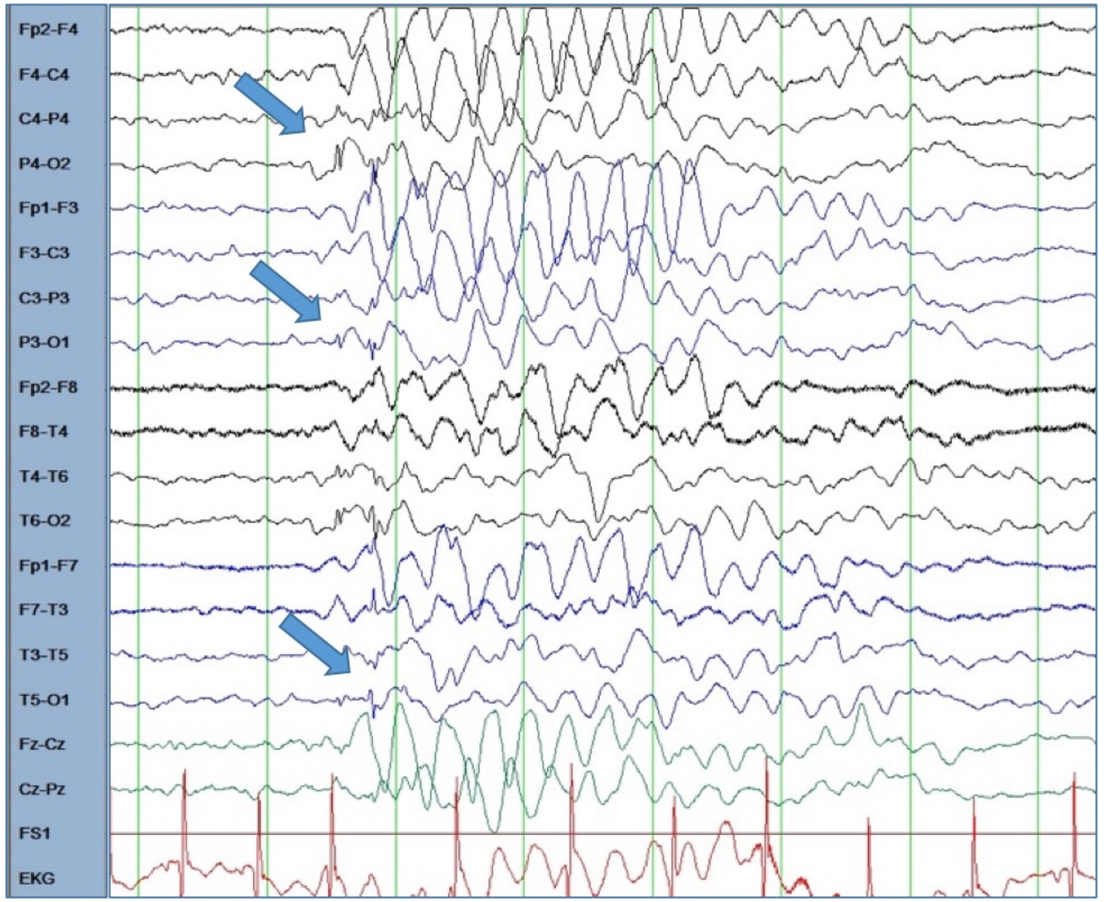
The electrophysiological footprint of *CACNA1A* disorders

Elisabetta Indelicato[1] · Iris Unterberger[2] · Wolfgang Nachbauer[1] · Andreas Eigentler[1] · Matthias Amprosi[1] · Fiona Zeiner[3] · Edda Haberlandt[3,4] · Manuela Kaml[2] · Elke Gizewski[5] · Sylvia Boesch[1]

85 EEG recordings from 38 **genetically confirmed** patients performed 1994-2019 + Review of the literature

- Seizures and interictal epileptic discharges (IEDs) at EEG were recurrently observed in EA2
- Seizures were typically reported in children and young adults before the onset of paroxysmal ataxia.
- Absences and 3 Hz Spike-Wave discharges were the most common pattern



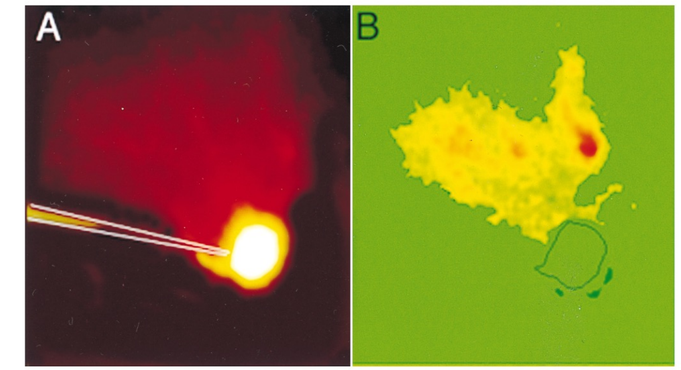


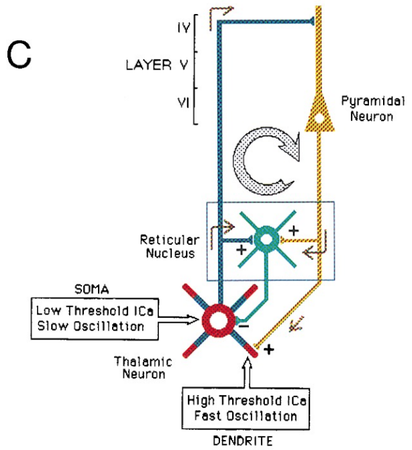
Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 724–728, January 1997
Neurobiology

Dendritic calcium conductances generate high-frequency oscillation in thalamocortical neurons

(thalamus/dendrites/*in vitro*/gamma band frequency/calcium currents)

CHRISTINE PEDROARENA AND RODOLFO LLINÁS





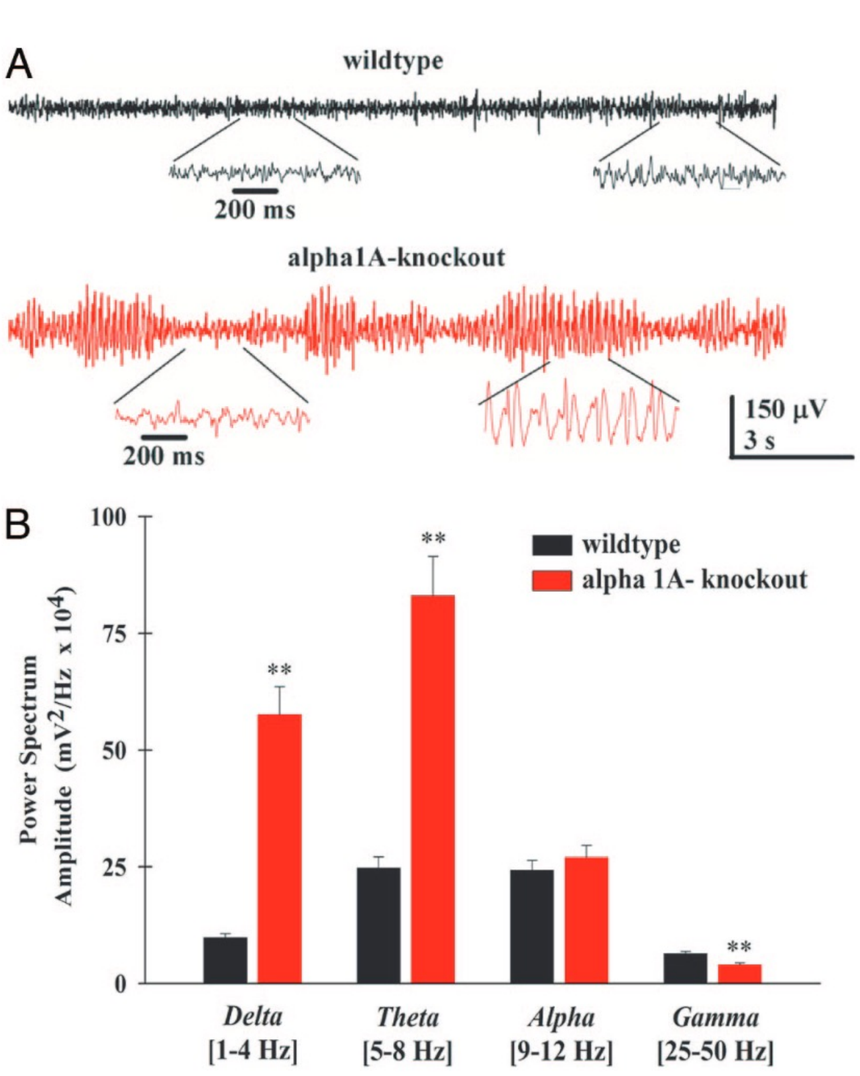
PNAS

γ-Band deficiency and abnormal thalamocortical activity in P/Q-type channel mutant mice

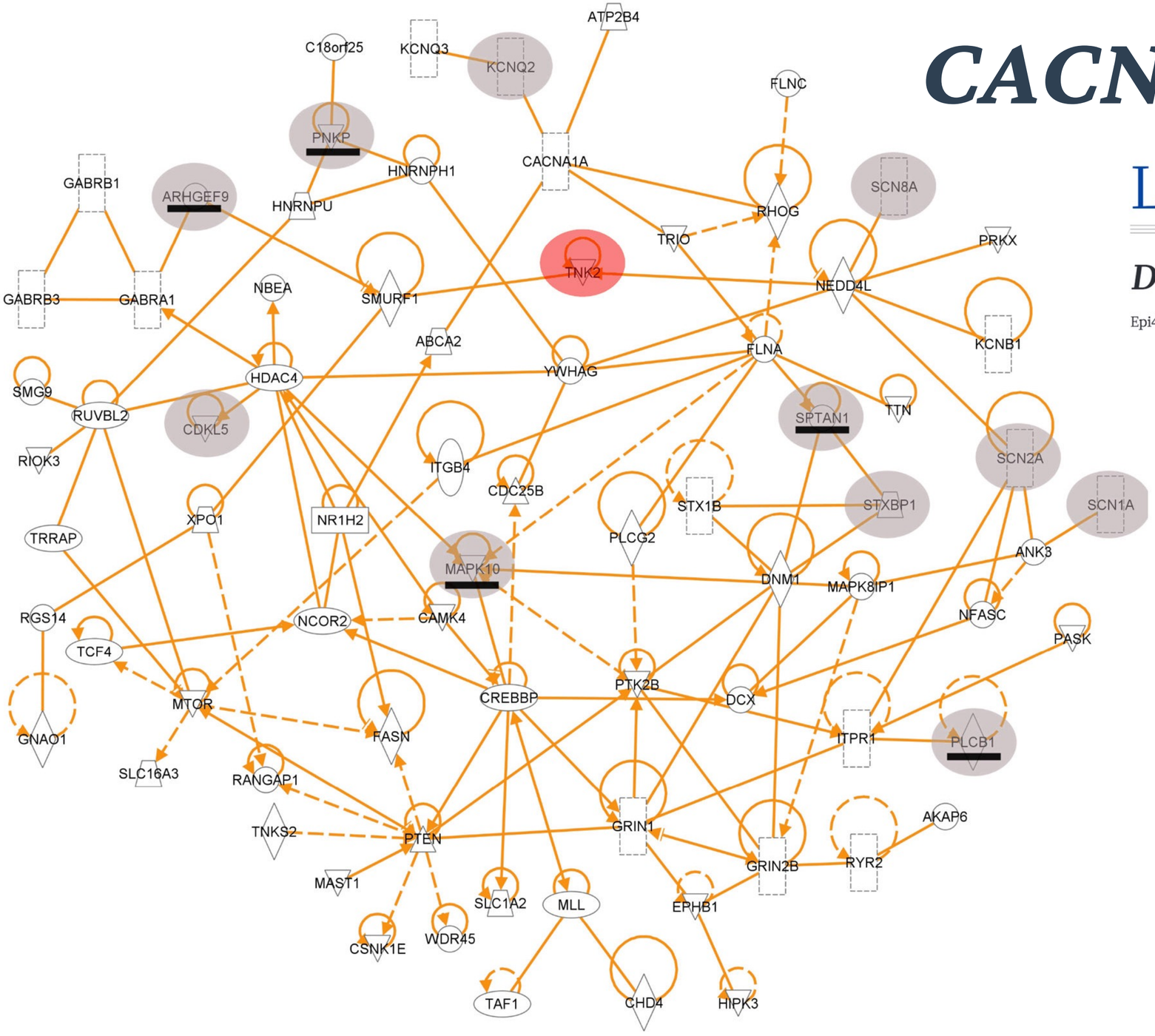
Rodolfo R. Llinás*†, Soonwook Choi*‡§, Francisco J. Urbano*¶, and Hee-Sup Shin†‡§

*Department of Physiology and Neuroscience, New York University School of Medicine, 550 First Avenue, New York, NY 10016; ‡Center for Neural Science, Korea Institute of Science and Technology, Seoul 136-791, Korea; §Department of Neuroscience, University of Science and Technology, Daejon 305-333, Korea; and ¶Laboratotio de Fisiología y Biología Molecular, Instituto de Fisiología, Biología Molecular y Neurociencias, Universidad de Buenos Aires–Consejo Nacional de Investigaciones Científicas y Técnicas de Argentina, Ciudad Universitaria, C1428EHA Buenos Aires, Argentina

Contributed by Rodolfo R. Llinas, September 4, 2007 (sent for review June 7, 2007)



CACNA1A and Epilepsy



LETTER

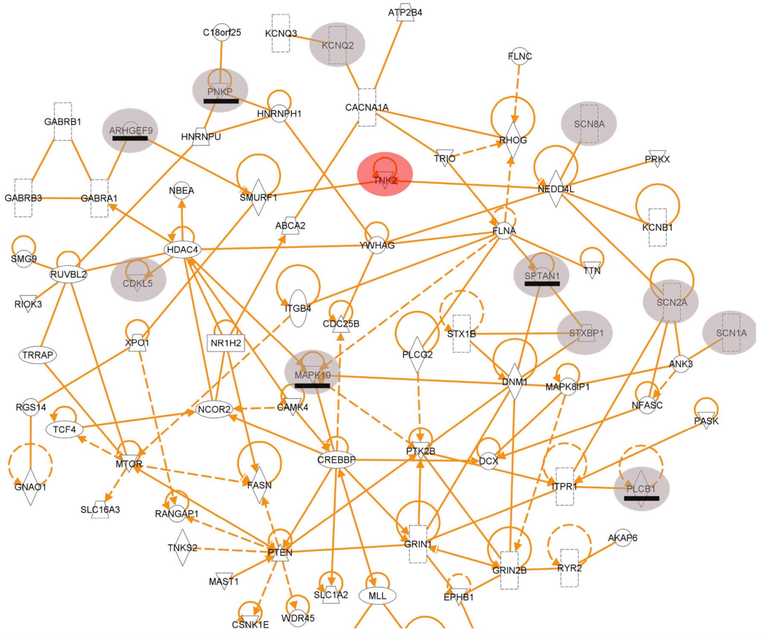
doi:10.1038/nat

De novo mutations in epileptic encephalopathies

Epi4K Consortium* & Epilepsy Phenome/Genome Project*

Detection of ***de novo missense mutations*** in the setting of severe pediatric syndromes with developmental delay and therapy resistant epilepsy (“Developmental and/or epileptic encephalopathies”)

CACNA1A and Epilepsy



CACNA1A-associated epilepsy: Electroclinical findings and treatment response on seizures in 18 patients

Marie Le Roux [a, *], Magalie Barth [b], Sophie Gueden [a], Patrick Desbordes de Cepoy [c], Alec Aeby [d], Catheline Vilain [e], Edouard Hirsch [f], Anne de Saint Martin [g], Vincent des Portes [h], Gaëtan Lesca [i], Audrey Riquet [j], Laurence Chaton [k], Nathalie Villeneuve [l], Laurent Villard [m, n], Claude Cances [o], Luc Valton [p, q], Florence Renaldo [r], Anne-Isabelle Vermersch [s], Cecilia Altuzarra [t], Marie-Ange Nguyen-Morel [u], Julien Van Gils [v], Chloé Angelini [v], Arnaud Biraben [w], Lionel Arnaud [x], Florence Riant [y], Patrick Van Bogaert [a, z]

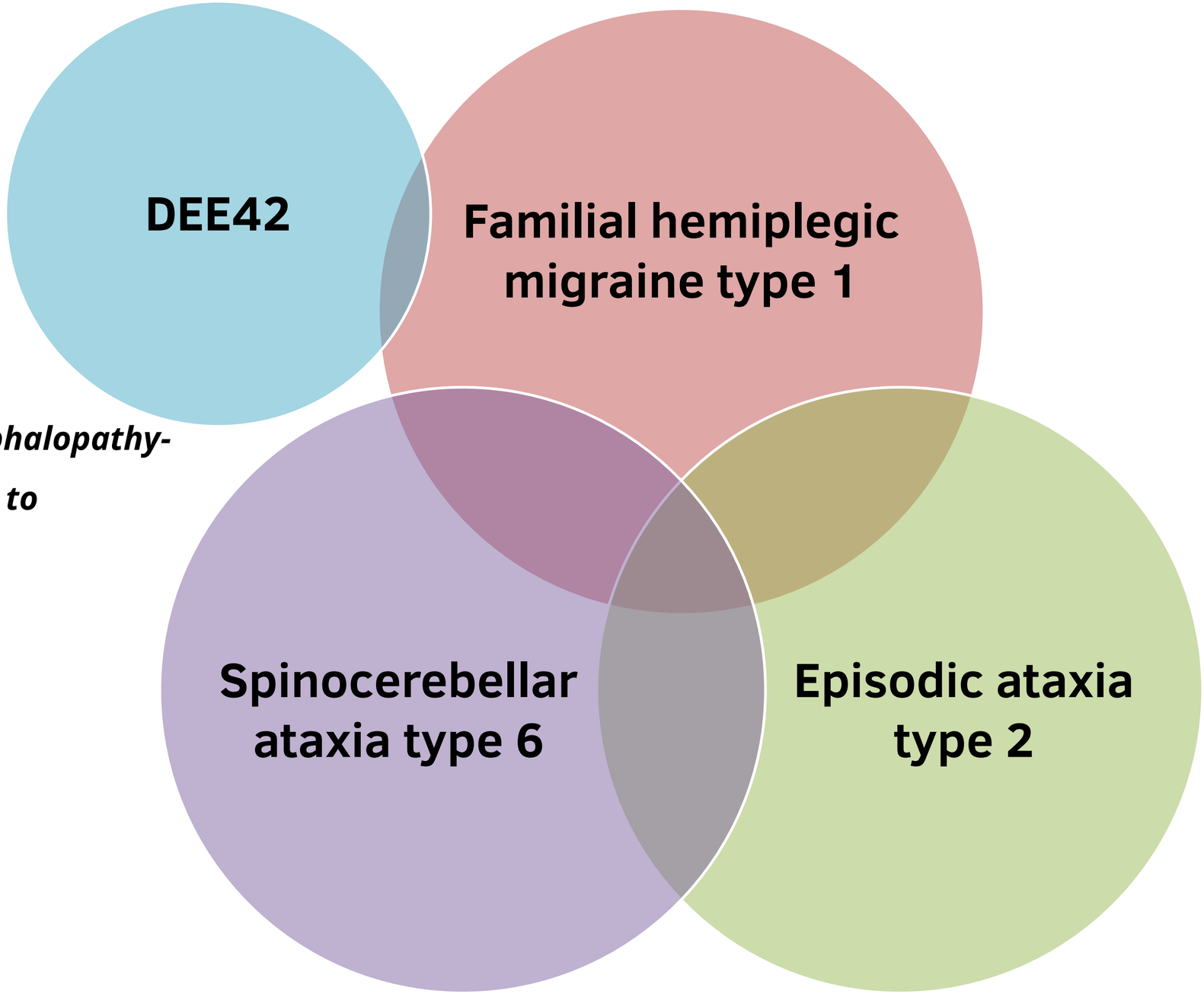
De Novo Mutations in *SLC1A2* and *CACNA1A* Are Important Causes of Epileptic Encephalopathies

Epi4K Consortium*

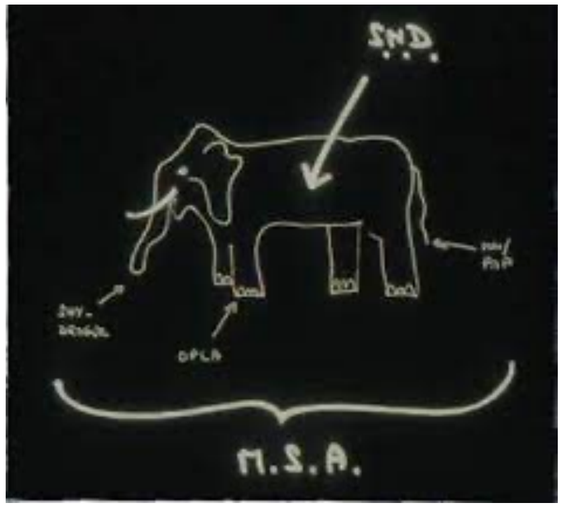
1. **In FHM1** seizures concomitant with severe migraine attacks accompanied by fever and coma state. Particularly frequent is the description of seizures following trivial head trauma in patients bearing the S218L mutation. Epileptic seizures in the intervals are rare.

2. **In EA2 families/LoF mutations** epilepsy is frequently described as “independent” manifestation usually occurring in children before the onset of paroxysmal ataxia. Absence epilepsy and its correlating EEG changes (3 Hz spike-waves complexes) are the most reported manifestation. Description of epilepsy/seizure in adults with EA2 phenotypes are rare. In adults focal seizures as well as well-defined localized EEG foci have been described.

3. ***De novo* missense *CACNA1A* mutations** recurrently cause severe early onset epilepsy which phenotypically may present as classical developmental-epileptic encephalopathies such as Dravet Syndrome, Lennox-Gastaut-Syndrome and epilepsy of infancy with migrating focal seizures. They often present with early episodes of status epilepticus, especially triggered by fever. Both novel missense mutations and well-known *CACNA1A* variants have been associated with these severe phenotypes, first of all the S218L. In some children both severe epilepsy and episodes of flaccid hemiparesis can be noticed, a phenotype that overlaps with earlier reports of FHM1 families with a particularly severe disease



The term "developmental and epileptic encephalopathy-42" (DEE42) (OMIM #601011) has been coined to describe such new disease entities.



Quinn N, JNNP 1989

Paroxysmal vertigo

Epilepsy

BPTI/PTU

Cerebellar ataxia

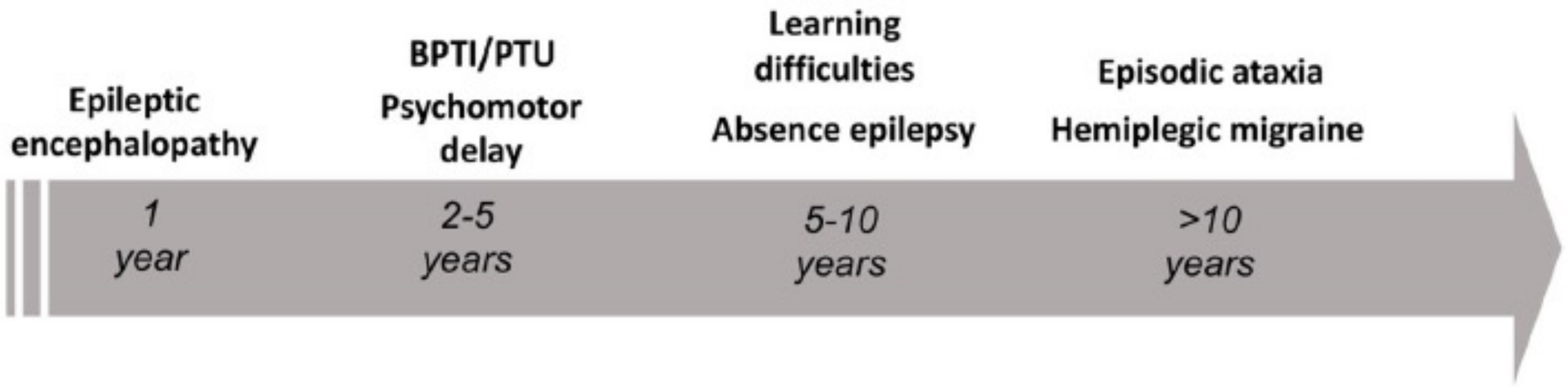
CACNA1A

migraine

psychomotor delay

From Genotype to Phenotype: Expanding the Clinical Spectrum of *CACNA1A* Variants in the Era of Next Generation Sequencing

*Elisabetta Indelicato and Sylvia Boesch**



Expanding the phenotype with age-dependent manifestations which precede the typical attacks of hemiplegic migraine or episodic ataxia

Question 3: When would you order a CACNA1A testing?

a. Recurring episodes of hemiplegic migraine

b.Absence epilepsy & chronic cerebellar signs

c. Epileptic encephalopathy

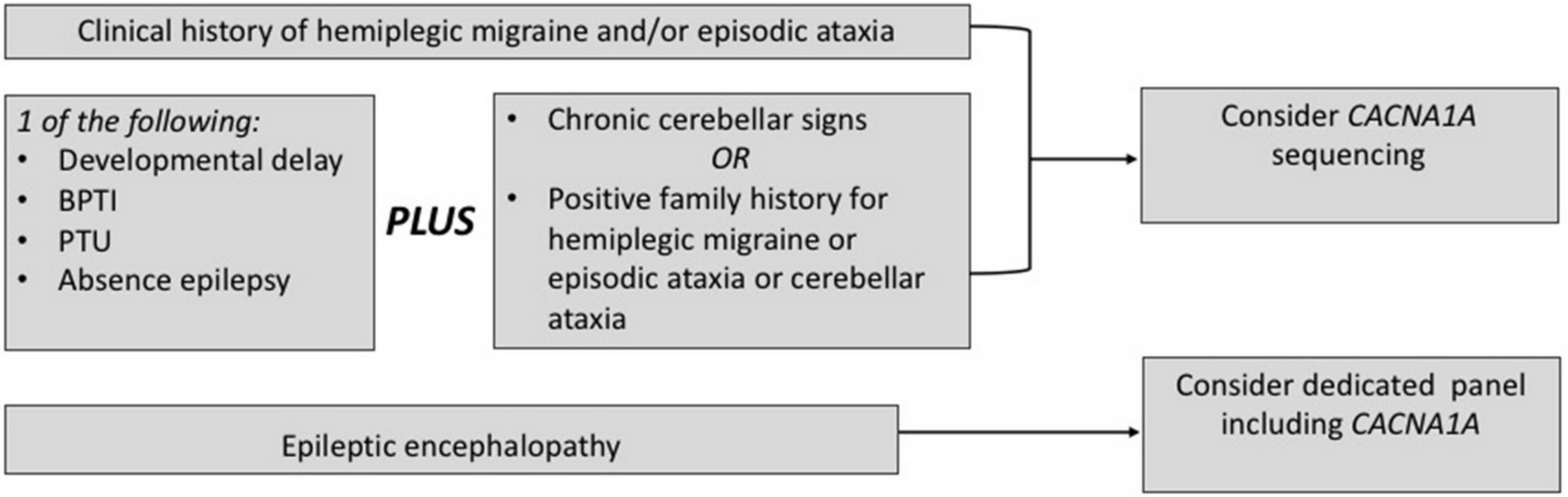
d. Recurring episodes of paroxysmal ataxia

Diagnosis

frontiers in Neurology

From Genotype to Phenotype: Expanding the Clinical Spectrum of *CACNA1A* Variants in the Era of Next Generation Sequencing

*Elisabetta Indelicato and Sylvia Boesch**



Therapy

A serendipitous discovery

Case Reports > Ann Neurol. 1978 Jun;3(6):531-7. doi: 10.1002/ana.410030614.

Effects of acetazolamide on myotonia

R C Griggs, R T Moxley 3rd, J E Riggs, W K Engel

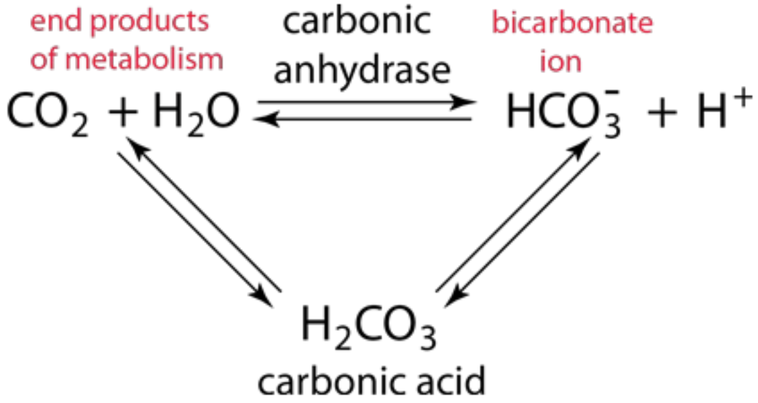
Case Reports > Neurology. 1983 Sep;33(9):1212-4. doi: 10.1212/wnl.33.9.1212.

Acetazolamide-responsive episodic ataxia syndrome

N L Zasorin, R W Baloh, L B Myers

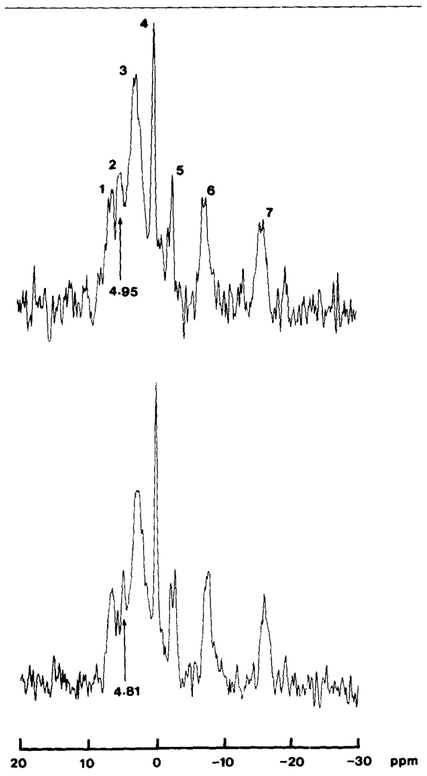
Acetazolamide is a carbonic anhydrase inhibitor. The inhibition of carbonic anhydrase in the kidney hampers the reabsorption of bicarbonate as well as of sodium and chloride, which goes along with excretion of water along with ions resulting in a diuretic effect.

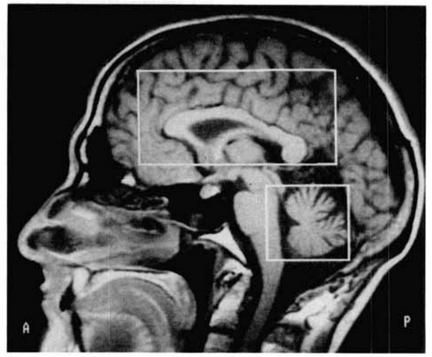
The consequence at a systemic level is a decrease in blood pressure, intracranial and intraocular pressures. Furthermore, bicarbonate excretion increases the pH of the blood as well as of the cerebrospinal fluid. The clinical application of acetazolamide span from the altitude sickness to glaucoma, intracranial hypertension to epilepsy



Familial Periodic Cerebellar Ataxia: A Problem of Cerebellar Intracellular pH Homeostasis

P. G. Bain, MA, MRCP,* M. D. O'Brien, MD, FRCP,* S. F. Keevil, MA, MSc, MIPSM,† and D. A. Porter, BSc‡





The beneficial effect of acetazolamide in *CACNA1A* disorders is believed to directly derive from the pH alterations elicited by the drug. Earlier studies applying phosphorous magnetic resonance spectroscopy in small non-genetically confirmed cohorts revealed that pH in the cerebellum is higher in patients compared to controls and normalizes upon treatment.

Changes in extra- and intracellular pH influences the potassium currents as well as the opening of Na^+ and Ca^{2+} channels and may thus mitigate the effect of an abnormal opening kinetics in the setting of *CACNA1A* mutations

This positive effect is not restricted to P/Q channel mutations, as ACZ improves the manifestations of further ion channel disorders, such as hypokalemic periodic paralysis.

Case Reports > Neurology. 1999 Jul 13;53(1):38-43. doi: 10.1212/wnl.53.1.38.

A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia

S Battistini [1], S Stenirri, M Piatti, C Gelfi, P G Righetti, R Rocchi, F Giannini, N Battistini, G C Guazzi, M Ferrari, P Carrera

Ten years of follow-up in a large family with familial hemiplegic migraine type 1: Clinical course and implications for treatment

Spinocerebellar ataxia type 6 with positional vertigo and acetazolamide responsive episodic ataxia

Joanna C Jen, Qing Yue, Juliana Karrim, Stanley F Nelson, Robert W Baloh

Case Reports > J Neurol Neurosurg Psychiatry. 2003 May;74(5):688-9. doi: 10.1136/jnnp.74.5.688.

Schizophrenia and episodic ataxia type 2

S Mechtcheriakov, M A Oehl, A Hausmann, W W Fleischhacker, S Boesch, M Schocke, E Donnemiller

Acetazolamide was primarily applied in EA2, but it has been also proven effective in the prevention of hemiplegic migraine (Battistini et al., 1999; Indelicato et al., 2017), as well as in the treatment of paroxysmal dizziness that predates chronic ataxia in SCA6 (Jen et al., 1998). Sparse reports suggested that acetazolamide may also mitigate some chronic features. Our recommendation is a trial of acetazolamide also in primary chronic courses, as a positive effect on fluctuations may also contribute to disease stabilization. In our clinical experience, acetazolamide contributed also to the stabilization of psychopathological status in *CACNA1A* patients with concomitant schizophrenia (Mechtcheriakov et al., 2003).

Usual daily dosage: 250 to 1000 mg (bid/tid).

Aminopyridines

Clinical Trial > Neurology. 2004 May 11;62(9):1623-5.
doi: 10.1212/01.wnl.0000125691.74109.53.

Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine

M Strupp [1], R Kalla, M Dichgans, T Freilinger, S Glasauer, T Brandt

Randomized Controlled Trial > Neurology. 2011 Jul 19;77(3):269-75.
doi: 10.1212/WNL.0b013e318225ab07. Epub 2011 Jul 6.

A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias

M Strupp [1], R Kalla, J Claassen, C Adrion, U Mansmann, T Klopstock, T Freilinger, H Neugebauer, R Spiegel, M Dichgans, F Lehmann-Horn, K Jurkat-Rott, T Brandt, J C Jen, K Jahn

RESEARCH

Fampridine and Acetazolamide in EA2 and Related Familial EA

A Prospective Randomized Placebo-Controlled Trial

Aminopyridines are potassium channel blockers which have been originally applied in the treatment of down-beat nystagmus (Strupp et al., 2003). The beneficial effect on nystagmus may derives from an increasing inhibitory firing of the Purkinje cells. An earlier report described a beneficial effect of 4-aminopyridines in 2 patients with EA2 who no longer responded to acetazolamide (Strupp et al., 2004). This observation was corroborated in an observational study (Strupp et al., 2004) as well as in a randomized, double-blind, placebo-controlled, crossover trial, comparing 4-aminopyridine and placebo (Strupp et al., 2011).

However, 4-aminopyridine is not licensed for other indications and its availability may be limited. Instead, the prolonged-release form fampridine (Fampyra, Biogen) holds an approval for the symptomatic treatment of gait disturbances in multiple sclerosis and has been recently investigated in a cross-over trial versus acetazolamide and placebo in a group of patients with episodic ataxia with and without confirmed *CACNA1A* mutation (Muth et al., 2021). Fampridine was effective in reducing the number of attacks to 63% compared to placebo. In comparison, acetazolamide appeared to be likely more effective (reduction of attacks to 52%), though it was, as expected, far less well tolerated.

Usual daily dosage: 10-20 mg/die

Migraine Prophylaxis

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Safety and efficacy of flunarizine in childhood migraine: 11 years' experience, with emphasis on its effect in hemiplegic migraine

BASHEER PEER MOHAMED[1] | PETER J GOADSBY[1,2] | PRAB PRABHAKAR[1]

Flunarizine in a non-selective Ca^{2+} channel blocker which is approved also in the treatment of common migraine and has been proven to be safe and effective in children (Peer Mohamed et al., 2012). Experimental evidence suggests that blocking of Ca^{2+} and Na^{+} currents induced by flunarizine raises the threshold for the cortical spreading depression phenomenon underlying migraine (Eikermann-Haerter et al., 2012; Ye et al., 2011). Flunarizine may be particularly beneficial in the treatment of migraine with aura and several reports confirmed its effectiveness in FHM1. Common side effects include sedation as well as depressive mood and weight gain. Flunarizine also increases the risk of developing a pharmacologically induced parkinsonism after long term use (Karsan et al., 2018).

Usual daily dosage: 10 mg/die (evening)

Original Article

Cephalalgia
An International Journal of Headache
International Headache Society

Ten years of follow-up in a large family with familial hemiplegic migraine type 1: Clinical course and implications for treatment

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102417715229
journals.sagepub.com/home/cep
SAGE

Topiramate is an established migraine prophylaxis which bears carbon anhydrase inhibition properties and has been reported to be effective in sparse reports in both FHM1 and EA2 (Gonzalez-Mingot et al., 2022; Indelicato et al., 2017). In the clinical experience of ours and others (Pelzer et al., 2013) topiramate is generally better tolerated in *CACNA1A* patients as in common migraineurs. Side effects of topiramate partly overlap with those of acetazolamide, due to clear overlapping mechanisms. Furthermore, topiramate may have central side effects such as impaired concentration, speech disorders and cognitive disturbances which are reversible upon drug withdrawal. Topiramate and to less extent acetazolamide also have an anorexiant effect which may be advantageous in the clinical practice.

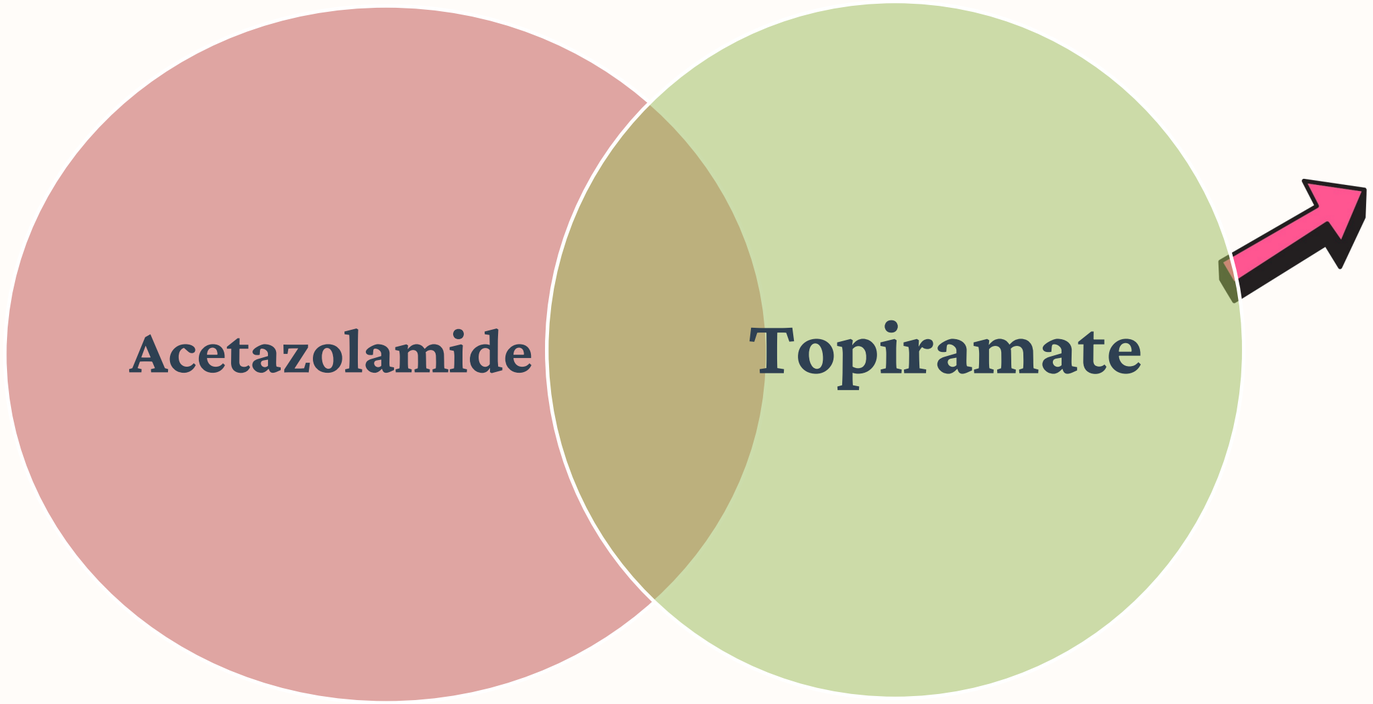
Usual daily dosage: 50-100 mg/die (bid)

Treatment of EA2/FHM1 spells

- Up to date, no specific treatment is available which effectively abates ataxia or hemiplegic migraine spells.
- One single report described abating aura manifestation upon administration of intranasal **ketamine** (Kaube et al., 2000). The mechanism of action is unclear and this finding has not been replicated.
- Two reports about **Verapamil** in non genetically confirmed FHM and SHM (Yu & Horowitz, 2001 & 2003)
- In the acute treatment of severe hemiplegic attacks with brain edema, **an empirical symptomatic management with corticosteroid or hypertonic saline** should be considered.
- The treatment of the migraine related headache relies on the same therapeutics available for common migraine, with a controversial **caveat for triptans**. Since triptans are powerful vasocontricting agents, their application in FHM was believed to possibly aggravate neurological deficits and leading to migrainous strokes. Currently, the US Food and Drug Administration approved package labelling states that triptans are contraindicated in patients with hemiplegic migraine. Some retrospective case series showed a safe profile for triptans in the treatment of hemiplegic migraine (Artto et al., 2007; Mathew et al., 2016).

Epilepsy

Data on therapy of *CACNA1A* related epilepsy are controversial and systematic analysis are lacking. Generally, early onset severe phenotypes present with the stigmata of a therapy refractory epilepsy, while later onset epileptic syndromes appear to be prone to a good seizure control upon classical antiepileptic drugs (AED) (Le Roux et al., 2021; Niu et al., 2022; Verriello et al., 2021).



- Approved AED
- Na^+ channel blocker, AMPA inhibition, GABA enhancer, weak carbonic anhydrase inhibition
- In current series (Le Roux 2021, Zhang 2020) add on therapy with topiramate beneficial concerning seizure control, better than ACZ

Epilepsy

Valproate → additional therapy described to be beneficial both in epilepsy and migraine (Niu et al., 2022; Pelzer et al., 2013; Zhang et al., 2020).

Ketogenic Diet → resulted in clinical improvement in 1 out of 4 patients (Le Roux et al., 2021)

Vagus nerve stimulation → yielded no benefit in 4 implanted patients (Le Roux et al., 2021) .

Pyridoxine → The singular description of a “dramatic” improvement of therapy resistant absence seizure to in one child (Du et al., 2017), was not replied up to now in further reports.

Question 4: 25 yo, 4-5 HM attacks per year, mostly “severe” attacks. Overweight. Which would be your treatment strategy?

a. No prophylaxis

b. 4-aminopyridin trial

c. Topiramate trial

d. Flunarizine trial

Compound	Dosage	Mechanisms of Action	Application
Acetazolamide	250-1000 mg/daily	carbon anhydrase inhibition	First line therapy for EA2, as well as prevention of paroxysmal manifestation in FHM1
4-aminopyridine	10-15 mg/daily	K^+ channel blocker	EA2, interictal nystagmus, episodic ataxia in other settings (e.g. SCA6)
Fampridine	20 mg/daily	K^+ channel blocker (prolonged release form of 4-AP)	as 4-AP
Flunarizine	5-10 mg/daily	Ca^{2+} channel blocker	First line migraine prophylaxis in FHM1
Topiramate	50-100 mg/daily	Na^+ channel blocker, AMPA inhibition, GABA enhancer, weak carbonic anhydrase inhibition	Overlap phenotypes episodic ataxia/hemiplegic migraine as well as overlap with epileptic manifestations

Open issues and future directions

- Age dependent manifestations: separate entities or phenotypical continuum ?

Open issues and future directions

- Therapeutic issues:
  - Management of chronic manifestations (cerebellar ataxia, psychiatric manifestations)
  - Effect of acetazolamide on early manifestations

Open issues and future directions

- Multicentric prospective studies, raising awareness, patient empowerment

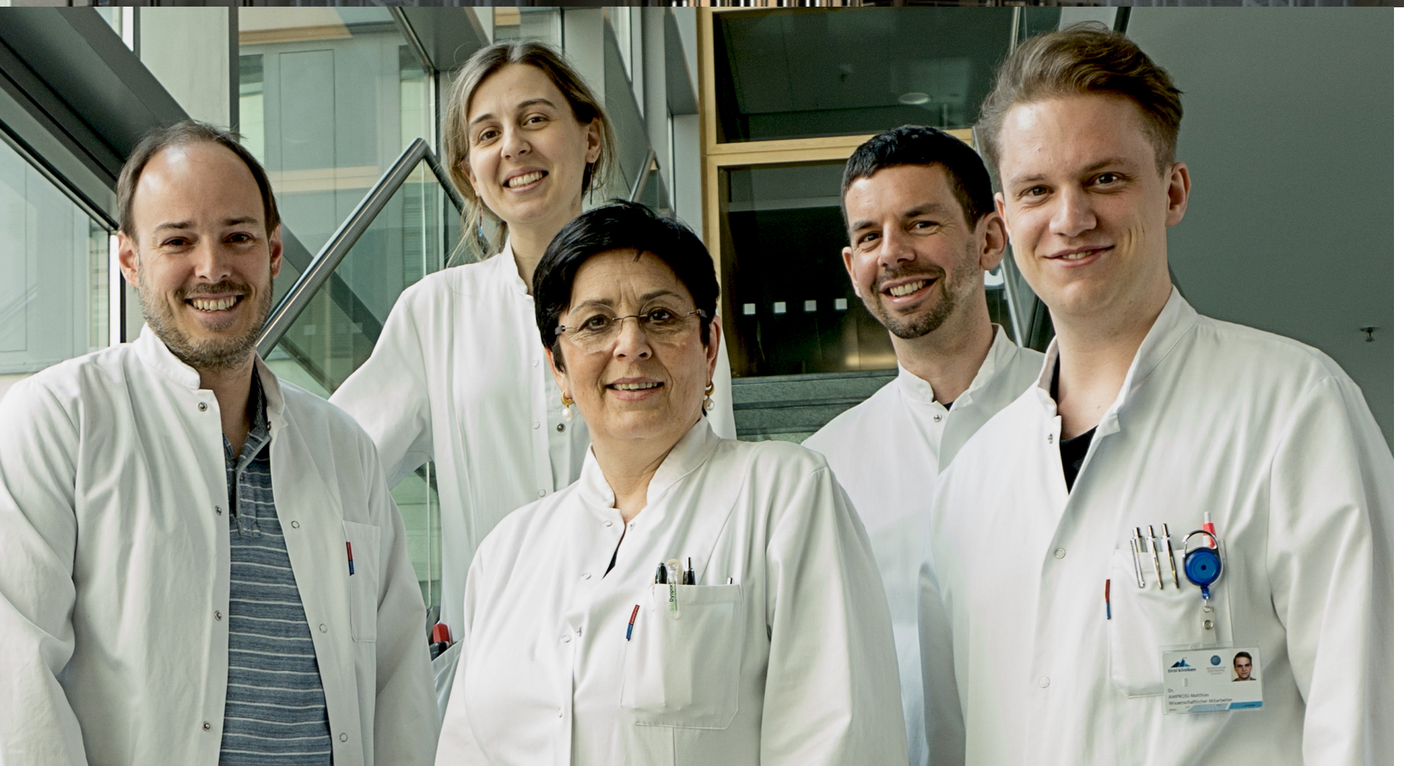
CACNA1A FOUNDATION

ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

https://www.cacna1a.org/

Take home messages

- Non polyglutamine *CACNA1A* mutations are associated with a broader phenotype than previously thought
- Especially neurodevelopmental phenotypes, neuropsychiatric manifestations and epilepsy emerged as relevant manifestations
- Despite poor clinical evidence from randomized trials, several compounds has a clinically proven efficacy in preventing hemiplegic migraine or episodic ataxia attacks.
- Evidence for a specific AED treatment or acute treatment of HM/EA is lacking



Center for Rare Movement Disorders
Department of Neurology
Medical University of Innsbruck
Austria

European Reference Network | Neurological Diseases (ERN-RND)

elisabetta.indelicato@i-med.ac.at

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

NEXT Webinar

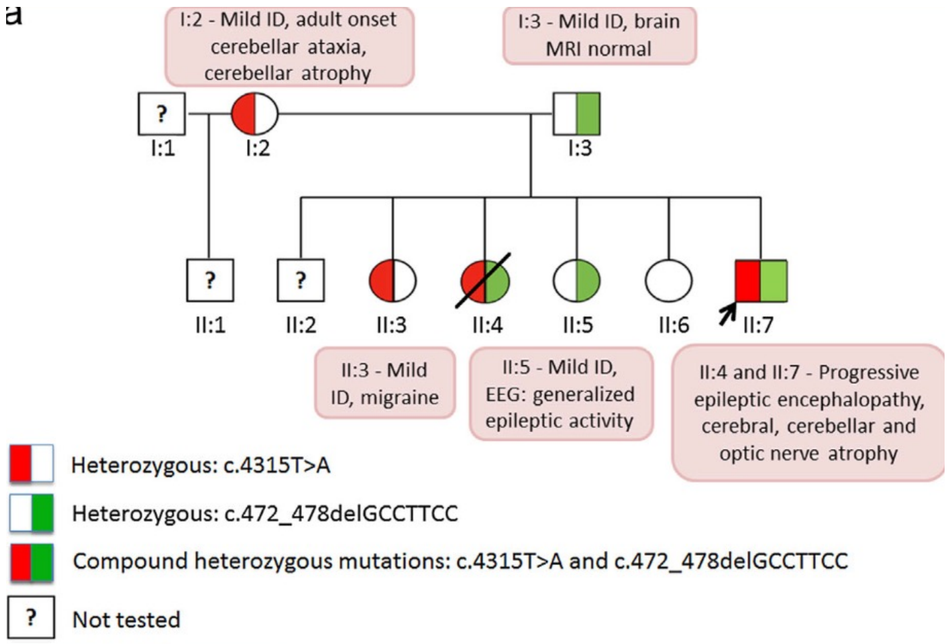
‘Krabbe disease – natural history and treatment options’

by Ingeborg Krägeloh-Mann & Samuel Gröschel,
University Hospital Tübingen, Germany

11. October 2022

Biallelic *CACNA1A* Mutations Cause Early Onset Epileptic Encephalopathy with Progressive Cerebral, Cerebellar, and Optic Nerve Atrophy

Karit Reinson,[1,2] Eve Õiglane-Shlik,[2,3] Inga Talvik,[2,3] Ulvi Vaher,[3] Anne Õunapuu,[4] Margus Ennok,[4,5] Rita Teek,[1,2] Sander Pajusalu,[1,6] Ülle Murumets,[1] Tiiu Tomberg,[7] Sanna Puusepp,[1] Andres Piirsoo,[6] Tiia Reimand,[1,2,6] and Katrin Õunap[1,2]*



ARTICLE

Check for updates

Biallelic variants in genes previously associated with dominant inheritance: *CACNA1A*, *RET* and *SLC20A2*

A. Arteche-López[1]✉, MI. Álvarez-Mora[1,2], MT. Sánchez Calvin[1], JM. Lezana Rosales[1], C. Palma Milla[1], M. J. Gómez Rodríguez[1], I. Gomez Manjón[1], A. Blázquez[3,4], A. Juarez Rufián[1], P. Ramos Gómez[1], O. Sierra Tomillo[1], I. Hidalgo Mayoral[1], R. Pérez de la Fuente[1], IJ. Posada Rodríguez[5], LI. González Granado[6,7], Miguel A. Martin[3,4], JF. Quesada-Espinosa[1] and M. Moreno-García[1]

Biallelic *CACNA1A* variants: Review of literature and report of a child with drug-resistant epilepsy and developmental delay

Vivien M. Y. Wong-Spracklen[1] | Anna Kolesnik[2] | Josefine Eck[2] | Saras Sabanathan[3] | Olivera Spasic-Boskovic[4] | Anna Maw[1] | Kate Baker[2,5]