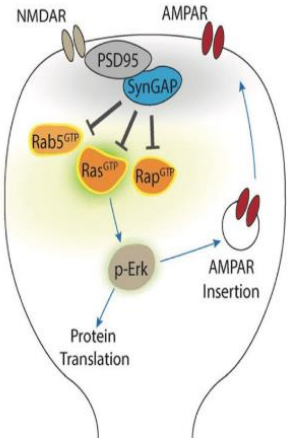
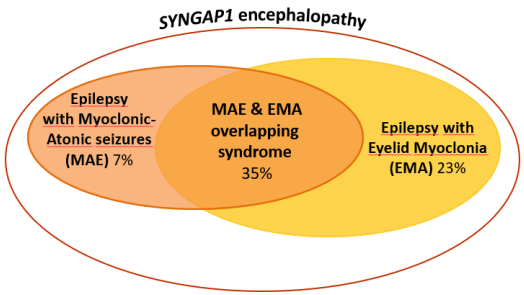
EpiCARE



SYNGAP1

From discovery to syndromology



PD Dr. med. Celina von Stülpnagel
Dr. Danique Vlaskamp

Webinar
15-07-2021

Outline

Part 1

- SYNGAP1 Protein Function
- EEG Findings in *SYNGAP1*
- Eating epilepsy

Part 2

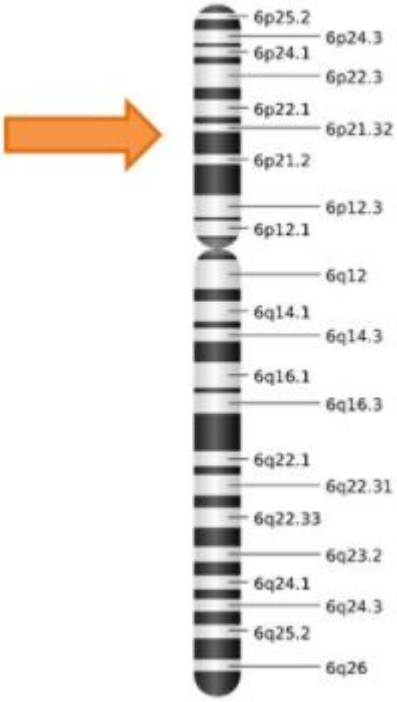
- *SYNGAP1* Syndromology

Part 3

- Treatment

QUESTIONS

SYNGAP1, a new gene identified



Background

- *SYNGAP1* codes for Synaptic Ras GTPase-activating protein 1 on short arm of Chr. 6 (6p21.3)
- Function of *SYNGAP1* contains regulation of the density of NMDA-rezeptors and AMPA-rezeptors.
- Important for cognition and functioning of synapses

Clement et al. Cell 2012; Komiyama et al. J. Neurosci 2002; Kim et al. J Neurosci 2003

Background

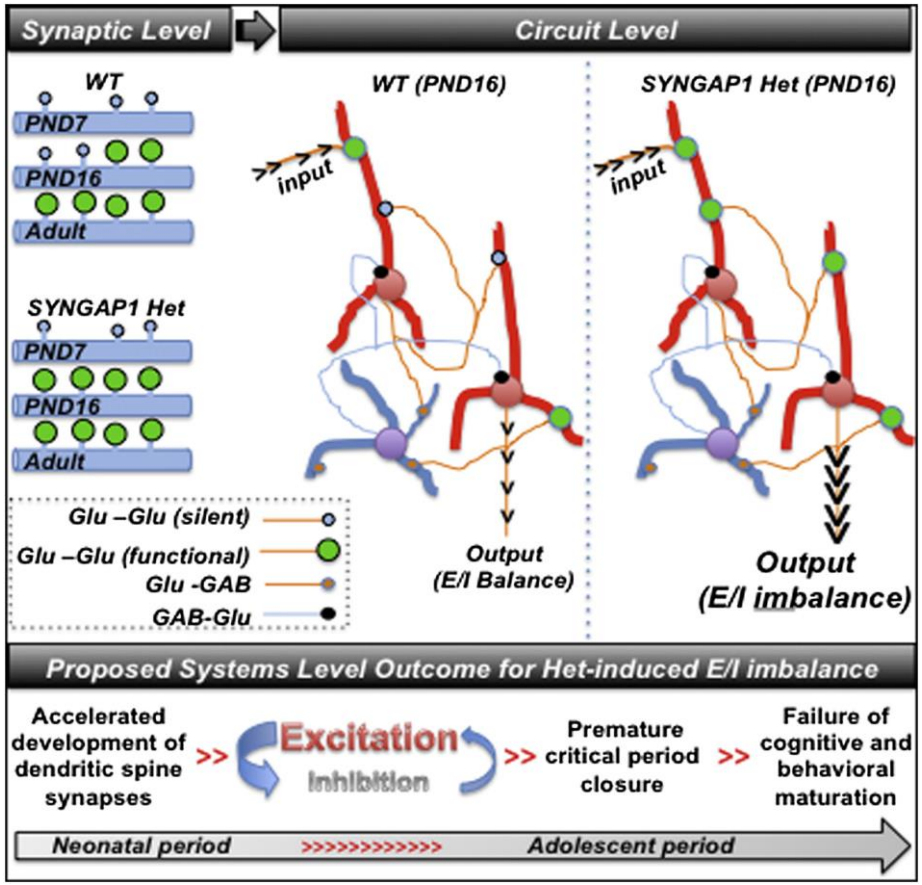
Mutations that cause intellectual disability (ID) and autism spectrum disorder (ASD) commonly in genes that encode for synaptic proteins.

SYNGAP1 mouse model of ID/ASD:

Dendritic spine synapses develop prematurely during the early postnatal period ➡ premature spine maturation dramatically enhanced excitability in the developing hippocampus ➡ emergence of behavioral abnormalities

Clement et al. Cell 2012

Background



Clement et al. Cell 2012

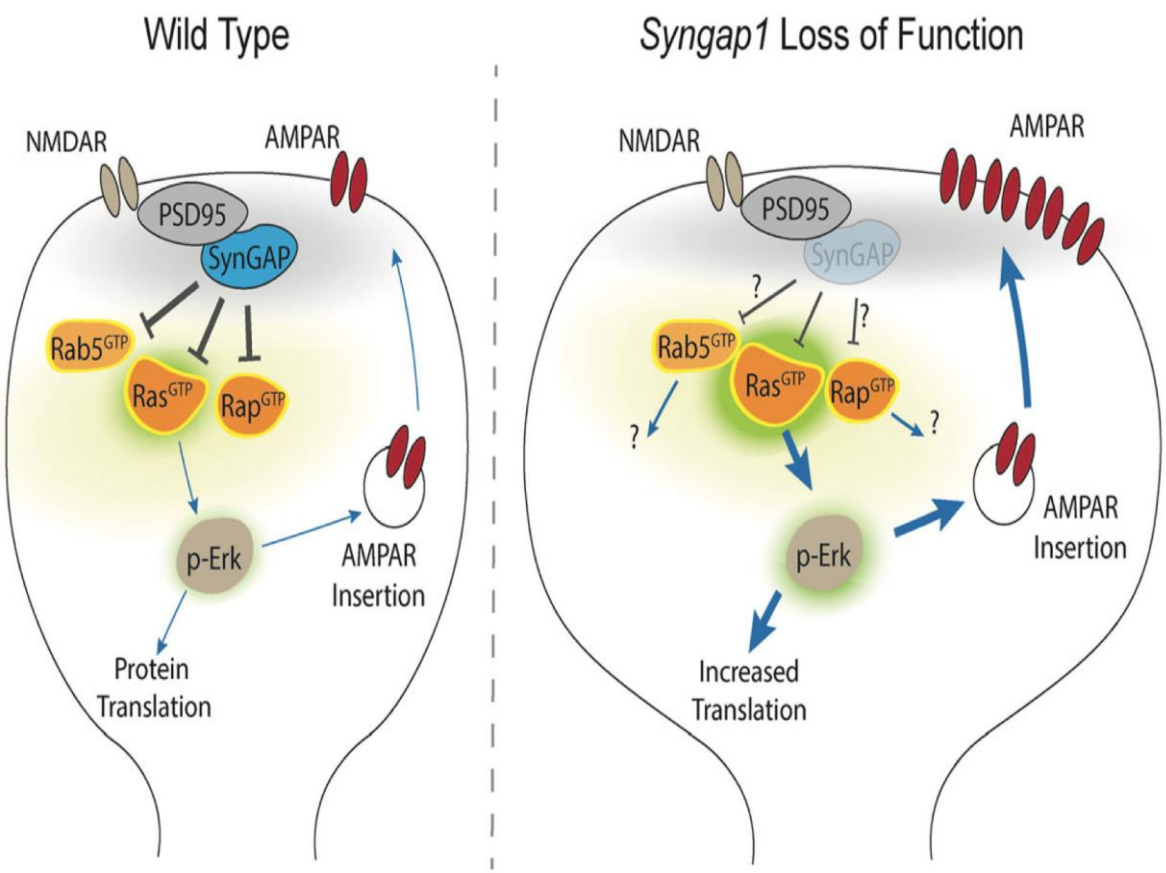
Background- Protein Function

Findings by the SYNGAP1 mouse model

- Pathogenic *SYNGAP1* mutations promote early maturation of hippocampal spine synapses
- Mutations lead to neonatal hyperactivity of the hippocampal trisynaptic circuit
- Mutations have greatest impact during the first 3 weeks of development
- Reversal of mutations in adults does not improve behavior and cognition

Clement et al. Cell 2012

Pathomechanism *SYNGAP1*



Weldon M, Kilinc M, Lloyd Holder J Jr, Rumbaugh G.
J Neurodev Disord. 2018 Feb 5;10(1):6.

SYNGAP1

- Mutation in *SYNGAP1* cause “autosomal dominant mental retardation type 5” (MRD5).
- *SYNGAP1* one of most important genes for intelligence impairment (ID), mutation are found in 0.7 - 1% of ID.

Muhia et al. Euro J Neurosci 2010; Aceti et al. Biol Psychiatry 2015; Vissers et al. Nat Genet. 2010; Rauch et al. Lancet 2012; Allen et al. Nature 2013

SYNGAP1

Mutations in SYNGAP1 in autosomal nonsyndromic mental retardation

Fadi F Hamdan [1], Julie Gauthier, Dan Spiegelman, Anne Noreau, Yan Yang, Stéphanie Pellerin, Sylvia Dobrzeniecka, Mélanie Côté, Elizabeth Perreau-Linck, Lionel Carmant, Guy D'Anjou, Eric Fombonne, Anjene M Addington, Judith L Rapoport, Lynn E Delisi, Marie-Odile Krebs, Faycal Mouaffak, Ridha Joober, Laurent Mottron, Pierre Drapeau, Claude Marineau, Ronald G Lafrenière, Jean Claude Lacaille, Guy A Rouleau, Jacques L Michaud, Synapse to Disease Group

Affiliations + expand

PMID: 19196676 PMCID: PMC2925262 DOI: 10.1056/NEJMoa0805392

Free PMC article

Erratum in

N Engl J Med. 2009 Oct 29;361(18):1814. Perreault-Linck, Elizabeth [corrected to Perreau-Linck, Elizabeth]

Abstract

Although autosomal forms of nonsyndromic mental retardation account for the majority of cases mental retardation, the genes that are involved remain largely unknown. We sequenced the autosomal gene SYNGAP1, which encodes a ras GTPase-activating protein that is critical for cognition and synapse function, in 94 patients with nonsyndromic mental retardation. We identifie de novo truncating mutations (K138X, R579X, and L813RfsX22) in three of these patients. In contrast, we observed no de novo or truncating mutations in SYNGAP1 in samples from 142 subjects with autism spectrum disorders, 143 subjects with schizophrenia, and 190 control subjects. These results indicate that SYNGAP1 disruption is a cause of autosomal dominant nonsyndromic mental retardation.

SYNGAP1- phenotypes

- Autism spectrum disorder (ASD)
- Developmental delay
- Acquired microcephaly
- Different epilepsies (including epileptic encephalopathy)
- …

Muhia et al. Euro J Neurosci 2010; Aceti et al. Biol Psychiatry 2015; Vissers et al. Nat Genet. 2010; Rauch et al. Lancet 2012; Allen et al. Nature 2013

SYNGAP1

Human Mutation
Variation, Informatics, and Disease
OFFICIAL JOURNAL HGV HUMAN GENOME VARIATION SOCIETY

Research Article

Mutations in *SYNGAP1* Cause Intellectual Disability, Autism, and a Specific Form of Epilepsy by Inducing Haploinsufficiency

Martin H. Berryer, Fadi F. Hamdan, Laura L. Klitten, Rikke S. Møller, Lionel Carmant, Jeremy Schwartzentruber, Lysanne Patry, Sylvia Dobrzeniecka, Daniel Rochefort ... See all authors

First published: 15 November 2012 | https://doi.org/10.1002/humu.22248 | Citations: 105

Communicated by Mark H. Paalman
Contract grant sponsors: Canadian Institute of Health Research; Réseau de Médecine Génétique Appliquée; Scottish Rite Charitable Foundation; FORGE Canada.

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ABSTRACT

De novo mutations in *SYNGAP1*, which codes for a RAS/RAP GTP-activating protein, cause nonsyndromic intellectual disability (NSID). All disease-causing point mutations identified until now in *SYNGAP1* are truncating, raising the possibility of an association between this type of mutations and NSID. Here, we report the identification of the first pathogenic missense mutations (c.1084T>C [p.W362R], c.1685C>T [p.P562L]) and three novel truncating mutations (c.283dupC [p.H95PfsX5], c.2212_2213del [p.S738X], and (c.2184del [p.N729TfsX31]) in *SYNGAP1* in patients with NSID. A subset of these patients also showed ataxia, autism, and a specific form of generalized epilepsy that can be refractory to treatment. All of these mutations occurred de novo, except c.283dupC, which was inherited from a father who is a mosaic. Biolistic transfection of wild-type *SYNGAP1* in pyramidal cells from cortical organotypic cultures significantly reduced activity-dependent phosphorylated extracellular signal-regulated kinase (pERK) levels. In contrast, constructs expressing p.W362R, p.P562L, or the previously described p.R579X had no significant effect on pERK levels. These experiments suggest that the de novo missense mutations, p.R579X, and possibly all the other truncating mutations in *SYNGAP1* result in a loss of its function. Moreover, our study confirms the involvement of *SYNGAP1* in autism while providing novel insight into the epileptic manifestations associated with its disruption.

SYNGAP1

SYNGAP1 Mutation in Focal and Generalized Epilepsy: A Literature Overview and A Case Report with Special Aspects of the EEG

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Neuropediatrics 2015;46:287–291.

Abstract

Background *SYNGAP1*, which encodes a RAS-GTPase-activating protein, is located on the short arm of chromosome 6. Heterozygous *SYNGAP1* gene mutations have been associated with autism spectrum disorders, delay of psychomotor development, acquired microcephaly, and several forms of idiopathic generalized epilepsy. Here, we report a patient with a new *SYNGAP1* stop mutation, and compare the phenotype with published cases with *SYNGAP1* mutations and epilepsy.

Patient This 15-year-old nondysmorphic girl with intellectual disability developed drop attacks at the age of 2 years, later clonic and clonic–tonic as well as myoclonic seizures predominantly during sleep. The epilepsy was well-controlled by valproic acid (VPA) and later on with levetiracetam. Electroencephalogram (EEG) showed a complete EEG-normalization with eye opening as well as photosensitivity. Magnetic resonance imaging was normal. Genetic analysis revealed a de novo heterozygous stop mutation (c.348C > A, p.Y116*) in exon 4 of the *SYNGAP1* gene.

Discussion The main clinical features of our patient (i.e., intellectual disability and idiopathic epilepsy) are compatible with previous reports on patients with SYNGAP1 mutations. The unusual feature of complete EEG normalization with eye opening has not been reported yet for this genetic abnormality. Furthermore, our case provides further support for efficacy of VPA in patients with *SYNGAP1* mutation–related epilepsy.

Keywords
- *SYNGAP1* new stop mutation
- photosensitivity
- EEG normalization by eye opening

Case 1

- Normal pregnancy and birth, as early development
- 2.5 y: delay in speech development
- 12 y: neuropsychological testing: learning disability; intellectual impairment and autistic characteristic signs
- 2 y: first epileptic seizure (drop attacks ➡ clonic and GTCS)
- AED: STM+ CLB ➡ STM; with 6 y.: VPA
- 11-13 y: +LEV; then all AED stopped

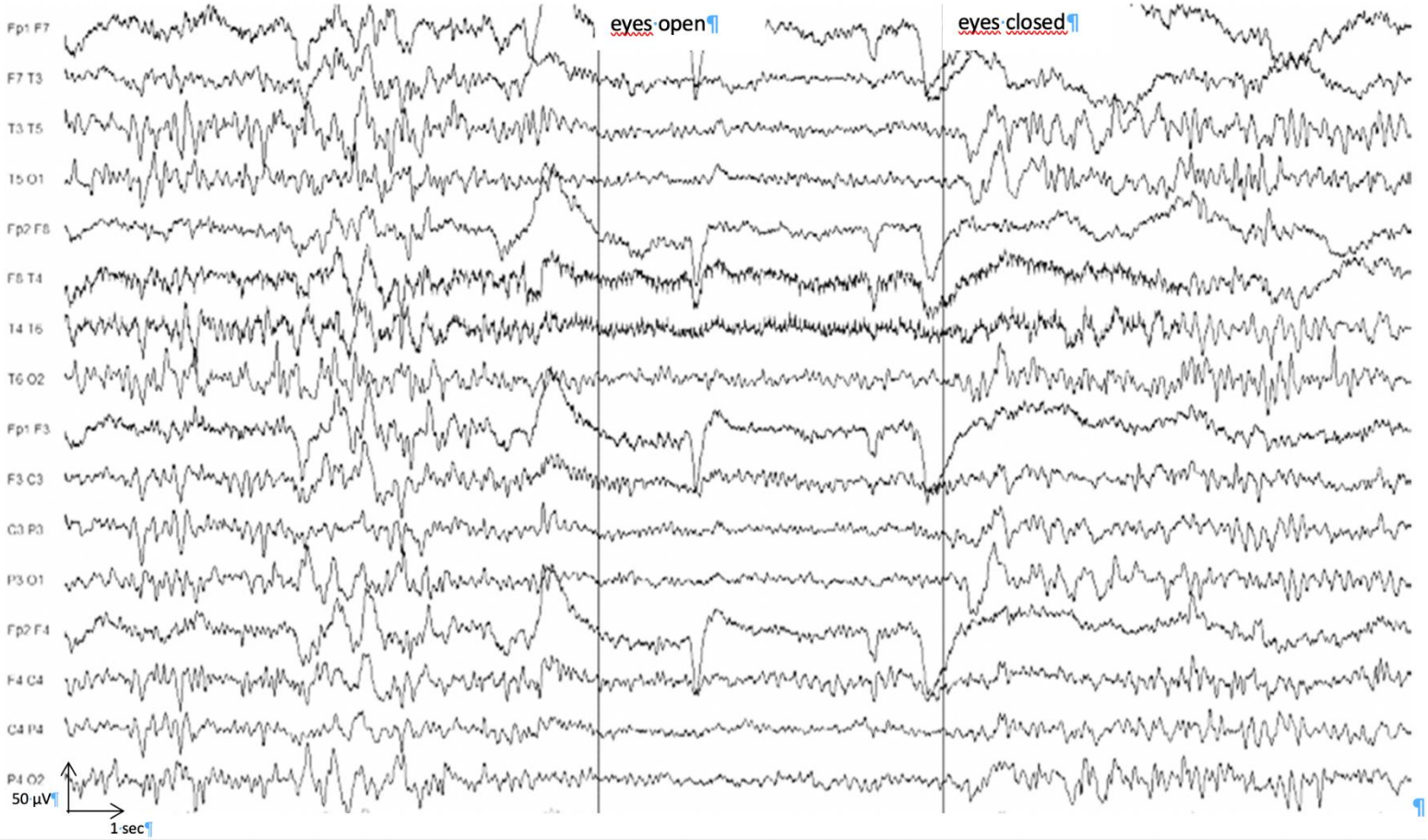
Case 1

- EEG:
  - without AED worse
  - 2 GTCS (one during fotostimulation)
  - new: normalization of paroxysmal activity by eye opening

- NGS-panel: heterozygote Mutation c.348C > A, p.Y116 in Exon 4 of *SYNGAP*1

Case 1

Figure 1: EEG with normalization of paroxysmal activity by eye opening



Case 1

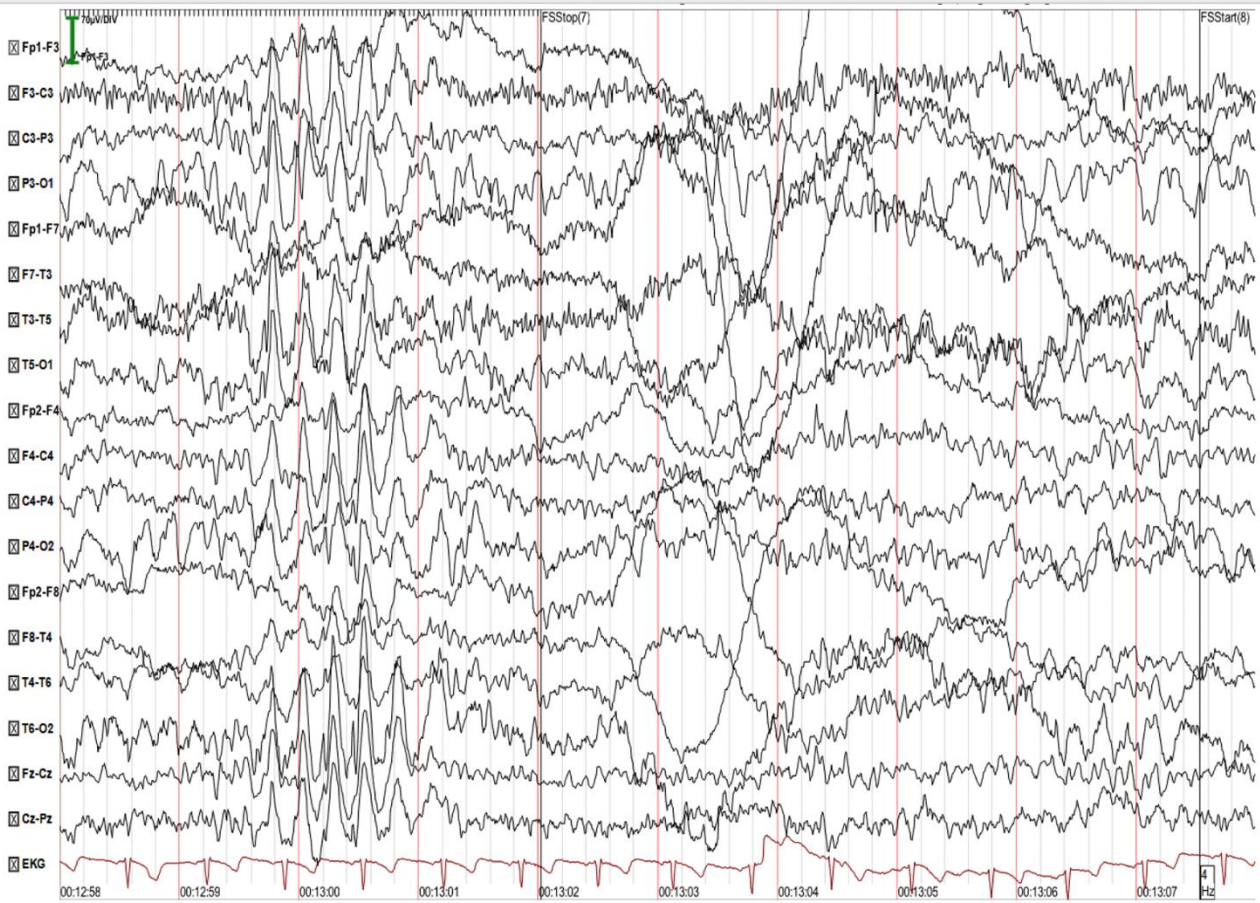


Figure 2 a: EEG under photostimulation

SYNGAP1

JMG Online First, published on March 17, 2016 as 10.1136/jmedgenet-2015-103451

ORIGINAL ARTICLE

Genetic and neurodevelopmental spectrum of *SYNGAP1*-associated intellectual disability and epilepsy

Cyril Mignot,[1,2,3] Celina von Stülpnagel,[4,5] Caroline Nava,[1,6] Dorothée Ville,[7] Damien Sanlaville,[8,9,10] Gaetan Lesca,[8,9,10] Agnès Rastetter,[6] Benoit Gachet,[6] Yannick Marie,[6] G Christoph Korenke,[11] Ingo Borggraefe,[12] Dorota Hoffmann-Zacharska,[13] Elżbieta Szczepanik,[14] Mariola Rudzka-Dybała,[14] Uluç Yiş,[15] Hande Çağlayan,[16] Arnaud Isapof,[17] Isabelle Marey,[1] Eleni Panagiotakaki,[18] Christian Korff,[19] Eva Rossier,[20] Angelika Riess,[21] Stefanie Beck-Woedl,[21] Anita Rauch,[22] Christiane Zweier,[23] Juliane Hoyer,[23] André Reis,[23] Mikhail Mironov,[24] Maria Bobylova,[24] Konstantin Mukhin,[24] Laura Hernandez-Hernandez,[25] Bridget Maher,[25] Sanjay Sisodiya,[25] Marius Kuhn,[26] Dieter Glaeser,[26] Sarah Wechuysen,[6,27] Candace T Myers,[28] Heather C Mefford,[28] Konstanze Hörtnagel,[29] Saskia Biskup,[29] EuroEPINOMICS-RES MAE working group, Johannes R Lemke,[30] Delphine Héron,[1,2,3,4] Gerhard Kluger,[4,5] Christel Depienne[1,6]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2015-103451).

For numbered affiliations see end of article.

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Received 12 August 2015
Revised 15 February 2016
Accepted 16 February 2016

ABSTRACT

Objective We aimed to delineate the neurodevelopmental spectrum associated with *SYNGAP1* mutations and to investigate genotype–phenotype correlations.

Methods We sequenced the exome or screened the exons of *SYNGAP1* in a total of 251 patients with neurodevelopmental disorders. Molecular and clinical data from patients with *SYNGAP1* mutations from other centres were also collected, focusing on developmental aspects and the associated epilepsy phenotype. A review of *SYNGAP1* mutations published in the literature was also performed.

Results We describe 17 unrelated affected individuals carrying 13 different novel loss-of-function *SYNGAP1* mutations. Developmental delay was the first manifestation of *SYNGAP1*-related encephalopathy; intellectual disability became progressively obvious and was associated with autistic behaviours in eight patients. Hypotonia and unstable gait were frequent associated neurological features. With the exception of one patient who experienced a single seizure, all patients had epilepsy, characterised by falls or head drops

INTRODUCTION

The human *SYNGAP1* gene on chromosome 6p21.3 encodes the synaptic RAS-GTPase-activating protein 1, a protein of the post-synaptic density (PSD) of glutamatergic neurons.[1 2] SYNGAP1 interacts with PSD95 (*DLG4*) and SAP102 (*DLG3*), and is able to positively or negatively regulate the density of N-Methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at the glutamatergic synapses and mediate signalling downstream of glutamate receptor activation.[3 4] While complete *Syngap1* deficiency in mice is lethal at early postnatal stages, heterozygous *syngap1* +/- mice are viable but show behavioural and cognitive disturbances.[5–8] *Syngap1* haploinsufficiency disrupts the excitatory/inhibitory balance in the developing hippocampus and cortex and results in accelerated glutamatergic synapse maturation. When this process occurs during critical developmental windows, it alters the synaptic plasticity necessary for

SYNGAP1

Results:

- Description of 17 non-related patients with 13 different new loss-of-function *SYNGAP1* mutations (8m/9f; mean age:10.3y. (3-29 y.))
- Developmental delay was first manifestation of *SYNGAP1*- Encephalopathy
- Intelligence impairment became more and more obvious and was related in 8 patients with autistic behavior.

SYNGAP1

Mutations all over the gene except for spliced 3‘ and 5‘ exons.

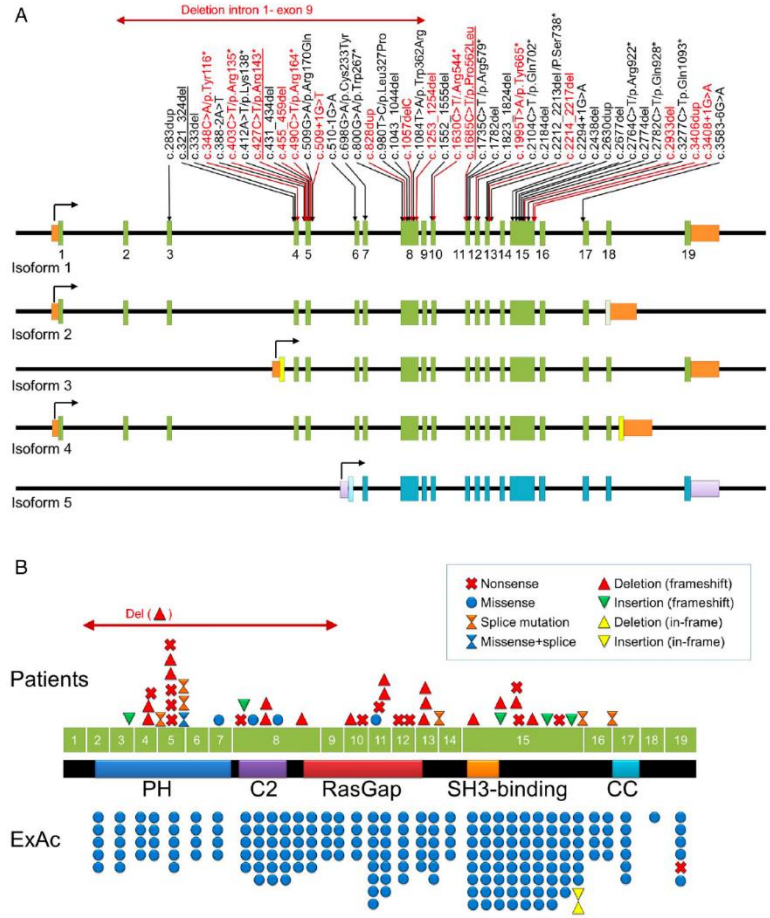

Figure 1 Summary of *SYNGAP1* mutations identified in this study and the literature. (A) Location of mutations on the different *SYNGAP1* isoforms. Mutations in red correspond to the patients identified in this study. Mutations in black correspond to previously published patients. Recurrent mutations are underlined. Isoform 1 corresponds to the longest isoform (NM_006772.2, N-terminus: SYNGAP A, C-terminus: SYNGAP α2); isoform 2 is obtained through alternative splicing of exons 18 and 19 and differs in its C-terminus (SYNGAP β: 1265–1343: RLMLVEEELR…NGEFRNTADH →SPSLQADAGGGGAAPGPPRHG); isoform 3 is obtained through alternative transcription start site usage involving an additional exon and differs in its N-terminus (SYNGAP B: 1–98: MSRSRASIHR…PVEGRPHGEH→MGLRPPTPSP…RRCSSCCFPG); isoform 4 is obtained through alternative splicing of exon 19 and differs in its C-terminus (SYNGAP γ: 1296–1343: ERQLPPLGPTNPRV…LQITENGEFRNTADH→LLIR). Isoform 5 corresponds to a rat isoform obtained through transcription start site usage (SYNGAP C); its existence in humans has not been demonstrated and therefore remains putative. Note that other isoforms, not represented on this schematic, have been described in rodents but not yet in humans, in particular isoform α

SYNGAP1

- Neurological assessment: often hypotonia and unsteady gait/ataxia
- MRI: either normal or unspecific findings

SYNGAP1

- Except for one patient all had epilepsy
- Seizure-Semiology: atonic or myoclonic seizures, (myoclonic) absences, and/or eyelid myoclonia
- Often trigger for seizures (n=7): PS (n=5) or Fixation OFF Sensitivity (FOS) (n=2), eating (1x).
- Severity of epilepsy did not correlate with occurrence of autistic features or the severity of cognitive impairment

SYNGAP1

Patients with mutations in Exon 4 - 5 more responsible to pharmaco-therapy than patients with mutations in Exon 8-15.

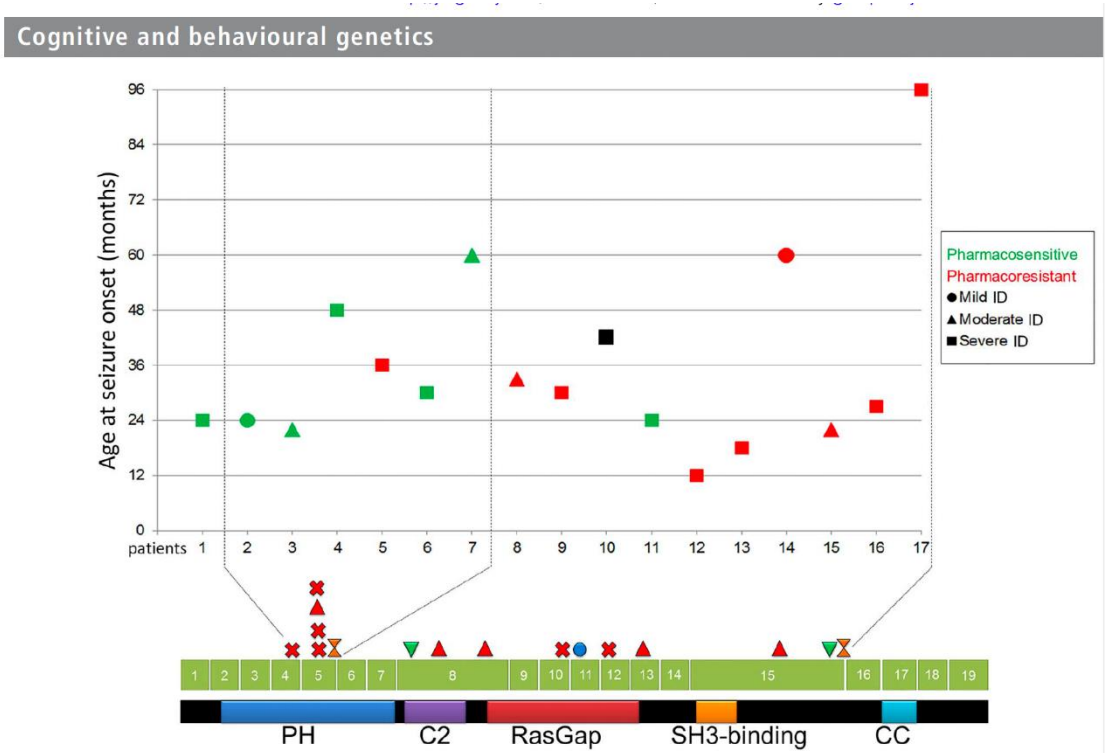

Figure 3 Graphical representation of clinical data (age at epilepsy onset, level of intellectual disability (ID) and pharmacoresistance or pharmacosensitivity) in our patients series. X-axis indicates the number of the patient, ordered by the position of the mutation on the gen patient 1, who corresponds to the patient with the intragenic *SYNGAP1* deletion. Y-axis indicates the age at seizure onset (in months). Th proportion of patients with mild (circles), moderate (triangles) and severe (squares) ID is not different in the pharmacoresistant (red) and i pharmacosensitive (green) groups. One patient (black square, patient 10), who had a single afebrile seizure and was thus not considered having epilepsy, was not considered for this analysis. The age at the first seizure is neither related to the resistance or sensitivity of the ep antiepileptic drug nor to the position on the gene. The age at seizure onset is not correlated with the level of ID. The mutations of most p with pharmacosensitive epilepsy cluster in exons 4–5, whereas those of most patients with pharmacoresistant epilepsy spread over exons 8 (p=0.001).

SYNGAP1

- in EEGs of 15 new patients two distinct EEG patterns
  - P1:rythmic posterior/diffuse delta waves (FOS)
  - P2: diffuse polyspike and wave discharges
- both triggered by eye closure
- FOS and eye closure main seizure triggers!

> Clin Neurophysiol. 2021 Apr;132(4):841-850. doi: 10.1016/j.clinph.2021.01.014. Epub 2021 Feb 3.

SYNGAP1-DEE: A visual sensitive epilepsy

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Affiliations + expand

PMID: 33639450 DOI: 10.1016/j.clinph.2021.01.014

Abstract

Objective: To further delineate the electroclinical features of individuals with SYNGAP1 pathogenic variants.

Methods: Participants with pathogenic SYNGAP1 variants and available video-electroencephalogram (EEG) recordings were recruited within five European epilepsy reference centers. We obtained molecular and clinical data, analyzed EEG recordings and archived video-EEGs of seizures and detailed characteristics of interictal and ictal EEG patterns for every patient.

Results: We recruited 15 previously unreported patients and analyzed 72 EEGs. Two distinct EEG patterns emerged, both triggered by eye closure. Pattern 1 (14/15 individuals) consisted of rhythmic posterior/diffuse delta waves appearing with eye-closure and persisting until eye opening (strongly suggestive of fixation-off sensitivity). Pattern 2 (9/15 individuals) consisted of diffuse polyspike-and-wave discharges triggered by eye closure (eye-closure sensitivity). Both patterns presented in 8/15. Including archived video-EEG clips of seizures from 9/15 patients, we analyzed 254 seizures. Of 224 seizures experienced while awake, 161 (72%) occurred at or following eye closure. In 119/161, pattern 1 preceded an atypical absence, myoclonic seizure or myoclonic absence; in 42/161, pattern 2 was associated with eyelid myoclonia, absences and myoclonic or atonic seizures.

Conclusions: Fixation-off and eye closure were the main triggers for seizures in this SYNGAP1 cohort.

Significance: Combining these clinical and electroencephalographic features could help guide genetic diagnosis.

SYNGAP1, eating epilepsy

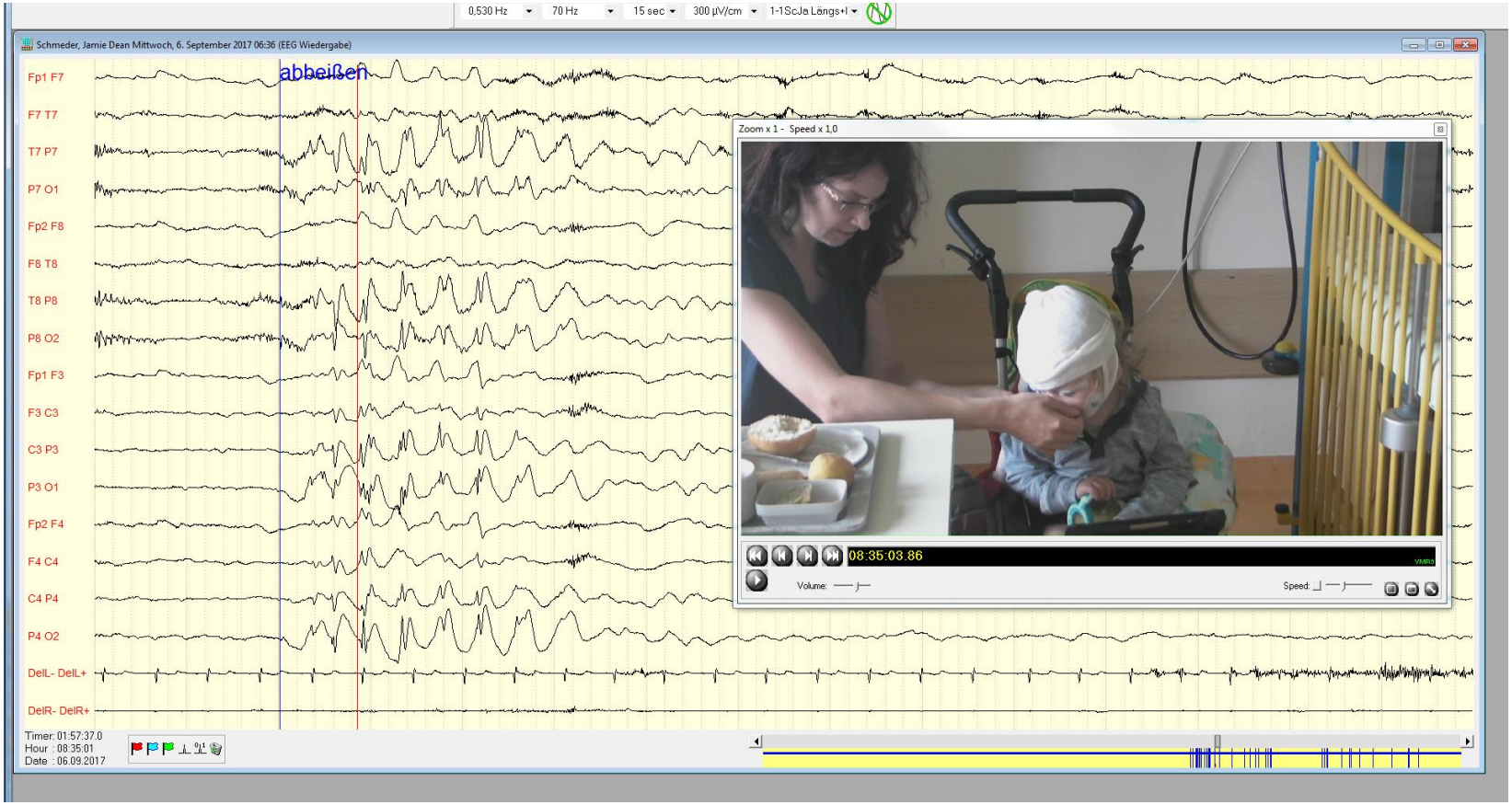
SYNGAP1 and eating epilepsy

- 1/17 patients in *SYNGAP1* publication with seizures triggered by chewing

- Further index patient:
  - 4-year-old boy, no family history
  - at 3 months: motoric developmental delay
  - At 2.5 yr. drop attacks
  - + eyelid myoclonia and atonic seizures
  - VPA → seizure reduction
  - cMRT: normal
  - Epilepsiepanel: *SYNGAP1* mutation

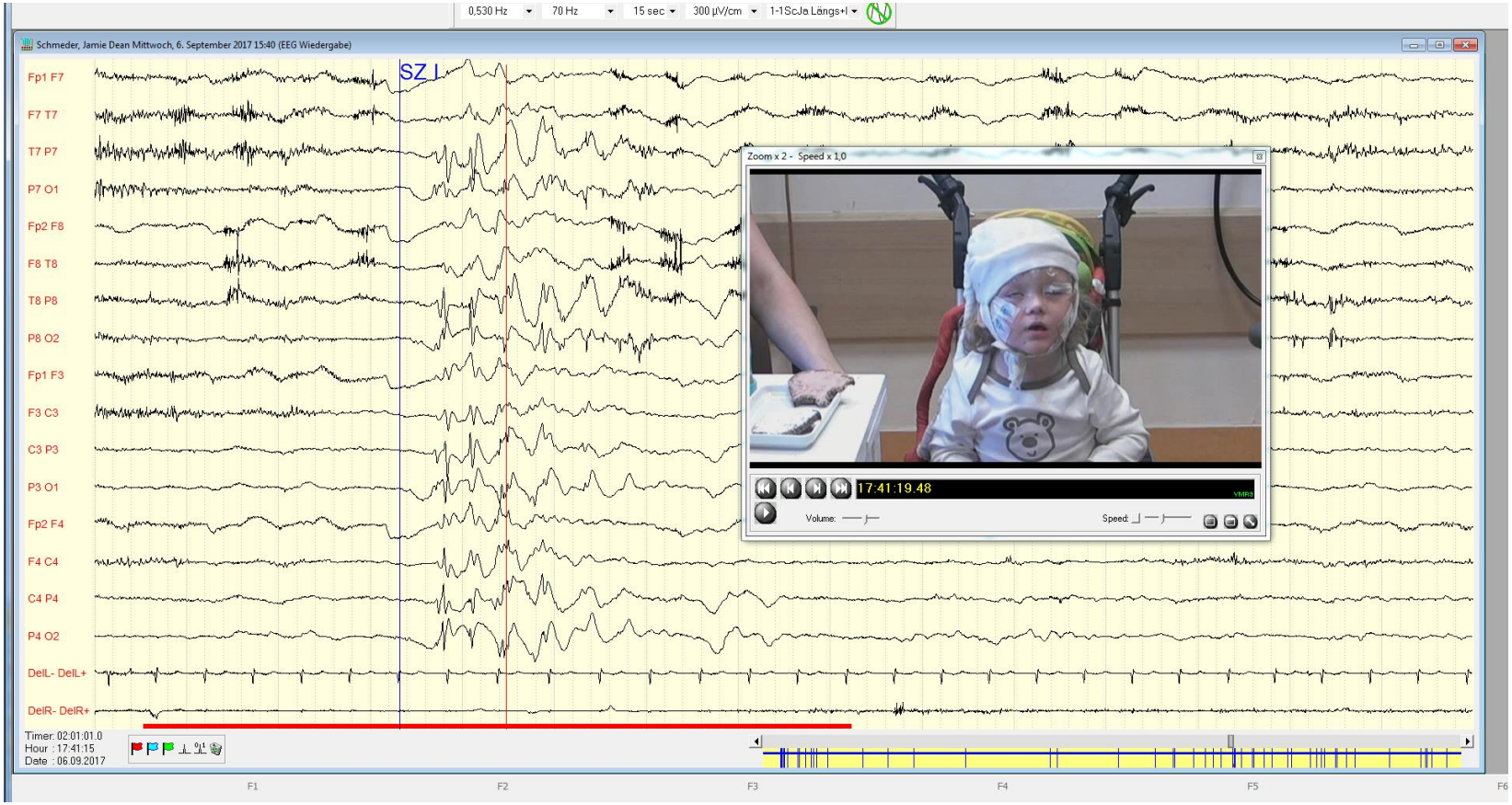
Mignot C et al J Med Genet 2016

SYNGAP1 and eating epilepsy



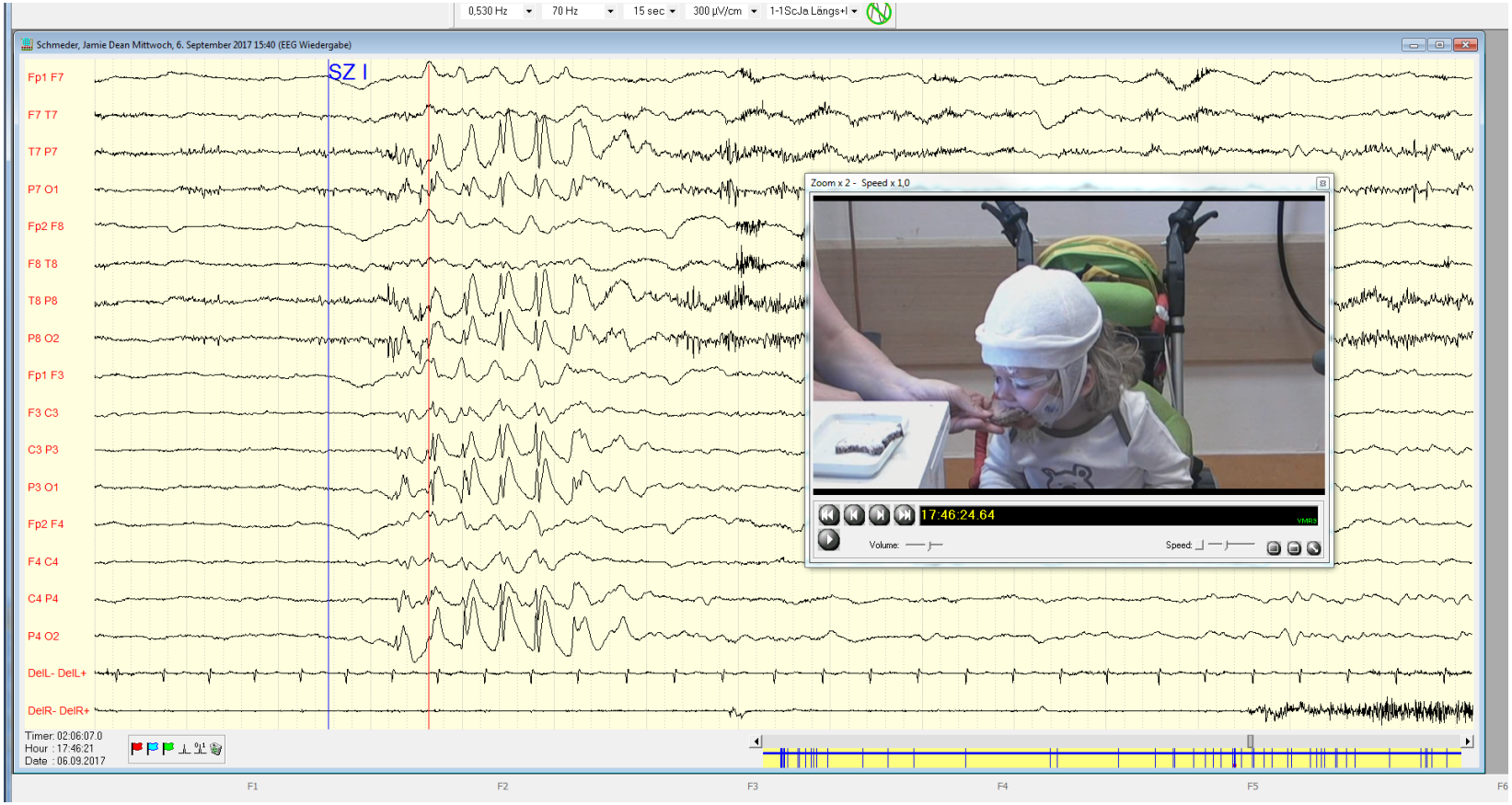
von Stülpnagel C et al Seizure 2019

SYNGAP1 and eating epilepsy



von Stülpnagel C et al Seizure 2019

SYNGAP1 and eating epilepsy



von Stülpnagel C et al Seizure 2019

SYNGAP1 and Eatingepilepsy

von Stülpnagel C et al Seizure 2019

SYNGAP1 and eating epilepsy

Eating seizures: bilateral eyelid myoclonia, upward starring, followed by short tonic head propulsions/thoraxpropulsions and sometimes short tonic extensions of head and neck

EEG:

- similar focal EEG-pattern with 1-5 sec. high amplitude, irregular 3/sec spike-wave complexes with start from left temporo-occipital, rights temporo-occipital or bi occipital/ temporo-occipital

SYNGAP1 and eating epilepsy

Seizure: European Journal of Epilepsy 65 (2019) 131–137

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

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

Chewing induced reflex seizures ("eating epilepsy") and eye closure sensitivity as a common feature in pediatric patients with *SYNGAP1* mutations: Review of literature and report of 8 cases

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SYNGAP1 encephalopathy

A distinctive generalized developmental and epileptic encephalopathy

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Neurology® 2019;92:e96-e107. doi:10.1212/WNL.0000000000006729

SYNGAP1 and eating epilepsy

Retrospective study with 8 *SYNGAP1* patients and eating epilepsy (EE):

- 4 girls (age: 4–14 yr.; mean 6.9 yr.; median: 5.75 yr.)

- all severe language developmental delay
- cognition: (mean age:5.6 yr)
  - moderate-severely impaired in 6
  - 1 patient each with moderate or severe impairment.

- first seizure around 3.5 yr. (1 -7.5 yr.)

SYNGAP1 and Eatingepilepsy

EE:

- main seizure type: bilateral eyelidmyoclonia (7 pat.)
- with additional short absences with 3 pat.
- subtle atonic components in further 3 pat.
- 1 pat. atonic headdrops
- 1 pat. besides eyelidmyoclonia short retropulsive movements of head and neck and atonic phase at the end.
- 1 pat. tonic head extensions more to the right side and upward gaze for 7 sec. (eating as toddler) and as child eyelidmyoclonia with oral stimulation.

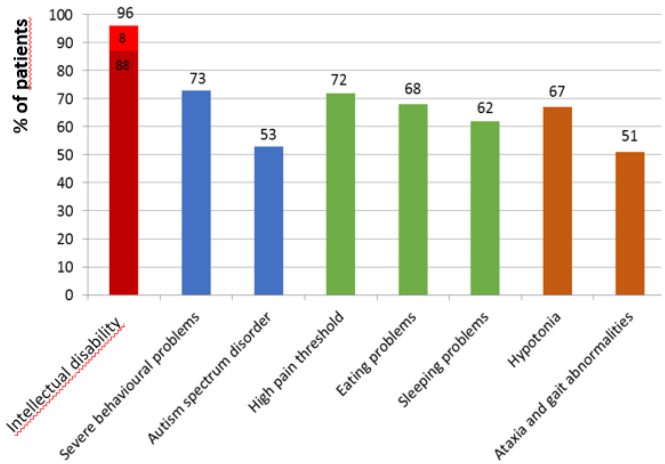
SYNGAP1 and Eatingepilepsy

von Stülpnagel C et al Seizure 2019

SYNGAP1 and Eatingepilepsy

EEG:

- 1-5 sec. high amplitude, irregular 3/sec spike-wave complexes with beginning left temporo-occipital, right temporo-occipital or bi-occipital/ temporo-occipital
- spike-wave complexes bioccipital and generalizied
- multifokale irregular spikes and polyspikes right fronto-temporal and left temporo-occipital (Pat#2)



SYNGAP1, the broader clinical picture

ARTICLE OPEN ACCESS

SYNGAP1 encephalopathy

A distinctive generalized developmental and epileptic encephalopathy

Danique R.M. Vlaskamp, MD, Benjamin J. Shaw, MD, Rosemary Burgess, PhD, Davide Mei, MSc, Martino Montomoli, MD, Han Xie, PhD, Candace T. Myers, PhD, Mark F. Bennett, PhD, Wenshu XiangWei, BSc, Danielle Williams, BappSc, Saskia M. Maas, MD, Alice S. Brooks, MD, Grazia M.S. Mancini, MD, PhD, Ingrid M.B.H. van de Laar, MD, Johanna M. van Hagen, MD, PhD, Tyson L. Ware, FRACP, Richard I. Webster, MBBS, MSc, FRACP, Stephen Malone, FRACP, Samuel F. Berkovic, MD, FRS, Renate M. Kalnins, MBBS, Federico Sicca, MD, G. Christoph Korenke, MD, PhD, Conny M.A. van Ravenswaaij-Arts, MD, PhD, Michael S. Hildebrand, PhD, Heather C. Mefford, MD, PhD, Yuwu Jiang, MD, PhD, Renzo Guerrini, MD, FRCP, and Ingrid E. Scheffer, MBBS, PhD, FRACP

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Neurology® 2019;92:e96-e107. doi:10.1212/WNL.0000000000006729

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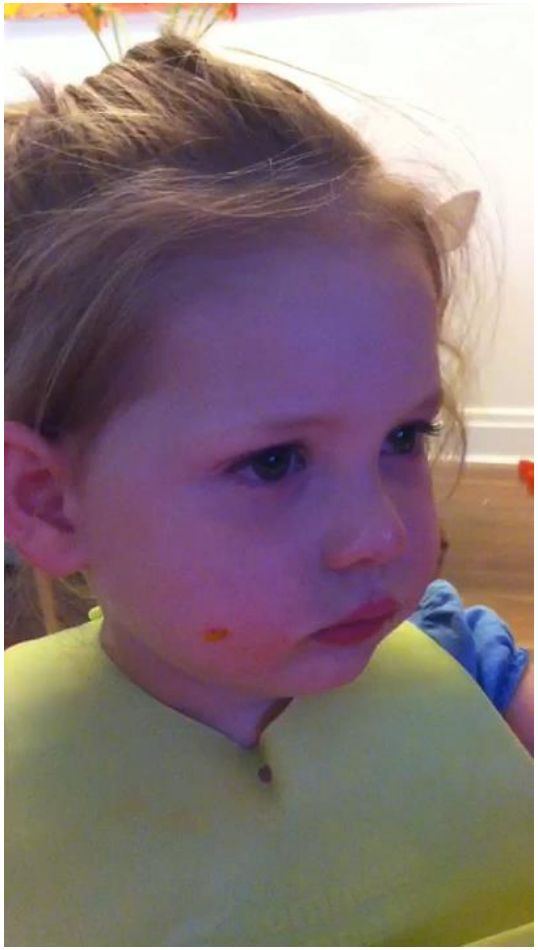
UNIVERSITY of WASHINGTON

Inspiration for study



Patient recruitment (n = 66)

- Investigators' practices and research databases (n = 39)




- Facebook (n = 27)

Bridge the Gap
SYNGAP
Education & Research Foundation

Patient cohort (n = 57)

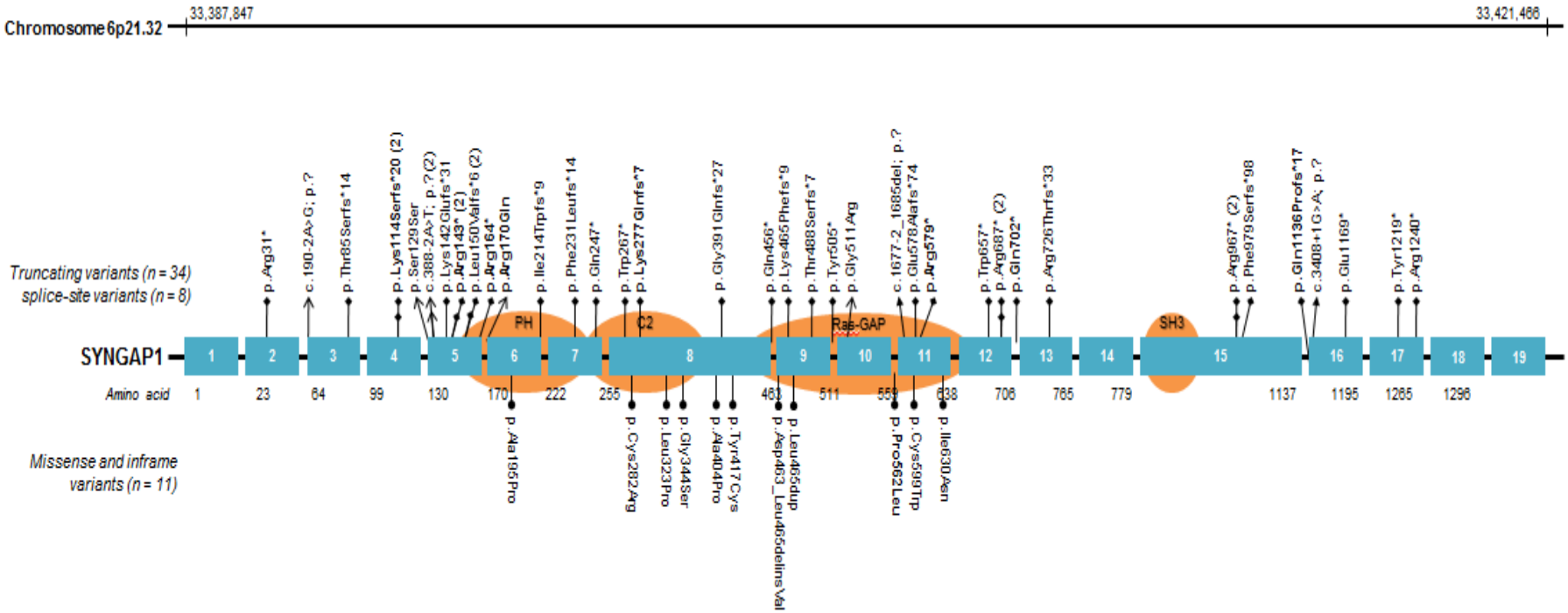
57 with pathogenic mutation

53% male

Median age 8 yrs (range 18 m – 33 yrs)

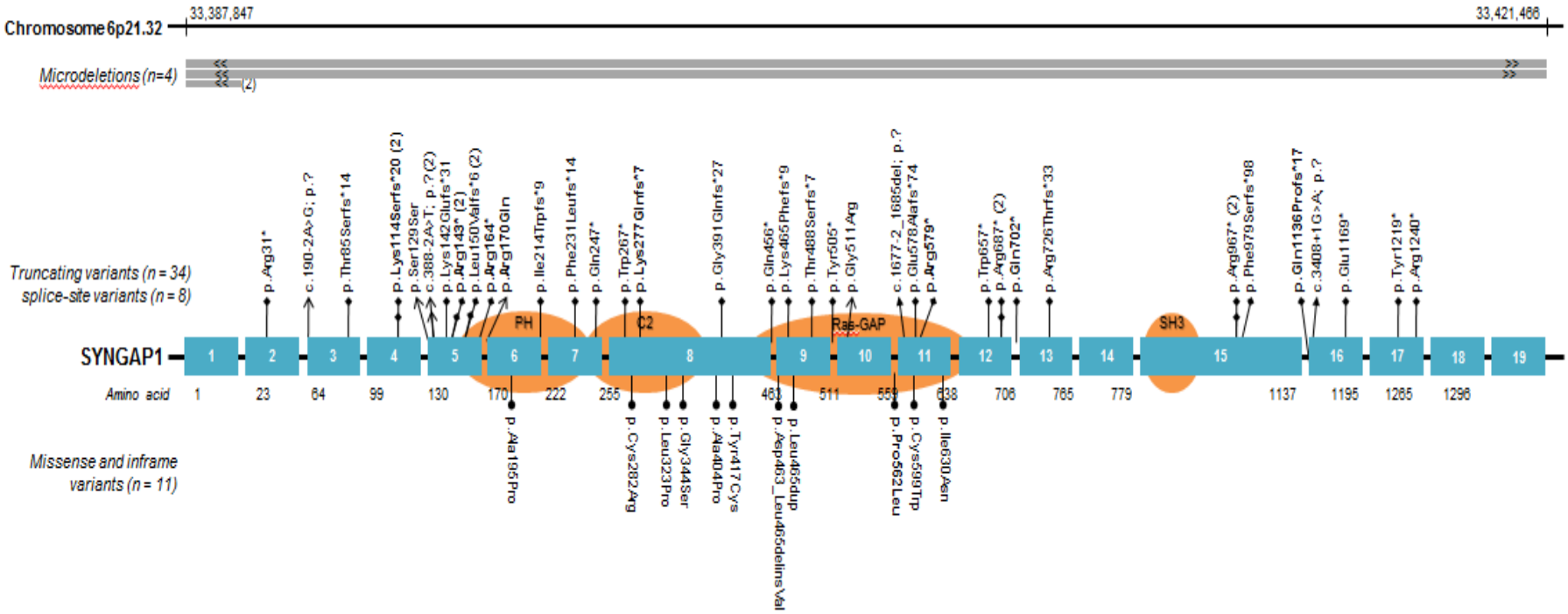
46 novel patients, 35 novel unique mutations

SYNGAP1 genotypes



Both truncating and missense variants were identified

SYNGAP1 genotypes



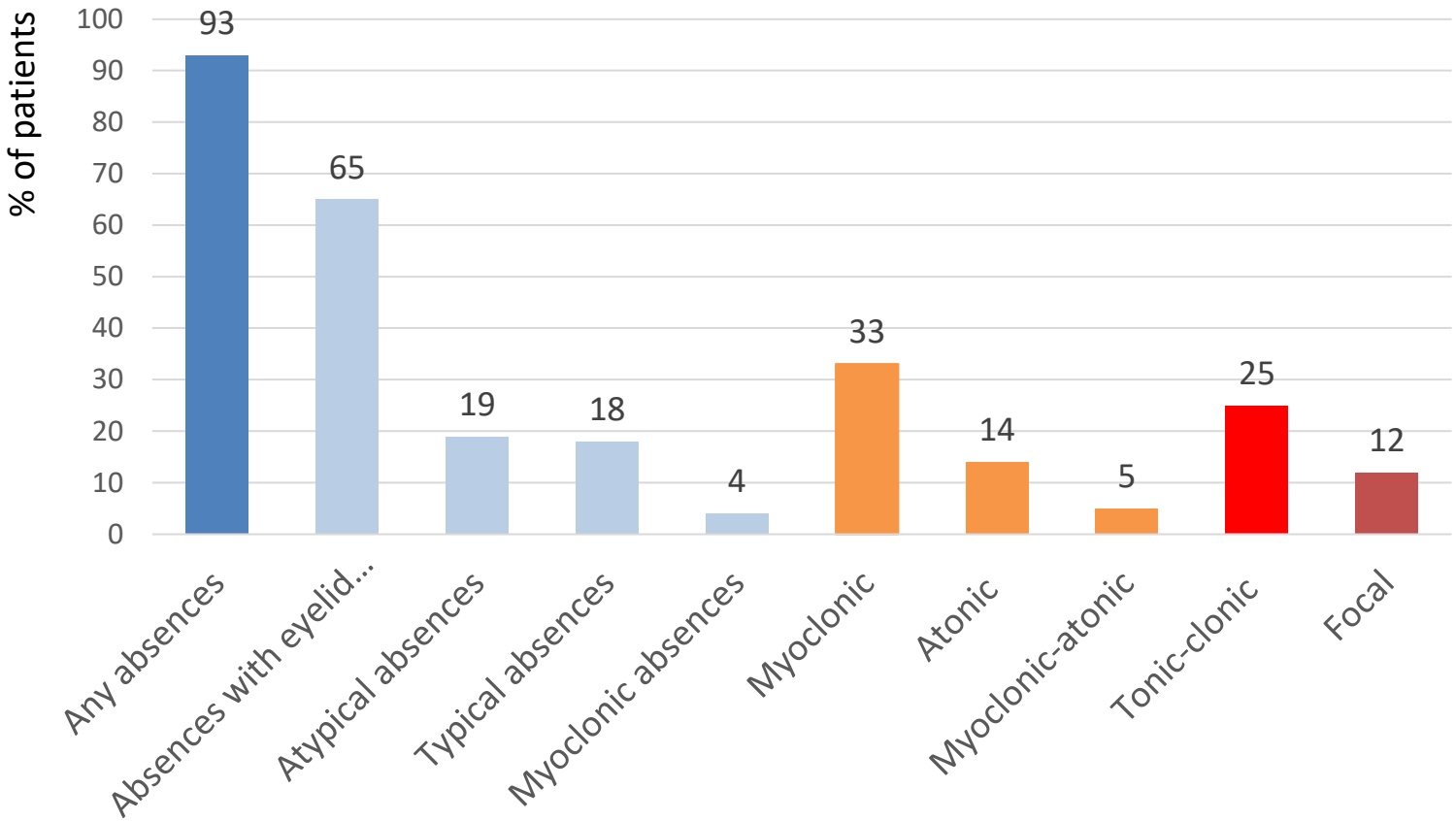
Microdeletions were identified in patients with similar phenotypes

Seizures

- Seizures diagnosed in 56/57 patients
  - Median age at onset: 2 years (4 m – 7 y)
- Seizures remitted in 10 (18%)
  - Median age at offset: 7 years (3 y – 13 y)
- Multiple seizures types in 61%

Most patients have multiple seizure types with onset in childhood

Seizure types



Seizure types are most often generalized

Seizures can be subtle

Seizures often misinterpreted as behavior

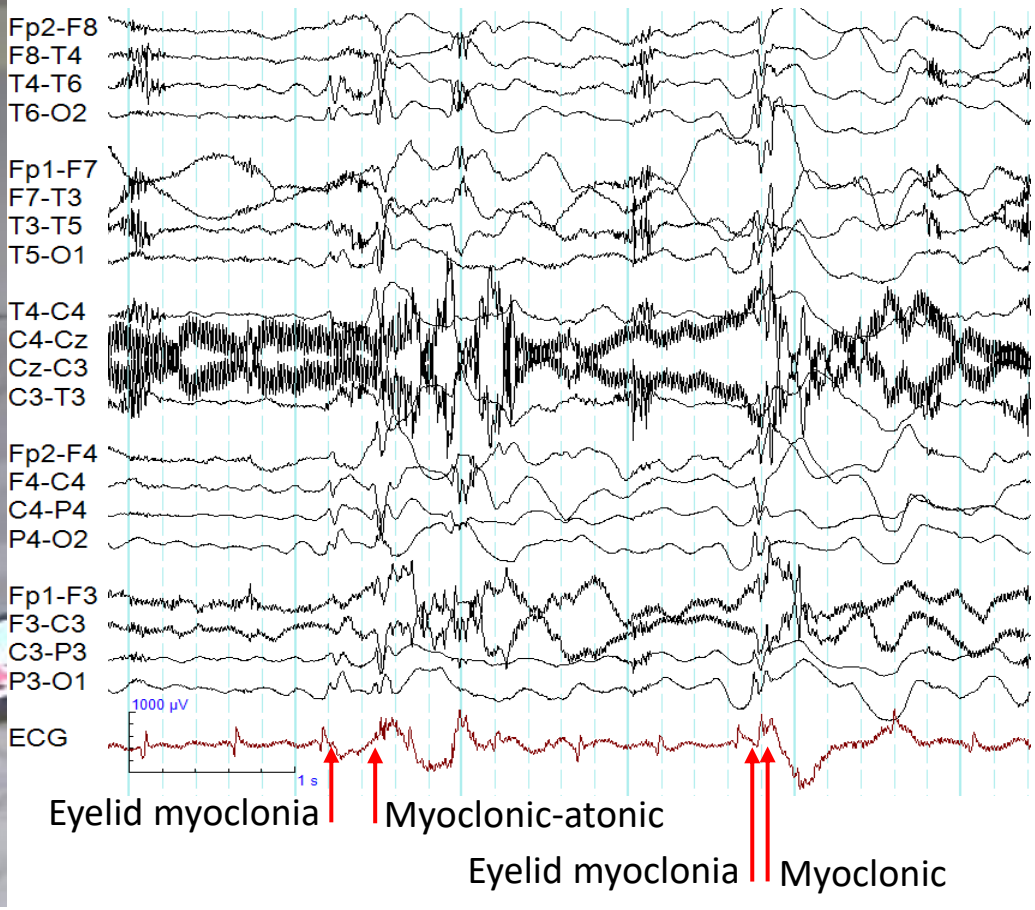
Reflex seizures

Seizures induced by eating in 25%

Novel seizure type (n = 13)

Eyelid myoclonia	→	myoclonic – atonic seizure	(n = 5)
	→	atonic seizures	(n = 8)

Eyelid myoclonia – myoclonic – atonic seizure



Novel type of drop attack for *SYNGAP1*

EEG results (n = 52)

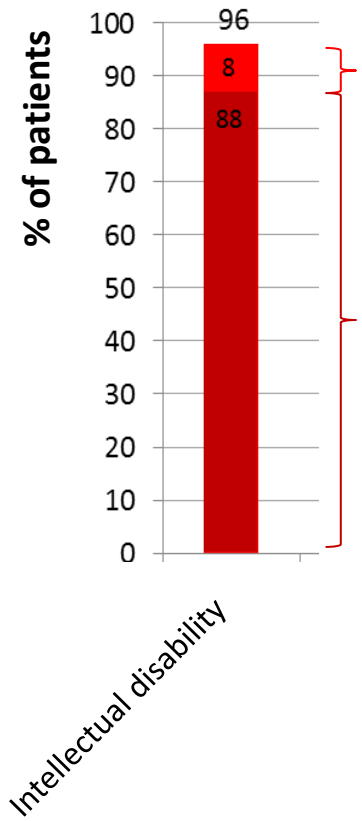
- Generalized discharges in 77%
- Focal/multifocal discharges in 54%

- Photosensitivity in 55% of tested patients (n=31)

- Slow background in 50%

The EEG shows both generalized and focal discharges

Intellectual disability (ID)

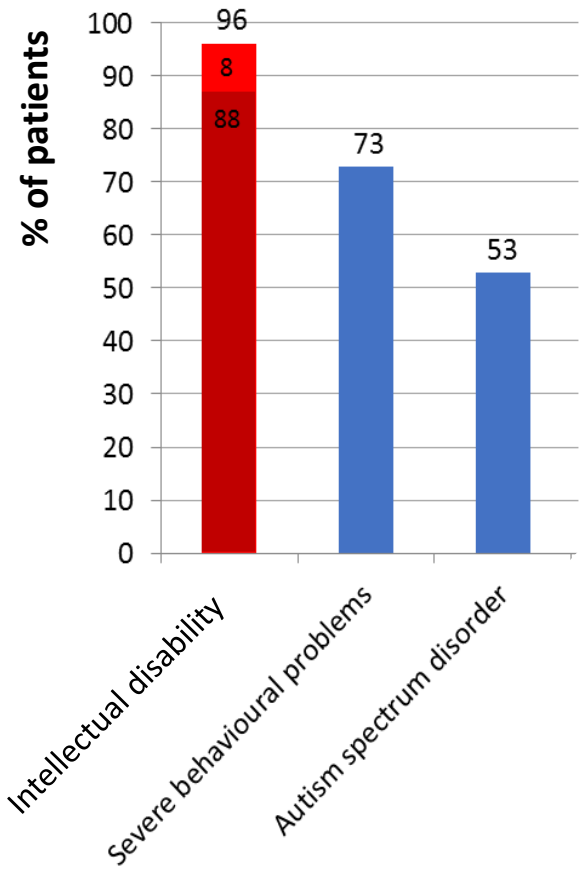


5 / 57 had mild ID

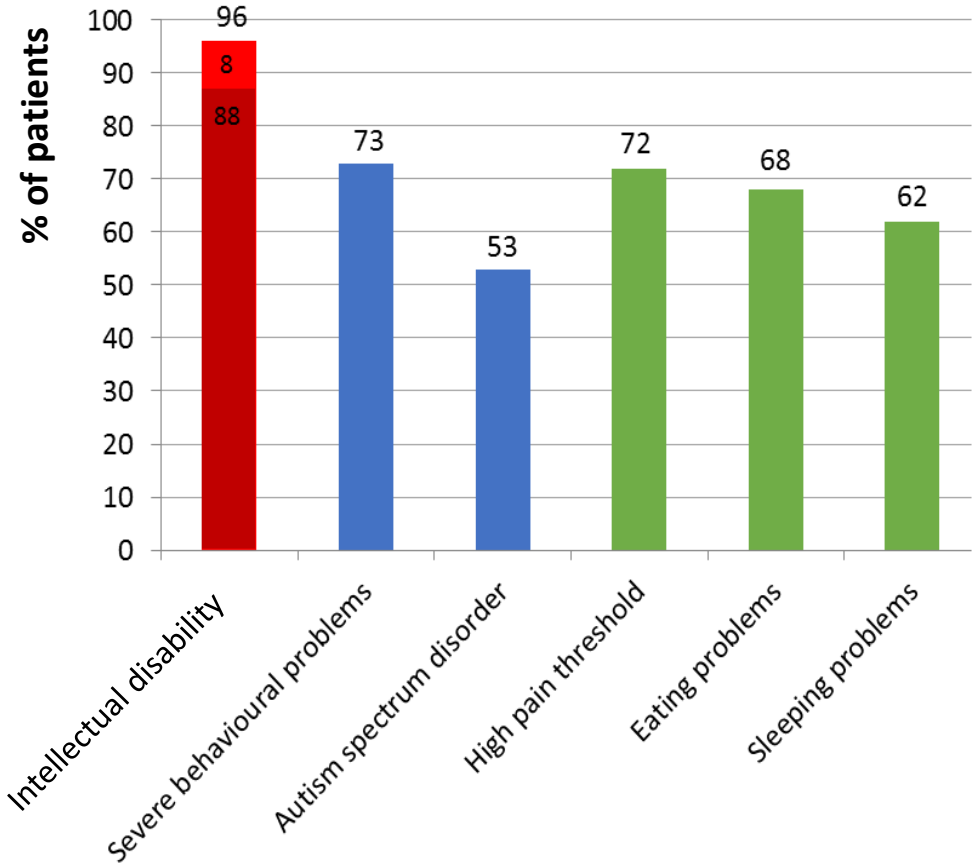
50 / 57 had moderate to severe ID

Patients have developmental delay with regression

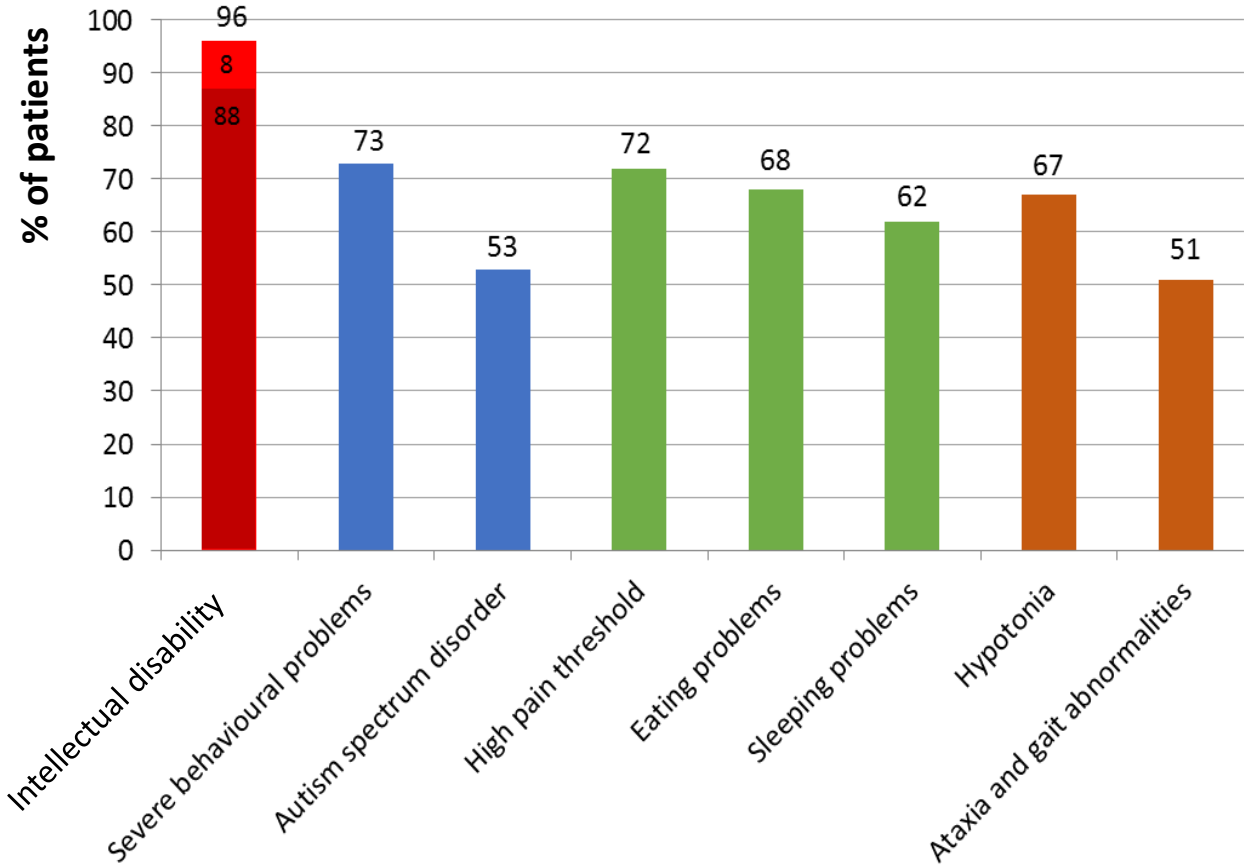
SYNGAP1 comorbidities



SYNGAP1 comorbidities



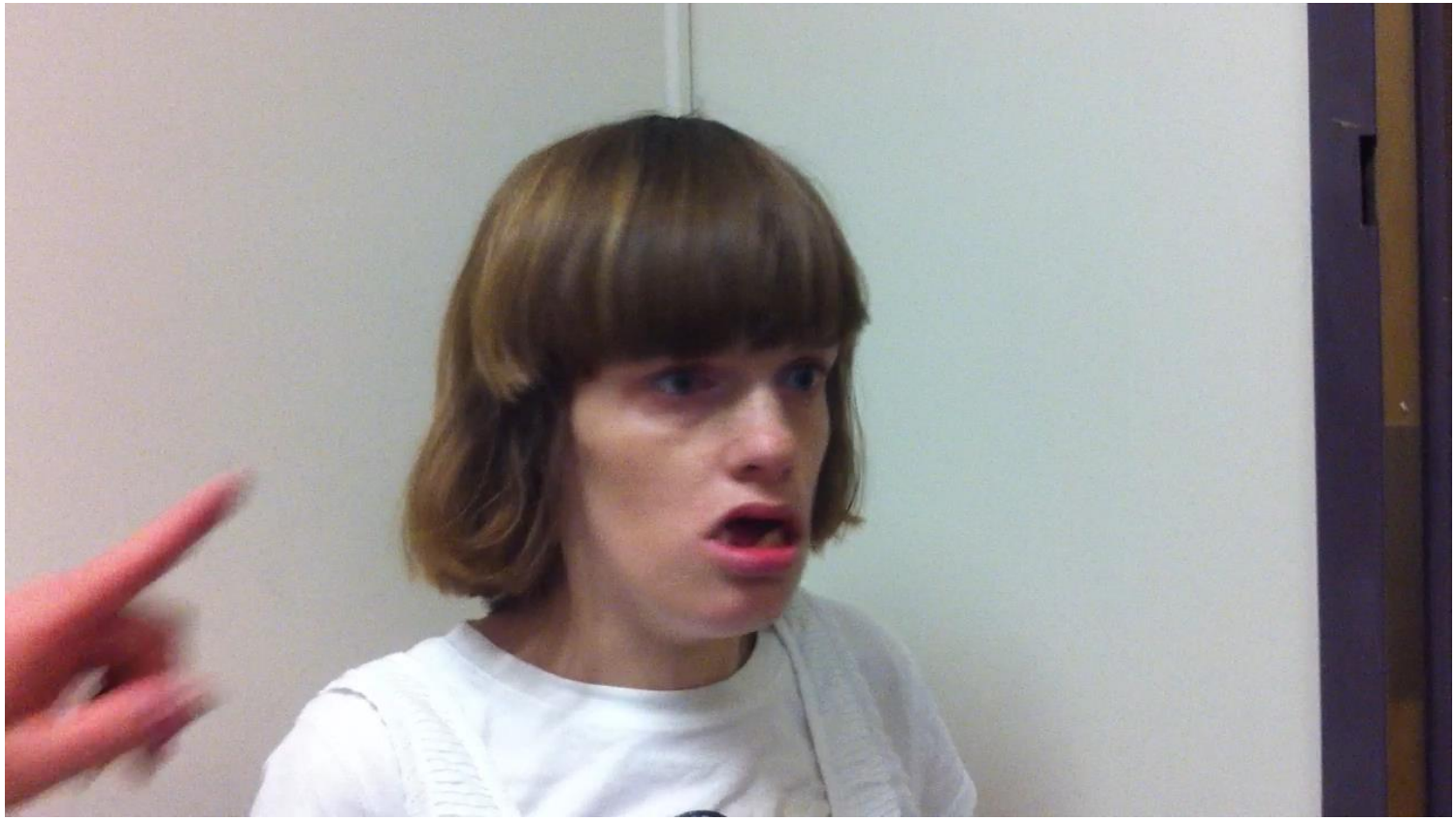
SYNGAP1 comorbidities



Gait difficulties

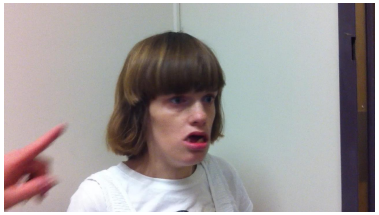
Gait difficulties in a 10 year old boy

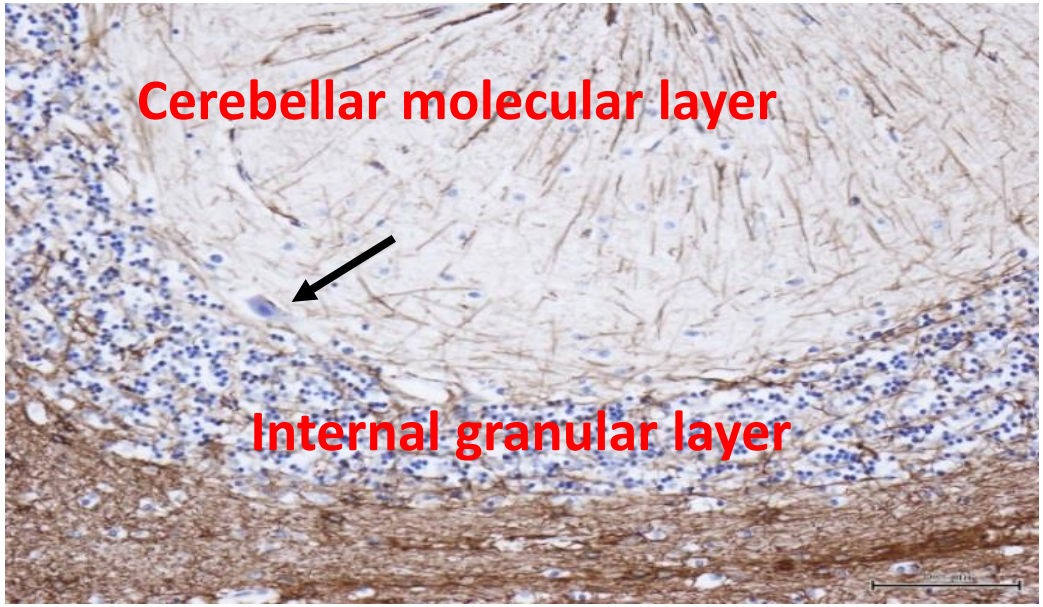
Brain pathology in *SYNGAP1* encephalopathy



Older patient with focal seizures

Brain pathology in *SYNGAP1* encephalopathy



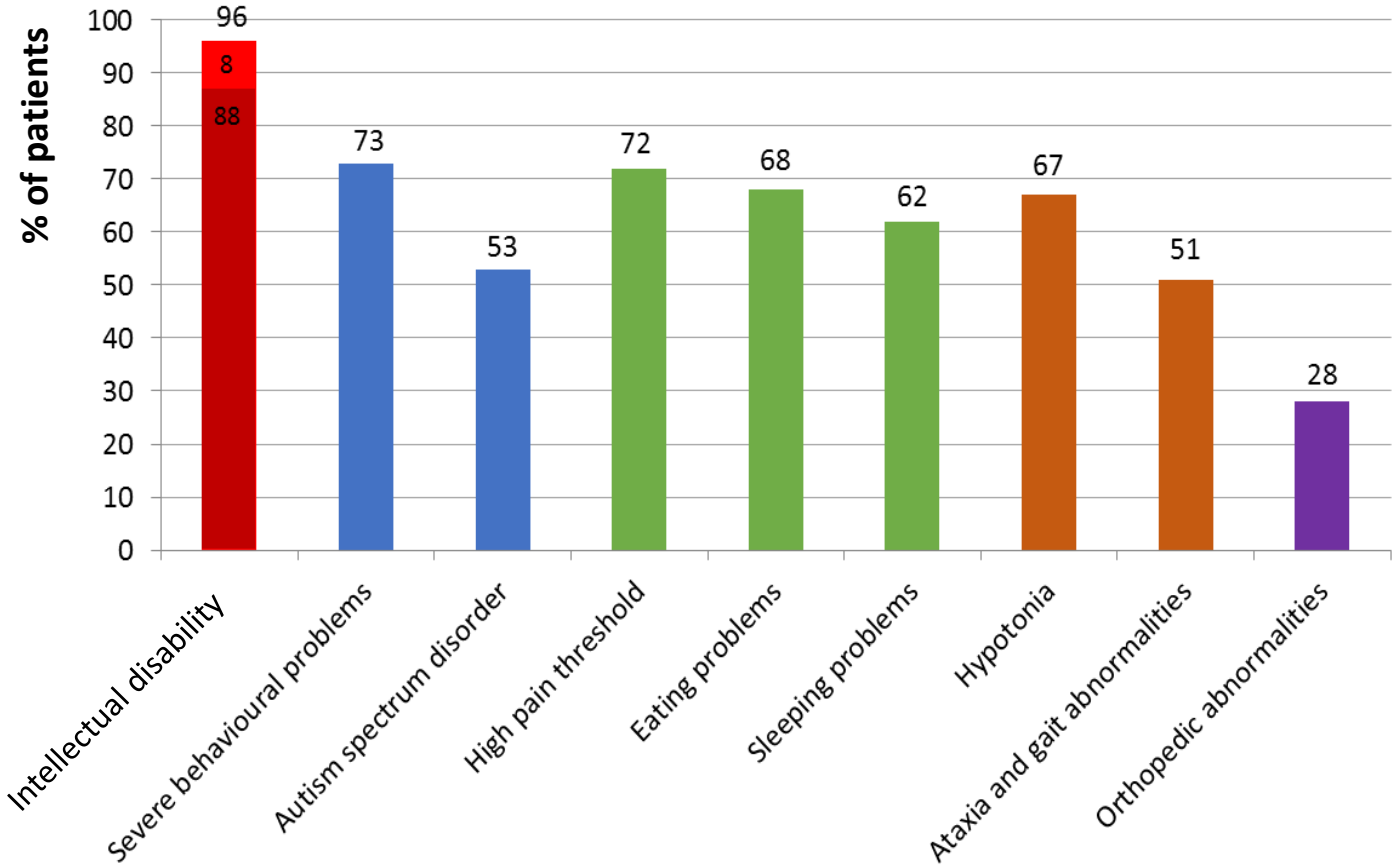


Astrocytosis

Loss of purkinje cells

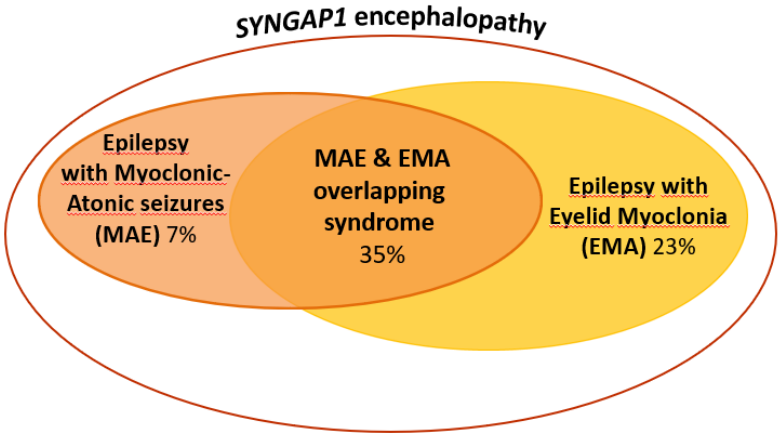
Loss of purkinje cells likely relates to ataxia

SYNGAP1 comorbidities



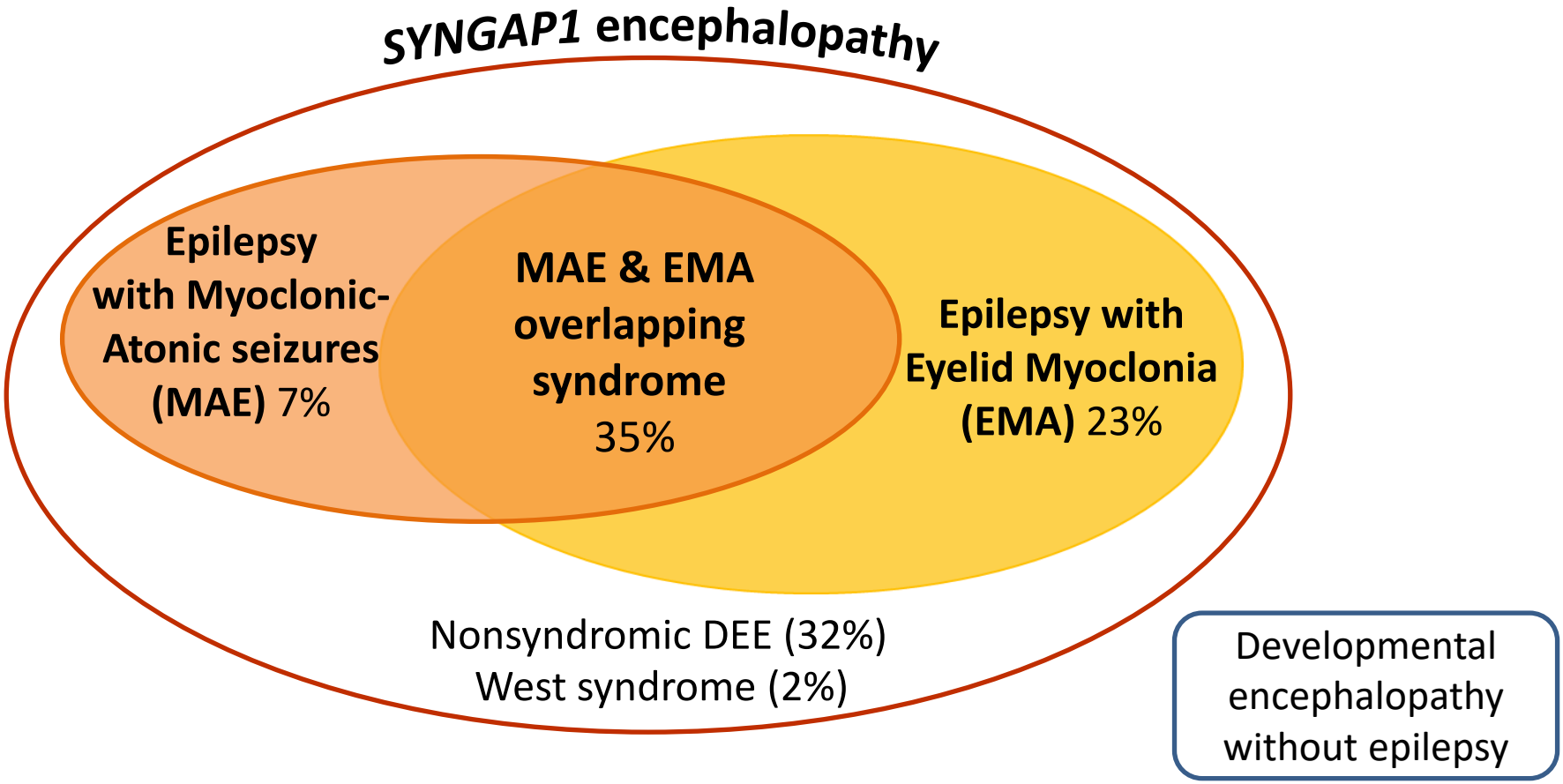
Dysmorphology

SYNGAP1 has subtle dysmorphic features



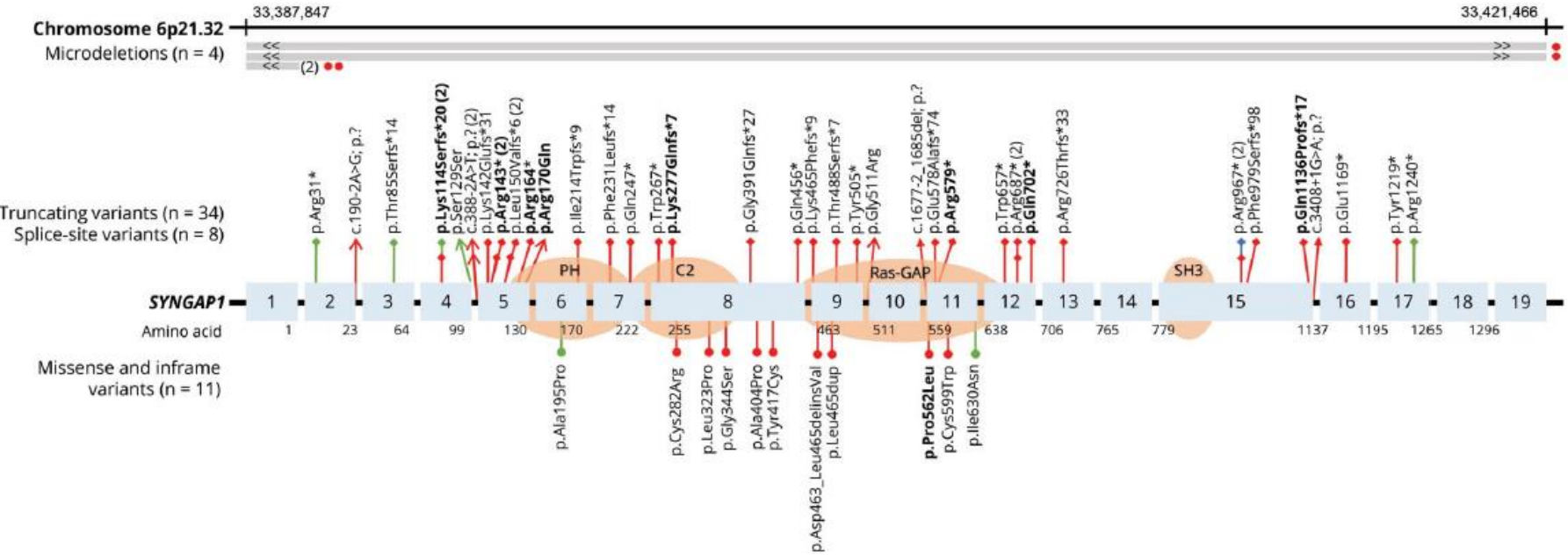
SYNGAP1 syndromology

SYNGAP1 epileptology



SYNGAP1 encephalopathy is a MAE & EMA overlapping syndrome

Genotype-phenotype correlation



No clear genotype-phenotype correlation exists

Treatment in *SYNGAP1*

Epilepsy treatment

April 14, 2020; 94 (15 Supplement) THURSDAY, APRIL 30

Developing targeted therapies for epileptic encephalopathy due to SYNGAP1 mutations (5191)

Jimmy Holder, Lunhui Lin, Ridhima Vij

First published April 14, 2020,

CITATION | PERMISSIONS | MAKE COMMENT

Gene Therapy for SynGAP1 Deficiency

Treatment for the cause of MRD5 intellectual disabilit

Published: 9th March 2021

Re-expression of SynGAP protein in adulthood improves translatable measures of brain function and behavior

; K Creson, Camilo Rojas, Ernie Hwaun, Thomas Vaissiere, Murat Kilinc, Andres Jimenez-Gomez, Jimmy Lloyd Holder Jr, Jianrong Tang, Laura L Colgin see all »

The Scripps Research Institute, United States; University of Texas at Austin, United States; Baylor College of Medicine, United States

Research Article Apr 26, 2019

Novel therapies on the horizon

Epilepsy treatment

- 20 different anti-epileptic drugs
- Valproate most often commenced (64%)
- Lamotrigine most often continued (77%)

Anti-epileptic drug	Commenced in n	Continued in n
Valproate (VPA)	45	29 (64.4)
Lamotrigine (LTG)	22	17 (77.3)
Levetiracetam (LEV)	19	8 (50.0)
Clobazam (CLB)	15	6 (40.0)
Topiramate (TPM)	11	6 (54.5)
Ethosuximide (ETX)	10	2 (20.0)
Clonazepam (CZP)	10	5 (50.0)
Zonisamide (ZNS)	7	2 (28.6)
Cannabidiol (CBD)	6	5 (83.3)
Ketogenic diet	6	3 (50.0)
Carbamazepine (CBZ)	3	2 (66.7)
Nitrazepam (NZP)	4	-
Steroid	4	-
Pyridoxine	3	-
Lacosamide (LCM)	3	-
Rufinamide	3	-
Vigabatrin (VGB)	2	-
Phenytoin (PHE)	1	-
Lorazepam (LZP)	1	-
Perampanel	1	-

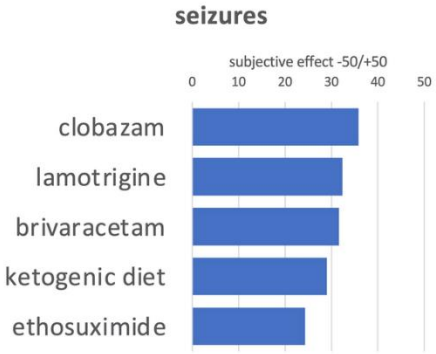
Most patients had therapy-resistent epilepsy

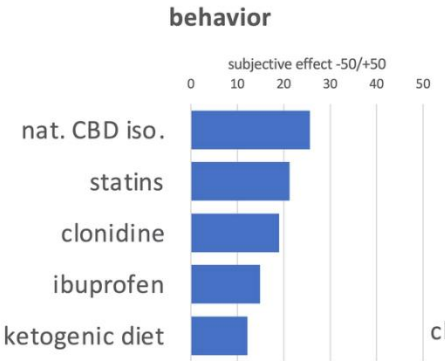
SYNGAP1-Epilepsy Treatment

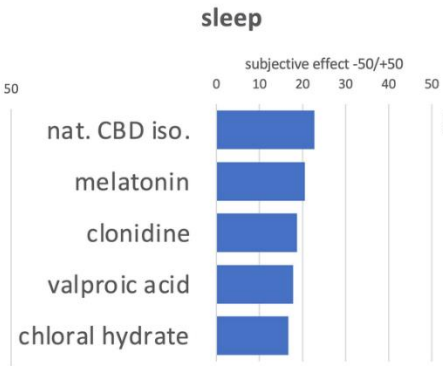
PATRE

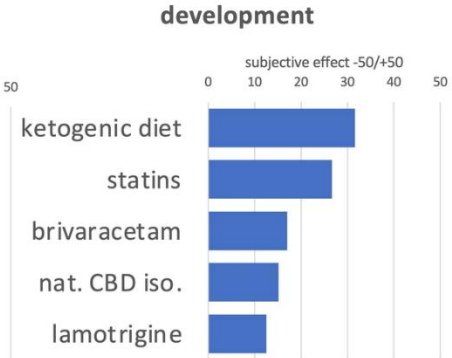
PATient based phenotyping and evaluation of therapy for Rare Epilepsies

TOP 5 drugs
from a survey with parents of 48 SYNGAP1 patients in collaboration with









Eschermann K, Kiwull L. et al. submitted

SYNGAP1-Epilepsy Treatment

> Epilepsia Open. 2020 Jul 1;5(3):496-500. doi: 10.1002/epi4.12411. eCollection 2020 Sep.

Add-on cannabidiol significantly decreases seizures in 3 patients with SYNGAP1 developmental and epileptic encephalopathy

Mathieu Kuchenbuch [1 2 3], Gianluca D'Onofrio [1], Nicole Chemaly [1 2], Giulia Barcia [2 4], Théo Teng [1], Rima Nabbout [1 2 3]

Affiliations + expand

PMID: 32913957 PMCID: PMC7469777 DOI: 10.1002/epi4.12411

Free PMC article

Abstract

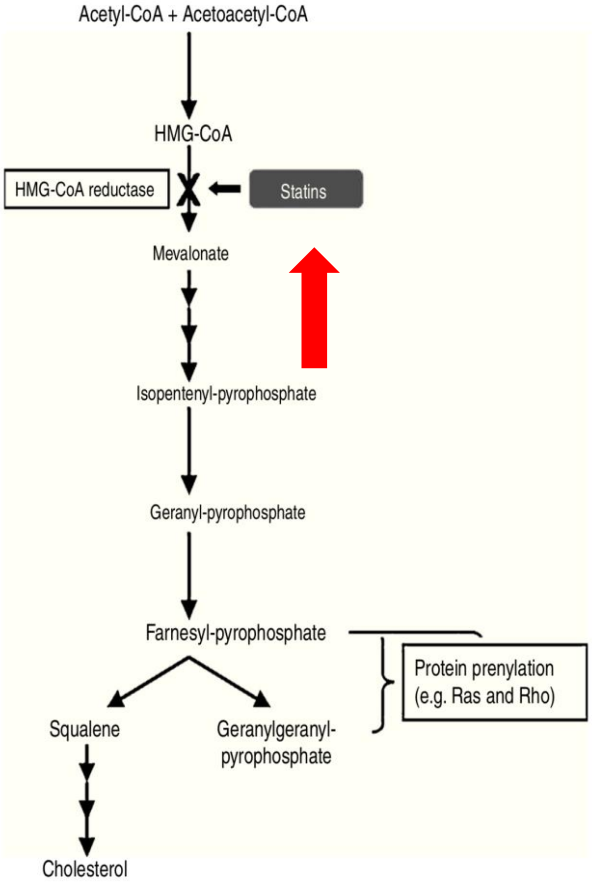
Mutations in *SYNGAP1* are associated with developmental delay, epilepsy, and autism spectrum disorder (ASD). Epilepsy is often drug-resistant in this syndrome with frequent drop attacks. In a prospective study of add-on cannabidiol (CBD), we identified three patients with *SYNGAP1* mutations: two boys and one girl. Seizure onset was at 3.5, 8, and 18 months (M), respectively, with numerous atypical absences per day associated with eyelid myoclonia (2/3 patients), upper limb myoclonic jerks (2/3 patients), and drop attacks (all patients). Seizures were resistant to at least 5 antiepileptic drugs (AEDs). After CBD introduction, two patients were responders since M2 and achieve a seizure reduction of 90% and 80%, respectively, at M9 with disappearance of drop attacks. EEGs showed an improvement regarding background activity and interictal anomalies. The last patient showed a late response at M7 of treatment with an 80% decrease in seizure frequency. Caregiver in all three evaluated as much improved the status of their children. Treatment was well-tolerated in all, and no major adverse events (AEs) were reported. CBD showed efficacy in patients with drug-resistant epilepsy due to *SYNGAP1* mutations. Other patients with rare genetic developmental and epileptic encephalopathies with drug-resistant epilepsies might benefit from CBD.

Case 1

- 19 yrs.: EEG-worsening with generalized polyspike waves and occipital spikes
- 20 yrs.: GTCS after sleep deprivation and single myoclonic seizures every morning after waking-up
- Longterm-Video-Monitoring (52h): 100 episodes with epileptic discharges as well as 4 myoclonic seizures/24h
- N1-Trial with rosuvastatin 5 mg/d for 18 months in monotherapy → seizure situation improved: no GTCS /less myoclonic seizures

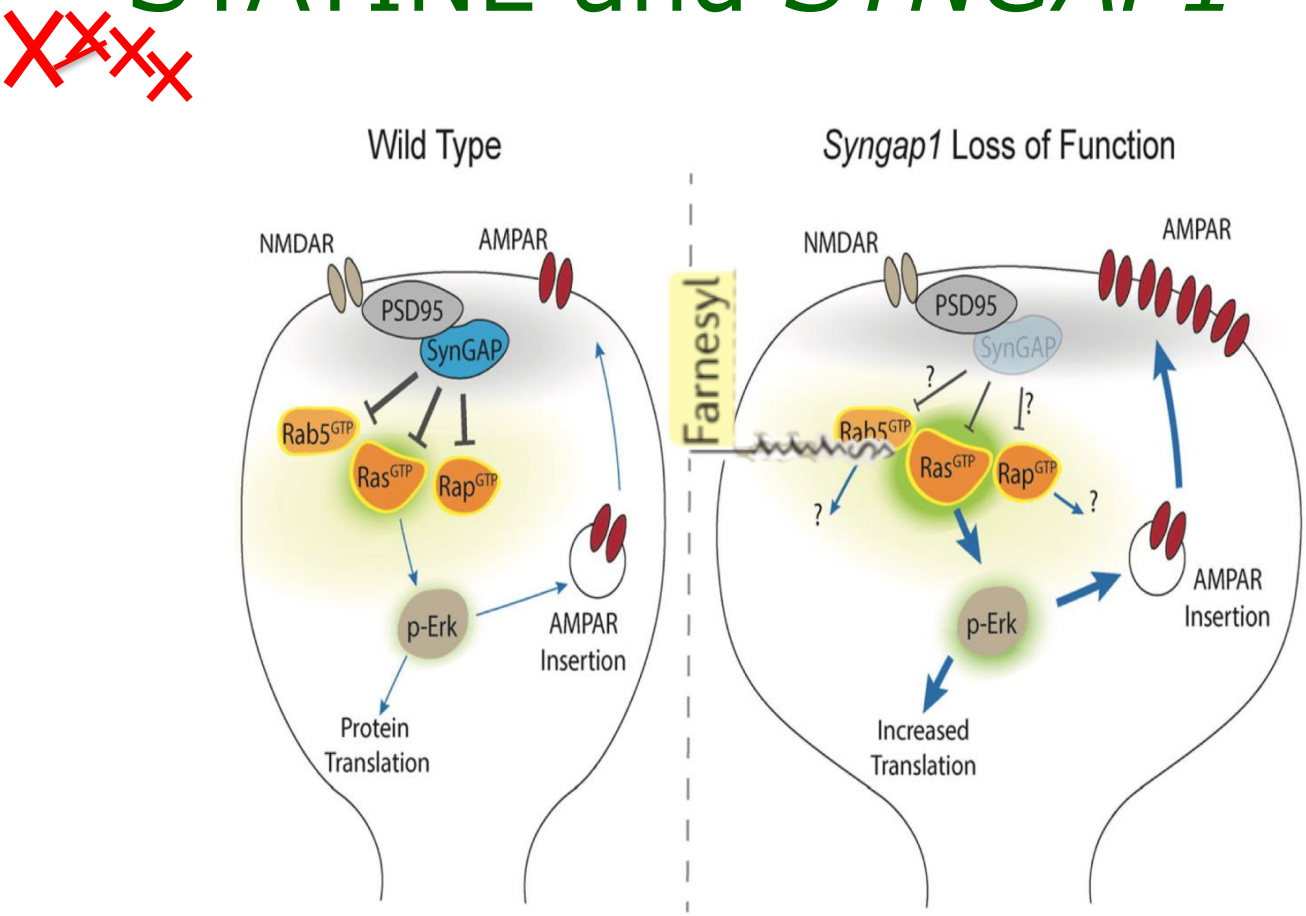
Kluger G. et al. Neuropediatrics. 2019

Mode of Action Statines



Rose; Al-Janabi, et al. Porto Biomedical Journal. 2017.

STATINE and *SYNGAP1*



Weldon M et al. J Neurodev Disord. 2018

Take home messages

- *SYNGAP1* is a distinctive generalized DEE
  - Combines features of MAE and EMA
  - Seizures can be triggered by eating
  - Fixation off Sensitivity and Eyeclosure triggers seizures
  - Array of comorbidities
    - » Intellectual disability, behavioural problems, a high pain threshold and ataxia
- Early recognition of seizures might improve outcome

Questions?

NETRE

frontiers in Neurology

REVIEW
published: 14 January 2021
doi: 10.3389/fneur.2020.622510

Network for Therapy in Rare Epilepsies (NETRE): Lessons From the Past 15 Years

Celina von Stülpnagel[1,2], Andreas van Baalen[3], Ingo Borggraefe[1], Kirsten Eschermann[2], Till Hartlieb[2,4], Lorenz Kiwull[1,2,5], Milka Pringsheim[2,4], Markus Wolff[6], Manfred Kudernatsch[2,7], Gert Wiegand[3,8], Pasquale Striano[9,10], Gerhard Kluger[2,4*] and NETRE Consortium*

- non-sponsered and non-funded
- initiated to share treatment experiences among clinicians
- coordinators for different genes (>270 groups)
- Quarterly newsletter

- Contact:

celina.Steinbeisvon@med.uni-muenchen.de

Acknowledgements

SYNGAP1 Facebook group

Special thanks to Danielle Williams

Patients and families

Epilepsy research centre Melbourne, Australia

Benjamin J. Shaw

Rosemary Burgess

Mark Bennett

Michael S. Hildebrand

Samuel F. Berkovic

Ingrid E. Scheffer

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