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

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**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 centers were also collected, focusing on developmental aspects and the associated epileptic 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 behaviors in half of the 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, characterized by falls or head drops due to atonic or myoclonic seizures, (myoclonic) absences, and/or eyelid myoclonia. Photosensitivity was frequent. Seizures were pharmacoresistant in half of the patients. The severity of the epilepsy did not correlate with the presence of autistic features or with the severity of cognitive impairment. Mutations were distributed throughout the gene, but spared spliced 3' and 5' exons. Seizures in patients with mutations in exons 4-5 were more pharmacoresponsive than in patients with mutations in exons 8-15.

**Conclusion:** *SYNGAP1* encephalopathy is characterized by early neurodevelopmental delay typically preceding the onset of a relatively recognizable epilepsy comprising generalized seizures (absences, myoclonic jerks) and frequent photosensitivity.

## 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 NMDA and AMPA receptors at the glutamatergic synapses and mediate signaling downstream of glutamate receptor activation [3, 4]. While complete *Syngap1* deficiency in mice is lethal at early post-natal stages, heterozygous *syngap1*+/- mice are viable but show behavioral and cognitive disturbances [5, 6, 7, 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 the refinement of connections that ultimately shape cognitive and behavioral modalities [4, 9]. Different SYNGAP1 protein isoforms exist and are generated through alternative splicing and alternative promoter usage, in a process regulated by synaptic activity and postnatal age in mice. Two of the main SYNGAP1 mouse isoforms that differ in their N-terminal and C- terminal sequences, have opposite effects on glutamate activation pathway [10]. Although several isoforms have also been described in humans, their specific role has not yet been established.

Recently, several groups have independently reported *de novo SYNGAP1* mutations in patients with intellectual disability (ID), epileptic encephalopathy (EE) or autism spectrum disorders (ASD) identified by exome sequencing [11, 12, 13, 14, 15] or direct sequencing of the *SYNGAP1* gene through a candidate gene approach [16, 17, 18, 19, 20, 21, 22, 23, 24]. Recently, seven *SYNGAP1* mutations were identified by

exome sequencing in a series of 1,133 patients, 83% of whom had ID, indicating a frequency of *SYNGAP1* mutation of ~0.74% in patients with ID [25]. One patient with a chromosomal translocation interrupting *SYNGAP1* [26] and five patients with 6p21.3 deletions encompassing *SYNGAP1* [23, 27, 28, 29, 30] have also been reported. Thus, to date, *SYNGAP1* appears one of the most relevant ID-causing genes, with mutations possibly explaining 0.7 to 1% of ID. Genotype-phenotype correlations have not been clearly established. Moreover, because most patients with *SYNGAP1* mutation were identified in large-scale exome or panel studies, the clinical features and the natural history of the *SYNGAP1*-associated ID and epilepsy remain to be precisely described. Here, we have gathered the molecular and clinical data of 15 unreported and two previously reported patients to investigate in more detail the *SYNGAP1* mutational and neurodevelopmental spectra.

## METHODS

**Patients.** We analyzed 251 patients with variable neurodevelopmental phenotypes including ID, EE and ASD (see Supplementary Methods for details) by exome sequencing (n=59) or direct sequencing of genes encoding synaptic proteins (n=192). One additional patient had an intragenic *SYNGAP1* deletion identified by microarray-based comparative genomic hybridization (array-CGH). Clinical and molecular data of 13 additional patients with *SYNGAP1* mutation, identified in 12 other centers, were collected: all patients with a mutation introducing a premature termination codon or occurring *de novo* (i.e. proven pathogenic), with the exception of patients with genomic deletions encompassing other genes than *SYNGAP1*, were eligible for inclusion. Patients #2 and #10 have been previously reported [12, 24]. Each patient's referring physician filled out a table with detailed developmental, neurological, behavioral and epileptic medical history, including EEG and imaging data if available. Most patients were evaluated according to developmental scales routinely used in enrolled centers by clinicians trained in neurodevelopment or neuropsychologists (for example Brunet-Lezine, HAWIK-IV, or SON-R2 scales). The sex ratio was 8 males / 9 females. Mean age at the time of the study was 10.3 years (range 3-29 years). Informed written informed consent was locally obtained for all participants. This study was approved by INSERM (RBM C12-06) and the ethical CCPRB committee from La Pitié-Salpêtrière (Paris, France).

**Exome sequencing**. The exome of index cases or parent-offspring trios was sequenced by IntegraGen (Evry, France) or by the Genotypic and sequencing facility of ICM [31]. Exons were captured from fragmented genomic DNA samples using the SureSelect Human All Exon 50Mb exome kit (Agilent Technologies) or the SeqCap

EZ Solution-Based Enrichment v3.0 (Roche), and paired-end 150-base massive parallel sequencing was carried out on an Illumina HiSeq2500 or a NextSeq500, according to manufacturers' protocols. Bioinformatics analyses were respectively done using the in-house pipeline developed by Integragen SA, as previously described [31] or by the iCONICS ICM facility platform as follows: sequencing reads passing quality filtering were aligned to the human reference genome (hg19) with Burrows-Wheeler Aligner (BWA) [32]; GATK [33] was used to recalibrate base quality scores, realign around indels, and mark duplicate reads. Variants were filtered based on their impact on the gene (missense, nonsense, frameshift, splice site-altering variants) and a minor allele frequency lower than 1% in databases (Exome Variant Server, 1000 Genomes, HapMap, Exome Aggregation Consortium, and in-house databases). Calling of *de novo* variants in trios was done using the Eris interface (Integragen SA) or Polyweb (University Paris-Descartes).

***SYNGAP1* screening and Sanger sequencing.** All exons and intron-exon junctions of *SYNGAP1* (NM_006772.2) and 18 other synaptic genes were amplified using the Fluidigm Access Array technology (IFC Controller AX, FC1 Cycler, 48x48 Access Arrays) and sequenced on a MiSeq Illumina sequencer as paired-end 2 x 250 bp reads. Alignment of reads on the human reference was performed with BWA and GATK, and additional bioinformatics steps including filtering for novel coding variants, were done using an in-house pipeline. Mutations identified by next generation sequencing (exome or panel) were validated by Sanger sequencing. *De novo* occurrence was tested by analyzing available parents. The predicted effect of mutations was interpreted with Alamut 2.2 (Interactive Biosoftware).

**SYNGAP1 isoforms and genotype-phenotype correlations.** Human *SYNGAP1* cDNA and protein sequences were retrieved from NCBI and Uniprot, aligned using Clustalw2 (http://www.ebi.ac.uk/Tools/msa/clustalw2/) and compared to mouse and rat isoforms [10]. We first assessed genotype-phenotype correlations in the 17 affected individuals from our cohort.

**Review of individuals with previously published *SYNGAP1* mutations**. The terms 'SYNGAP1' and 'mutation' were used to search for articles reporting patients with SYNGAP1 mutation in Pubmed. In addition, SYNGAP1 mutations and variants present in the HGMD professional (Biobase) and Exac databases were retrieved, listed and visualized on the schematic representation of the *SYNGAP1* gene. Statistical analysis was done using the Fisher exact test.

## RESULTS

**Genetic analyses and review of *SYNGAP1* mutations.** In our cohort of 251 patients with neurodevelopmental disorders, we identified 3 patients (1.2%) with novel *de novo* pathogenic heterozygous mutations of *SYNGAP1* using exome or panel sequencing. One additional patient had a *SYNGAP1* deletion of 16.6 Kb encompassing exons 2-9, identified by array-CGH. We collected additional phenotypic information for two cases published previously [12, 24] and 11 additional patients with *SYNGAP1* mutations identified in other centers (Table 1 and Supplementary Table 2).

*SYNGAP1* mutations occurred *de novo* in all 12 patients for whom DNA of both parents was available and, with the exception of one *de novo* missense mutation, all of them introduced a premature termination codon in the protein sequence (Table 1 and Figure 1). None of the mutations were reported in control databases (Exome Variant Server, 1000Genomes, HapMap, Exome Aggregation Consortium). The single missense mutation of this study (c.1685C>T, p.Pro562Leu, rs397514670), also identified in a previously reported patient [20], altered a highly conserved amino acid of the RasGap/GTPase domain of the protein (up to yeast) and was predicted damaging by SIFT and Polyphen-2.

In total, 47 patients (including two monozygotic twins [23]) carrying 43 different point mutation or indels limited to the *SYNGAP1* gene have been described to date (Figure 1 and Supplementary Table 3). Three recurrent mutations (c.321_324del, c.427C>T/ p.Arg143*, c.1685C>T/ p.Pro562Leu) were found in 2 patients each. Pathogenic mutations in *SYNGAP1* are distributed throughout the gene, especially in exons 5, 8, and 15, which are amongst the largest exons of *SYNGAP1.* Interestingly, the two first and two last exons, which are alternatively spliced and included in 3 out of 5

SYNGAP1 isoforms, but also exons 9 and 16, present in all known isoforms seem to be spared (Figure 1).

**Clinical and neurodevelopmental features of *SYNGAP1*-related encephalopathy (Table 1 and Supplementary Table 1).** All patients with *SYNGAP1* anomalies of our series had ID which was evaluated as severe in 10 patients, moderate in five and mild in two. The mean age of sitting unsupported was 12 months (median age 10 months, n=15) and of walking 27.7 months (median age 24 months, n=15). Half of the patients could walk by age 2 years and 75% by age 3 years. All patients had speech delay: 12 of them spoke first words at a mean age of 2.5 years and five patients did not speak at age 10 years or older. In most patients, both receptive and expressive languages were affected. Two patients had mild ID, including one without motor delay. In those, mild, progressive language delay and behavioral anomalies were the most prominent features.

Eight out of 16 patients (50%) older than 3 years old were diagnosed with ASD. Patients with ASD had remarkably poor verbal and non verbal communication abilities as well as impaired social interactions (Supplementary Table 1). Half of the patients (n=4/8) with severe ID, 1/5 with moderate ID and 2/2 with mild ID were diagnosed with ASD. Independent from a formal diagnosis of ASD, many of the patients exhibited stereotypies (n=10), temper tantrums, aggressiveness, self-injurious behavior and/or restlessness (n=7).

Neurological examination, performed at a mean age of 8.9 years, was considered normal in two patients. Gait was clumsy or unsteady in five patients and ataxic in five others. Truncal hypotonia was reported in 10 patients and facial hypotonia in four. Some patients had orthopedic problems, such as *pes planus* and rotation of the hips.

Brain MRI performed in all 17 patients (mean age 5.4 years) was either normal or revealed nonspecific features (arachnoid cysts in two patients, mild myelination delay in one, and signal abnormities in another).

Epilepsy was diagnosed in 16/17 patients (Table 2). The only patient without epilepsy, who was aged 5 at the time of this study, had a single afebrile seizure at the age of 3.5 years. Excluding this patient, first seizures occurred at a mean age of 3 years (range: 1-8 years) and consisted of drop-attacks, massive myoclonic jerks, atonic seizures, myoclonic absences or absences. A diagnosis of Doose syndrome (DS) and epilepsy with myoclonic absences (EMA) was made in three and one patients, respectively. The others were diagnosed with unclassified genetic generalized epilepsy (GGE). None had a diagnosis of Lennox-Gastaut syndrome (LGS).

The epilepsy responded to a single anti-epileptic drug (AED), mostly sodium valproate, in seven patients and was pharmacoresistant in nine. During the active phases of epilepsy, seizures occurred daily in five patients, 10 times per day or more in two and 100 times daily or more in two others. Seizures were of short-duration and the most frequent seizure types were typical or atypical absences (n=9), massive myoclonic jerks with or without falls (n=7), eyelid myoclonia (n=3), clonic or tonic clonic seizures (n=3), myoclonic absences (n=3) and atonic seizures (n=2). Head drops or falls were relatively frequent (n=5) and reported as myoclonic-astatic, atonic seizures or drop-attacks. Eight patients had several seizure types. No patients had status epilepticus and exacerbation by fever was mentioned in four. We found no correlations between the diagnosis of ASD and the age at epilepsy onset. The proportion of patients with ASD was identical among those with pharmacoresistant (n=5/10) and pharmacosensitive epilepsy (n=3/6).

The most frequent anomalies reported on EEG traces (Figure 2) from 16 patients were ictal or interictal bursts of spikes, spike-waves or slow waves that were either generalized (n=13), generalized with a posterior predominance or posterior only (n=5). Paroxysmal anomalies were localized to central regions in six instances. Triggers of seizures were identified in seven patients, including photosensitivity (PS, n=5), fixation-off sensitivity (FOS, n=1), PS and FOS (n=1), and chewing (n=1).

**Genotype/phenotype correlations.** We observed no definite correlation between the location of the mutation on the gene and the severity of ID or ASD diagnosis. However, schematic representation of the clinical features of our 17 patients, ordered by the position of the mutation on the gene (Figure 3), revealed that the epilepsy of patients with mutations in exons 4-5 was mainly pharmacosensitive (5/6 patients) whereas that of patients with mutations in exons 8-15 was mainly pharmacoresistant (8/9, p=0.01).

## DISCUSSION

In this study, we collected the comprehensive molecular and clinical data of the largest series of patients with *SYNGAP1* mutation so far in order to describe more accurately the neurodevelopmental and epileptic phenotype and to address genotype-phenotype correlations. Delineation of the phenotype from 36 patients with *SYNGAP1* mutations showed that it includes mild to severe ID in all, generalized epilepsy in most and autistic behavior in a half of them (Supplementary Table 3). In the present study, we describe the phenotype of 17 cases with *SYNGAP1*-associated encephalopathy, bringing the total number of reported patients with *SYNGAP1* mutations to 47.

**Neurological examination in *SYNGAP1*-associated encephalopathy**. Truncal hypotonia, sometimes in association with facial hypotonia, was the main recurrent feature in our patients, in line with previous series [20, 23]. Likewise, ataxia, with a broad-based or clumsy gait, was frequent in our patients and recurrently mentioned in others [20, 23]. Gait abnormalities are probably due to a combination of hypotonia, lack of global coordination, poor motor control, inattentiveness and orthopedic issues. Occipitofrontal circumference (OFC) was normal in 78% of patients from the literature and in 100% of ours. Though microcephaly has been mentioned in some cases [17, 20, 23], it seems to be not a common aspect in patients with SYNGAP1 mutations.

As with previously-reported patients, MRI in our patients showed either no or nonspecific features, implying that brain imaging is not helpful in the diagnosis of *SYNGAP1*-related disorders.

**The neurodevelopmental phenotype in *SYNGAP1*-associated encephalopathy.** In our series as well as in the literature, early motor delay with severe language impairment is the first manifestation of *SYNGAP1* encephalopathy. Fourteen patients of our series acquired a few words between 1 and 4 years old but only three patients were able to speak simple sentences. These data highlight that language acquisition in most patients with *SYNGAP1* mutation rapidly reaches a plateau. It may even be subjected to regression, since seven of our patients acquired a few words but eventually lost them again during the first years of life.

Slowing of global development and seizures appeared to occur concurrently in some patients, suggesting that *SYNGAP1* mutation might be a cause of EE, as previously suggested [18]. By definition, EE is an epileptic disorder in which the "epileptic

activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone" [34]. The concept of EE may apply to specific syndromes (West syndrome and LGS) usually associated with ID or to epileptic individuals with an encephalopathic course [34]. West syndrome and LGS were not diagnosed in our patients. However, retrospective analysis of the clinical history of some of them may illustrate an "encephalopathic course" apparently related to frequent daily seizures. As an example, patient #14 in whom first seizures occurred up to 100 times a day had increasing behavioral disturbances and a concomitant stagnation of cognitive acquisition; her language and communication skills significantly improved once the epilepsy was controlled. On the contrary, the epilepsy of patient #4 responded to sodium valproate alone at 4 years old but her cognitive evolution was very poor at 10 years. Beyond these particular clinical histories, a global view of the epilepsy and neurodevelopmental disorder in our series shows that the level of ID is not related to the resistance or sensitivity of the epilepsy to AED (Figure 3). In addition, the age at first seizure does not correlate with the resistance to AED and is not clearly linked to the severity of ID. Finally, among the eight patients with language regression reported here, two of them only had a concomitant first seizure. Epilepsy in the others started several months or years after language regression. The contribution of interictal EEG abnormalities to cognitive regression is theoretically possible, but cannot be demonstrated since EEG were recorded after the first seizure. Consequently, while the concept of EE may possibly correspond to the encephalopathic course of a subgroup of patients with pharmacoresistant epilepsy in our series, evidence to extend this concept to *SYNGAP1*-related neurodevelopmental disorder in general is lacking.

**Epilepsy in *SYNGAP1*-associated encephalopathy.** *SYNGAP1* mutation rate was 0.74% in a large series of 940 patients with ID [25], and up to 1% (5/500) in another large series of patients with EE [18]. Overall, about 85% patients with *SYNGAP1* mutations had seizures. This suggests that epilepsy is extremely common in the *SYNGAP1*-associated encephalopathy and that *SYNGAP1* is one of the most frequently mutated genes in patients with ID and epilepsy. All patients in our series had generalized seizures, like those reported in a previous study [20], only a few of them also experienced focal clonic or tonic clonic seizures. Generalized bursts of spikes, spike-waves and slow waves, sometimes with an occipital predominance, were the main recurrent EEG features in our patients. Thus, falls and myoclonic jerks, (typical or atypical) absences, sometimes in combination, define the most common seizures types that, together with the finding of interictal generalized and/or occipital anomalies on EEG, may guide toward the diagnosis of *SYNGAP1* mutation in patients with ID.

Though most of our patients with *SYNGAP1* mutations had a diagnosis of unclassified GGE, seizure types were suggestive of epilepsy syndromes associated with ID, particularly EMA and DS, which diagnosis have been suggested in 3 and 1 patient(s), respectively. To our knowledge, two other patients with EMA were found to carry a *de novo* genetic anomaly affecting *SYNGAP1*: one with a frameshift mutation [20] and another with a gene interruption due to a balanced translocation [26]. However, the sequencing of *SYNGAP1* in four other patients with EMA and in another one with DS failed to reveal any mutations. This result is in agreement with a previous work in which a single *SYNGAP1* mutation was identified in three patients with EMA, 10 with DS and two with LGS [20]. This suggests that *SYNGAP1* mutations are relatively uncommon causes of these epilepsy syndromes.

Photosensitivity has been mentioned in previously reported *SYNGAP1* patients [17, 23], but has not been emphasized. The fixation-off phenomenon has been described once [24]. In our series, photosensitivity as a trigger for seizure was found in half of the patients. Parents or caregivers of four patients noticed it as sensitivity to sunlight, artificial light or the television. This high rate of photosensitivity is significant since clinical photosensitivity is found in only 10% of patients with epilepsy in the 7-19 years old group [35]. We assume that photosensitivity may have not been detected in some of our patients because it is an age-dependent phenomenon with a peak around puberty; it could therefore still appear in some of them; or because of the poor cooperation of patients during the recording. These data suggest that photosensitivity, when present, might be a diagnostic clue from the EEG of an underlying *SYNGAP1* mutation.

**Genotype/phenotype correlations.** Although patients with *SYNGAP1* mutations show a common core clinical picture, the phenotype is relatively variable, particularly regarding the severity of ID, pharmacoresistance and the presence of ASD. Since *SYNGAP1* is a complex gene, giving rise to several protein isoforms with opposite effects on the glutamate activation pathway, via alternative splicing and transcription start sites [10], it was tempting to speculate that the location of the mutation on the gene could correlate to the clinical outcome. However, we found little correlation between the location of the mutation and the severity of ID, epilepsy and/or ASD. Yet, the epilepsy of patients with mutations in exons 4-5 appeared more pharmacosensitive than that of patients with mutations in exons 8-15. Interestingly, exons 4 and 5 are not present in SYNGAP C, an isoform obtained through alternative promoter usage, which existence has been demonstrated in mice and rats. Although

this isoform has not been shown to exist in humans as well, our results suggest that it could also exist and have a different function, as already proven for isoforms α1 and α2, which differ in their C-terminus. Further study is necessary to confirm this finding, and decrypt the precise function of each human SYNGAP1 isoform and its relationship with the human pathology characteristics.

Nevertheless, the comparison of the clinical features of patients with identical mutations revealed significant clinical differences (Supplementary Tables 2 and 3), confirming that there is a real variability of the phenotype that depends on other factors than the mutation itself. On the contrary, monozygotic twins had strikingly similar phenotypes, suggesting that these modifier factors could be of genetic origin [23].

**ASD in *SYNGAP1*-associated encephalopathy and hypothetical consequences of *SYNGAP1* mutations on brain development.** Although all patients with validated pathogenic *SYNGAP1* mutations reported to date had ID, only half of them had a diagnosis of ASD (including data from the literature and our series). In our series, the presence of autistic traits was neither limited to patients with moderate or severe ID, nor to those with pharmacoresistant or early-onset epilepsy. Thus, ASD, like epilepsy, could be considered as an additional feature of the *SYNGAP1*-related phenotype in the context of ID, irrespectively of its severity, rather than an "isolated" diagnosis.

This observation is in agreement with previous studies showing that many neurodevelopmental disorders are caused by mutations in genes encoding synaptic proteins, and more specifically constituents of the post-synaptic density [36]. The fact that a subset of patients with *SYNGAP1* mutations exhibit autistic behaviors suggests

that a single mutation in a synaptic gene is not sufficient to cause ASD and that the genetic or epigenetic background of the patient probably plays an important role in the occurrence of autistic features in a context of intellectual development impairment. Many genes mutated in patients with ASD and ID are linked with neuronal signaling pathways and may alter the synaptic plasticity underlying the building, refinement and consolidation of neuronal networks associated with learning and adaptive behaviors, with the balance between inhibitory and excitatory signals being determinant in this process [37, 38, 39]. Given the function of the SYNGAP1 protein in regulating excitatory inputs downstream of NMDA receptors, the *SYNGAP1*-associated encephalopathy is likely a manifestation of the disruption of this balance. ASD as well other neurodevelopmental disorders could in many cases result from the interruption or impairment of the maturation processes of neuronal networks that are driven by neuronal activity during a critical period of brain development [39]. This scenario is particularly relevant to the fact that the clinical and morphological consequences of *SYNGAP1* haplo-insufficiency in mice, *i.e.* behavioral disturbances and premature dendrite elongation, are restricted to gene disruption during a given period of brain development [4, 9]. Following this hypothesis, *SYNGAP1* encephalopathy may be regarded as an example of premature closing of the time-window for cognitive development in humans. In the *SYNGAP1*-associated encephalopathy, disruption of the excitatory/inhibitory balance, which is also a cause of epilepsy, may therefore prematurely end the maturation process of synapses and lead to ID, ASD and epilepsy by a common pathophysiological mechanism.

## URLS/RESOURCES

NCBI Pubmed: http://www.ncbi.nlm.nih.gov/pubmed

Uniprot: http://www.uniprot.org/

Exome Variant Server: http://evs.gs.washington.edu/EVS/;

ExAC Browser (Beta) | Exome Aggregation Consortium:

http://exac.broadinstitute.org/

BIOBASE HGMD Professional: http://www.biobase-international.com/product/hgmd


## ACKNOWLEDGMENT

The authors thank the families for their participation in this study, the iCONICS facility, especially Ivan Moszer and Justine Guegan, for bioinformatic analysis of exome and panel sequencing data, Patrick Nitschké and the Paris-Descartes Bioinformatics Platform for access to the Polyweb interface, and the DNA and cell bank of the U1127 for DNA extraction and collection.

## FUNDING

This study was financially supported by INSERM, Fondation de France (FdF - Engt n°15144 to D. Héron), Agence Nationale de la Recherche (ANR SAMENTA SynDivAutism), Assistance Publique des Hôpitaux de Paris (APHP) and the “Investissements d’Avenir” program ANR-10-IAIHU-06 (IHU-A-ICM). C. Depienne and C. Nava are members of the Bio-Psy Labex.


## COMPETING INTERESTS

The authors declare no competing interests.

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## FIGURE LEGENDS

**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 alpha 1, which differs in the C-terminus (QTRV). (B) Schematic representation of the mutations (above) and the variants present in the Exome Aggregation (ExAc) database (below) on the longest SYNGAP1 isoform (NM_006772.2) and corresponding protein domains.

**Figure 2.** EEG samples from patients exemplifying electroencephalographic findings in *SYNGAP1*-related encephalopathy. (A) Sample demonstrating normalization of

paroxysmal activity by eye opening, i.e. fixation-off sensitivity, in Patient #2. (B) Sample showing paroxysmal activity under photic stimulation, i.e. photosensitivity, in Patient #2. (C) Sample from Patient #1: burst of generalized spikes concomitant of a rapid eye deviation (fast rhythms are due to benzodiazepine therapy). (D) Sample from Patient #12 showing the appearance of generalized spike-wave complexes with a low degree of bilateral synchronization after eye closure (fixation off phenomenon).

**Figure 3.** Graphical representation of clinical data (age at epilepsy onset, level of 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 gene, except patient 1, who corresponds to the patient with the intragenic *SYNGAP1* deletion. Y-axis indicates the age at seizure onset (in months). The proportion of patients with mild (circles), moderate (triangles) and severe (squares) ID is not different in the pharmacoresistant (red) and in the pharmacosensitive (green) groups. One patient (black square, patient 10), who had a single afebrile seizure and was thus not considered strictly as epileptic, was not considered for this analysis. The age at the first seizure is neither related to the resistance or sensitivity of the epilepsy to AED, nor to the position on the gene. The age at seizure onset is not correlated with the level of ID. The mutations of most patients with pharmacosensitive epilepsy cluster in exons 4-5 whereas those of most patients with pharmacoresistant epilepsy spread over exons 8-15 (p=0.001).

## SUPPLEMENTARY DATA

**Supplementary Table 1.** Additional data to Table 1.

**Supplementary Table 2.** Molecular data of patients with *SYNGAP1*-associated encephalopathy reported in the literature and in the present study. Lines with recurrent mutations are highlighted in green.

**Supplementary Table 3.** Clinical data of patients with *SYNGAP1*-associated encephalopathy from the literature. Patients reported in two articles [21,30] were not included because of insufficient clinical data.

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39 Meredith RM. Sensitive and critical periods during neurotypical and aberrant neurodevelopment: a framework for neurodevelopmental disorders. *Neurosci Biobehav Rev* 2015;**50**:180-8.

Table 1. Molecular and clinical data from the 17 patients with *SYNGAP1* mutations*. (1)

| **Patient ID** | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age at the time of the study (years)** | | 14 | 15 | 8.5 | 10.8 | 15 | 11 | 5 | 9.8 | 5.5 |
| **Sex** | | M | F | F | M | F | M | F | F | F |
| **Ancestry** | | Guinean | European | European | European | Moroccan | Malian | European | European | European |
| **Genetics** | Mutation type | intragenic deletion | nonsense | nonsense | nonsense | frameshift | nonsense | splice site | frameshift | frameshift |
| | Mutation | c.68-1518-?_1530+?del | c.348C>A | c.403C>T | c.427C>T | c.455_459del | c.490C>T | c.509+1 G>T | c.828dup | c.1057delC |
| | Protein level | p.? | p.Tyr116* | p.Arg135* | p.Arg143* | p.Arg152Glnfs*14 | p.Arg164* | p.? | p.Lys277Glnfs*7 | p.Leu353Trpfs*13 |
| | Location in gene | intron 1 - exon 9 | exon 4 | exon 5 | exon 5 | exon 5 | exon 5 | intron 5 | exon 8 | exon 8 |
| | Inheritance | *de novo* | *de novo* | *de novo* | *de novo* | *de novo* | *de novo* | *de novo* | parents not tested | parents not tested |
| **Level of intellectual disability / Age at evaluation** | | severe / 10 y | mild / 12 y | moderate / 5.5 y | severe / 10.8 y | severe / 11 y | severe / 11 y | moderate / 5 y | moderate / 4.5 y | moderate / 5.5 y |
| **Developmental stages** | Age of sitting / walking | 7 m / 24 m | 10 m / < 18 m | 10 m / 20 m | 10 m / 24 m | 16 m / 36 m | 8 m / 20 m | 10 m / 22 m | 9 m / 15 m | NA / 24 m |
| | Age of first words / first sentences | 4 y / no sentences | 14 m / NA | 33 m / no sentences | 5 y (5 words) / no sentences | 4 y transient "mama" "papa" / no sentences | NA / no sentences | 3 y / 5 y | 23 m | 36 m / no sentences |
| | Current language ability | single words | NA | ~ 50 words | 10 words | absence of speech | few words at 11 y | 5-word sentences | short sentences | 15 words |
| | Regressive episode during the development / Age | slowing of development with untreated epilepsy / 2y | no | no | no | possible (loss of few acquired words) | no | loss of few dissylable words after 20 m | no | NA |
| **Autism spectrum disorder** | | no | yes | no | yes | yes | yes | no | no | no |
| **Clinical Examination** | Age at examination | 14 y | 12 y | 5.5 y | 10.8 y | 11 y | 10 y | 5 y | 6 y | 5.5 y |
| | Height in cm (SD) / weight in kg (SD) / head circumference in cm (SD) | 133 (-0.5) / 28 (-0.5) / 50.5 (-1) | 173 (+2.5) / 40 (-1) / 53 (-1) | 151 (+1) / 53 (+3) / 53.5 (-0.5) | NA | 156 (-0.75) / 62 (+0.25) / NA | 143 (+4) / 35 (+3.5) / 51 (-0.5) | 15 (-1.5) / 103 (-1.5) / 49 (-1.5) | 105 (-0.5) / 16 (-1) / 52 (+0.5) | 110 (-1.5) / 17.9 (-1.5) / 50.5 (-0.5) |
| | Neurologic examination | normal | normal | global hypotonia, gait ataxia | truncal hypotonia | nystagmus during the 1st year (possibly caused by myopia), clumsy gait | facial and truncal hypotonia, broad based gait | truncal hypotonia | facial hypotonia with drooling, gait ataxia | truncal hypotonia, walking with inwards rotation of hips |

Table 1. Molecular and clinical data from the 17 patients with *SYNGAP1* mutations*. (2)

| **Patient ID** | | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **Summary** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age at the time of the study (years)** | | 5 | 3 | 22 | 12 | 8 | 8.2 | 29 | 10 | mean 11.4 |
| **Sex** | | M | M | F | M | F | M | M | M | M=8, F=9 |
| **Ancestry** | | European | Iraqi | European | Turkish | European | European | European | European | nonsense 7; frameshift 5; splice 2; missense 1; intragenic deletion 1 |
| **Genetics** | Mutation type | nonsense | nonsense | missense | nonsense | frameshift | frameshift | frameshift | splice site | |
| | Mutation | c.1253_1254del | c.1630C>T | c.1685C>T | c.1995T>A | c.2214_2217del | c.2933del | c.3406dup | c.3408+1G>A | |
| | Protein level | p.Lys418Argfs*54 | p.Arg544* | p.Pro562Leu | p.Tyr665* | p.Glu739Glyfs*20 | p.Pro978Hisfs*99 | p.Gln1136Profs*17 | p.? | |
| | Location in gene | exon 8 | exon 10 | exon 11 | exon 12 | exon 13 | exon 15 | exon 15 | intron 15 | |
| | Inheritance | *de novo* | *de novo* | *de novo* | parents not tested | *de novo* | *de novo* | parents not tested | *de novo* | |
| **Level of intellectual disability / Age at evaluation** | | severe / 4 y | severe / 3 y | severe / 22 y | severe / 12 y | mild / 8 y | moderate / 5 y | severe / 8.5 y | severe / 10 y | mild n=2; moderate n=5; severe n=10 / mean age eval. 8.7 y |
| **Developmental stages** | Age of sitting / walking | 15-18 m / 36 m | 12 m / walks only with aid | 12 m / 38 m | NA / 36 m | 8 m / 18 m | 10 m / 18 m | 16 m / 30 m | 25 m / 4.5 y | mean 12 m / 27.7 m |
| | Age of first words / first sentences | ~29 m transient "mama", "papa" / no sentences | 3 y "papa" only / no sentences | no words / no sentences | no words / no sentences | 12 m / 6 y | 3 y / no sentences | 17 m / no sentences | no words / no sentences | mean age first words 2.6 y |
| | Current language ability | absence of speech | absence of speech | absence of speech | absence of speech | 120 words, 3 to 4-word sentences | 5 words | absence of speech | absence of speech | absence of speech 7; speaks words 5; associates words or simple sentences 3 |
| | Regressive episode during the development / Age | since age of 36 months-loss of "mama", "papa" | no | 12m - with febrile seizures | no | 14 months | no | loss of words at age 18-30 m | possible (loss of 2-syllable words) | n=7 |
| **Autism spectrum disorder** | | yes | too young to be evaluated | no | no | yes | no | yes | yes | yes 8; no 8 |
| **Clinical Examination** | Age at examination | 5.2 y | 3 y | 22 y | 12 y | 8 y | 7 y | 8.5 y | 6.6 y | mean 8.9 y |
| | Height in cm (SD) / weight in kg (SD) / head circumference in cm (SD) | 149 (+1.5) / 48.6 (+2) / 52 (-1.5) | 105 (-0.5) / 20 (+1.5) / 49.3 (-1) | 93 (0) / 13.8 (0) / 48 (-2) | 146.5 (+1) / 35 (+0.5) / 55 (+1) | NA /21 (-1) / 54 (+1) | 116 (+1) / 21 (+1) / 50 (0) | 124 cm (-1.5) / 22 kg (-1.8) / 50.8 cm (-1.7) | 116 cm (+0.4) / 22.3 kg (+0.7) / 51.3 cm (+0.4) | normal OFC 15/15 |
| | Neurologic examination | truncal hypotonia, broad based gait, hypotonic-atactic movements | truncal hypotonia, swallowing difficulties | mild gait ataxia, flexion deformity of left hip, hyperlordotic lumbar spine | hyperactive deep tendon reflexes, unsteady gait | motor slowness and moderate akinesia, ataxic gait, truncal hypotonia, dystonic postures of hands and feet, plastic hypertonia | truncal hypotonia, orthostatic truncal tremor, slight pyramidal tetraparesis, gait ataxia | truncal hypotonia | truncal hypotonia, orofacial hypotonia, wide-based gait | clumsy/ataxic gait 10, truncal hypotonia 10, facial hypotonia 4, normal exam 2 |

* patients are ordered by mutation from the 5' end of the gene. NA: not available; m: months; y: years; mean age eval.: mean age at evaluation; SD: standard deviation.

Table 2. Epilepsy features in SYNGAP1-related encephalopathy. (1)

| Patient ID | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age at seizure onset (m:months or y:years)** | | 24 m | 24 m | 22 m | 4 y | 3 y | 30 m | 5 y | 33 m | 30 m |
| **Seizure type at onset** | | myoclonic jerks (falls) | drop attacks | febrile seizure | GTCS, abs. | tonic febrile and afebrile, myoclonic jerks | not defined | abs. | abs. | head nodding, abs. |
| **Seizure types during disease course** | | myoclonic abs., eye myoclonia | GTCS, clonic, drop attacks, myoclonic jerks, | atypical abs., myoclonic jerks, atonic seizures | abs. | head falls, massive myoclonic jerks of arms, myoclonic abs. | abs. | abs. | abs. | myoclonic jerks (mainly arms) |
| **Epilepsy syndrome** | | EMA | DS then atypical GGE | unclassified GGE | unclassified GGE with absences | unclassified GGE | unclassified GGE with absences | unclassified GGE with absences | unclassified GGE with absences | unclassified GGE with absences |
| **Febrile seizures** | | no | yes | yes | no | rare | no | no | no | no |
| **Status epilepticus** | | no | no | no | no | no | no | no | no | no |
| **Frequency of seizures** | | >10 daily then 2/day presently nearly seizure-free | daily -> one per week-> almost seizure free | 1-2/month | seizure free for several years | controlled | <1/day | several/day | daily | up to 100/day |
| **Lifetime / current anti-epileptic treatment** | | VPA | VPA then LEV | LEV | VPA | VPA, OXC, LTG, LEV, CBZ / VPA + LTG | VPA, CBZ | LTG | VPA, LTG / LTG | VPA, ETH, LEV, CLN*, ketogenic diet / none |
| **Pharmoresistance** | | no | no | no | no | partial | no | no | yes | yes |
| **EEG** | Age at examination | 9 y | 2 to 15 y | 4.5 y | 9 y | 1 to 5 y | 3 to 8 y | 5 y | 8.5 y | 5 y |
| | Main abnormalities | generalized bursts of S | generalized PsW and photoconvulsions | frontal and generalized SpW and PSW | irregular spike-slow-wave-complexes: generalized, maximum frontal; beta-waves | 1 y: normal; 3.5 y: generalized bursts of S, S + SW in posterior areas; 5 y: slow background activity, fronto-temporal bursts of SW | bi-occipital SW, S and SpW, bi-central anomalies | NA | diffuse SpW, PSp or PSW | bursts of bilateral S and PSp with maximum in posterior regions |
| | Triggers of seizures | none | PS | no | none | none | none | NA | none | chewing, emotions |

Table 2. Epilepsy features in SYNGAP1-related encephalopathy. (2)

| Patient ID | | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | Summary |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age at seizure onset (m:months or y:years)** | | one seizure at 3.5 y | 24 m | 12 m | <2 y | 5 y | 22 m | 27 m | 8 y | mean 35.4 m, median age 28.5 m, 75th centile 39 m |
| **Seizure type at onset** | | non febrile | febrile seizure | febrile seizures | astatic seizures | eyelid myoclonia | atonic | myoclonic seizures | NA | |
| **Seizure types during disease course** | | NA | eyelid myoclonia | eyelid myoclonia, atypical abs., myoclonic jerks | myoclonic astatic | eyelid myoclonia, myoclonic abs. | GTCS, focal, atypical abs., myoclonic jerks | myoclonic jerks, GTCS, atypical abs. | atypical absences | myoclonic jerks 7, atypical abs. 5, abs. 4, eyelid myoclonia 3, clonic or GTCS 3, myoclonic abs.3, atonic 2 |
| **Epilepsy syndrome** | | NA | unclassified GGE | unclassified GGE | DS | unclassified GGE | DS | unclassified GGE | unclassified | unclassified 12 , DS 3, EMA 1 |
| **Febrile seizures** | | no | yes | yes | no | no | no | no | no | yes 4 |
| **Status epilepticus** | | no | no | no | no | no | clusters of seizures/no status epilepticus | no | no | n=0 |
| **Frequency of seizures** | | only one until now | several/day | several/month | 10/day | 100/day | several/day | several/day | 4-8/month | |
| **Lifetime / current anti-epileptic treatment** | | no | VPA | LEV, TPM | VPA, ZNM, LTG | LEV, ETH | VPA, LTG + VPA, LTG, LEV, CLN, ACTH | VPA, CBL, TPM / ketogenic diet | VPA | |
| **Pharmoresistance** | | not applicable | no | yes | yes | yes | yes | yes | partial | yes 9, no 7 |
| **EEG** | Age at examination | 1.8 and 2.5 y | 3 y | 3 to 8 y | 2 to 10 y | 2 to 5 y | 7 | 8.5 y | 2.3 y | |
| | Main abnormalities | 1st: SW; 2nd: no abnormalities | abnormal background, generalized slowing, recorded seizures with eyelid myoclonia and generalized seizure patterns | bursts of S and SW in the occipital region after eye closure | generalized SpW | 2y: normal; 5y: ictal bursts of diffuse PSW with posterior predominance after eyes closer and photic stimulation | focal SpW in central-parietal areas, generalized S and PSW | generalized PSW and frontal Sw | multifocal SW | |
| | Triggers of seizures | none | PS | FOS | PS | PS, FOS | none | none | PS | PS 4, FOS 1, PS + FOS 1, other 1 |

GTCS: generalized tonic-clonic seizures; abs.: absences; EMA: epilepsy with myoclonic absences; GGE: genetic generalized epilepsy; DS: Doose syndrome. Anti-epileptic drugs: VPA: valproic acid, LEV: levetiracetam, ETH: ethosuximide, OXC: oxcarabzepine, CBZ: clobazam, ZNM: zonisamide, LTG: lamotrigin, TPM: topiramate, CLN: clonazepam, ACTH: adrenocorticotropic hormone. EEG: electroencephalogram; SW: slow waves; S: spikes; SpW: spike-waves; PSW: polyspike-waves; PSp: polyspikes; PS: photosensitivity; FOS: fixation off sensitivity.
*epilepsy aggravated

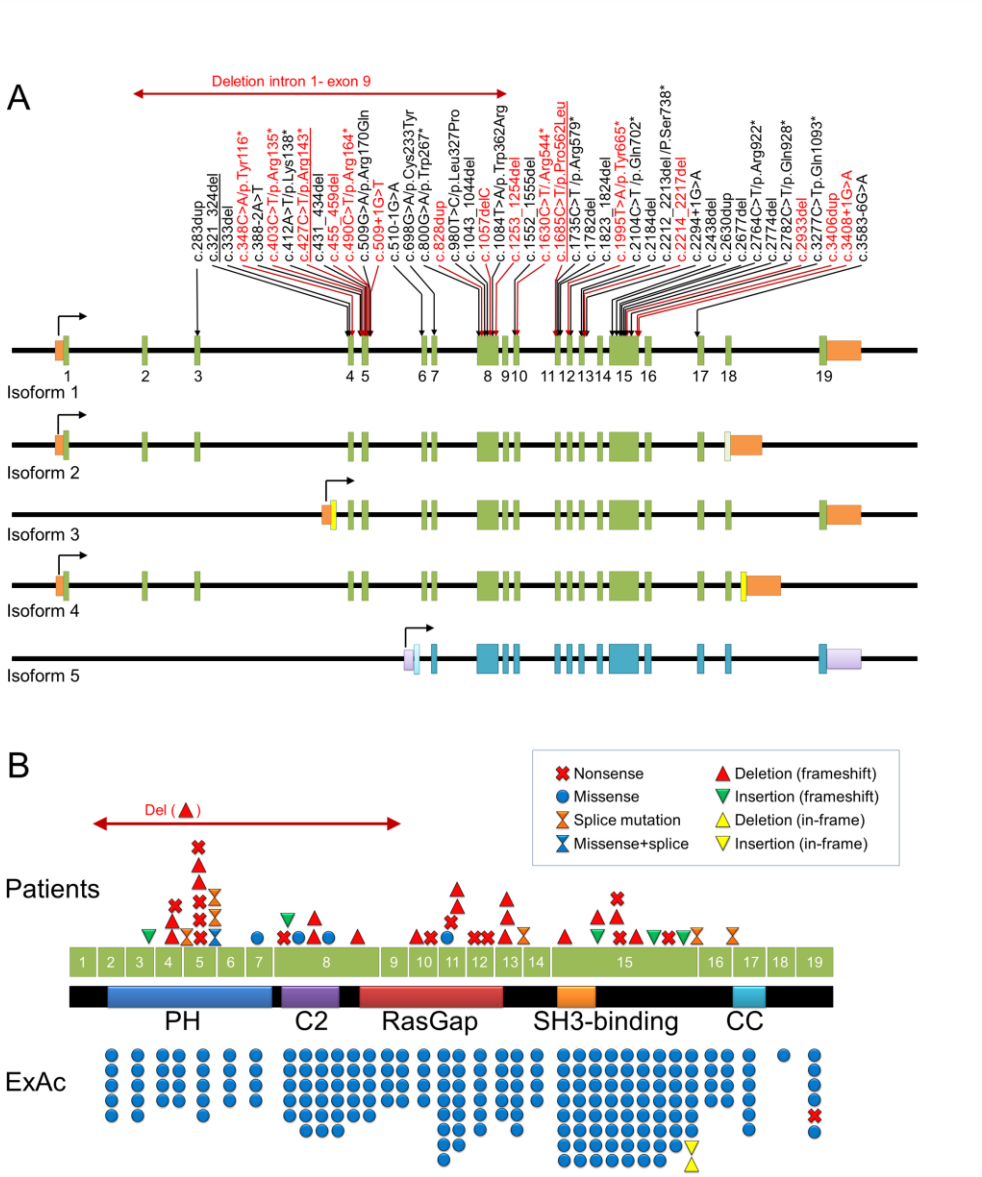

A
Deletion intron 1- exon 9
c.283dup
c.321_324del
c.333del
c.348C>A/p.Tyr116*
c.388-2A>T
c.403C>T/p.Arg135*
c.412A>T/p.Lys138*
c.427C>T/p.Arg143*
c.431_434del
c.455_459del
c.490C>T/p.Arg164*
c.509G>A/p.Arg170Gln
c.509+1G>T
c.510-1G>A
c.698G>A/p.Cys233Tyr
c.800G>A/p.Trp267*
c.828dup
c.980T>C/p.Leu327Pro
c.1043_1044del
c.1057delC
c.1084T>A/p.Trp362Arg
c.1253_1254del
c.1552_1555del
c.1630C>T/p.Arg544*
c.1685C>T/p.Pro562Leu
c.1735C>T/p.Arg579*
c.1782del
c.1823_1824del
c.1995T>A/p.Tyr665*
c.2104C>T /p.Gln702*
c.2184del
c.2212_2213del /P.Ser738*
c.2214_2217del
c.2294+1G>A
c.2438del
c.2630dup
c.2677del
c.2764C>T/p.Arg922*
c.2774del
c.2782C>T/p.Gln928*
c.2933del
c.3277C>Tp.Gln1093*
c.3406dup
c.3408+1G>A
c.3583-6G>A
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Isoform 1
Isoform 2
Isoform 3
Isoform 4
Isoform 5
B
Nonsense
Missense
Splice mutation
Missense+splice
Deletion (frameshift)
Insertion (frameshift)
Deletion (in-frame)
Insertion (in-frame)
Del ( )
Patients
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
PH
C2
RasGap
SH3-binding
CC
ExAc

Figure 1.

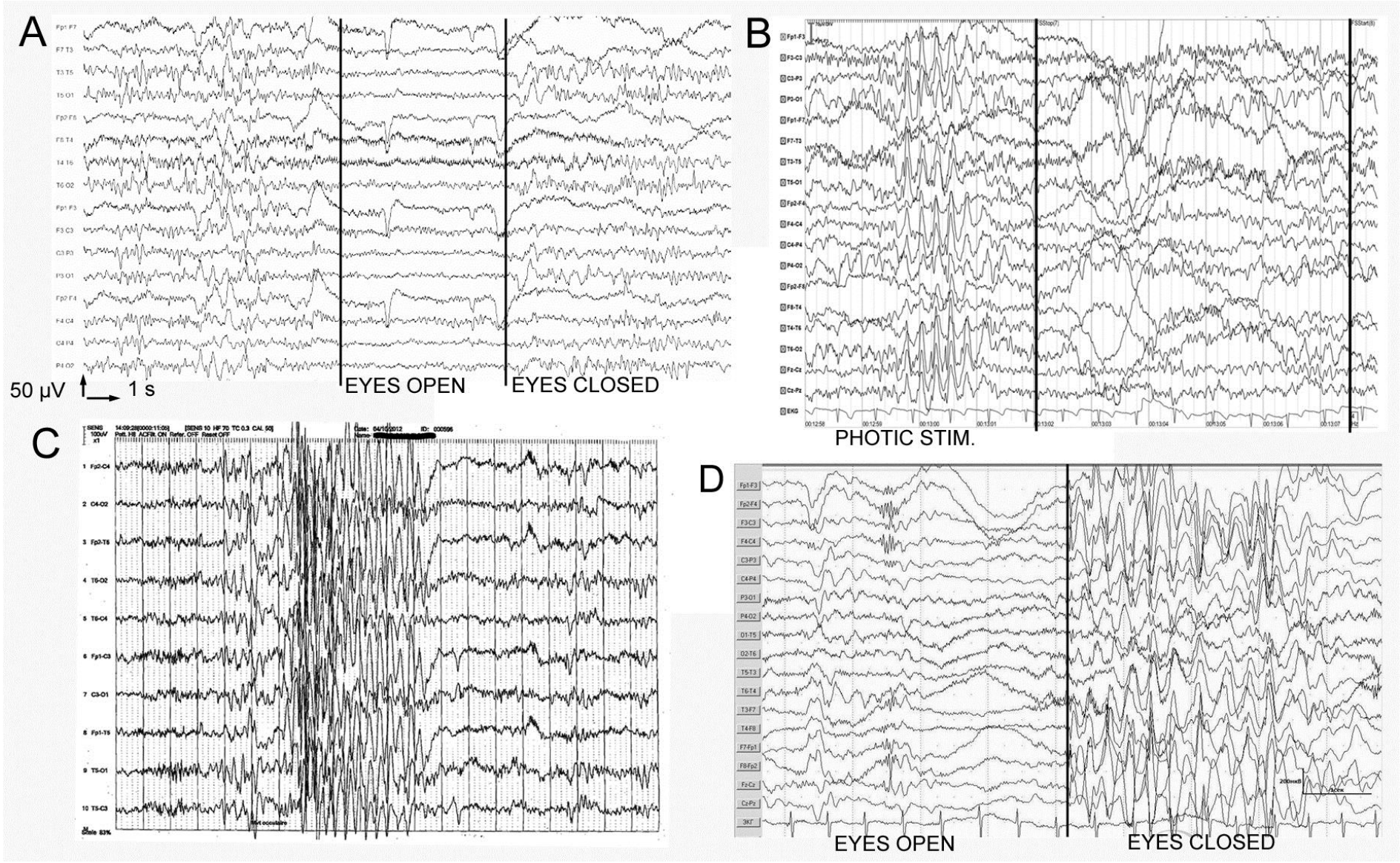

A
50 µV
1 s
EYES OPEN
EYES CLOSED
B
PHOTIC STIM.
C
D
EYES OPEN
EYES CLOSED

Figure 2

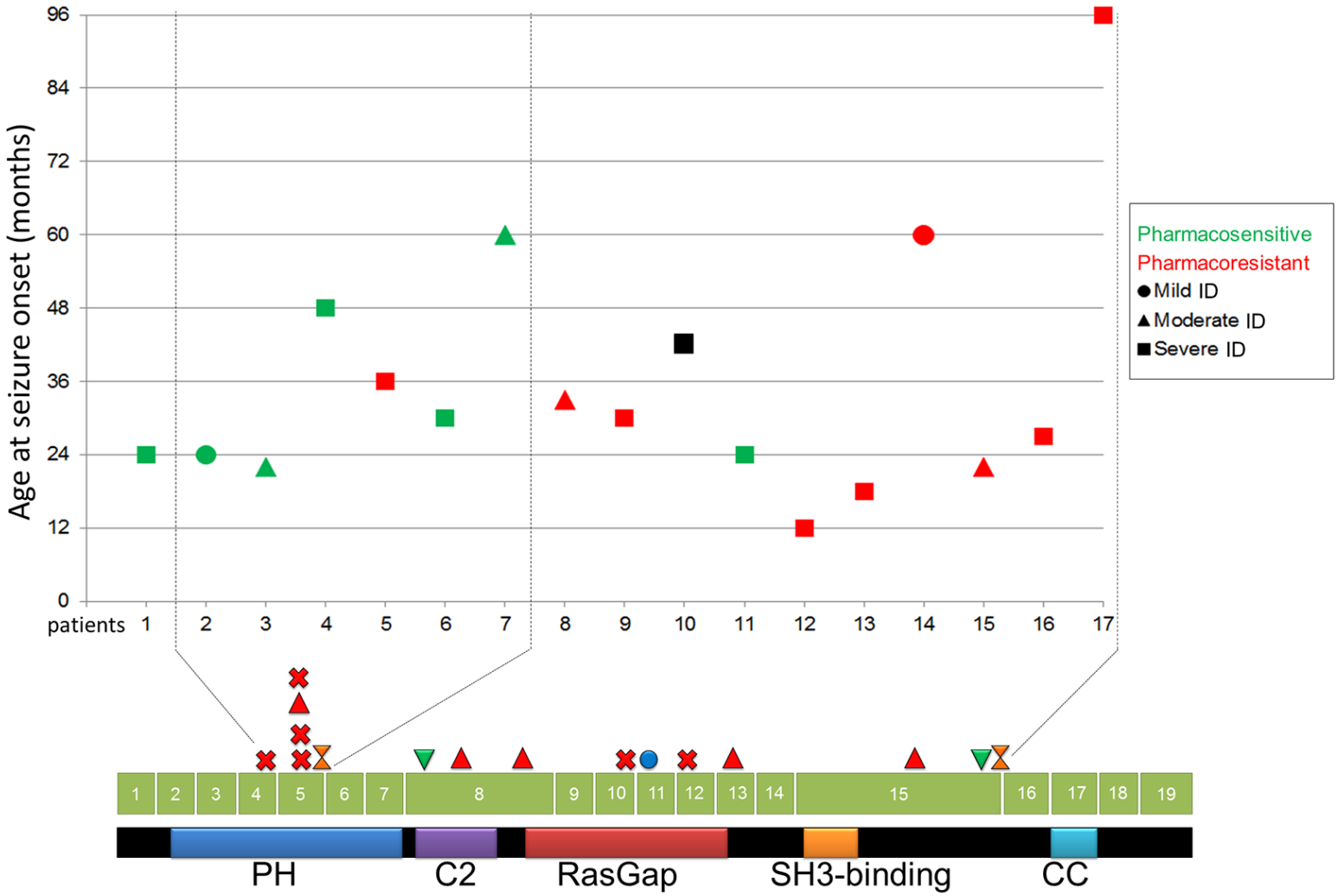
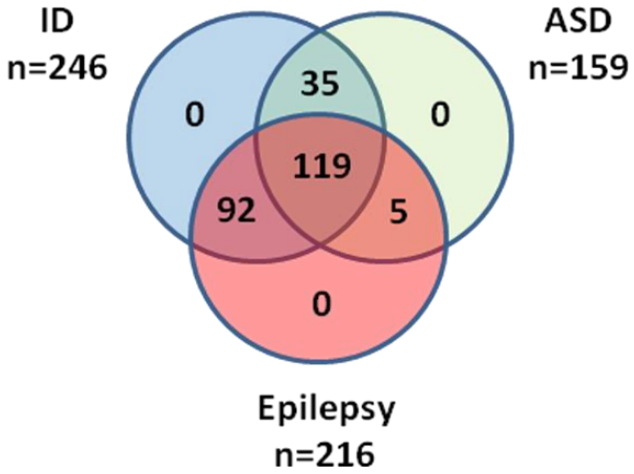

Age at seizure onset (months)
96
84
72
60
48
36
24
12
0
patients 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Pharmacosensitive
Pharmacoresistant
Mild ID
Moderate ID
Severe ID
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
PH
C2
RasGap
SH3-binding
CC

Figure 3.

**Supplementary Methods.**
Clinical characteristics of the 251 patients with variable neurodevelopmental phenotypes included in this study (ID: intellectual disability, ASD: autism spectrum disorder).




Among epileptic patients, 158 had a non-syndromic or unclassified epilepsy. The epilepsy type or the main seizure type in the 58 other patients were the following: West syndrome (n=24), epilepsy with myoclonic absences (n=5), Doose syndrome/ epilepsy with myoclonic atonic seizures (n=1), malignant migrating partial seizures of infancy (n=1), unspecified neonatal epileptic encephalopathy (n=7), myoclonic epilepsy (n=4), absence epilepsy (n=3), generalized epilepsy with tonic-clonic seizures (n=13).

Supplementary Table 1. Complement to genetic and clinical data of the 17 patients with *SYNGAP1* mutations. (1)

| Patient ID | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Genetics** | Family history | none | cousin with absence epilepsy | none | none | none | none | none | none | none |
| | Parental age at birth | Mo=35, Fa=18 | NA | Mo=34, Fa=35 | Mo=40, Fa=36 | Mo=40, Fa=47 | NA | Mo=40, Fa=30 | Mo=28, Fa=28 | NA |
| | Other significant genetics abnormalities | none | none | array-CGH: Xp22.33 dup 491 kb - 511 kb (inherited from healthy father) | *de novo* VOUS: *RANBP2:* c.8146G>A (p.K2716E); *KLHL8:* c.95C>G (p.S32L) | variant in *MBD5* inherited from one parent | none | none | none | RBFOX1-deletion (hq19 chr16:6340454-6814185) |
| | Method of molecular diagnosis | microarray analysis | CeGat panel | CeGat panel | WES | SYNGAP1 testing | WES | panel (genetikum ® ) | SYNGAP1 testing | CeGat panel |
| **Neonatal period** | Pregnancy and delivery | probably normal, fullterm | unremarkable | Apgar 8/10/10 | unremarkable, cesarean section week 39, Apgar scores 10/10 | unremarkable | twin pregnancy, born at 8 months, delivery unremarkable | unremarkable | mild gestational diabetes, fullterm, Apgar 10 | unremarkable |
| | Birth length in cm (perc) / weight in g (perc) / head circumference in cm (perc) | NA | 52 (50th) / 3010 (50th) / 34 (25th) | 55 (90th) / 4125 (96th) / 36.5 (98th) | 49 (10-50th) /3160 (10-50th)/ 34 (10-50th) | 50 (10-50th) / 3230 (10-50th) / 34.5 (10-50th) | NA / 2740 (NA) / 34 (NA) | 52 / 3880 / 36 | 48 (10th) / 3300 (25th) / 33 (25th) | 48 (10th)/ 3420 (10-50th) / NA |
| | Neonatal findings | NA | none | none | muscular hypertonia during first months | none | none | none | none | none |
| **Autism spectrum disorder** | Alteration of nonverbal communication | mild | mild | moderate | no | moderate | severe | NA | mild | severe |
| | Repetitive behaviours | no | no | no | yes | yes | yes | little | no | no |
| | Stereotypies | no | no | no | yes | yes | yes | no | yes | no |
| | Social interactions | normal | no social reactions to peers, lack of eye-contact, no empathy | altered | normal | very poor | very poor | altered | altered | altered |
| | Behaviour troubles | temper tantrum then peaceful behaviour | aggr. especially after acoustic or tactile stimuli | severe social anxiety | hetero- / autoagr. | anxiety | restlessness, aggr. | autoaggr., temper tantrum | temper tantrum, occasional aggr. | anxiety, incontrolled panic attacks |
| **Brain imaging (age)** | | normal (9 y) | normal (13 y) | normal (3.8 y) | myelination not yet complete (4 y) | normal (2 and 9 y) | normal with small cyst in the right pontocerebellar angle | normal (2 y) | normal (4 y) | normal (3 y) |

Supplementary Table 1. Complement to genetic and clinical data of the 17 patients with *SYNGAP1* mutations. (2)

| Patient ID | | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|
| **Genetics** | Family history | none | none | none | none | none | none | none | none |
| | Parental age at birth | Mo=34, Fa=35 | Mo=46, Fa=38 | NA | Mo=30, Fa=33 | Mo=26, Fa=26 | Mo=31, Fa=27 | Mo=37, Fa=40 | Mo=31, Fa=28 |
| | Other significant genetics abnormalities | none | VOUS inherited from the mother: *SCN9A:* c.4282G>A and c.5624G>A, *ARX* c.1462A>G | none | none | none | none | array-CGH: 3q12.2-12.3 dup 1.55-1.60 MB (inherited from healthy father) | none |
| | Method of molecular diagnosis | WES | CeGaT panel | WES | WES | WES | MIP gene panel | CeGaT panel | MR-Panel (Kingsmore Panel) |
| **Neonatal period** | Pregnancy and delivery | unremarkable | pathologic, otherwise normal delivery, Apgar 10/10 | IVF; emergency LSCS at 36 weeks due to reduced fetal movements | unremarkable | unremarkable | born at 37 WG, premature detachment of the placenta, Apgar 10 | gestation diabetes, Apgar 9/10/10 | 36+6 week of pregnancy, APGAR 8/8/8, intensive care |
| | Birth length in cm (perc) / weight in g (perc) / head circumference in cm (perc) | 49 (10th) /3160 (25th) / 36 (50th) | NA | 47 (50th) / NA / NA | 50 (50th) / 3500 (50th) / 34 (10-50th) | 49 (10-50th) / 3120 (10-50th) / 34 (10-50th) | 52 (90-97th) / 2700 (25th) /33 (10th) | 49 (14th) / 3350 (46th) / 35 (52th) | 47.5 (<10th) / 2490 (50th) / 33,5 (>50th) |
| | Neonatal findings | none | none | slow to suck and feed | none | none | hyperbilirubinemia | none | hypotonia, bradycardia, hypothermia, hyperbilirubinemia |
| **Autism spectrum disorder** | Alteration of nonverbal communication | moderate-severe | moderate-severe | moderate | moderate | NA | NA | severe | severe |
| | Repetitive behaviours | no | yes | no | no | NA | NA | yes | yes |
| | Stereotypies | yes | yes | yes | no | yes | yes | yes | yes |
| | Social interactions | very poor | very poor | altered | altered | NA | NA | very poor | poor |
| | Behaviour troubles | hetero- / autoaggr. | NA | NA | aggr. | NA | NA | auto- and hetero-aggr. | altered |
| **Brain imaging (age)** | | arachnoid cysts (1.8 y) | normal (3 y) | normal (8 y) | normal (8 y) | normal (5 y) | slight dilatation of the anterior horns of lateral ventricles (3 and 5 y) | normal (28 m and 6 y) | bilateral T2 hypersignal of fasciculus longitudinalis medialis, piritrigonal white matter and central parts of centrum semiovale (15 m) |

Mo: mother; Fa: father; VOUS: variant of unknown signification; WES: whole exome sequencing; ID: intellectual deficiency; NA: not available; m: months; y: years; aggr.: aggressiveness; SD: standard deviation; WG: weeks of gestation; IVF: in vitro fertilization; LCSC: lower segment Caesarean section.

Supplementary Table 2. Molecular data of patients with *SYNGAP1* encephalopathy reported in the literature and in the present study.

| Type | Mutation nomenclature (GRCh37) | Exon | Isoform | Domain | Expected effect | Mutation type | Base change (NM_006772.2) | Amino acid change | Inheritance | Patient ID | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Point | Chr6:g.33393668dup | 3 | 1, 2, 4 | | Hap | frameshift | c.283dup | p.His95Profs*5 | Mosaic father | Patient 1 | Berryer et al, 2013 |
| Point | Chr6:g.33399963_33399966del | 4 | 1, 2, 3, 4 | | Hap | frameshift | c.321_324del | p.Lys108Valfs*25 | de novo | R0038372 | Hamdan et al., 2011 |
| Point | Chr6:g.33399963_33399966del | 4 | 1, 2, 3, 4 | | Hap | frameshift | c.321_324del | p.Lys108Valfs*25 | de novo | T19988 | Carvill et al., 2013 |
| Point | Chr6:g.33399975del | 4 | 1, 2, 3, 4 | | Hap | frameshift | c.333del | p.Lys114Serfs*20 | de novo | 217-14271-3940 | O'Roak et al., 2014 |
| Point | Chr6:g.33399990C>A | 4 | 1, 2, 3, 4 | | Hap | nonsense | c.348C>A | p.Tyr116* | de novo | Patient #2 | von Stüpnagel et al., 2015; this study |
| Point | Chr6:g.33400460A>T | intron 4 | 1, 2, 3, 4 | | Hap | splice | c.388-2A>T | p.? | de novo | T15924 | Carvill et al., 2013 |
| Point | Chr6:g.33400477C>T | 5 | 1, 2, 3, 4 | | Hap | nonsense | c.403C>T | p.Arg135* | de novo | Patient #3 | This study |
| Point | Chr6:g.33400486A>T | 5 | 1, 2, 3, 4 | | Hap | nonsense | c.412A>T | p.Lys138* | de novo | R0033401 | Hamdan et al., 2009 |
| Point | Chr6:g.33400501C>T | 5 | 1, 2, 3, 4 | | Hap | nonsense | c.427C>T | p.Arg143* | de novo | T22387 | Carvill et al., 2013 |
| Point | Chr6:g.33400501C>T | 5 | 1, 2, 3, 4 | | Hap | nonsense | c.427C>T | p.Arg143* | de novo | Patient #4 | This study |
| Point | Chr6:g.33400505_33400508del | 5 | 1, 2, 3, 4 | | Hap | frameshift | c.431_434del | p.Thr144Serfs*29 | de novo | 259214 | Parker et al., 2015 |
| Point | Chr6:g.33400529_33400533del | 5 | 1, 2, 3, 4 | PH | Hap | frameshift | c.455_459del | p.Arg152Glnfs*14 | de novo | Patient #5 | This study |
| Point | Chr6:g.33400564C>T | 5 | 1, 2, 3, 4 | PH | Hap | nonsense | c.490C>T | p.Arg164* | de novo | Patient #6 | This study |
| Point | Chr6:g.33400583G>A | 5 (last nucleotide) | 1, 2, 3, 4 | PH | Hap | missense +splice | c.509G>A | p.Arg170Gln | de novo | 259840 | Parker et al., 2015 |
| Point | Chr6:g.33400584G>T | intron 5 | 1, 2, 3, 4 | PH | Hap | splice | c.509+1 G>T | p.? | de novo | Patient #7 | This study |
| Point | Chr6:g.33402928G>A | intron 5 | 1, 2, 3, 4 | PH | Hap | splice | c.510-1G>A | p.? | de novo | Patient 16 | De Ligt et al., 2012 |
| Point | Chr6:g.33403326G>A | 7 | All | PH | mis | missense | c.698G>A | p.Cys233Tyr | de novo | 12804.p1 | O'Roak et al., 2014 |
| Point | Chr6:g.33405482G>A | 8 | All | C2 | Hap | nonsense | c.800G>A | p.Trp267* | de novo | T15923 | Carvill et al., 2013 |
| Point | Chr6:g.33405510dup | 8 | All | C2 | Hap | frameshift | c.828dup | p.Lys277Glnfs*7 | NA | Patient #8 | This study |
| Point | Chr6:g.33405662T>C | 8 | All | C2 | mis | missense | c.980T>C | p.Leu327Pro | de novo | LEM300468 + LEM300469 | Parker et al., 2015 |
| Point | Chr6:g.33405725_33405726del | 8 | All | C2 | Hap | frameshift | c.1043_1044del | p.Val348Alafs*70 | de novo | Patient 8 | Vissers et al., 2010 |
| Point | Chr6:g.33405739del | 8 | All | C2 | Hap | frameshift | c.1057del | p.Leu353Trpfs*13 | NA | Patient #9 | This study |
| Point | Chr6:g.33405766T>A | 8 | All | C2 | mis | missense | c.1084T>A | p.Trp362Arg | de novo | Patient 2 | Berryer et al, 2013 |
| Point | Chr6:g.33405935_33405936del | 8 | All | RASGAP | Hap | frameshift | c.1253_1254del | p.Lys418Argfs*54 | de novo | ER53899 and Patient #10 | Rauch et al., 2012; this study |
| Point | Chr6:g.33406572_33406575del | 10 | All | RASGAP | Hap | frameshift | c.1552_1555del | p.Tyr518Asnfs*8 | de novo | 259041 | Parker et al., 2015 |
| Point | Chr6:g.33406650C>T | 10 | All | RASGAP | Hap | nonsense | c.1630C>T | p.Arg544* | de novo | Patient #11 | This study |
| Point | Chr6:g.33408514C>T | 11 | All | RASGAP | mis | missense | c.1685C>T | p.Pro562Leu | de novo | Patient 3 | Berryer et al, 2013 |
| Point | Chr6:g.33408514C>T | 11 | All | RASGAP | mis | missense | c.1685C>T | p.Pro562Leu | de novo | Patient #12 | This study |
| Point | Chr6:g.33408564C>T | 11 | All | RASGAP | Hap | nonsense | c.1735C>T | p.Arg579* | de novo | R0032180 | Hamdan et al., 2009 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Point | Chr6:g.33408612del | 11 | All | RASGAP | Hap | frameshift | c.1782del | p.Leu595Cysfs*55 | de novo | 212-21043-1 | O'Roak et al., 2014 |
| Point | Chr6:g.33408652_33408653del | 11 | All | RASGAP | Hap | frameshift | c.1823_1824del | p.Phe608Trpfs*9 | de novo | 13073.p1 | O'Roak et al., 2014 |
| Point | Chr6:g.33409031T>A | 12 | All | RASGAP | Hap | nonsense | c.1995T>A | p.Tyr665* | NA | Patient #13 | This study |
| Point | Chr6:g.33409140C>T | 12 | All | RASGAP | Hap | nonsense | c.2104C>T | p.Gln702* | de novo | T2528 | Carvill et al., 2013 |
| Point | Chr6:g.33409426del | 13 | All | RASGAP | Hap | frameshift | c.2184del | p.Asn729Thrfs*31 | de novo | Patient 5 | Berryer et al, 2013; Dyment et al, 2015 |
| Point | Chr6:g.33409454_33409455del | 13 | All | | Hap | frameshift | c.2212_2213del | p.Ser738* | de novo | Patient 4 | Berryer et al, 2013 |
| Point | Chr6:g.33409456_33409459del | 13 | All | | Hap | frameshift | c.2214_2217del | p.Glu739Glyfs*20 | de novo | Patient #14 | This study |
| Point | Chr6:g.33409537G>A | intron 13 | All | | Hap | splice | c.2294+1G>A | p.? | de novo | R0034526 | Hamdan et al., 2011; Xiong et al., 2015 |
| Point | Chr6:g.33410767del | 15 | All | SH3 | Hap | frameshift | c.2438del | p.Leu813Argfs*23 | de novo | R0033475 | Hamdan et al., 2009 |
| Point | Chr6:g.33410959dup | 15 | All | | Hap | frameshift | c.2630dup | p.Thr878Aspfs*60 | de novo | BO14/09 | Rauch et al., 2012 |
| Point | Chr6:g.33411006del | 15 | All | | Hap | frameshift | c.2677del | p.Gln893Argfs*184 | de novo | R0034759 | Hamdan et al., 2011 |
| Point | Chr6:g.33411093C>T | 15 | All | | Hap | nonsense | c.2764C>T | p.Arg922* | de novo | 264135 | Parker et al., 2015 |
| Point | Chr6:g.33411103del | 15 | All | | Hap | frameshift | c.2774del | p.Leu925Profs*152 | de novo | 259606 | Parker et al., 2015 |
| Point | Chr6:g.33411111C>T | 15 | All | | Hap | nonsense | c.2782C>T | p.Gln928* | de novo | 258913 | Parker et al., 2015 |
| Point | Chr6:g.33411262del | 15 | All | | Hap | frameshift | c.2933del | p.Pro978Hisfs*99 | de novo | Patient #15 | This study |
| Point | Chr6:g.33411606C>T | 15 | All | | Hap | nonsense | c.3277C>T | p.Gln1093* | de novo | Pat. 8 "258536" | Parker et al., 2015 |
| Point | Chr6:g.33411735dup | 15 | All | | Hap | frameshift | c.3406dup | p.Gln1136Profs*17 | NA | Patient #16 | This study |
| Point | Chr6:g.33411738G>A | intron 15 | All | | Hap | splice | c.3408+1G>A | p.? | de novo | Patient #17 | This study |
| Point | Chr6:g.33414346G>A | intron 16 | All | CC | Hap | splice | c.3583-6G>A | p.Val1195Alafs*27 | de novo | APN-139 | Redin et al., 2014 |

| **Type** | **Mutation nomenclature (GRCh37)** | **Type** | | | | **Size** | **Genes altered** | **Consequence** | **Inheritance** | | **Reference** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CNV | Chr6:33389736-33406339 | Deletion | All | PH, C2, RASGAP | Hap | 16.6 Kb | SYNGAP1 (intron 1 - exon 9) | p.? | de novo | Patient #1 | This study |
| CNV | Chr6:33356364-33406339 | Deletion | All | PH, C2, RASGAP | Hap | 50 Kb | SYNGAP1 (5'UTR-exon 9) + 3 others | p.? | de novo | Case report | Writzl et al., 2013 |
| CNV | Chr6:33291871-33404064 | Deletion | All | PH, C2, RASGAP | Hap | 112 Kb | SYNGAP1 ('UTR-intron8) + 5 others | absence of protein synthesis | de novo | Case report | Pinto et al., 2010 |
| CNV | NA | Deletion | All | All | Hap | 300 Kb | Entire gene + 6 others | absence of protein synthesis | de novo | Case report | Zollino et al., 2011 |
| CNV | Chr6:33201710-33595089 | Deletion | All | All | Hap | 393 Kb | Entire gene + 18 others | absence of protein synthesis | de novo | Case report | Parker et al., 2015 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CNV | Chr6:33273955–34086729 | Deletion | All | All | Hap | 813 Kb | Entire gene + 18 others | absence of protein synthesis | de novo | Case report | Krepischi et al., 2010 |
| CNV | t(6;22)(p21.32;q11.21) | Balanced translocation | | | | | Interrupts SYNGAP1 | p.? | de novo | Case report | Klitten et al., 2013 |

Hap: haploinsufficiency.

Supplementary Table 3

| **Reference** | | | | |
|---|---|---|---|---|
| **Patient** | 259041 | 259840 | 258913 | 264135 |
| **Sex** | F | F | F | F |
| **Age (in years)** | 7 | 8 | 7 | 3 |
| **Developmental/neurological evaluation** | | | | |
| **Evaluation of developmental delay/intellectual disability** | moderate | moderate | moderate | moderate |
| **Age of sitting** | 20 m | 7 m | 12 m | 24 m |
| **Age of walking** | 24 m | 36 m | 60 m | does not walk |
| **Evaluation of speech** | 50 words, two-word sentences | single words | single words | no speech |
| **Neurological signs** | unsteady gait | wide-based gait | wide-based gait | NA |
| **OFC** | -1.6 SD | + 0.8 SD | - 2.6 SD | - 2.5 SD |
| **Behavior** | aggressiveness, routine-orientated | autism, aggressiveness, routine-orientated, obsessions | aggressiveness, routine-orientated, stereotypies | autism, aggressiveness, obsessions |
| **Brain MRI** | NA | normal | normal | normal |
| **Epilepsy** | no epilepsy | yes | yes | yes |
| **Epilepsy onset** | NA | 6 y | 2 y | 2 y |
| **Seizure types** | NA | mj, abs | mj, abs, drop at | abs, drop at |
| **Epilepsy outcome** | NA | NA | NA | NA |
| **EEG** | NA | NA | NA | NA |

NA=not available or not applicable; F= female; M=male; m= months; y=years; ADHD=
Seizures: a = aura; abs = absences; atyp abs = atypical absences; drop at = drop attac
EEG: DS= diffuse slowing; ETPs= epileptic potentials; GPSW= generalized poly spike

| **Parker et al. Am J Med Genet 2015** | | | | |
|---|---|---|---|---|
| 259214 | 259606 | 258536 | Pat. 8 "258536" | LEM300469 |
| M<br>8 | F<br>12 | F<br>5 | F<br>8 | M<br>14 |
| | | | | |
| moderate | moderate | moderate | moderate | severe |
| 15 m | NA | 7 m | 12 m | 24-36 m |
| 17 m | 24 m | 19 m | 30 m | > 60 m |
| 200 single words | 20 single words | 2-word sentences | 4-word sentences | absent |
| NA | wide-based gait | unsteady gait | NA | ataxic gait |
| - 1.1 SD | - 1.83 SD | - 2.9 SD | 0 SD | - 0.98 SD |
| autism, aggressiveness, obsessions | aggressiveness, stereotypies | autism, aggressiveness, obsessions | ASD | autism, laughter outbursts, routine-orientated, obsessions |
| normal | normal | NA | NA | normal |
| no epilepsy | yes | no epilepsy | yes | yes |
| NA | 3 y | NA | 5 y | 13 m |
| NA | head drops & blinking, PS | NA | abs, drop at | FS, abs, drop at, occasional tc, mj |
| NA | NA | NA | NA | NA |
| NA | NA | NA | NA | NA |

attention deficit hyperactivitiy disorder; ASD = autistic spectrum disorder; EE= epileptic
ks; FDS = focal discognitive seizures; FS = febrile seizures; GTCS = generalized tonic
waves;  GSW= generalized spike waves; MFD= multi focal discharges; GS=generalize

| | Redin et al. J Med Genet 2014 | Carvill et al. Nat Genet 2013 | | | | |
|---|---|---|---|---|---|---|
| LEM300468 | APN-139 | T15923 | T22387 | T19988 | T15924 | T2528 |
| M<br>14 | M<br>6 | F<br>26 | F<br>7 | M<br>18 | M<br>11 | M<br>26 |
| | | | | | | |
| severe | moderate | severe | severe | moderate | severe | moderate |
| 24-36 m | delayed | NA | NA | NA | NA | NA |
| > 60 m | delayed | NA | NA | NA | NA | NA |
| absent | absent | NA | NA | NA | NA | NA |
| ataxic gait | hypotonia, cerebellar syndrome | NA | NA | NA | NA | NA |
| - 1.2 SD | NA | NA | NA | NA | NA | NA |
| autism, laughter outbursts, routine-orientated, obsessions | stereotypic movements, hetero and auto-aggressiveness | ASD | ASD | NA | ASD | NA |
| normal | NA | NA | NA | NA | NA | NA |
| yes | NA | yes | yes | yes | yes | yes |
| 13 m | NA | 36 | 10 | NA | 6 | 18 |
| FS, abs, drop at, occasional tc, mj | NA | atyp abs, a, FDS, mj | abs, mj | FDS | abs, tc | FS; abs, a, FDS, mj, tc, NCS |
| NA | NA | EE | EE | EE | EE | EE |
| NA | NA | SSW, MFD | GSW | MFD, DS | GSW, MFD, GPSW | SSW, bioccipital ETPs, DS |

: encephalopathy; EEG= electro encephalogram; mod.= moderate; MRI= magnetic resonance imagir
clonic seizures; myo abs = myoclonic absence; myo at = myoclonic atonic; mj = myoclonic jerks; PC
ed spikes; GSW=slow waves; poly-SW= poly spike waves; SSW= slow spike waves

| Berryer et al. Hum Mutat 2013 | | | | | de Light et al. New Engl J Med 2012 | Hamdan e |
|---|---|---|---|---|---|---|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 16 | Patient 1 R0034759 |
| F | M | F | M | F | M | F |
| 16 | 3.5 | 4.3 | 2.5 | 9.3 | 7.7 | 3.7 |
| | | | | | | |
| moderate | moderate | mild | moderate | moderate/severe | moderate | moderate/severe |
| 6 m | NA | NA | 9 m | NA | 12 m | NA |
| 10.5 m | 30 m | 15 m | 21 m | 26 m | 22 m | 22 m |
| impaired | absent | delayed | absent | impaired | absent | absent |
| none | hypotonia | none | hypotonia | ataxic gait | NA | hypotonia |
| normal | normal | normal | "microcephaly" | normal | normal | normal |
| recurrent seasonal depression | ASD | autism, irritability, automutilations, sleeping difficulties | sleeping difficulties and aggressiveness | ASD | self-mutilation, inappropriate laughters | attention deficit; aggressive adverse behavior |
| normal | normal | NA | normal | normal | normal | normal |
| yes | yes | no epilepsy | yes | yes | yes | yes |
| 18 | 30 | NA | 36 | 38 | 60 | 29 |
| myo abs, abs, mj | drop at, abs | NA | NA | drop at, abs | NA | head drop, abs |
| poor control | poor control | NA | NA | good control | NA | good control |
| GSW posterior predominance | GSW posterior predominance | "intermittent and slow dysfunction in the occipital regions" | bursts of GS + GSW bioccipital predominance | "abnormal bursts, in the right vertex region, of poorly formed waves during sleep" | NA | GSW posterior predominance |

ıg; TPM = topiramate; VPA = valproic acid; OFC=occipitofrontal
:S = partial complex seizures; tc = tonic-clonic; PS: photosensitivity

| et al. Biol Psychiatr 2011 | | Hamdan et al. Am J Hum Genet 2011, New Engl J Med 2009 and Biol Psychiatr 2011 | | | Vissers et al. Nat Genet 2010 | Rauch et al. La |
|---|---|---|---|---|---|---|
| Patient 2 R0038372 | Patient 3 R0034526 | Patient 1 R0033401 | Patient 2 R0032180 | Patient 3 R0033475 | Patient 8 | BO14/09 |
| M | M | F | F | F | F | F |
| 4 | 13 | 4.4 | 5.8 | 12 | NA | 11 |
| | | | | | | |
| moderate/severe | moderate/severe | moderate | moderate | moderate | mild/moderate | moderate/severe |
| NA | NA | NA | NA | NA | 19 m | 15 m |
| 17 m | 24 M | 24 M | 21 m | 24 m | NA | 24 m |
| impaired | impaired | impaired | impaired | impaired | absent | absent |
| normal | normal | hypotonia | hypotonia | normal | hypotonia | NA |
| normal | normal | normal | NA | NA | normal | normal |
| ADHD; aggressiveness; temper tantrums | autism, mood instability, temper tantrums | no ASD | no ASD | no ASD | NA | auto-aggressive behaviour |
| mildly enlarged ventricles | NA | normal | normal | normal (TDM) | mild myelination dealy (10 m) | normal |
| yes | no epilepsy | yes | yes | no epilepsy | yes | yes |
| 24 | NA | 15 | 28 | NA | 48 | 26 |
| FS, mj,abs | NA | febrile and afebrile GTCS; PCS | myo at | NA | NA | abs, atonic seizures |
| good control | NA | good control by TPM | good control by VPA | NA | NA | NA |
| bioccipital SSW | NA | bioccipital spikes during light stimulation | bioccipital spikes during light stimulation | NA | NA | NA |

| ıncet 2012 | Klitten et al. Epilepsia 2011 | Writzl et al. Am J Med Genet 2013 | Zollino et al. Eur J Hum Genet 2011 | Krepischi et al. Am J Med Genet 2010 |
|---|---|---|---|---|
| ER53899 | | | | |
| M<br>5 | M<br>25 | M<br>9 | F<br>5 | M<br>6.8 |
| | | | | |
| severe | severe | moderate | severe | moderate |
| 17 m | NA | 10 m | NA | 6.5 m |
| 36 m | 36 m | 29 m | NA | 16 m |
| absent | impaired | impiaired | impaired | impaired |
| hypotonia | NA | NA | normal | NA |
| normal | NA | normal | normal | normal |
| ADS, stereotypies | ASD | none | ASD, stereotypies | NA |
| arachnoid cyst | NA | normal | normal | NA |
| NA | yes | yes | yes | NA |
| NA | 13 | 48 | 3 | NA |
| NA | abs, myo abs, atyp abs, drop at with mj | abs, head nodding | myo at, | NA |
| NA | poor control | good control VPA | positive effect by VPA and TPM | NA |
| NA | GSW, GPSW | MFD | MFD;SSW; Sp and Poly-SPW; subcontinuous during sleep and were reminiscent of the EEG features of the Lennox–Gastaut syndrome | NA |

| summary |
| --- |
| n=35 |
| sex ratio M/F : 0.84<br>mean 10 y |
| |
| mild 1; mild/moderate 1; moderate 20; moderate/severe 5, severe 8 |
| mean 14.8 m, median 12 m |
| mean 25.3 m; median 24 m |
| absent speech 11; single words 4; 2-4-word sentences 3; "impaired" 12 |
| none 6; unsteady gait/ataxia 8; hypotonia 8 |
| normal 22; microcephaly (≤ -2.5 SD) 6 |
| ASD 20; aggressiveness 11; stereotypies 5 |
| normal 19; minor nonspecific findings 3 |
| yes 26; no 6 |
| mean 30 m; median 24 m; 75th centile 3.5 years |
| abs 19; mj 10; drop at 8; tc 4; FDS/PCS 4; myo abs 2; GTCS 1; PS 1 |
| NA 20; EE 5; poor control 3; good control 7 |
| occipital predominance of anomalies 8; PS 2 |