■ Original article

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Epilepsy features in *ARID1B*-related Coffin-Siris syndrome

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INTRODUCTION

Coffin–Siris Syndrome (CSS) is a rare congenital malformation syndrome, caused by mutations in the *ARID1B* gene in over half of the cases (Kosho and Okamoto, 2014; Tsurusaki et al, 2012).

Cardinal clinical features include variable degrees of developmental and cognitive delay predominantly affecting speech, hypotonia, dysmorphic facial features and hypertrichosis (Schrier Vergano et al, 2013).

To date, the reported data on the epilepsy features of these patients are sparse and the EEG documentation is lacking.

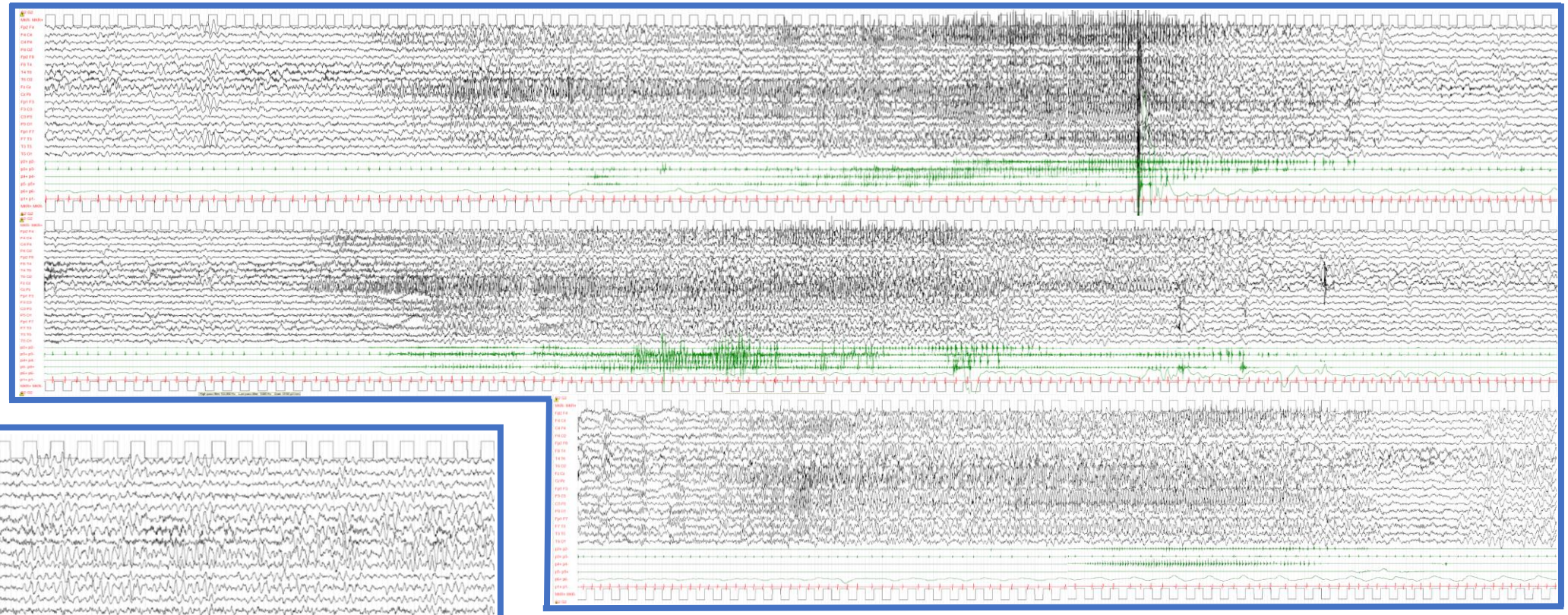
METHODS

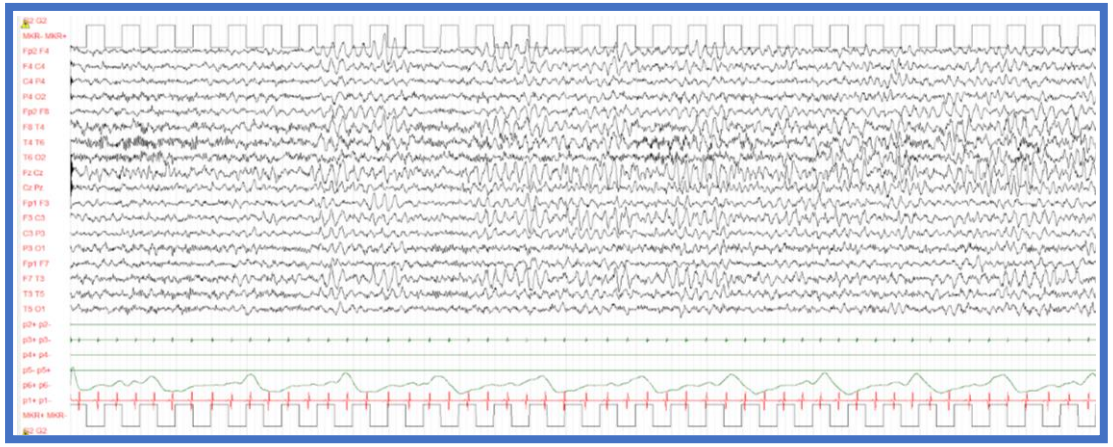
We report seven patients with CSS and confirmed pathogenic *ARID1B* mutation, collected within the framework of the Genetic Commission of the Italian League Against Epilepsy (LICE), focusing on epilepsy and its electroclinical features.

Furthermore, a literature review was performed on PubMed, using the following search terms: (("Seizures"[Mesh]) OR ("Epilepsy"[Mesh])) AND (("Coffin-Siris syndrome" [Supplementary Concept]) OR CSS OR "Coffin-Siris" OR ARID1B).

Patient 1 [1/2] Stormy epilepsy onset at 1 year and 4 months: focal motor seizures, in sleep and wakefulness, without fever, rapidly increased up to 70 per day, CBZ gradually reduced frequency and duration after one month until complete seizure freedom at 45 days after onset. CBZ, NZP, VPA, LEV, PB and PHT sequentially added as polytherapy.

Ictal EEG: focal discharge of polyspikes over the vertex region soon involving the motor areas of both hemispheres, asynchronously (with alternating side predominance) and sometimes independently. Detailed semiology: breathing changes, upper and lower limb hypertonia evolving to a tonic-vibratory phase, followed by clonic twitches asynchronously affecting both sides of the body.





Interictal EEG: intermittent medium-voltage theta activity over the vertex region, spreading to the centrotemporal areas of both hemispheres; absence of clear-cut epileptiform abnormalities.

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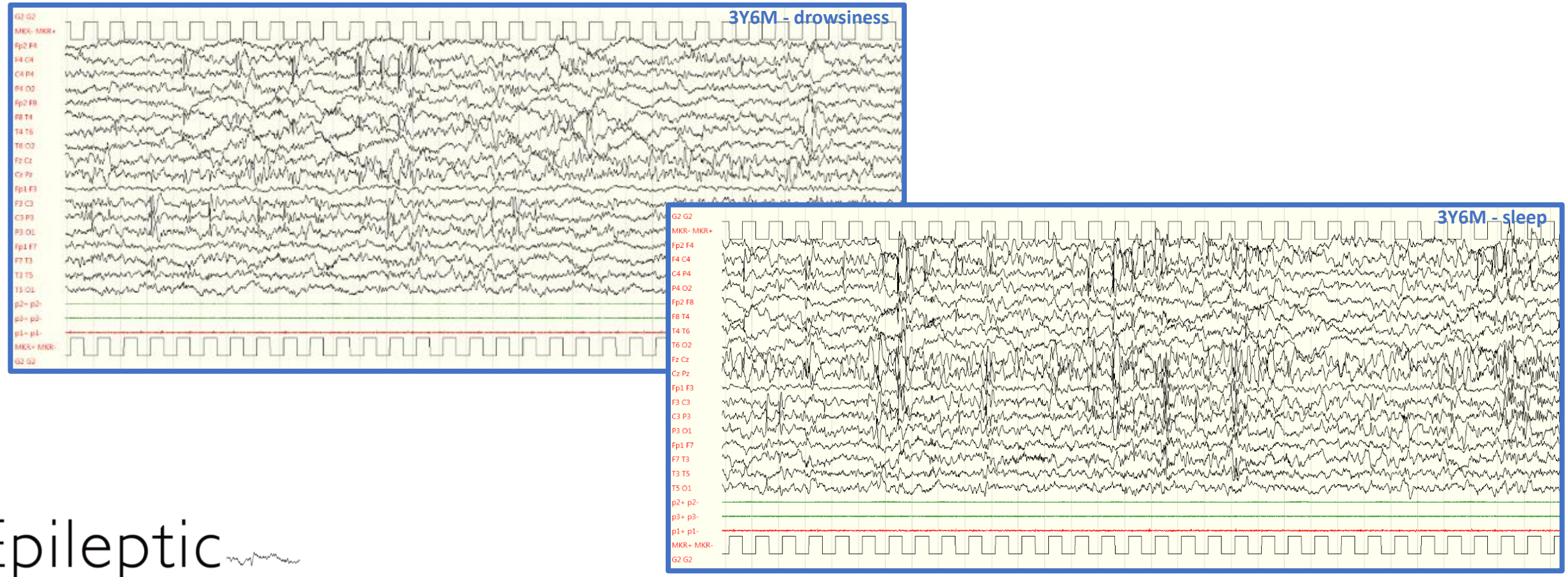
Patient 1 [2/2] Comprehensive metabolic testing and Array-CGH were negative. A 149-gene panel for epilepsy revealed a *de novo* heterozygous stop-gain mutation [c.5547del (p.Leu1850*)] in *ARID1B*.

During the 24-month follow-up period, the antiseizure therapy was gradually simplified with transition to CBZ monotherapy.

Since then, only one isolated seizure occurred by the age of two years and three months, during fever.

At the age of 3 years and 6 months, interictal epileptiform abnormalities, asynchronous over the Rolandic regions of both hemispheres, became evident during drowsiness and sleep.



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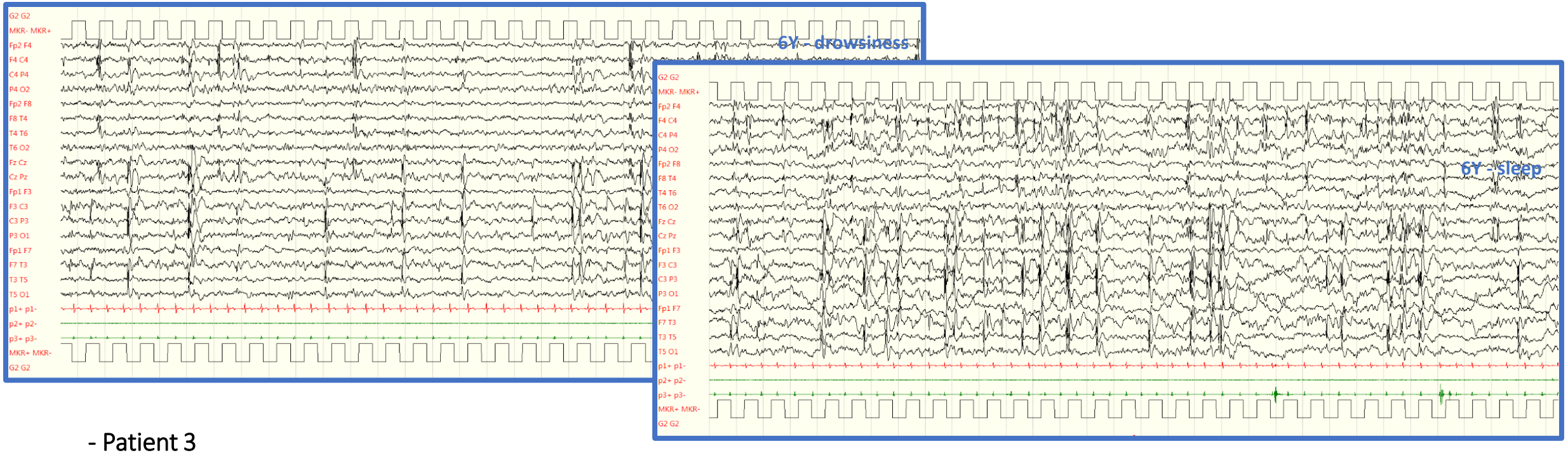
Patient 2 Epilepsy onset: 2 years and 10 months. Tonic-vibratory seizures, isolated, during sleep, each one lasting less than 1 minute, varying in frequency from 1 up to 5 per year. Seizures occurred in a cluster only once, and this happened during fever. The Array-CGH analysis revealed a 5.4-Mb *de novo* deletion (del 6q25.2q25.3) including *ARID1B*.

The interictal EEG by the age of 3 years and 6 months showed epileptiform abnormalities asynchronously on the Rolandic regions of the two hemispheres, later-on increasing in frequency, especially during sleep with an EEG pattern of continuous spike and wave during sleep (CSWS) by the age of 6 years.



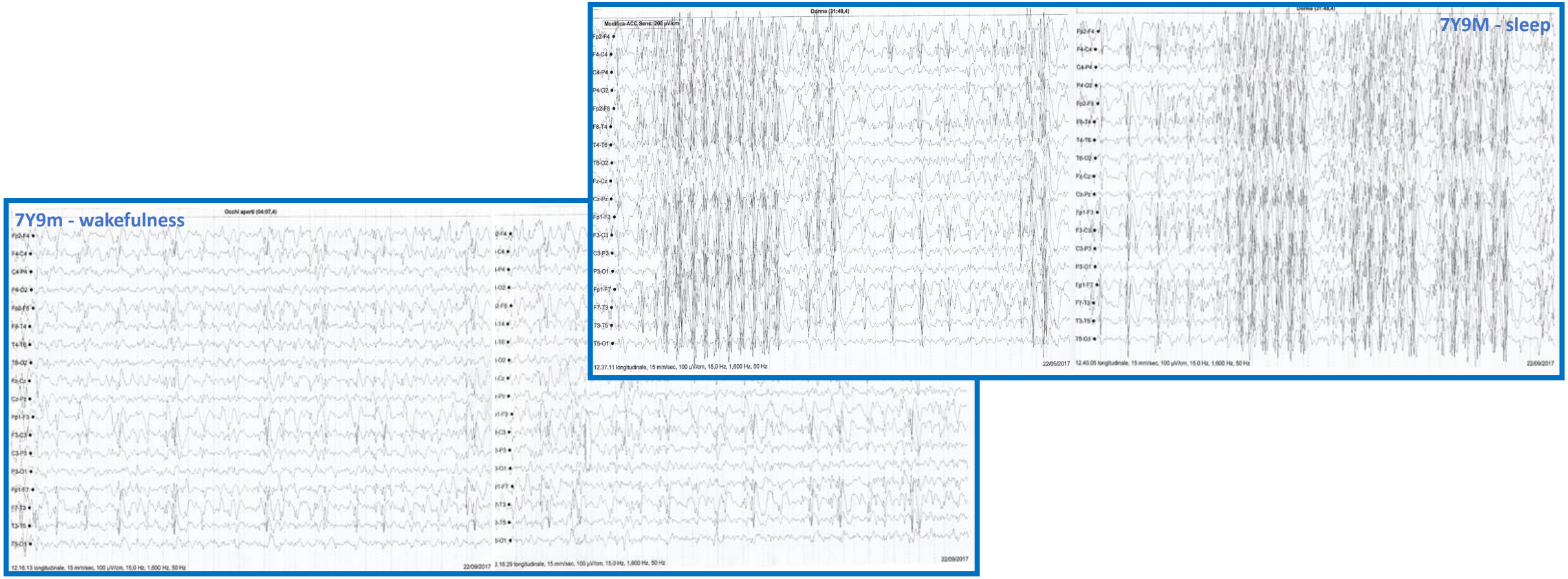
- Patient 3

One seizure, with convulsive semiology, during fever, at the age of 1 year and 9 months. Interictal EEG: unusual theta activity over the frontal-centro-parietal areas and, by the age of 4 years, isolated sharp waves asynchronously in the centro-parietal regions of both hemispheres and over the vertex.

CSS-specific genetic testing: *de novo* heterozygous frameshift mutation leading to a premature stop [c.1382_1391delGGGCGGCGGC (p.Ala464SerfsTer35)] in *ARID1B*.

Patient 4 Focal clonic seizures (with hemifacial and upper limb jerks) and tonic seizures by the age of 2 years and 6 months, frequently triggered by fever.

From the age of 4 years, the interictal EEG showed asynchronous centrotemporal paroxysms, enhanced during sleep, which evolved – by the age of 6 years – with an EEG pattern of CSWS. By the age of 7 years and 9 months, diffuse spike-wave and polyspike-wave discharges with hard-to-notice clinical correlate (sometimes subtle jerking, suggestive for myoclonic-atonic phenomena) were recorded both in sleep and awake EEG recordings. Metabolic investigations were unremarkable. Whole-exome sequencing: heterozygous *de novo* mutation [c.2270C>T (p.Ala757Val)] in the exon6 of the *ARID1B* gene.



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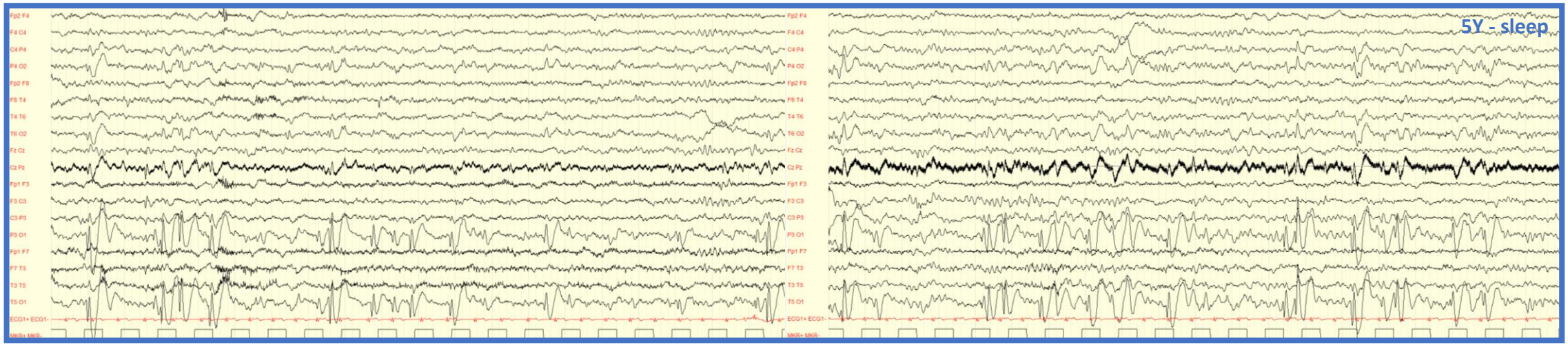
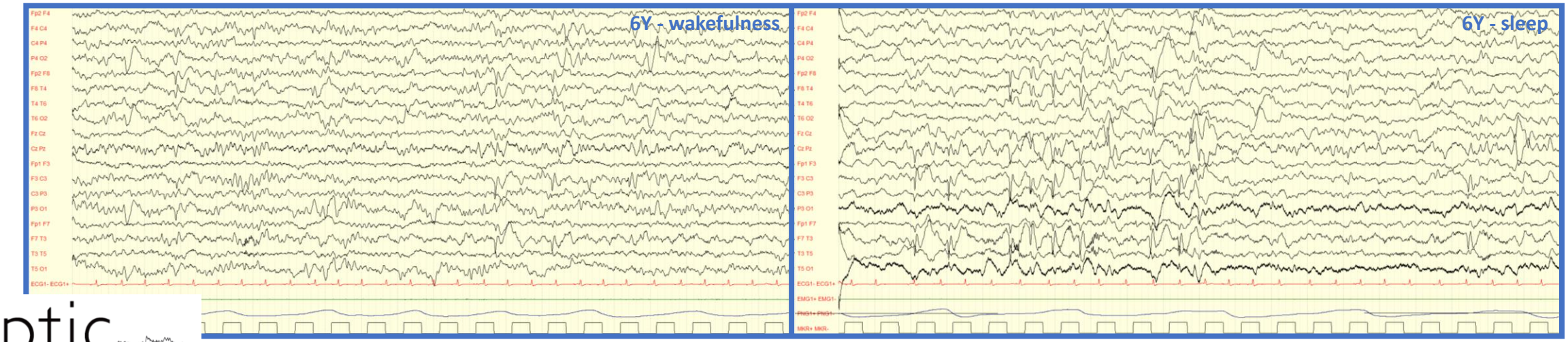
Patient 5 From the age of 4 years and 11 months, focal-onset seizures (motion arrest, staring, and oroalimentary automatisms) evolving to a tonic or tonic-clonic phase, mainly during sleep, presenting up to 4 times per month initially, controlled with CBZ. Interictal EEG: medium-voltage asynchronous spike-waves, predominant in the posterior regions at onset, from the age of 6 years clearly prevalent over the centrotemporal regions of both hemispheres and increasing in frequency during sleep. CSS-specific genetic testing: *de novo* heterozygous frameshift mutation [c.5265_5266delAG (p.Glu1756LysfsTer3)] in *ARID1B*.





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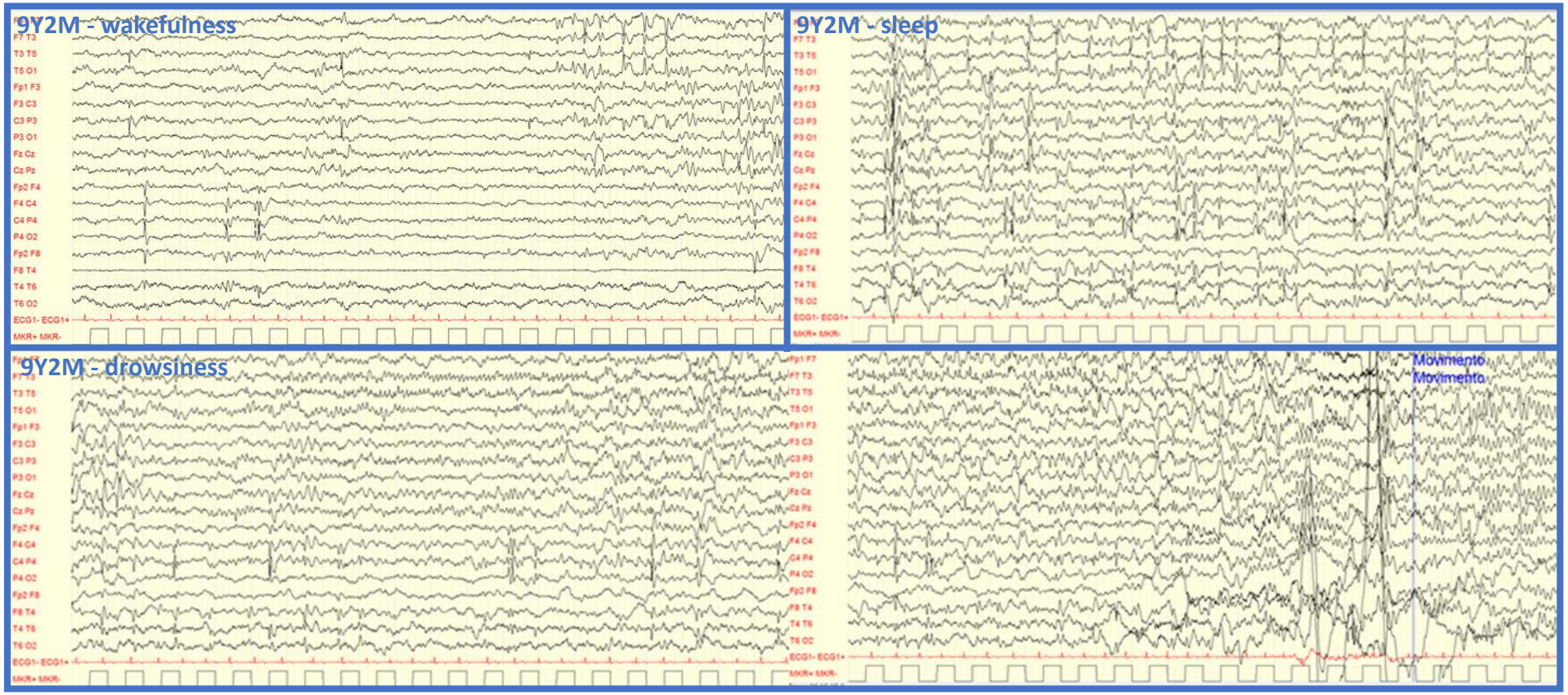
Patient 6 First seizure at 9 years 2 months: impaired awareness, drooling and predominant right upper limb hypertonia and clonic movements, during drowsiness, self-remitting within 1 min. Nap EEG recorded 1 week later: interictal multifocal paroxysms asynchronously on the fronto-centro-temporal regions, activated by sleep. An electrographic seizure (low-voltage fast activity discharge arising from the left hemisphere, lasting 10 seconds, not associated with clinical manifestation) was also recorded during drowsiness. LEV was started, with subsequent reduction of interictal abnormalities and seizure freedom. A *de novo* heterozygous stop-gain mutation [c.382G>T p.Glu1276*] in the *ARID1B* gene was found.



Patient 7 At the age of 6 years, asymmetric tonic seizures, exclusively during sleep, with >yearly frequency. Seizure freedom after VPA introduction and optimization. Interictal EEG: isolated focal abnormalities over the right temporal and parietal lobes, sometimes spreading to homologous contralateral regions, activated both in amplitude and frequency during sleep. Genetic testing: *de novo* mutation c.2002_2006delinsTTC; p.(Asn668PhefsTer18) in *ARID1B*.

LITERATURE REVIEW

1/3 of subjects with *ARID1B* mutations experience seizures. Onset: from birth to 14 years, median 4 years. Good response to standard ASMs (van der Sluijs et al, 2019).

Case reports:

- Sylvester et al, 1976: epileptic fits in infancy, diminished in frequency by the age of 2 and a half and ceased at 14 years.

- Bender et al, 2011: diagnosis of “partial epilepsy” at the age of 4 years; “simple” and “complex partial” seizures with clonic activity involving either side of the body, predominantly the arm, associated with Todd’s paralysis, predominantly nocturnal, with monthly frequency and prominent during febrile illnesses; bout of prolonged seizure activity lasting more than 30 minutes (status epilepticus); interictal paroxysmal abnormalities arising independently in the centrotemporal regions of both hemispheres, abnormal sleep architecture.

- Takenouchi et al, 2016: seizure onset at the age of 3 years, electroencephalographic abnormalities, treated with VPA.
Sonmetz et al, 2016: a single seizure with fever at 2 months of age, from the age of 13 recurrent afebrile GTCSs (three-four times monthly), successfully treated with OXC.

- Curcio et al, 2020 (two patients): focal onset seizures by the age of 5 years, isolated and brief in duration, both during wakefulness and sleep, satisfactorily treated with CBZ and VPA, respectively; focal interictal paroxysms enhanced by sleep, localized in the left frontal-central-temporal region in the first patient and over the temporal-occipital region in the second.

SUMMARY OF FINDINGS

The analysis of our patients and of those previously described in the literature reveals common epilepsy features, summarized in the table.

	Age at first seizure	Epilepsy onset	SE	ASMs*	Fever susceptibility	Age at remission	Seizure semeiology (state)	FIPA (region)	FIPA activation in sleep
Patient 1	1y4m	Id	Y	CBZ	Y	NA	T, TV (w, s)	Y (V, C-P)	Y
Patient 2	2y10m	Id	N		Y	NA	T, TV (s)	Y (C-P)	Y (continuous)
Patient 3	1y9m	-	N	-	Y	-	TC	Y (V, C-P)	N/NA
Patient 4	2y6m	Id	N	CBZ, VPA, CLB, ETS	Y	NA	C, T, M, AA (w, s)	Y (C-T)	Y (continuous)
Patient 5	4y11m	Id	N	CBZ	N	NA	T, TC (s)	Y (O to C-T)	Y
Patient 6	9y3m	Id	N	LEV	N	NA	T (s)	Y (F-C-T)	Y
Patient 7	6y6m	Id	N	VPA	N	7y6m	T (s)	Y (P-T)	Y (continuous)
Sylvester, 1976	<2y	Id	N/NA	NA	NA	14y	NA	NA	NA
Bender, 2011	4y	Id	Y	NA	Y	NA	C, TC (s>w)	Y (C-T)	Y (continuous)
Takenouchi, 2016	3y	Id	N/NA	VPA	NA	NA	NA	Y	NA
Sonmetz, 2016	2m	13 y	N	OXC	Y	14y	GTC	NA	NA
Curcio, 2020	5y	Id	N	CBZ	N	6y	TC (w, s)	Y (F-C-T)	NA
	5y6m	Id	N	VPA	N	7y6m	NM, TC (w, s)	Y (T-O)	Y
mean/percentage	3y9m	4y8m	15%	-	55%	-	-	100%	100%

SE: status epilepticus.

ASMs: antiseizure medications (excluded those administered during SE);
CBZ clobazam,
VPA valproate,
CLB clobazam,
ETS ethosuximide,
LEV levetiracetam,
OXC oxcarbazepine.

FIPA: focal interictal paroxysmal abnormalities.

NA: not applicable.

Seizure semiology:
T tonic,
C clonic,
M myoclonic,
TV tonic-vibratory,
TC: tonic-clonic,
AA atypical absences,
NM focal non-motor.

DISCUSSION - ARID1B-related CSS epilepsy phenotype:

Onset in the first years of life: 4Y2M in our patients, 2Y9M in the literature (mean)

"Rolandic trait" similar to the one observed in other genetically determined syndromic entities (Musumeci et al, 1988; Lewis et al, 2020)

focal seizures mainly arising from the motor areas

interictal paroxysmal abnormalities (100%), predominant in the **centrotemporal** areas

marked activation of focal abnormalities **during sleep** (100%),
with possible evolution to an EEG pattern of **CSWS**
(eventual associated cognitive regression is difficult to evaluate
because of the pre-existing severe neurodevelopmental impairment*)
*this implies that these patients cannot be diagnosed as ESES, although a phase of epileptic encephalopathy cannot be excluded

Possible **age-related postero-anterior** dysfunctional hyperexcitability **gradient** (14% of our patients, 17% in the literature),
consistent with a "childhood seizure-susceptibility syndrome" (Panayiotopoulos, 1993; Caraballo et al, 2008)

developmental delay, predominantly affecting speech, detected **before the epilepsy onset** in all cases

fever susceptibility: 57% of our patients, 33% in the literature

status epilepticus: 14% of our patients, 17% in the literature

Spectrum of "self-limited focal epilepsies of childhood"