



Review

Candidate Genes for Eyelid Myoclonia with Absences, Review of the Literature

Sonia Mayo ^{1,*}, Irene Gómez-Manjón ^{1,2,†}, Fco. Javier Fernández-Martínez ^{1,2,†}, Ana Camacho ^{3,‡}, Francisco Martínez ^{4,5,‡} and Julián Benito-León ^{6,7,8,‡}

- ¹ Genetics and Inheritance Research Group, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), 28041 Madrid, Spain; irenegomezmanjon@hotmail.com (I.G.-M.); ffernandezm@salud.madrid.org (F.J.F.-M.)
 - ² Department of Genetics, Hospital Universitario 12 de Octubre, 28041 Madrid, Spain
 - ³ Department of Neurology, Division of Pediatric Neurology, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, 28041 Madrid, Spain; acamacho@salud.madrid.org
 - ⁴ Traslational Research in Genetics, Instituto de Investigación Sanitaria La Fe (IIS La Fe), 46026 Valencia, Spain; martinez_fracas@gva.es
 - ⁵ Genetics Unit, Hospital Universitario y Politecnico La Fe, 46026 Valencia, Spain
 - ⁶ Department of Neurology, Hospital Universitario 12 de Octubre, 28041 Madrid, Spain; jbenitol67@gmail.com
 - ⁷ Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28031 Madrid, Spain
 - ⁸ Department of Medicine, Universidad Complutense de Madrid, 28040 Madrid, Spain
- * Correspondence: soniamayodeandres@gmail.com; Tel.: +34-91-779-2603
† S.M., I.G.-M. and F.J.F.-M. contributed equally to this work and should be considered joint first authors.
‡ A.C., F.M. and J.B.-L. contributed equally to this work and should be considered joint senior authors.



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Abstract: Eyelid myoclonia with absences (EMA), also known as Jeavons syndrome (JS) is a childhood onset epileptic syndrome with manifestations involving a clinical triad of absence seizures with eyelid myoclonia (EM), photosensitivity (PS), and seizures or electroencephalogram (EEG) paroxysms induced by eye closure. Although a genetic contribution to this syndrome is likely and some genetic alterations have been defined in several cases, the genes responsible for have not been identified. In this review, patients diagnosed with EMA (or EMA-like phenotype) with a genetic diagnosis are summarized. Based on this, four genes could be associated to this syndrome (*SYNGAP1*, *KIA02022/NEXMIF*, *RORB*, and *CHD2*). Moreover, although there is not enough evidence yet to consider them as candidate for EMA, three more genes present also different alterations in some patients with clinical diagnosis of the disease (*SLC2A1*, *NAA10*, and *KCNB1*). Therefore, a possible relationship of these genes with the disease is discussed in this review.

Keywords: Jeavons syndrome; eyelid myoclonia with absences; candidate genes; *SYNGAP1*; *KIA02022*; *NEXMIF*; *RORB*; *CHD2*

1. Introduction

In 1977, Jeavons described something that is now known as Jeavons syndrome (JS): “Eyelid myoclonia and absences show a marked jerking of the eyelids immediately after eye closure and there is associated brief bilateral spike-and-wave activity. The eyelid movement is like rapid blinking and the eyes deviate upwards, in contrast to the very slight flicker of eyelids which may be seen in a typical absence in which the eyes look straight ahead. Brief absences may occur spontaneously and are accompanied by 3 c/s spike-and-wave discharges. The spike-and-wave discharges seen immediately after eye closure do not occur in the dark. Their presence in a routine EEG is a very reliable warning that abnormality will be evoked by photic stimulation” [1].

JS, also known as eyelid myoclonia with absences (EMA), is a childhood onset epileptic syndrome with manifestations involving a clinical triad of absence seizures with eyelid

myoclonia (EM), photosensitivity (PS), and seizures or electroencephalogram (EEG) paroxysms induced by eye closure [2].

EMA is considered as a separate entity among genetic generalized epilepsies (GGE) associated with EM and brief absences related to generalized paroxysmal activity on EEG triggered by eye closure or intermittent photic stimulation (IPS) [3,4]. However, epilepsy with eyelid myoclonias has only been recently recognized as a distinct epilepsy syndrome by the International League Against Epilepsy (ILAE) [5].

A family history of seizures or epilepsy is common in those cases (seen in 40–80%) [4,5]. Additionally, reports of affected identical twins suggest its genetic etiology [4,6–8]. Despite this, there is actually no known gene accepted as pathogenic for this disease [5,9]. Moreover, different case reports have proposed several candidate genes [2,10–13].

EMA onset is typically in childhood, with a peak at 6–8 years. However, the time of seizure onset may be difficult to be exactly established, as eyelid jerks are frequently misinterpreted as tics or mannerisms, and absences may be overlooked [3]. The presence of massive myoclonus, intellectual disability (ID), or slowing of the EEG background are not typical features of the syndrome and may also cause delay in making the correct diagnosis [14]. More frequent in females, some patients show resistance to antiepileptic therapy [3,4].

In clinical practice, however, syndromes may overlap and cases may present with unusual manifestations, posing a diagnostic challenge [14]. The phenotypic and genetic heterogeneity may lead to underestimation of the clinical presentation, making the diagnosis more difficult [15]. In this review, based on different reported cases, we present four candidate genes for EMA and three other genes that might also be related to the disease. Moreover, we discuss their possible relation with the disease in order to improve the knowledge of this syndrome.

2. Results and Discussion

2.1. *SYNGAP1*

SYNGAP1 (MIM *603384) is located on 6p21.32 [16]. This gene encodes a brain-specific synaptic Ras GTPase activating protein that is a member of the N-methyl-D-aspartate receptor complex [17]. Primarily expressed in excitatory neurons, it regulates dendritic spines structure, function, and plasticity, with major consequences for neuronal homeostasis and development, crucial for learning and memory [18]. Heterozygous loss of function variants in *SYNGAP1* are associated with developmental delay (DD), ID, epilepsy, and autism spectrum disorder (ASD) (MIM # 612621; ORPHA 544254) [19,20].

In 2011, Klitten et al. described a patient with epilepsy with myoclonic absences and a balanced translocation disrupting *SYNGAP1* [12]. This patient presented DD, ID, and ASD, but also eyelid winking and absences associated with eye deviation, being resistant to treatment (Table 1).

Mignot et al. (2016) presented a series of 17 unrelated patients with ID and epilepsy, mainly pharmacoresistant (>55%), carrying 13 different loss-of-function *SYNGAP1* mutations [21]. Three of them presented EM and suffered from seizures triggered by PS or EEG alteration after eye closure. Even more, one of them carry the missense alteration c.1685C>T (p.Pro562Leu), which has also been described in another patient diagnosed with EMA with myoclonic-atonic epilepsy (MAE) [22,23] (Table 1). However, this mutation was also recently reported by Lo Barco et al. (2021) in a patient without EM [24].

Table 1. Cont.

	AED Treatment	VPA, LTG, CLB	VPA	LEV, TPM	LEV, ETX	CBZ, VPA, LEV, ETX, LTG	VPA	VPA, LEV, LTG, ETX, CBD	VPA	VPA, CLZ, CBZ	
Genetic information	Genetic test	karyotype	gene panel NGS	WES	WES	NGS panel	NR	NR	NR	NR	
	Genomic change (Hg19)	NR	chr6:33406650; C>C/T	chr6:33408514; C>C/T	chr6:33409458_33409461delAGCG	chr6:33414346; G>G/A	chr6:33391277; C>C/T	chr6:33399974; CA>CA/C	chr6:333400498_33400501delAAAC	chr6:33400501; C>C/T	
	cDNA/aa change	(truncate gene) ish, 46,XY,t(6;22)(p21.32;q11.21)dn	c.1630C>T, p.Arg544*	c.1685C>T, p.Pro562Leu	c.2214_2217delAGCG, p.Glu739Glyfs*20	c.3583-6G>A, p.Val1195Alafs*27	c.91C>T, p.Arg31*	c.333delA, p.Lys114Serfs*20	c.424_427delAAAC, p.Lys142Glyfs*31	c.427C>T, p.Arg143*	
	Inheritance	de novo	de novo	de novo	de novo	(parent not tested)	de novo	de novo	de novo	de novo	
Others information	FISH (probe RP11.497A24)	VUS inherited from the mother: SCN9A: c.4282G>A and c.5624G>A; ARX: c.1462A>G	-	-	Karyotype and anlysis for AS with normal results. CSF glucose normal	-	-	-	-		
Family History	- (epilepsy)	-	-	-	- (epilepsy or ID)	- (seizures, ID or ASD)	- (seizures, ID or ASD)	- (seizures, ID or ASD)	-	Sister, father, and many paternal relatives with learning difficulties. Maternal cousin ASD	
B											
	Reference	Flaskamp 2019 ^{1,2} /Von Stülpnagel 2019	Flaskamp 2019 ^{1,2}	Flaskamp 2019 ^{1,2}	Flaskamp 2019 ^{1,2} /The DDD Study 2017	Flaskamp 2019 ^{1,2}	Flaskamp 2019 ¹	Flaskamp 2019 ¹	Flaskamp 2019 ^{1,2}	Flaskamp 2019 ^{1,2}	
	Patient	8/7	9/8	11	12	13/241	15	17	18	20	21
	gender	female	female	male	female	male	female	female	male	female	female
	Age	8 yr	6 yr	6 yr	4 yr 8 months	7 yr 10 months	9.5 yr	5 yr 2 months	5 yr 10 months	15 yr 1 months	10 yr 5 months
	DD/ID	+ (moderate-severe)	+ (moderate-severe)	+ (severe)	+ (severe)	+ (severe)	+ (severe)	+ (severe)	+ (severe)	+ (moderate)	+ (moderate)
Clinical features	Behavioral features	regression, tantrums, self-injury, tichotillomania, high pain threshold, eating disorder, sleeping problems	ASD, echolalia, high pain threshold, eating disorder, sleeping problems	aggression, high pain threshold	regression, ASD, tantrums, self-injury, aggression. high pain threshold, sleep problems	Tantrums, aggression, high pain threshold, sleep problems	ASD traits, stereotypes, odontoprisis, high pain threshold	odontoprisis, high pain threshold	regression, obsession, self-injury, aggression, high pain threshold, sleep problems, eating disorder	ASD, self-injury, aggression, sleep problems, high pain threshold, oral hypersensitivity	regression, ASD, severe tantrums, self-injury, aggression, sleep problems, high pain threshold, oral hypersensitivity
	Other parametres	hypotonia, hyperlaxity, 2 café au lait spots, small capillary hemangioma, constipation, hearing loss after infection/ ataxia, problems in fine motor skills	hypotonia, hyperlaxity, hearing loss after recurrent otitis/ ataxia		hypotonia, ataxia, constipation, reflux, absence of language	pes planus, strabismus, constipation, hearing loss	nystagmus	Congenital hipdyslocation, absence of language	hypotonia, poor balance and coordination, absence of language	hypotonia, hypermobility, scoliosos, constipation	congenital nystagmus, hypotonia, a few cafe au lait macules, constipation

Table 1. Cont.

Epilepsy	Age of onset	8/16 months	12–13 months	4 yr	23 months	2 yr	2 yr	3.5 yr	3 yr	12–14 months	2 yrs
	Abscence seizures	+	+	NR	+(AA)	NR	NR	NR	NR	+(MA)	
Epilepsy	Eyelid myoclonia	+	+	+	+	+	+	+	+	+	+
	Photosensitivity	+	+	NR	NR	NR	NR	+	NR	+	+
Epilepsy	Other seizures	MS, MA. Triggered by touch and thinking of eating/GS, MJ, atonic drops. Reflex seizures while chewing	MS, MA. Triggered by thinking of eating/GS, MJ, atonic drops. Reflex seizures while chewing	MS, DA. Triggered by fever and infection	MS, AS	MS, AS, bilateral TCS. Triggered by eating (chocolate), fever and fatigue	Bi- and unilateral TCS	MJ, MS	Triggered by fatigue	atonic DA, nocturnal TS. Triggered by PS and eating	MJ, bilateral TCS
	EEG	others	Intal: 3 Hz GSW (EM-MAT). Interictal:G(P)SW	Intal: 2.5–3.5 Hz GSW (EM-MAT). Inerictal: 2.5–3.5 Hz GSW	BG poor. Ictal: Bilateral occipital sharps, followed by MFD (EM). Interictal: MFD	BG: slow. Ictal: GPSW (MS), 1.5–2 Hz GSW (AA). Interictal: GSW facilitated by eye closure	Interictal: GSW	BG: slow. Ictal: FD (unilateral TCS). Interictal: 3–4 Hz GSW, MFD	BG: slow. Interictal: 1.5–3 Hz GSW, MFD	Interictal: 3 Hz GSW, bifrotal SW	BG: slow. Ictal: GSE (MA). Inerictal: MFD
MRI	Cranial	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal (discrete hippocampal tissue loss, not progressive and without sclerosis)	Normal
Treatment	AED	VPA, LEV, TPM, CLB, LTG, ETX, LCM, ZNS, CLZ, CBD, PHT	CLB, LCM, ZNS, CLZ, CBD	VPA, LEV, TPM	CLB, TPM, NZP, LTG, VPA, CLZ	VPA, CLB	VPA, CLZ, LEV, TPM	VPA, CLZ, LEV, CLB	VPA	VPA, LEV, LTG	VPA
	Other	KD	KD, mAD				Vitamin B6				
Genetic information	Genomic change (Hg19)	chr6:33400509_33400521dup		chr6:33403058delC	chr6:33403318dupC	chr6:33403367; C>C/T	chr6:33405511_33405512insC	chr6:33406048; C>C/T	chr6:33406202delC	chr6:33406324; C>C/G	chr6:33408547G >GGCTGC
	cDNA/aa change	c.435_447dup, p.Leu150Valfs*6		c.639delC, p.Ile214Trpfs*9	c.690dupC, p.Phe231Leufs*14	c.739C>T, p.Gln247*	c.822_823insC, p.Lys277Glnfs*7	c.1366C>T, p.Gln456*	c.1393delC, p.Leu465Phefs*9	c.1515C>G, p.Tyr505*	c.1718_1719insGCTGC, p.Glu578Alafs*74
Genetic information	Inheritance	de novo/mosaic parent		de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
	Family History	sisters		-(seizures, ID or ASD)	-(seizures, ID or ASD)	Maternal aunt and distant relative epilepsy, other distant relatives ASD	-(seizures, ID or ASD)	-(seizures, ID or ASD)	Maternal grandfather post-stroke epilepsy	Paternal uncle moderate ID	-(seizures, ID or ASD)

Table 1. Cont.

C											
Reference	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ¹	Vlaskamp 2019 ¹ /Carvill 2013	Vlaskamp 2019 ¹	Vlaskamp 2019 ¹	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ¹	Vlaskamp 2019 ¹	Vlaskamp 2019 ¹	
Patient	23	24	25	26/T2528	27	30	31	32	33	35	
Clinical features	gender	female	female	male	male	male	female	male	female	male	male
	Age	11 yr 11 months	7 yr	11 yr 7 months	30/26 yr	6 yr	3 yr 11 months	11 yr 2 months	33 yr	15 yr 3 months	4 yr 9 months
	DD/ID	+ (severe)	+ (severe)	+ (moderate)	+ (moderate)	+ (severe)	+ (severe)	+ (severe)	+ (moderate-severe)	+ (severe)	+ (moderate-severe)
	Behavioral features	regression, ASD, tantrums, self-injury, aggression. Sleep problems, high pain threshold, eating difficulties	regression, ASD, aggression, sleep problems, high pain threshold	ASD, self injury, aggression, sleep problems, high pain threshold	regression, OCD symptoms, tantrums, aggression	regression, ASD, high pain threshold	ASD, tantrums, self-injury, aggression, sleep problems, high pain threshold, oral hypersensitivity	regression, ASD, tantrums, aggressive, sleep problems, high pain threshold, eating difficulties	regression, ASD, self-injury, aggression, poor concentration, high pain threshold	regression, ASD, aggression, sleep problems, high pain thresholds, eating difficulties	ASD, aggression, sleep problems, high pain threshold
Other parametres	hypotonia, constipation	congenital hisdysplasia, hypotonia, ataxic gait	pes planus, hypotonia, unsteady gait, constipation	mild two/three syndactly, irregular tremor upper extremities, osteopenia	Unsteady gait	hypotonia, unsteady gait, constipation, chronic idiopathic tromnocytopenic purpura, absence of language	microcephaly, short stature, borderline hypotonia, ataxia, Hemangioma nasal cavity	Hypotonia, coordination disorder/ataxia	right pes planus, left pes caves, hypotonia, bilateral pyramidal syndrome, unsteady gait, orthotics, hyperflexibility	mild hypotonia	
Epilepsy	Age of onset	2 yr	6 months	9.5 yr	18 months	2 yr	18 months	2 yr 3 months	8 months	18 months	2 yr 1 month
	Absence seizures	NR	NR	NR	+	NR	NR	NR	NR	NR	NR
	Eyelid myoclonia	+	+	+	+	+	+	+	+	+	+
	Photosensitivity	NR	NR	NR	+	NR	NR	NR	+	NR	NR
Other seizures	FS, bilateral TCS (with fiver)	bilateral TCS (with fiver), atonic DA. Triggered by fatigue and illness	Triggered by eating	FS, aura, FIAS, MJ, NCSE, bi- and unilateral TCS, MS. Triggered by PS	Triggered by hunger, self-induced with hyperventilation, fatigue and stress	TCS (with fiver)	Atonic DA. Triggered by sounds, fatigue, and drop in emperature	GTCS. Triggered by PS	-	Triggered by eating	
EEG	others	IBG: Slow. Ictal: 2-3 Hz GSW with frontal maximum, (EM-AS). Interictal: MFD	Interictal: 2.5 Hz GSW	NR	BG: slow. Interictal: occipital 2 Hz GSW, occipital FD/bi-occipital ED, DS, SSW	BG: iregular. Ictal: GSW (EM). Interictal: 2-3 Hz GSW, irregular GPSW, MFD	interictal: epileptiform discharge	Ictal: irregular GSW followed by slower discharges (EM), GPSW (EM). Interictal: G(P)SW, bifrotal SW, FD	NR	BG: slow Ictal: GSW (EM). Interictal: temporo-occipital SW, 10% generalized activity in 24 hours.	BG: right occipital slowing. Ictal: eyeblink without ictal correlate. Interictal: only in sleep: right occipital slowing, focal sharp waves
Cranial MRI	Normal	Normal	Normal	Normal	Patent cavus vergae	Atypical WM abnormalities	Normal	NR	Enlarged ventricles	Normal	

Table 1. Cont.

Treatment												
	AED	VPA, LEV		VPA, LEV	-	VPA, LTG, CLB	VPA, LEV, ETX, ZNS, CBD, LTG	-	VPA, CLB, TPM, LTG	VPA, CBZ, TPM	VPA, LEV, LTG	-
Genetic information												
	Genetic test	NR		NR	NR	NGS panel	NR	NR	NR	NR	NR	NR
Genetic information												
	Genomic change (Hg19)	chr6:33409006;G>G/A		chr6:33409095;C>C/T	chr6:33409095;C>C/T	chr6:33409140;C>C/T	chr6:33409419_3349422del	chr6:33411265_33411267delinsCA	chr6:33411735dupC	chr6:33412317;G>G/T	chr6:33414426;T>T/G	chr6:33393573;A>A/G
Genetic information												
	cDNA/aa change	c.1970G>A, p.Trp657*		c.2059C>T, p.Arg687*	c.2059C>T, p.Arg687*	c.2104C>T, p.Gln702*	c.2177_2180delGGAA, p.Arg726Thrfs*33 de novo	c.2936_2938delinsCA, p.Phe979Serfs*98 de novo	c.3406dupC, p.Gln1136Profs*17 de novo	c.3505G>T, p.Glu1169* de novo	c.3657T>G, p.Tyr1219* de novo	c.190-2A>G, (splice acceptor site) de novo
Genetic information												
	Inheritance	unknow		de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
Family History												
	Family History	Distant relative ASD		Paternal grandmother GTCS 16–20 y. Distant relative ASD	- (seizures, ID or ASD)	Distant relative epilepsy	- (seizures, ID or ASD)	Maternal aunt ID. Paternal first cousin post-traumatic epilepsy	Maternal uncle ID post-meningitis. Distant relative epilepsy	Maternal and paternal first cousins learning difficulties	Distant relative ASD	- (seizures, ID or ASD)
D												
Clinical features	Reference	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ¹ /Parrini 2017	Vlaskamp 2019 ¹	Vlaskamp 2019 ^{1,2,c}	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ^{1,2,a} /Berruyer 2013 ^a	Vlaskamp 2019 ^{1,2}	Vlaskamp 2019 ^{1,2}	Von Stülpnagel 2019 ^{2,c}	Von Stülpnagel 2019
	Patient	36	39/1190N	41	45	46	50	51/3	52	53	1	2
Clinical features	gender	female	female	female	male	male	male	female	female	female	male	male
	Age	8 yr 11 months	16.4/17 yr	6 yr 8 months	3 yr 2 months	10 yr	15 yr 1 month	9.1/4.2 yr	8 yr 3 months	7 yr months	5 yr	14 yr
Clinical features	DD/ID	+ (mild)	+ (moderate-severe)	+ (moderate-severe)	+ (severe)	+ (moderate)	+ (severe)	+ (moderate/mild)	+ (severe)	+ (mild)	+ (moderate)	+ (moderate-severe)
	Behavioral features	regression, ASD traits, tantrums, self-injury, aggressive	regression, Aggressive, REM sleep behavioral disorder, ASD	regression, ASD, sleep problems, high pain threshold	regression, ASD traits	regression, ASD, tantrums, OCD, echolalia, high pain threshold, eating difficulties	regression, ASD, eating disorder	regression, ASD, self-injury, sleep problems, high pain threshold, eating disorder	regression, ASD, tantrums, self-injury, sleep problems, high pain threshold	tantrums, aggressive, sleep problems	regression, ASD	ASD
Clinical features	Other parametres	Few café au lait macules	pronated foot, coordinarition disorder, ataxic gait	hypotonia	hypospadie, 6th toe, hypotonia, nystagmus	weakness, clinodactyly toes, hypotonia, constipation, coeliac disease	obesity, ataxia with wide-based gait	Hypotonia, unsteady gait with poor balance, gross and fine motor dyspraxia	macrocephaly, knee hyper-extension, pes planus, pronated feet, hypotonia, wide-based gait with poor balance, constipation	pes caves, hypotonia, balance issues	Height <3p. Tongue hypotonia and horizontal nystagmus. Postaxial hexadactylia and hypospadias	Abnormal gait; poor coordination; dysarthria. Abnormal facial shape (triangular), large anteverted ears, wide mouth, thin lips, pointed chin

Table 1. Cont.

	Age of onset	<2 yr	6.7/5 yr	4.5 ys	2.5 yr	2.8 yr	2.5 yr	18 months	18 months	2.5 yr	2.5 yr	20 months
Epilepsy	Absence seizures	NR	NR	+ (typical)	NR	NR	+ (typical)	NR	NR	NR		
	Eyelid myoclonia	+	+	+	+	+	+	+	+	+	+	+
	Photosensitivity	NR	+	+	+	-	+	-	NR	-	-	+
	Other seizures	Triggered by eye closure, hunger and fatigue	Triggered by PS	-	MAt, MS, atonic DA. Triggered by eating and stress	Triggered by visual patterns	bilateral TCS (with fever). Triggered by PS and noise	bilateral TCS, myoclonic DA. Triggered by eating	Triggered by eating, eye closure and fatigue	Triggered by illness and fatigue	Atonic head dropping	+ FS, GTCS, episodes characterized by loss of consciousness, backward eyeball rolling, MS; generalized with head atonia and EM; status epilepticus.
EEG	others	Ictal: GD (EM-MAt). Interictal: 2–3 Hz GSW, frequent GD, induced by eye closure	Ictal: G(P)SW (EM) Interictal: G(P)SW	Ictal: G(P)SW (EM)	NR	BG: slowing. Interictal: GPS, 3.5–4 GSP, FD	Interictal: GD, MFD, spikes, G(P)SW	BG slow	Interictal: GSW	BG: gegeralized slowing. Interictal: MFD	1–3 s lasting high amplitude 3/s SW complexes with bilateral initiation and occipital predominance but never lateralized. Triggered by heat, fatigue, stress, and orofacial stimuli	slowed BG activity (theta); spikes and polyspikes over the occipital regions; abnormalities are worsened by sleep. Triggered by PS, autoinduced, and eating.
MRI	Cranial	Normal	Normal	Mega cisterna magna fossa posterior	Normal	Normal	Normal	Small hyperintens subcortical WM lesions (bi-frontal, periventricular), possibly post-anoxic leukopathy	Stable mild enlarged ventricles and pineal cyst	Normal	Slight frontal dilatation of the external spaces of cerebrospinal fluid and an age-appropriate myelination	Normal
Treatment	AED	VPA, CLB, LTG	LZP, RUF, VPA	LEV, ZNS, RUF, VPA	VPA, LTG	VPA	Hydrocortison, VGB, NZP	VPA	VPA, LEV, ETX, CLZ, LTG, CBD	VPA, ZNS, LEV, PER, CBD	VPA, LTG	VPA, LTG, LEV, CLB
	Other	NR	NR	NR	NR	NR	NR	NR	NR	KD	NR	NR

Table 1. Cont.

	Genetic information												
	Genetic test	NR	NGS panel (95 genes)	NR	NR	NR	NR	NR	NR	NR	NR	gene panel NGS	NR
	Genomic change (Hg19)	chr6:33400029; G>G/A	chr6:33400583; G>G/A	chr6:33408504_33408514delAG CGTGTCC	chr6:33405650; T>T/C	chr6:33405712; G>G/A	chr6:33406199; T>T/TTCC	chr6:33408514; C>C/T	chr6:33408626; C>C/G	chr6:33408718; T>T/A	chr6:33405650; T>T/C	chr6:33400462; C>C/T	
	cDNA/aa change	c.387G>A, p.Ser129Ser (splice donor site)	c.509G>A, p.Arg170Gln	c.1677-2_1685del, (splice acceptor site)	c.968T>C, p.Leu323Pro	c.1030G>A, p.Gly344Ser	c.1390delinsTTCC, p.Leu465dup	c.1685C>T, p.Pro562Leu	c.1797C>G, p.Cys599Trp	c.1889T>A, p.Ile630Asn	c.968T>C, p.Leu323Pro	c.388C>T, p.Gln130Ter	
	Inheritance	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
	Others information							de novo Karyotype, aCGH, MECP2 mutation and X-fragile analysis, without relevant results					
	Family History	- (seizures, ID or ASD)	- (seizures, ID or ASD)	- (seizures, ID or ASD)	Paternal uncle epilepsy and behavioural problems	- (seizures, ID or ASD)	Mother FS. Paternal uncle learning difficulties	Maternal first cousin ASD	- (seizures, ID or ASD)	- (seizures, ID or ASD)	- (epilepsy or DD)	NR	
E													
	Reference	Kuchenbuch 2020 ^d	Kuchenbuch 2020 ^e	Lo barco 2021 ^e	Lo barco 2021	Lo barco 2021	Lo barco 2021 ^d	Lo barco 2021 ^b	Lo barco 2021	Lo barco 2021			
	Patient	1	3	2	4	5	6	8	9	10			
Clinical features	gender	male	male	male	male	female	male	male	female	female	female		
	Age	5.6 yr	3.5 yr	3 yr 4 months	11 yr 3 months	6 yr 3 months	5 yr 4 months	6 yr 6 months	14 yr	7 yr			
	DD/ID	NR	NR	+ (severe/moderate)	+ (severe)	+ (severe/moderate)	+ (moderate)	+ (severe)	+ (severe/moderate)	+ (severe/moderate)	+ (severe/moderate)		
	Behavioral features	motor stereotypies, heteroaggressivity, ASD	NR	ASD, behavior disorder	ASD, behavior disorder	ASD, behavioral and sleep problems	ASD, behavior disorder	ASD, feeding problems	ASD, behavioral and sleep problems	ASD, feeding problems	ASD, behavioral and sleep problems	ASD, behavioral and sleep problems	
Other parametres	NR	NR	NR	head growth slowdown, absence of language	growth delay, absence of language	NR	nystagmus, absence of language	head growth slowdown, absence of language	head growth slowdown, absence of language	head growth slowdown, absence of language	head growth slowdown, absence of language		
Epilepsy	Age of onset	3.5 yr	8 months	8 months	27 months	18 months	36 months	20 months	20 months	30 months			
	Absence seizures	+ (AA)	+ (MA)	+ (AA, AAM)	+ (AA)	+ (AA, AAM, AAOC, AAA)	+ (AA, AAOC, MA)	+ (AAM)	+ (AA, AAM)	+ (AAM)			
	Eyelid myoclonia	+	+	NR	+	+ (EMA)	+	NR	NR	NR	NR		
	Photosensitivity	+	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Other seizures	FS, MS, upper limb MJ, DA. Triggered by sleep and IPS	DA, upper limb MJ, reflex seizures self-induced by eye closure	MS, FS	DA	AS	NR	MS, TS	MS	NR				

Table 1. Cont.

EEG	PPR others	NR NR	NR 2-HZ GPSW	+ Sleep: Sporadic low-voltage multifocal spikes; sporadic bursts of generalized irregular polyspike or PSW in sleep. EM, AA, AAM, F. Self stimulation with eyes closure.	- Wake: (P)SW on frontal regions; Sleep: higher frequency of generalized discharges. EM, AA. Self stimulation with eyes closure.	+ Sleep: Multifocal spikes, prominent on frontal and occipital regions; bursts of generalized irregular polyspike or PSW. EM, EMA, AA, AAOC, AS, MS, AAA. Self stimulation with eyes closure.	+ Sleep: Low-voltage centrooccipital spikes. AA, AAOC, MA	- Wake: Diffuse GPSW; Sleep: PSW on frontal regions. EM, EMA, AA, AAM, MS, AS, MATS. Self stimulation with eyes closure.	+ Wake: Diffuse SW, predominant on frontal regions; Sleep: Numerous frontal SW. EMA, AAM	- Wake: Temporoparietal SW; Sleep: PSW on frontal regions
MRI	Cranial	Normal	NR	Normal	Normal	Bilateral hypersignal of WM (4 yr); cerebellar atrophy (6 yr)	Normal	Aspecific WM hypersignal	NR	Defect in frontal lobes development
Treatment	AED Other	VPA, LEV, ETX, LTG, CBD KD	ETX, LEV, LTG, VPA, CLB, ZNS, PER, CBD KD	VPA, ETX, ZNS, LTG KD	LEV, VPA KD	VPA, CLB, ETX, LTG, RUF, ZNS KD, VNS	LEV, VPA, LTG, ETX KD	LEV, VPA, TPM, CLB, CLZ, ZNS, LTG, PER KD	VPA, LEV, TPM KD	LEV, VPA, LTG, ETX, CLB, CLZ, ZNS
Genetic inform	Genomic change (Hg19) cDNA/aa change Inheritance	chr6:33409002; G>G/T c.1966G>T, p.Glu656*	chr6:33409095; C>C/T c.2059C>T, p.Arg687*	chr6:33409095; C>C/T c.2059C>T, p.Arg687*	chr6:33411544delA c.3215_3224del, p.Lys1072Serfs*2	chr6:33405604; T>T/C c.922T>C, p.Trp308Arg	chr6:33409002; G>G/T c.1966G>T, p.Glu656*	chr6:33414346; G>G/A c.3583-6G>A, p.Val1195Alafs*27	chr6:33411127; A>A/G c.2798A>G, p.His933Arg	chr6:33400531-33400532insG c.456insG, p.Thr153Aspfs*15 de novo
Family History	NR	Paternal grandmother with unspecified epilepsy	NR	NR	NR	NR	NR	NR	NR	NR

¹ Syndromic diagnosis of EMA; ² Syndromic diagnosis of MAE; ^{a,b,c,d,e} Different cases with the same genomic change. aa: amino acid; aCGH: Array comparative genomic hybridization; AS: Angelman syndrome; ASD: Autism spectrum disorder; CSF: Cerebrospinal fluid; DD: Developmental delay; DDD: Deciphering Developmental Disorders; del: deletion; EEG: Electroencephalogram; FOS: Fixation of the sensitivity; ID: Intellectual disability; IPS: Intermittent Photic Stimulation; MRI: Magnetic resonance imaging; NGS: Next generation sequencing; NR: not reported; p: percentile; OCD: Obsessive compulsive disorder; PPR: Photoparoxysmal response; PS: Photosensitivity; REM: Rapid eye movement; VUS: variant of unknown significance; WES: whole exome sequencing; WM: White matter; yr: year; -: Feature not found. Seizure types: AA: Atypical absence; AAA: Atypical absences with atonic phenomena, AAM: Atypical absence with myoclonia; AAOC: Atypical absences with oculoclonic movements; AS: Atonic seizures; DA: drop attack; EM: Eyelid myoclonia; F: focal seizures; FIAS: Focal impaired awareness seizures; FS: Febrile seizures; GS: Generalized seizures; GTCS: Generalized tonic clonic seizures; MA: Myoclonic absence; MAT: myoclonic-atic seizures; MATS: Myoclonic-atic-tonic seizures; MFD: multifocal discharges; MJ: Myoclonic jerks; MS: Myoclonic seizures; NCSE: Non-convulsive status epilepticus; TCS: Tonic-clonic seizures; TS: Tonic seizure. EGG: BG: Background; DS: diffuse slowing; ED: epileptiform discharge; FD: focal discharges; GD: General discharges; GPSW: Generalized polyspike wave; GSW: Generalized spike wave, PSW: polyspike wave; SSW: slow spike and wave; SW: spike wave. Treatment: CBD: cannabidiol; CBZ: carbamazepine; CLB: clobazam; CLZ: clonazepam; KD: Ketonic diet; ETX: ethosuximide; LCM: lacosamide; LEV: levetiracetam; LTG: lamotrigine; LZP: Lorazepam; AD: modified Atkins diet; NZP: nitrazepam; PER: perampanel; PHT: Phenytoin; RUF: Rufinamide; TPM: topiramate; VGB: vigabatrin; VNS: vagal nerve stimulation; VPA: valproate; ZNS: zonisamide.

Vlaskamp et al. (2019) explored the relationship between EMA and MAE [23]. From a cohort of 57 cases with *SYNGAP1* mutations or microdeletions, the most common epilepsy phenotype was an overlapping syndrome combining the features of these two epilepsy syndromes (20/57, 35%), followed by the diagnosis of EMA in 13 patients (23%). DD/ID (32/33) and ASD (24/33) were also prevalent in those cases (Table 1). According to the results of Vlaskamp et al., absences with EM and PS were found in more than 50% of the cases with epilepsy and *SYNGAP1* alteration. Myoclonic (33%) and atonic (8%) seizures were also recurrent in their patients with EM. Moreover, in those cases, EM has an earlier onset and the cognitive outcome is worse than the classic syndrome of EMA. Therefore, they concluded that the more severe cases of EMA might be explained by *SYNGAP1* mutations, especially in those individuals with earlier onset of EM or myoclonic or atonic seizures [23].

In this sense, Kuchenbuch et al. (2020) presented three cases with different *de novo* mutations in *SYNGAP1* and epilepsy [25]. Although not all the clinical data are available, two of these cases presented EM and absences induced by PS or eye closure (Table 1). These two cases presented also myoclonic jerks and the EM onset was before 3 years of age (8 months and 2.5 years, respectively) [25]. In addition, the *SYNGAP1* variants of these two cases were also reported by Lo Barco et al. (2021) in two other cases with EMA (p.Glu656*) and EM (p.Arg687*) in a cohort of 15 patients with cognitive disability and pathogenic *SYNGAP1* variants, of which 14 were epileptic [24]. According to the clinical and EEG data, five of these patients presented EMA, with an onset age of three years or below, presence of myoclonic (60%) and atonic (40%) seizures in three and two cases respectively, and with uncontrolled seizures despite of the treatment in four cases. Moreover, two more cases of this series also presented EM and absences (Table 1) [24].

Finally, other publications gather more patients with alterations in *SYNGAP1* and a phenotype resembling EMA. Okazaki et al. (2017) published a case with a EMA-like phenotype that was carrier of a variant in this gene (p.Val1195Alafs*27) [26]. This alteration was previously identified in a male patient with moderate ID, no speech, psychomotor delay, and behavioral disorders, but without epilepsy [27]. However, this was also later described by Lo Barco et al. in a patient with EMA [24] (Table 1). Von Stülpnagel et al. (2019) published four cases with *SYNGAP1* pathogenic variants and EM typically initiated by eye closure [28]. It should be noted that two of them, which were also reported by Vlaskamp et al., were carrier siblings of a variant probably inherited from one of their parents as a result of gonadal mosaicism. Moreover, other variant (p.Leu323Pro) has also been described by Vlaskamp et al. in a patient with a very similar phenotype except for the photosensitivity (Table 1). Furthermore, four more cases of the series from Vlaskamp et al. were previously reported in different publications [22,29–31]. Therefore, a total of 49 patients with a phenotype of EMA or EMA-like, carriers of 44 different pathogenic variants in *SYNGAP1*, have been reported (Table 1).

2.2. KIA2022/NEXMIF

NEXMIF (MIM *300524), also known as *KIAA2022*, is located on Xq13.3 [32]. *NEXMIF* encodes for the X-linked Intellectual Disability Protein Related to Neurite Extension (XPN) [33]. Highly expressed in the early brain development, it participates in neurite outgrowth and regulates neuronal migration and cellular adhesion, critical for developing neuronal circuits [33–35]. Loss of function of *NEXMIF* causes mental retardation X-linked 98 (MRX98; MIM # 300912) [36]. Like most of X-linked disorders, males tend to be more severely affected than females, whereas carrier females present a wide phenotypic variability and may be unaffected as a result of random X-chromosome inactivation (XCI). MRX98 is a neurodevelopmental disorder characterized in males by delayed motor milestones, lack of language development, moderate to profound ID, behavioral abnormalities such as ASD, hypotonia, postnatal growth restrictions, dysmorphic facial features, and often early-onset seizures [36,37]. Compared with its hemizygous male counterpart, the heterozygous

female disease has less severe ID, but is more often associated with a severe and intractable myoclonic epilepsy [38,39].

In 2017, Borlot et al. published the case of a woman with EMA syndrome carrier of a *de novo* *NEXMIF* deletion of 77Kb, detected by genome-wide oligonucleotide array, within a cohort of 143 adults with unexplained childhood-onset epilepsy and ID [40]. One year later, Myers et al. reported two other sisters diagnosed with MAE with a point mutation at *NEXMIF* (p.Arg322*) in their search of parental gonadal mosaicism in apparently *de novo* epileptic encephalopathies [41]. These two cases and their clinical features have recently been reviewed by Stamberger et al. (2021) [42]. Analyzing the phenotype of 87 patients with *NEXMIF*-related encephalopathy, 10 females were diagnosed with EMA, 2 of them with an earlier onset (one year or younger), and 5 more cases (2 males and 3 females) presented a combination of EMA and MAE syndromes, including the case reported by Myers et al. (2018) (Table 2) [42]. According to Stamberger et al., there was no correlation between phenotype and XCI status in their series, based on 1) the comparison of females with skewed and random XCI and 2) the families with sisters each presenting skewed and random XCI (families F4 and F7). However, it is interesting that in those families, both cases with a skewed XCI were diagnosed with MAE-EMA syndrome without photosensitivity, and their sister with a random inactivation presented a less severe phenotype. Moreover, XCI testing was performed in blood cells, so that the inactivation rate in neuronal cells is in fact unknown. Additionally, it is remarkable that from the two males, one presented the alteration in a 30% somatic mosaicism, which may lead to clinical repercussions equivalent to XCI in females (Table 2). On the other hand, the majority of patients with *NEXMIF*-related encephalopathy had drug-resistant epilepsy. Although specific information for each patient was not available, only 16% of the patients from the total cohort were seizure-free. It is outstanding that only 7% of the females, compared to 47% of males, were seizure-free ($p = 0.001$ Fisher's exact) [42].

Finally, two more female patients with alterations in the *NEXMIF* gene and a phenotype resembling EMA have been reported. Wu et al. (2020) described a woman with refractory epilepsy and EEG features similar to those described in EMA who was a carrier of a nonsense variant in *NEXMIF* (p.Leu355*) (Table 2) [43]. Samanta and Willis (2020) identified a frameshift mutation (p.Asp573Serfs*11) in a girl with intractable seizures diagnosed with EMA [2]. She presented a XCI classified as random (ratio 74:26) (Table 2). Based on the results of Viravan et al. (2011) on occipital lobe relation to eye movements in JS, Samanta and Willis proposed that functional brain mosaicism, as a result of random XCI, causes a cellular interference effect responsible for the variable symptoms, with a predominant involvement of a circuit encompassing the occipital cortex and the cortical/subcortical systems physiologically involved in the motor control of eye closure and eye movements [2,44].

Summarizing, a total of 15 female patients and 2 males (one of which was a mosaic for the alteration) have been reported with pathogenic variants in *NEXMIF* and clinical features of EMA (Table 2).

Table 2. Summary of the cases reported with a pathogenic (or probably pathogenic) alteration in *NEXMIF* (NM_001008537.3) and an EMA/EMA-like phenotype.

A									
Reference	Samanta 2020 ¹	Wu 2020	Stamberger 2021 ^{1,2}	Stamberger 2021 ^{1,2}	Stamberger 2021 ^{1,2}	Stamberger 2021 ¹	Stamberger 2021 ¹	Stamberger 2021 ^{1,2} /Myers 2018 ²	
Patient			1 (F1)	2 (F2)	4 (F4)	7 (F5)	8 (F6)	10 (F7)/T990 (family 12)	
gender	Female	Female	Male	Male	Female	Female	Female	Female	
Age	9 yr	29 yr	8 yr	12 yr	12 yr	14 yr	18 yr	28 yr	
DD/ID	+ (mild)	+ (mild)	+ (severe)	+ (moderate)	+ (severe)	+ (moderate)	+ (moderate)	+ (moderate-severe)	
Clinical features	Behavioral features	ADHD	NR	Regression, ASD, behavioral problems	Regression, ASD, severe tantrums	Regression, ASD, ADHD	Regression, obsessive, repetitive behaviours, anxiety	Regression, stereotypes, aggressive behaviour, impulsive, attention problems, anxiety	ASD traits
	Other parametres	mild hypotonia	Minor dysmorphic features (flat nasal bridge and ocular hypertelorism), diabetes mellitus type 2	Scaphocephaly, mild facial dysmorphisms (deep set eyes, wide spaced teetch, prominent lower lips, protruding tongue; tapering fingers), hypotonia/hupertonia, esotropia	NR	Upslanting palpebral fissures, hypoplastic eyelashes, small rounded nasal tip	ventricular septal defect; primary enuresis	NR	overweight, prominent eyebrows, hirsutism, polycystic ovarian syndrome
Epilepsy	Age of onset	2 yr	6 yr	21 months	15 months	12–14 months	2 yr	3 yr	19 months
	Absence seizures	+	+ (AAS)	+	+	+	+	+	+
	Eyelid myoclonia	+	+ (rare)	+	+	+	+	+	+
	Photosensitivity	+	+	+	-	-	-	+	-
Other seizures	Rapid eye blinking with upward eye rolling associated with head bobbing	GTCS, brief blanking, behavioral arrest and states of prolonged confusion	AS, MS. Triggered by PS	MS, MAS, GTCS, NCSE. Triggered by temperature (hot)	Head nods, drop attack, AS, MS, likely NCSE. Triggered by fever, temperature, eye closure	MS, NCSE (absence status)	nocturnal MS, rare GTCS	MS, DA, GTCS, NCSE	
EEG	PPR	+	+	NR	NR	NR	NR	NR	NR
	others	3 Hz GSW. Eyelid jerking, generalized epileptiform discharges induced by eye cosure	Interictal: paroxysmal GPSW induced by eye closure, PS. Ictal: persistent 1.5–2.5 Hz semi-rhythmic GPSW. Epileptiform discharges induced by eye closure	Interictal: BG slowing, 2.5–3 Hz GPSW, PFA. Ictal: 2.5 Hz GPSW. Triggered by sleep abd IPS	Interictal: BG slowing, 2.5–4 Hz G(P)SW. Ictal: 2.5–4 Hz GPSW (MS, MAS, head drops). Triggered by sleep, eye closure	Interictal: BG slowing, G(P)SW. Ictal: irregular G(P)SW (eyeclosure with EM). Triggered by eye closure, possible IPS	Interictal: excessive beta activity, G(P)SW. Ictal: irregular GSW (A-EM, MS). Triggered by eye closure, IPS	Interictal: BG slowing 2.5–5 Hz G(P)SW, MFD. Ictal: G(P)SW (EM, MS), NCSE in sleep. Triggered by sleep, eye closure, IPS	Interictal: BG slowing, G(P)SW, PFA, left rhythmic delta activity, MFD
MRI	Cranial	Normal	Normal	Short medulla, thin, dysmorphic CC, asymmetrical hippocampi, right incompletely rotated, delayed myelination subcortical WM and increased FL/T2 signal in posterior PVWM	Slightly small cerebellar vermis and mild tonsillar ectopia, bulky amygdalas and hippocampal heads.	Normal	Possible minimal atrophy superior cerebellar vermis	Normal	Normal

Table 2. Cont.

A									
Reference	Samanta 2020 ¹	Wu 2020	Stamberger 2021 ^{1,2}	Stamberger 2021 ^{1,2}	Stamberger 2021 ^{1,2}	Stamberger 2021 ¹	Stamberger 2021 ¹	Stamberger 2021 ^{1,2} /Myers 2018 ²	
Patient			1 (F1)	2 (F2)	4 (F4)	7 (F5)	8 (F6)	10 (F7)/T990 (family 12)	
Treatment	AED	ETX, LTG, MPH, GF, RD, LEV, VPA, RUF, TPM, ZNS	CBZ, VPA, MZN, LTG, LEV, TPM	VPA, LTG, LEV	ETX, VPA, FBM, RUF, TPM, CLB, CBZ, LEV, PLP, CLZ, VGB, LTG, GB, CS	CS, CLB, LEV, VPA.	ETX, ZNS, PB, CS, VPA, LTG, AZA, CLB, LEV, ATD, CBD	CS, NZP, LTG, CBZ, VPA, TPM, CLB, ZNS, ETX	CS, VPA, LEV, LCM, TPM, AZA, PB, ETX, LTG, PER, BRV, CBD
	Other	KD, mAD, LHID, DAP	GPO, STG		KD		KD	KD	
Genetic information	Genetic test	NGS panel (1148 genes)	WES	NR	NR	NR	NR	NR	NR
	Genomic change (Hg19)	chrX:73962671_73962674 del	ChrX:73963328; AG>AG/A-	chrX:73963494; C>C/A	chrX:73961747; G>G/C	chrX:73962951; G>G/A	chrX:73962417; G>G/A	chrX:73961593; G>G/T	chrX:73963428; G>G/A
	cDNA/aa change	c.1718_1721delATCA, p.Asp573Serfs*11	c.1063delC, p.Leu355*	c.898G>T, p.Glu300*	c.2645C>G, p.Ser882*	c.1441C>T, p.Arg481*	c.1975C>T, p.Gln659*	c.2799C>A, p.Tyr933*	c.964C>T, p.Arg322* inherited (paternal gonadal mosaicism likely)
	Inheritance	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	NR	inherited (maternal)	<i>de novo</i>	<i>de novo</i>	
	Others information	CXI 74:26 (random). CSF GLUT1 and aCGH normal	CXI 51:49 (random)	NR	~30% mosaicism for NEXMIF alteration	CXI ~90:10 (skewed). SCN1A:p.(Met1977Val), paternal - VUS	CXI~60:40 (random)	CXI~50:50 (random)	CXI~80:20 (skewed)
Family History		No family history of ID nor epilepsy	Family history of GEFS+ and hypotonia: Father: seizures, hypotonia, speech/language delay, unilateral hearing loss. Sister: FS. Paternal grandfather, paternal aunt and two paternal uncles: childhood epilepsy +- FS. Paternal cousin: FS	Maternal great-great-grandmother: epilepsy	Two sisters carriers of the alteration with ID but without seizures (patient 5 and 6). Two more affected siblings not included in the study with ID without seizures. One other sister is carrier with no disease activity to date. Carrier mother has mild ID			Epileptic sister, also with MAE, carrier of the alteration (patient 9).	

Table 2. Cont.

B										
Reference	Stamberger 2021 ^{1,#}	Stamberger 2021 ^{1,#}	Stamberger 2021 ¹	Stamberger 2021 ^{1,&}	Stamberger 2021 ¹	Stamberger 2021 ¹	Stamberger 2021 ¹ /Borlot 2017 ¹	Stamberger 2021 ¹	Stamberger 2021 ^{1,2,&}	
Patient	13 (F10)	15 (F12)	16 (F13)	18 (F15)	23 (F20)	33 (F30)	34 (31)/27	37 (F34)	41 (F38)	
gender	Female	Female	Female	Female	Female	Female	Female	Female	Female	
Age	8 yr	12 yr	10 yr	15 yr	16 yr	15 yr	26/23 yr	10 yr	4 yr	
DD/ID	+ (mild)	+ (moderate)	+ (moderate)	+ (mild)	+ (moderate)	+ (moderate)	+ (mild)	+ (moderate)	+ (mild)	
Clinical features	Behavioral features	Aggressive behaviour, attention problems	ADHD	ASD, Agressive behaviour	Self-abasement, ASD traits (social difficulties)	NR	Easily frustrated	Depression, anxiety	Attention deficiency and problems linked to communication difficulties during infancy, decreased satiety, tics (blinking), ASD traits.	-
	Other parametres	overweight, gastro-oesophageal reflux disease	NR	Mild facial dysmorphisms (short philtrum, low-set hairline, mild prognathism with frontal bossing)	NR	Hypotonia, hypermovility	NR	overweight, gastro-oesophageal reflux disease as infant/-	Low set backward rotated ears, protruding underlip, hypotonia	Mild hypotonia and hyperlaxity
Epilepsy	Age of onset	1 yr	9 monts	2–4 months	2–4 yr	18 months	6.5 yr	16 months	30 months	2 yr 10 months
	Absence seizures	+	+	+	+	+	+	+	+	NR
	Eyelid myoclonia	+	+	+	+	+	+	+	+	+
Other seizures	Photosensitivity	NR	NR	-	NR	+	-	-	-	+
	MS, GTCS. Triggered by sleep deprivation	Triggered by fever, eye closure	Triggered by fever, eye closure	Triggered bu eye closure	GTCS	GTCS, NCSE (absences), Triguered by PS	NR	Single GTCS/BCS	MS	AS (head drops) MS (blinking). Triggered by PS
EEGG	PPR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	others	Interictal: mild BG slowing, >3 Hz G(P)SW, MFD, GPFA. Ictal: G(P)SW (Absences +-EM), GSW (MS). Triggered by sleep, IPS, hiperventilation	Interictal: normal BG, G(P)SW in sleep, MFD. Ictal: GSW (EM), Triggered by sleep, eye closure	Interictal: normal BG, G(P)SW in sleep, MFD. Ictal: 3 Hz irregular GPSW (EM). Triggered by sleep	Interictal: BG asimmetry, near continuous G(P)SW during wakefulness. Ictal: EM with impaired awareness	Interictal: Normal BG, MFD with (P)SW, multiple spikes. Triggered by hyperventilation, IPS, sleep, eye closure	Interictal: G(P)SW, PFA. IctalG(P)SW (EM, MS). Triggered by hyperventilation, IPS, eye closure, fixation of sensitivity	Interictal and ictal: sharply contoured runs of alpha activity at times/polyspike and generalized spike waves induced by eye closure	Interictal: multiple spikes and spike-wave. Ictal: quick frontal and central activity (MS). Triggered by eye closure	Interictal: BG slowing, G(P)SW, MFD, bifrontal disrhythmic delta activity during sleep. Ictal: GPSW (MS). Triggered by sleep
Cranial MRI	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Treatment	AED	ETX, LEV, VPA	LTG, CLZ, LCM, VPA, ETX, CLB, LEV	ETX, CLZ, VPA	VPA, LTG	LEV, CLZ, ZNS, VPA, ETX, OXC, LTG	VPA, CLB	TPM, CBZ, VPA	LEV, LTG, ETX, VPA	CBD, VPA, CLB, LEV
	Other					KD, VNS	vitamin B6			

Table 2. Cont.

B										
Reference	Stamberger 2021 ^{1,#}	Stamberger 2021 ^{1,#}	Stamberger 2021 ¹	Stamberger 2021 ^{1,&}	Stamberger 2021 ¹	Stamberger 2021 ¹	Stamberger 2021 ^{1/Borlot 2017¹}	Stamberger 2021 ¹	Stamberger 2021 ^{1,2,&}	
Patient	13 (F10)	15 (F12)	16 (F13)	18 (F15)	23 (F20)	33 (F30)	34 (31)/27	37 (F34)	41 (F38)	
Genetic information	Genetic test	NR	NR	NR	NR	NR	aCGH	NR	NR	
	Genomic change (Hg19)	chrX:73962510; G>G/A	chrX:73962510; G>G/A	chrX:73961016; C>C/A	chrX:73961500; G>G/C	chrX:73964056; C>C/T	chrX:73963740; G>G/A	ChrX:73930523_74007913 del (0.08 Mb, 1 gene)	chrX:73960934dupT	chrX:73961500; G>G/C
	cDNA/aa change	c.1882C>T, p.Arg628*	c.1882C>T, p.Arg628*	c.3376G>T, p.Glu1126*	c.2892C>G, p.Tyr964*	c.336G>A, p.Trp112*	c.652C>T, p.Arg218*	Xq13.3 del (Ex 2–4)	c.3458dupA, p.Asn1153Lysfs*8	c.2892C>G, p.Tyr964*
	Inheritance	NR	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	<i>de novo</i>	NR
Others information		CXI~65:35 (random)	CXI~65:35 (random)		3p24.1(30,414,405–30,878,291)x3, maternal - VUS ADGRV1: p.(Asp2942His), maternal - VUS		CXI ~60:40 (random)			
Family History							Maternal distant cousin: GTCS and learning disability. Distant maternal relative: absence seizures in childhood. Sister of paternal grandmother: "drop seizures" and questionable DD	Sister with normal development exhibited epilepticus status due to a fall in bicycle, attention deficiency		

¹ Syndromic diagnosis of EMA; ² Syndromic diagnosis of MAE; ^{#,&} Different cases with the same genomic change. aa: amino acid; aCGH: Array comparative genomic hybridization; ADHD: Attention deficit hyperactivity disorder; AED: Antiepileptic drug; ASD: Autism spectrum disorder; CC: corpus callosum; CSF: Cerebrospinal fluid; CXI: X-inactivation; DD: Developmental delay; del: deletion; EEG: Electroencephalogram; Ex: exon; ID: Intellectual disability; IPS: Intermittent Photic Stimulation; MRI: Magnetic resonance imaging; NGS: Next generation sequencing; NR: not reported; PPR: Photoparoxysmal response; PS: Photosensitivity; PVWM: Periventricular white matter; VUS: variant of unknown significance; WM: White matter; yr: year; -: Feature not found. Seizure types: AAS: Atypical absence status; AS: Atonic seizures; DA: drop attack; EM: Eyelid myoclonia; FS: Febrile seizures; GTCS: Generalized tonic clonic seizures; MAS: Myoclonic-atic seizures; MFD: multifocal discharges; MS: Myoclonic seizures; NCSE: Non-convulsive status epilepticus; PFA: paroxysmal fast activity. EGG: BG: Background; GPFA: Generalized paroxysmal fast activity; GPSW: Generalized polyspike wave; GSW: Generalized spike wave, PFA: paroxysmal fast activity. Treatment: AZA: acetazolamide; ATD: Amantadine; BRV: brivaracetam CBD: cannabidiol; CBZ: carbamazepine; CLB: clobazam; CLZ: clonazepam; CS: corticosteroids; KD: Ketonic diet; DAP: dexamphetamine; ETX: ethosuximide; FBM: felbamate; GB: gabapentin; GF: guanfacine; GPO: glimepiride; LCM: lacosamide; LEV: levetiracetam; LHID: low hypoglycemic index diet; LTG: lamotrigine; mAD: modified Atkins diet; MPH: methylphenidate; MZN: midazolam; NZP: nitrazepam; OXC: oxcarbazepine; PB: phenobarbital; PER: perampanel; PLP: Piridoxal phosphate; RD: risperidone; RUF: Rufinamide; STG: sitagliptin; TPM: topiramate; VGB: vigabatrin; VNS: vagal nerve stimulation; VPA: valproate; ZNS: zonisamide.

2.3. RORB

RORB (MIM * 601972) is located on 9p21.13 [45]. This gene encodes for a nuclear receptor, retinoid-related orphan receptor β (ROR β), involved in neuronal migration and differentiation [46]. Recent evidences have point out that mutations in this gene may contribute to susceptibility to epilepsy (MIM # 618357) [47].

In 2012, Bartnik et al., within a cohort of 102 patients, described a case with epilepsy and EM with generalized tonic-clonic seizures (GTCS), carrier of a 2.57 Mb deletion of 6 genes including *RORB* [48]. A few years later, Rudolf et al. (2016) described a family with four affected family members of EMA with rare GTCS carriers of a nonsense variant in *RORB* (p.Arg66*) [49]. Other sporadic cases were also reported by these authors with different alteration on *RORB*, including two more cases with absences, EM and GTCS (Table 3). Sadleir et al. (2020) identified four novel *RORB* variants in 11 affected patients from four families with different epileptic syndromes [50]. Of this series, one case was diagnosed with EMA and occipital lobe epilepsy, presenting also GTCS. Moreover, another patient from a different family also presented absences with EM and GTCS, but was diagnosed with juvenile absence epilepsy and idiopathic photosensitive occipital lobe epilepsy (Table 3). Although the predominant epileptic phenotype of this cohort was represented by the overlap of photosensitive generalized and occipital epilepsy, the authors underlined the important role of occipital cortex in starting epileptic discharge in idiopathic generalized epilepsies such as EMA [50]. Finally, Morea et al. (2021) described another case with a *RORB* variant diagnosed with EMA [11].

Even though only six patients with *RORB* alterations, from three different families, have been clearly diagnosed with EMA, interestingly, five of them also presented GTCS. Moreover, four more patients presented EM and absences with GTCS.

Table 3. Cont.

Reference	Bartnik 2012	Rudolf 2016 ¹	Rudolf 2016 ¹	Rudolf 2016 ¹	Rudolf 2016 ¹	Rudolf 2016	Rudolf 2016	Sadleir 2020 ¹	Sadleir 2020	Morea 2021 ¹	
Patient	12	4	13	14	20	9A1117	GE0705	Family C II-2	Family D II-1	Case report	
Genetic information	Genetic test	aCGH	WES	WES	sanger sequencing	WES	aCGH	aCGH	aCGH	Sanger sequencing	NGS
	Genomic change (Hg19)	chr9:7474,400_77306932 del (2.57 Mb, 6 genes)			chr9:77249649; C>C/T		chr9:70984481_79549501 del (8.5 Mb, 47 genes)	chr9:77261322_77313598 del (52Kb)	Min:chr9:77249078_77251973del2896 Max:chr9:77248677_77251984del3308	chr9:77286755; A>A/T	9q21
	cDNA/aa change				c.196C>T, p.Arg66*			9q31.13 del (Ex 5–10)	c.96_237del141, p.Gly32_Ala79del48	c.1162A>T, p.Ile388Phe inherited (paternal)	NR
	Inheritance	de novo			(probably) Inherited		de novo	de novo	inherited (maternal)		de novo
Others information	FISH: 9q21.13 (RP 11-243A1)		aCGH array normal			Karyotype: mos 47,XX,+r[20]/46,XX,-21,+der(9)t(9;21)[5]/46,XX [25]. aGCH array: mosaic gain 9p. FISH: 9q13q21.13 del (RP11-404E6), mosaic i(9p), der(9)t(9;21) and r(9)	qPCR to validate the result	NR	NR		
Family History	Father Asperger syndrome	Family members: Patient 20; Patient 13 (Mother); Patient 14 (maternal aunt); Patient 4 (maternal grandmother). Other two carriers: Patient 23 (sister): One episode of absence seizure (probably GGE with no EEG); Patient 10 (maternal great-aunt): EEG with isolated high-amplitude spike during IPS but seizure state not confirmed. Several antecedents of PS without seizures				Maternal uncle and two of her first cousins had GTCS	No family history of seizures	Alteration inherited from her mother (normal intelligence and no seizures). Her son, with intractable DEE and severe ID, has the same microdeletion	Alteration inherited from his father, diagnosed with early onset abcense epilepsy and occipital lobe epilepsy, who also presented GTCS	-	

¹ Syndromic diagnosis of EMA. aa: amino acid; aCGH: Array comparative genomic hybridization; ADHD: Attention deficit hyperactivity disorder; AED: Antiepileptic drug; ASD: Autism spectrum disorder; DD: developmental delay; DEE: developmental and epileptic encephalopathy; del: deletion; EEG: Electroencephalogram; Ex: exon; GGE: genetic generalized epilepsy; ID: Intellectual disability; IPS: Intermittent Photic Stimulation; MRI: Magnetic resonance imaging; NGS: Next generation sequencing; NR: not reported; PPR: Photoparoxysmal response; yr: year; -: Feature not found. Seizure types: FS: Febrile seizures; GTCS: Generalized tonic clonic seizures; TA: typical absence; TC: tonic-clinic seizure. EGG: BG: background; CTS: centro-temporal spike; GPSW: Generalized polyspike wave; GSW: Generalized spike wave. Treatment: CBZ: carbamazepine; CLB: clobazam; ETX: ethosuximide; KD: Ketonic diet; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; TPM: topiramate; VGB: vigabatrin; VPA: valproate.

2.4. *CHD2*

CHD2 (MIM *602119) is located on 15q26.1 [51]. It encodes a member of the chromodomain helicase DNA-binding (CHD) family of proteins, of which the canonical function is the gene expression regulation by epigenetic changes in chromatin [52]. Loss of function of *CHD2* is identified as a cause of developmental epileptic encephalopathy (DEE) [52], being associated with childhood-onset epileptic encephalopathy (EEOC; MIM #615369) and MAE (ORPHA 1942) [53,54]. Usually, it is also characterized by cognitive regression, ID, ASD-like phenotype, and resistance to antiepileptic drugs (AED) treatment [52].

Two publications of 2015 underline the association of *CHD2* variants with photosensitivity in epilepsy, with seven patients with EMA between both articles [55,56]. Thomas et al. presented four cases with EMA, out of 10 patients with *de novo* *CHD2* alterations [56]. The four cases also have GTCS; in addition, other common features associated to *CHD2* deficiency were present (ID (4/4), ASD (3/4) and regression (3/4)) (Table 4). On the other hand, Galizia et al. presented the results of a *CHD2* screening in a series of more than 500 patients with photosensitive epilepsy [55]. From 36 patients with EMA, all with photoparoxysmal response, three cases presented unique variants in *CHD2* (Table 4). Based on the highest frequency of alterations among EMA patients compared to the rest of the series (8/544), the authors considered *CHD2* as an important contributor to EMA [55].

Although the number of reported cases with EMA and pathogenic variants in *CHD2* is low, it should also be considered in the screening for the genetic causes of this pathology.

Table 4. Summary of the cases reported with a pathogenic (or probably pathogenic) alteration in *CHD2* (NM_001042572) and an EMA/EMA-like phenotype.

	Reference	Galizia 2015 ¹	Galizia 2015 ¹	Galizia 2015 ¹	Tomas 2015 ¹ /Carvill 2013 ²	Tomas 2015 ¹	Tomas 2015 ¹	Tomas 2015 ¹ /Mullen 2013
	Patient	7	8	9	5/T38	6	8	9/15 [57]
Clinical features	gender	NR	NR	NR	Male	Female	Male	Female
	Age	NR	NR	NR	18/17 yr	13 yr	14 yr	36/26 yr
	DD/ID	NR	NR	NR	+ (moderate-severe/moderate)	+ (moderate-severe)	+ (mild)	+ (mild)
	Behavioral features	ASD	NR	NR	ASD, regression, aggression/ASD, No regression	ASD, ADHD, aggression	ADHD, regression, aggression	autistic traits, regression, aggression
Other parametres	nephrolithiasis, migraine, scoliosis	NR	NR	Transient ataxia on valproate	Short stature	Short stature, ataxia	NR	
Epilepsy	Age of onset	NR	NR	NR	12 months	30 months	30 months	34 months
	Absence seizures	+	+	+	+ (AMA, MA; TA)/+	+ (TA)	+	+
	Eyelid myoclonia	+	+	+	+	+	+	+
	Photosensitivity	+	+	+	+ (Self induced with TV)	+ (Self induced with TV)	+ (Self induced with TV; photic stimulation)	+ (Self induced with TV or light)
	Other seizures	NR	NR	NR	MS, FS, GTCS/AS, FS, MJ, TC	MS (self-induced with TV), TS, GTCS	AS, GTCS, MS (self-induced with TV), NCSE, CSE	GTCS, MS (self-induced with TV or light),
EEG	PPR	+	+	+	- (interictal and BG)	- (interictal and BG)	+ (grade 4)	NR
	others	NR	NR	NR	3–4-Hz GPSW during atonic myoclonic absence seizures. 9 yr: Diffusely slow BG with symmetrical theta and 3 Hz delta. 14 yr: Normal BG for brief bursts of 3–4 Hz regular rhythmic GSW/3.8 Hz GSW	3 yr: Slow BG for age. Inter-ictal GSW GPSW, bi frontal slow spike wave (2 Hz). Eye flickering—bursts of 2 Hz bifrontal spike and wave. 4 yr: EMA, GSW, GPSW. Activated by eye closure. 7 yr: Normal BG, irregular GSW with a frontal predominance. GSW on eye closure and during eyelid myoclonia	32 months: Normal BG, frontal predominant GSW, GPSW. 5.5 yr: Normal BG, multifocal GSW. 11 yr: Diffusely slow BG, 3 Hz GSW, bifrontal spikes, activated in sleep, 4–5 Hz posteriorly dominant GSW on eye closure. 12 yr: Continuous slowing in wake and marked generalized epileptiform activity in sleep. 14 yr: Diffuse theta slowing, active interictal GSW GPSW discharges >3 Hz increased by hyperventilation	5 yr: Generalized epileptiform discharges every 1–2 minutes
MRI	Craneal	NR	NR	NR	Normal	Generalized cerebellar atrophy with large v4 and prominent folia. The posterior corpus callosum is foreshortened and smaller posteriorly	Atrophy between scans, markedly in the cerebellum. The corpus callosum is hypoplastic posteriorly with a small splenium	Normal

Table 4. Cont.

	Reference	Galizia 2015 ¹	Galizia 2015 ¹	Galizia 2015 ¹	Tomas 2015 ¹ /Carvill 2013 ²	Tomas 2015 ¹	Tomas 2015 ¹	Tomas 2015 ¹ /Mullen 2013
	Patient	7	8	9	5/T38	6	8	9/15 [57]
Genetic data	Genetic test	NGS	NGS	NGS	target NGS	target NGS	target NGS	aCGH
	Genomic change (Hg19)	chr15:93540316; A> A/-	chr15:93545442; ->-/A	chr15:93482909; C>C/T	chr15:93545504_93545507del	chr15:93557956delG	chr15:93521611; C>C/T	chr15:91027533_93477874 del
	cDNA/aa change	c.3725delA, p.Lys1245Asnfs*4	c.4173dupA, p.Gln1392Thrfs*17	c.C653T, p.Pro218Leu	c.4235_4238 delAAGG, p.Glu1412Glyfs*64	c.4720delG, p.Gly1575Valfs*17	c.2725C>T, p.Gln909*	15q26 del (2.4 Mb)
	Inheritance	NR	de novo	inherited	de novo	de novo	de novo	de novo
Family History	NR	NR	Inherited from unaffected mother	NR	NR	NR	NR	

¹ Syndromic diagnosis of EMA; ² Syndromic diagnosis of MAE. aa: amino acid; aCGH: Array comparative genomic hybridization; ADHD: Attention deficit hyperactivity disorder; AED: Antiepileptic drug; ASD: Autism spectrum disorder; DD: developmental delay; del: deletion; EEG: Electroencephalogram; ID: Intellectual disability; MRI: Magnetic resonance imaging; NGS: Next generation sequencing; NR: not reported; PPR: Photoparoxysmal response; yr: year. Seizure types: AMA: Atonic myoclonic absence; AS: Atonic seizure; CSE: Convulsive status epilepticus; FS: Febrile seizures; GTCS: Generalized tonic clonic seizures; MA: Myoclonic absence; MJ: Myoclonic jerks; MS: Myoclonic seizures; NCSE: Non-convulsive status epilepticus; TA: typical absence; TC: tonic-clinic seizure, TS: Tonic seizure. EGG: BG: Background; GPSW: Generalized polyspike wave; GSW: Generalized spike wave.

2.5. Other Genes of Interest

Three publications present different patients with clinical diagnosis of EMA and with a pathogenic variant in three candidate genes for the disease: *SLC2A1*, *KCNB1*, and *NAA10*. The possible implication of these genes in EMA is discussed below.

SLC2A1 (MIM *138140) is located in 1p34.2 and encodes for the major glucose transporter in the brain, GLUT1 [58]. It is responsible for the well-known GLUT1 deficiency syndrome and encephalopathy characterized by a childhood-onset epilepsy refractory to treatment, but with a wide phenotypic variability (MIM #606777; ORPHA 71277) [59,60]. In this sense, Madann et al. reported a pathogenic variant in *SLC2A1* in a family with Glut1-deficiency syndrome and JS [13]. The index case was a 9-year-old boy with intractable seizures since 4 months of age, and frequent absences with EM since 3 years of age. EEG showed eye closure sensitivity (eye closure triggered eyelid myoclonia with absences) and photosensitivity suggestive of EMA. He also presented multifocal seizures and paroxysms of intermittent involuntary gaze; sleep EEG showed multifocal interictal discharges and MRI was normal. Moreover, he had DD, mild ID, gait ataxia, scanning speech, and microcephaly. His father had a history of infantile-onset generalized epilepsy with generalized tonic-clonic seizures and ID, and his paternal uncle also had childhood-onset epilepsy. Metabolic results were suggestive of Glut1-deficiency syndrome; therefore, *SLC2A1* was sequenced. A pathogenic variant was detected in both the index case and his father (c.376C>T; p.Arg126Cys), in a hotspot located at a transmembrane domain of the GLUT1, that had been previously reported in other cases with the metabolic syndrome and typical absence seizures or myoclonic absences as the most prevalent seizure type but without EM or EMA features [61,62]. After different unsuccessful treatments with AEDs (valproate, phenobarbital, benzodiazepines, phenytoin, and topiramate), once the molecular diagnosis was known, a ketogenic diet allowed complete seizure remission. However, since it was a targeted study, other genetic causes in the index case could contribute to or be responsible for the EMA phenotype. Furthermore, a screening study of *SLC2A1* performed at 25 GGE-EM patients, including 8 cases of EMA, did not identify any variant that could confirm the role of *SLC2A1* in EMA or other GEE with EM [63]. Based on these cases, although EMA could be included within the wide phenotypic spectrum for non-classic GLUT1 deficiency syndrome, more evidence is required.

KCNB1 (MIM *600397) is located in 20q13.13 [64]. It encodes for a brain potassium channel (Kv2.1) and its alteration causes a developmental epileptic encephalopathy (DEE26) (MIM # 616056) [65]. In 2017, from a cohort of six patients with *de novo* mutations in *KCNB1*, Marini et al. described two patients with a phenotype resembling EMA. The first case (patient 3) was carrier of a missense variant and was diagnosed with JS [66]. This patient was a 22-year-old female who had had epilepsy since 6 months of age, with bilateral myoclonic jerks. From 7 years of age, she developed absences with EM, frequently on eye closure or autoinduced, with persistent generalized PS. EEG showed generalized spike- and polyspike-wave discharges with a prominent generalized photoparoxysmal response, several episodes of myoclonia and absences with EM were recorded. She also presented myoclonic and tonic-clonic seizures. Tried with several AEDs (Carbamazepine, valproic acid, levetiracetam, lamotrigine, ethosuximide, clonazepam, and topiramate), she finally became seizure-free with a combination of three of them. She had a delayed early development, evolving into mild cognitive impairment with motor and verbal dyspraxia, poor coordination, and moderate ID [66]. Her *KCNB1* variant (c. 916C>T; p.Arg306Cys) was located in the voltage-sensor domain of the protein, which was previously reported in a patient with DD and infantile-onset seizure refractory to therapy but without EMA [67]. A new case with this mutation was also recently reported by Minardi et al. (2020) in a series of 71 patients with DEE [68]. However, few specific clinical data for this case were provided, and EM or EMA-like features were not included among them. On the other hand, the series reported by Marini et al. included a second case with generalized epilepsy with myoclonic seizures and EM with PS; however, unfortunately, this patient was not clearly identified in the article [66]. Therefore, although the data reported by Marini et al.

were promising, stronger evidence and casuistry are required to consider this gene as a candidate for EMA.

Finally, *NAA10* (MIM *300013) is located in Xq28 [69]. It encodes for an N- acetyltransferase and it is responsible for the Ogden syndrome in male carriers, a rare syndrome characterized by postnatal growth failure, developmental delay, hypotonia, and variable dysmorphic features (MIM # 300855) [70]. Although epilepsy is not associated to this syndrome, Valentine et al. (2018) describe a case with JS and a *de novo* variant in this gene [10]. The female patient, at the age of 3 years, presented initial seizures described as eye rolling and blank stares without generalized or focal body twitching. At first, she was diagnosed with absence epilepsy. Her seizures were frequently triggered by light stimulation. EEG showed a photoparoxysmal response, characterized by generalized spike-and-slow wave discharges, and numerous eyelid myoclonias with or without absences were recorded. Moreover, her seizures were intractable despite of the AED treatment (clonazepam, levetiracetam, lamotrigine, valproic acid, topiramate, rufinamide, clobazam, intravenous immunoglobulin, modified Atkins diet, and vagal nerve stimulator). Therefore, her epilepsy was consistent with EMA. She also presented DD, normal growth, self-injurious behavior and stereotypies, mild generalized hypotonia, and mild dysmorphisms (clinodactyly, mild ptosis, down slanting palpebral fissures, and tented upper lip) [10]. This patient's *NAA10* variant (c.346C>T; p.Arg116Trp) was previously reported in a female patient with random XIC and without known seizure activity, but with other clinical features (normal growth, moderate ID, hypotonia, attention deficit hyperactivity disorder (ADHD), and developmental coordination disorder) [71]. This variant was also reported by Popp et al. (2015) in a male patient with a more severe phenotype (postnatal growth retardation, severe ID, truncal hypotonia and hypertonia of extremities, autistic features, and aggressive behavior) [72]. Moreover, EEG under photic stimulation of this reported male showed generalized epileptic form activity. However, the clinical differences might be due to the inactivation pattern of X chromosome in females, as commented for *NEXMIF* above.

More cases need to be collected to be able to consider these genes as candidates for EMA. However, in the next-generation-sequencing era, the screening for alteration in those genes in EMA-like patients is manageable and will allow to clarify their promising role in the disease.

2.6. General Overview of Genetic Interactions

As mentioned before, the seven genes are expressed in the brain and their function are of great relevance for neuronal development, migration, function, or genetic regulation; however, there is no clear relationship among them. Looking for possible interactions, *NEXMIF*, highly expressed in fetal and adult brain [73], might be related to *RORB*, involved in neuronal migration and differentiation [46], and to *SLC2A1*, essential to provide the requirements of glucose at the brain among other tissues [74] (Figure 1) [75]. However, further studies, including in vitro and animal model assays, would be required to confirm this hypothesis.

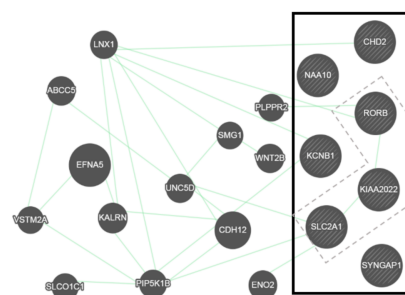


Figure 1. Prediction of the genetic interactions performed by Genemania (<http://genemania.org/>) (accessed on 15 April 2021) [75].

2.7. Animal Models

Gene editing techniques have facilitated the generation of mouse models of human diseases; however, very little is known specifically about EMA. *SYNGAP1* haploinsufficient young mice showed a reduced fluorothyl-induced seizure threshold and were prone to audiogenic seizures [76]. Furthermore, it is worth noting that in the former study, photo-stimulation evoked signals originating in the dentate gyrus were dramatically amplified as they spread through the hippocampus, instead of attenuated as it occurs in wild type animals. In addition, germline *Syngap1* mutations in mice induced a persistent form of stabilized cortical hyperexcitability that lasted into adulthood, with the seizure threshold remaining reduced [77]. Interestingly, restoration of the gene in adult mice was able to improve behavioral and electrophysiological measures of memory and seizures [78]. Finally, the phenotype of the epileptogenesis in a *Syngap1*^{+/-} mouse model have been recently described [79]. On the other hand, loss of *NEXMIF* gene expression in neurons of Knock-out (KO) mice results in a significant decrease in synapse density and synaptic protein expression [80]. These animals presented severe seizures, although further studies are required to characterize the epileptic phenotype in Nexmif KO mouse models.

3. Methods

Systematic literature research of PubMed was performed to identify eligible articles until 31 March 2021 (see Appendix A for complete search terms). The search identified 66 potential articles.

Reviews, clinical trials, and articles in a different language than English were excluded. We screened the titles and abstracts to check if they were within the scope of this review. In some cases, when abstracts were not available or more information was required to decide, a quick review of the whole article was carried out. At this stage, a total of 21 original articles, mainly case reports, containing data dealing with candidate genes for EMA, were obtained (Figure 2). For each of the seven selected genes, a literature research was also performed to look for more cases with an EMA-like phenotype. This selection was based on different number of cases for each gene: 49 for *SYNGAP1* (Table 1); 17 for *NEXMIF* (Table 2); 10 for *RORB* (Table 3); 7 for *CHD2* (Table 4); 2 cases for *KCNB1*; and 1 case each for *SLC2A1* and *NAA10*. It is also remarkable that some of these cases were reported in different publications (Tables 1, 2 and 4).

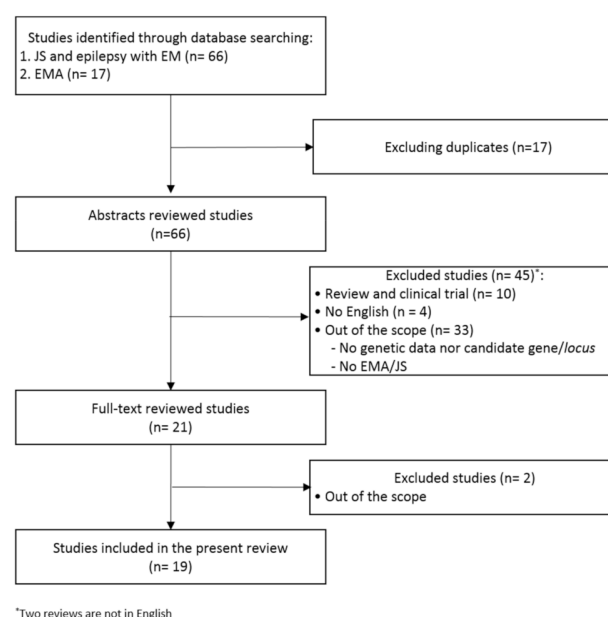


Figure 2. Flow diagram summarizing the systematic search, screening, and studies selection for this review.

4. Conclusions

Loss of function of *SYNGAP1*, in addition to its association with DD, ID, and ASD, might be considered in epileptic patients with EMA, especially in those cases with earlier onset of EM, pharmacoresistance, or myoclonic or atonic seizures.

The phenotype spectrum of *NEXMIF* in females (or mosaic males) may also include EMA-like, probably associated with pharmacoresistance. Since this gene is located in the X chromosome, XCI in the brain can cause specific cellular mosaicism that might be responsible for the EMA phenotype in those cases.

In patients with alterations in *SYNGAP1* or *NEXMIF*, clinical features of EMA may overlap with MAE syndrome, presenting manifestations of both pathologies. It is also remarkable that despite the relative low number of cases with pathogenic alteration in those genes, two families presented a probably gonadal mosaicism: one family presented with a frame shift mutation in *SYNGAP1* (p.Leu150Valfs*6) and the other with a nonsense variant in *NEXMIF* (p.Arg322*) (Tables 1 and 2). The recurrence of gonadal mosaicism is very variable depending on the disease but has to be taken into account for correct genetic counseling [81].

Regarding *RORB* and *CHD2*, although the number of cases with EMA is significantly lower, they should be taken into account, especially in those cases with GTCS.

In relation to other genes, a few cases of EMA have been reported with variants in *SLC2A1*, *KCNB1*, or *NAA10*. There is not enough information to establish a clear relationship, but as more and more exome and genome studies in EMA patients are performed, it is expected that their role in the molecular diagnosis of this pathology will be clarified.

It is remarkable that two of the seven genes are located in the X chromosome, *NEXMIF* and *NAA10*. Although males show an apparently more severe phenotype, females more often present severe and intractable epilepsy. As mentioned before, random XCI in the brain might lead to cellular interference responsible for the epilepsy and could also explain the higher prevalence of EMA in females.

Finally, an animal model is a great tool to study the pathobiology of complex human disease that affect organs such as the brain. Although mouse models have shown some results regarding *SYNGAP1* and *NEXMIF* haploinsufficiency, no specific data have been collected for EMA. Therefore, to establish the possible interaction between these seven genes, or their direct implication into the pathology, further functional studies are required.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

PubMed search terms:

1. ((Jeavons Syndrome) OR (epilepsy with eyelid myoclonias)) AND (genetic OR gene OR genes)
2. (“Eyelid myoclonia with absences”) AND (genetic OR gene OR genes)

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AED	Antiepileptic drugs
ASD	Autism spectrum disorder
CHD	Chromodomain helicase DNA-binding
DD	Developmental delay
DEE	Developmental epileptic encephalopathy
EEOC	Childhood-onset epileptic encephalopathy
EEG	Electroencephalogram
EM	Eyelid myoclonia
EMA	Eyelid myoclonia with absences
GGE	Genetic generalized epilepsies
GTCS	Generalized tonic-clonic seizures
ID	Intellectual disability
ILAE	International League Against Epilepsy
IPS	Intermittent photic stimulation
JS	Jeavons syndrome
KO	Knock-out
MAE	Myoclonic-atonic epilepsy
MRX98	Mental retardation X-linked 98
PS	Photosensitivity
XCI	X-Chromosome Inactivation
XPN	X-linked Intellectual Disability Protein Related to Neurite Extension

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