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

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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-ataxic 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. Summary of the cases reported with pathogenic (or probably pathogenic) alteration in SYNGAP1 (NM_006772) and an EMA/EMA-like phenotype.

| Reference  | Klitten 2011 | Mingot 2016 | Mingot 2016 | Okazaki 2017 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 |
|------------|--------------|-------------|-------------|-------------|---------------|---------------|---------------|
| Patient    | 11           | 12          | 14          | 1           | 4             | 5             | 7             |
| gender     | Male         | Male        | Female      | Male        | Male          | Male          | Male          |
| Age        | 25 yr        | 3 yr        | 22 yr       | 8 yr        | 4 yr          | 3 yr 10 months| 8 yr 3 months |
| DD/ID      | + (Severe)   | + (Severe)  | + (Severe)  | + (Mild)    | +            | + (Mild)      | + (Severe)    |
| Behavioral features | ASD traits, anxious behavior | Repetitive behaviours, stereotypies | Stereotypies | ASD, stereotypies | NR | NR | - |
| Other parameters | Absence of language | Absence of language, truncal hypotonia, swallowing difficulties | Absence of language, mild gait ataxia, flexion deformity of left hip, hyperlordotic lumbar spine, microcephaly | Motor slowness and moderate akinesia, ataxic gait, truncal hypotonia, dystonic postures of hands and feet, plastic hypotonia | Hypotonia, hypersalivation | Hypotonia | - |
| Age of onset | 13 months    | 2 yr        | 1 yr        | 5 yr        | 1 yr and 5 months | 16 months    | 2.5 yr        |
| Absence seizures | + (MA, AA) | + (AA) | + (MA) | NR | + (MA) | NR | NR |
| Eyelid myoclonia | + (eyelid winking) | + | + | NR | + | + | + |
| Photosensitivity | NR | + | NR | + | + | + | + |
| Other seizures | DA with MJ | FS | FS, MJ | NR | MS | Triggers by PS, sleep deprivation and fatigue | MS | Triggers by PS, sleep deprivation and fatigue |
| Epilepsy  | Interictal: generalized synchronous 3–7 Hz (P)SW | Abnormal BG, generalized slowing, EM, and generalized seizure patterns. Triggered by photosensitivity | Bursts of spikes and slow waves in the occipital region after eye closure. Triggered by photosensitivity | Ictal: bursts of diffuse PSW with posterior predominance after eyes closer and plastic stimulation. Triggered by Photos and PS | Ictal: diffuselow or SW activity with occipitalto central predominance. Interictal: bilateral frontal spikes. Sleep: rhythm, generalized 2–3-Hz delta activity, without visible seizures. Normal BG | Ictal: GSW (myoclonic). Interictal: GSW | Ictal: GSW (myoclonic). Interictal: GSW |
| EEG others | BG slow | Ictal: GSW (myoclonic) | Interictal: GSW | BG slow | Interictal: Frequent 2.5–4 Hz GSW, after eye closure in trains, MFD | Interictal: GPW | sleep: frequent seizures while falling asleep |
| Cranial MRI | NR | Normal | Normal | Normal | Normal | Normal | Normal |

Notes:
- MA, AA: Moderate and mild motor and mild language delay.
- PSW: Paroxysmal slow waves.
- EM: Emergence myoclonus.
- MFD: Myoclonus, facial dyskinesia.
- FOS: Photo-synchronous or photoparoxysmal response.
| AED Treatment | VPA, LTG, CLB | VPA | LEV, TPM | LEV, ETX | CBZ, VPA, LEV, ETX, LTG | VPA | VPA, LEV, LTG, ETX, CBD | VPA |
|---------------|---------------|-----|----------|----------|-------------------------|-----|------------------------|-----|
| **Genetic Information** | | | | | | | | |
| Genetic test | karyotype | NGS | chr:33406650; C>C/T | chr:33406650; C>C/T | chr:33406650; C>C/T | chr:33406650; C>C/T | chr:33406650; C>C/T | chr:33406650; C>C/T |
| Genomic change | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T | chr6:33406650; C>C/T |
| Others | FISH (probe RP11.497A24) |  |  |  |  |  |  |  |
| **Others Information** | | | | | | | | |
| Inheritance | de novo | VUS inherited from the mother: SCN9A: c.4282G>A and c.5624G>A; ARX: c.1462A>G | c.1630C>T, p.Arg544* | c.1685C>T, p.Pro562Leu | c.2214_2217delAGCG, p.Glu739Glyfs*20 | c.3583-6G>A, p.Val1195Alafs*27 | - | - |
| **Behavioral Features** | | | | | | | | |
| Gender | male | female | male | female | male | female | male | female |
| Age | 8 yr | 6 yr | 4 yr 8 months | 9.5 yr | 5 yr 2 months | 9 yr | 5 yr 10 months | 15 yr 1 months |
| DD/ID | + (moderate-severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (moderate) |
| **Clinical Features** | | | | | | | | |
| Hypotonia, hyperlaxity, 2 cafe 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, reflex, absence of language | pes planus, strabismus, constipation, hearing loss after recurrent otitis/ataxia | nystagmus | Congenital hip dysplasia, absence of language | | | |
| **Others** | | | | | | | | |
| Family History | - (epilepsy) | - | - | - | - (epilepsy or ID) | - (seizures, ID or ASD) | - (seizures, ID or ASD) | Sister, father, and many paternal relatives with learning difficulties. Maternal cousin ASD |
| B | | | | | | | | |
| **Reference** | Vlaskamp 2018 | Vlaskamp 2018 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 |
| Patient | 8/7 | 9/8 | 11 | 12 | 13/241 | 15 | 17 | 20 | 21 |
| Age | 8 yr | 6 yr | 4 yr 8 months | 9.5 yr | 5 yr 2 months | 9 yr | 5 yr 10 months | 15 yr 1 months | 10 yr 5 months |
| DD/ID | + (moderate-severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (severe) | + (moderate) | + (moderate) |
| Behavioral features | regression, tantrums, self-injury, tichotillomania, high pain threshold, eating disorder, sleeping problems | 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 | | | | |
| Other parameters | hypotonia, hyperlaxity, 2 cafe au lait spots, small capillary hemangioma, constipation, hearing loss after infection/ataxia, problems in fine motor skills | hypotonia, ataxia, constipation, reflex, absence of language | pes planus, strabismus, constipation, hearing loss | nystagmus | Congenital hip dysplasia, absence of language | | | | | |
| 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 |
| **Absence seizures** | + | + | NR | + (AA) | NR | NR | NR | NR | NR | + (MA) |
| **Eyelid myoclonia** | + | + | NR | NR | NR | NR | NR | + | + | + |
| **Photosensitivity** | + | + | NR | NR | NR | NR | NR | + | + | + |
| **Other seizures** | MS, MA. Triggered by touch and thinking of eating/GS, MJ, atonic drops. Reflex seizures while chewing | MS, DA. Triggered by fever and infection | 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** |
|----------------|
| **Intal** | 3 Hz GSW (EM-MAI) | Intal: 2.5–3.5 Hz GSW (EM-MAI). Inerictal: 2.5–3.5 Hz GSW | BG poor. Ictal: Bilateral occipital sharp wave, followed by MFD (EM). Inerictal: MFD | BG: slow. Ictal: GPSW (MS), 1.5–2 Hz GSW (AA). Interictal: GSW facilitated by eye closure | Intercital: GSW | BG: slow. Ictal: FD (unilateral TCS). Intercital: 3–4 Hz GSW, MFD | BG: slow. Interictal: 1.5–3 Hz GSW, MFD | Intercital: 3 Hz GSW, bifrontal SW | BG: slow. Ictal: GSE (MA). Interictal: MFD | BG: slow. Interical: 3 Hz GSW, also following eye closure, PD |
| **MRI** |
|----------------|
| **Cranial** | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal (discrete hippocampal tissue loss, not progressive and without sclerosis) | Normal |

| **AED** |
|----------------|
| **VPA, LEV, TPM, CLB, LTG, ETO, LCM, ZNS, CLZ, CBD, PHT KD** | VPA, LEV, TPM | CLB, TPM, NZP, LTG, VPA, CLZ | VPA, CLB | VPA, CLZ, LEV, TPM | Vitamin B6 | VPA | VPA | VPA | VPA | VPA |

| **Genomic information** |
|----------------|
| **Genomic change (Hg19)** | chr6:33400529_33400521dup | chr6:33403058delC | chr6:3340318dupC | chr6:3340367; C>C/T | chr6:33405511_33405512insC | chr6:33406048; C>C/T | chr6:33406202delC | chr6:33406324; C>C/T | chr6:33406420delC | chr6:33408547C >GGCTGC |
| **cDNA/aa change** | c.435_447dupC, 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 | c.1393delC, p.Leu465Phefs*9 | c.1515C>G, p.Tyr505* | c.1718C>G, p.Glu578Asafs*7 | c.1718C>G, p.Glu578Asafs*7 |
| **Inheritance** | de novo/mosaic parent | de novo | 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) | Maternal grandfather post-stroke epilepsy | Maternal uncle moderate ID | (seizures, ID or ASD) |
Table 1. Cont.

| Reference | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 |
|------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Patient    | 23            | 24            | 25            | 26/27528       | 27            | 30            | 31            | 32            | 33            |
| gender     | female        | female        | male          | male          | male          | 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 |
| DD/ID      | + (severe)    | + (severe)    | + (moderate)  | + (severe)    | + (severe)    | + (severe)    | + (moderate-severe) | + (severe)    | + (moderate-severe) |
| Clinical features | regression, ASD, aggression, sleep problems, high pain threshold | regression, ASD, aggression, sleep problems, high pain threshold | regression, ODD symptoms, tantrums, aggression | regression, ASD, aggression, sleep problems, high pain threshold, oral hypersensibility | regression, ASD, aggression, sleep problems, high pain threshold, eating difficulties | regression, ASD, aggression, sleep problems, high pain thresholds, eating difficulties | ASD, aggression, sleep problems, high pain threshold |
| Other parameters | hypotonia, constipation | congenital dysplasia, hypotonia, ataxic gait | mild two/three syndactyly, irregular tremor upper extremities, osteopenia | Unsteady gait | hypotonia, unsteady gait, constipation, chronic idiopathic trypomocystopenic purpura, absence of language | microcephaly, short stature, borderline hypotonia, ataxia, Hemangiomna nasal cavity | Hypotonia, coordination disorder, ataxia |
| Age of onset | 2 yr | 6 months | 9.5 yr | 18 months | 2 yr | 18 months | 2 yr | 2 yr 3 months | 8 months |
| Absence seizures | NR | NR | + | NR | NR | + | NR | + | NR |
| Eyelid myoclonia | + | + | + | + | + | + | + | + | + |
| Photosensitivity | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Other seizures | FS, bilateral TCS (with fiver), atomic DA. Triggered by fatigue and illness | bilateral TCS (with fiver), atomic DA. Triggered by fatigue and illness | Triggered by eating | FS, aura, FIAS, MJ, NCSE, bv- and unilateral TCS, MS. Triggered by PS | TCS (with fiver) | Atticogenic 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 | IBG: slow. Interictal: occipital 2 Hz GSW, occasional FD/bi-occipital ED, DS, SSW | IBG: irregular. Ictal: GSW (EM). Interictal: 2-3 Hz GSW, irregular GPSW, MFD | IBG: irregular GSW followed by slower discharges (EM). GPSW (EM). Interictal: GP(SW, bifrontal SW, FD | IBG: slow Ictal: GSW (EM). Interictal: tempor-opercular SW, 10% generalized activity in 24 hours. | NR | IBG: right occipital slowing, Ictal: eyeblink without lctal correlate. Interictal: only in sleep: right occipital slowing, focal sharp waves |
| Cranial MRI | Normal | Normal | Normal | Normal | Normal | Atypical WM abnormalities | Normal | NR | Enlarged ventricles |

**C**

| Reference | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 |
|------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Patient    | 34            | 35            | 36            | 37            | 38            | 39            | 40            |
| gender     | female        | male          | male          | male          | male          | female        | male          |
| Age        | 16 yr         | 16 yr         | 16 yr         | 16 yr         | 16 yr         | 16 yr         | 16 yr         |
| DD/ID      | + (severe)    | + (severe)    | + (moderate)  | + (severe)    | + (severe)    | + (severe)    | + (severe)    |
| Clinical features | regression, ASD, aggression, sleep problems, high pain threshold | regression, ASD, aggression, sleep problems, high pain threshold | regression, ODD symptoms, tantrums, aggression | regression, ASD, aggression, sleep problems, high pain threshold, oral hypersensibility | regression, ASD, aggression, sleep problems, high pain threshold, eating difficulties | regression, ASD, aggression, sleep problems, high pain thresholds, eating difficulties | ASD, aggression, sleep problems, high pain threshold |
| Other parameters | hypotonia, constipation | congenital dysplasia, hypotonia, ataxic gait | mild two/three syndactyly, irregular tremor upper extremities, osteopenia | Unsteady gait | hypotonia, unsteady gait, constipation, chronic idiopathic trypomocystopenic purpura, absence of language | microcephaly, short stature, borderline hypotonia, ataxia, Hemangiomna nasal cavity | Hypotonia, coordination disorder, ataxia |
| Age of onset | 2 yr | 6 months | 9.5 yr | 18 months | 2 yr | 18 months | 2 yr | 2 yr 3 months | 8 months |
| Absence seizures | NR | NR | + | NR | NR | + | NR | + | NR |
| Eyelid myoclonia | + | + | + | + | + | + | + | + | + |
| Photosensitivity | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Other seizures | FS, bilateral TCS (with fiver), atomic DA. Triggered by fatigue and illness | bilateral TCS (with fiver), atomic DA. Triggered by fatigue and illness | Triggered by eating | FS, aura, FIAS, MJ, NCSE, bv- and unilateral TCS, MS. Triggered by PS | TCS (with fiver) | Atticogenic 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 | IBG: slow. Interictal: occipital 2 Hz GSW, occasional FD/bi-occipital ED, DS, SSW | IBG: irregular. Ictal: GSW (EM). Interictal: 2-3 Hz GSW, irregular GPSW, MFD | IBG: irregular GSW followed by slower discharges (EM). GPSW (EM). Interictal: GP(SW, bifrontal SW, FD | IBG: slow Ictal: GSW (EM). Interictal: tempor-opercular SW, 10% generalized activity in 24 hours. | NR | IBG: right occipital slowing, Ictal: eyeblink without lctal correlate. Interictal: only in sleep: right occipital slowing, focal sharp waves |
| Cranial MRI | Normal | Normal | Normal | Normal | Normal | Atypical WM abnormalities | Normal | NR | Enlarged ventricles |
Table 1. Cont.

| Treatment | Genetic test | Genomic change (Hg19) | Inheritance | Family History |
|-----------|--------------|-----------------------|-------------|----------------|
| AED       | Genetic information | c.1970G>A, p.Trp657* | Distant relative ASD | Paternal grandmother GTCS 16–20 y. Distant relative ASD |
| Other     | genetic test NR | chr6:33409006;G>G/A | de novo | - (seizures, ID or ASD) |
| VPA, LEV | Genetic information | chr6:33409095;C>C/T | de novo | Paternal first cousin post-traumatic epilepsy |
| VPA, LEV | Genetic information | chr6:33409410;C>C/T | de novo | Maternal and paternal first cousins learning difficulties |
| ZNS, CBD | Genetic information | chr6:334422del | de novo | Distant relative ASD |
| LEV, VPA | Genetic information | chr6:334422del | de novo | - (seizures, ID or ASD) |
| LTG, CLB | Genetic information | chr6:334422del | de novo | Maternal aunt ID. |
| VPA, LEV, | Genetic information | chr6:33411265_33411735delinsCA | de novo | Maternal uncle ID post-meningsitis. Distant relative epilepsy |
| ETX, ZNS, | Genetic information | chr6:33411265_33411735delinsCA | de novo | Distant relative ASD |
| CBD, LTG | Genetic information | chr6:33411265_33411735delinsCA | de novo | - (seizures, ID or ASD) |
| VPA, LEV, | Genetic information | chr6:33411265_33411735delinsCA | de novo | Maternal and paternal first cousins learning difficulties |
| LEV | Genetic information | chr6:33411265_33411735delinsCA | de novo | Distant relative ASD |
| LTG - VPA, | Genetic information | chr6:33411265_33411735delinsCA | de novo | - (seizures, ID or ASD) |
| CLB | Genetic information | chr6:33411265_33411735delinsCA | de novo | Maternal and paternal first cousins learning difficulties |
| TPM | Genetic information | chr6:33411265_33411735delinsCA | de novo | Distant relative ASD |
| LTG | Genetic information | chr6:33411265_33411735delinsCA | de novo | - (seizures, ID or ASD) |
| Other KD | Genetic information | chr6:33411265_33411735delinsCA | de novo | Maternal and paternal first cousins learning difficulties |
| KD | Genetic information | chr6:33411265_33411735delinsCA | de novo | Distant relative ASD |

**Clinical features**

| Reference | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Vlaskamp 2019 | Von Stülpnagel 2019 | Von Stülpnagel 2019 |
|-----------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|----------------------|----------------------|
| Patient | 36 | 39/1190N | 41 | 45 | 46 | 50 | 51/3 | 52 | 53 | 1 |
| gender | female | female | female | male | male | female | female | male | 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 yr | 7 yr months | 5 yr | 14 yr |
| DD/ID | + (mild) | + (moderate-severe) | + (moderate-severe) | + (severe) | + (severe) | + (moderate/mild) | + (severe) | + (mild) | + (moderate) | + (moderate-severe) |
| Behavioral features | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | regression, ASD traits | ASD |
| Other parameters | Few café au lait macules | pronated foot, coordination disorder, ataxic gait | hypotonia | hypoplasia, 6th toe, hypotonia, nystagmus | obesity, ataxia with wide-based gait | Hypotonia, unsteadiness with poor balance, gross and fine motor dyspraxia | pes cavus, hypotonia, balance issues | Height <3p. | Tongue hypotonia and horizontal nystagmus. Postaxial hypothenar hypoplasia and hypoplasia | Abnormal gait; poor coordination; dysarthria. Abnormal facial shape (triangular), large antverted, ears, wide mouth, thin lips, pointed chin |
Table 1. Cont.

| Epilepsy | EEG | MRI | Treatment |
|----------|-----|-----|-----------|
| **Age of onset** | **Absence seizures** | **Eyelid myoclonia** | **Photosensitivity** |
| <2 yr | NR | + (typical) | NR |
| 6.7/5 yr | NR | + | - |
| 4.5 yr | + | + | + |
| 2.5 yr | + | + | + |
| 2.8 yr | + | + | + |
| 2.5 yr | + | + | + |
| 18 months | NR | + | - |
| 18 months | NR | + | - |
| 2.5 yr | NR | + | - |
| 2.5 yr | NR | + | - |
| 20 months | NR | + | - |
| **Other seizures** | **Triggered by eye closure, hunger and fatigue** | **Triggers by PS** | **Triggers by visual patterns** |
| **EEG** | **Ictal:** GD (EM-MAt). | **Interictal:** 2–3 Hz GSW, frequent GD, induced by eye closure | **Interictal:** GD, MFD, spikes, G(P)SW |
| **Others** | **Ictal:** G(P)SW (EM). | **Interictal:** G(P)SW (EM) | **Interictal:** GSW |
| **BG:** Slowing. | **Interictal:** G(S)W, GSP, 3.5–4 GSP, FD | **BG slow** | **BG:** Generalized slowing. **Interictal:** MFD |
| **MRI** | **Cranial** | **Normal** | **Normal** |
| **Mega cisterna magna fossa posterior** | **Normal** | **Normal** | **Normal** |
| **Small hyperintens subcortical WM lesions (bi-frontal, peri-ventricular), possibly post-anoxic leukoapathy** | **Stable mild enlarged ventricles and pineal cyst** | **Normal** | **Normal** |
| **Hydrocortison, VGB, NZP** | **VPA, LEV, ETX, CLZ, LTG, CBD** | **VPA, LEV, ZNS, PER, CBD** | **VPA, LTG, LEV, CLB** |
| **Treatment** | **AED** | **VPA, CLB, LTG** | **LEZ, RUE, VPA** |
| **Other** | **NR** | **NR** | **NR** |

Note: FS, GTCS, episodes characterized by loss of consciousness, backward eyeball rolling, MS, generalized with head atonia and EM, status epilepticus.
| Table 1. Cont. |
|----------------|
| Genetic test  | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) | NR | NGS panel (95 genes) |
| Genomic change (Hg19) | chr6:33400029, G>G/A | chr6:33400583, G>G/A | chr6:33408504, G>G/A | chr6:33406580, T>T/C | chr6:33405712, G>G/A | chr6:33406199, C>C/T | chr6:33408514, C>C/T | chr6:33406718, C>C/T | chr6:33405650, T>T/C | chr6:33408626, C>C/G | chr6:33408718, C>C/G | chr6:33405650, T>T/C | chr6:33406199, C>C/T | chr6:33408514, C>C/T |
| cDNA/aa change | chr6:33400583, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33400583, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33400583, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln | chr6:33405650, p.599G>A, p.Arg170Gln |
| Paternal uncle epilepsy and behavioural problems | head growth slowdown, 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 | head growth slowdown, 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 | head growth slowdown, 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 |
| Mother FS. Paternal uncle learning difficulties | head growth slowdown, 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 | head growth slowdown, 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 | head growth slowdown, 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 |
| Other parameters | head growth slowdown, 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 | head growth slowdown, 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 | head growth slowdown, 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 |

## Clinical features

| Reference | Kuchenbuch 2020 | Kuchenbuch 2020 | Lo barco 2021 | Lo barco 2021 | Lo barco 2021 | Lo barco 2021 | Lo barco 2021 | Lo barco 2021 | Lo barco 2021 |
|-----------|----------------|----------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Patient   | 1              | 2              | 3              | 4              | 5              | 6              | 7              | 8              | 9              |

### 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) | + (AA) | + (AA) | + (AA) | + (AA) | + (AA) | + (AA) | + (AA) | + (AA) |
| Photosensitivity | + | + | + | + | + | + | + | + | + |

**Others**

| FS, MS, upper limb MJ, DA. Triggered by sleep and IPS | MS, FS | DA | MS | TS | MS | NR |
|---|---|---|---|---|---|---|

**Family History**

1. (seizures, ID or ASD)
2. (seizures, ID or ASD)
3. (seizures, ID or ASD)
4. (seizures, ID or ASD)
5. (seizures, ID or ASD)
6. (seizures, ID or ASD)
7. (seizures, ID or ASD)
8. (seizures, ID or ASD)
9. (seizures, ID or ASD)
10. (seizures, ID or ASD)

**Epilepsy**

1. (seizures, ID or ASD)
2. (seizures, ID or ASD)
3. (seizures, ID or ASD)
4. (seizures, ID or ASD)
5. (seizures, ID or ASD)
6. (seizures, ID or ASD)
7. (seizures, ID or ASD)
8. (seizures, ID or ASD)
9. (seizures, ID or ASD)
10. (seizures, ID or ASD)
Table 1. Cont.

| EEG   | PPR | NR | NR | 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, AA, AAM, MATS. Self stimulation with eyes closure. | Wake: Diffuse GPSW; Sleep: PSW on frontal regions. EM, AA, AAM. Self stimulation with eyes closure. | Wake: Temporoparietal SW; Sleep: PSW on frontal regions |
|-------|-----|----|----|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| others | NR  | 2-HZ GPSW | | | | | | |

| MRI | Cranial | Normal | NR | Bilateral hypersignal of WM (4 yr); cerebellar atrophy (6 yr) | Normal | Bilateral hypersignal of WM (4 yr); cerebellar atrophy (6 yr) | Normal | Aspecific WM hypersignal | NR | Bilateral hypersignal of WM (4 yr); cerebellar atrophy (6 yr) |
|------|---------|--------|----|-----------------------------------------------------------------|--------|-----------------------------------------------------------------|--------|-----------------------|----|-----------------------------------------------------------------|
| AED  | VPA, LEV, ETX, LTG, CBD | ETX, LEV, LTG, VPA, CLB, ZNS, PER, CBD | VPA, ETX, ZNS, LTG | VPA, LEV, VPA | LEV, VPA, ETX, LTG, RUF, ZNS | LEV, VPA, LTG, ETX | LEV, VPA, CLB, CLZ, ZNS, LTG, PER | LEV, VPA, TPM | LEV, TPM |
| Other | KD | KD | KD | KD | KD | KD | KD | KD |

| Genomic change (Hg19) | chr6:33409002; G>G/T | chr6:33409095; C>C/T | chr6:33411544delA | chr6:33409092; T>T/C | chr6:33409092; G>G/T | chr6:33414346; G>G/A | chr6:33411127; A>A/G | chr6:33400531-33400532insG |
|-----------------------|----------------|----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| cDNA/aa change | c.1966G>T, p.Glu656* | c.2059C>T, p.Arg687* | c.3215_3224del, p.Lys1072Serfs*2 | c.922T>C, p.Trp308Arg | c.1966G>T, p.Glu656* | c.3583-6G>A, p.Val1195Alafs*27 | c.2798A>G, p.His933Arg | c.456insG, p.Thr153Aspfs*15 |
| Inheritance | de novo | de novo | de novo | de novo | de novo | de novo | de novo | de novo |

| Family History | NR | NR | NR | NR | NR | NR | NR | NR |
|----------------|----|----|----|----|----|----|----|----|

1 Syndrome diagnosis of EMA; 2 Syndrome diagnosis of MAE; 3 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 atomic phenomena, AAM: Atypical absence with myoclonia; AAOC: Atypical absences with oculoclonic movements; AS: Atomic 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; MAE: Myoclonic-ataonic 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 (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].

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 women 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 Wills 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.

| Patient | Reference | Clinical features | Other parameters | Other seizures | EEG | MRI |
|---------|-----------|------------------|-----------------|----------------|-----|-----|
|         |           | gender | Age | DD/ID | Behavioral features | Other parameters | Epilepsy | PPR | other |
| 1 (F1)  | Samanta 2020 1 | Female | 9 yr | + (mild) | ADHD | Mild hypotonia | 2 yr | + | 3 Hz GSW, Eyelid jerking, generalized epileptiform discharges induced by eye closure |
| 2 (F2)  | Wu 2020 | Male | 29 yr | + (mild) | Regression, ASD, behavioral problems | NR | + (AAS) | + | + (rare) |
| 4 (F4)  | Stamberger 2021 1,2 | Male | 8 yr | + (severe) | Scaphocephaly, mild facial dysmorphism (deep set eyes, wide spaced teeth, prominent lower lips, protruding tongue; tapering fingers), hypotonia/hypertonia, esotropia | NR | + | + | + |
| 7 (F5)  | Stamberger 2021 1,2 | Female | 12 yr | + (moderate) | Regression, ASD, severe tantrums | Upplanting palpebral fissures, hypoplasic eyelashes, small rounded nasal tip | 12-14 months | + | + |
| 8 (F6)  | Stamberger 2021 1,2 | Female | 12 yr | + (severe) | Regression, ASD, ADHD | Ventricular septal defect; primary enuresis | 2 yr | + | + |
| 10 (F7) | Myers 2018 2 | Female | 14 yr | + (moderate) | Regression, stereotypes, agressive behaviour, repetitive behaviours, anxiety | NR | + | + | + |
| 12      | Stamberger 2021 1,2 | Female | 16 yr | + (moderate) | ASD traits | Overweight, prominent eyebrows, hirsutism, polycystic ovarian syndrome | 19 months | + | + | + |
| 12      | Myers 2018 2 | Female | 28 yr | + (moderate-severe) | | | | | |

### Notes:
- **Behavioral features:** ADHD: Attention Deficit Hyperactivity Disorder, NR: Not recorded.
- **Other parameters:** Mild hypotonia, Minor dysmorphic features (flat nasal bridge and ocular hypertelorism), diabetes mellitus type 2.
- **Other seizures:** Rapid eye blinking with upward eye rolling, associated with head bobbing.
- **EEG:** PPR: Paroxysmal PPR, Others: 3 Hz GSW, Eyelid jerking, generalized epileptiform discharges induced by eye closure.
- **MRI:** Cranial: Normal, Normal, Normal.
- **Clinical features:** Gender: Female, Male, Female, Male, Female, Female, Female, Female, Female.
- **Age:** 9 yr, 29 yr, 8 yr, 12 yr, 12 yr, 14 yr, 18 yr, 28 yr.
| Reference       | Samanta 2020 | Wu 2020 | Stamberger 2021 | Stamberger 2021 | Stamberger 2021 | Stamberger 2021 | Stamberger 2021 | Stamberger 2021 |
|-----------------|--------------|---------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient         | 1 (F1)       | 2 (F2)  | 4 (F4)         | 7 (F5)          | 8 (F6)          | 10 (F7)/T990    |                 |                 |
| Treatment       | AED          | Other   |                |                 |                 |                 |                 |                 |
| Genetic test    | NGS panel (1148 genes) | WES | NR | NR | NR | NR | NR | NR |
| Genomic change  | chrX:73962671, ChrX:73963328, del | chrX:73963494, C>G/A | chrX:73961747, G>G/C | chrX:73962951, G>G/A | chrX:73962417, G>G/A | chrX:73961593, G>G/G | chrX:73963428, G>G/A |
| Genomic         | c.1063delC, p.Leu335* | c.898G>T, p.Ser882* | c.1441C>T, p.Arg481* | c.2645C>G, p.Tyr933* | c.1975C>T, p.659* | c.2799C>A, p.Tyr933* | c.964C>T, p.Arg322* |
| Information     | CXI 74:26 (random), CSF GLUT1 and aCGH normal | CXI 51:49 (random) | NR | ~30% mosaicism for \(5\) 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). |
| Patient | Age | DD/ID | Gender | Clinical features | Other parameters | Other seizures | Epilepsy | EEG | Cranial MRI | Treatment |
|---------|-----|-------|--------|------------------|------------------|---------------|---------|-----|-------------|-----------|
| F10     | 8 yr| (mild)| Female | Mild facial dysmorphisms (short philtrum, low-set hairline, mild prognathism with frontal bossing) | BMI, gastroesophageal reflux disease | NR | 1 yr | Intercital: mild BG slowing, >3 Hz G(P)SW, MFD, GPCA. Ictal: G(PSW) in sleep, MFD. Ictal: 3 Hz irregular GPSW (EM). Triggered by sleep, epilepsy. | Normal | AED: ETX, LEV, VPA |
| F12     | 12 yr| (mild)| Female | ADHD | Mild facial dysmorphisms (short philtrum, low-set hairline, mild prognathism with frontal bossing) | BMI, gastroesophageal reflux disease | NR | 9 months | Intercital: normal BG, G(P)SW in sleep, MFD. Ictal: GSW (EM), Triggered by sleep, epilepsy. | Normal | AED: LEV, VPA, LTG, CLZ, LCM, VPA, ETX, CLB, LEV |
| F13     | 10 yr| (moderate)| Female | ASD, Aggressive behaviour | NR | NR | 2–4 months | Intercital: normal BG, G(P)SW in sleep, MFD. Ictal: 3 Hz irregular GPSW (EM). Triggered by sleep, epilepsy. | Normal | AED: LEV, VPA, CLZ, ZNS, VPA, ETX, OXC, LTG |
| F15     | 15 yr| (mild)| Female | Self-abasement, ASD traits (social difficulties) | NR | GTCS (absences), Triggered by PS | 18 months | Intercital: normal BG, MFD with (P)SW, multiple spikes. Triggered by hyperventilation, IPS, sleep, epilepsy. | Normal | Other: KD, VNS, vitamin B6 |
| F20     | 16 yr| (moderate)| Female | Hypotonia, hypermovility | NR | GTCS | 6.5 yr | Intercital: normal BG, MFD with (P)SW, multiple spikes. Triggered by hyperventilation, IPS, sleep, epilepsy. | Normal | Other: CBD, VPA, CLB, LEV |
| F30     | 15 yr| (moderate)| Female | Easily frustrated | NR | GTCS | 16 months | Intercital: normal BG, MFD with (P)SW, multiple spikes. Triggered by hyperventilation, IPS, sleep, epilepsy. | Normal | Other: TPM, CBZ, VPA, vitamin B6 |
| F34     | 26/23 yr| (moderate)| Female | Depression, anxiety | NR | NR | 30 months | Intercital: multiple spikes and spike-wave. Ictal: quick frontal and central activity (MS). Triggered by eye closure | Normal | Other: LEV, LTG, ETX, VPA |
| F38     | 4 yr| (mild)| Female | Low set backward rotated ears, protruding underlip, hypotonia | Mild hypotonia and hyperlaxity | NR | 2 yr 10 months | Intercital: BG slowing, G(P)SW, MFD, bifrontal dysrhythmic delta activity during sleep. Ictal: GPSW (MS). Triggered by sleep | Normal | Other: LEV, LTG, ETX, VPA |

**Reference:** Stamberger 2021

*B*:** Stamberger 2021/1, Stumberger 2021/2, Stamberger 2021/3, Stamberger 2021/4, Borlot 2017

**Treatment:**
- AED: LTG, LEV, VPA
- Other: LEV, CLZ, LCM, VPA, ETX, CLB, LEV
| Patient | Reference |
|---------|-----------|
| 13 (F10) | Stamberger 2021 |
| 15 (F12) | Stamberger 2021 1,2,4 |
| 16 (F13) | Stamberger 2021 1,2,4 |
| 18 (F15) | Stamberger 2021 1,2,4 |
| 23 (F20) | Stamberger 2021 1,2,4 |
| 33 (F30) | Stamberger 2021 1,2,4 |
| 34 (31)27 | Borlot 2017 1 |
| 37 (F34) | |
| 41 (F38) | |

**Genetic information**

| Patient | Reference |
|---------|-----------|
| 13 (F10) | NR |
| 15 (F12) | NR |
| 16 (F13) | NR |
| 18 (F15) | NR |
| 23 (F20) | NR |
| 33 (F30) | NR |
| 34 (31)27 | aCGH |
| 37 (F34) | NR |
| 41 (F38) | NR |

**Genomic change (Hg19) cDNA/aa change**

| Patient | Reference |
|---------|-----------|
| 13 (F10) | chrX:73962510; G>G/A c.1882C>T, p.Arg628* de novo |
| 15 (F12) | chrX:73961016; C>C/A c.3376G>T, p.Glu1126* |
| 16 (F13) | chrX:73961500; G>G/C c.2892C>G, p.Tyr964* |
| 18 (F15) | chrX:73964056; C>C/T |
| 23 (F20) | chrX:73963740; G>G/A |
| 33 (F30) | chrX:73930523_74007913 del (0.08 Mb, 1 gene) |
| 34 (31)27 | chrX:7390934dupT |
| 37 (F34) | c.3458dupA, p.Asn1153Lysfs*8 de novo |
| 41 (F38) | c.2892C>G, p.Tyr964* |

**Inheritance**

| Patient | Reference |
|---------|-----------|
| 13 (F10) | de novo |
| 15 (F12) | de novo |
| 16 (F13) | de novo |
| 18 (F15) | de novo |
| 23 (F20) | de novo |
| 33 (F30) | de novo |
| 34 (31)27 | de novo |
| 37 (F34) | de novo |
| 41 (F38) | de novo |

**Others information**

| Patient | Reference |
|---------|-----------|
| 13 (F10) | CXI~65:35 (random) |
| 15 (F12) | CXI~65:35 (random) |
| 16 (F13) | CXI~65:35 (random) |
| 18 (F15) | CXI~65:35 (random) |
| 23 (F20) | CXI~65:35 (random) |
| 33 (F30) | CXI~65:35 (random) |
| 34 (31)27 | CXI~65:35 (random) |
| 37 (F34) | CXI~65:35 (random) |
| 41 (F38) | CXI~65:35 (random) |

**Family History**

| Patient | Reference |
|---------|-----------|
| 13 (F10) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 15 (F12) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 16 (F13) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 18 (F15) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 23 (F20) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 33 (F30) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 34 (31)27 | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 37 (F34) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |
| 41 (F38) | Maternal distant cousin: GTCS and learning disability. Sister of maternal grandmother: "drop seizures" and questionable DD |

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1 Syndromic diagnosis of EMA; 2 Syndromic diagnosis of MAE; 3 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; CF: 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-atonic 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: azetazolamide; ATD: Amanadrine; BRV: brivaracetam CBD: cannabidiol; CBZ: carbamazepine; CLB: clobazam; CLZ: clonazepam; CS: corticosteroids; KD: Ketonic diet; DAP: dexamethasime; ETX: ethosuximide; FBM: felbamate; GB: gabapentin; GF: guanfacine; GPO: glimepiride; LCM: lacosamide; LEV: levetiracetam; LHD: low hypoglycemic index diet; LTG: lamotrigine; mAD: modified Atkins diet; MPH: methylphenidate; NZIP: nitrazepam; OXC: oxcarbazepine; PB: phenobarbital; PER: perampanel; PLP: Piridoxal phosphate; RD: risperidone; RUF: Rufinamide; STG: sitagliptin; TPM: topiramate; VGR: vigabratin; 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 (RORβ), 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 absences 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. Summary of the cases reported with a pathogenic (or probably pathogenic) alteration in RORB (NM_006914) and an EMA/EMA-like phenotype.

| Reference       | Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|-----------------|---------|---|---|---|---|---|---|---|---|---|----|----|----|
| Bartnik 2012    | Male    | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Female  | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Male    | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Female  | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Female  | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Male    | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Rudolf 2016     | Female  | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Family C II-2   | Female  | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Family D II-1   | Male    | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|
| Case report     | Male    | NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR| NR|

**Clinical features**

- **gender**: Male, Female
- **Age**: 2 yr, 3 yr, 9 yr, 11 yr, 5 yr 5 months, 4 yr 9 month, 3 yr, 4 yr 9 month, 3 yr, 10 yr, 4 yr
- **DD/ID**: NR, + (mild), + (mild), NR, NR, NR, NR, NR, NR, NR, NR, NR, NR
- **Behavioral features**: + (mild), + (mild), NR, NR, NR, NR, NR, NR, NR, NR, NR, NR, NR
- **Epilepsy**: Age of onset: 2 yr, 13 yr, 3 yr, 9 yr, 11 yr, 5 yr 5 months, 4 yr 9 month, 3 yr, 10 yr, 4 yr
- **Absence seizures**: NR, +, +, +, NR, NR, NR, NR, NR, NR, NR, NR, NR
- **Eyelid myoclonia**: NR, +, +, +, +, +, +, +, +, +, +, +, +
- **Photosensitivity**: NR, +, +, +, +, +, +, +, +, +, +, +, +
- **Other seizures**: GTCS, GTCS, GTCS, GTCS, GTCS, GTCS, FS, TC, nocturnal GTCS, GTCS, occipital seizures, GTCS, occipital seizures, induced by television and videogame exposure
- **EEG**: PPR, NR, +, +, +, +, +, NR, NR, NR, NR, NR, NR, NR
- **Cranial MRI**: NR, NR, NR, NR, NR, NR, NR, Normal, Normal, Normal, Normal, Normal, Normal
- **AED**: NR, 3 treated with VPA, one with ETX and PB, CBZ, VPA, ETX, VGB, CLB, LTC, TPM, LEV, TEX, VPA, LTC, LEV, KD, LTG, VPA, VPA, LEV, LTG, VPA, ETX, LEV
- **Other**: Normal, Normal, Normal, Normal
Table 3. Cont.

| Reference | Bartnik 2012 | Rudolf 2016 | Rudolf 2016 | Rudolf 2016 | Rudolf 2016 | Sadleir 2020 | Sadleir 2020 | Morea 2021 | Case report |
|-----------|--------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-------------|
| **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 | WES | aCGH | aCGH | Sanger sequencing | | NGS |
| Genomic change (Hg19) | chr9:7474,400_77306932 del | chr9:7724649; C>C/T | chr9:70984481_7945901 del (8.5 Mb, 47 genes) | | | | | | |
| cDNA/aa change | | | | | | | | | |
| Inheritance | de novo | (probably) Inherited | | | | | | | |
| **Others information** | | | | | | | | | |
| FISH: 9q21.13 | | | | | | | | | |
| (RP 11-243/A1) | aCGH array normal | | | | | | | | |
| qPCR to validate the result | NR | | | | | | | | |
| Karyotype: mos 47,XX,+r[20]/46,XX,-21,+der(9)(9:21) | | | | | | | | | |
| [3]/46,XX,[25] | | | | | | | | | |
| aCGH array: mosaic gain 9p. | | | | | | | | | |
| FISH: 9q13q21.13 del (RP11-404E6), mosaic i(9p), der(9)t(9;21) and r(9) | | | | | | | | | |
| **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 | | | | | | | | | |
| Maternal uncle 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 absence 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-clonic 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; LGf: 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                     | Patient | Galizia 2015 ¹ | Galizia 2015 ¹ | Galizia 2015 ¹ | Tomas 2015 ¹/Carvill 2013 ² | Tomas 2015 ¹ | Tomas 2015 ¹/Mullen 2013 ³ |
|-------------------------------|---------|----------------|----------------|----------------|----------------------------|-------------|---------------------------|
| Clinical features             |         |                |                |                |                            |             |                           |
| Gender                        | Female  | Male           | Male           | Female         | Male                       | Female      | Female                    |
| Age                           | 18/17 yr| 13 yr          | + (moderate-severe) | 14 yr          | + (mild)                   | 56/26 yr    |                           |
| DD/ID                         | + (moderate-severe) | + (moderate-severe) | + (mild) |                       |                           |             |                           |
| Behavioral features           | ASD     | ASD, aggression| ASD, ADHD, aggression | ADHD, regression, aggression |                      |                           |                           |
| Other parameters              | nephrolithiasis, migraine, scoliosis | Transient ataxia on valproate | Short stature |                           | Short stature, ataxia |             |                           |
| Epilepsy                      |         |                |                |                |                            |             |                           |
| Age of onset                  | 12 months | 30 months | 30 months | 34 months |                          |             |                           |
| Absence seizures              | + (AMA, MA, TA) | + (TA) | +               | + (Self induced with TV) | + (Self induced with TV) | + (Self induced with TV or light) |                           |
| Eyelid myoclonia              | + (Self induced with TV) | + (Self induced with TV) | +               | + (Self induced with TV) | + (Self induced with TV or light) | + (Self induced with TV or light) |                           |
| Photosensitivity              | +       | +             | +             | +             | + (Self induced with TV or light) | + (Self induced with TV or light) | + (Self induced with TV or light) |                           |
| Other seizures                | MS, FS, GTCS/AS, FS, MJ, TC | MS (self-induced with TV), TS, GTCS | AS, GTCS, MS (self-induced with TV), NCSE, CSE |                           |                           |                           |                           |
| EEG                           |         |                |                |                |                            |             |                           |
| PPR                           | +       | +             | +             | +             | + (interictal and BG)      | + (interictal and BG) | + (grade 4) |                           |
| others                        | 3-4-Hz GPSW during atonic myoclonic absence seizures | 3 yr: Slow BG for age. Inter-ictal GSW GPSW, 3 Hz and 4 Hz | 3 yr: Normal BG, frontal predominant GSW, GPSW | 3 yr: Generalized epileptiform discharges >3 Hz increased by hyperventilation |                           |                           |                           |
| MRI                           |         |                |                |                |                            |             |                           |
| Craneal                       | Normal  | Normal         | Normal         | Normal         | Normal                     | Normal      |                           |

NR: Not reported.
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 [97]               |
| Genetic data         | NGS            | NGS            | NGS            | target NGS                  | target NGS   | target NGS   | aCGH                    |
| Genomic change       | chr15:93540136; A⇒/A    | chr15:93545442; A⇒/A | chr15:93489290; C⇒C/T | chr15:9354504_93545907del | chr15:93557956delG |
| Inheritance          | NR             | NR             | NR             | de novo                     | de novo      | de novo      | de novo                 |
| cDNA/aa change       | c.3725delA, p.Lys1245Asnfs*4 | c.4173dupA, p.His1392Thrfs*17 | inherited |
|                      | de novo        |                |                |                             |              |              |                         |
| Family History       | NR             | NR             | NR             | de novo                     | NR           | NR           | de novo                 |

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-clonic 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. Trialed 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](image-url)

**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 causes 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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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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