



# Phenotypic and genetic spectrum of epilepsy with myoclonic atonic seizures

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#### Abstract

**Objective:** We aimed to describe the extent of neurodevelopmental impairments and identify the genetic etiologies in a large cohort of patients with epilepsy with myoclonic atonic seizures (MAE).

**Methods:** We deeply phenotyped MAE patients for epilepsy features, intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder using standardized neuropsychological instruments. We performed exome analysis (whole exome sequencing) filtered on epilepsy and neuropsychiatric gene sets to identify genetic etiologies.

**Results:** We analyzed 101 patients with MAE (70% male). The median age of seizure onset was 34 months (range = 6-72 months). The main seizure types were myoclonic atonic or atonic in 100%, generalized tonic-clonic in 72%, myoclonic in 69%, absence in 60%, and tonic seizures in 19% of patients. We observed intellectual disability in 62% of patients, with extremely low adaptive behavioral scores in 69%. In addition, 24% exhibited symptoms of autism and 37% exhibited attention-deficit/hyperactivity symptoms. We discovered pathogenic variants in 12 (14%) of 85 patients, including five previously published patients. These were pathogenic genetic variants in *SYNGAPI* (n = 3), *KIAA2022* (n = 2), and *SLC6A1* (n = 2), as well as *KCNA2*, *SCN2A*, *STX1B*, *KCNB1*, and *MECP2* (n = 1 each). We also identified three new candidate genes, *ASHIL*, *CHD4*, and *SMARCA2* in one patient each.

**Significance:** MAE is associated with significant neurodevelopmental impairment. MAE is genetically heterogeneous, and we identified a pathogenic genetic etiology in 14% of this cohort by exome analysis. These findings suggest that MAE is a manifestation of several etiologies rather than a discrete syndromic entity.

#### KEYWORDS

Doose syndrome, epilepsy/seizures, genetics, myoclonic atonic epilepsy

## 1 | INTRODUCTION

Epilepsy with myoclonic atonic seizures (MAE), also known as myoclonic atonic epilepsy or Doose syndrome, is a rare epilepsy syndrome that occurs in 0.3%-2.2% of children with epilepsy.<sup>1,2</sup> Children with MAE usually have normal development prior to seizure onset between 7 months and 6 years. Seizure types include myoclonic atonic, atonic, myoclonic, generalized tonic-clonic, absence, and tonic seizures. Electroencephalogram (EEG) may exhibit irregular generalized spike-wave or polyspike-wave complexes.<sup>2</sup> However,

#### Key Points

- MAE is associated with significant neurodevelopmental impairment
- MAE is genetically heterogeneous, and a genetic etiology was identified in 14% of this cohort by exome analysis
- Severe neurodevelopmental comorbidity was observed in MAE patients with identified genetic etiology

the variable combination of seizure types and developmental profile prior to seizure onset is open to interpretation, such that the phenotypic and nosological boundaries for this disorder remain debated.<sup>3</sup>

The spectrum of neurodevelopmental comorbidity in MAE has not been systemically described. Intellectual disability (ID) has been reported in 34%-60% of patients assessed with variable psychometric tools and different cognitive definitions.<sup>2-6</sup> Adaptive functioning, a collection of age-appropriate conceptual, social, and practical skills to enable a person to function in everyday life, has not been previously explored. Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) symptoms have been documented in 5%-45% of very small case series and case reports.<sup>7,8</sup>

The importance of genetic factors in MAE was recognized through family history and EEG studies in its first description.<sup>2</sup> Early twin studies and rare Mendelian pedigrees offered a glimpse of the genetic basis of MAE.<sup>9,10</sup> Subsequently, the era of gene discovery through next generation sequencing and the recognition of the role of de novo variants in epileptic encephalopathies (EE) and neurodevelopmental disorders has led to a multitude of gene associations for MAE.

Pathogenic variants in *SCN1B*,<sup>9</sup> *SCN1A*,<sup>10</sup> *SLC2A1*,<sup>11</sup> *CHD2*,<sup>12</sup> *SYNGAP1*,<sup>13</sup> *KCNA2*,<sup>14</sup> *STX1B*,<sup>15</sup> *SLC6A1*,<sup>16</sup> *TBC1D24*,<sup>17</sup> *KIAA2022*,<sup>18</sup> *SCN2A*,<sup>19</sup> *GABRB3*,<sup>20</sup> *KCNT1*,<sup>21</sup> *STXBPI*,<sup>21</sup> *MECP2*,<sup>21</sup> and *AP2M1*<sup>22</sup> have been reported in individuals with MAE, some overlapping with this cohort. However, although the number of implicated genes has expanded to 16, the number of identified patients for each gene remains small, with the most enriched gene, *SLC6A1*, accounting for only 3.7%. In addition, most gene discoveries were made in the context of EE patient cohorts, with very few MAE-specific discovery cohorts.

Here, we set out to provide a multifaceted analysis of the condition and describe deep phenotyping and exome sequencing in a cohort of 101 MAE patients. We present assumed pathogenic variants in seven unpublished and five previously described cases from single gene discovery studies.<sup>13-15,18,19,23</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

MAE patients fulfilling the criteria of (1) onset of myoclonic, myoclonic atonic, or atonic seizures between 7 months and 6 years; (2) presence of generalized spike or polyspike-wave EEG discharges; and (3) exclusion of other epilepsy syndrome<sup>24,25</sup> were recruited through three cohorts. These were (1) the EuroEPINOMICS Rare Epilepsy Syndrome MAE cohort,<sup>14</sup> (2) an Italian cohort collected through a tertiary pediatric neurology center at the Meyer Children's Hospital,

and (3) a UK cohort (award ref MR/J011231/1, ethics ref 09/H0713/76). Written informed consent was obtained from all parents/legal guardians of participating patients.

### 2.2 | Phenotyping methods

Medical notes including seizure types, presence of febrile convulsions, and EEG reports were obtained from referring clinical collaborators for the UK and Italian cohorts. Details from the EuroEPINOMICS cohort were available through an online password-protected platform.

All UK cases were phenotyped for adaptive functioning skills, ASD, ADHD, and behavioral screening rated by parent/carer and teacher where indicated. Additionally, families that lived close to King's Health Partners, London were invited for deep phenotyping for cognition using the Wechsler Preschool and Primary Scale of Intelligence—Third UK Edition (WPPSI), Bayley Scales of Infant and Toddler Development—Third Edition (Bayleys), and Developmental, Dimensional and Diagnostic Interview (3di) rapid assessment. Deep phenotyping was assessed by a neuropsychologist or pediatric neurologist (S.T., A.S., M.A., D.K.P.).

#### 2.2.1 | Adaptive behavior

Adaptive behavior was measured with the Adaptive Behaviour Assessment System (ABAS II) Parent Form. The ABAS II explores three domains: conceptual, social, and practical. The general adaptive composite score is derived from the sum of the three domains.

#### 2.2.2 | Autism

Autism was measured with the Social Communication Questionnaire (SCQ) Autoscore Form: Lifetime and the 3di rapid assessment computerized interview.

#### 2.2.3 | Behavior

Behavior was measured using Conners' Comprehensive Behavioural Rating Scale (CBRS). The presence of significant ADHD symptoms was assumed when a T score > 70 was surpassed in subscale N. We also used the Strength and Difficulties Questionnaire (SDQ) as a behavioral screening questionnaire (www.sdqinfo.com). The SDQ has an impact supplement that enquires about chronicity, distress, social impairment, and burden to others. The scores were classified as close to average, slightly raised, high, or very high.

## 2.3 | Analysis

SCQ scores were distributed by gender and compared with the Avon Longitudinal Study of Parents and Children (ALSPAC) population cohort (<http://www.bris.ac.uk/alspac/sci-com>). Comparisons were performed using Student *t* test. SDQ comparisons using chi-square test were made with a normative sample of 10 298 British children aged 5-15 years and with 73 children with established epilepsy excluding MAE.<sup>26,27</sup>

## 2.4 | Exome sequencing

Exome sequencing was performed at two centers. The EuroEPINOMICS cohort was sequenced at the Wellcome Trust Sanger Institute (Hinxton, Cambridgeshire, UK), and techniques have been described before.<sup>28</sup> BAM files from the EuroEPINOMICS cohort were converted back to FASTQ files, and variant calling was reperformed using the Guy's Genomics Facility pipeline consistent with the remainder of the cohort. The Italian and UK cohorts were sequenced at the Guys Genomics Facility (Guy's Hospital, London, UK). DNA libraries were prepared using the SureSelect Human All Exon 50 Mb Kit (Agilent Technologies). Samples were multiplexed (four samples on each lane), and 100-bp paired-end sequencing was performed on the Illumina HiSeq system. Sequencing reads were aligned using Novoalign (<http://www.novocraft.com>). FastQC was used to perform quality control on FASTQ files. Variant calling was performed with SAMtools, and annotation was performed using ANNOVAR (<http://annovar.openbioinformatics.org>). A read depth of 10 reads was the minimum cutoff, and heterozygous variants were called if the alternate allele was present in >20% of total reads. All genetic variants are reported in human genome build GRCh37 (hg19) coordinates.

All variants of interest were annotated for minor allele frequency to the 1000 Genome Project ([www.internationalgenome.org](http://www.internationalgenome.org)), Exome Variant Server (<http://esp.gs.washington.edu>), Exome Aggregation Consortium (ExAC; <http://exac.broadinstitute.org>), and the Genome Aggregation Database (<http://gnomad.broadinstitute.org>). Missense variants were annotated with a Combined Annotation Dependent Depletion (CADD) score (<http://cadd.gs.washington.edu>), Sorting Intolerant From Tolerant (<http://sift.jcvi.org>), and PolyPhen (<http://genetics.bwh.harvard.edu>). Splice site prediction tools were AdaBoost and random forest provided by ANNOVAR. In addition, candidate genes were annotated with a residual variation intolerance score (RVIS) (<http://genic-intolerance.org>) and the ExAC Z score for missense variants. Gene expression in human central nervous system tissues was reviewed using GENEVESTIGATOR (<http://genevestigator.com>).

## 2.5 | Gene and variant filtering

Variants were selected when not observed in 1000 Genome Project, Exome Variant Server, and ExAC and in genes overlapping with two gene lists: (1) the epilepsy-associated gene list (Table S1), consisting of 100 reported epilepsy-associated genes identified through various epilepsy sequencing studies; and (2) the neuropsychiatric gene list (Table S2), consisting of 2105 genes curated from de novo sequencing studies of ID,<sup>29-31</sup> developmental disorders,<sup>32</sup> EE,<sup>33</sup> and ASD.<sup>34-36</sup> For variants matching a gene in the neuropsychiatric gene list, variants were reviewed if they had more than one filtered variant per gene with a CADD score > 20. All selected variants were then assessed based on genotype-phenotype correlation through PubMed literature search, gene intolerance, and gene expression (as above), and in some instances by locus-specific databases.

Sanger sequencing using standard methods from polymerase chain reaction (PCR) fragments was used to confirm all variants and for inheritance studies. Individual variants were classified as likely benign, variant of uncertain significance (VUS), pathogenic, or candidate variants. Variants were considered pathogenic if they were not present in control population data, were nonsynonymous, were splice site altering, were nonsense or frameshift, predicted damaging by one or more prediction tools, had consistent phenotype-genotype characteristics for gene, and were de novo. Likely benign variants did not have supportive phenotype-genotype correlations. VUS had unclear phenotype-genotype correlations and/or were inherited from an unaffected parent. Candidate variants were variants identified in genes that are not known to be associated with an epilepsy phenotype. Variants were interrogated by a pediatric neurologist, a molecular geneticist, and a bioinformatics scientist (S.T., D.K.P., L.A.).

# 3 | RESULTS

## 3.1 | Phenotype

We assembled 101 MAE patients (EuroEPINOMICS cohort, *n* = 31; Italian cohort, *n* = 13; UK cohort, *n* = 57) for phenotyping. There were 71 males (70.3%) and 30 females (29.7%). Table 1 details the main clinical characteristics of this cohort and compares it with previously published cohorts.

### 3.1.1 | Onset

The median age at seizure onset was 34 months (range = 6-72 months) based on 100 probands. Twenty (21.0%) of 95 patients had evidence of a developmental epileptic encephalopathy where developmental delay was reported prior to epilepsy onset; of these patients with prior developmental delay,

**TABLE 1** Main clinical characteristics of epilepsy with myoclonic atonic seizures cohorts

Cohorts	This cohort	Caraballo et al 2013	Trivisano et al 2011	Kilaru & Bergqvist 2007	Nabbout et al 2003	Oguni et al 2002a	Kaminska et al 1999	Doose et al 1970
Cases, n	101	69	18	23	22	81	55	51
Boys, %	70	67	89	83	—	75	78	71
Febrile seizures, %	38	13	—	17	—	—	16	22
Family history of Ep/FS, %	37/6	39/11	—	39/—	13/18	14/18	12/—	40/—
Mean age of onset, mo	32	39	43	36	40	32	35.6	36–48
Myo-atonic, %	100	100	100	61	100	100 <sup>a</sup>	86	59
GTCS, %	72	72	78	70	77	93	87	71
Myoclonic, %	69	100	67	61	87	43	98	10
Absence, %	60	55	89	52	44	54	76	59
Tonic, %	19	40	39	0	27	—	46	2
Focal, %	4	—	—	—	8	—	0	6

Abbreviations: —, not available; Ep, epilepsy; FS, febrile seizures; GTCS, generalized tonic-clonic seizures; Myo-atonic, myoclonic atonic and/or atonic seizures.

<sup>a</sup>This cohort was ascertained to assess treatment responsiveness of myoclonic atonic or atonic seizures, and therefore all patients had this seizure type.

nine reported isolated speech delay prior to seizure onset. Six patients had missing information about early development. Twenty-eight (38.3%) of 73 patients had a personal history of febrile convulsions.

### 3.1.2 | Family history

A family history of epilepsy was reported in 36 of 95 probands; a first-degree family member in 14 (of which one had MAE) and second- or higher-degree family member in 22. A family history of febrile seizures was reported in six probands; family history was missing in six.

### 3.1.3 | Seizures

Seizure types at onset were generalized tonic-clonic seizures (GTCS) in 52 patients, myoclonic atonic or atonic in 31, myoclonic in 13, and absence in four of 100 patients. Seizure type at onset was missing for one patient. During the epilepsy course, mainly generalized seizure types were reported (see Table 1). Clinical examination, available in 92 patients, was abnormal in 21 (22.8%), including tremor and/or ataxia in 15, pyramidal or motor signs in three, dysmorphism in two, and microcephaly in one. Dysmorphic features were described as prominent forehead, small eyes, large mouth, and syndactyly in one patient; and frontal balding, broad nasal bridge, thick alae nasi, broad and long philtrum, thin upper vermillion and thick lower vermillion, skin wrinkling, upturned nasal tip, and anterior projection of the upper lip over premaxilla in the other patient.

### 3.1.4 | EEG

EEG background was slow during the epilepsy course in 16 of 70 (22.8%) patients. EEG background data were not available for the EuroEPINOMICS cohort. One hundred patients had abnormal generalized epileptiform activity of spike-wave discharges. Additional EEG features comprised polyspike and wave in 31 and focal epileptiform activity in seven.

### 3.1.5 | Neuroimaging

Computed tomography and/or magnetic resonance imaging reports were available for 78 patients. This was reported normal in 72 patients, with generalized cerebral volume loss in two, nonspecific focal signal alteration in two, and immature myelination and benign hydrocephalus in one patient each.

### 3.1.6 | Remission

Data regarding seizure remission, where seizure freedom was achieved for >2 years with or without antiepileptic drugs, were obtained for 72 patients within the UK and Italian cohorts. Twenty-four of 72 (33.3%) patients fulfilled this definition of seizure remission. There was no statistical difference in the median age of seizure onset in both groups (32.5 months in remission group compared with 33.5 months in nonremission group, Mann-Whitney *U* test, *P* = .93). The most common antiepileptic drugs used



in both groups were sodium valproate and clobazam, suggesting patients likely to go into remission would respond to these medications.

## 3.2 | Neurodevelopmental comorbidity

### 3.2.1 | Cognition

ID was reported by the referring clinician in 61 (62.8%) of 97 patients. Deep phenotyping with formal cognitive testing was available in 19 (WPPSI/Wechsler Intelligence Scale for Children,  $n = 14$ ; Bayleys,  $n = 5$ ) and showed eight with moderate to severe ID (intelligence quotient [IQ] < 70), five with mild ID (IQ = 7-85), and six as normal (IQ > 85).

### 3.2.2 | Adaptive behavior

Forty-six of 56 (response rate = 81%) ABAS II Parent Forms in the UK cohort were returned. Extremely low adaptive scores, which indicated a percentile rank  $\leq 2$ nd, were seen in 27 (58.6%) patients for the conceptual, 15 (32.6%) for the social, and 31 (67.3%) for the practical domain. Correspondingly, 32 (69.5%) patients had extremely low general adaptive composite scores. Figure S1 shows the distribution of individual domain scores of the ABAS II.

### 3.2.3 | Autism

Fifty (38 males, 12 females) of 57 (response rate 87%) SCQ questionnaires were returned in the UK cohort. Fifteen (30%) patients reached the threshold for suspecting ASD with a score of  $\geq 15$ . The mean score of 10.1 (SD = 7.41) was significantly higher in both males and females when compared with the ALSPAC cohort ( $P < .0001$ ; see Table S3). In addition, 3di interviews were conducted with one or both parents of 19 patients. Based on the results of the 3di interview, eight patients had an ASD diagnosis. MAE patients reported the most difficulties in the social reciprocity domain, with a mean score of 8.43 (SD = 6.89) within the abnormal range for that subscale. Based on clinician report, two (25%) of eight patients in the Italian cohort and three (12%) of 25 patients in the EuroEPINOMICS cohort reported a diagnosis of ASD. Considering all these measures, 20 (24.1%) of 83 patients reported either a diagnosis or symptoms of ASD.

### 3.2.4 | Behavior

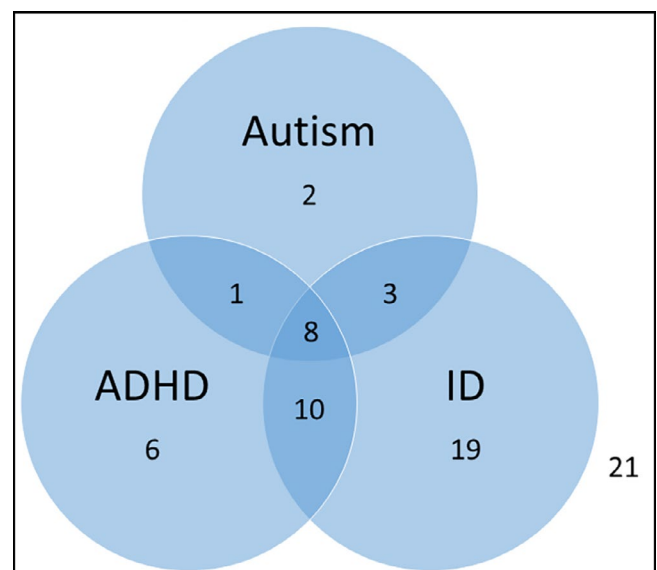
Fifty of 56 SDQs (response rate = 89%) were returned in the UK cohort. High scores were returned in seven (14%)

with emotional problems, 17 (34%) with conduct problems, 19 (38%) with hyperactivity problems, 21 (42%) with peer problems, 18 (36%) with prosocial problems, and 31 (62%) reporting these problems to significantly impact the family and child. The scores were significantly higher ( $P < .0001$ ) in all domains except emotional symptoms when compared with a normative sample of British children, but were not significant when compared with children with established epilepsy excluding MAE (see Table S4).<sup>26,27</sup>

ADHD symptoms were ascertained through clinician reports in the Italian and EuroEPINOMICS cohorts and through the Parent and Teacher CBRS in the UK cohort. Two (25%) of eight patients in the Italian cohort, 13 (50%) of 26 patients in the EuroEPINOMICS cohort, and 13 (32.5%) of 40 UK patients reported ADHD symptoms. Therefore, the estimated prevalence of ADHD symptoms in the entire cohort was 28 (37.8%) of 74 patients. Both parent and teacher CBRS scores were available in 34 UK patients. Table S5 details the results of the parent and teacher CBRS scores.

### 3.2.5 | Multiple neurodevelopmental comorbidities

Patients for whom data for ID, ASD, and ADHD were available were analyzed for multimorbidity. Fifty of 70 (71.4%) patients had at least one comorbidity, and 22 of 70 (31.4%) had two or more comorbidities (Figure 1).



**FIGURE 1** Venn diagram demonstrating neurodevelopmental multimorbidity in 70 epilepsy with myoclonic atonic seizures patients. ADHD, attention-deficit/hyperactivity disorder; ID, intellectual disability

### 3.3 | Exome sequencing

Of the 101 probands assembled in the phenotyping cohort, we exome sequenced 85 (EuroEPINOMICS cohort,  $n = 31$ ; Italian cohort,  $n = 13$ ; UK cohort,  $n = 41$ ).

#### 3.3.1 | Gene filtering using epilepsy-associated genes

##### *Pathogenic variants*

Pathogenic variants in eight epilepsy-associated genes were identified in 12 patients (Table 2). This included seven unpublished and five previously described patients with variants in *KCNA2* ( $n = 1$ ),<sup>14</sup> *KIAA2022* ( $n = 2$ ),<sup>18</sup> *SCN2A* ( $n = 1$ ),<sup>19</sup> *SLC6A1* ( $n = 2$ ), *STX1B* ( $n = 1$ ),<sup>15</sup> *SYNGAP1* ( $n = 3$ ),<sup>13</sup> *KCNB1* ( $n = 1$ ), and *MECP2* ( $n = 1$ ). Of these, *KCNB1* (voltage-gated potassium channel subfamily B member 1) variants have not been previously associated with MAE but have been reported in patients with EE and infantile epilepsy.<sup>37</sup> Subject 00 533 and the two other reported probands with the p.Arg306Cys variant all have an early onset epilepsy associated with severe ID. However, seizure types and EEG features in these patients were variable.<sup>37,38</sup>

##### *Likely benign variants and variants of uncertain significance*

Six different variants from six different genes were classified as likely benign, and 15 variants in 12 genes were classified as VUSs (see Tables S6 and S7 and Appendix S1 for further discussion of each gene).

#### 3.3.2 | Gene filtering using neuropsychiatric genes

Twenty-one genes from the neuropsychiatric gene set had nonsynonymous variants with CADD > 20 in the MAE cohort. There were no recurrent variant matches with the MAE cohort and the gene set variants. Eighteen genes were deprioritized due to RVIS > 25th percentile and negative ExAC Z score; or conflicting gene function; or inadequate nervous system expression; or unsupportive heterozygosity types or lack of segregation. Three genes, *ASH1L*, *CHD4*, and *SMARCA2*, remained as possible candidate genes (Table 3).

*ASH1L* (absent, small or homeotic disc 1 like histone lysine methyltransferase) encodes histone methyltransferase, which is involved in histone and chromatin modification and gene regulation. *Ash1L* is enriched in the brain in mice, and a role in epigenetic modification in brain functioning was implicated when in *Ash1L* knockout mice the activity-dependent repression of neurexin 1 $\alpha$ , a presynaptic adhesion molecule required for synaptic formation, was completely abolished.<sup>39</sup>

*CHD4* (chromodomain helicase DNA binding protein 4) is an adenosine triphosphate (ATP)-dependent chromatin remodeler involved in epigenetic regulation of gene transcription, DNA repair, and cell cycle progression.<sup>40</sup> It is also a paralogue of *CHD2*, which is associated with MAE.<sup>12</sup> *SMARCA2* mutations are associated with Nicolaides-Baraitser syndrome. It is one of six genes that encode the SWItch/sucrose nonfermentable like chromatin remodeling complex and alters chromatin structure through ATP hydrolysis. Subject 3003 301, with a de novo p.Gln1241Glu *SMARCA2* variant, was subsequently identified as also having clinical features compatible with a diagnosis of Nicolaides-Baraitser syndrome along with MAE.<sup>23</sup>

## 4 | DISCUSSION

This paper uses a large cohort of patients with MAE ( $n = 101$ ) to describe the phenotypic variability in seizures and a high incidence of neurodevelopmental comorbidities. We report a genetic cause in 14% with some associated motor symptoms. The findings pose questions for the nosological boundaries of MAE and overlap with genetic generalized epilepsies (GGEs) and developmental epileptic encephalopathies (DEEs).

Although the most frequent seizure types in MAE are as expected (myoclonic atonic or atonic seizure, 100%; GTCS, 72.7%; and myoclonic seizures, 68.2%),<sup>3,5,6,41</sup> a minority of MAE patients have focal seizures, some (6.9%) with additional focal epileptiform activity on EEG. Focal EEG features have been reported in up to 39% of MAE cohorts<sup>40</sup> and have been proposed as a marker of poor prognosis in MAE.<sup>42</sup> However, we were not able to confirm this hypothesis in this cohort, as two of seven patients with focal EEG abnormalities achieved seizure remission, compared to 22 of 70 patients without focal abnormalities.

Approximately 20% of patients had evidence of a DEE with developmental or speech delay prior to onset of seizures, a much higher frequency of antecedent impairments than was previously appreciated. ID was reported in 61 (62.8%) of 97 patients, and the impact of these deficits is reflected in extremely low adaptive functioning in 32 (69.5%) of 46 patients. ASD symptoms occurred in 24.1%, possibly due to predisposing factors such as ID, early onset of seizures, and EE. ADHD symptoms, predominantly inattentive, were identified in 37.8%, in keeping with other pediatric epilepsies.

The variation in phenotype overlaps with other epilepsy syndromes, and we recognize that the current concept of MAE provides a phenotypic bridge between GGEs and DEEs, including Lennox-Gastaut syndrome. For example, antecedent neurodevelopmental impairments and autistic and cognitive deficits are more characteristic of DEE.<sup>43</sup> Moreover, Eschbach et al reported that more than one-half of a cohort of 77 patients with suspected MAE undergo epilepsy diagnosis

TABLE 2 Pathogenic epilepsy with myoclonic atonic seizures variants

Subject	Gene	c.DNA:protein change	Inheritance	SIFT, PP2, CADD	gnomAD MAF	Seizure phenotype	EEG	Additional clinical features
8MAE23 <sup>14</sup>	KCNA2	c.T788C:p.Ile263Thr	De novo	0 (P), 0.977 (P), 22.7	Novel	7 y M, seizure onset at 11 mo with myoclonic and MA seizures. Seizure-free since 4 y	Multifocal sharp waves and spikes	Early developmental delay, mild-moderate ID
00533	KCNBJ	c.C916T:p.Arg306Cys	De novo	0 (P), 1.0 (P), 29.7	Novel	6 y F, seizure onset at 7 m with MA, myoclonic, and atonic seizures	GSW and polyspikes and multifocal spikes	ID
138J	KIAA2022	c.1261_1270del:p.Leu421fs	NK	—	Novel	10 y F, seizure onset at 21 mo with MA seizures	GSW and polyspikes	ID
EG1263 <sup>18</sup>	KIAA2022	c.C964T:p.Arg322*	De novo	1 (T), —, 37	Novel	11 y F, seizure onset at 30 mo with myoclonic, atonic, tonic, and focal seizures. Ongoing seizures	Polyspike wave and focal discharges	Mild ID, ASD, ADHD
291J	MECP2	c.C673A:p.Pro225Thr	De novo	0.05 (P), 0.998 (P), 24.4	Novel	15 y F, seizure onset at 6 y with MA and tonic seizures	Disorganized background with bilateral GSW	Prior febrile convulsions, ID, cerebellar signs
9329 <sup>19</sup>	SCN2A	c.C2790A:p.His930Gln	De novo	0 (P), 0.999 (P), 27.2	Novel	4 y M, seizure onset at 17 mo with atonic and GTC seizures	Generalized epileptic activity	ASD, ADHD
00587	SLC6A1	c.A419G:p.Tyr140Cys	De novo	0 (P), 1 (P), 27.6	Novel	16 y F, seizure onset at 2 y with MA seizures then myoclonic seizures, absence seizures, and nonconvulsive status	Generalized epileptic activity	Early speech delay, ID
00595	SLC6A1	c.C1155G:p.Phe385Leu	De novo	0.03 (P), 0.012 (T), 32	Novel	8 y M, seizure onset at 13 mo with myoclonic seizure, then MA seizures	GSW provoked by posterior eye closure sensitivity	Early developmental delay, ID, ASD
18_P <sup>15</sup>	STX1B	c.G676C:p.Gly226Arg	De novo	0 (P), 1 (P), 32	Novel	6 y F, seizure onset at 13 mo with GTC, MA, myoclonic, and tonic seizures	Generalized epileptic activity	Prior febrile convulsions, moderate ID, hypotonic with unsteady gait
4MAE10 <sup>13</sup>	SYNGAP1	c.T1995A:p.Tyr665*	De novo	0.85 (T), —, 35	Novel	12 y M, seizure onset at 1 y with atonic and MA seizures. Ongoing seizures	GSW, photosensitive	Severe ID with absent speech, unsteady gait

(Continues)



TABLE 2 (Continued)

Subject	Gene	c.DNA:protein change	Inheritance	SIFT, PP2, CADD	gnomAD		Seizure phenotype	EEG	Additional clinical features
					MAF	MAF			
00512	<i>SYNGAP1</i>	c.2176_2179del:p.Arg726fs	De novo	—	Novel	Novel	3 y 9 mo M, seizure onset at 2 y with MA and absence seizures	GSW	Early developmental delay, ID, ASD, ataxia
00514	<i>SYNGAP1</i>	c.2562_2578del:p.Arg854fs	De novo	—	Novel	Novel	5 y M, seizure onset at 17 mo with MA, atonic, and absence seizures	Slow background and GSW	Early developmental delay, ID, ASD, ADHD, hypotonia, and ataxia

Abbreviations: —, not available; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CADD, Combined Annotation Dependent Depletion; EEG, electroencephalogram; F, female; gnomAD, Genome Aggregation Database; GSW, generalized spike wave; GTC, generalized tonic-clonic; ID, intellectual disability; M, male; MA, myoclonic atonic; MAF, minor allele frequency; NK, not known; P, pathogenic; PP2, PolyPhen-2; SIFT, Sorting Intolerant from Tolerant; T, tolerated.

TABLE 3 Candidate gene variants

Subject	Gene, RVIS/ExAC Z	c.DNA:protein change	Inheritance	SIFT, PP2, CADD	gnomAD		Seizure phenotype	EEG	Additional clinical features
					MAF	MAF			
00530	<i>ASH1L</i> , 2.22%/3.05	c.C4024T:p.Arg1342*	De novo	1 (T), —, 38	Novel	Novel	7 y M, seizure onset at 6 mo with MA, myoclonic, GTC, absence, and tonic seizures. Seizures refractory to treatment	GSW and polyspike; focal activity maximal in right temporal region	Moderate to severe ID, ASD, ADHD
00526	<i>CHD4</i> , 2.82%/7.05	c.A2687G:p.His896Arg	NK	0 (P), 0.993 (P), 24.6	Novel	Novel	5 y 8 mo F, seizure onset 2 y 11 mo with GTC, MA, atonic, and absence seizures. Seizures refractory to treatment	GSW	Severe ID
3003301 <sup>23</sup>	<i>SMARCA2</i> , 1.82%/5.57	c.C3721G:p.Gln1241Glu	De novo	0.5 (T), 0.954 (P), 22.5	Novel	Novel	5 y F, seizure onset at 14 mo with MA and GTC seizures. Seizure-free since 4 y	Generalized spike wave and polyspike	Severe ID, ASD, severe feeding difficulties, dysmorphism

Abbreviations: —, not available; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CADD, Combined Annotation Dependent Depletion; ExAC, Exome Aggregation Consortium; F, female; gnomAD, Genome Aggregation Database; GSW, generalized spike wave; GTC, generalized tonic-clonic; ID, intellectual disability; M, male; MA, myoclonic atonic; MAF, minor allele frequency; NK, not known; P, pathogenic; PP2, PolyPhen-2; RVIS, residual variation intolerance score; SIFT, Sorting Intolerant from Tolerant; T, tolerated.

switching.<sup>40</sup> However, we believe that the MAE concept remains broadly useful to guide treatment and prognosis.

Unsurprisingly, cases with neurodevelopmental symptoms or neurological signs were more likely to have an identified genetic etiology. ID was reported in 11 of 12 (3/3 candidate) patients, ASD in five of 12 (2/3 candidate) patients, and ADHD in three of 12 (1/3 candidate) patients. ID, ASD, and epilepsy share causative genes and biological pathways including gene transcription regulation, neurotransmission, and maintenance of synaptic structure. These neurodevelopmental comorbidities may be a primary feature of the genetic disease rather than secondary to disturbance of brain function due to excessive epileptiform activity (an epileptic encephalopathy). Abnormal neurological findings were reported in 21 of 92 patients, higher than the 12% in previous smaller MAE series.<sup>2,41</sup> Ataxia and tremor have been recognized in MAE patients with pathogenic variants in *SLC2A1*,<sup>11</sup> *STX1B*,<sup>15</sup> and *SLC6A1*<sup>16</sup> and occurred in our probands with pathogenic variants in *SYNGAP1* (n = 3) and *MECP2* (n = 1). These motor signs may be useful in suggesting specific genotype correlation in MAE.

The expansion of the phenotype has consequently led to expansion of the genetic spectrum. We identified pathogenic variants in 12 (14.1%) of 85 patients. These included seven unpublished and five previously described patients with *KCNA2* (n = 1),<sup>14</sup> *KIAA2022* (n = 2),<sup>18</sup> *SCN2A* (n = 1),<sup>19</sup> *SLC6A1* (n = 2), *STX1B* (n = 1),<sup>15</sup> *MECP2* (n = 1), *KCNBI* (n = 1), and *SYNGAP1* (n = 3).<sup>12</sup> We also present candidate genes *ASHIL*, *CHD4*, and *SMARCA2*<sup>21</sup> in one patient each.

Gene-specific features were observed. Our subjects with *SYNGAP1* variants all had seizure onset in infancy, ID, ataxia, and hypotonia consistent with a *SYNGAP1* encephalopathy.<sup>13</sup> The two female subjects with p.Leu421fs and p.Arg322\* *KIAA2022* variants both have MAE comorbid with ID. Subject 291J with a de novo *MECP2* p.Pro225Thr variant has overlapping clinical features found in classic Rett syndrome of cerebellar signs and an EEG with a disorganized background. De novo *MECP2* variants are recognized as causative for MAE and other epilepsies.<sup>21,44</sup> A potential clinical implication is that children with Rett syndrome have an increased risk of life-threatening arrhythmias associated with prolonged QT<sub>c</sub> interval and should avoid drugs known to prolong QT<sub>c</sub> interval. It is unknown whether this also applies to patients with an *MECP2*-associated epilepsy.

Atypical EEG features should prompt a search for a genetic etiological link as demonstrated in our cases with *KCNA2* and *KCNBI*. Moreover, subject 00595 with an *SLC6A1* variant had an unusual EEG feature of posterior eye closure sensitivity with 3- to 4-Hz spike-wave complexes on the posterior third of the head provoked by eye

closure, similarly identified in one of seven other MAE cases with *SLC6A1* variants.<sup>16</sup>

Finally, we identified *ASHIL* and *CHD4* as candidate genes in this paper. Seven other de novo *ASHIL* variants have been reported in ID/ASD patients.<sup>45,46</sup> Only one case has been described with an epilepsy phenotype; the patient had a missense *ASHIL* variant of unknown inheritance, leaving its pathogenic role uncertain.<sup>46</sup> The highly conserved p.Arg1342\* variant identified here is located between two annotated protein domains, like other reported mutations.<sup>46</sup> A de novo *CHD4* variant has been reported in a single patient with EE, and individuals with overlapping phenotypes of developmental delay, hearing loss, macrocephaly, distinct facial dysmorphisms, palatal abnormalities, ventriculomegaly, and hypogonadism but no epilepsy.<sup>33,47</sup> The variant p.His896Arg identified in subject 00526 is located within the ATPase/helicase domain and may disrupt the ATPase activity of *CHD4*. Further studies are required to understand the phenotypic variability of *CHD4* mutations.

There were several limitations in this study. The ascertainment of patients may have been biased toward more severe phenotypes. Patients were recruited from different European countries, which may have contributed to phenotypic heterogeneity. Many cases were phenotyped through screening questionnaires, which does not substitute for direct neuropsychological testing. Whole exome sequencing has poor capacity to identify structural variants and somatic mosaic variants, and this was not investigated. Additionally, in silico prediction tools were available only for missense variants, and the role of indels and frameshift variants may be underestimated.

Several lines of enquiry remain for the unsolved MAE cases. While there are remaining undiscovered genes within the exome space, the impact of variants in noncoding regions, regulatory regions, and microRNAs remain to be interrogated and may be revealed with whole genome sequencing. Copy number variations (CNVs) in this cohort were not investigated, but from previous studies we would expect a frequency of pathogenic CNVs in 5% of cases.<sup>48,49</sup> Somatic mosaic variants are increasingly recognized in early onset genetic disease and remain challenging to investigate.<sup>50</sup> Susceptibility genetic factors and rare variants contributing to specific phenotypic features such as seizure types and EEG features remain undetermined.

In summary, we demonstrated that MAE is associated with significant neurodevelopmental comorbidity and the yield of identifying a possible monogenetic etiology was about 14% in this cohort. An identifiable genetic etiology was more likely in patients with associated neurodevelopmental disorders and brings the possibility of personalized medicine closer, such as the use of the ketogenic diet in patients with *GLUT1* deficiency, sodium channel blockers in patients with

*KCNQ2*, *SCN2A*, and *SCN8A* mutations, and the promise of gene-specific small molecular ion channel modulators and antisense oligonucleotides. This genetic heterogeneity suggests a concept that the MAE phenotype might be a common manifestation of several etiologies rather than a discrete syndromic entity.

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## CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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## APPENDIX 1

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