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Epilepsy in *KAT6A* syndrome: Description of two individuals and revision of the literature

Serena Troisi [a,b,*], Silvia Maitz [c], Mariasavina Severino [d], Alice Spano [c], Gerarda Cappuccio [f], Nicola Brunetti-Pierri [e,f], Annalaura Torella [f,g], Vincenzo Nigro [f,g], Tudp [h], Leonilda Bilo [a], Antonietta Coppola [a]

[a] Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy
[b] Pediatric Neurology, Department of Neuroscience, Santobono-Pausilipon Children's Hospital, Naples, Italy
[c] Clinical Pediatric Genetics Unit, Pediatrics Clinics, MBBM Foundation, S. Gerardo Hospital, Monza, Italy
[d] Neuroradiology Unit, "IRCCS Istituto Giannina Gaslini", Genoa, Italy
[e] Department of Translational Medicine, Federico II University, Naples, Italy
[f] Telethon Institute of Genetics and Medicine, Pozzuoli, Naples, Italy
[g] Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[h] Telethon Undiagnosed Disease Program, Italy

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ABSTRACT

Pathogenic variants in *KAT6A*, encoding a histone acetyltransferase, have been identified as a cause of a developmental disorder with a definite clinical spectrum including intellectual disability, speech delay, dysmorphic facial features, microcephaly, cardiac and gastrointestinal defects. Seizures have been described in a minority of patients without a detailed characterization.

In this work we focus on epilepsy in *KAT6A* syndrome, reporting two affected girls with history of seizures, bearing a *KAT6A* de novo heterozygous variant, of which one is novel. We describe the different epilepsy phenotypes of these two patients and compare them to the other individuals in literature presenting with epilepsy.

1. Introduction

KAT6A syndrome is a rare genetic neurodevelopmental disorder caused by mutations in the gene encoding lysine acetyltransferase 6A gene (*KAT6A,* NM_006766). The *KAT6A* gene encodes for histone acetyltransferase and acts as a co-activator for several transcription factors. Since the early descriptions, the core features of this condition include intellectual disability with speech delay, typical dysmorphisms, microcephaly, feeding difficulties, cardiac defects, frequent infections, gastrointestinal complications (Arboleda et al., 2015; Tham et al., 2015). A series of cases detected by exome sequencing (ES) enabled a detailed definition of the genotype-phenotype spectrum of *KAT6A* syndrome with late-truncating mutations, affecting exons 16 and 17, being associated with a more severe phenotype (Kennedy et al., 2019). Seizures have been reported in a minority of patients (about 9%) (Kennedy et al., 2019) and without complete clinical and electroencephalographic data. Here, we describe two children with epilepsy carrying *KAT6A* de novo heterozygous variants detected by ES; one of the two variants has never been reported in literature to date. Interestingly, these two individuals presented with different forms of epilepsy that we described in great detail and compared to the epilepsy reported in other patients.

2. Patients' report

Patient #1. The patient is a 17-year-old girl, only child of healthy unrelated parents. Her family history reports a maternal uncle with febrile seizures in childhood. She was born by cesarean section after 38 weeks of gestation complicated by threats of miscarriage in the first trimester. At birth, her weight was 2540 g (<5th percentile, −1.7 SD), her length was 48 cm (10th-25th percentile, −0,6 SD), the head circumference was 31.5 cm (<5th percentile, −2.2 SD). Apgar scores were 9 at 1 min and 9 at 5 min. On the second day of life, she was diagnosed with sepsis requiring treatment with intravenous antibiotics. Sleep disturbances were noted from few months of age, along with

* Corresponding author. Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University Via Pansini 5, 80131, Naples, Italy.
E-mail addresses: serena.troisi@gmail.com, s.troisi@santobonopausilipon.it (S. Troisi).

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Fig. 1. Facial features of patient#1 at the age of 16 years old showing bitemporal narrowing, broad nasal tip, thin and tented upper lip (A) and patient#2 showing blepharophimosis, hypertelorism, epicanthal folds, depressed nasal bridge, broad nasal tip, and short philtrum (B).

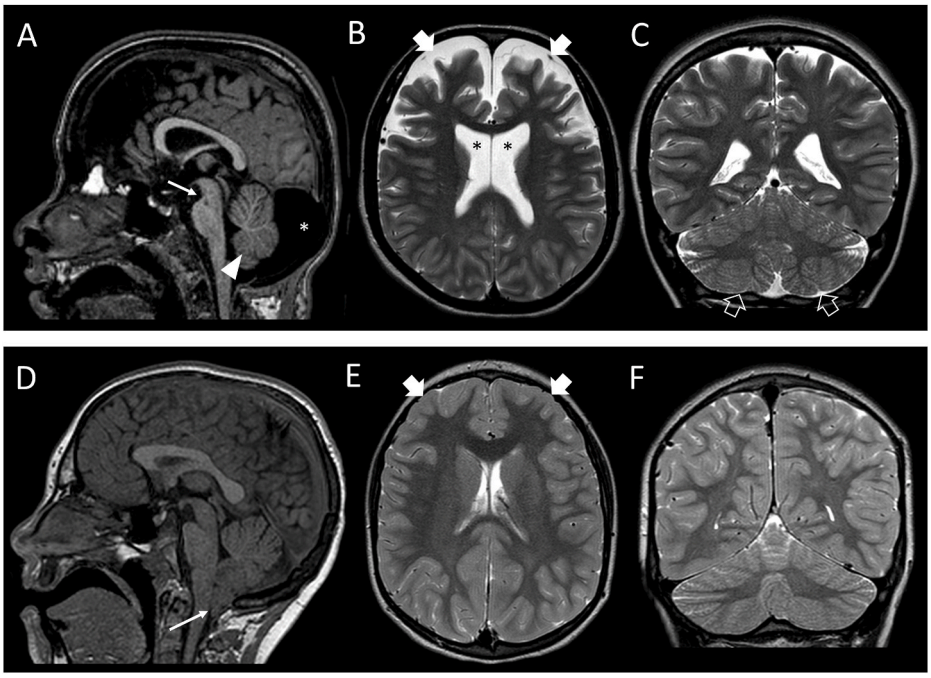

Fig. 2. Brain MRI of patient#1 (A–C) at 14 years of age and patient#2 at 7 years of age (D–F). A) Sagittal T1-weighted image shows an abnormal pontomesencephalic junction (arrow), small inferior cerebellar vermis (arrowhead) and megacisterna magna (asterisk). (B) Axial T2-weighted image reveals markedly reduced volume of the frontal lobes, reduction of periventricular white matter and enlargement of the subarachnoid spaces (arrows) and lateral ventricles (asterisks). (C) coronal T2-weighted image depicts abnormal foliation at the level of inferior cerebellar hemispheres (arrows). D) Sagittal T1-weighted image shows caudal cerebellar tonsils through the foramen magnum (arrow), consistent with Chiari I malformation. E) Axial and F) coronal T2-weighted images show small frontal lobes (arrows) and normal cerebellar hemispheres.

recurrent respiratory infections and feeding difficulties with gastro-esophageal reflux. At 4 years of age, she underwent surgery for intestinal malrotation and at 16 years of age, a second surgery, for bowel obstruction due to a volvulus was performed.

Neurological and epilepsy history: Epilepsy onset was at 3 months of age when daily right hemiclonic seizures appeared during sleep. She was then started on phenobarbital that reduced seizure frequency to a monthly occurrence. During her first years, neurologic examinations reported global developmental delay: she was hypotonic, never sat without support, never walked nor spoke, and never acquired sphincter control. Since the age of 11 years, she presented with bilateral tonic seizures and episodes of "loss of awareness" during wakefulness. Valproic acid and oxcarbazepine were added without significant benefit. At 15 years of age, the physical evaluation showed microcephaly (head circumference was 50 cm, <3rd percentile, −3.7 SD), dysmorphisms including coarse face, bitemporal narrowing, broad nasal tip, thin and tented upper lip, short philtrum (Fig. 1 A), severe scoliosis, and neck hemangioma. Her body mass index (BMI) was 13 kg/m^2 (<3rd percentile, −5.6 SD). Neurological examination showed severe intellectual disability with absent language, truncal hypotonia, tetraparesis with limb hypertonia. At that time, she was having two type of seizures: major episodes of tonic asymmetric seizures sometimes preceded by bilateral spasms occurring at a monthly frequency; weekly clusters of minor focal seizures characterized by impaired awareness, sudden interruption of her motor activity, slow eyelid myoclonia and nystagmus. In one episode, a cluster proceeded to a non-convulsive status epilepticus which ceased under intravenous diazepam. Oxcarbazepine was discontinued and lacosamide was added with a disappearance of the major tonic seizures and a reduction of the minor focal seizures to one per week. Brain MRI performed at the age of 14 years showed marked reduction of the volume of the frontal lobes, abnormal ponto-mesencephalic junction, mild cerebellar vermis hypoplasia, abnormal foliation in the inferior portions of the cerebellar hemispheres, and megacisterna magna (Fig. 2A–C). The EEG performed at the age of

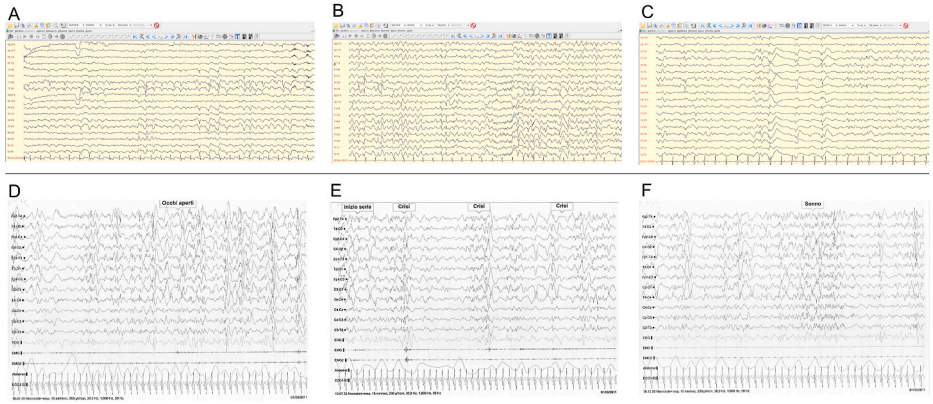

Fig. 3. Electroencephalogram findings of patient#1 at 17 years old (A–C) and of patient#2 at 8 months (D–F). A) awake EEG showing severe slowing of background activity with disorganized and diffuse theta-delta rhythm and superimposed sharp and slow wave complexes over both occipital regions. B) The sleep EEG recording revealed worsening of epileptiform activity spreading to the parietal and vertex electrodes. C) Irregular K complexes were recorded. D) awake EEG showing disorganized background activity with high amplitude theta-delta rhythm with superimposed multifocal epileptiform discharges; E) ictal sleep EEG showing a high amplitude and slow electrodecremental wave followed by a diffuse flattening of the background activity. These abnormalities were time locked with a spasm as demonstrated by the electromiographic activity over EMG and EMG2 channels (deltoids); F) interictal sleep EEG showing both slow and sharp waves over the posterior regions and asyncronous spikes over the frontal regions.

17 years, showed a severe slowing of the background activity represented by disorganized and diffuse theta-delta rhythm. Epileptiform activity, namely sharp and slow wave complexes were present over both the occipital regions and spreading to the parietal and vertex electrodes. The sleep EEG recording revealed worsening of this epileptiform activity; although irregular, K complexes were observed (Fig. 3A–C).

Genetic investigations: She underwent several genetic investigations including array-CGH, Sanger sequencing of *MECP2* and *ZEB2* genes, and next generation sequencing (NGS) of 55 genes causing intellectual disability. All were reported as negative. A trio-based ES disclosed a de novo heterozygous variant in the exon 17 of *KAT6A* gene (NM_006766: c.4645G > A, p. Gly1549Ser), that has been previously reported as pathogenic (Kennedy et al., 2019).

Patient #2. The patient is a 9 years old girl born from healthy unrelated parents with unremarkable family history. She was born at 38 weeks of gestation by caesarian section. At birth, her weight was 2930 g (10th-25th percentile, −1 SD), her length was 50.5 cm (50th-75th percentile, +0.4 SD), the head circumference was 33 cm (10th percentile, −1.2 SD). The Apgar scores was 6 both at 1 and at 5 min because of respiratory distress requiring ventilation and neonatal intensive cure admission. At birth she presented with interatrial septal defect that required surgery at 1 year of age. In the first years of life she suffered from frequent upper respiratory tract infections, sleep disturbances with difficulty in falling asleep, gastroesophageal reflux and constipation. At 6 years of age she entered the first grade at school with support; no behavioral problems were reported.

Neurological and Epilepsy history: Seizures onset was at 5 months with daily clusters of symmetric spasms characterized by flexion of the arms, extension of the legs and eyes' rolling. At 8 months typical spasms were captured on EEG recording. The spasms were associated with a high amplitude and slow electrodecremental wave followed by a diffuse flattening of the background activity which was otherwise disorganized and mixed with high amplitude multifocal epileptiform discharges (Fig. 3D–F). She was commenced on antiseizure medication with vigabatrin without benefit. ACTH and valproic acid were started and spasms' frequency was dramatically reduced. At three years of age she became seizure-free, the EEG evaluation showed the absence of epileptic abnormalities and one year later antiseizure medications were discontinued. Since then, she remained seizure and medication free with no relapse. Motor milestones were significantly delayed: the patient started walking without support at 4 years of age, she never spoke and never acquired sphincter control. At 3 years of age, the developmental profile evaluated with the Griffiths Mental Development Scales-Extended Revised test showed a psychomotor delay in all the items corresponding to an age-equivalent of 16 months. Brain MRI studies, performed at 3 and 7 years of age, showed small frontal lobes and Chiari type 1 malformation (CM1) (Fig. 2D–F). At 7 years of age, a physical examination reported microcephaly (49 cm, <3° percentile, −1.1 SD), facial dysmorphisms (blepharophimosis, hypertelorism, epicanthal folds, depressed nasal bridge, broad nasal tip, short philtrum), pectus carinatum, kyphoscoliosis and popliteal hemangioma (Fig. 1B). Neurological examination showed moderate intellectual disability (IQ = 50) with absent language, broad based gait, limb hypertonia, poor motor coordination.

Genetic investigations: Array-CGH, Sanger sequencing of *KAT6B, RAI1, CDKL5, EZH2*, genes and NGS panel of nine genes associated with Rett and Angelman syndrome (*UBE3A, TCF4, SLC9A6, MECP2, CNTNAP2, NRXN1, ZEB2, EHMT1, ATRX*) resulted negative. Trio-based ES revealed a de novo heterozygous nonsense variant in exon 17 in *KAT6A* gene (NM_006766: c.3844G > T, p. Gly1282Ter), deemed pathogenic according to ACMG guideline, absent from population databases (now registered in the LOVD website as individual ID #00383157).

3. Discussion

KAT6A-related syndrome presents with various degrees of developmental delay and a spectrum of manifestations recently delineated by Kennedy et al. (2019) in a cohort of 76 cases. In this cohort, epilepsy was present in seven patients. Here we have reported the clinical history of two further individuals harboring de novo *KAT6A* heterozygous variants. One variant was previously reported by Kennedy et al. (2019) in a child with severe developmental delay, seizures, feeding difficulties, gastrointestinal disturbances and normal brain MRI, whereas the other variant has not been previously reported. Consistent with the phenotype of individuals with *KAT6A* mutations, both girls herein described developed severe life-threatening neonatal problems, and showed typical facial dysmorphisms, intellectual disability with marked expressive speech delay. Gastrointestinal problems including non-specific feeding difficulties and dysfunctional intestinal motility are common in *KAT6A*-related syndrome and were present in both our cases. However, they were particularly severe in patient#1 who required surgical correction for intestinal malrotation and volvolus.

Both our patients developed early onset seizures but the type of seizures, response to medication and outcomes were inconsistent, although precise comparison was not possible because of the different ages of the two individuals. Patient#1 suffered from focal to bilateral seizures, resistant to antiseizure medications with only limited benefit achieved with lacosamide. Given the EEG abnormalities mainly arising from the occipital regions and the brain abnormalities, her epilepsy was classified as a focal of possibly structural origin. Patient#2 presented with infantile spasms consistent with West syndrome, responsive to

Table 1
Summary of clinical features of individuals with *KAT6A* variants and seizures.

		Kennedy et al. *2019*							*Trinh* et al. *2017*
		Kennedy et al. 2019				Tham et al. 2015		Millan et al. 2016	
case		patient#a	patient#b	patient#c	patient#d	patient#e	patient#f	patient#g	patient#h
sex/age		F/9	M/13	M/14	F/7	F/deceased	F/4	M/30	M/39
mutation	**type**	frameshift	missense	splicing	frameshift	nonsense	frameshift	splicing	missense
	inheritance	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
	exon	7	17	8	10	16	17	16	17
	coding DNA	c.1308_1309insCGCAA	c.4645G > A	c.1364-2A > T	c.1639_1640del	c.3116_3117delCTinsAA	c.3831_3832insAG	c.3040-1_3040delGA	c.5924A > G
	protein change	p. Tyr437Argfs*43	p. Gly1549Ser	acceptor splice site	p. Met547Glufs*3	p.Ser1039*	p.Arg1278Ser*17	splice site	p. Asn1975Ser
epilepsy	**seizures**	several focal seizures between ages 2-3	no information	absences	absences with eyelid myoclonia	no information	transient infantile spasms which responded to ACTH	focal seizures with secondary generalisation	no information except treatment with levetiracetam and lamotrigine
	age at onset/ offset	2–3 years	NA	NA	NA	NA	NA	9 yo	38 yo/NA
	EEG description (age)	normal (2 yo)	NA	*abnormal* EEG	NA	focal left temporal discharge general spike-slow wave	NA	NA	NA
neuroimaging		NA	NA	NA	NA	Brain MRI: Cavum septum pellucidum, foramen cecum epidermoid, craniosynostosis	Brain MRI: negative	Brain MRI: absence of olfactory bulb	NA
patient		**patient#a**	**patient#b**	**patient#c**	**patient#d**	**patient#e**	**patient#f**	**patient#g**	**patient#h**
other clinical features	**Dysmorphisms**	+	+	+	+	+	+	+	+
	ID (degree)	+ (mild)	+(severe)	+(moderate)	+ (mild)	+(NA)	+ (NA)	+ (NA)	+ (mild)
	Speech delay	+	+	+	+	+	+	+(absent)	–
	GI disturbances/ feeding problems	–	+	NA	+	+	+	+	–
	Microcephaly (A = acquired)	–	NA	–	–	–	+	–	+
	Congenital heart defects	+	–	–	–	+	–	–	–
	sleep disturbances	–	+	–	–	NA	NA	NA	NA
	frequent infections	–	–	+	–	NA	NA	NA	NA

NA: information not available.

ACTH and valproic acid. She had a remission within the third year of life and successfully discontinued her medication.

Epilepsy has been reported in a minority of *KAT6A* cases and a detailed characterization of seizures semiology, frequency, outcome, EEG and antiseizure treatment response has not been specifically documented. In our literature revision and including our two individuals, we identified 90 patients with *KAT6A* mutations (Tham et al., 2015; Kennedy et al., 2019; Urreizti et al., 2020; Rochtus et al., 2020; Millan et al., 2016; Efthymiou et al., 2018; Marji et al., 2021; Trinh et al., 2018; Taşkıran et al., 2021). Seizures were described in 17/90 (18.9%) subjects (see Table 1 summarizing the epileptic features of the present cases and those from the literature). Notably, a previously reported individual harboring the same de novo *KAT6A* missense variant p. Gly1549Ser detected in our case #1, presented with an overlapping clinical phenotype including seizures, although no further details about epilepsy history are described (Kennedy et al., 2019).

Taşkiran et al. (2021) disclosed *KAT6A* variants though ES in two patients with non-syndromic intellectual disability: seizures were reported only in the girl who presented with a previously described variant and not in the other girl with a novel one (c.1312C > T, p.Arg438*).

No definitive conclusion about the semeiology of seizures in *KAT6A* syndrome is possible because of limited data. However, taking into consideration our cases and those reported in the literature, infantile spasms were reported in three patients and seem to be a possible clinical presentation during the first months of life (Tham et al., 2015; Rochtus et al., 2020). Similarly to one of the case described by Tham et al. (2015), our patient#2 suffered from infantile spasms responsive to ACTH and with a favorable outcome. Of note, although a clear evidence of infantile spasms was not elicited by report in patient#1, spasms preceding asymmetric tonic seizures were reported at an older age (15 years old). Focal seizures were reported in four individuals, in two cases resulting in focal to bilateral seizures, as in our patient#1 (Kennedy et al., 2019; Millan et al., 2016; Efthymiou et al., 2018; Marji et al., 2021). Electroencephalographic focal discharges were described in another case by Tham et al. (2015) without any clinical detail. Brain MRI was performed and reported as altered only in one patient with focal seizures, showing absence of the olfactory bulb (Millan et al., 2016). "Absences" were mentioned in four cases without any precise EEG description; in two individuals eyelid myoclonia were described, as in our patient#1 associated with nystagmus (Kennedy et al., 2019; Urreizti

Efthymiou et al. *2018*	*Rochtus* et al. *2020*	*Urreitzi* et al. *2020*			*Marji* et al. *2021*	*Taşkiran* et al. *2021*	this report	
patient#i	patient#j	patient#k	patient#l	patient#m	patient#n	patient#o	patient#1	patient#2
M/21	F/17	M/10	M/11	M/8	F/16	F/6.5	F/17	F/9
nonsense	nonsense	nonsense	nonsense	missense	frameshift	nonsense	missense	nonsense
de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo
16	17	17	17	7	17	17	17	17
c.3338C > G	c.3496delA	c.3385C > T	c.3640A > T	c.1075G > A	c.4254_4257del	c.3385C > T	c.4645G > A	c.3844G > T
p. Ser1113*	p. Arg1166AspfsTer10	p. Arg1129*	p.Lys1214*	p.Gly359Ser	p.Glu1419fs	p.Arg1129*	p. Gly1549Ser	p.Glu1282*
focal and generalized seizures	Infantile spams	absences	"two episodes of loss of consciousness"	absences with eyelid myoclonia	focal seizures treatment: levetiracetam	no information	focal seizures, eyelid myoclonia, atypical absences, tonic seizures, spasms	Infantile spasms
NA/3 years	first months/NA	9 yo/11 yo	6 yo	16 months/ present	NA	NA	3 months/present	5 months/3 yo
NA	NA	normal (11 yo)	NA (6 yo)	spike wave anomalies (3 yo)	NA	NA	delta background activiy, occipital and diffuse epileptiform discharges	frequent diffuse and multifocal epileptiform discharges, some burst related to spasms
Brain MRI: negative	NA	negative	Brain MRI: posterior right insula polymicrogyria, delayed myelination, Chiari I malformation	Brain MRI: negative	CT: pancraniosynostosis	NA	Brain MRI: small frontal lobes, abnormal ponto-mesencephalic junction, mild cerebellar vermis hypoplasia, megacisterna magna	Brain MRI: small frontal lobes and Chiari I anomaly
patient#i	**patient#j**	**patient#k**	**patient#l**	**patient#m**	**patient#n**	**patient#o**	**patient#1**	**patient#2**
+	NA	+	+	+	+	+	+	+
+ (NA)	+ (NA)	+ (severe)	+ (NA)	+ (NA)	+ (severe)	+ (moderate/ severe)	+ (severe)	+ (moderate)
+	+ (absent)	+	+	+	+	+ (absent)	+ (absent)	+ (absent)
–	NA	+	+	+	NA	NA	+	+
+	+	+	+	+	NA	+	+	+ (A)
–	NA	+	+	–	NA	NA	–	+
NA	NA	–	+	+	NA	NA	+	+
NA	NA	–	+	–	NA	NA	NA	NA

et al., 2020). Doubtful "staring episodes" were reported in a girl with a truncating variant in exon 17, severe phenotype, early death because of gastrointestinal complications and CM1 on brain MRI. These clinical manifestations were not classified as seizures by the authors and no information about EEG were provided (Kennedy et al., 2019). Subtle episodes with little clinical expression could be misdiagnosed especially in such patients with complex phenotypes and epilepsy's incidence could be underestimated in these cases.

We also focus on type of mutations and involved exons in subjects with seizures harboring *KAT6A* variants. The *KAT6A* gene comprises 18 exons, 16 of which are coding. It encodes a member of the MYST family of proteins that acetylate lysine residues in histone H3 and H4. In addition, it acts as a co-activator for several transcription factors. The protein is composed of five domains: a nuclear localization one (NEMM), a double C2H2 zinc finger domain that binds to acetylated histone tails, a histone acetyl-transferase (HAT) domain, followed by the ED (glutamate/aspartate-rich domain), and a serine- and methionine-rich (SM) transactivation domain (Klein et al., 2014). Pathogenic variants in the last two exons (16 and 17) are harbored by the majority of individuals with *KAT6A* syndrome, and specifically by 65 out of 90 subjects (72.2%). Both individuals herein reported harbor *KAT6A* variants in exon 17. Adding our report to the other 15 individuals with seizures in literature, 13 subjects (86.7%) harbored a variant either in exons 16 or 17. About 76% of the mutations are loss-of-function (nonsense, frameshift or splicing), including our patient#2 with a nonsense mutation (c.3844G > T) never reported before and likely pathogenic due to consistent phenotype. Missense variants are reported in the other four individuals and they all involve serine residues: they include our patient#1, patient#b from Kennedy et al. (2019) bearing the same variant (p.Gly1549Ser), patient#h from Trihn et al. (2018) presenting with a mild phenotype and recent patient#m from Urreitzi et al. (2020) harboring a missense mutation with functional reduction of *KAT6A* mRNA. Kennedy et al. (2019) already highlighted that more severe phenotypes with typical syndromic features are prevalent in late-truncating mutations.

Data about brain MRI are available only in about 40% of patients (including our report, 33/88) and it is normal in the majority of subjects with *KAT6A* syndrome. Neuroimaging findings are otherwise nonspecific and include craniosynostosis, microcephaly, CM1, thin corpus callosum, pituitary gland malformations, megacisterna magna, and delayed myelination (Kennedy et al., 2019; Urreizti et al., 2020; Marji et al., 2021; Zwaveling-Soonawala et al., 2017). Similarly, in the present individuals we observed CM1 in one subject (patient#2), while the other had mild cerebellar dysplasia, abnormal pontomesencephalic junction, inferior vermis hypoplasia and megacisterna magna (patient#1). Including our patient#2, CM1 was reported in about 18% of patients (6/33) whose MRI data are described in literature. This finding could be interesting, given the role of *KAT6A* in chromatin remodeling. In a recent work by Sadler et al. (2021), ES performed in a large cohort of individuals with CM1 revealed an association with rare de novo variants

in chromodomain (CHD) genes as *CHD3* and *CHD8*, that are also involved in dynamic change of chromatin structure.

Interestingly, in both patients the volume of the frontal lobes was reduced, with widening of the subarachnoid spaces and lateral ventricles in one of them. Future studies with quantitative assessment of cerebral white and gray matter volume are needed to investigate if this might be an additional underestimated feature of *KATA6A* syndrome.

In conclusion, to date epilepsy is reported in nearly one fifth of the patients affected by *KAT6A* syndrome. With the regard to the specific type, infantile spasms responsive to antiseizure medications (Tham et al., 2015; Rochtus et al., 2020), focal seizures (Kennedy et al., 2019; Millan et al., 2016; Efthymiou et al., 2018) and "absences" (Kennedy et al., 2019; Urreizti et al., 2020) are possible phenotypes. Given the *forme fruste* presentation of certain seizures, they are probably underestimated. The description of further cases with epilepsy is crucial to broaden the knowledge about epilepsy in *KAT6A* syndrome and help clinicians in the management of these patients.

Author statement

The first author of the manuscript and the corresponding author (if different) certify on honor, on behalf of all co-authors, that they have been granted a permission to publish signed by the patient himself (or by his legal representatives) for each patient whose facial features are identifiable in the photographs illustrating this article. The authors maintain in their files a copy of this consent, which will be forwarded to Elsevier in case of complaints or legal proceedings.

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