



Epilepsy, status epilepticus, and hemiplegic migraine coexisting with a novel *SLC4A4* mutation

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Abstract

Background Recessive mutations in the *SLC4A4* gene cause a syndrome characterised by proximal renal tubular acidosis (pRTA), mental retardation, dental and ocular abnormalities, and hemiplegic migraine. Rare cases involving the development of epilepsy or its severe complication—status epilepticus—have been described.

Methods The clinical and genetic status of four affected members in a Spanish family was studied. The *SLC4A4* gene mutation was detected with a next-generation sequencing (NGS) panel in the proband, and Sanger confirmed the putative mutations in affected relatives. In silico analysis was performed to elucidate the putative effect of mutation on the splicing process.

Results A novel mutation, c.2562+2T>G, was identified in the homozygous state in all diseased members of the family. This mutation affected a canonical splice site and is predicted to abolish the wild-type donor site, which predicts a premature truncated NBCe1 protein with cotransport activity. The resulting protein lacks the 190 amino acids of the carboxyl-terminus, and the effect is likely to be a loss of function. All patients suffered from severe pRTA and ocular abnormalities, and the adults also suffered from neurological complications, such as hemiplegic migraine and/or epilepsy. Two developed life-threatening status epilepticus, although they fully recovered and remained free of seizures with valproate.

Conclusion These results expand the clinical and mutational spectra of *SLC4A4*-related disease and have implications for understanding the potential role of NBCe1 in the pathophysiologic processes of hemiplegic migraine and epilepsy/status epilepticus associated with the mutation.

Keywords Status epilepticus · NBCe1 · Roma ancestry · Seizures · Paroxysmal movement disorders

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Introduction

Mutations in the *SLC4A4* gene, a member of the solute carrier family, cause a rare autosomal recessive syndrome characterised by altered renal function, which is occasionally associated with other manifestations, including familial hemiplegic migraine (FHM). The gene encodes for the sodium bicarbonate cotransporter NBCe1. NBCe1 and its splice variants are expressed in different organs, including the kidney, eyes, pancreas, and brain. In the brain, the more frequent variants are NBCe1B and NBCe1C, which are mainly expressed by astrocytes and thought to modulate neuronal excitability, acting as acid extruders to regulate local pH.

Fifteen mutations have been described to date, including nonsense [1, 2], missense [1, 3–9], and frame-shift mutations [3, 10]; deletion [11]; a 3' UTR mutation, creating a AU-rich element [12]; and, just recently, two compound heterozygous mutations, one of which involves a splice site [13, 14]. Despite

encoding a splice variant in the central nervous system (CNS), not all described *SLC4A4* mutations lead to the development of neurological symptoms. These mutations are summarised in Table 1.

In this study, we describe four affected patients with a novel mutation, c.2562+2T>G, affecting a splice site in the *SLC4A4* gene in a gipsy family with origin in Northern Spain. The phenotype was of severe proximal renal tubular acidosis (pRTA), band keratopathy, and dental hypoplasia, with major neurological symptoms that included hemiplegic migraine, episodic ataxia, epilepsy, and status epilepticus, which is a rare complication of *SLC4A4* mutations.

Methods

Patients

All studies were undertaken with the understanding and written consent of all subjects or next-of-kin involved and conformed with the World Medical Association Declaration of Helsinki. The institutional review board at the Health Institute in Hospital La Fe approved this study.

Genetic analysis

Genomic DNA was extracted from the peripheral leukocytes of the family members by standard procedures. DNA from the index patient was analysed by next-generation sequencing (NGS) using the *SureSelect custom Constitutional Panel*

17 Mb based on the Agilent *SureSelectQXT* solution-capture enrichment protocol (Agilent, CA, USA). The *Alissa Clinical Informatics Platform* was used to align the obtained sequences against the genome reference sequence and to perform the calling of variants (*Align&Call* software). The focus of the analysis was on the main causative genes, and the filtering and interpretation of data were carried out with *Alissa Interpret* on the bases of the minor allele frequency ($\leq 1\%$ in the control population) and the type of variant.

The splicing effect was assessed with Human Splicing Finder 3.1 software, the Berkeley Drosophila Genome Project Splice Site Prediction by Neural Network, and the NetGene2 Server. Pathologic variants were confirmed by Sanger sequencing. Segregation analysis was performed in all affected patients.

CT perfusion study and MRI acquisition

Multimodal stroke CT imaging included non-enhanced CT (NECT), an angio-CT (CTA) of the cervical and intracranial arteries, and CT perfusion (CTP). The study was performed on a Philips 256 detector CT scanner (Brilliance iCT, Philips Healthcare, Cleveland, USA). For dynamic contrast-enhanced CTP and CTA, iopamidol (Isovue-370; Bracco, Milan, Italy) was injected intravenously followed by saline flush. The commercial software provided by the manufacturer was used to generate the perfusion parametric maps, including the mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV).

Table 1 Known *SLC4A4* gene mutations affecting the CNS

Variant	Effect in NBCe1	Neurological signs or symptoms	Bibliography
$\Delta 65$ bp Frameshift Location: C-terminal tail	Frameshift in exon 23 introduces a premature stop codon for both NBCe1A (S982NfsX4) and NBCe1B (S1026NfsX4) + abolishes the translation of NBCe1C, the C-terminal variant skipping exon 24→cytosolic retention and failure to induce a functional activity in mammalian cells	Homozygosis: • Hemiplegic migraine • Migraine stupor • Migraine-associated epileptic seizures • Complex partial status epilepticus Heterozygosis (dominant negative effect of the mutant protein through hetero-oligomer formation with the wild-type protein: migraine with or without aura)	[3, 15]
L522P Missense Location: TM4	Intracellular retention	Homozygosis: hemiplegic migraine and ataxia	[6, 7, 16–18]
$\Delta 231$ 1A Frameshift Location: IL4	Truncation of all NBCe variants	Homozygosis: migraine with aura	[10]
R510H Missense Location: TM4	Intracellular retention	Homozygosis: migraine without aura	[1] [3, 8, 19] [16]
R881C Missense Location: TM12	Intracellular retention	Homozygosis: migraine without aura	[3, 8, 20]

MRI examination was performed on a 3T MRI scanner (Signa HDxt, GE Healthcare, Milwaukee, USA) using a transmit–receive head coil array with 8 elements. The brain MRI protocol included sagittal 3D T1-weighted, coronal 2D FLAIR, axial 2D T2*-weighted, axial 2D T2-weighted, axial 2D diffusion-weighted images (DWI), and 3D time-of-flight (TOF) angiography.

EEG acquisition and status epilepticus definition

We performed routine video EEG for 30 min using the international 10–20 system placement (Fig. S1) and 21 contact electrodes, with both bipolar and monopolar montages. The bandpass filters were set at 0.5 and 120 Hz. Status epilepticus was defined clinically as a continuous seizure or intermittent seizures without full recovery of consciousness between seizures for more than 5–10 min, and it was defined electrically using the Salzburg criteria [15].

Results

Clinical features of proband and affected relatives

The proband (IV:3) was a 28-year-old woman born to consanguineous healthy parents with origin in a Roma ancestry family from Northern Spain. There was no history of inherited diseases in her family, taken that her grandfather died young of a chronic renal disease. She was being followed up since childhood because of blood acidosis due to pRTA and band keratopathy. She had short stature and slight mental retardation. At age 25, she had already consulted the Neurology Department in our hospital and had been studied due to self-limited episodes of ataxia as well as paraesthesia and hemiparesis. Due to her chronic kidney disease, a kidney transplant was performed in 2016. The graft finally had to be excluded by embolisation because of secondary hypokalaemia and severe metabolic acidosis. The patient was since then on a conventional haemodialysis programme. She had been admitted to the intensive care unit (ICU) on two occasions due to a decrease in her level of consciousness of unclear cause, attributed to hydro-electrolyte disturbances.

In 2017, she was admitted to the hospital due to low-grade fever (37.8 °C) and generalised weakness. Her blood pressure levels were normal, she was drowsy and did not collaborate in the examination, she did not present meningism, and she lacked initial focal deficits. Additional laboratory tests showed hyponatraemia (127 mmol/l), hypokalaemia, hyperazotaemia, and metabolic acidosis with elevated C-reactive protein (30 mg/l). Her cerebrospinal fluid (CSF) was normal (leukocytes, 1/μl; glucose, 72 mg/dl; and protein, 33 mg/dl). Underlying infection was ruled out. Twenty-four hours later,

she presented an abrupt episode of left hemiparesis, increased muscle tone in the left arm, and decreased level of consciousness. It is associated with preferential gaze to the right, unintelligible speech, and supranuclear left facial paralysis. An urgent CT protocol was performed to rule out stroke (Fig. 1a). NECT showed a subtle sulcal effacement and mild loss of cortico-subcortical differentiation in the right parieto-occipital convexity, and the CTA revealed engorged leptomeningeal vessels obliterating the sulci within the areas of effacement. CTP was unremarkable, MTT was slightly prolonged, CBF was decreased, and CBV was increased, excluding acute ischaemia. A brain MRI, 48 h later, (Fig. 1b) showed increased signal and mild swelling of the cortex and juxtacortical white matter and sulcal effacement in the right hemisphere in T2-weighted sequences, with hyperintensity in DWI corresponding to cytotoxic oedema. MRI TOF showed asymmetry in vascularisation between both hemispheres, which was more prominent in the right hemisphere. Differential diagnosis initially considered hemiplegic migraine and focal seizures with secondary generalisation, but at the time, there was no EEG documentation. The trigger of the episode was thought to be metabolic acidosis and electrolyte imbalance.

The patient recovered consciousness within hours, while the hemiparesis gradually resolved after 9 days. On the 10th day, during haemodialysis, the patient experienced ocular deviation to the left and hypertonia in the left arm, followed by generalised tonic–clonic seizures, blood oxygen desaturation, and lingual bite. Drugs used in situ were 500 mg levetiracetam, 5 mg diazepam, and 2 mg midazolam, but they were unable to terminate the crisis. Non-convulsive status was reported on EEG, showing focal epileptiform activity in the right frontotemporal region with a rhythmicity at 2–3 Hz that evolved to a frequency of 0.5 Hz immediately before a general depression of electric activity for 3–6 s (Fig. 2). She was admitted to the ICU where she was intubated and connected to mechanical ventilation. Intravenous treatment with propofol and valproate (500 mg bid) was initiated. After 4 days of stay, she recovered her state of consciousness and was released to the medical ward where evolution was good, and at follow-up MRI, abnormalities were resolved (Fig. 1c). She was discharged from the hospital 20 days after admission with valproic acid (VA) (500 mg/12 h). Motor recovery was complete in the next clinical visit, and during follow-up, the patient had not experienced new episodes of hemiplegic migraine or epilepsy.

The proband had two siblings (see pedigree in Fig. 3). Her older sister (IV:2) was a 33-year-old healthy female. Her brother (IV:4) was a 27-year-old male and had similar clinical features as the proband. He had short stature, psychomotor delay, and severe pRTA with blood acidosis. For this reason, he received a renal transplantation in 2005. On several occasions, he visited our Paediatrics Department for

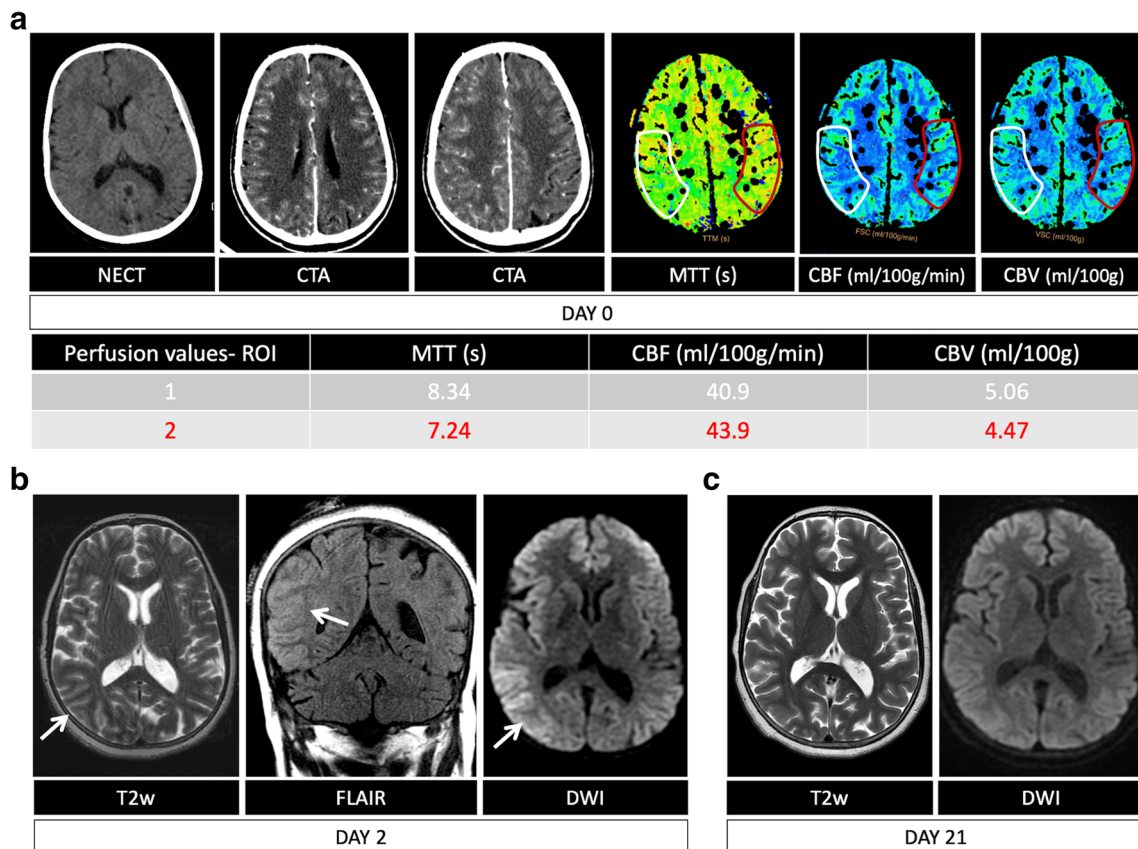


Fig. 1 MRI findings in the proband during seizures. **a** Coinciding with acute loss of consciousness and loss of strength in the left arm, non-enhanced CT (NECT) showed subtle sulcal effacement and loss of cortico-subcortical differentiation in the right parieto-occipital convexity. Angio-CT (CTA) revealed swollen leptomeningeal vessels obliterating the sulci within the same area. Perfusion CT (CTP) was visually unremarkable; although the mean transit time (MTT) was slightly prolonged, cerebral blood flow (CBF) decreased, and cerebral blood volume (CBV) increased, excluding acute ischaemia. **b** Brain MRI performed 48 h after

the acute episode showed increased signal and mild swelling of the cortex and juxtacortical white matter and sulcal effacement in the right hemisphere on axial T2w and coronal FLAIR sequences (white arrows). On diffusion-weighted MRI, these regions were slightly hyperintense, but the apparent diffusion values were normal (not shown), corresponding to vasogenic oedema. MRI TOF showed asymmetry in vascularisation, which was more prominent in the right hemisphere. **c** On day 21, the MRI changes were resolved

self-limited ataxia episodes and frequent migraine episodes with limb paresis, and he was diagnosed with epilepsy in 2007. Similar to her sister, he also had bilateral blindness secondary to cataracts and band keratopathy. In 2017, the patient was admitted to the ICU for an episode of abrupt decreased levels of consciousness in the context of electrolyte disbalance (hyponatraemia, 118 mg/dl) preceded by drowsiness and vomit. CT scan and MRI showed signs of cortical oedema. Video EEG at the recovery phase showed diffuse slow basal brain bioelectric activity with bilateral delta waves at 2–3 Hz with generalised injury signs with right predominance and epileptiform activity, as sharp waves, in the left frontal area. He gradually recovered with propofol, levetiracetam, lacosamide, sodium correction, and anti-oedema measures. Retrospectively, it is thought that the patient developed non-convulsive status, and, thus, cortical oedema was considered a secondary event. He was released with levetiracetam, without new seizures or neurological symptoms.

Two cousins of the proband with homozygous mutation (IV:5, 21-year-old and IV:6, 9-year-old) had neurological symptoms but no seizures to date.

Genetic analysis, identification of the *SLC4A4* mutation, and in silico analysis

The genetic study was initially carried out in patient IV:5 by NGS, leading to the identification of a novel mutation in homozygosis in the *SLC4A4* gene (OMIM 603345, ENST00000340595.3, NM_003759.3): c.2562+2T>G. This variant affects the second nucleotide after the end of exon 17, which is a canonical splice site that is a known mechanism of disease, and it was considered pathogenic according to the ACMG classification [16] (Fig. 4a). It is a novel variant since it was not found in GenomAD exomes, GenomAD genomes, and 1000G control databases. The presence of mutation in the proband and in the affected relatives (IV:3, IV:4, and IV:6) was assessed by Sanger sequencing.

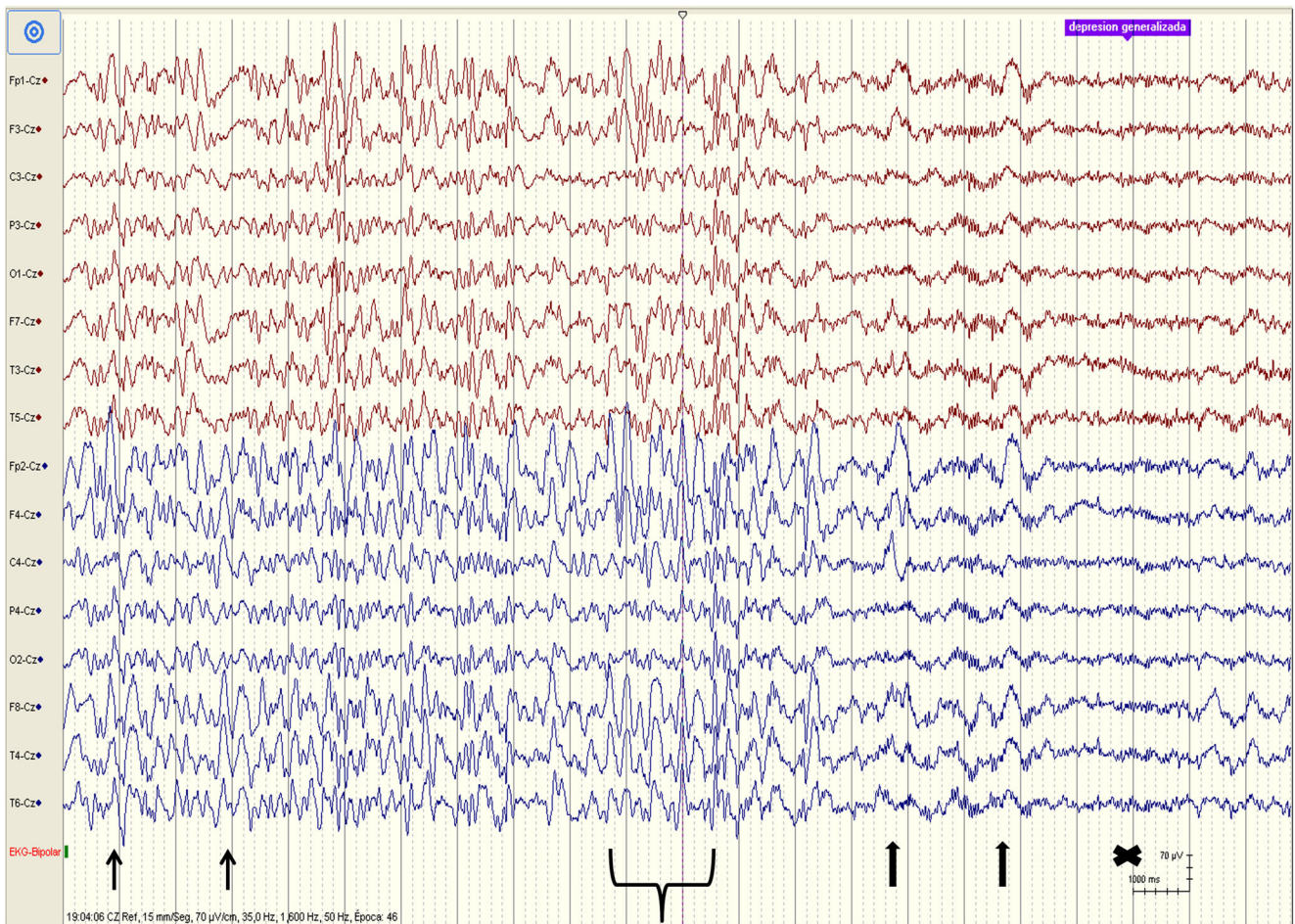


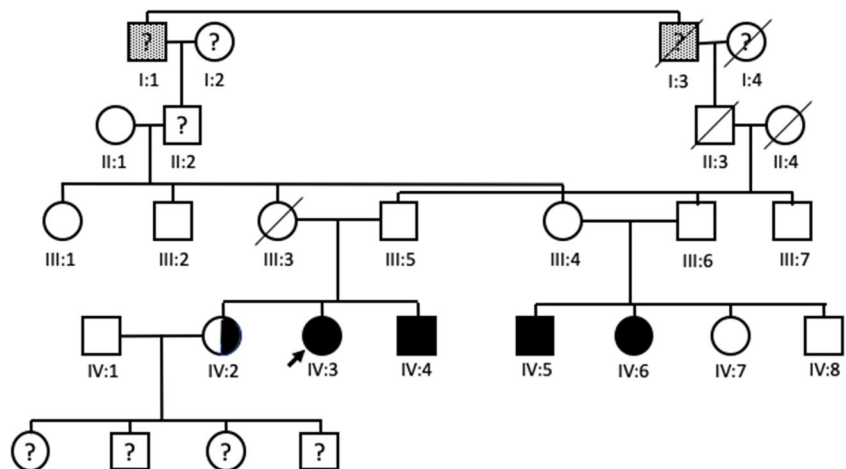
Fig. 2 EEG of the proband during non-convulsive status. The recording showed background activity consisting of high-amplitude waves. Irregular high-voltage sharp waves (thin arrow) were recorded with interspersed biphasic spikes in the right frontotemporal region (Fp2, F4, F8, T4, and T6), which occasionally projected to contralateral homonymous areas. These anomalies had a tendency for rhythmicity at

2–3 Hz (outline key) and slowed down to a frequency of 0.5 Hz (thick arrow) before ending with a general bioelectric depression for 3–6 s (cross). During the 30 min of recording, 10 episodes of similar electrical characteristics suggestive of non-convulsive status with probable origin in the right frontotemporal region were registered

The *in silico* analysis of the mutation was carried out with different software: *Human Splicing Finder*, *NetGene2*, and *Berkeley Drosophila Genome Project Splice Site Prediction*

by *Neural Network*. For this purpose, a sequence of 500 nucleotides comprising exon 17 and intronic flanking sequences containing either the WT or the mutant sequence was

Fig. 3 Pedigree. The proband belongs to a family of Roma ancestry with origin in a small village in Northern Spain. Several consanguineous marriages are depicted



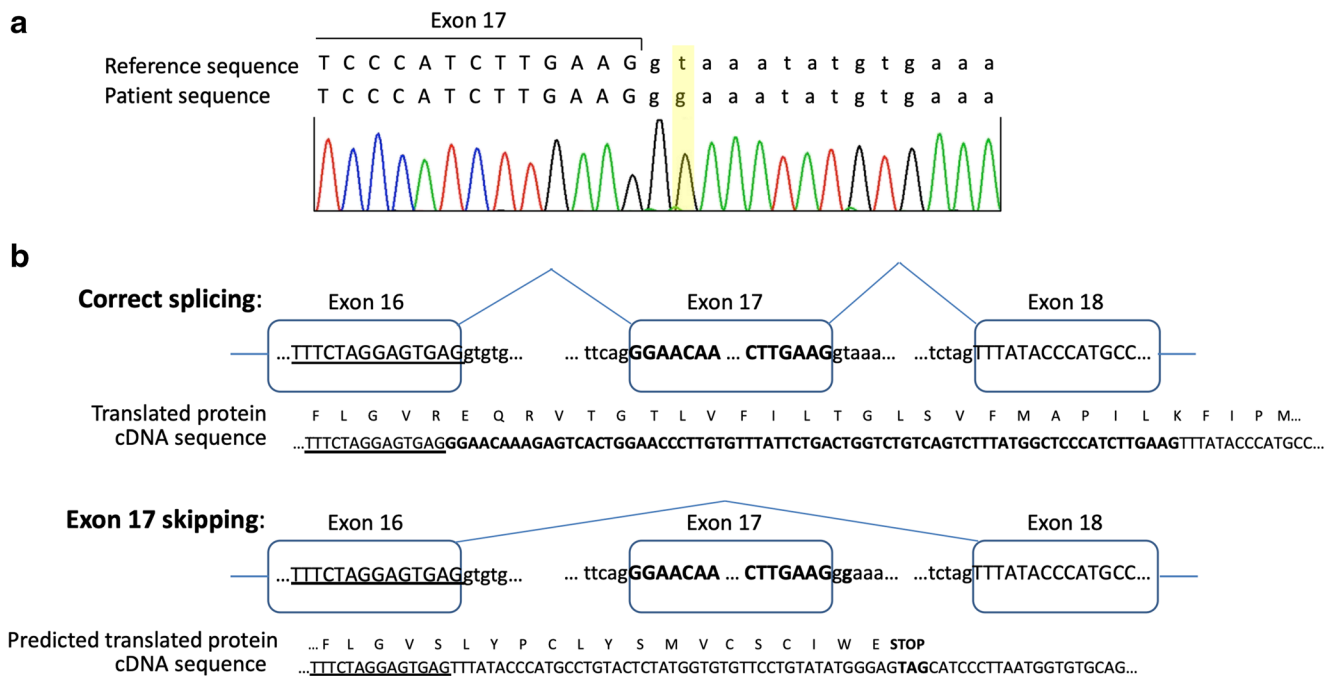


Fig. 4 Genetic and in silico analysis. **a** Electropherogram of the patient. The mutation c.2562+2T>G in *SLC4A4* appears highlighted. **b** Schematic representation of the processing of the wild-type sequence and the

expected exon 17 skipping when the mutation is present. In the lower region of the diagrams, the expected cDNA sequences and the putative translated proteins are transcribed

analysed. *Human Splicing Finder* and *NetGene2* software suggested that the donor splice site was abolished, and no novel donor site predictions were indicated. The *Berkeley Drosophila Genome Project Splice Site Prediction by Neural Network* indicated the consensus donor splice site with a score of 0.98 and a second putative donor site with a score of 0.75. In the presence of the mutation, the consensus donor site was abolished, whereas the secondary donor site was maintained. However, its location 31 bp upstream of the beginning of exon 17 and low score make its use unlikely. The abolishment of the donor splice site usually leads to exon skipping, which would generate a premature truncated protein of 845 amino acids in length instead of the wild-type (WT) protein of 1035 amino acids (Fig. 4b) that lacks the 190 amino acids of the carboxyl-terminus, and the effect on its cotransport activity is likely to be a loss of function.

Discussion

In this study, we report a family of gipsy ethnicity in which a novel mutation was found in the *SLC4A4* gene (c.2562+2T>G) affecting a canonical splice site, which expresses as a renal, ocular, and neurological syndrome. This is, to our knowledge, the first homozygous mutation affecting a splice site associated with epilepsy and/or status epilepticus.

The *SLC4A4* gene has been recently identified as the cause of a syndrome whose main sign is metabolic acidosis secondary to failure in the acidification of urine by the kidney. The cotransporter of sodium and bicarbonate encoded by the gene, NBCe1, presents abnormal function that is responsible for this condition. Extrarenal symptoms associated with the *SLC4A4* mutation are due to the expression of NBCe1 in other organs, such as the CNS. In the brain, two splicing variants, mainly NBCe1C but also NBCe1B, are expressed by astrocytes and neurons. The loss of function of NBCe1B in astrocytes is suggested to produce an alteration of synaptic pH that is responsible for hyperexcitability. Only 5 out of 15 known mutations of the *SLC4A4* gene affect the CNS, and reported cases describe migraine with or without aura, hemiplegic migraine, episodic ataxia, and, in only one case, epilepsy and stupor (Table 1). The only described mutation in a splice site affects exon 12 (NBCe1A) and is associated with renal dysfunction without neurological symptoms [14].

Currently, it is estimated that “genetic epilepsies” represent more than 30% of all epilepsies. Relevant diagnostic advances have been achieved thanks to the use of NGS-based molecular techniques, leading to the identification of new causative genes. *SLC4A4* is a cause of hemiplegic migraine (HM), a rare form of migraine presentation. It is associated with a complex aura that includes, by definition, a motor deficit. However, while the mutation on other SLC transporters has been associated with epilepsy and epileptic syndromes [17, 18], the

association of *SLC4A4* with epilepsy is rare. There are only two reported cases in siblings with the $\Delta 65$ pb mutation [3]. In both cases, epilepsy developed as complex partial status epilepticus and unexplained self-limited loss of consciousness, respectively. The effect of the $\Delta 65$ pb mutation is a frameshift in exon 23 (C-terminal tail) with a premature stop codon that affects membrane expression in all variants, but, specifically, it abolishes translation of the NBCe1C variant. The mutation c.2562+2T>G is expected to break the donor splice site and cause exon 17 skipping, which leads to a premature stop codon that results in a truncated protein of 845 amino acids in length instead of the WT protein of 1035 amino acids that lacks the 190 amino acids of the carboxyl-terminus. Although aberrant mRNAs are usually degraded by the nonsense-mediated decay (NMD) mechanism through exon skipping, the activation of cryptic splice sites or intron retention, which is not assessed with *in silico* analysis, could result in a defective protein. The link between mutations that affect the translation of the C-terminus (and, therefore, NBCe1 splicing variant C) and epilepsy should be confirmed in additional studies.

The type of genetic variant identified in a specific gene might influence the therapeutic strategy. Valproate acid was effective at keeping the proband free of seizures during follow-up. This antiepileptic drug exhibits its pharmacologic effects by acting on γ -aminobutyric acid (GABA) levels in the CNS, blocking voltage-gated ion channels, and inhibiting histone deacetylase. It may also exert antiepileptic effects by reducing the high-frequency firing of neurons by voltage-gated sodium, potassium, and calcium channel blockade. In other *SLC* mutations that affected a sodium bicarbonate transporter and that were associated with epilepsy [17], seizures were well controlled with zonisamide therapy but did not respond to lamotrigine. This suggests that wide-spectrum antiepileptic drugs might be more effective at treating epilepsy associated with *SLC* mutations than sodium blockers alone. Nevertheless, metabolic acidosis was a trigger for hemiplegic migraine episodes and preceded seizures in the described case, and, therefore, besides the use of antiepileptic drugs, maintaining blood bicarbonate within an acceptable range may also contribute to avoid neurological complications.

This mutation has only been described in a gipsy family with origin in Northern Spain. In many disorders, founder mutations have been identified in Spanish gipsy populations [19–21]. It is possible that the novel mutation c.2562+2T>G might be a frequent alteration in patients of Roma ancestry suffering from this condition and may be associated with a founder mutation.

Conclusions

In patients of Roma ancestry with pRTA, ocular abnormalities, and neurological symptoms, including epilepsy, the

SLC4A4 mutation c.2562+2T>G should be suspected, and these patients might be valproate acid responders. *SLC4A4* mutations in the C-terminal position could be pathogenically linked to epilepsy in relation to a potential loss of defective function in the NBCe1C variant, although this hypothesis needs further investigation.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10072-020-04961-x>.

Author contributions SGP and TJ designed the study and wrote the manuscript. RGR helped collect data and design figures. MM was the neuro-radiologist that analysed CT and MRI data. AGV and PR performed and interpreted EEG data. SGP and SD were the attending physicians of the proband during admittance and follow-up, and SD is the head of the Headache Unit and helped revise the final manuscript. All authors read and approved of the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request. 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.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical approval The institutional review board at the Health Institute in Hospital La Fe approved this study.

Informed consent statement All studies were undertaken with the understanding and written consent of all subjects or next-of-kin involved and conformed with the World Medical Association Declaration of Helsinki.

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