Original article

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Epilepsy in *KCNH1*-related syndromes

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ABSTRACT – *Aim*. *KCNH1* mutations have been identified in patients with Zimmermann-Laband syndrome and Temple-Baraitser syndrome, as well as patients with uncharacterized syndromes with intellectual disability and overlapping features. These syndromes include dysmorphic facial features, nail hypo/aplasia, thumb and skeletal anomalies, intellectual disability, and seizures. We report the epilepsy phenotype in patients with *KCNH1* mutations.

Methods. Demographic data, electroclinical features, response to antiepileptic drugs, and results of significant diagnostic investigations of nine patients carrying mutations in *KCNH1* were obtained from referring centres.

Results. Epilepsy was present in 7/9 patients. Both generalized and focal tonic-clonic seizures were observed. Complete seizure control was achieved with pharmacological treatment in 2/7 patients; polytherapy was required in 4/7 patients. Status epilepticus occurred in 4/7 patients. EEG showed a diffusely slow background in 7/7 patients with epilepsy, with variable epileptiform abnormalities. Cerebral folate deficiency and an increase in urinary hypoxanthine and uridine were observed in one patient.

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Conclusions. Epilepsy is a key phenotypic feature in most individuals with *KCNH1*-related syndromes, suggesting a direct role of *KCNH1* in epileptogenesis, although the underlying mechanism is not understood.

Key words: Zimmermann-Laband syndrome, Temple-Baraitser syndrome, genetic epilepsy, undefined intellectual disability, *KCNH1*-related encephalopathy

KCNH1 (potassium channel, voltage-gated, subfamily h, member 1; OMIM-603305) encodes a voltage-gated potassium channel (Kv10.1), with prominent expression in the brain, where it is involved in the regulation of neurotransmitter release and synaptic transmission (Mortensen *et al.,* 2015; Haitin *et al.,* 2013). *KCNH1* mutations have been recently demonstrated to have a pathogenic role in two rare disorders: Zimmermann-Laband syndrome (ZLS- OMIM 135500) and Temple Baraitser syndrome (TMBTS- OMIM 611816) (Kortüm *et al.,* 2015; Simons *et al.,* 2015). These syndromes include dysmorphic facial features, nail hypo/aplasia, thumb and skeletal anomalies, intellectual disability, and seizures (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Simons *et al.,* 2015). Overlapping clinical presentations have been reported in four cases from a cohort of individuals with uncharacterized intellectual disability (Bramswig *et al.,* 2015). Here, we phenotype the epilepsy features of patients with *KCNH1*-related syndromes.

Patients and methods

The clinical history, including medical history and developmental course, seizure semiology, clinical examination, antiepileptic drugs treatment, EEG monitoring, and laboratory and neuroradiological data, was collected for nine cases with *KCNH1*-related disorders. Of the eight published cases, five had ZLS and three uncharacterized intellectual disability (Rauch *et al.,* 2012; Castori *et al.,* 2013; Campeau *et al.,* 2014; Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Nair *et al.,* 2015; Simons *et al.,* 2015). A new case of a 12-month-old child with ZLS was also included.

The genetic mutations were identified through whole-exome sequencing (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015). It was not possible to detect any of the patients' mutations in their parents by Sanger sequencing (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015). Parental mosaicism was similarly excluded (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015). Parental written informed consent was obtained for all subjects.

Results

Demographic, electroclinical, and genetic features of nine patients (six female; aged 12 months to 28 years) are summarized in *table 1*.

Seizure semiology

Epilepsy was present in 7/9 patients. Seizure onset ranged from birth to eight months in 4/7 patients, while in Patients 1, 7 and 9, onset was at 10 years, 18 months, and 33 months, respectively. Febrile seizures were observed in Patient 3 only.

Focal seizures (including clonic and versive seizures) occurred in six patients, while generalized seizures (including myoclonic, tonic, clonic, and tonic-clonic) were reported in six patients (*table 2*). Photosensitive absence seizures were observed in Patients 3 and 9. Four of seven patients had convulsive status epilepticus (*table 2*).

Other clinical features

All patients had the previously reported phenotypic hallmarks of *KCNH1* disorders (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Simons *et al.,* 2015). Nail hypo/aplasia was observed in all patients, except Patient 3.

Neonatal problems, including neonatal asphyxia, respiratory distress, jaundice, neonatal seizures, and feeding difficulties, were observed in 4/9 patients. Six of nine patients had hypotonia and 3/8 patients had movement disorders including tremor, choreoathetosis, oculo-motor apraxia, and ataxia.

EEG findings

EEG studies showed diffuse background slowing in 8/9 patients (*table 1*). Multifocal epileptiform abnormalities with prominent fronto-temporal foci were observed in 6/7 patients, while occipital foci were found in 3/7 patients (*table 2*). A generalized spike-wave after photic stimulation was detected in two patients (*table 2*). As an example, EEG features of Patient 4 are shown in *figure 1*.

Other diagnostic investigations

MRI showed non-specific abnormalities in 3/9 patients: ventricular asymmetry, cystic enlargement of the subarachnoid spaces of the temporal lobes and dilatation of cavum vergae, increased extra-axial spaces, and corpus callosal hypoplasia (*table 1*).

Table 1. Demographic, molecular genetics, and electro-clinical data of the reported series.

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Clinical diagnosis	Zimmermann-Laband syndrome	Zimmermann-Laband syndrome	Zimmermann-Laband syndrome	Zimmermann-Laband syndrome	Zimmermann-Laband syndrome	Zimmermann-Laband syndrome	Undefined intellectual disability	Undefined intellectual disability	Undefined intellectual disability
Reference	Patient 1 Kortüm *et al.*, 2015	Patient 2 Kortüm *et al.*, 2015	Patient 4 Kortüm *et al.*, 2015	Patient 5 Kortüm *et al.*, 2015	Patient 6 Kortüm *et al.*, 2015	Unpublished	Patient 1 Bramswig *et al.*, 2015	Patient 2 Bramswig *et al.*, 2015	Patient 3 Bramswig *et al.*, 2015
Age and gender	14 Years, F	28 years, M	14 years, F	10 years, M	8 years, F	12 months, M	15 years, F	5 years, F	5 years, F
Place of birth	Germany	Australia	Italy	Italy	India	USA	Germany	Germany	The Netherlands
***KCNH1* gene mutation**	c.1399A>G p.Ile467Val	c.974C>A p.Ser325Tyr c.1066G>C p.Val356Leu	c.1405G>A p.Gly469Arg	c.1054C>G p.Leu352Val	c.1399A>G p.Ile467Val	c.1042G>A p.Gly348Arg	c.1070G>A; p.Arg330Gln	c.1070G>A; p.Arg330Gln	c.1070G>A; p.Arg357Gln
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Gestation and delivery	Normal gestation Natural delivery	Normal gestation Forceps delivery	Normal gestation Caesarean section because of foetal sufferance	Normal gestation Natural delivery	Normal gestation Natural dystocic delivery (meconium stained liquor, absent crying, requiring meconium suction and stimulation)	Normal gestation Natural delivery	Normal gestation Caesarean section	Normal gestation Caesarean section	Normal gestation Caesarean section

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Apgar scores	10-10-10	Not available	8-9	7-9	4-8	Not available	10-10-10	6-10-10	4-5-8
Perinatal problems	Muscle hypotonia Feeding difficulties	Absent nails, floppy, back arching, athetosis Poor temperature regulation Feeding difficulties Recurrent cyanosis Seizures	None	None	Neonatal seizures	Lethargic state, Respiratory distress Bradikinesia, Jaundice, Feeding difficulties	None	Cyanosis because of a nuchal cord	Respiratory distress Hypotonia
Motor developmental milestones	HC: 12m TC: 18m SW: 5y, 2m AW: 5y 6m	HC: 12m TC: 3y SW: non verbal AW: non-ambulant	HC: 3m TC: 7m SW: 13m AW: 17m	HC: 10m TC: 12m SW: 18m AW: 24m	HC: 14m TC: 2y, 7m SW: 3y AW: 3y, 4m	HC: poor TC: poor SW: not achieved AW: not achieved	HC: Unknown TC: Unknown SW: not achieved AW: not achieved	HC: Unknown TC: Unknown SW: Unknown AW: 2y 6m	HC: Unknown TC: 6 m SW: 21 m AW: 3y 6m

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Neurocognitive profile and results of cognitive tests (if available)	Intellectual disability	Severe intellectual disability	Intellectual disability; FSIQ 55 at the WISC-III (VIQ: 80; PIQ: 41)	Intellectual disability	Intellectual disability 47 at Seguin foam board test	Not done	Intellectual disability	Intellectual disability	Intellectual disability
Muscle tone	Hypotonia	Normal	Hypertonia	Hypotonia	Normal	Hypotonia	Hypotonia	Hypotonia	Hypotonia in the neonatal period; Hypertonia in the following ages
Movement disorders	None	Choreo-athetosis	Oculo-motor apraxia; Ataxia;	Ataxia;	None	None	None	None	None
Age at seizure onset	10y, 6m	Apnoeic episodes as neonate Seizure diagnosis at 6m of age	6m	8m	1m	No seizures	18m	No seizures	2y 9m

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Seizure types at onset	Generalized tonic-clonic seizures	Tonic	Clonic and myoclonic seizures	Focal clonic secondary generalized seizures	Clonic	No seizures	Focal tonic-clonic secondary generalized seizures	No seizures	Focal seizures (Upward gaze deviation)
Seizure types during follow-up	Generalized tonic-clonic seizures	Tonic seizures Myoclonic seizures; Generalized tonic-clonic seizures; status epilepticus; focal seizure evolving to bilateral tonic-clonic	Simple febrile seizures; Focal motor seizures; Generalized tonic-clonic seizures.	Focal motor secondary generalized seizures; Clonic, myoclonic and generalized tonic clonic-seizures.	Focal motor seizures; Generalized tonic-clonic seizures.	No seizures	Focal tonic-clonic secondary generalized seizures; Tonic seizures.	No seizures	Focal seizures (Upward gaze deviation)
Episodes of status epilepticus	No	Yes (Convulsive and non-convulsive status epilepticus)	No	Yes (Convulsive status epilepticus)	Yes (Convulsive status epilepticus)	No seizures	No	No	Yes (Convulsive status epilepticus)

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
EEG pattern	Slow background activity; Multifocal sharp waves and sharp slow waves with prominence in fronto-temporal regions.	Slow background activity; Multifocal sharp and slow discharges predominantly from right occipital and bilateral frontal regions; slow spike wave	Slow background activity; Fronto-temporal sharp waves and sharp slow waves; Photosensitivity.	Slow background activity; Multifocal spikes, spike and waves and spike and slow-waves with prominence in fronto-temporal (in some traces in occipital) regions.	Slow background activity; Multifocal spikes, spike and waves and spike and slow-waves with prominence in fronto-temporal regions.	Slow background activity	Sharp slow waves in the right parieto-occipital zone (rarely in the temporal zone); Diffuse sharp and slow waves during sleeping	Normal	Slow background activity Left central-temporal focus with sharp slow waves and peek waves during wakefulness. During photostimulation, bicentral sharp waves and peek waves from the flash frequency of about 10 Hz During sleeping, bicentral (right>left), left parietal and right temporal sharp waves and peek waves.

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Magnetic resonance imaging	Ventricular asymmetry	Normal	Normal	Cystic enlargement of subarachnoid spaces at the temporal lobes and mild dilatation of cavuum vergae	Normal	Increased extra-axial spaces	Normal	Corpus callosum hypoplasia	Normal
Metabolic abnormalities	None	None	None	Low 5-methyltetrahydrofolate; Increased urinary hypoxanthine and uridine.	None	Hypothyroidism	None	None	None
Antiepileptic drugs	VPA	CBZ, LTG , CLB, TPM, VPA, CZP	Monotherapy with PB in the first year of life; Monotherapy with CBZ after the first year of life	PB, VPA, NTZ, P, LEV, ETS, RFM, FA, TPM, LTG	Monotherapy with PHT in the first months; PHT+ VPA at school age	No drugs	VPA, OXC, SUL, LEV, LAC	No drugs	CZP, NTZ, CHL

Table 1. (*Continued*)

PATIENTS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Level of seizure control	No seizure control	No seizure control with CBZ, VPA, CZP; Reduction of seizure between 50 and 75% with LTG, TPM and CLB; TPM controlled status episodes; myoclonic seizures responded to CLB	No seizure control with PB; Complete seizure control with CBZ.	PB: Complete seizure control for 6 months; VPA: Transient reduction of seizures of 50%; LEV: Transient reduction of seizures of 50%; NTZ: No seizure control; ETS: No seizure control; P: No seizure control; RFM: worsening of seizures; TPM: reduction of seizure of 50%, LTG: reduction of seizure by 50%;	Complete seizure control with the association PTH+ VPA	Not applicable	Transient seizure reduction of less than 25% with OXC; No seizure control with VPA, SUL, LEV and LAC	Not applicable	Seizure reduction of less than 25% with NTZ
Side effects of the antiepileptic treatments	None	Depression with TPM	None	Worsening of seizures with RFM	None	Not applicable	Somnolence with VPA and OXC; Transient skin reaction with OXC; Sleep disturbances with SUL	Not applicable	None

HC: head control; TC: trunk control; SW: supported walking; AW: autonomous walking; y: years; m: months; WISC-III: Wechsler Intelligence Scale for Children III; FSIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; VPA: valproic acid; CBZ: carbamazepine; LTG: lamotrigine; CLB: clobazam; PB: phenobarbital; LEV: levetiracetam; NTZ: nitrazepam; ETS: ethosuximide; P: prednisone; RFM: rufinamide; FA: folinic acid; PHT: phenytoin; TPM: topiramate; CZP: clonazepam; OXC: oxcarbazepine; SUL: sulthiame; LAC: lacosamide; CHL: chlorydral.

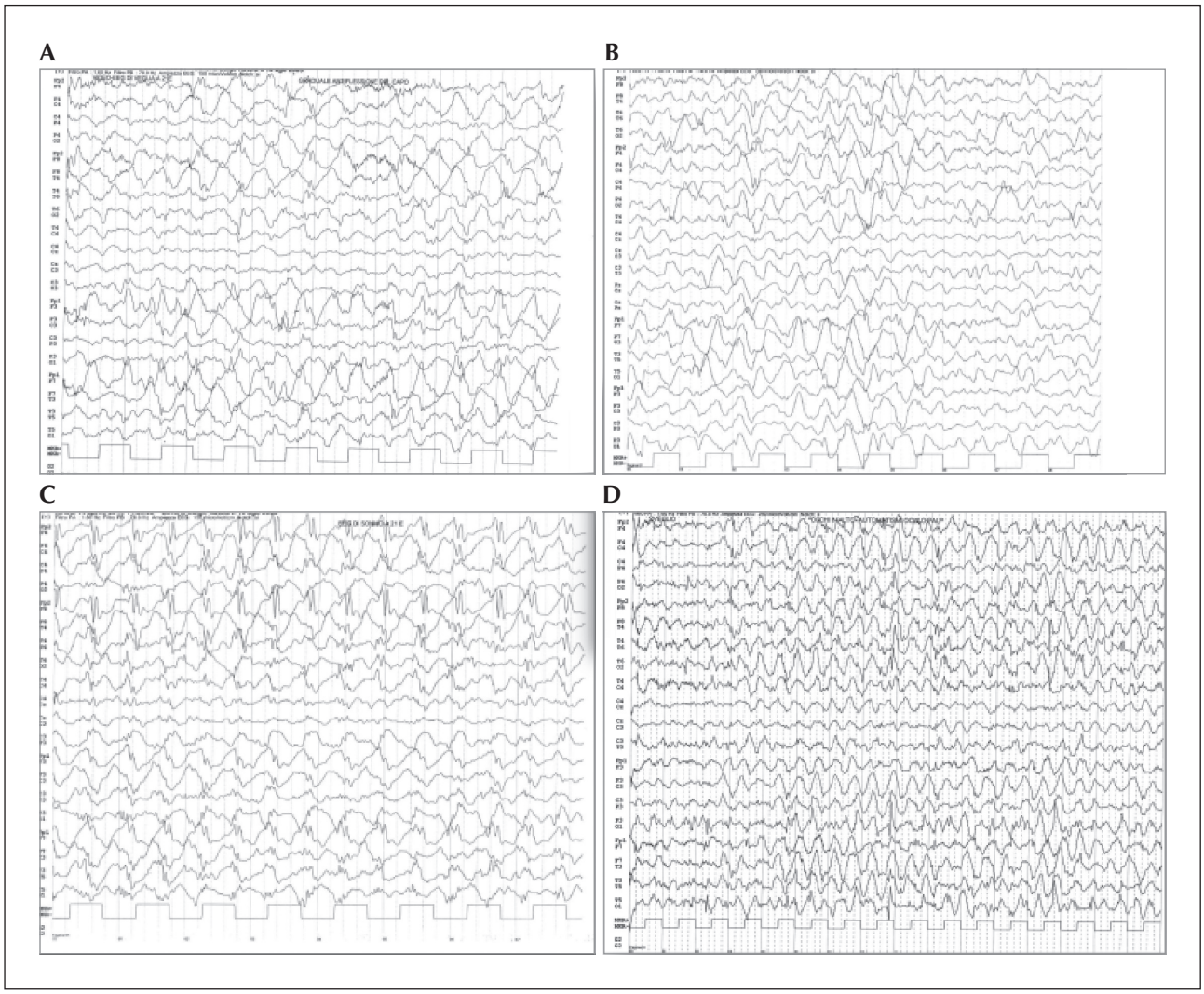

Figure 1. EEG of Patient 4 showing: (A) multifocal spikes, high-voltage atypical 1.5-2-Hz spike and waves and sharp slow waves during an episode of head drop; (B) diffuse high-voltage 2-3-Hz delta activity associated with prominent posterior spikes and sharp slow waves; (C) multifocal spike and waves and sharp slow waves with prominence in frontal regions; (D) high-voltage delta waves associated with prominent anterior spikes and sharp waves during an episode with up-gaze and oculo-palpebral automatisms.

Patient 4 had decreased 5-methyltetrahydrofolate in CSF and increased urinary hypoxanthine and uridine. Oral supplementation with folinic acid (15 mg three times/week) was of no benefit in terms of seizure frequency or severity.

Antiepileptic drugs treatment

Four of seven individuals had daily seizures, while seizure control was eventually achieved with pharmacological treatment in 3/7 patients. Complete seizure control was obtained with monotherapy in one patient (carbamazepine in Patient 3). Patient 5 responded to valproic acid with phenytoin. Topiramate and lamotrigine resulted in significant seizure reduction in Patients 2 and 4. Transient seizure reduction was observed in Patient 7 with oxcarbazepine and Patient 9 with nitrazepam.

Poor seizure control was obtained with clonazepam (Patient 2), nitrazepam (Patient 2 and 4), ethosuximide (Patient 4), prednisone (Patient 4), and lacosamide (Patient 7). Rufinamide caused seizure exacerbation and severe asthenia in Patient 4.

Other symptoms, eventually related to antiepileptic treatment included depression in adolescence (Patient 2: topiramate), somnolence (Patient 7: valproic acid and oxcarbazepine), skin reactions (Patient 7: oxcarbazepine), and sleep disturbances (Patient 7: sulthiame). Episodes of status epilepticus were controlled with intravenous benzodiazepines in Patients 2, 4 and 9, while Patient 5 required phenytoin.

Table 2. Epileptological features of all the published patients with *KCNH1*-related disorders.

FEATURES	OUR SERIES	Kortüm *et al.*, 2015 (patients not included in our series)	Simons *et al.*, 2015	Bramswig *et al.*, 2015 (patients not included in our series)	Total
Focal seizures	Patients 2, 3, 4, 5, 7, 9	Seizures type not available for Patient 3	Patient B	Patient 4	8/16 patients
Generalized seizures	Patient 1, 2, 3, 4, 5, 7	Seizures type not available for Patient 3	Patient A, D	Patient 4	9/16 patients
Focal secondary generalized seizures	Patients 2, 4, 7	Seizures type not available for Patient 3	None reported	Patient 4	4/16 patients
Episodes of status epilepticus	Patient 2, 4, 5, 9	Data not available for Patient 3	Data not available	None	4/16 patients
Febrile seizures	Patient 3	Data not available for Patient 3	Patient C	None	2/16 patients
Photosensitivity	Patient 3, 9	Data not available for Patient 3	Data not available	None	2/16 patients
Background slowing on EEG	Patients 1, 2, 3, 4, 5, 6, 7, 9	Data not available for Patient 3	Patients A, B	None	10/16 patients
Multifocal epileptic abnormalities	Patients 1, 2, 3, 4, 5, 9	Data not available for Patient 3	Patients C	Data not available	7/16 patients
Frontal secondary generalized epileptic abnormalities on EEG	Patients 1, 2, 3, 4, 5, 9	Data not available for Patient 3	Patients C	Data not available	7/16 patients
Occipital secondary generalized epileptic abnormalities on EEG	Patients 2, 4, 7	Data not available for Patient 3	Patients C	Data not available	4/16 patients
Monotherapy	Patients 3, 5	Data not available for Patient 3	Patients A, C, D	None	5/16 patients
Polytherapy	Patients 2, 4, 7, 9	Data not available for Patient 3	Patient B	Patient 4	6/16 patients
Seizure control	Patients 3 ,5	Patient 3	Patients A, B, C, D	Patient 4	8/16 patients
Poor or lacking seizure control	Patients 1, 7, 9	None	None	None	3/16 patients
No information on seizure outcome	None	None	Patients E and F	None	2/16 patients

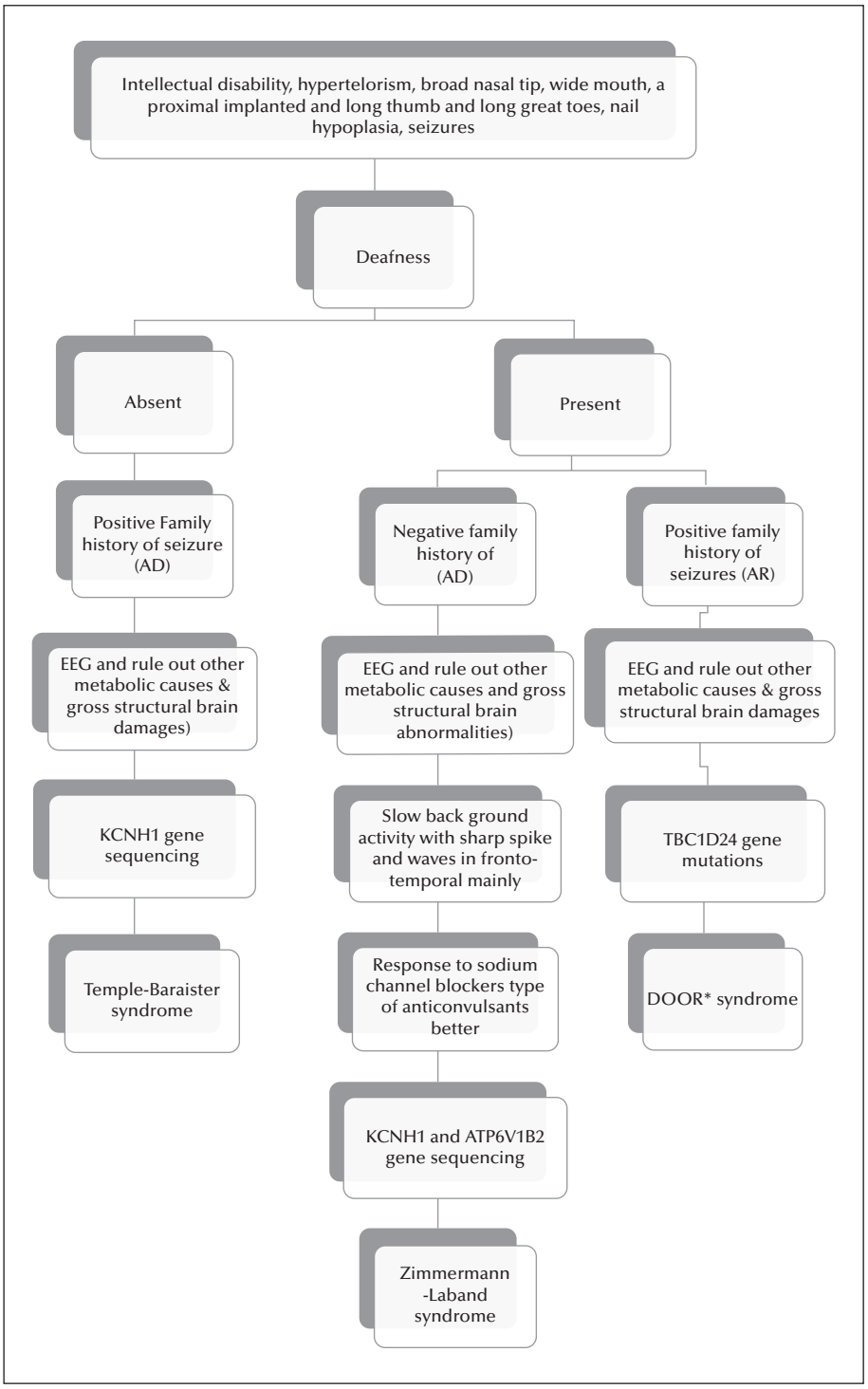

Figure 2. Suggested diagnostic flow chart for suspected *KCNH1*-related disorders.
AD: autosomal dominant; AR: autosomal recessive; KCNH1: potassium channel, voltage-gated, subfamily h, member 1; ATP6V1B2: ATPase, h+ transporting, lysosomal, 56/58-kd, v1 subunit b, isoform 2; TBC1D24: TBC1 domain family, member 24; DOORS: deafness, onychodystrophy, osteodystrophy, intellectual disability, and seizures syndrome; (*see Campeau *et al*., 2014).

Discussion

Epilepsy is a key manifestation in *KCNH1* disorders, reported in 15/16 patients (six with ZLS, six with TMBTS, and three uncharacterized with intellectual disability with overlapping phenotypic features of ZLS/TMBTS). Two mothers of patients with TMBTS, mosaic for the *KCNH1* mutation, also had seizures but without other hallmarks of TMBTS/ZLS (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Simons *et al.,* 2015). A diagnostic flow chart is suggested in *figure 2*.

All 10 reported *KCNH1* mutations (five with ZLS and four with TMBTS) result in a gain of Kv10.1 channel function (Kortüm *et al.,* 2015; Simons *et al.,* 2015). The mechanism by which *KCNH1* mutations cause epilepsy remains to be elucidated; a possible mechanism could be that gain of Kv10.1 channel function results in increased potassium conductance with subsequent inhibition of sodium and calcium currents and perturbation of neurotransmitter release (Ufartes *et al*., 2013; Kortüm *et al.,* 2015; Mortensen *et al.,* 2015). Hippocampal hyperexcitability, with an increased predisposition to seizures and EEG abnormalities, has been reported in mice after deletion and pharmacological block of Kv12.2 (another member of the KCNH family encoded by *KCNH3*) (Zhang *et al.,* 2010). This is unlikely to be relevant to *KCNH1* mutations because a loss of function of the Kv10.1 channel is better tolerated (Kortüm *et al.,* 2015; Simons *et al.,* 2015).

We did not find a clear relationship between our patients' mutations and their epilepsy phenotypes which were heterogeneous with regards to seizure type, EEG features, and refractoriness. Reported patients with different *KCNH1* mutations had infrequent seizures comprising both focal motor seizures and generalized tonic-clonic seizures with seizure control, while, in two cases, seizure outcome was not described (*table 2*) (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Simons *et al.,* 2015). Our EEG studies showed background slowing in 8/9 patients and in two published patients, consistent with their severe intellectual disability (*table 2*) (Simons *et al.,* 2015). With time, focal epileptiform abnormalities with secondary generalization were seen in the fronto-temporal region in 7/16 and the occipital region in 4/16 subjects (*table 2*).

It is unknown whether the cerebral folate deficiency and abnormal levels of urinary hypoxanthine and uridine of Patient 4 have any diagnostic relevance for subjects with *KCNH1* mutations, as only Patient 4 underwent these metabolic investigations. Potassium channel openers prevented the antidepressant effects of folic acid in mice that underwent forced swimming tests (Budni *et al.,* 2012). Similarly, a gain of function resulting in a persistent open state of Kv10.1 due to *KCNH1* mutations could induce folate depletion and subsequent cortical hyperexcitability leading to epileptogenesis. Folate depletion could also result from secondary inhibition of sodium currents with mechanisms comparable to the action of a sodium blocker, such as phenytoin (Kortüm *et al.,* 2015). A third hypothesis could be based on the role of 5-methyltetrahydrofolate as a non-specific biomarker of cerebral dysfunction (Pérez-Dueñas *et al.,* 2011).

Data on the antiepileptic treatment was available for 12/15 published patients (Bramswig *et al.,* 2015; Kortüm *et al.,* 2015; Simons *et al.,* 2015). Monotherapy was effective in 5/12 patients, while 6/12 patients required polytherapy (*table 2*). The inhibition of sodium currents, secondary to the persistent open state of Kv10.1, could have been worsened by rufinamide in Patient 4 who experienced seizure exacerbation. This seizure worsening could also result from specific drug dosages or drug combinations. A similar worsening in patients with *KCNH1* mutations might be expected with potassium channel openers, such as retigabine. No experience with this drug has been described in patients with *KCNH1* mutations, but the theoretical possibility of exacerbation of the persistent pathological open state of Kv10.1 would suggest that retigabine should be avoided in this population. Potassium channel blockers could be considered in pre-clinical models, but channel specificity, passage through the blood-brain barrier, and toxicity would need to be carefully considered.

Two patients in our series did not have seizures. Patient 6 was a 12-month-old boy with developmental delay, hypothyroidism, hypersomnolence, and EEG background slowing. He had the same mutation as Patient 3 from the series of Kortüm *et al.,* who had infrequent seizures beginning in adolescence (Kortüm *et al.,* 2015). Patient 8 was a 4-year-old girl with severe developmental delay, autistic features, hypotonia, and a normal EEG. Patient 7 and 9 in our series, with an identical mutation, had epileptic seizures requiring polytherapy.

Conclusions

Seizure types in *KCNH1*-related syndromes included both generalized and focal motor seizures, evolving to bilateral tonic-clonic seizures. EEGs were characterized by generalized background slowing with multifocal epileptiform abnormalities. *KCNH1* sequencing is strongly recommended when epilepsy is associated with typical facial dysmorphic features, nail hypo/aplasia, thumb/skeletal anomalies, and intellectual disability resembling Zimmermann-Laband or Temple-Baraitser syndrome (see the suggested diagnostic flow chart in *figure 2*). □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the main clinical features of *KCNH1*-related syndromes?

(2) How many patients with *KCNH1* pathogenic gene mutations presenting with epilepsy are published in the literature?

(3) What are the main EEG features of epileptic patients with *KCNH1* pathogenic gene mutations?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".