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Clinical letter

Two Chinese siblings with two novel *KCTD7* mutations have dystonia or seizures and epileptic discharge on electroencephalograms

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Dear editor

Many potassium channel gene mutations are reportedly associated with genetic forms of epilepsy, such as progressive myoclonic epilepsy (PME). In 2007, a homozygous mutation of the gene encoding potassium channel tetramerization domain-containing protein 7 (KCTD7) was first reported in three siblings from a consanguineous family with PME with autosomal recessive inheritance [1]. PME associated with *KCTD7* mutations has been reported in 42 patients from 33 families to date [2,3]. Here, we describe one Chinese girl presenting with paroxysmal non-epileptic myoclonus that was thought to be dystonia, asynchronous epileptic discharge which were not seen simultaneously with the motor manifestations on electroencephalogram (EEG) (Fig. 1) and intellectual disability. Her older brother had similar symptoms. He had dystonia but few atypical absences or generalized tonic-clonic seizures during EEG. The phenotypic features are summarized in Table 1.

To identify the mutations, we conducted whole exome sequencing (WES) on the two siblings and their parents. We used Sanger sequencing to validate probable pathogenic variants, and parental origin was determined by WES. A novel compound heterozygous mutation c.440 T > C (p.Leu147Pro) and c.520 G > A (p.Ala174Thr) in *KCTD7* was identified in these two siblings. The mutations were derived from their healthy parents (Fig. 1). No candidate variant was found in any other gene. The two novel mutations identified in the patients were not found in 1000 control samples. We used PolyPhen2, SIFT and Mutation Taster software to evaluate how the missense mutations affected protein function (Table 1), which could help us predict their possible pathogenicity. Residues Leu147 and Ala174 of KCTD7 are conserved during evolution.

This is a report of *KCTD7* mutations associated with paroxysmal dystonia or seizures, asynchronous epileptic discharge on EEG and intellectual disability in one family. Presently, 42 patients with *KCTD7* mutations reportedly exhibit continuous multifocal epileptic myoclonus, aggravated by action and posture, that has been diagnosed as PME [2,3]. In one patient, myoclonus was associated with opsoclonus and ataxia, which prompted the authors to consider a diagnosis of opsoclonus-myoclonus syndrome. All 42 reported patients had epileptic discharge on EEG and had homozygous or compound heterozygous mutations in the *KCTD7* gene.

The two siblings had frequent generalized multifocal spike-wave and spike-slow wave discharges on EEG, but EEG showed no changes during paroxysmal myoclonus. These siblings developed non-epileptic myoclonus-dystonia before 3 years and 9 months of age. The older brother had atypical absences and generalized tonic-clonic seizures at 3 years and 9 months of age, which suggests that *KCTD7* may cause non-epileptic myoclonus-dystonia, but as the disease progresses, epilepsy may occur. *KCTD17,* another *KCTD* family gene mutation, has a primary role in autosomal dominant myoclonus-dystonia [4]. Therefore, we suspect that *KCTD7* mutations might tend to cause non-epileptic myoclonus-dystonia.

Our findings expand the phenotype and genotype of *KCTD7*. Therefore, we conclude that *KCTD7* should be considered a candidate gene for non-epileptic myoclonus-dystonia, asynchronous epileptic discharge on EEG and intellectual disability.

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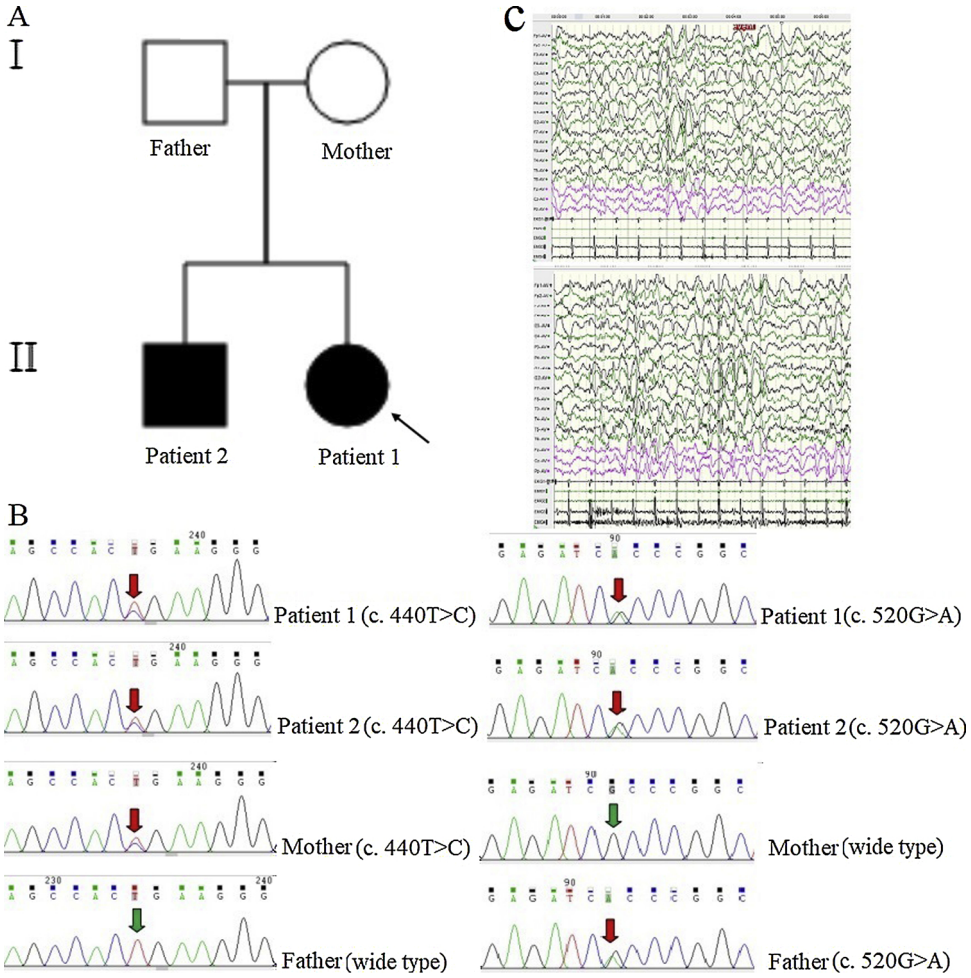

Fig. 1. A: Family pedigree. The proband is depicted in arrow pointing. B: The two novel mutations of KCTD7. C: Frequent generalized multifocal spike-waves, spike-slow waves discharges on interictal EEG and no epileptic dischage on ictal EEG of patient 1.

Table 1
The summary of phenotypic and genotypic features of two patients.

	patient 1	patient 2
clinical features		
Sex	Female (index patient)	Male (older brother)
Age until follow-up	3 years, 9 months	9 years, 11 months
Age of onset	2 years	1 years, 9 months
Perinatal history	Normal	Normal
Episodes of dystonia	1. Sudden onset of blink of eyes, sometimes with asymmetric limb myoclonus, conscious, no nystagmus or strabismus, lasted several seconds, and occurring dozens of times per day. 2. Sudden onset of hypotonia of trunk and limbs, couldn't control the head and sit alone, sometimes with minipolymyoclonus of limbs or fingers spontaneously, lasted several seconds to several hours, and occurring dozens of times per day. 3. Paroxysmal loss able of walk, couldn't walk for 1-2 months and then can walk for 4-5 months without help. Slurred speech and salivate	Similar to patient 1 but no blink of eyes, paralysis occur at 3 year, 2 months
Epileptic seizures	No	Atypical absence and generalized tonic clonic seizures occur at age of 3 year, 9 months, 1 time per 2-3 months
Treatment	No response to levetiracetam, nitrazepam, clobazam, topiramate and madopar	No response to levetiracetam, valproate, lamotrigine, clobazam, topiramate, phenobarbital and methylprednisolone. paralysis occur after treatment of rituximab
Development milestones	Moderate to severe delay. could speak 2-3 words but slurred speech, and could not sit independently until follow up.	Severe delay. no language and movement after 3 years, 2 months old
Interictal EEG	Frequent generalized multifocal spike-waves, spike-slow waves discharges	Similar to patient 1
Ictal EEG	No epileptic dischage	90% were no epileptic dischage. Capture few atypical absence and generalized tonic clonic seizures

(*continued on next page*)

Table 1 (*continued*)

	patient 1	patient 2
Physical examinations	Hypotonia, myodynamia IV level, normal tendon reflex on upper limb, no tendon reflex on lower limb, negtive babinski sign	Loss of weight, hypertonia, myodynamia I level, brisk tendon reflex on upper limb, no tendon reflex on lower limb, negtive babinski sign
Brain MRI and metabolic workup	Normal	Normal
***KCTD7* mutaions**		
cDNA (NM_153033.4)	c. 440 T > C c. 520 G > A	Same as patient 1
Protein	p.Leu147Pro p.Ala174Thr	
Parental derivation	Mother Father	
Pathogenicity Prediction		
PolyPhen2	Benign Possibly damage	
SIFT	Damaging Damaging	
Mutation Taster	Disease causing Polymorphism	

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