

KCNN2 mutation in autosomal-dominant tremulous myoclonus-dystonia

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Background and purpose: Despite recent advances in neurogenetics that have facilitated the identification of a number of dystonia genes, many familial dystonia syndromes remain without known cause. The aim of the study was to identify the cause of autosomal dominant tremulous myoclonus-dystonia in a UK kindred with affected individuals in three generations.

Methods: Known genetic causes of myoclonus-dystonia were excluded. We combined clinical and electrophysiological phenotyping with whole-exome sequencing and Sanger sequencing to identify candidate causal variants in a family with tremulous myoclonus-dystonia.

Results: The core phenotype consisted of childhood-onset dystonia predominantly affecting hands and neck, with a fast tremor with superimposed myoclonus and, in some individuals, subtle cerebellar signs. We identified a novel missense variant in potassium calcium-activated channel subfamily N member 2 (*KCNN2*) [NM_021614:c.1112G > A:p.(Gly371Glu)], which was the only variant that we were able to identify as segregating with the phenotype over three generations. This variant, which is absent from the most recent version of gnomAD, was predicted to be deleterious by SIFT and PolyPhen-2 and had an overall CADD score of 29.7.

Conclusions: *KCNN2*, a member of the KCNN family of potassium channel genes, is highly conserved across species and in humans is highly expressed in the brain, particularly the cerebellum. *KCNN2* mutations have never been described as pathological in human disease, but are recognized abnormalities in two rodent models of fast, jerky tremor. Segregation, absence of the variant in the normal population and *in-silico* prediction of a deleterious effect together with animal models compatible with the clinical phenotype are all in line with *KCNN2* mutations being a plausible cause underlying myoclonus-dystonia.

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing

abnormal movements, postures or tremor [1]. Dystonia may occur as a solitary clinical feature ('isolated dystonia') or may be part of a 'combined dystonia' syndrome when associated with other movement disorders, e.g. myoclonus in 'myoclonus-dystonia' syndromes. Epsilon-sarcoglycan (*SCGE*) mutations account for approximately one-third of familial myoclonus-dystonia cases with autosomal dominant inheritance (reviewed in [2]). In the remaining cases, a

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number of different (often rare) genetic causes have been discovered, such as mutations in *KCTD17*, *ANO3*, *SCN8A*, *RELN*, *ADCY5* or *TITF1* [2,3]. We used exome and Sanger sequencing to investigate the cause of autosomal dominant myoclonus-dystonia in a British pedigree with multiple affected individuals, in which known genetic causes had been excluded. We discovered a novel heterozygous missense variant in potassium calcium-activated channel subfamily N member 2 (*KCNN2*) (NM_021614:c.1112G>A: p.(Gly371Glu)) segregating with the disease over the three generations. This variant is predicted to have a deleterious effect on the protein.

Methods

All family members available for assessment underwent a detailed medical interview and a videotaped movement disorder-focused neurological examination. We performed electroencephalography (EEG)–electromyography recording in the index case. Written informed consent was obtained from all participants prior to sample collection and the study was approved by our UCLH/UCL ethics committee.

Sample preparation

DNA from clinically diagnosed cases and unaffected family members was extracted from whole blood using a Nucleon™ BACC3 Genomic DNA Extraction Kit (GE Healthcare, Chicago, IL, USA). All samples were checked for integrity on agarose gel and quantified using Qubit (Invitrogen, Inc., Carlsbad, CA, USA).

Exome sequencing

Three affected samples and one unaffected sample were included in the exome-sequencing experiment (III:5, IV:6, IV:7, IV:8). Exome sequencing was performed using SureSelect Exome Capture Kit version 4 (Agilent, Santa Clara, CA, USA) and sequencing on HiSeq2500 (Illumina, San Diego, CA, USA) using 100-bp paired-end reads, according to the manufacturer's instructions. Average on-target coverage of at least 30× was obtained for all included samples.

Data analysis

Exome sequencing data analysis was performed according to standard GATK (v3) best practices [4,5] using a single informatics pipeline and performing joint variant calling of single nucleotide variants and short insertions and deletions (indels) across all samples. In brief, sequencing reads were aligned to the

human reference genome (GRCh37/hg19) using bwa (v0.7.12) [6], duplicate reads were flagged using samblaster (v0.1.21) [7] and realignment around indels and base quality scores was recalibrated using GATK. Variant recalibration was performed using GATK's variant quality score recalibration. Variants that did not meet the variant quality score recalibration threshold of 99.9 were excluded. Variants then underwent a stage of genotype refinement, where population priors from the 1000 Genomes phase 3 dataset [8] were used to improve call estimates. Individual genotypes with a phred-scaled quality score below 20 and with coverage below 8 were set to missing. Annotation of variants was performed with snpEff (v4.2) [9] and dbNSFP v2.9 [10] using GRCh37/hg19 as reference. The variants were filtered to obtain rare exonic and splice-site variants classified as deleterious. Variants with a minor allele frequency higher than 0.1% in the gnomAD database [11] were excluded. The predicted functional impact of the variants was evaluated using the *in-silico* tools SIFT [12], PolyPhen-2 [13], MutationTaster [14] and CADD [15].

Sanger sequencing

Candidate variants were confirmed by Sanger sequencing when DNA was available. DNA was amplified by polymerase chain reaction using FastStart PCR Master Mix (Roche Diagnostics Corp., Risch-Rotkreuz, Switzerland) and sequenced with BigDye terminator version 3.1 (Applied Biosystems, Foster City, CA, USA) sequencing chemistry in an ABI3730XL genetic analyzer as per manufacturer's instructions. Primers are available upon request. The sequences were analysed using Sequencher software version 4.2 (Gene Codes, Ann Arbor, MI, USA).

Results

Clinical and neurophysiological investigations

We studied a British family with eight affected individuals over three generations (Fig. 1), suggesting an autosomal-dominant inheritance pattern. A summary of symptoms and clinical signs in all affected family members can be found in Table 1.

Index case/IV:8

A 32-year-old woman with normal birth and developmental history had onset at the age of 6 years of writing difficulties, whereby she was noted to press the pen very hard on the paper. Moreover, bilateral hand tremor with superimposed fast jerks was noted, causing her to spill or throw things inadvertently.

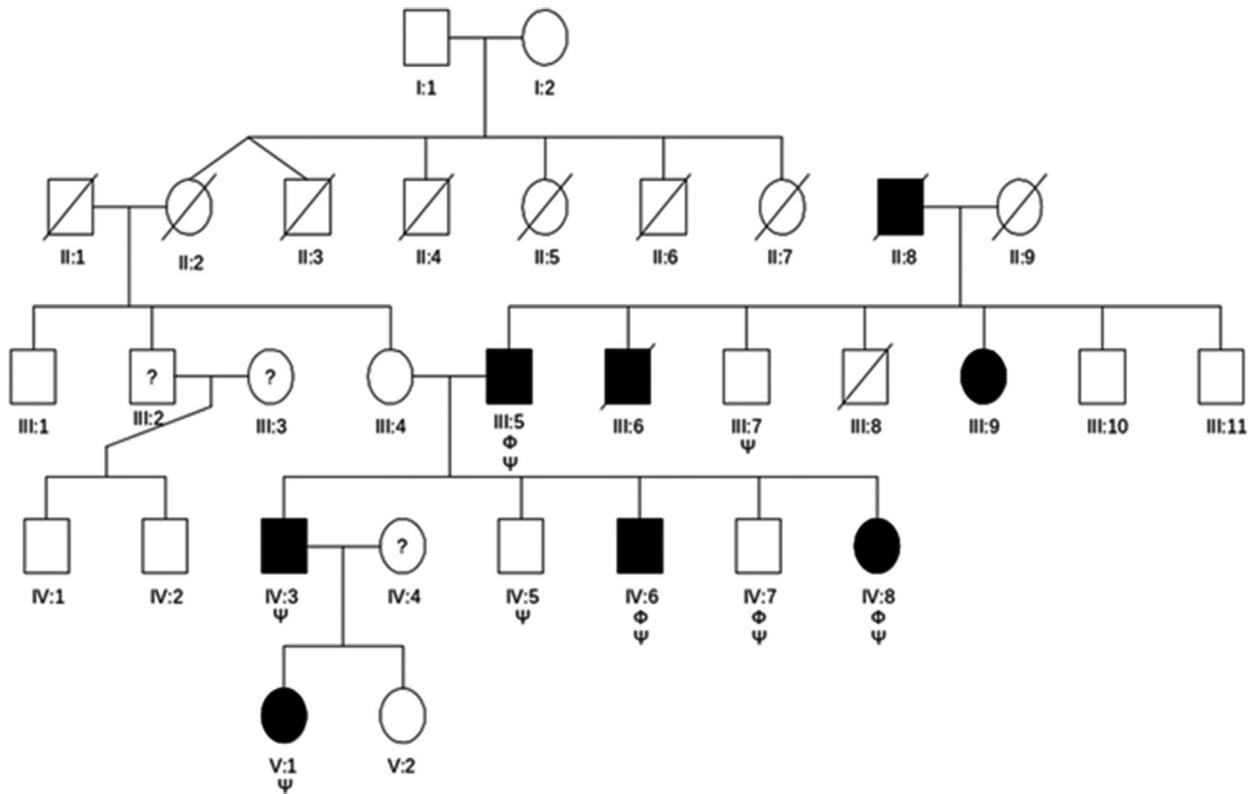


Figure 1 Pedigree of the British family with the *KCNN2* mutation. Only the NM_021614:c.1112G>A:p.(Gly371Glu) variant segregated with myoclonus-dystonia in this family. White represents unaffected individuals and black represents affected family members. Individual IV:8 is the index case. Φ, samples were whole exome sequenced with candidate variants in the three affected individuals, confirmed by Sanger sequencing when DNA was available. Ψ, Samples tested for segregation of *KCNN2*.

These symptoms initially worsened over the ensuing years but later plateaued. There was no diurnal fluctuation. Early alcohol responsiveness was lost over time.

Past medical history was significant for anxiety disorder, right eye congenital ptosis, strabismus and amblyopia suggestive of Duane’s syndrome and polycystic ovaries.

On examination (Video S1), she had torticollis to the right, dystonic posturing of the hands (right more than left) and clear writer’s cramp. A high-frequency, low-amplitude tremor affected the hands, most prominently on action and posture. Superimposed on this were non-stimulus-sensitive, small-amplitude myoclonic jerks mainly affecting the hands and craniocervical region (neck, shoulders and face) and, rarely, the legs. Apart from the known congenital Duane’s syndrome (near-complete right-eye ptosis, amblyopia and abduction with a tendency to deviate upwards on lateral gaze to the right), broken pursuits and rotatory end-gaze nystagmus were noted. She had slight difficulty performing tandem gait. The remainder of the examination was normal. Treatment with Clonazepam 0.25 mg proved beneficial.

IV:6

Her brother, aged 35 years, was similarly, but more severely affected. His symptoms started at the age of 6 years and comprised hand and head tremor, jerks and balance problems. He needed a typewriter at school because of writing difficulties and had physiotherapy because of his balance problems. His mother recalled that he had difficulty standing on one leg. Trials of beta-blockers and levodopa were not beneficial. There was no alcohol responsiveness of his symptoms. Examination showed tremulous segmental dystonia with mild torticollis and bilateral hand posturing, a jerky tremor of the head and hands and superimposed, small-amplitude myoclonic jerks most notably in the hands. Additionally, he had broken pursuit eye movements and rotatory gaze-evoked nystagmus. He had mild in-turning of the feet with subtle toe extension and slight difficulties on tandem gait.

III:5

The father of the index case, aged 63 years at examination, presented around the age of 12 years with

Table 1 Summary of the clinical information of affected family members

	IV:8 (index case)	IV:6	IV:3	V:1	III:5
Sex, age (years)	F, 31	M, 35	M, 39	F, 17	M, 63
Age at onset (years), first symptom	6, writer's cramp	5, hand and head tremor, jerks, balance problems	6, hand and head tremor	5, tremor and 'shivering jerks' of the hands	12, writing difficulties
Examination	Torticollis with occasional superimposed myoclonic jerks, dystonic hand posturing and writer's cramp; rest tremor with superimposed myoclonic jerks of the hands; high-frequency, small-amplitude postural tremor of the hands with superimposed distal > proximal myoclonus; tremor and myoclonus partly occurring in a 'shivering attack-like fashion'. Broken pursuit, rotatory end-gaze nystagmus. Congenital Duane's syndrome	Tremulous torticollis, rest tremor with superimposed myoclonic jerks of the hands, high-frequency small-amplitude postural tremor of the hands with superimposed distal > proximal myoclonus. Dystonic posturing of the hands; mild in-turning of the feet with striatal extension of the toes. Broken pursuit, hypermetric saccades, rotatory end-gaze nystagmus, mild difficulties with tandem gait	Dystonic posturing of the left hand, mild postural jerky tremor of both hands ^a	Tremor of head and hands ^a	Jerky hand tremor on posture and action with mild terminal component, mild hand posturing; borderline oculomotor abnormalities (broken pursuit)

^aNo data on eye movements for these individuals as eye movement examination was not feasible on video call. F, female; M, male.

writing difficulties due to cramping of his hand. Over the years, he developed shaking of his hands, but without any difficulties in his day-to-day life. On examination, he had mild asymmetric hand posturing with a jerky hand tremor on posture and action with mild terminal component and few superimposed, non-stimulus-sensitive jerks. There was also mild hand posturing, and mildly broken pursuit.

Neurophysiology

The EEG–electromyography polygraphic recording was performed in the index case. Bilateral frontocentral regions and right limb muscles (trapezius, biceps, extensor carpi radialis, first dorsal interosseus) were simultaneously recorded.

The patient was recorded for about 40 min. At rest and when attempting to move, she exhibited a 5–6-Hz tremor of her limb with superimposed jerks of >100 ms in duration. With the arms outstretched against gravity, there were no sudden interruptions of muscle activity. EEG jerk-locked back averaging was not performed due to muscular EEG artefacts. There were no electrophysiological features supporting the diagnosis of cortical myoclonus (i.e. burst duration, cranial-caudal progression, and both positive and negative myoclonus).

Genetic investigations

From the exome-sequencing data in the four individuals, no deleterious variants in the myoclonus-dystonia candidate genes *SCGE*, *KCTD17*, *ANO3*, *SCN8A*, *RELN*, *ADCY5* and *TITF1* were found to segregate in the family.

After Sanger sequencing validation and genotyping of an additional four family members, the only variant that we were able to identify as segregating with the phenotype in the family was *KCNN2* [NM_021614:c.1112G>A:p.(Gly371Glu)]. Individuals deemed unaffected who were tested did not carry the variant. The *in-silico* tools SIFT, PolyPhen-2 and MutationTaster predicted the variant as having a deleterious consequence. The high CADD score of 29.7 also suggested a damaging effect of the variant. Additionally, in the gnomAD database, there is a report of a single individual carrying a variant in the same position; however, the nucleotide change is not the same as in our family.

This novel variant occurs in an evolutionary conserved amino acid. As a result, a larger and negatively charged amino acid is introduced in the protein, which may lead to a disruption of the local structure. This variant appears to be located between transmembrane domains 6 and 7, closer to 7 (Fig. 2).

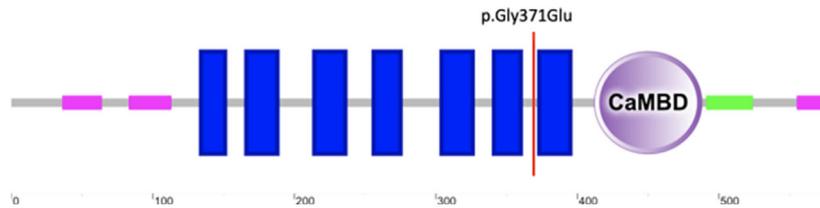


Figure 2 Schematic representation of *KCNN2* (NP_067627.2) domains. The red line represents the p.(Gly371Glu) mutation. Pink blocks represent low-complexity regions. Blue blocks represent transmembrane domains. Green block represents coiled coil region. CaMBD, calmodulin-binding domain. Adapted from https://smart.embl.de/smart/show_motifs.pl?ID=Q9H2S1. [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

We performed exome and Sanger sequencing in a UK kindred affected by autosomal-dominant myoclonus-dystonia and identified a missense variant in *KCNN2* [chr5:113798856:G>A in hg19, which translates to NM_021614:c.1112G>A:p.(Gly371Glu)] as the only variant segregating with the phenotype over three generations. Additionally, this variant, which is absent from the most recent version of gnomAD, was predicted to be deleterious by SIFT and PolyPhen, and obtained an overall CADD score of 29.7.

The phenotype consisted of tremulous dystonia predominantly affecting hands and neck, with superimposed myoclonus and subtle cerebellar eye signs. Onset was typically in infancy with writer's cramp and/or tremor, similar to other cases of non-SGCE myoclonus-dystonia [16]. The phenotype was different from the classic myoclonus-dystonia due to SGCE mutations, which consists of 'lightening' jerks mainly affecting the neck and arms, whereas here, myoclonus is more distal, sometimes occurring in a 'shivering-like fashion'. Different to classic SGCE-dystonia there are also cerebellar eye signs to variable degrees, ranging from mildly broken pursuit to end-gaze nystagmus. There was some intrafamilial variability regarding severity of symptoms, ranging from no problems with activities of daily living to the requirement for medical treatment, physiotherapy and other aids in younger years. Nonetheless, in adulthood there were no major limitations to their professional or private life.

The gene *KCNN2* is a member of the KCNN family of potassium channel genes and is located on 5q22.3. It is encoded by eight exons, with four intron–exon junctions within the core domain and three intron–exon boundaries at the C-terminus of the hSK2 channel sequence [17]. It shows a high degree of conservation across species [17,18]. In humans, it is strongly expressed in the liver and brain (particular the cerebellum, caudate nucleus and hippocampus) [19]. There are four different SK2 channel isoforms (SK2-std, SK2-long, SK2-ssv and SK2-hib) in the human brain

[20] with important roles in the regulation of neuronal excitability and modulation of spike-firing frequency and calcium transients in dendritic spines [21].

KCNN2 mutations have not previously been described in human neurological disease, but are described as underlying abnormalities in two rodent models of tremor. The 'tremor-dominant Kyoto rats' have a phenotype consisting of a rapid tremor with superimposed myoclonic jerks (very similar to our patients), which is caused by autosomal dominant missense mutations (c. 866T>A, p. I289N) in *KCNN2* [22]. *In-silico* prediction of pathogenicity with PROVEAN software indicated the I289N mutation to be deleterious [22]. Furthermore, *in-vitro* experiments with I289N mutant *KCNN2* HEK cells showed a significant reduction of K⁺ currents [22]. The mouse 'frissonnant' mutant phenotype is caused by recessively inherited deletions, disrupting both the first and second coding exons of the *KCNN2* gene, resulting in a truncated, non-functional protein [23]. Expression studies showed complete absence of normal *Kcn-n2* transcripts but abnormal truncated variants in the brain of animals. Intracellular electrophysiological recordings of brain slices revealed permanent alterations of the after-hyperpolarization and firing behaviour of neurons [23]. The frissonnant mutation occurred spontaneously in the stock of C3H mice of the Pasteur Institute in Paris. 'Frisonnant' is French for shuddering and the mice show a constant rapid tremor [23,24].

These rodent models would lend further support to the notion that the identified missense mutation in *KCNN2* is indeed pathogenic. Alongside phenotypic similarities (tremor, myoclonus), both animal models and patients show normal brain morphologies (brain pathology in mice [22]; brain magnetic resonance imaging in patients).

KCNN2 seems a biologically plausible candidate gene to explain the neurological signs in this kindred. The predominant cerebellar gene expression correlates well with the observed subtle clinical cerebellar signs. In addition, the role of the cerebellum in the

pathophysiology in dystonia is becoming increasingly evident [25,26].

The present study has some limitations. We were not able to confirm *KCNN2* mutations in other kindreds with myoclonus-dystonia (screening included a cohort of 28 SGCE-negative myoclonus-dystonia cases), which may indicate that *KCNN2* mutations are a rare cause of tremulous myoclonus-dystonia, and functional data, e.g. patch-clamp experiments, are lacking. However, segregation, absence of the variant in the normal population and *in-silico* prediction of a deleterious effect together with animal models compatible with the clinical phenotype are all in line with *KCNN2* mutations being a plausible causative gene underlying myoclonus-dystonia. So far, there has been only one publication about the possible role of *KCNN2* mutations in human disease. Raghuram *et al.* [27] described a heterozygous variant in *KCNN2* and homozygous variants in *ZNF135* in a patient with progressive spastic ataxia with epilepsy. Functional studies of that *KCNN2* variant, a single nucleotide duplication leading to a translational frame shift and a premature stop codon, in HEK cells and a knock-in mouse model suggested that this particular *KCNN2* variant was not causative for the phenotype, but the *ZNF135* mutations.

In summary, further research with screening in larger cohorts will be needed to investigate the role of *KCNN2* in human neurological disease and to establish the full clinical spectrum. We hope that our report will encourage other investigators to search for *KCNN2* mutations in their kindreds. The availability of an animal model of this genetic disorder is fortuitous and may provide an opportunity to test novel treatment strategies.

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University Press, 2017). He has received honoraria/personal compensation for participating as a consultant/scientific board member from Ipsen, Allergan and Merz, and honoraria for speaking at meetings and from Allergan, Ipsen, Merz, Sun Pharma, Teva, UCB Pharmaceuticals, American Academy of Neurology and International Parkinson's Disease and Movement Disorders Society.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. The index case, individual IV:8. She has dystonic posturing of the hands and torticollis to the right. She has a high-frequency, small-amplitude tremor with superimposed jerks affecting the hands more than the neck. Eye movement examination reveals broken pursuit and a subtle rotatory gaze-evoked nystagmus, alongside congenital Duane's syndrome with limitation of abduction and narrowing of the palpebral fissure of the right eye.

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