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Clinical letter

# Progressive myoclonus epilepsy caused by a gain-of-function *KCNA2* mutation

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## 1. Introduction

We describe the novel phenotypic features of an adult male patient carrying a p.Arg297Gln (c.890G > A) mutation of the *KCNA2* gene encoding the voltage-gated potassium channel KV1.2. This mutation has been previously reported in patients presenting with epileptic encephalopathy (MIM # 616366) and early-onset polymorphic seizures [1–3] but, unlike the other cases, the clinical aspects of our patient included prominent and worsening action myoclonus consistent with progressive myoclonus epilepsy (PME).

## 2. Case report

The patient was born to healthy, non-consanguineous parents after a physiological pregnancy, and his early physical and psychomotor development was normal. He started walking at the age of 14 months but appeared to be clumsy; his speech was slurred, and the movements of mainly his upper limbs became jerky. His first tonic seizure occurred at the age of three years. He started treatment with valproate but continued to experience rare generalised seizures, occasionally elicited by intermittent photic stimulation during EEG. The movement disorder slowly worsened, but he maintained an independent gait and fulfilled many tasks at home. He attended school with support, but never got a job.

The results of various laboratory diagnostic tests were normal, including blood acanthocytes, organic acids, very long-chain fatty acids, hexosaminidase A activity, and screening of the *CSTB*, *EPM2A*, *NHLRC1, PRICKLE1*, *LASS1*, *KCDT7*, *NEU1*, *SCARB2* and *DRPLA* genes. Furthermore, analysis of the genes involved in hereditary ataxia (*SCA1, SCA2* and *SCA28*) showed that they were wild-type.

## 3. Neurophysiological findings and neuroimaging

We first observed the patient when he was 22 years old. EEG revealed slow background activity, rare spikes on the posterior derivations, and bilateral spikes during light sleep. Intermittent photic stimulation at 1 Hz triggered occipital spikes with 1:1 responses (Fig. 1A–C), and a polygraphic recording revealed a particular movement disorder characterised by the co-existence of 6 Hz tremor during posture maintenance and irregularly repetitive myoclonic jerks during active hand movements (Fig. 1D). Jerk-locked back averaging analysis of the jerks recorded on the right wrist extensor (130 epochs) showed an EEG transient on the left centro-parietal EEG channels whose positive peak preceded the averaged jerks by 20–22 ms (Fig. 1F). Somatosensory evoked potentials showed greater N20-P25 amplitude ( = 18 μV; normative values: 3.15 ± 2.9 μV) and increased central conduction time (N20 latency: 27.5 ms; N13-N20: 14 ms) (Fig. 1E). The results of an ophthalmological examination and retinal optical coherence

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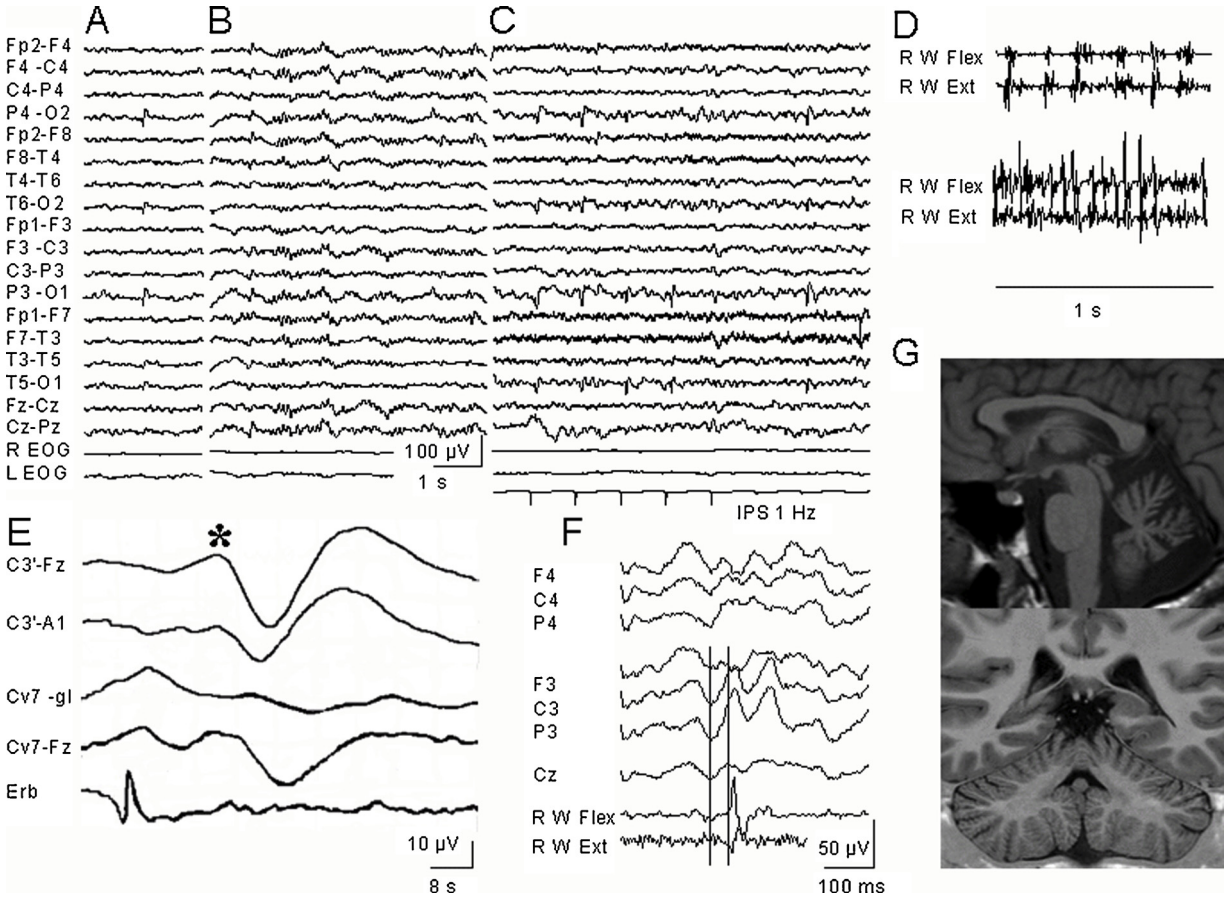


**Fig. 1. A–C**: EEG epochs during wakefulness, light sleep, and intermittent photic stimulation (IPS) at 1 Hz. **D**: Epochs of EMG traces during active muscle contraction showing bursts related to tremor (top) and myoclonic jerks (bottom). **E**: Traces of somatosensory evoked potentials: the asterisk indicates the N20 wave. **F**: Jerk-locked back averaging: the vertical lines indicate the delay between the EEG positive peak and the onset of the averaged jerk (about 20 ms). **G**: Sagittal T1-wi and coronal inversion recovery brain MRI scan recorded at the age of 22 years and showing mild cerebellar atrophy mainly of the vermis.

tomography were normal. Brain MRI revealed mild cerebellar atrophy associated with cisterna magna (Fig. 1G).

Suspecting a genetic cause of the disease, we analysed the patient's DNA by NGS panel customised for epileptic encephalopathies and PME and found a *de novo* heterozygous mutation p.Arg297Gln (c.890 G > A) in the *KCNA2* gene. This missense variant is included in the human database (rs786205232), but SIFT and PolyPhen scores predict it plays a pathogenic role (http://sift.jcvi.org/; http://genetics.bwh.harvard.edu/pph2/). The analysis did not reveal any other significant variant.

## 4. Discussion

This is the first description of a case of PME caused by a heterozygous gain-of-function c.890C > A mutation in *KCNA2*. The mutation leads to the amino acid substitution p.Arg297Gln, which involves the second of the critical arginine residues in the S4 voltage sensor of the voltage-gated potassium channel KV1.2. The previously described phenotype in seven patients bearing the same mutation includes recurrent seizures at onset, cognitive impairment and ataxia. [3] Like these subjects, our patient showed ataxia and psychomotor delay, whereas epilepsy was delayed and limited to relatively rare seizures that were associated with prominent cortical myoclonus consistent with PME.

PMEs are genetically heterogeneous, but share the common symptoms and signs of cortical myoclonus, seizures and ataxia; their neurophysiological features include the presence of EEG spikes, photoparoxysmal responses, and often-increased SEP amplitude, all of which were also observed in our patient. Moreover, central conduction slowing in our patient is also seen in the case of other forms of PME, including the later stages of classical Unverricht-Lundborg disease.

Mutations in other potassium channels are known to cause PME. An Arg320His mutation in *KCNC1* causes a PME similar to Unverricht-Lundborg disease, and homozygous mutations in *KTCD7* first described in a large consanguineous Moroccan family with PME were subsequently confirmed in other families of various ethnic origins. Table 1 shows all of the different forms of PME associated with potassium channelopathy.

The potassium channel dysfunctions involved in the other PME phenotypes have been demonstrated by studies aimed at characterising mutated *KCNC1* and *KTCD7*. [4] It can be assumed that the c.890 G > A mutation in the *KCNA2* channel (a member of the delayed rectifier class of potassium channels) leads to a gain of function by greatly increasing the potassium current and shifting its activation to more hyperpolarised potentials. The effect of the increased neuronal excitability is currently unclear, [4] but it may involve complex local mechanisms or circuitry rearrangements such as those leading to changes in channel inactivation at nearly resting potentials in excitatory neurons or a decrease in the excitability of inhibitory neurons.

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**Table 1**
Comparison of the forms of PME associated with *KCNA2*, *KCNC1*and *KTDC7* mutations.

| Characteristics | KCNA2 (our patient) | KCNC1 | KTDC7 |
|---|---|---|---|
| Disease onset | 14 months | 3–15 years | 0.5-3 years |
| Ataxia | Present | Always reported | Nearly always reported |
| Myoclonus | Present | Always reported | Seen in > 50% of cases |
| Cognitive decline | Mild–moderate | Mild or absent | Severe |
| Mode of inheritance | Autosomal dominant, *de novo* | Autosomal dominant, usually *de novo* (specific mutation) | Autosomal recessive |
| Seizures | Rare | Variable frequency | Very frequent |
| | | Oliver et al, 2017[a] | Van Bogaert, 2016[b] |

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