V374A KCND3 Pathogenic Variant Associated With Paroxysmal Ataxia Exacerbations

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Abstract

Objective
Ataxia channelopathies share common features such as slow motor progression and variable degrees of cognitive dysfunction. Mutations in potassium voltage-gated channel subfamily D member 3 (KCND3), encoding the K+ channel, Kv4.3, are associated with spinocerebellar ataxia (SCA) 19, allelic with SCA22. Mutations in potassium voltage-gated channel subfamily C member 3 (KCNC3), encoding another K+ channel, Kv3.3, cause SCA13. First, a comprehensive phenotype assessment was carried out in a family with autosomal dominant ataxia harboring 2 genetic variants in KCNC3 and KCND3. To evaluate the physiological impact of these variants on channel currents, in vitro studies were performed.

Methods
Clinical and psychometric evaluations, neuroimaging, and genotyping of a family (mother and son) affected by ataxia were carried out. Heterozygous and homozygous Kv3.3 A671V and Kv4.3 V374A variants were evaluated in Xenopus laevis oocytes using 2-electrode voltage-clamp. The influence of Kv4 conductance on neuronal activity was investigated computationally using a Purkinje neuron model.

Results
The main clinical findings were consistent with adult-onset ataxia with cognitive dysfunction and acetazolamide-responsive paroxysmal motor exacerbations in the index case. Despite cognitive deficits, fluorodeoxyglucose (FDG)-PET displayed hypometabolism mainly in the severely atrophic cerebellum. Genetic analyses revealed the new variant c.1121T>C (V374A) in KCND3 and c.2012T>C (A671V) in KCNC3. In vitro electrophysiology experiments on Xenopus oocytes demonstrated that the V374A mutant was nonfunctional when expressed on its own. Upon equal co-expression of wild-type (WT) and V374A channel subunits, Kv4.3 currents were significantly reduced in a dominant negative manner, without alterations of the gating properties of the channel. By contrast, Kv3.3 A671V, when expressed alone, exhibited moderately reduced currents compared with WT, with no effects on channel activation or inactivation. Immunohistochemistry demonstrated adequate cell membrane translocation of the Kv4.3 V374A variant, thus suggesting an impairment of channel function, rather than of expression. Computational modeling predicted an increased Purkinje neuron firing frequency upon reduced Kv4.3 conductance.

Conclusions
Our findings suggest that Kv4.3 V374A is likely pathogenic and associated with paroxysmal ataxia exacerbations, a new trait for SCA19/22. The present FDG PET findings contrast with a previous study demonstrating widespread brain hypometabolism in SCA19/22.

*These authors contributed equally to this work.

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Heterozygous mutations in potassium voltage-gated channel subfamily D member 3 ( KCND3), encoding the voltage-dependent potassium channel Kv4.3, are associated with spinocerebellar ataxia (SCA) 19, allelic with SCA22.1–3 So far, only 10 articles describing patients with SCA19/22 have been published.2–10 The phenotype is variable and includes, besides ataxia, other movement disorders, variable degrees of cognitive impairment and epilepsy.1–10 The only fluorodeoxyglucose (FDG) PET study on SCA19 demonstrated widespread hypometabolism.9 Genetic variants in KCND3 are also associated with cardiac arrhythmia and sudden unexpected death (SUD).6,13,12

Functional analyses of some of the KCND3 mutations demonstrated either channel dysfunction or reduced cell membrane trafficking.2–5,10,13 These abnormalities are often attenuated by co-expression of potassium channel interacting protein 2 (KChIP2).4,5,10,12 Here, we report 2 members of a family affected by ataxia and intellectual disability associated with the new V374A variant in KCND3. In addition, the index case suffered from paroxysmal ataxia exacerbations responsive to acetazolamide (ACZ). Our results demonstrate a downsizing of current upon co-expression of wild-type (WT) Kv4.3 with the V374A mutant compared with WT Kv4.3 expressed alone, suggesting a decreased expression of functional channels in the membrane.

**Methods**

Both patients provided written and oral consent to this study approved by the ethical committee in Stockholm. Clinical assessment included examination with Scale for Assessment and Rating of Ataxia, Index of Non-Ataxia Symptoms, psychometric testing, and neuroimaging. Neuroimaging included MRI and 18F-FDG PET, whereas psychometric evaluation included a comprehensive test battery (e-Methods, links.lww.com/NXG/A348). The index case was investigated with massive parallel sequencing and candidate variants verified with Sanger sequencing. Injection of complementary RNA encoding channel subunits into Xenopus laevis oocytes and subsequent oocyte voltage-clamp recordings were performed as described previously.14 Finally, a computational analysis of the mutational effects of Kv4.3 channels on a Purkinje neuron model was performed using the program NEURON7.7,15,16 Briefly, this model incorporates resurgent and nonresurgent Nav channels, Kv1, Kv3, Kv4 channels, P-type calcium channels, calcium-activated Kv channels, hyperpolarization-activated cation channels, and leak currents (e-Methods).

**Immunocytochemistry**

HEK293T cells were transfected according to previous descriptions,2,3 the mean fluorescence density of Alexa Fluor 633 of whole cell body, membrane (Fm), and cytoplasm (Fc), and the Fm/Fc ratio was calculated (e-Methods, links.lww.com/NXG/A357).

**Data Availability**

Anonymized data will be shared by the investigators upon request.

**Results**

**Clinical Findings**

Two patients, mother and son, in a Swedish family were diagnosed with adult-onset slowly progressive cerebellar ataxia and bradyphrenia (figure e-1, links.lww.com/NXG/A348). Both patients were also diagnosed with learning difficulties (table 1) and have attended special schools. Common features for these patients include normal general intellectual ability despite low results in cognitive screening tests. Low performance in the following cognitive domains was evident in both patients: information processing speed, visuo-spatial episodic memory, spatial/visual construction, verbal concept formation, phonemic word fluency, and executive function (table 2). Despite these deficits, IQ scores were 90 and 95, respectively. The index case (II:1) is a 35-year-old man who suffered from paroxysmal ataxia exacerbations when exposed to accelerations/decelerations, such as when riding an elevator, bus, or train. These episodes, witnessed in 2 occasions by 2 of the authors (J.W. and M.P.), were responsive to ACZ. Patient II:1 was also treated with clonazepam and mesalazine, and the latter was for ulcerative colitis. Patient I:1 (62 years old) was not treated with any psychotropic drugs. Cerebellar atrophy was severe in the index case and milder in patient I:1; in both cases, FDG PET demonstrated moderate-to-severe hypometabolism in the cerebellum (vermis and upper cerebellar hemispheres) and subtle hypometabolism in the prefrontal cortex (figure e-2, links.lww.com/NXG/A349). We did not find evidence of parkinsonism, epilepsy, polyneuropathy, cardiac signs, or arrhythmias.

**Genetic Analyses**

Pathologic CAG expansions associated with SCA 1, 2, 3, 6, 7, dentatorubropallidoluysian atrophy as well as copy number variations were ruled out in the index case. Both patients carry the variants c.1121T>C (V374A) in KCND3 and c.2012T>C (A671V) in potassium voltage-gated channel subfamily C

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**Glossary**

ACZ = acetazolamide; Fc = fluorescence density of Alexa Fluor 633 cytoplasm; FDG = fluorodeoxyglucose; Fm = fluorescence density of Alexa Fluor 633 membrane; GOF = gain of function; KCNC3 = potassium voltage-gated channel subfamily C member 3; KCND3 = potassium voltage-gated channel subfamily D member 3; KChIP2 = potassium channel interacting protein 2; LOF = loss of function; SCA = spinocerebellar ataxia; SUD = sudden unexpected death; WT = wild-type.
member 3 (KCNC3). The variant c.1121T>C (V374A) in KCND3 has not been reported before, whereas c.2012T>C (A671V) in KCNC3 has a minor allele frequency = 0.00016% in the European population (e-Methods, links.lww.com/NXG/A357). Heterozygous variants in KCNC3 are associated with SCA13; therefore, we hypothesize a synergistic effect of the 2 K+ channel variants.

**In Vitro Studies**

**Kv4.3 V374A Disrupts Potassium Conductance**

Oocytes injected with complementary RNA encoding Kv4.3 + KChIP2 (WT:V374A, 1:0) exhibited peaked currents with swift N-type inactivation (figure 1A), consistent with previous descriptions of Kv4.3 currents.17 Cells expressing Kv4.3 + Kv4.3 V374A + KChIP2 (WT:V374A, 0.5:0.5) showed smaller currents maintaining the peaked character without shifting the voltage dependence of channel activation (figure 1B) or inactivation (figure e-3, links.lww.com/NXG/A350). In cells expressing Kv4.3 V374A + KChIP2 (WT:V374A, 0:1) alone, virtually no voltage-dependent currents were observed (figure 1C). WT:V374A, 0.5:0.5 demonstrated an average peak current reduction of ~80% as compared to WT:V374A, 1:0 (figure 1D). A simple scaling effect suggests a reduction of functional Kv4.3 channels in the membrane, with no effect of the V374A mutation on conductance or inactivation curves (figure e-3). Conversely, expression of Kv3.3 + A671V (WT: A671V, 0:1:0.5) resulted in currents similar to those of cells expressing Kv3.3 WT (WT:A671V, 1:0) alone, whereas Kv3.3 A671V (WT:A671V, 0:1) alone exhibited slightly reduced currents compared with WT (figure e-4, links.lww.com/NXG/A351). Again, for A671V, no effects were observed on activation or inactivation curves (figure e-5, links.lww.com/NXG/A352). Application of 100 μM ACZ to oocytes expressing Kv4.3 + Kv4.3 V374A, 1:0, 0.5:0.5, or 0:1, respectively, did not modify the currents (data not shown).

**Kv4.3 Channel Modulates Purkinje Neuron Excitability**

The effect of reducing the number of functional Kv4.3 channels on neuronal excitability was analyzed using a Purkinje neuron model incorporating Kv1, Kv3, and Kv4 channels.15 Based on the similar kinetic properties of Kv4.3 + Kv4.3 V374A, 1:0 and 0.5:0.5, the maximum Kv4 conductance (Kv4 bar) was reduced according to the I-V relationships (figure 1D). In contrast to the WT:V374A, 1:0, the WT: V374A, 0.5:0.5 model demonstrated lower action potential amplitudes and higher firing frequency, indicating modified excitability properties (figure e-6A, links.lww.com/NXG/A353). Action potential slope analysis corroborated the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The Main Features in Both Patients Are Ataxia and Intellectual Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotype features</strong></td>
<td><strong>II:1 (index case)</strong></td>
</tr>
<tr>
<td>axial ataxia</td>
<td>Y</td>
</tr>
<tr>
<td>dysarthria</td>
<td>Y</td>
</tr>
<tr>
<td>age at ataxia onset/current age, y/sex</td>
<td>25/35/M</td>
</tr>
<tr>
<td>reflexes</td>
<td>normal</td>
</tr>
<tr>
<td>cognitive impairment</td>
<td>Y</td>
</tr>
<tr>
<td>impaired smooth pursuit/ nystagmus</td>
<td>Y/Y</td>
</tr>
<tr>
<td>other features</td>
<td>paroxysmal ataxia exacerbation; increased muscle tone in legs</td>
</tr>
<tr>
<td>SARA score at last examination</td>
<td>13</td>
</tr>
<tr>
<td>EEG</td>
<td>slow activity in the temporo-parietal regions</td>
</tr>
<tr>
<td>ENeG</td>
<td>normal</td>
</tr>
<tr>
<td>MRI of the brain</td>
<td>marked cerebellar atrophy (vermis and superior part of the cerebellar hemispheres)</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>cerebellar hypometabolism; subtle hypometabolism in prefrontal cortex</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>normal</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>ulcerative colitis</td>
</tr>
</tbody>
</table>

Abbreviations: ENeG = electroneurography; KCND3 = potassium voltage-gated channel subfamily D member 3; SARA = Scale for the Assessment and Rating of Ataxia. Range or SARA score is 0–40 points (>3 points indicate ataxia). This syndrome is associated with the novel c.1121T>C (V374A) in KCND3. \(^a\) Treated with metformin and enalapril.
dynamic differences induced by WT:V374A, 0.5:0.5, with a slower increase in voltage for the reduced amplitude action potentials (figure e-6B). The firing frequency was increased 2.9-fold by WT:V374A, 0.5:0.5, compared with 1:0, and detailed analysis of peak amplitudes revealed a 22 mV reduction for 0.5:0.5 (figure e-6, C and D). Also, peak width and hyperpolarization were increased for WT:V374A, 0.5:0.5 (figure e-6, E and F).

Immunohistochemistry
HEK293T cells transiently transfected to express Kv4.3 WT:V374A, 1:0, 0.5:0.5, and 0:1, separately, displayed a high level of Kv4.3 protein at the cell surface. The Fm/Fc ratio of Kv4.3 WT protein remained at a similar level with or without Kv4.3 V374A (figure e-7, links.lww.com/NXG/A354).

Discussion
Paroxysmal ataxia exacerbations responsive to ACZ and the KCND3 variant V374A are new findings for SCA19. Hypometabolism limited to the cerebellum is unexpected, considering the range of cognitive deficits in this family. These findings contrast with the widespread brain hypometabolism in another SCA19 family.9 In our studies, the failure of the Kv4.3 V374A mutant to produce appreciable Kv4.3 currents when expressed alone, along with the conservation of WT channel kinetic properties in the face of a downscaling of current amplitudes, suggests a reduction of functional WT Kv4.3 channels in the membrane upon co-expression with the mutant channel. Our findings neither support a synergistic effect between Kv4.3 V374A and Kv3.3 A671V. However, some caution is required since heterologous expression systems such as Xenopus oocytes may not completely mirror mammalian expression and/or trafficking of ion channels.

Kv4 channels are made of up 4 alpha subunits (figure e-8, links.lww.com/NXG/A355)19; thus, incorporation of mutant subunits that are incompatible with channel function can be expected to decrease the number of functional channels by more than 50% (i.e., a dominant-negative effect).20 The Kv4.3 V374A variant is located in the pore loop between transmembrane helices S5 and S6 near the selectivity filter; the part of the protein forming the ion conduction pathway, crucial to the channel’s ability to pass current. Of interest the majority of the 13 reported pathogenic variants in KCND3 associated with SCA19 are located in the pore loop or in the nearby extracellular ends of S5 and S6 (figure e-6, links.lww.com/NXG/A353). Judging by our immunohistochemistry data, V374A appears to be localized to the cell membrane, contrary to other pathogenic KCND3 variants.2,3 Despite the relatively conservative amino acid substitution, the V374A variant reduced Kv4.3 peak currents by ~81% when co-expressed at a

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**Table 2** Summary of Cognitive Features in 2 Patients From a Family With SCA19 Associated With the Novel Pathogenic Variant V374A in KCND3

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Neuropsychological test</th>
<th>I:1 At age 63 (z score)</th>
<th>I:1 At age 35 (z score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief cognitive status examination</td>
<td>MoCA</td>
<td>12/30 (−7.0)a</td>
<td>21/30 (−2.91)a</td>
</tr>
<tr>
<td>General intellectual ability IQ</td>
<td>Ravens progressive matrices</td>
<td>19 (−0.67); IQ = 90</td>
<td>36 (−0.33); IQ = 95</td>
</tr>
<tr>
<td>Verbal episodic memory</td>
<td>RAVLT learning</td>
<td>14 (−4.72)a</td>
<td>40 (−0.83)</td>
</tr>
<tr>
<td>Visuo-spatial episodic memory</td>
<td>ROCFT (delayed recall)</td>
<td>2 (&lt;−3)a</td>
<td>10.5 (&lt;−3)a</td>
</tr>
<tr>
<td>Working memory</td>
<td>Digit span/WAIS-III</td>
<td>4 (−2.33)a</td>
<td>9 (−1.67)a</td>
</tr>
<tr>
<td>Spatial/visual construction</td>
<td>ROCFT copy</td>
<td>3.5 (−8.44)a</td>
<td>19.5 (−4.30)a</td>
</tr>
<tr>
<td>Verbal concept formation</td>
<td>Similarities/WAIS-III</td>
<td>8 (−2.0)a</td>
<td>13 (−1.67)a</td>
</tr>
<tr>
<td>Phonemic word fluency</td>
<td>COWAS/FAS</td>
<td>7 (−1.65)a</td>
<td>11 (−2.29)a</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>SDMT</td>
<td>16 (−3.56)a</td>
<td>19 (−5.41)a</td>
</tr>
<tr>
<td>Executive function</td>
<td>TMT B</td>
<td>200 (−3.0)a</td>
<td>394 (−14.0)a</td>
</tr>
<tr>
<td>Motor speed</td>
<td>FT dominant hand</td>
<td>5 (−3.98)a</td>
<td>44 (−0.95)</td>
</tr>
<tr>
<td></td>
<td>FT nondominant hand</td>
<td>22 (−1.39)</td>
<td>35 (−2.18)a</td>
</tr>
</tbody>
</table>

Abbreviations: COWAT = Controlled Oral Word Association Test; FAS = the letters used in the phonological word fluency test; FT = Finger-tapping test; FT = Finger-tapping test; KCND3 = potassium voltage-gated channel subfamily D member 3; MoCA = Montreal cognitive assessment; RAVLT = Rey Auditory Verbal Learning Test; ROCFT = Rey-Osterrieth Complex Figure Test; SCA = spinocerebellar ataxia; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; WAIS-III = Wechsler Adult Intelligence Scale, third edition.

* A z score <−1.5 SD is compatible with a significant deficit.
0.5:0.5 ratio with WT Kv4.3 subunits, consistent with a dominant-negative effect. In comparison, the SCA19/22-associated Kv4.3 T352P variant, in the presence of 1:1 KChIP2, has been suggested to reduce the peak current by 52%.13 Of interest the adjacent pathogenic variant Kv4.3 M373I, also in the presence of KChIP2, did not affect the expression level in oocytes as measured by current amplitudes.13 Given its critical location, it may be that the V374A mutation perturbs the ability of the channel to conduct potassium ions.

KCND3 mutations are also associated with arrhythmia and SUD. We hypothesize that gain-of-function (GOF) variants, reported for SUD, mainly influence the cardiac action potential, whereas loss-of-function (LOF) variants, associated with SCA19/22, mainly modulate neuronal excitability. Purkinje neuron simulations with a 80% reduction of Kv4.3 channel conductance (e.g., 0.5:0.5, WT:V374A) demonstrated rapid firing, whereas corresponding simulations with only a slightly increased Kv4.3 channel conductance (103%; corresponding to GOF mutations) demonstrate reduced firing frequencies (and no firing with further increased Kv4 conductance). The increase in firing frequency following Kv4.3 inhibition is in line with previous pharmacologic and genetic experiments with dopamine21 and pyramidal neurons, respectively.22 By contrast, a ventricular cell model23 exhibited slightly shortened action potentials following ~80% reduction in the number of Kv4 channels, whereas a 50%–100% increase in Kv4 channels, corresponding to GOF variants, prolonged the action potentials substantially11 (figure e-9, links.lww.com/NXG/A356). Hypothetically, KChIP2 may be involved in regulating the Kv4.3 expression in pathologic conditions—for GOF (LOF) variants, reduced (increased) KChIP2 levels may decrease (increase) the number of Kv4.3 channels. Theoretically, such differences may explain why concomitant ataxia and arrhythmia have not been reported. Expression of KChIP2 has recently been demonstrated to modulate the balance between Kv4.3 and voltage-gated sodium channel 5 (Nav1.5).24 However, the GOF variant Kv4.3 L450F has been reported separately in a patient with Brugada syndrome25 and a patient with ataxia,4 illustrating the complexity in elucidating genotype-phenotype correlations for KCND3.

Although ACZ demonstrated clinical efficacy in the index case, no in vitro effects were observed on Kv4.3 V374A.
Instead, carbonic anhydrase inhibition by ACZ and subsequent pH reduction could indirectly modulate ion channels, thereby possibly mediating the therapeutic effect and attenuating paroxysmal ataxia exacerbations. Decreased neuronal excitability in numerous SCAs associated with LOF variants (SCA27—indirectly Nav1.6, SCA13—Kv3.3, and SCA6—Cav2.1) has been described.26 For Kv4.3 LOF, increased Purkinje neuron excitability was observed in the simulations. Based on this, evaluation of drugs reducing neuronal excitability, e.g., Nav channel blockers, in a Kv4.3 LOF model may provide further insights of therapeutic relevance.

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Appendix

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<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>Martin Paucar, MD, PhD</td>
<td>Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden</td>
<td>Patient care; study concept and design; analysis and interpretation of data; drafting and revising the manuscript</td>
</tr>
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<td>Richard Ågren, MD, PhD</td>
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<td>Immunohistochemistry; revising the manuscript</td>
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</tr>
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</tr>
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</tr>
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<td>Daniel Nilsson, PhD</td>
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<td>Obtaining and interpretation of genetic data; revising the manuscript</td>
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</tbody>
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References
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