

# Epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome in a European child with *KCNJ10* mutations: A case report

SAGE Open Medical Case Reports  
Volume 5: 1–6  
© The Author(s) 2017  
Reprints and permissions:  
sagepub.co.uk/journalsPermissions.nav  
DOI: 10.1177/2050313X17723549  
journals.sagepub.com/home/sco



Antigone Papavasiliou<sup>1</sup>, Katerina Foska<sup>1</sup>,  
John Ioannou<sup>1</sup> and Mato Nagel<sup>2</sup>

## Abstract

**Background:** Epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome is a multi-organ disorder that links to autosomal recessive mutations in the *KCNJ10* gene, which encodes for the Kir4.1 potassium channel. It is mostly described in consanguineous, non-European families.

**Case Report:** A European male of non-consanguineous birth, with early-onset, static ataxic motor disorder, intellectual disability and epilepsy, imitating cerebral palsy, presented with additional findings of renal tubulopathy, sensorineural deafness and normal neuroimaging leading to the diagnosis of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. The patient was heterozygous for two *KCNJ10* mutations: a missense mutation (p.R65C) that is already published and a not yet published duplication (p.F119GfsX25) that creates a premature truncation of the protein. Both mutations are likely damaging. Parental testing has not been performed, and therefore, we do not know for certain whether the mutations are on different alleles. This young man presents some clinical and laboratory features that differ from previously reported patients with epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome.

**Conclusion:** The necessity of accurate diagnosis through genetic testing in patients with static motor disorders resembling cerebral palsy phenotypes, atypical clinical features and noncontributory neuroimaging is emphasized.

## Keywords

Epilepsy, ataxia, sensorineural deafness, tubulopathy/seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance syndrome, *KCNJ10* gene, ataxic cerebral palsy

Date received: 9 February 2017; accepted: 7 July 2017

## Introduction

Identifying neurogenetic syndromes in patients who display static motor disorders resembling cerebral palsy, intellectual disability and seizures of undetermined etiology is challenging. A Swedish population-based study indicated that an estimated 40% of cerebral palsy cases without a specific etiologic diagnosis were of genetic origin.<sup>1</sup> Molecular genetic testing has facilitated diagnosis of neurogenetic disorders with phenotypes fulfilling criteria for cerebral palsy including the necessary criterion of absence of clinical or neuroradiological regression over time.<sup>2</sup> This testing is increasingly used in the assessment of atypical cerebral palsy cases, where brain magnetic resonance imaging (MRI) images are normal and in the ataxic and hypotonic subgroups. De novo point mutations were recently shown in ataxic cerebral palsy, and it has been suggested

that these findings could be relevant to other subtypes of cerebral palsy.<sup>3</sup>

Epilepsy, ataxia, sensorineural deafness, tubulopathy (EAST) syndrome, characterized by ataxia, developmental delay and epileptic seizures, in association with renal tubulopathy, sensorineural deafness and hypokalemic,

<sup>1</sup>Department of Pediatric Neurology, Pendeli Children's Hospital, Athens, Greece

<sup>2</sup>Laboratory for Molecular Diagnostics, Weisswasser, Germany

### Corresponding Author:

Antigone Papavasiliou, Department of Pediatric Neurology, Pendeli Children's Hospital, 8 Hippocrates Street, Palia Pendeli, 15236 Athens, Greece.

Email: theon@otenet.gr



**Table 1.** *KCNJ10* mutations identified on the reported patient.

Number	Transcript	Exon/intron	Codon	Protein	DNA	Zygoty
1	NM_002241.4	2	65	p.R65C (CGC>TGC)	c.193C>T	Heterozygous
2	NM_002241.4	2	119	p.F119GfsX25	c.297_354dup	Heterozygous

hypomagnesemic metabolic alkalosis, is a relevant example for this discussion. This syndrome links to autosomal recessive mutations in *KCNJ10* (potassium channel, inwardly rectifying subfamily J, member 10), which encodes the Kir4.1 potassium channel.<sup>4,5</sup> *KCNJ10* is expressed in the renal distal convoluted tubule, cochlear stria vascularis, brain glial cells and other tissues.

*KCNJ10* mutations have been described in five children as EAST syndrome<sup>6</sup> and as seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance (SeSAME) syndrome in five other children,<sup>7</sup> in essence referring to the same clinical entity. Most of these children came from consanguineous families of non-European origin. Although such diagnosis is likely to be very infrequent, it is important to recognize this syndrome in order to assure symptomatic management and inform the families of its static course.<sup>8</sup>

The aim of this article is to present a case report of a European male of non-consanguineous origin, with mutation of the *KCNJ10* and the features of EAST/SeSAME syndrome in comparison with the previously reported patients. The importance of identifying cerebral palsy imitators in those patients who display static motor disorders of undetermined etiology is stressed.

## Case report

A 14-year-old Greek male, born to healthy non-consanguineous parents, at term and without perinatal complications, was evaluated for uncontrolled epilepsy. He displayed generalized motor seizures at 3.5 months of age, eventually controlled by anticonvulsants. He showed developmental delay with head control at 4.5 months and ambulation at 19 months with a broad-based unsteady gait. He was diagnosed with ataxic cerebral palsy. In addition, he displayed a delay in speech and generalized learning difficulties at school. Tubulopathy was identified at the age of 8 years. Bartter syndrome was erroneously diagnosed at first. The patient received treatment with potassium gluconate, magnesium, spironolactone and indomethacin. At the same age, sensorineural deafness was detected and a hearing aid was used. At the start of his teenage years, this young man had infrequent secondarily generalized focal motor seizures unresponsive to several medication changes. At 14 years of age, he was a pleasant, cooperative teenager with mild intellectual disability and normal cranial nerve examination (II–XII), normal muscle strength in the upper and lower extremities, mild spastic hypertonia in the lower limbs, increased deep tendon

reflexes and bilateral Babinski signs. There was mildly decreased superficial sensation in the lower extremities and no disturbance of position sensation or vibration. Romberg sign was absent. His gait was broad based and slow and he was unable to walk in tandem. Examination for cerebellar signs revealed the absence of tremor and dysmetria, while rapid alternating movements were slow and uncoordinated, resulting in dysdiadochokinesis.

Wakefulness and sleep electroencephalogram (EEG) showed slow background rhythms and no epileptiform activity. Brain computed tomography (CT) and MRI were normal. Nerve conduction studies revealed mild abnormalities on two occasions without important differences between the two tests. The motor conduction velocities on the second measurement were 41.3 m/s for the right median nerve, 38.2 m/s for the right peroneal nerve and 40.8 m/s for the left peroneal nerve. The sensory conduction velocities were 38.6 m/s for the right median nerve, 42.9 m/s for the right ulnar nerve and 42.3 m/s for the right sural nerve. There were no other abnormalities in these electrophysiological studies. Laboratory tests showed normal serum vitamin E, B12, folic acid and plasma very-long-chain fatty acid (VLCFA).

The patient's epilepsy was fully controlled with topiramate and carbamazepine. At F/U, the ataxia remained stable, as was the spasticity, with independent home ambulation and need for support in the community. Episodic weakness appeared on many occasions, without evidence of electrolyte disturbance or clinically overt seizures, and this responded to adjustment of the anticonvulsants. Overall status was consistent with a static disorder of movement, with activity limitations, also associated with intellectual disability and epilepsy. Nevertheless, the unremarkable neuroimaging, the renal tubulopathy and sensorineural deafness, led us to obtain consent from the family to search for a neurogenetic syndrome, specifically for *KCNJ10* mutations associated with EAST syndrome. The patient was heterozygous for two *KCNJ10* mutations: a missense mutation (p.R65C) that is already published<sup>9</sup> and a not yet published duplication (p.F119GfsX25) that creates a premature truncation of the protein (Table 1). Both mutations are likely damaging. The missense mutation p.R65C has been also listed as disease causing in various databases including OMIM (Online Mendelian Inheritance in Man).<sup>10</sup> In addition, prediction software agrees. As for the truncating frameshift mutation p.F119GfsX25, it is noted that truncating mutations in particular when occurring at the beginning of the protein are most likely damaging. Prediction software agrees here too.

Parental testing has not been performed, and therefore, we do not know for certain whether the mutations are in different alleles, but this also seems quite likely as the missense mutation has already been described in a patient not harboring the additional duplication (and that the same mutation occurred twice is not impossible but very unlikely). This patient's static clinical course has been ascertained for the following 10 years.

## Discussion

This European male with *KCNJ10* mutations presented with an early onset, non-progressive disorder of movement and posture of central origin, causing activity limitations, developmental delay and seizures. In the absence of neuro-metabolic deviations, these symptoms satisfied the criteria for the initial diagnosis of ataxic cerebral palsy,<sup>2</sup> but further findings proved that this was a cerebral palsy imitator. It is likely that similar misdiagnoses occur as a result of genetic testing being generally expensive or unavailable worldwide. Clinicians should therefore be aware that many neuro-genetic syndromes exist with a phenotype resembling cerebral palsy and a static course.

This patient presented with the typical characteristics of EAST syndrome together with certain clinical and laboratory features that differ from previously reported patients with the EAST/SeSAME syndrome (Table 2). Clinical and laboratory heterogeneity in this syndrome has been reported even between family members sharing the same mutation with each other.

The young man referred to in this report came from non-consanguineous ancestry, contrary to publications that report on patients from consanguineous ancestry. For EAST syndrome, consanguinity was previously reported as follows: four patients from a Pakistani family,<sup>6</sup> one from Arabic parents,<sup>6</sup> one patient from an Algerian family, two siblings from Indian parents and one from Iranian parents.<sup>9</sup> For SeSAME syndrome, consanguineous families were reported from Afghanistan and Turkey.<sup>7</sup> In total, 11 out of the 22 reported patients were of consanguineous origin, 5 were of no consanguineous origin and for the remaining 5, no information was available. European ancestry is also rare among the reported patients.

Most of the reported patients had delayed psychomotor development and gait ataxia, as was the case with our patient. Some children were unable to walk in contrast to our patient who has maintained ambulation, albeit slow and unsteady. The nature of the syndrome's motor disorder has not been clearly demonstrated.<sup>8</sup> In some of the reported cases, there was cerebellar dysfunction, such as intention tremor<sup>7</sup> and dysdiadochokinesis.<sup>6</sup> The latter was present in our patient as well. Spasticity was also observed in our patient, contributing to gait instability. Spasticity was also described in one of the Scholl's patients.<sup>12</sup> The static clinical course of this patient is consistent with previous observations.<sup>8</sup> The

majority of the previously reported patients presented with generalized seizures and three had focal seizures. In our patient, both focal and generalized seizures were described. Most of the reported EEGs were unremarkable. Background abnormalities (as observed in the young man that we describe in this case report) and/or epileptiform activity were present in some reports. The clinical and EEG features of our patient point toward a symptomatic focal epilepsy presenting with focal or secondarily generalized seizures of early onset. Seizure onset in infancy has been observed in most literature reports. Nerve conduction velocities in both our patient and in a patient with SeSAME syndrome were reduced, but these were normal in the remaining reported cases.<sup>5,8</sup> In the case of the patient reported to within this article, no interpretation for the delayed nerve conduction velocities can be offered. However, peripheral nerve dysfunction is not a frequent finding in patients with EAST syndrome.

Renal ultrasound was normal in both our patient and the previously reported cases. Brain MRI was normal in our patient and in several of the reported cases. Nevertheless, MRI abnormalities in the cerebellum, the brainstem and the corpus callosum have been reported previously.<sup>7,8,11,12</sup> It is possible that with higher resolution MRI, abnormalities could be detected in those patients with unremarkable findings. The MRI findings that have been reported so far are subtle and of uncertain clinical significance<sup>7,8,11,12</sup> and do not allow for conclusions as to the type and extent of brain lesions induced by different *KCNJ10* mutations.

Different mutations in *KCNJ10* were identified in patients with EAST/SeSAME syndrome, as well as in our patient who is heterozygous for two different mutations. However, the lack of genetic testing of his parents does not allow for any conclusions to be drawn regarding the origin of these mutations, that is, whether these were de novo or inherited from his parents.

Table 3 shows the autosomal recessive *KCNJ10* mutations, identified in EAST/SeSAME syndrome and the respective references. The available reports describe many different spontaneous pathogenic mutations in *KCNJ10*. Most of these are homozygous,<sup>6,9,11–13,14,15</sup> but there are also heterozygous and compound heterozygous mutations.<sup>7,16</sup> Our patient has the same missense mutation (p.R65C) as patient 1, described in family 1 of Freudenthal et al.'s<sup>9</sup> report; this mutation is heterozygous, while Freudenthal et al.'s patient is homozygous. Clinical description of Freudenthal et al.'s patient is limited, but all the main features of the syndrome are present. In contrast to our patient, Freudenthal et al.'s patient is of consanguineous origin. Abdelhadi et al.<sup>15</sup> report that among the 14 different pathogenic mutations of *KCNJ10* published so far, the missense mutation c.194G>C, replacing arginine with proline at the position 65 in the protein structure (p.R65P), is the most frequent of all.

In summary, EAST/SeSAME syndrome should be considered in patients with renal tubular disorders in association with developmental delay, ataxia, epilepsy and sensorineural deafness. Neurogenetic syndromes may present as cerebral

**Table 2.** Clinical features of reported patients.

Reference	Patient number/sex	Ancestry	Consanguinity	Onset of seizures	Type of seizure	Developmental delay	Sensorineural deafness	Ataxia	Ability to walk independently	Ability to speak	Prematurity	Age at last follow-up (years)
Papavasiliou et al.	Index case/ male	Greece	No	Infancy—unspecified age	Generalized and focal	Yes	Yes	Yes	Yes	Yes	No	24
Scholl et al. <sup>7</sup>	444-1/female	Afghanistan	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	No	No	N/A	N/A
	632-1/N/A	Canada	No	Infancy—unspecified age	Generalized	Yes	Yes	Yes	N/A	N/A	N/A	N/A
	632-2/N/A	Canada	No	Infancy—unspecified age	Generalized	Yes	Yes	Yes	N/A	N/A	N/A	N/A
	404-1/N/A	Turkey	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	N/A	N/A	N/A	N/A
Bockenbauer et al. <sup>6</sup>	327-1/N/A	Great Britain	N/A	N/A	Generalized	Yes	Yes	Yes	N/A	N/A	N/A	N/A
	1-1/female	Pakistan	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	Yes	Speech delay	No	14.9
Kara et al. <sup>11</sup> Scholl et al. <sup>12</sup>	1-2/male	Pakistan	Yes	Infancy—unspecified age	Generalized and focal	Yes	N/A	Yes	No	Speech delay	No	9.0
	1-3/female	Pakistan	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	Yes	Speech delay	No	6.4
	1-4/female	Pakistan	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	Yes	Speech delay	No	4.6
	2-1/male	Arabia	Yes	Infancy—unspecified age	Generalized	Yes	Yes	Yes	No	Speech delay	No	3.0
Freudenthal et al. <sup>9</sup>	Male	N/A	No	Infancy—unspecified age	Generalized	Yes	Yes	Yes	No	Yes	N/A	N/A
	100-3/female	Somalia	N/A	Infancy—unspecified age	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A
	100-1/female	Somalia	N/A	Infancy—unspecified age	N/A	Yes	No	Yes	Yes	Yes	N/A	N/A
	100-2/male	Somalia	N/A	Infancy—unspecified age	N/A	Yes	No	Yes	Yes	Yes	N/A	N/A
Family 1	100-7/female	Somalia	N/A	Infancy—unspecified age	N/A	N/A	Yes	N/A	N/A	N/A	No	N/A
	1-1/male	Algeria	Yes	Infancy—unspecified age	N/A	v	Yes	Yes	N/A	N/A	N/A	N/A
	2-1/male	Afro-Caribbean	No	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A
	2-2/female	Afro-Caribbean	No	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A
Family 3	3-1/male	India	Yes	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A
	3-2/female	India	Yes	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A
Family 4	4-1/male	Iran	Yes	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A
			Yes	Infancy—unspecified age	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A

N/A: not available.

**Table 3.** *KCNJ10* gene mutations.

Reference	Patient number	Protein	DNA	Zygoty	Type of mutation	
Papavasiliou et al.	Patient 1	p.R65C (CGC>TGC)	c.193C>T	Heterozygous	Missense	
Scholl et al. <sup>7</sup>	Patient 444-1	p.F119GfsX25	c.297_354dup		Frameshift	
		p.T164I	c.491C>T	Homozygous	Missense	
	Patient 632-1	p.A167V	c.500C>T	Heterozygous	Compound missense	
		p.R297C	c.889C>T			
	Patient 632-2	p.A167V	c.500C>T	Heterozygous	Compound missense	
		p.R297C	c.889C>T			
Bockenbauer et al. <sup>6</sup>	Family 1	Patient 1-1	p.R199X	c.595C>T		
		Patient 1-2	p.R65P	c.194G>C	Homozygous	Missense
		Patient 1-3	p.R65P	c.194G>C	Homozygous	Missense
		Patient 1-4	p.R65P	c.194G>C	Homozygous	Missense
	Family 2	Patient 2-1	p.G77R	c.229G>C	Homozygous	Missense
		Boy, 8years old	R204H	N/A	Homozygous	N/A
	Kara et al. <sup>11</sup> Scholl et al. <sup>12</sup>	Patient 100-3	T57I	ACA>ATA	Homozygous	Missense
		Patient 100-1	T57I	ACA>ATA	Homozygous	Missense
		Patient 100-2	N/A	N/A	N/A	N/A
		Patient 100-7	T57I	ACA>ATA	Homozygous	Missense
Freudenthal et al. <sup>9</sup>	Family 1	Patient 1-1	p.R65C	c.193C>T	Homozygous	Missense
	Family 2	Patient 2-1	p.F75L	c.225T>G	Homozygous	Missense
		Patient 2-2	p.F75L	c.225T>G	Homozygous	Missense
	Family 3	Patient 3-1	c.775delG	p.V259fsX259	Homozygous	Frameshift
		Patient 3-2	c.775delG	p.V259fsX259	Homozygous	Frameshift
	Family 4	Patient 4-1	p.R297C	c.889C>T	Homozygous	Missense
Parrock et al. <sup>13</sup>	Patient 1	p.F75C	N/A	Homozygous	N/A	
	Patient 2	p.A167V	N/A	Homozygous	N/A	
	Patient 3	p.V91fsI97X	c.272delT	Homozygous	N/A	
	Patient 4	p.A167V	N/A	Homozygous	N/A	
Thompson et al. <sup>14</sup>	Patient 2	p.R65P	N/A	Homozygous	Missense	
	Patient 3	p.R297C	N/A	Homozygous	N/A	
Reichold et al. <sup>16</sup>	Patient 1	p.R65P	c.194G>C	Heterozygous	N/A	
	Patient 2	p.G77R	c.229G>C	Homozygous	N/A	
	Patient 3	p.R175Q	c.524G>A	Homozygous	N/A	
	Patient 4	p.R199X	c.595C>T	Heterozygous	N/A	
Abdelhadi et al. <sup>15</sup>	Family 7	Patient 12	p.R65P	c.194G>C	Homozygous	Missense

N/A: not available.

palsy imitators, and therefore, patients should be genetically investigated if the history and the neuroimaging do not clarify the etiology, in order to ensure appropriate management, prognosis and genetic counseling.

### Acknowledgements

The authors wish to thank the patient and the family for consenting for this publication.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Ethical approval

Our institution does not require ethical approval for publishing case reports.

### Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

### Informed consent

Written informed consent was obtained from the parents and assent from the patient for the anonymized information to be published in this case report.

## References

1. Costeff H. Estimated frequency of genetic and nongenetic causes of congenital idiopathic cerebral palsy in west Sweden. *Ann Hum Genet* 2004; 68: 515–520.
2. Smithers-Sheedy H, Badawi N, Blair E, et al. What constitutes cerebral palsy in the twenty-first century? *Dev Med Child Neurol* 2014; 56(4): 323–328.
3. Parolin Schnekenberg R, Perkins EM, Miller JW, et al. De novo point mutations in patients diagnosed with ataxic cerebral palsy. *Brain* 2015; 138: 1817–1832.
4. Williams DM, Lopes CM, Rosenhouse-Dantsker A, et al. Molecular basis of decreased Kir4.1 function in SeSAME/EAST syndrome. *J Am Soc Nephrol* 2010; 12: 2117–2129.
5. National Center for Biotechnology Information, US National Library of Medicine. KCNJ10 potassium channel, inwardly rectifying subfamily J, member 10 [*Homo sapiens* (human)], <http://www.ncbi.nlm.nih.gov/gene/376> (accessed September 2015).
6. Bockenbauer D, Feather S, Stanescu HC, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *N Engl J Med* 2009; 360: 1960–1970.
7. Scholl UI, Choi M, Liu T, et al. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. *Proc Natl Acad Sci U S A* 2009; 106: 5842–5847.
8. Cross HJ, Arora R, Heckemann RA, et al. Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. *Dev Med Child Neurol* 2013; 55: 846–856.
9. Freudenthal B, Kulaveerasingam D, Lingappa L, et al. KCNJ10 mutations disrupt function in patients with EAST syndrome. *Nephron Physiol* 2011; 119(3): 40–48.
10. OMIM, <http://www.omim.org/entry/602208?search=KCNJ10&highlight=kcj10#0010>
11. Kara B, Ekici B, Ipekei B, et al. KCNJ10 gene mutation in an 8-year-old boy with seizures. *Acta Neurol Belg* 2013; 113: 75–77.
12. Scholl UI, Dave HB, Lu M, et al. SeSAME/EAST syndrome—phenotypic variability and delayed activity of the distal convoluted tubule. *Pediatr Nephrol* 2012; 11: 2081–2090.
13. Parrock S, Hussain S, Issler N, et al. KCNJ10 mutations display differential sensitivity to heteromerisation with KCNJ16. *Nephron Physiol* 2013; 123: 7–14.
14. Thompson DA, Feather S, Stanescu HC, et al. Altered electroretinograms in patients with KCNJ10 mutations and EAST syndrome. *J Physiol* 2011; 589(Pt 7): 1681–1689.
15. Abdelhadi O, Iancu D, Tekman M, et al. Founder mutation in KCNJ10 in Pakistani patients with EAST syndrome. *Mol Genet Genomic Med* 2016; 4(5): 521–526.
16. Reichold M, Zdebik AA, Lieberer E, et al. KCNJ10 gene mutations causing EAST syndrome (epilepsy, ataxia, sensorineural deafness, and tubulopathy) disrupt channel function. *Proc Natl Acad Sci U S A* 2010; 107(32): 14490–14495.