A novel CLCN2 homozygous mutation related to subclinical leukodystrophy: a case report

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Background:

Mutations in the *CLCN2* gene encoding CLC-2, a chloride channel implicated in brain ion and water homeostasis, are associated with leukoencephalopathy with ataxia (LKPAT; OMIM 615651), a rare form of autosomal recessive leukoencephalopathy. LKPAT is characterized by a specific MRI pattern of white matter anomalies on brain MRI, including signal abnormalities in the posterior limbs of the internal capsules, pyramidal tracts in the pons, and middle cerebellar peduncles (1).

So far, only 7 patients have been reported (four adults, three children), whose clinical features varies from the absence of neurological symptoms (2) to mild cerebellar ataxia with a variable combination of chorioretinopathy, visual field defects, optic neuropathy and headache. Very recently a patient presenting with paroxysmal kinesigenic dyskinesia has been described (3).

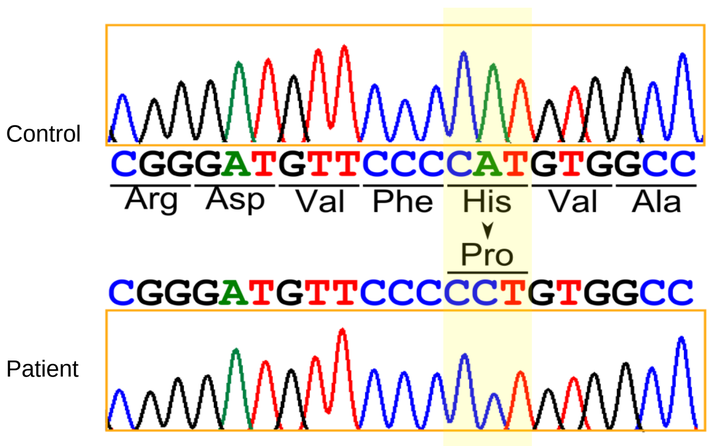
Case report:

Proband was a 52-year old woman presenting only with a mild bilateral optic atrophy. Her clinical neurologic examination was unremarkable except for bilateral optic disk pallor. Brain MRI showed symmetrical white matter anomalies compatible with the characteristic pattern of LKPAT. Despite the absence of auditory symptoms, a significant increase in the ponto-mesencephalic conduction time was detected at BAEPs. VEPs were normal.

Genetic analysis:

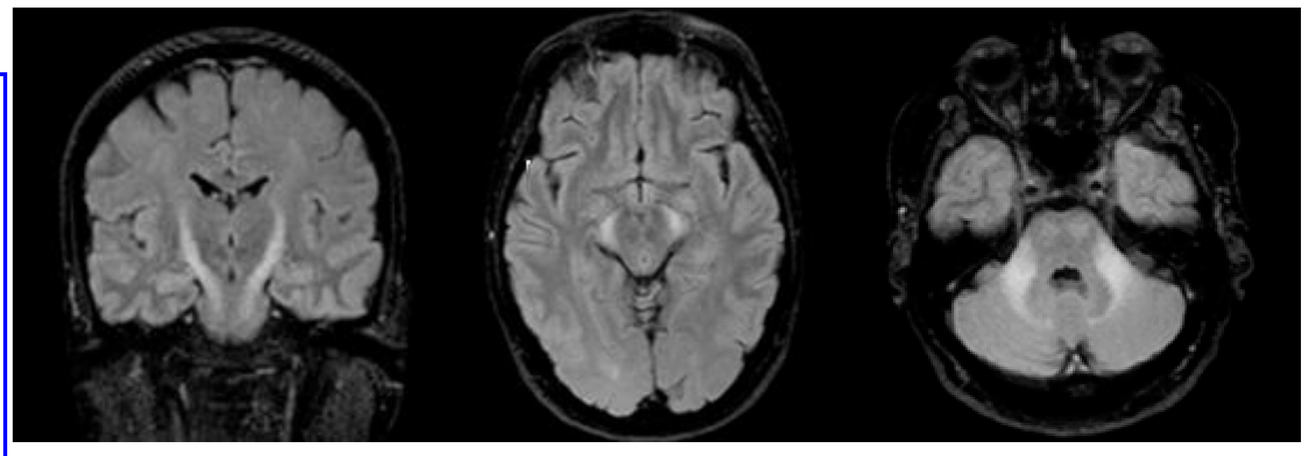
A novel homozygous missense mutation in exon 16, c.1769A>C (p.His590Pro) was found by *CLCN2* Sanger sequencing.

The mutation is not reported as polymorphism in the databases (dbSNP138, ExAC), and it is expected to be pathogenetic based on bioinformatic analyses (SIFT, Mutation taster, PHD-SNP).

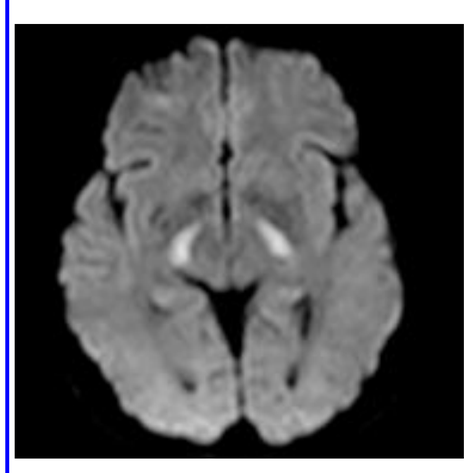


Human	DVPHVAL		
Rhesus	DVPHVAL	Opossum	DVPHVAL
Mouse	DVPHVAL	Chicken	QVVAV--
Rabbit	DVPHVAL	X-tropicalis	NIPFVTL
Cow	DVPHVAL	Zebrafish	DVRYITL
Elephant	DVPHVAL		

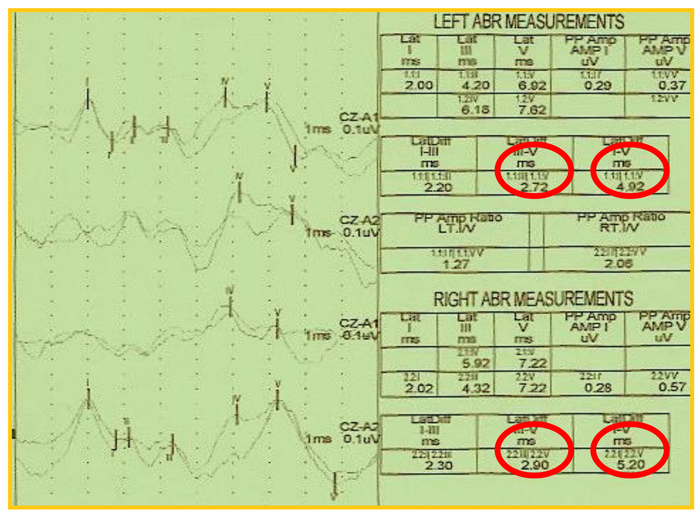
Software	Information	Description	Value output	bibliography
SIFT	Pathogenic or not predictors	damaging	0	Ng and Henikoff (2001)
PolyPhen-2	Pathogenic or not predictors	possibly damaging	0.77	Adzhubei IA et al. (2010)
I-Mutant	Stability changes prediction	increase stability	-0.01	Capriotti et al. (2005)
Mutation t@ster	Pathogenic or not predictors	damaging	0.97	Schwarz et al., (2014)
SNAP-F	Pathogenic or not predictors	Non-neutral	3	Bromberg and Rost (2007)
PHD-SNP	Pathogenic or not predictors	Disease	5	Capriotti et al. (2006)



MRI: T2-weighted images showing signal anomalies in the posterior limbs of internal capsules, pons, midbrain cerebral peduncles, and middle cerebellar peduncles.



MRI: Diffusion-weighted images showing high signal in the posterior limbs of the internal capsules.



BAEPs: bilateral increase in ponto mesencephalic conduction time

Conclusions:

We present a novel case of LKPAT, detected by the characteristic MRI pattern.

Clinical phenotype was extremely mild, confirming the broad clinical features associated with LKPAT.

We speculate that LKPAT white matter anomalies are likely due to water imbalance/intramyelinic oedema, not impairing the axonal function.

Specific MRI patterns are an important guide to diagnose rare forms of adult leukoencephalopathies to be confirmed by genetic tests.

Bibliography:

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