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CASE REPORT

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A Tunisian patient with CLCN2-related leukoencephalopathy

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Abstract

CLCN2-related leukoencephalopathy (CC2L OMIM#: 615651) is a recently identified rare disorder. It is caused by autosomal recessive mutations in the *CLCN2* gene and leads to the dysfunction of its encoded CLC-2 chloride channel protein with characteristic brain MRI features of leukoencephalopathy. We report the first Tunisian patient with clinical features of ClCN-2-related leukoencephalopathy. A 54-year-old female with a family history of leukemia, male infertility, motor disability, and headaches who initially presented with a tension-type headache and normal physical examination. At the follow-up, she developed mild gait ataxia and psycho-cognitive disturbances. A previously reported homozygous NM_004366.6(CLCN2):c.1709G > A (p.Trp570Ter) stop gained mutation was identified. This report expands the knowledge related to CC2L and highlights the clinical features in affected individuals of African descent.

KEYWORDS

CLCN2, CLCN2-related leukoencephalopathy, MRI

1 | INTRODUCTION

CLCN2-related leukoencephalopathy (CC2L), which is also known as leukoencephalopathy with ataxia (LKPAT; OMIM#: 615651), is a recently identified as a rare autosomal recessive disorder; it is caused by mutations in the *CLCN2* gene and results in CLC-2 chloride channel dysfunction and myelin microvacuolization.[1–3] CC2L is characterized by nonspecific neurologic findings, mild visual impairment resulting from chorioretinopathy or optic atrophy,[4] male infertility,[5] and characteristic findings in brain MRI.[6] Neurological deficits (e.g., mild ataxia, cognitive impairment, and headaches) are mild and lack specific manifestations. Patients are reported to remain ambulatory during follow-ups.

However, as specific clinical patterns of the disease, retinopathy and male infertility may be diagnostic clues that prompt, to a certain extent, a clinical suspicion of CC2L. Since the identification of CC2L in 2013 by Depienne et al., only 18 cases have been reported. Most patients show mild clinical phenotypes with prolonged survival. Herein, we report the first Tunisian patient with a previously reported *CLCN2* pathogenic mutation and a remarkable family history.

2 | CASE REPORT

A 56-year-old woman, born from a consanguineous marriage (Figure 1), initially presented to our clinical

department at the age of 27 with chronic headaches, which have been evolving for 5 years. Her family history was remarkable for male infertility (individuals II.4 and II.5) and headaches [sister: individual II.3 and (children: individuals III.2 and III.3)]. Her older son also showed psychiatric disturbances and aggressiveness. In addition, early infant deaths, leukemia, diabetes, and motor disability were observed in other family members.

The initial neurological examination, standard biological investigations, and brain CT scan were normal. The diagnosis of chronic tension-type headache was retained according to the international classification of headache disorders (second edition published in 2004).

After 7 years of follow-up, during which the patient remained stable, she started complaining of gait disturbances and difficulties performing daily fine task activities (Table 1). Moreover, she complained of memory disturbances. Neurological examination revealed cerebellar ataxia manifesting as dysarthria and broad-based gait associated with mild spastic paraplegia with brisk tendon reflexes in the lower limbs. A neuropsychological test revealed a mild memory deficit and a depressive mood.

Given the progression of symptoms, conventional cerebral magnetic resonance imaging (MRI) was performed. Cerebral MRI (Figure 1) showed confluent white matter abnormalities with hypointense T1- and hyperintense T2-weighted signals, with the symmetrical involvement of internal capsules (Figure 1C), cerebral peduncles (Figure 1B), and middle cerebellar peduncles (Figure 1A). Diffusion-weighted imaging (DWI) showed hyperintensity in the pathological areas without restriction on the apparent diffusion coefficient (ADC) map. No enhanced lesion was observed on the postgadolinium T1-weighted sequence.

Biological work-up (including blood cell count, liver enzymes, renal function, glycemia, and lipid profile) as well as specific blood tests (amino and organic acids chromatography – lactic/pyruvic acid and cupric concentrations) were normal. Thyroid check-up revealed hypothyroidism. Thyroid ultrasound did not show signs of thyroiditis. Immunological work-up showed positive antiperoxidase antibodies and negative antithyroglobulin antibodies.

Based on the suggestive characteristic brain MRI features of leukoencephalopathy, the diagnosis of CLCN2 leukoencephalopathy was suspected.

Exome sequencing was performed using the TruSight® One Sequencing Panel and reagents provided by Illumina TruSight One Sequencing Panel (Illumina Inc). The panel covers 4813 disease-associated genes. Fast read files were generated from the sequencing platform via the Illumina pipeline.

A previously reported homozygous variant, c.1709G > A, p.Trp570Ter,[6,7] was detected and then confirmed by Sanger sequencing (Figure 2). The nonsense mutation introduces a stop codon at position 570, which results in protein truncation of 1882 amino acids.

Functional studies show that Trp570Ter results in decreased protein expression and abnormal protein localization.[6] This variant is predicted to cause the loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay.

3 | DISCUSSION

In this study, we report a case of an adult woman, who is born of a consanguineous union, with a confirmed CLCN2 mutation. This is the fifth reported patient with a CLNC2-related leukoencephalopathy from North Africa.

The c.1709G > A mutation, identified in our patient, has been previously reported as an apparently homozygous pathogenic variant in two unrelated North African patients with an adult-onset leukodystrophy.[6] It has also been reported in an individual with idiopathic-generalized epilepsy; however, no further information was provided.[7] The other two patients have been reported to carry homozygous mutations c.430-435del[6] and c.1769A > C,[1] respectively. The latter was reported as a subclinical form of CC2L, which was discovered after an incidental detection of asymptomatic bilateral optic atrophy in an adult Moroccan woman.

The clinical features manifested by our patient and the reported patients carrying the same c.1709G > A mutation in the *CLCN-2* gene are summarized in Table 1. Our patient showed a similar clinical phenotype of slow progression of symptoms and mild cerebellar ataxia. However, headaches (which were the most prominent clinical feature lasting for several years as unique clinical manifestation), psycho-cognitive disturbances, as well as spastic paraplegia have not been previously associated with this mutation. Although headache has been associated with the CLCN2-related leukoencephalopathy, it remains unclear whether it is a feature of this condition or a coincidental finding. Moreover, our patient had hypothyroidism with positive antithyroid antibodies. Zhuoxin Guo et al. reported a combined endocrinological disturbance (hyperthyroidism and hyperparathyroidism) in their patient. Endocrine involvement may be explained by the high expression of CLC2 in the glands; however, further studies are needed.[8]

Other family members presented with a clinical phenotype that could be related to CLC2 (i.e., headaches, psychiatric disturbances, and azoospermia). Unfortunately, these symptomatic patients died, and genetic confirmation could not be performed.

Our patient's two brothers presented with azoospermia. Association between CCL2 and azoospermia has been reported once. One male with azoospermia (but without neurological dysfunction) was found to have CC2L during a work-up for infertility.[5] Another male with a history of

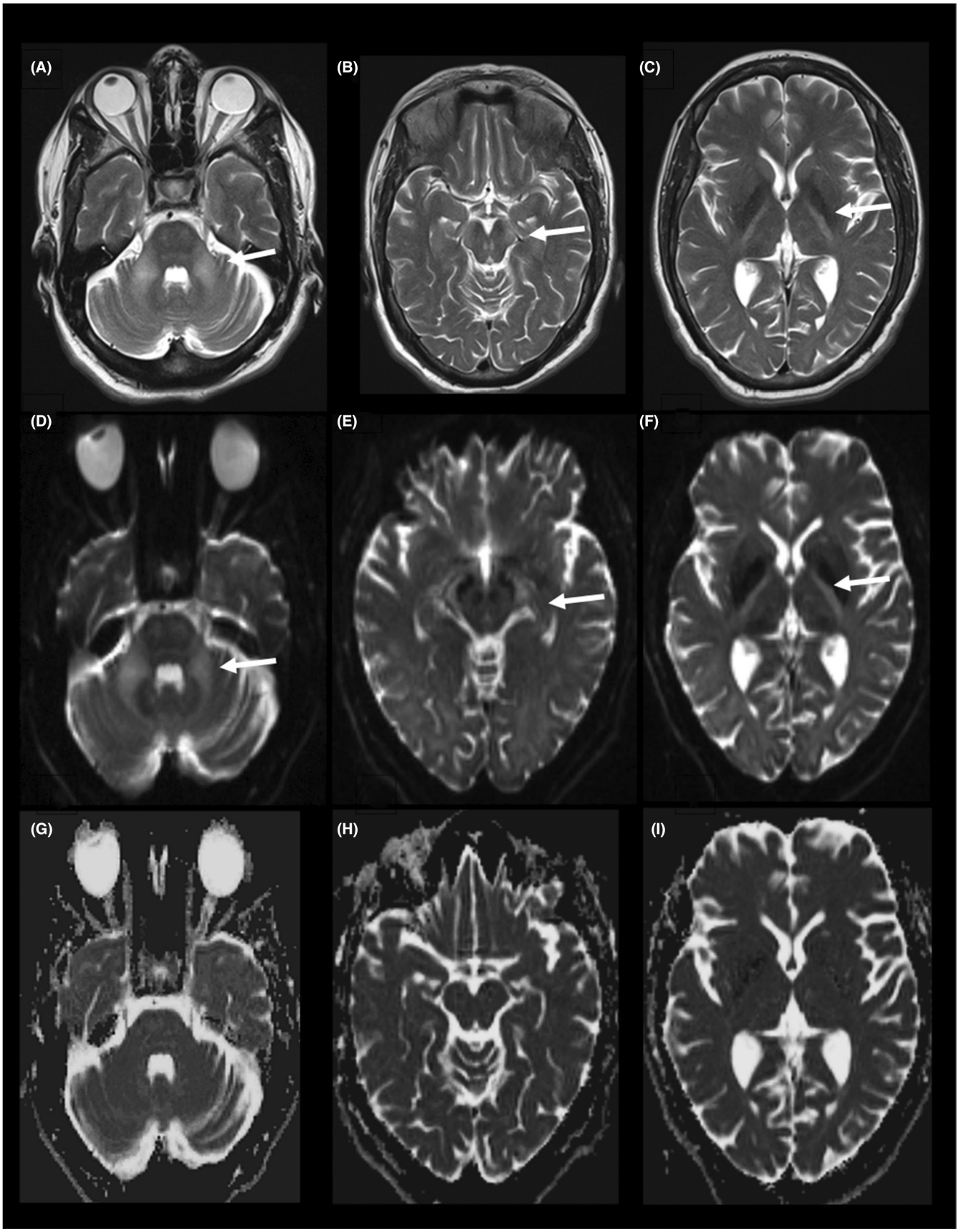

FIGURE 1 Cerebral MRI axial T2 weighted sequences (A–C) showing hyper T2 signal in the middle cerebellar peduncles (A), cerebral peduncles (B), and posterior limb of the internal capsule (C). Diffusion-weighted sequences (D–F) showing hyperintensity in the middle cerebellar peduncles (D), cerebral peduncles (E), and posterior limb of the internal capsule (F). Apparent diffusion coefficient (ADC) map (G–I) does not show a restriction of the diffusion

TABLE 1 Clinical features of our patient and the previously reported patients with CLCN-2 c.1709G > A nonsense mutation

	P1	P2	P3
Years of birth	1948	1952	1964
Sex-ancestry	F/North Africa	F/North Africa	F/North Africa
Consanguineous parents	No	No	Yes
Affected family members	No	No	Yes
Early psychomotor development	Normal	Normal	Normal
Age at first sign	44 years	54 years	45 years
Presenting signs	Action tremors, mild ataxia	Tinnitus, vertigo	Headache
Disease course	Stable	Progressive	Progressive
Signs of deterioration	None	Deafness	Psycho-cognitive disturbances, gait ataxia spasticity
Headache	No	No	Yes
Cognitive level	No	No	Mild memory deficit
Vision	Normal	20/80 right eye 20/400 letf eye	–
Visual field defects	No	Yes	–
Retina and optic nerves	Normal	Retinoschesis, bilateral optic neuropathy	Normal
Nystagmus	No	No	Yes
Hearing	Normal	Perceptive hearing loss	Tinnitus
Spasticity	No	No	Yes
Ataxia	Mild	Mild	Mild
Reporting authors	[6]		Our patient

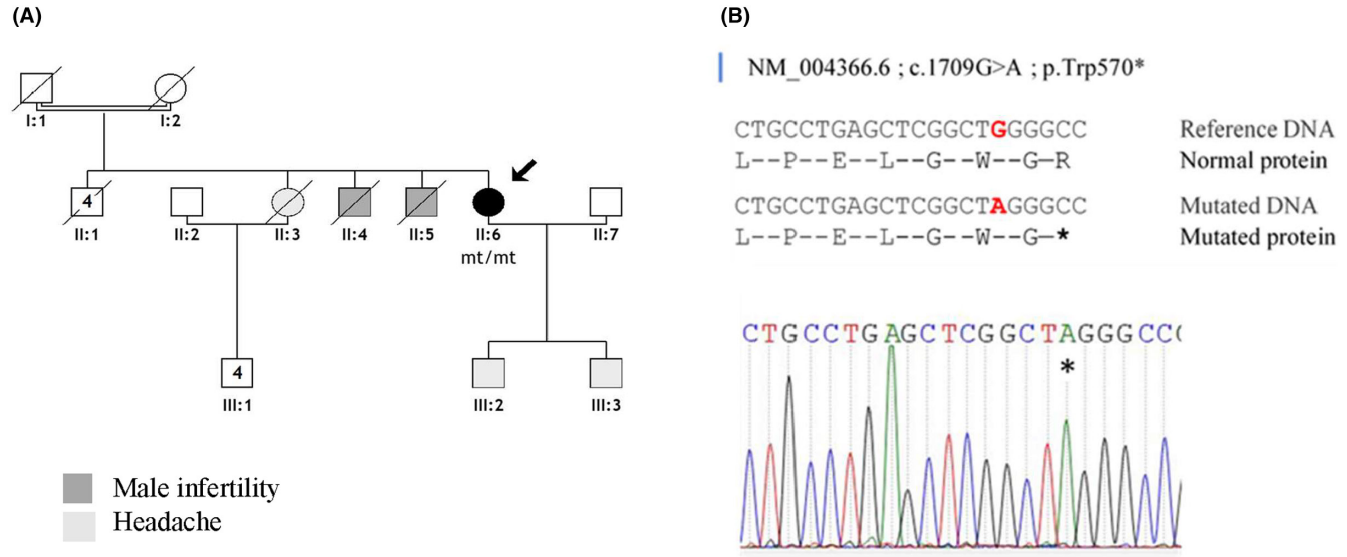

FIGURE 2 Pedigree and molecular findings. A. Pedigree of the index patient II.6. Her two brothers (II.4 and II.5) and sister (II.3) had suggestive symptoms of CLCN-2 related leukoencephalopathy. B. Sequencing chromatograms. Mutation confirmation of the homozygous c.1709G > A nonsense mutation (mt/mt) by forward primer indicated by an asterisk

infertility was diagnosed with CC2L when he was investigated for severe headaches.

MRI findings in patients with CC2L are essential for the clinician to guide the genetic diagnosis. The major criteria are the involvement of the posterior limbs of internal capsules, cerebral peduncles, and middle cerebellar peduncles.[2] Our findings were in accordance with the major brain MRI features.

Since its discovery in 2013, *CLCN2*-related leukoencephalopathy has been reported in 15 probands[9] with 18

pathogenic variants. Consequently, the phenotypic spectrum may only be partially known, and statements about the relative frequency of features are of limited value.

CLCN2-related leukoencephalopathy should be suspected in individuals with suggestive neurological, visual, and brain MRI findings. Another supportive finding may be male infertility caused by oligospermia/azoospermia.

The prevalence of CC2L is unknown. The small number of known affected individuals suggests that the disease is exceedingly rare. However, numerous individuals with CC2L may also remain undiagnosed because they stay asymptomatic at an advanced age, lack a specific clinical phenotype, or have findings (e.g., headaches or infertility due to azoospermia or oligozoospermia) that do not prompt evaluation by brain MRI.

In conclusion, we report the first Tunisian and the fifth North African patient with CC2L. Owing to the small number of known affected individuals to date, our report is valuable to the literature because it expands knowledge about the disorder. Moreover, our patient had the same p.Trp570Ter mutation as two other patients from the same origin, which indicates a possible high prevalence of this variant.

AUTHOR CONTRIBUTIONS

All the authors provided consent for the publication of this manuscript. All the authors have contributed to the work according to all four criteria listed under authorship in author guidelines.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of National Institute Mongi Ben Hamida of Neurology, Tunis, Tunisia. All the tests were carried out in compliance with the institution's specified rules and regulations. Furthermore, the patient's written informed consent was acquired for the publishing of this case report.

CONSENT

The patient's written informed consent was acquired for the publishing of this case report.

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