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Clinical short communication

Clinical, neuroimaging and genetic findings in the Japanese case series of *CLCN2*-related leukoencephalopathy

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ABSTRACT

Biallelic loss-of-function variants in *CLCN2* lead to *CLCN2*-related leukoencephalopathy (CC2L), also called leukoencephalopathy with ataxia (LKPAT). CC2L is characterized clinically by a spectrum of clinical presentations including childhood- to adult-onset mild ataxia, spasticity, cognitive decline, and vision loss as well as typical MRI findings of symmetrical high signal intensities on the DWIs/T2WIs of the middle cerebellar peduncles (MCPs). We searched for pathogenic variants of *CLCN2* in a case series of undiagnosed leukoencephalopathy accompanied by MCP signs, which led to the identification of four Japanese patients with CC2L. All the patients carried at least one allele of c.61dupC (p.Leu21Profs*27) in *CLCN2*, including compound heterozygosity with either the novel pathogenic variant c.983 + 2 T > A or the previously reported pathogenic variant c.1828C > T (p.Arg610*). Of note, all the four previously reported cases from Japan also harbored c.61dupC, and no reports of this variant have been documented from outside Japan. The allele frequency of c.61dupC in the Japanese population is 0.002152, raising the possibility of a relatively high prevalence of CC2L in Japan. Patients in this study developed symptoms after the age of 30, and demonstrated neurological signs including cerebellar ataxia, pyramidal signs, and mild cognitive impairment, consistent with previous reports. One male patient had two children, supporting preserved fertility, and another patient had calcifications in the cerebral and cerebellar surfaces. These findings provide valuable insights into the broader clinical and genetic spectra of CC2L in the Japanese population, and emphasize the importance of considering this disease in the differential diagnoses of leukoencephalopathy with MCP signs.

1. Introduction

CIC-2 is a member of the voltage-gated chloride channel family, broadly expressed in human tissues [1]. It plays an important role in ion and water homeostasis in the brain [2]. Loss-of-function variants in *CLCN2* impairs ClC-2 function through mechanisms involving reduced cellular and plasma membrane density, increased turnover, and impaired gating of ClC-2 [2,3], which is further supported by the observations of reduced ClC-2-mediated currents in oligodendrocytes of *Clcn2* knockout mice and in mammalian cells expressing the *CLCN2*

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variants [3,4]. Biallelic loss-of-function variants in *CLCN2*, the gene encoding CIC-2, cause a distinct form of leukoencephalopathy known as *CLCN2*-related leukoencephalopathy (CC2L) [2,5], which is also called leukoencephalopathy with ataxia (LKPAT; MIM #615651) [6]. CC2L is characterized by clinical manifestations ranging from childhood-onset mild ataxia, cognitive impairment, and headaches to adult-onset mild ataxia and decreased vision [2,6], and radiological manifestations with symmetrical high signal intensities in the posterior limbs of the internal capsules, cerebral peduncles, pyramidal tracts in the pons, and middle cerebellar peduncles (MCPs), along with mild signal abnormalities in cerebellar white matter on DWIs/T2WIs. Although more than 30 cases of CC2L have been reported to date, the clinical and radiological manifestations of CC2L are considerably variable, and the establishment of the disease spectrum still awaits further study of a larger number of patients with CC2L. We herein present four patients with biallelic pathogenic *CLCN2* variants to further characterize the clinical and radiological manifestations of this disease.

2. Methods

On the basis of a review of MRI findings of the patients with neurological diseases who had been referred to our laboratory for genetic testing of causative genes, we selected patients who had MRI findings with leukoencephalopathy and showing bilateral MCP signs in this study. Genomic DNAs were extracted from peripheral blood leukocytes with written informed consent from all the participants. Repeat primed PCR assays for expanded CGG repeats in *NOTCH2NLC* or in *FMR1* were conducted to exclude patients with neuronal intranuclear inclusion disease (NIID) [7] and fragile X-associated tremor/ataxia syndrome (FXTAS) [8]. Mutational analysis of *CLCN2* was conducted by PCR amplification of all the exons and flanking introns (Supplementary Table 1), followed by direct nucleotide sequence analysis in three patients. Whole-genome sequence (WGS) analysis employing NovaSeq6000 was conducted in seven patients. When multiple heterozygous pathogenic variants were identified, phasing was conducted by droplet digital PCR (ddPCR) [9] (Supplementary Table 2). For suspected homozygous variants, analysis of read depths of the whole genome sequence data was conducted to confirm the homozygosity of the variants. Copy number was determined by ddPCR for the samples genetically tested by direct nucleotide sequence analysis of their PCR products to confirm the homozygosity. The research project was approved by the institutional review board of the University of Tokyo.

3. Results

Of the 37 patients with MRI findings characterized by MRI findings of the white matter lesions with high T2/FLAIR and DWI signals and bilateral MCP signs, after excluding 22 patients with NIID and seven patients with FXTAS, we identified 8 patients from eight families (Supplementary Fig. 1). Pathogenic variants of *CLCN2* were identified in four patients from four independent families either in a homozygous or compound heterozygous state (Table 1). Specifically, Patients 2 and 4 had a homozygous c.61dupC variant (NM_004366.6) (Supplementary Figs. 2, and 3). Patients 1 and 3 had c.61dupC (p.Leu21Profs*27) / c.983 + 2 T > A and c.61dupC (p.Leu21Profs*27) / c.1828C > T (p.Arg610*) (NP_004357.3), respectively. The zygosities of these variants were confirmed to be compound heterozygous by ddPCR analysis in Patients 1 and 3 (Supplementary Figs. 4, and 5). While c.61dupC (p.Leu21Profs*27) and c.1828C > T (p.Arg610*) were previously reported as pathogenic [10–13], c.983 + 2 T > A is described neither in the ClinVar nor in the Human Gene Mutation Database (HGMD®) Professional version (https://www.hgmd.cf.ac.uk/ac/index.php). Reverse transcription-PCR (RT-PCR) analysis of RNA prepared from the cultured skin fibroblasts demonstrated that the amount of the cDNA corresponding to the wild-type sequence is substantially decreased in Patient 1, consistent with nonsense-mediated decay of the mutant mRNA with c.983 + 2 T > A. The minigene assay using HEK293 cells demonstrated absence of the correctly spliced form (exon 8-exon 9-exon 10) along with the aberrantly spliced forms including skipping of exon 9 (Supplementary Fig. 6) [14,15]. According to the ACMG guideline, this variant is

Table 1
Patients with CC2L in our study.

	Patient 1	Patient 2	Patient 3	Patient 4
Age at onset (y)	57	69	32	62
Age at presentation (y)	70	69	52	67
Sex	Male	Female	Male	Male
Variants	c.61dupC, p.Leu21Profs*27 c.983 + 2 T > A	c.61dupC, p.Leu21Profs*27 Homozygous	c.61dupC, p.Leu21Profs*27 c.1828C > T, p.Arg610*	c.61dupC, p.Leu21Profs*27 Homozygous
Parental consanguinity	Absent	Absent	Absent	Present
Ataxia	Truncal/limb ataxia	Truncal ataxia	Absent	Truncal/limb ataxia
Tendon reflexes	Increased tendon reflexes, jaw jerk	Absent	Increased tendon reflexes	Increased tendon reflexes, jaw jerk
Spasticity	Absent	Absent	Present	Absent
Babinski's sign	Present	Absent	Absent	Absent
Cognitive dysfunction	MMSE 26/30	Not assessed	Not assessed	MMSE 10/30; HDS-R 5/30; FAB 3/18
Psychiatric symptoms	Absent	Absent	Absent	Absent
Headache	Absent	Present	Present	Absent
Epilepsy	Absent	Absent	Absent	Absent
Deafness	Present	Absent	Present	Absent
Visual impairment	Absent (decreased potential in ERG, VEP P100 prolongation)	Present (blindness in the left eye, decreased visual acuity in the right eye)	Present (decreased visual acuity, uveitis, cataract, vitreomacular traction syndrome, Macular edema, right epiretinal membrane)	Absent
Infertility in men	Two children	Not applicable	No child	No child
Autonomic dysfunction	Decreased sweating, pollakiuria	Absent	Absent	Constipation, urinary incontinence, decreased CVR-R

All the patients listed in the table are from independent families. CC2L, *CLCN2*-related leukoencephalopathy; MMSE, Mini-Mental State Examination; HDS-R, Hasegawa Dementia Scale-Revised; FAB, Frontal Assessment Battery; VEP, visual evoked potential; ERG, electroretinogram; CVR-R, coefficient of variation of R-R intervals.

classified as pathogenic (PVS1, PM2, PM3) [16].

All the patients developed symptoms after the age of 30. Parental consanguinity was present only in Patient 2, whereas the other three patients did not report any parental consanguinity. Ataxia was observed in three patients (Patients 1, 2, and 4). Although increased tendon reflexes in the limbs were noted in three patients (Patients 1, 3, and 4), spasticity was observed only in Patient 3, and Babinski's signs were noted only in Patient 1. Cognitive impairment was evident in two patients, with the severity ranging from mild (MMSE score: 26/30 in Patient 1) to severe (MMSE score: 10/30 in Patient 4). Regarding autonomic dysfunction, Patient 1 showed decreased sweating and bladder urgency, while Patient 4 had constipation and urinary incontinence, and a reduced coefficient of variation of R-R intervals (CVR-R) on electrocardiogram of 0.80. However, orthostatic hypotension was observed neither in Patient 1 nor in Patient 4. MRI showed hyperintensities in the pyramidal tracts extending from the internal capsules to the cerebral peduncles and bilateral MCPs on T2/FLAIR and DWI in all the patients (Fig. 1), and only mild signal changes were observed in the cerebral white matter in these patients. In Patient 4, however, the hyperintense signal in the cerebral white matter was relatively more pronounced than in the other patients. In Patients 1 and 3, serial MRI findings remained unchanged over a 13-year period (data not shown). In Patient 4, head CT imaging showed calcification in the cerebellar hemispheres and frontal cortices.

4. Discussion

In the present study, we identified the four novel patients with CC2L who carried biallelic pathogenic variants in *CLCN2*, including a novel pathogenic variant. Although more than 30 cases of CC2L have been reported since the first report of CC2L in 2013 [2], only four cases of CC2L have been reported in Japan [10–13]. All the Japanese patients previously reported harbored the homozygous c.61dupC (p.Leu21Profs*27) variant, which was also present in all four patients in our study. The exclusive reporting of this variant from Japan suggests that this variant is an ancestry-specific causative variant for CC2L. The allele frequency of c.61dupC (p.Leu21Profs*27) in the Japanese population is 0.002152 according to the Japanese population database (jMorp 60KJPN: https://jmorp.megabank.tohoku.ac.jp/). Although the allele frequencies are much lower than that of c.61dupC (p.Leu21Profs*27), a considerable number of loss-of-function variants including nonsense, frameshift, and splicing variants in *CLCN2* are registered in the 60KJPN database (Supplementary Table 4). On the basis of these data, the frequency of individuals with CC2L carrying biallelic pathogenic *CLCN2* variants in the Japanese population is estimated to be approximately 0.000005915. Accordingly, given Japan's population of 125 million, the number of individuals with biallelic loss-of-function variants is estimated to be 740. Of note, the estimated frequency of individuals carrying biallelic pathogenic *CLCN2* variants with at least one c.61dupC (p.Leu21Profs*27) allele is 0.000005836. These results indicate that, despite the small number of reported cases of CC2L in Japan, a considerably large number of individuals with CC2L potentially exist, with the majority carrying the c.61dupC (p.Leu21Profs*27) variant (98.6 % of all the individuals with biallelic *CLCN2* variants). In addition, in our laboratory, after excluding 22 patients with NIID and seven patients with FXTAS from those with leukoencephalopathy with the bilateral MCP sign, CC2L was identified in four out of the remaining 8 patients.

CC2L patients typically present with characteristic MRI findings, whereas their clinical symptoms are generally mild, and the condition typically follows an indolent course [5,17]. These characteristic MRI findings, in which DWI signal changes are as pronounced as or even more pronounced than those on T2/FLAIR, and a reduction in ADC is observed in some cases, are attributed to intra-myelinic water rather than axonal degeneration [2]. This may underlie the relatively mild clinical symptoms compared with the imaging findings, and the indolent progression of CC2L [6,17]. In the present study, imaging abnormalities were detected in all the four patients after they reached their 30s. On the other hand, there have been multiple reports of patients with CC2L carrying the same c.61dupC (p.Leu21Profs*27) variant in whom imaging abnormalities were detected during childhood. For example, one patient was diagnosed at the age of 6 following an incidental episode of aseptic meningitis, and another was identified owing to a seizure beginning at 3 months of age, although no other neurological abnormalities were observed [10,11]. In the patients described in this study, it is also possible that earlier MRI studies might have revealed the similar signal abnormalities in the white matter. Given that MRI is relatively widely available in Japan, patients exhibiting the subtle MRI findings may well be identified compared to in other countries. All the patients in this study demonstrated imaging findings consistent with those in previously reported patients with variants other than the c.61dupC (p.Leu21Profs*27) variant. Although similar findings were not previously reported, of note Patient 4 showed calcification on the surfaces of the cerebral cortices and the cerebellar hemispheres. It is noteworthy that these calcifications were located in regions that are different from those of typical physiological calcification sites such as the basal ganglia or dentate nuclei. Additionally, no calcifications were observed in other organs on body CT images, and the levels of calcium, phosphate, and the parathyroid hormone were normal. Furthermore, based on experiments in mice, there has been a report suggesting that *CLCN2* variants can alter the intracellular concentration of calcium ions in the zona glomerulosa cells of the adrenal cortex [18], implying a potential link to the intracranial calcification observed in this case. Although multiple hereditary disorders are known to present with both leukoencephalopathy and intracranial calcification [19–21], and the link between these two conditions is not yet fully understood, attention should be paid to the possibility that patients with CC2L can also present with brain calcification.

CC2L can present with broad clinical manifestations [2,22]. In the present study, cerebellar ataxia was the most prominent manifestation, with some patients also exhibiting mild pyramidal signs and cognitive impairment, consistent with previous reports on variants other than c.61dupC (p.Leu21Profs*27) [2,6,22]. However, autonomic symptoms associated with CC2L have not been systematically reported. In this study, two of the four patients had some form of autonomic dysfunction. Although symptoms such as urinary incontinence and constipation may arise from other causes and warrant a careful differential diagnosis, these findings in two of our CCL2 patients suggest that they might be part of the phenotypic spectrum of CCL2, possibly resulting from damage to the autonomic nervous systems in the brainstem or spinal cord. Notably, Patient 1 is a male and has two children. Previous studies have shown that male infertility in CC2L is caused by oligospermia due to the loss of function of ClC-2 in Sertoli cells [23], and no previous studies have shown male patients with offspring. Although we neither confirmed the paternity of the two children by genetic testing nor perform fertility evaluations in this patient, the findings in Patient 1 suggest that male patients with CC2L may retain fertility potential.

5. Conclusion

We reported four Japanese patients with CC2L, including a patient carrying novel pathogenic variant of *CLCN2*. Although the patients in our study did not show considerable differences from those whose cases were reported in other countries, notable findings such as brain calcification, which was not previously reported, and autonomic dysfunction were observed, providing additional clinical insights into CC2L. Although the number of reported cases of CC2L is small, the estimated frequency of this disease may not be low in Japan. In cases of leukoencephalopathy with MCP signs, it is essential to consider CC2L in the differential diagnosis.

CRediT authorship contribution statement

Kenta Orimo: Writing – original draft, Formal analysis,

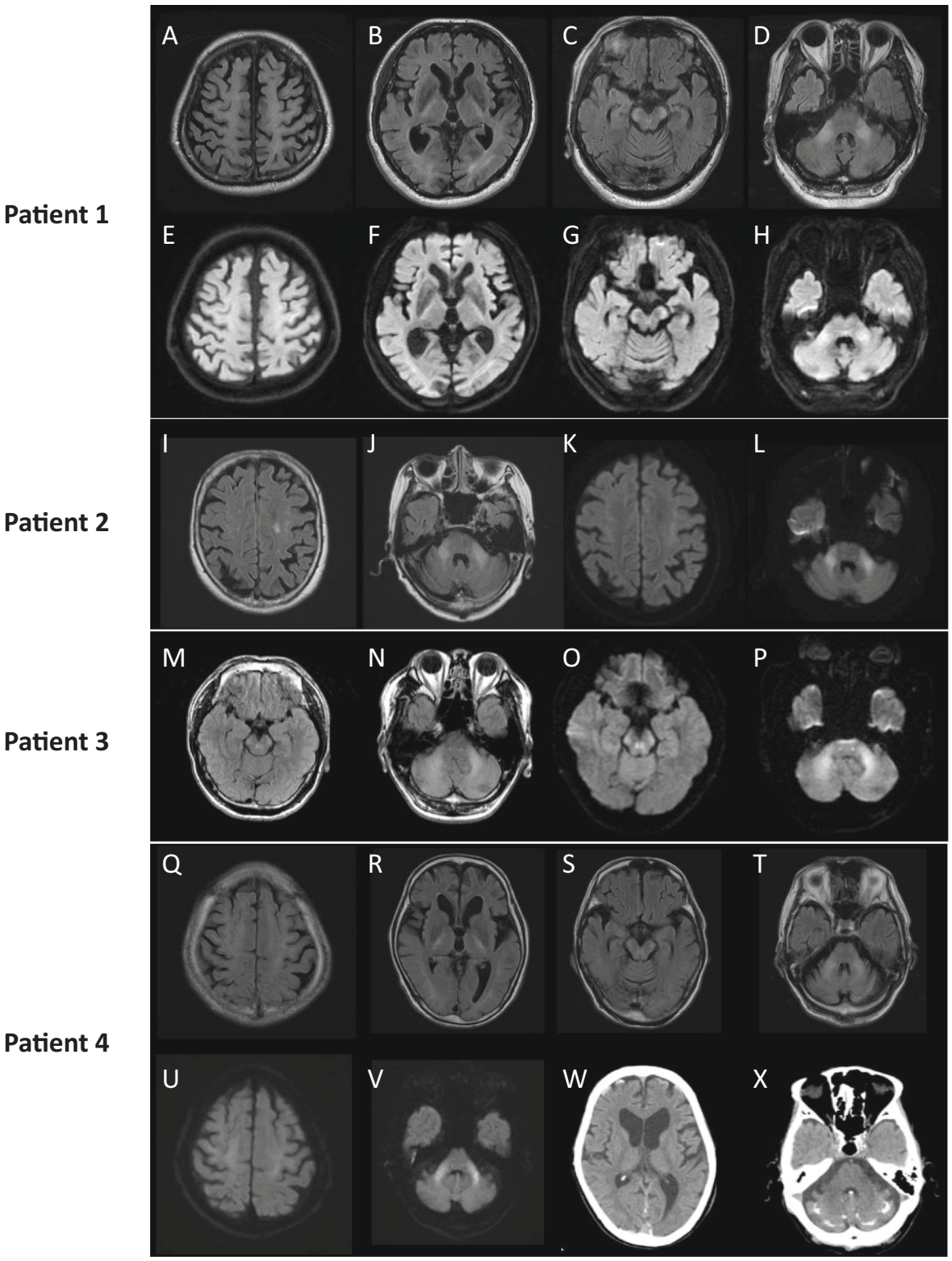

Fig. 1. MRI findings in patients with CC2L in this study. Brain MRI of Patient 1 (A– H) is shown. Axial FLAIR images (A– D) demonstrate symmetric hyperintensity lesions involving the cerebral white matter, posterior limb of internal capsules, cerebral peduncles, superior cerebral peduncles, and middle cerebellar peduncles. The corresponding regions manifest more prominent hyperintensity lesions in DWI than FLAIR (E– H). In the brain MRI of Patient 2 (I– L), although bilateral hyperintensity lesions in the middle cerebellar peduncles are observed, the signal changes in the cerebral white matter are very subtle. The brain MRI of Patient 3 (M– P) also shows symmetric hyperintensity lesions in the cerebral peduncles, superior cerebral peduncles, middle cerebellar peduncles, as well as central tegmental tracts. The brain MRI of Patient 4 also shows bilateral hyperintensity lesions in the cerebral white matter, posterior limb of internal capsules, cerebral peduncles, superior cerebral peduncles, and middle cerebellar peduncles on DWI and FLAIR, and the signal changes are slightly more pronounced than those in the other patients (Q– V). The head CT of Patient 4 shows calcification on the surfaces of the frontal lobe and cerebellar hemispheres not corresponding to the hyperintensity lesions on MRI (W, X).

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123486.

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