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ORIGINAL ARTICLE

Exome sequencing identifies a novel homozygous CLN8 mutation in a Turkish family with Northern epilepsy

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Abstract Neuronal ceroid lipofuscinosis (NCL), one of the most common neurodegenerative childhood-onset disorders, is characterized by autosomal-recessive inheritance, epileptic seizures, progressive psychomotor deterioration, visual impairment, and premature death. Based on the country of origin of the patients, the clinical features/courses, and the molecular genetics background of the disorder, 14 distinct NCL subtypes have been described to date. *CLN8* mutation was first identified in Finnish patients, and the condition was named Northern Epilepsy (NE); however, the severe phenotype of the *CLN8* gene was subsequently found outside Finland and named 'variant late-infantile' NCL. In this study, five patients and their six healthy relatives from a large Turkish consanguineous family were enrolled. The study involved detailed clinical, radiological and molecular genetic evaluations. Whole-exome sequencing and homozygosity mapping revealed a novel homozygous *CLN8* mutation, c.677T>C (p.Leu226-Pro). We defined NE cases in Turkey, caused by a novel mutation in *CLN8*. WES can be an important diagnostic method in rare cases with atypical courses.

Keywords CLN8 · NCL · Neuronal ceroid lipofuscinosis · Northern epilepsy

Introduction

Neuronal ceroid lipofuscinoses (NCLs) are progressive neurodegenerative childhood-onset disorders characterized by visual loss, seizures, and intellectual disability/developmental delay. Most are inherited in an autosomal-recessive manner but autosomal-dominant inheritance has also been described in some cases.

According to the age of onset and clinical and pathological findings, the NCLs have been classified into four main types, infantile (INCL), late-infantile (LINCL), juvenile (JNCL), and adult forms (ANCL) [1]. The current classification is based on genetic defects: CLN1 (OMIM# 256730)/*PPT1* gene (OMIM*600722), CLN2 (OMIM# 204500)/*TPP1* gene (OMIM*607998), CLN3 (OMIM#204 200)/*CLN3* gene (OMIM*607042), CLN4 (OMIM#1623 50)/*DNAJC5* gene (OMIM*611203), CLN5 (OMIM# 256731)/*CLN5* gene (OMIM*608102), CLN6 (OMIM# 601780)/*CLN6* gene (OMIM*602780), CLN7 (OMIM# 610951)/*MFSD8* gene (OMIM*611124), CLN8 (OMIM# 600143) and Northern Epilepsy (NE) (OMIM#610003)/*CLN8* gene (OMIM*607837), CLN10 (OMIM#610127)/*CTSD* gene (OMIM*116840), CLN11 (OMIM#614706)/*GRN* gene (OMIM*138945), CLN12 (OMIM#606693)/

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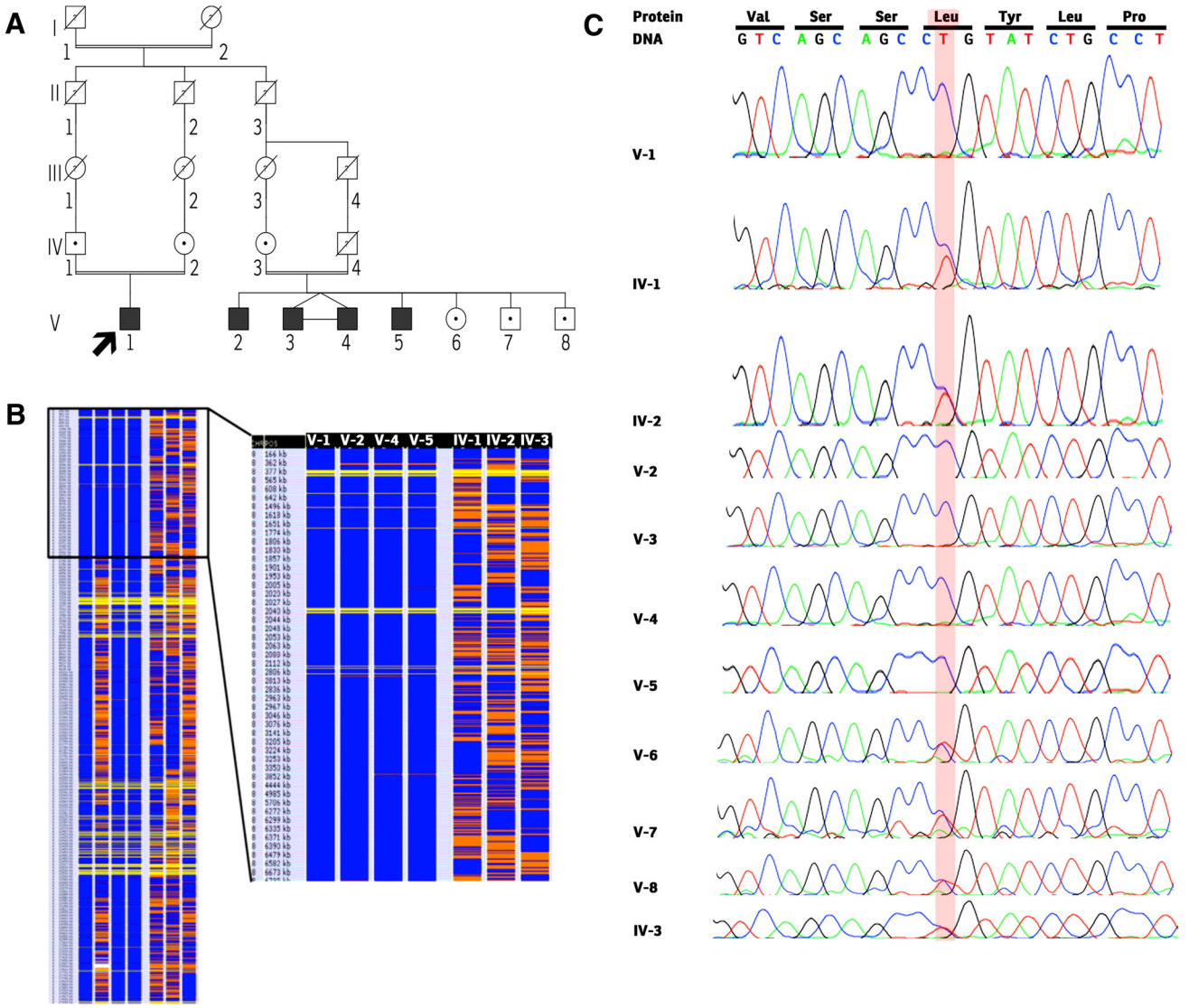

Fig. 1 **a** Pedigree of the family. The index patient is indicated by the *black arrow*. **b** Homozygosity map of chromosome 8. The homozygous region shared by affected individuals is surrounded with a *black rectangle*. **c** Sanger sequencing of the proband, his parents, and cousins. The first two lines show the protein and DNA sequences of wild-type CLN8, respectively. The mutated leucine residue and nucleotide are highlighted in *red*. Sanger sequencing revealed a homozygous c.677T>C variant in the proband, which was inherited from heterozygous parents (color figure online)

ATP13A2 gene (OMIM*610513), CLN13 (OMIM#615362)/*CTSF* gene (OMIM*603539), and CLN14 (OMIM#611726)/*KCTD7* gene (OMIM*611725) [2, 3], CLN9 (OMIM#609055) has not been molecularly characterized yet [4].

The CLN8 subtype was first described in Finland as progressive epilepsy with mental retardation (EPMR), also called NE [5]. EPMR is characterized by normal early development, slow deterioration of cognitive skills, and mildly reduced or normal visual acuity [5]. Subsequent studies described a variant late-infantile NCL (vLINCL) phenotype, distinct from NE, in different populations who showed rapid or slow clinical courses [6–10]. Here, we report the first case of NE with a novel *CLN8* variant in a large Turkish consanguineous family by using whole-exome sequencing (WES) (see Fig. 1).

Materials and methods

Human subjects

Five patients and their six healthy relatives from one consanguineous family were enrolled. Informed consent was obtained from all study participants. The consanguineous family originated from Turkey. The index patient,

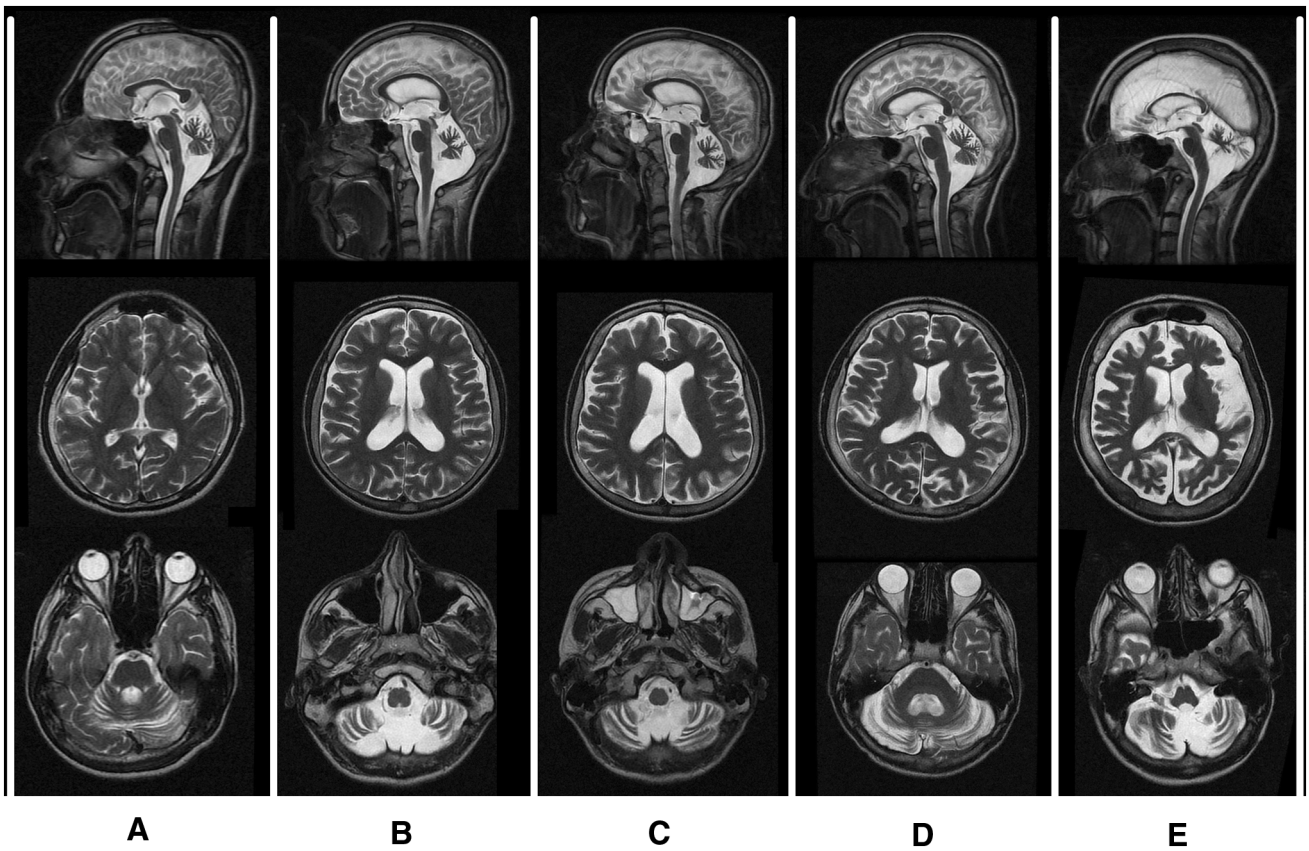

Fig. 2 MRI findings of the all patients: V-1, V-2, V-3, V-4, and V-5, respectively. **a** Mild cerebellar cortical atrophy. **b** Moderate-to-severe degree cerebral–cerebellar cortical atrophy and dilatation of the third and lateral ventricles secondary to atrophy. **c** Moderate-to-severe degree cerebral–cerebellar cortical atrophy and distinct dilatation of third and lateral ventricles. **d** Moderate-to-severe degree cerebral–cerebellar cortical atrophy and distinct dilatation of third and lateral ventricles. **e** Severe diffuse cerebral–cerebellar cortical atrophy, increased cerebrospinal fluid space, and distinct dilatation at the third and lateral ventricle

a 17-year-old male, was referred to our department because of intellectual disability and seizures. His parents were of Turkish origin and consanguineous. The prenatal period was unremarkable. The patient was born via a normal delivery at term with a birth weight of 2750 g. His first seizure started at age 10. Before the first seizure, his cognitive development had been normal. Initially, the seizures occurred every 2–3 months; later, the seizures started to take place 2–3 times every week. The seizures were kept under control with sodium valproate, oxcarbazepine, and clonazepam; he had no seizure for 2 years. His gait started to become impaired at the age of 14, and his speech has slowed down recently. An ophthalmological examination of the patient was normal. An extensive neurobiochemical evaluation, including urine organic acids, blood pyruvate, lactate, ammonia levels, and lysosomal enzyme screening, was normal. In a cranial MRI, subdural hematomas of 11 mm on the right and 10 mm on the left on the cerebral convexities and a mild degree of diffuse cerebellar cortical atrophy were observed (Fig. 2a).

Based on the index patient's clinical features, we examined the other affected family members. These findings are documented in Table 1.

Whole-exome sequencing (WES) and homozygosity mapping

DNA was extracted from lymphocytes according to standard protocols. WES was performed on seven samples (four affected individuals and three parents). Genomic DNA samples were prepared for massively parallel sequencing using the Illumina TruSeq Sample Preparation kit. Exonic regions were captured with the NimbleGen SeqCap EZ Human Exome Library (ver. 3.0) Kit. The Illumina TruSeq PE Cluster Kit (ver. 3)-cBot-HS was used for paired-end cluster generation, and the TruSeq SBS Kit (ver.3)-HS reagent kit was used for sequencing the post-capture libraries. Initial clustering was performed on an Illumina cBot machine. Paired-end sequencing was performed on an Illumina HiSeq 2500 system with a read

Table 1 Clinical features of all patients

	V-1 (index patient)	V-3	V-4	V-2	V-5
Age	17	18	18	21	31
Sex	M	M	M	M	M
Birth weight (g)	2750	2700	2850	2600	2700
Birth week	Term	Term	Term	Term	Term
Developmental milestones	Normal	Normal	Normal	Normal	Normal
Age at onset	10	8	8	8	8
Clinical course	Mild	Mild	Mild	Mild	Mild
Age at abnormal gait	14	14	14	15	16
Age at difficulty talking	16	15	15	16	18
Seizures	Generalized tonic–clonic seizure	Generalized tonic–clonic seizure	Generalized tonic–clonic seizure	Generalized tonic–clonic seizure	Generalized tonic–clonic seizure
Treatment	Valproate Oxcarbazepine Clonazepam	Valproate Clonazepam	Valproate Carbamazepine	Valproate Levetiracetam	Valproate
EEG	Normal	Normal	Normal	Normal	Normal
Ataxia	+	+	+	+	+
Cognitive decline	Mild	Mild	Mild	Moderate	Severe
Myoclonus	−	−	−	−	−
Biochemical Evaluation	Normal	Normal	Normal	Normal	Normal
Urine organic acids					
Blood pyruvate					
Blood lactate					
Blood ammonia					
Cerebral atrophy at MRI	+	+	+	+	+
Cerebellar atrophy at MRI	+	+	+	+	+

length of 110. All procedures were carried out according to the manufacturer's protocols. Base calling and image analysis were conducted using Illumina's Real-Time Analysis software (ver. 1.13) with default parameters.

Raw sequencing data were aligned to the hg19 reference human genome using BWA with standard parameters in paired-end (PE) mode [11] SAMtools [12] was then used to remove PCR duplicates. To calculate the coverage of targeted exome regions, BEDtools [13] was used. Nearly all targeted regions were covered at least four times, and the average sequencing depth of the regions was 54-fold. These values are the means of all samples. Each sample value is shown in Supplementary Table S1. To perform local realignment around indels, Genome Analysis Toolkit (ver. 1.6; GATK) IndelRealigner was used [14]. Then, SNPs and small indels were called using GATK UnifiedGenotyper. SnpEff was used for the functional annotation of variants, such as gene/exonic regions, minor allele frequencies, segmental duplications, and the effect of variants [15]. HomSI was used to show shared homozygous regions in the affected siblings (Fig. 1) [16].

All variants were filtered according to the following criteria, and results are outlined in Supplementary Table S1. First, the variants with genotype scores lower than 15 and coverage lower than 4 were removed using our in-house script. Then, candidate variants were sifted using FMFilter with respect to an autosomal-recessive mode of inheritance. Second, to filter the variants, we searched publicly available databases, such as the EVS (http://evs.gs.washington.edu/EVS/), ExAC (http://exac.broadinstitute.org/), and the 1000G Project (http://1000genomes.org/), and our in-house database, consisting of only Turkish samples ($n = 1182$). Finally, loss-of-function variants, such as frameshift/non-frameshift indels, non-synonymous variants, stops gained/lost, or splicing, were sifted. A non-synonymous variant located in the shared homozygous region in all patients in *CLN8* gene was selected after filtering.

Variant validation and segregation analysis

To verify and to test segregation of the identified WES-detected variant, PCR amplification from genomic DNA and Sanger sequencing were performed in the family members with available DNA (Fig. 1). Primer pair and PCR condition are available on request. The amplicon was

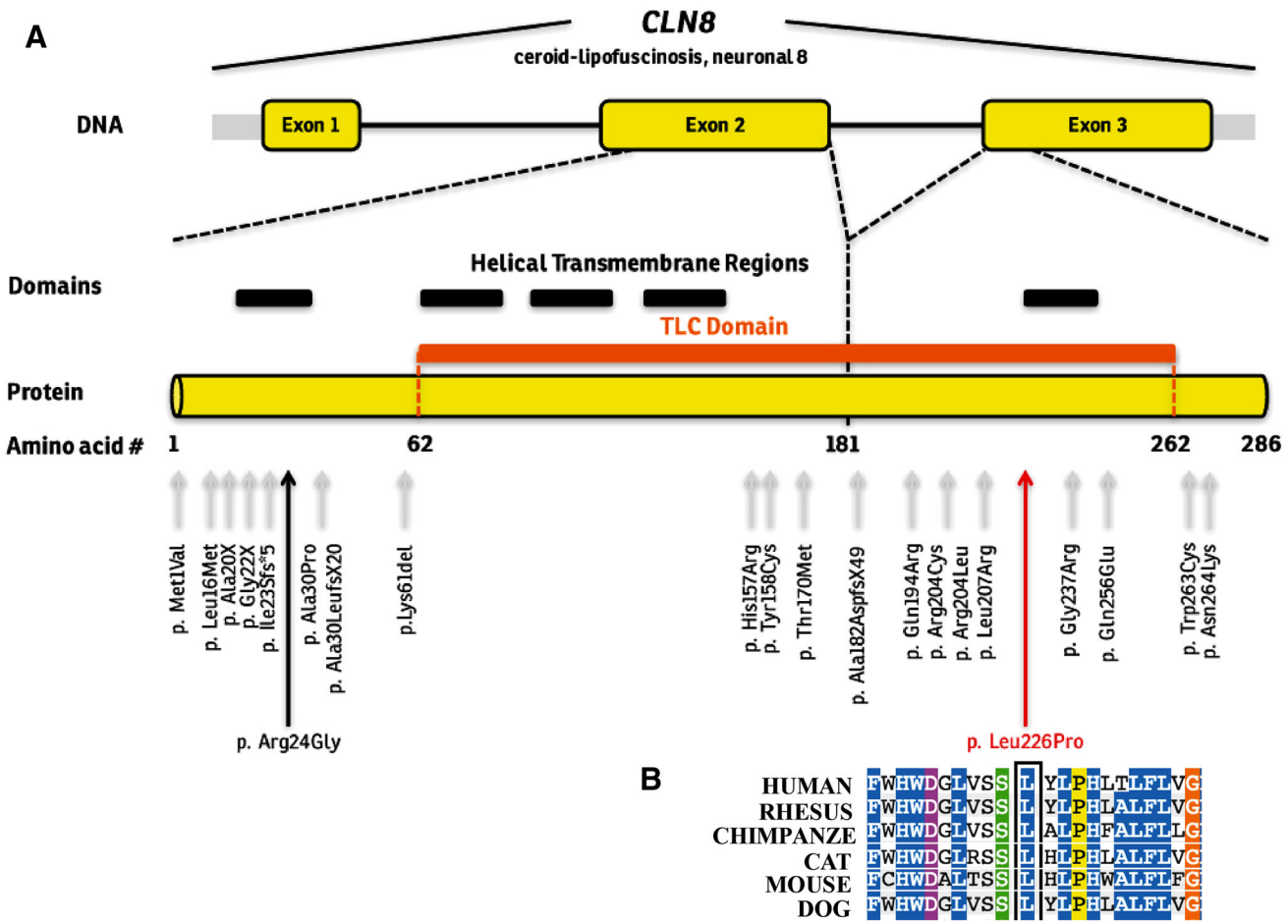

Fig. 3 **a** Structures of the CLN8 gene, encoded protein, protein domains, and mutations in the protein drawn from the literature. *Gray arrows* indicate mutations identified in vLINCL cases, *black arrow* shows the Northern epilepsy mutation, and the *red arrow* marks the variant identified in this study. **b** The conservation of 226th leucine residue among species (color figure online)

directly sequenced using ABI BigDye Terminator Sequencing Kit (Applied Biosystems, Darmstadt, Germany) and an automated capillary sequencer (ABI 3130; Applied Biosystems). To further identify the putative pathogenicity of the variants, we used in silico tools: SIFT (http://sift.jcvi.org/), Mutation Taster (http://www.mutationtaster.org/), and PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/index.shtml). Variant was named according to NM_018941.

Results

We assessed five patients from one pedigree who were all homozygous for a novel c.677T>C; p. (Leu226Pro) variant within exon 3 of the *CLN8* gene (variants numbered according to NM_018941 and NP_061764.2) by WES and confirmed by Sanger sequencing (Figs. 1, 3). This variant has not reported in a heterozygous or homozygous state in publicly available databases, such as the EVS, ExAC, and the 1000G Project or in our in-house database. Prediction analysis with in silico algorithms, such as Mutation Taster, Polyphen-2, and SIFT, showed this alteration to be pathogenic and disease-causing. The location of the variant was found to be in highly conserved region among species (Fig. 3b).

Discussion

We identified a novel homozygous *CLN8* missense variant in five affected kindred with a diagnosis of NE using WES. Of the four main forms of NCL, late-infantile NCL is subclassified into CLN2 (classic late-infantile), CLN1 (late-infantile), and CLN5-8 disease (variant late-infantile) [17]. Furthermore, CLN8 disease has been classified into NE and vLINCL. NE reported in Finland is a late-onset form, with slowly progressive epilepsy and intellectual disability [5]. The vLINCL phenotype has been reported in many countries. Most of the vLINCL patients show rapid

Table 2 Clinical variables of the CLN8 phenotypes

Phenotype	vLINCL8							Northern Epilepsy	
	Ranta et al. [9]	Canneli et al. [10]	Reinhardt et al. [7]	Reinhardt et al. [7]	Mahajnah and Zelnik [8]	Katata et al., 2015 [1]	Kohan et al., 2015 [29]	Herva et al. [5]	Index Patient, 2016
Geographical origin	Turkish	Italian	German	Pakistani	Israeli	Japanese	Argentinean	Finnish	Turkish
Consanguineous parents	4/6	1/3	−	+	+	NA	NA	+	+
Age at onset	4–7 years	4–6 years	3.5 years	4 years	4–5 years	3 years	3 years	5–10 years	8–12 years
Course	Rapid	Rapid	Rapid	Rapid	Slow-rapid	Rapid	Rapid	Slow	Slow
Visual impairment Eye findings	Visual deficit	Visual deficit	Visual deficit	Visual deficit	Visual deficit, Visual lost, optic atrophy, Retinal fibrosis	Visual deficit Bilateral retinal and macular degeneration	NA	Minimal visual deficit, no optic atrophy	No visual deficit, no optic atrophy
Seizures	+	+ Myoclonic, Tonic–clonic,	+	+ Drop attacks	+ Tonic–clonic	+ Drop, Myoclonic	+ Generalized tonic–clonic	+ Easily controlled	+ Generalized Tonic–clonic,
EEG	NA	NA	NA	NA	Multiple spikes and burst of generalized spike slow wave activity	Diffuse spikes and waves	NA	NA	Normal
Ataxia	+	+	NA	NA	-/+	+	+	NA	+
Developmental delay	+	+	+	+	+	+	+	+	−
Cognitive decline	+	+	+	+	+	+	+	+	+
Myoclonus	+	+	+	+		+	+	NA	−
Cerebral atrophy	NA	+	+	+	+	+	−	NA	+
Cerebellar atrophy	NA	+	+	+	+	+	+	NA	+
Other MRI findings	NA	None	None	None	Vermian atrophy, Enlarged cisterna magna, Increased ventricular size, Abnormal signals of the occipital periventricular white matter	Bilateral abnormalities around the lateral ventricles, Pontine atrophy	Severe hypotonia, Language never developed	NA	None
Other	NA	NA	Attention deficits, Sleep disturbances, Advanced spasticity	Dysphagia	Attention deficits, Behavioral difficulties, Horizontal nistagmus, Dementia	Left conjugate deviation, Rotational nistagmus, Chorea and athetosis, Dysphagia	NA	NA	None

Table 2 continued

Phenotype	vLINCL8							Northern Epilepsy	
	Ranta et al. [9]	Canneli et al. [10]	Reinhardt et al. [7]	Reinhardt et al. [7]	Mahajnah and Zelnik [8]	Katata et al., 2015 [1]	Kohan et al., 2015 [29]	Herva et al. [5]	Index Patient, 2016
Molecular Genetic Defects	p. L16M, p. T170M, p. A30fs20X, p. R204C, p. W263C	p. I23Sfs*5, p. Q194R, p. Y158C, p. A30P	p. R204L	p. G237R	p. Q256E	p. L207R	p. M1V p. N264K	p. R24G	p. L226P

NA not available

symptom progression, although some have a milder course [6–10]. Although vLINCL was reported previously in Turkish patients, NE has not been reported before in any country except Finland (Table 2; Fig. 3). This Finnish form is characterized by normal early development followed by drug-resistant epilepsy, starting at 5–10 years of age, slight motor dysfunction, slow progressive intellectual disability, and mildly reduced visual acuity [18]. In adulthood, the seizures become less frequent, but the slow deterioration of cognitive skills continues. Developmental milestones in all our patients were within the normal range until they had the first seizure. Epileptic seizures started at the age of 8–10 years in our patients. The onset ages of seizures in our patients were similar to those reported in Finnish patients; however, the frequency of seizures differed significantly: 1–2 times per week in Finnish patients and once every 2–3 months in our patients. There were 5-min intervals between the seizures in the twin patients. The 21-year-old patient had no seizure for 3 years and the 28-year-old had no seizure for 4 years.

Previous studies showed that a late-infantile NCL phenotype, distinct from Finnish NE, was the more typical CLN8 phenotype [9, 10, 19, 20]. To investigate the disease gene of the Turkish NCL variant, Ranta et al. reported *CLN8* mutations in nine families. In further studies, *CLN8* mutations with the late-infantile NCL phenotype were reported in patients from different countries of origin (Table 2). Additionally, Kousi et al. reported several *CLN8* mutations in Turkish patients but did not provided clinical details [21]. Symptoms of late-infantile NCL start at 2–7 years of age, followed by rapid disease progression with myoclonus, visual impairment, and loss of cognitive skills within 2 years from the time of onset [9]. In contrast to variant late-infantile CLN8 disease, the clinical course of our patients was slower, none of them had myoclonus or optical atrophy, and their visual acuity was normal. Clinical findings of our patients were consistent with NE.

A single mutation in *CLN8*, c.70C>G, resulting in an arginine-to-glycine substitution at codon 24 (p.Arg24Gly), was found in Finnish patients with the NE phenotype [22]. Although NE and vLINCL are related to *CLN8* mutations, the clinical phenotype is distinct between NE and other late-infantile-onset NCLs. Notably, NE starts at 5–10 years of age with frequent tonic–clonic seizures, followed by progressive intellectual disability [18, 23]. NE related to the *CLN8* mutation has not been reported previously in Turkey. Turkish patients reported in the literature related to the *CLN8* mutation demonstrated a more typical LINCL phenotype, with convulsions, motor impairment, myoclonus, intellectual disability, and visual loss [19]. The *CLN8* mutation in our patients was associated with a clinical course that was similar to that of NE patients previously reported in Finland. Development in our patients was

normal until the age of 8–10 years. Epileptic seizures started at the age of 8–10 and increased until puberty. Intellectual regression started after 14–15 years of age and was progressive with age. The c.677T>C variant described here has not been reported previously in NE patients.

The age at the first clinical manifestation of NE, 5–10 years, corresponds to the age of onset of juvenile NCL [24]. However, juvenile NCL typically starts with loss of vision due to retinal issues, particularly macular degeneration, followed by relatively rapid psychomotor deterioration and premature death, by 20–30 years of age [25]. In contrast, NE patients do not show initial visual loss or other ophthalmological signs, the course of psychomotor deterioration is much slower, and the patients usually survive until the age of 40–50 years [23]. Visual loss is not a prominent feature of NE; additionally, there is no myoclonus, and the clinical progression is slower. In our patients, there was typically no visual loss, optic atrophy, or myoclonus, and disease progression was slow. However, the apparently heterogeneous adult-onset forms of NCL (Kufs disease) including CLN4 disease caused by mutations in DNAJC5 and adult CLN6 disease both lead to dementia without visual loss but have a much later age of onset than our patients [26].

MRI findings were previously reported in patients with vLINCL. Thalamic signal changes on MRI have been reported in CLN 1/2 patients with vLINCL, and T2-weighted images show high signal intensities in the periventricular white matter. Severe cerebellar atrophy, evident on MRI, has been reported in CLN5 patients. In CLN8 patients, brain MRI revealed hyperintensity of the deep white matter of the centrum semiovale, as well as hypointense thalamic signals on T2-weighted images [27]. Katata reported bilateral periventricular hyperintensity in the white matter on T2-weighted images but no abnormal signals from the thalamus or posterior limb of the internal capsule in CLN8 patients [1]. Neuroradiological findings in patients with NE related to the CLN8 mutation were first defined by Hirvasniemi and Karuma [28]. Brain computed tomography (CT) scans showed that cerebellar and brainstem atrophy, apparent already in young adulthood, were the first signs, and the atrophy progressed in severity with age. Cerebral atrophy appeared later in these patients. They reported that only one of the seven patients under 30 years showed cerebral cortical atrophy and three patients showed central white matter atrophy, whereas all 12 patients older than 30 presented with cortical and/or central atrophy on CT. However, MRI findings in these patients were not given in detail. They reported that there was mild cerebellar atrophy in the MRI of a 16-year-old patient; however, another patient's MRI at 10 years old was normal. The MRI scan confirmed slight cerebral atrophy and moderate cerebellar–brainstem atrophy, with no specific localized finding. The signs of cerebellar atrophy appeared before those of cerebral atrophy [28].

In the cranial MRI examinations of our patients, diffuse cerebellar cortical atrophy was detected as the most common initial finding. At this stage, impairment in gait and speech as well as cerebellar system findings, such as dysmetria and dysdiadochokinesia, were apparent. Later, diffuse cerebral cortical atrophy started to develop following cerebellar atrophy. Radiological and clinical findings of the cerebellar and cerebral cortical atrophy were progressive and paralleled increases in age. Furthermore, thickening in the cranial diploe distance and hyperintense appearances in T1 and T2 images were observed in all our patients. Additionally, subdural hematomas were detected in two patients. These findings have not been reported before in patients with NE. We think that the subdural hematomas may stem from bleeding from the bridging veins, because of the shrinkage in cerebral volume due to the cerebral and cerebellar atrophy (Fig. 2).

To our knowledge, although NE was previously defined in Finland, NE due to the c.677 T>C missense mutation described in our patients has not been reported before. The consanguineous marriages between close relatives in this family might have caused this variant to be homozygous.

In conclusion, we defined NE cases in Turkey caused by a novel mutation in *CLN8*. We emphasize that WES can be an important diagnostic method in rare cases with atypical courses.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest as regards the reported study.

Ethical approval The authors declare that they acted in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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