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Original Article

A Novel Homozygous Variant in the *MCOLN1* Gene Associated With Severe Oromandibular Dystonia and Parkinsonism

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ABSTRACT: *Background:* Mucolipidosis type IV (MLIV) is a rare, progressive lysosomal storage disorder characterized by severe intellectual disability, delayed motor milestones and ophthalmologic abnormalities. MLIV is an autosomal recessive disease caused by mutations in the *MCOLN1* gene, encoding mucolipin-1 which is responsible for maintaining lysosomal function. *Objectives and Methods:* Here, we report a family of four Iranian siblings with cognitive decline, progressive visual and pyramidal disturbances, and abnormal movements manifested by severe oromandibular dystonia and parkinsonism. MRI scans of the brain demonstrated signal abnormalities in the white matter and thinning of the corpus callosum. *Results and Conclusions:* Whole-exome sequencing identified a novel homozygous variant, c.362C > T:p. Thr121Met in the *MCOLN1* gene consistent with a diagnosis of MLIV. The presentation of MLIV may overlap with a variety of other neurological diseases, and genetic analysis is an important strategy to clarify the diagnosis. This is an important point that clinicians should be familiar with. The novel variant c.362C > T:p. Thr121Met herein described may be related to a comparatively older age at onset. Our study also expands the clinical spectrum of MLIV associated with the *MCOLN1* variants and introduces a novel likely pathogenic variant for testing in MLIV cases that remain unresolved.

RÉSUMÉ : Un tout nouveau variant homozygote du gène *MCOLN1* associé à une dystonie oromandibulaire grave et au parkinsonisme *Contexte :* La mucolipidose de type IV (ML IV) est une maladie de surcharge lysosomale rare et évolutive, qui se caractérise par un déficit intellectuel grave, un retard des étapes du développement moteur et des anomalies oculaires. La ML IV est une maladie autosomique récessive, causée par des mutations du gène *MCOLN1*, qui code la mucolipine1, responsable du maintien de la fonction lysosomale. *Objectif et méthode :* Sera présentée, dans l'article, l'histoire d'une famille iranienne, comptant une fratrie de quatre membres atteints d'un déclin cognitif, de troubles visuels et pyramidaux progressifs et de mouvements anormaux qui se manifestent par une dystonie oromandibulaire grave et du parkinsonisme. Les examens par IRM du cerveau ont révélé des anomalies de la transmission des signaux dans la substance blanche et un amincissement du corps calleux. *Résultats et conclusion :* Grâce au séquençage de l'exome entier, l'équipe a découvert un tout nouveau variant homozygote, c.362C>T :p. Thr121Met, du gène *MCOLN1*, qui se montre compatible avec le diagnostic de la ML IV. Le tableau clinique de la ML IV peut coïncider avec celui de plusieurs autres maladies du système nerveux, et une analyse génétique représente une stratégie primordiale afin de clarifier le diagnostic. Il s'agit là d'un point important que devraient bien connaître les médecins. Le tout nouveau variant c.362C>T :p. Thr121Met ici décrit pourrait commencer à se manifester à un âge plus avancé que d'autres gènes du groupe. L'étude a aussi permis d'élargir le champ clinique de la ML IV associée aux variants *MCOLN1* et présente un tout nouveau variant, probablement pathogène, à soumettre à des tests dans les cas non résolus de ML IV.

Keywords: Lysosomal storage disorder; *MCOLN1*; mucolipin-1; mucolipidosis type IV; oromandibular dystonia; Parkinsonism

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Introduction

Lysosomal storage disorders are a group of over 50 metabolic disorders caused by defects in lysosomal degradation pathways.[1] A deficiency of lysosomal hydrolases or a defect along the lysosomal pathways causes the intralysosomal accumulation of undegraded substrates composed of mucopolysaccharides and lipids, called mucolipidosis.[1,2] In general, mucolipidosis can be classified into four

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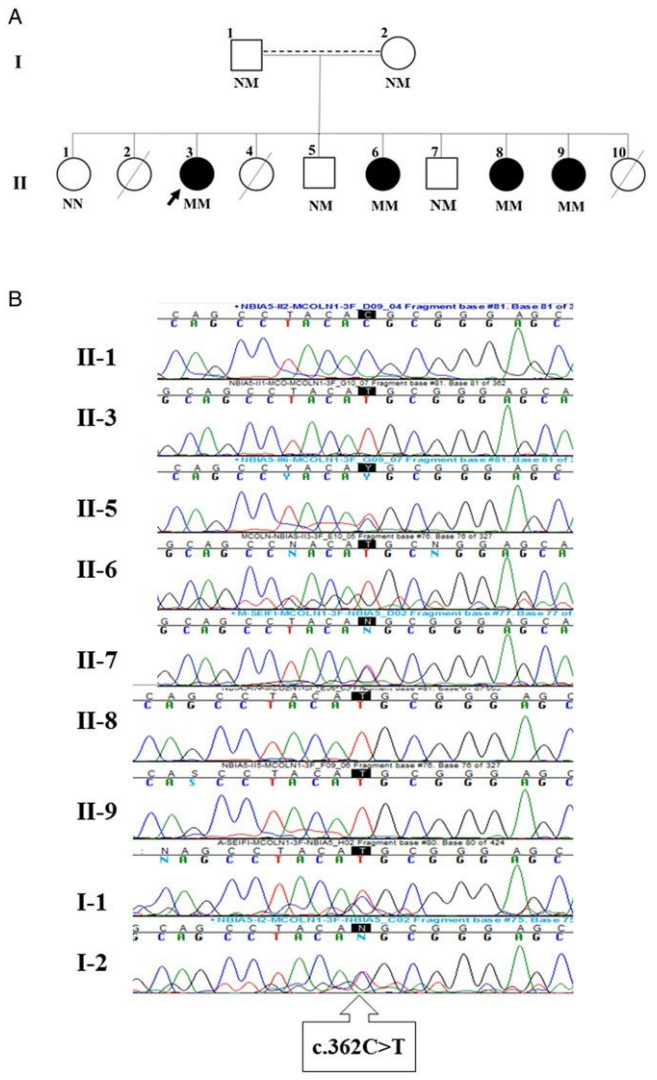

Figure 1. (A) Pedigree of the family in this study who carried a variant, c.362C > T:p. Thr121Met in the *MCOLN1* gene. Genotypes of *MCOLN1* are shown when individuals were assessed. The arrow denotes the proband. Dashed line shows the parents originated from nearby small villages, suggesting a common ancestry. Blank circles and squares: normal individuals; dark circles and squares: MLIV-affected individuals. (B) Sequence chromatograms of c.362C > T:p. Thr121Met variant in the *MCOLN1* gene in the family members. MLIV = mucolipidosis type IV; M = mutated allele; N = normal (wild type) allele.

types: I, II, III and IV.[1] Mucolipidosis type IV (MLIV: OMIM #252650) is an ultra-rare autosomal recessive progressive neurodegenerative disorder that appears during the first few years of life.[3,4] In addition to hypomyelinating leukodystrophy,[5] the disease manifests as severe psychomotor difficulties, hypotonia that gradually develops into spasticity, bilateral pyramidal tract signs, strabismus, visual impairment due to progressive retinal degeneration, corneal clouding and achlorhydria.[4,6,7] Marked clinical heterogeneity has been observed, even among siblings, and the disease may present with nonspecific symptoms, which makes diagnosis challenging.[1,8] The clinical and paraclinical characteristics of MLIV patients may overlap with a variety of other diseases; for example, the deposition of iron in the basal ganglia observed in some MLIV patients bears resemblance to neurodegeneration with brain iron accumulation (NBIA) cases.[4] MLIV is caused by biallelic variants in the *MCOLN1* gene (OMIM #605248), which encodes for transient receptor potential channel mucolipin-1 (TRPML1).[9] MLIV is thought to result from abnormal sorting and/or transport of macromolecules along the late endocytic pathway, while other mucolipidosis disorders are caused by deficiency of a specific metabolic enzyme.[10,11] Ethnically, MLIV is more frequent among Ashkenazi Jews than other ethnic groups.[4,12] Here, for the first time, we present the clinical manifestations of four MLIV siblings who carried a novel *MCOLN1* variant with prominent oromandibular dystonia and Parkinsonism.

Subjects and methods

Subjects

Four affected individuals of an Iranian family (Fig. 1A) who suffered from a progressive neurological disease were included. Although consanguinity was denied, the parents originated from nearby small villages, suggesting a common ancestry.

Patient II3

The proband (II3) was referred for genetic analysis at the age of 42 years. She was the result of an uneventful pregnancy with normal birth weight and normal psychomotor development up to the age of 6 years, when the first symptom, dysarthria, appeared followed by visual disturbance. She was unable to continue her schooling because of the progressive visual problem. She was initially diagnosed with retinitis pigmentosa (RP). The family has noticed progressive cognitive decline since the age of 12. In early adolescence, gait disturbance was added to her other problems due to the stiffness of her lower limbs (Table 1). She also has dysphagia, iron deficiency anemia (consumes iron supplements since ~ 10 year) and high levels of serum gastrin, 712 pg/mL (reference intervals 13−115 pg/mL) (Table 2) which supports the diagnosis of achlorhydria. Over time, all movements were reduced, including facial mimicry, and abnormal movements developed in the face and limbs, including the inability to close her jaw (jaw opening dystonia) and abnormal dystonic postures in the limbs. However, no dysmorphic feature was observed in the proband as well as in her affected sisters (II6, II8 and II9). In terms of quality of life, she has severe movement problems and is not able to walk without aid. She relies on other family members for all of her daily activities, including going to the bathroom and eating. She has an irritable mood and is restless. On neurologic examination, she had anarthria (which she has been suffering since the age of ~ 20 years) (based on her mother's explanation, she had severe dysarthria from 6 years old) and was unable to follow commands and cooperate for a complete examination due to severe cognitive dysfunction. Positive findings included optic atrophy and RP, a masked face, severe jaw opening dystonia, dystonic postures of the hands and legs, hypokinesia, spasticity in the lower limbs, increased deep tendon reflexes and bilateral Babinski signs. Because of Parkinsonism, dystonia and spasticity, she was not able to walk unaided (Video 1). There was no evidence of myopathy or neuropathy based on the results of the electromyography/ nerve conduction study, so we did not perform muscle biopsy.

Brain magnetic resonance imaging (MRI) revealed cerebellar atrophy, white matter hyperintensities on T2/FLAIR (fluid attenuated inversion recovery) and atrophy of the corpus callosum. Iron sensitive sequences (susceptibility weighted imaging or SWI) was normal (Fig. 2A, D, E).

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Table 1. Detailed clinical features of patients with *MCOLN1*-related phenotypes in the published literature**

Reference	Year	Genetics data		Age (y)	AAO	Sex	Consangouinity	Nationality
		Variant in cDNA level	Variant in amino acid level					
Bargal R, et al.	2002	c.163-197del, c.195-197insTCA	NR	Died at 37	8 m	M	NR	German
				Died at 33	Infantile	M	NR	German
Goldin E, et al.	2004	c.1207C>T	p. Arg403Cys	4	NR	F	NR	Canadian-Scottish
Dobrovolny R, et al.	2007	c.1084G>T, c.1704A>T	p. Asp362Tyr, p. Gly568=[#]	12	NR	F	NR	NR
[3]	2009	c.1367C>T	p. Ser456Leu	11	6 m	M	+	Turkish
[11]	2013	c.1307A>G	p. Tyr436Cys	6	1 y	M	+	Saudi Arabian
[6]	2015	c.395-397delCTG, c.468-474dupTTGGACC	p. Ala132del, p. Asn159Leufs*27	5	NR	M	NR	Italian
[5]	2016	c.1292G>A	p. Cys431Tyr	Died at 68	NR	M	+	Japanese
K. Gowda V, et al.	2017	c.771dupC	p. Val258Argfs*6	6	NR	M	+	NR
[19]	2018	c.551T>C	p. Ile184Thr	26	Adolescence	M	NR	NR
				22	Adolescence	F	NR	NR
[13]	2018	c.694A>C, c.785T>C	p. Thr232Pro, p. Phe262Ser	2	4 m	M	NR	French-Canadian
Meloche J, et al.	2018	c.405+1G>A	NR	NR	NR	M	NR	NR
[10]	2020	c.936-938del, c.1503dupC	p. Phe313del, p. Ile502Hisfs*106	4	1 y	F	NR	Japanese
[8]	2020	c.937-939delTTC	p. Phe313del	17	NR	M	NR	NR
[16]	2020	c.1256G>C	p. Arg419Pro	20	NR	F	NR	Pakistani
				23	NR	F	NR	
				27	NR	M	NR	
[17]	2021	c.1135-1G>C	Mis-splicing	NR	1 y	NR	NR	Ashkenazi Jewish
[1]	2022	c.237+5G>A	Mis-splicing	1.5	NR	F	+	Omani
				9	Infantile	M		
				13	Infantile	F	+	
				5	Infantile	M		
				9	Infantile	M		
				2	Infantile	M		
This study	2024	c.362C>T	p. Thr121Met	42	6 y	F	+	Iranian
				35	6 y	F		
				29	8 y	F		
				27	13 y	F		

Ophthalmologic consultation and fundus photos confirmed bilateral optic atrophy and RP (Fig. 3). Abdominal and heart MRIs to detect iron deposition (ferriscan) were done and revealed no pathologic iron deposition in the liver and heart (Supplementary file 1). Renal function tests such as blood urea nitrogen, creatinine and electrolytes were normal (Table 2). Her abdominal, including kidneys, ultrasound scan results were normal. Since there was no polysomnography study (PSG) for the proband, we could not say precisely whether there was any abnormal sleep pattern, but based on their healthy family members, there was no evidence of an abnormal sleep pattern such as nocturnal seizures, myoclonus or REM sleep behavior disorder.

Patient II6

The 35-year-old affected sister (II6) had normal psychomotor development in early childhood. The family noticed visual problems at the age of 6 years. She was unable to attend normal school due to her low intelligence quotient. Later, she developed dysarthria, dysphagia, slowness of movement and gait disturbance. She was not able to walk independently when she was 13 years old (Table 1). Similar to her sister, the patient had high levels of serum gastrin, 235 pg/mL and iron deficiency anemia (Table 2). She has been taking iron supplements since the age of 10 years. Her quality of life was similar that of to the proband. The examination was similar to the proband, including optic atrophy, RP, staring face,

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Table 1. Detailed clinical features of patients with *MCOLN1*-related phenotypes in the published literature** (*continued*)

		Neurological findings										Ophthalmic abnormalities				Brain MRI	
Reference	Year	Developmental delay	Intelectual disability/ cognitive decline	Dysarthria	Spasticity	Motor deficit	Babinski's sign	Clonus	Parkinsonism (hypokinesia/ bradykinesia/ rigidity)	Dystonia	Iron deficency anemia	Corneal opacities/ haziness	Cataract	RP	Nystagmus/ strabismus	Thin/atrophic/ hypoplastic corpus callosum	Iron accumulation
Bargal R, et al.	2002	+	+	NR	+	+	NR	NR	NR	NR	+	+	NR	NR	NR	NR	NR
		+	+	NR	+	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	NR	NR
Goldin E, et al.	2004	+	NR	NR	NR	+	NR	NR	NR	NR	+	+	NR	NR	NR	+	NR
Dobrovolny R, et al.	2007	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR	+	NR	NR
[3]	2009	+	NR	+	+	+	NR	+	NR	NR	+	+	NR	NR	+	+	+
[11]	2013	+	NR	+	+	+	+	+	NR	NR	+	+	NR	NR	NR	+	NR
[6]	2015	+	+	+	+	+	NR	NR	NR	NR	NR	+	NR	NR	NR	+	+
[5]	2016	NR	+	+	+	+	+	+	+	OMD	NR	NR	+	NR	NR	+	NR
K. Gowda V, et al.	2017	+	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	+	+	NR
[19]	2018	NR	NR	NR	NR	NR	NR	NR	+ (bradykinesia, tremor)	GD	NR	NR	NR	NR	NR	NR	NR
		NR	NR	NR	NR	NR	NR	NR	+ (bradykinesia)	GD	NR	NR	NR	NR	NR	NR	NR
[13]	2018	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	+	NR
Meloche J, et al.	2018	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
[10]	2020	+	NR	+	NR	+	NR	NR	NR	NR	+	NR	NR	NR	NR	+	NR
[8]	2020	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	+	NR
[16]	2020	NR	+	NR	NR	NR	NR	NR	NR	NR	NR	+	+	NR	NR	NR	+
		+	+	+	NR	NR	NR	NR	NR	NR	+	+	NR	+	NR	+	NR
		+	+	+	+	+	+	+	NR	NR	+	+	+	+	+	+	+
[17]	2021	+	NR	NR	+	NR	NR	NR	NR	NR	+	NR	NR	NR	NR	+	NR
[1]	2022	+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
		+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
		+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
		+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
		+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
		+	NR	NR	+	NR	NR	NR	NR	NR	+	+	NR	NR	+	+	NR
This study	2024	+	+	+	+	+	+	–	+	OMD	+	–	–	+	–	+	–
		+	+	+	+	+	+	–	+ (akinesia, rigidity)	OMD	+	–	–	+	–	+	–
		+	+	+	+	+	+	–	+ (hypokinesia)	OMD	+	–	–	+	–	+	–
		+	+	+	+	+	+	–	+ (hypokinesia, rigidity)	OMD	+	–	–	+	–	+	–

NR = not reported; *m* = month; *y* = year; *M* = male; *F* = female; RP = retinitis pigmentosa; OMD = oromandibular dystonia; GD = generalized dystonia.
#Synonymous variant "p. Gly568=" creates a novel donor splice site.
**Reference No. 4, which evaluated 26 cases of MLIV, was not included in the table due to its unavailability of the particular clinical information pertaining to these individuals.

Table 2. CBC and biochemical examinations of all affected individuals and their follow-ups in different times

Patient ID	Date	Gastrin (13-115 pg/ml)	WBC (4-11 10*3/μl)	RBC (4-5.1 10*6/μl)	HGB (11.5-15 g/dL)	HCT (34.4-45 %)	MCV (80-96 fL)	MCH (26-33 pg)	MCHC (32-36 g/dL)	RDW-CV (11-14.5 %)	RDW-SD (33.4-49.2 fL)	Hypochromia	Anisocytosis	TIBC (250-450 μl/dl)	BUN (8-20 mg/dL)
II3	14/11/2023	712	3.49	4.81	10	33.8	70.3	20.8	29.6	19.6	49.3	+	+	340	12
	15/7/2023	–	5.1	3.97	8.3	27.7	69.8	20.9	30	16.5	43.4	+	slight	–	–
	6/3/2023	–	3.4	4.54	9.1	32.6	71.8	20	27.9	15.4	42.7	+	+	–	–
	18/1/2018	–	4	4.93	13.4	39.3	79.7	27.3	34.2	15.5	–	–	–	–	10
II8	14/11/2023	383	6.56	4.56	13.3	42.4	93	29.2	31.4	13.8	45.1	–	–	223	–
	23/7/2023	–	7.7	4.63	13.7	41.1	88.8	29.6	33.3	13.7	45.8	–	–	–	–
	12/11/2022	–	7.3	4.77	13.5	40.3	84	28.3	33.5	13.6	–	–	–	–	–
	15/9/2021	–	10.4	4.28	11.9	36.7	85.7	27.8	32.4	13.4	–	–	–	–	–
	4/9/2013	–	6.5	5.2	11.4	35.2	68	22	32	26	–	+	+	–	–
II6	14/11/2023	235	5.87	4.09	11.8	37.5	91.7	28.9	31.5	13.8	44.4	–	–	248	16
	3/12/2022	–	5.5	4.74	13	39.3	83	27.4	33.1	13.1	–	–	–	–	–
II9	14/11/2023	>1000	6.99	4.91	12.7	40.6	82.7	25.9	31.3	15	44.9	–	–	390	–
	23/5/2023	–	6.7	4.88	11.8	36.7	75	24.2	32.2	15	–	+	slight	–	–

Patient ID	Urea (17-43 mg/dL)	Creatinine (0.6-1.3 mg/dL)	Uric acid (3.6-6.1 mg/dL)	eGFR (> 90 ml/min/ 1.73 m2)	Fe (39-149 μg/dL)	Ca (8.6-10.3 mg/dL)	P (2.6-4.5 mg/dL)	Ferritin (7-147 ng/mL)	S.G.O.T (Up to 31 U/L)	S.G.P.T (Up to 31 U/L)	ALP (64-306 (IU/L)	LDH (<480 U/L)	Bilirubin total (0.1-1.2 mg/ dL)	Bilirubin direct (Up to 0.3 mg/ dL)
II3	15	0.63	3.7	110.2	10	–	–	15	–	–	–	–	–	–
	30	0.7	3.6	–	55	8.9	3.6	6.41	29	25	106	160	–	–
	29	0.7	3.6	–	66	–	4.1	7.09	27	39	–	432	–	–
	–	0.5	–	–	–	9.3	3.2	14.2	26	18	65	195	–	–
II8	14	0.61	–	122	122	–	–	129	–	–	–	–	–	–
	36	1	–	–	134	10.1	3.2	9.56	41	44	84	–	–	–
	–	–	–	–	–	–	–	–	46	56	148	–	0.5	0.2
	40	0.7	–	–	–	8.9	3.5	–	–	–	–	–	–	–
	–	–	–	–	52	–	–	131	–	–	–	–	–	–
II6	36	0.79	4.5	97.2	86	–	–	72	–	–	–	–	–	–
	40	1.2	–	–	–	9.4	3.1	–	26	22	84	–	–	–
II9	19	0.79	–	102.1	44	–	–	10	–	–	–	–	–	–
	27	0.8	–	–	–	9.2	3.7	–	21	23	163	–	–	–

CBC = complete blood count; WBC = white blood count; RBC = red blood count; HGB = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; RDW = red cell distribution width; TIBC = total iron binding capacity; eGFR = estimated glomerular filtration rate; Fe = iron; Ca = calcium; P = phosphorus; SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; "-" = Not checked. All abnormal amounts shown in bold.
All of the patients are taking iron supplements during tests.

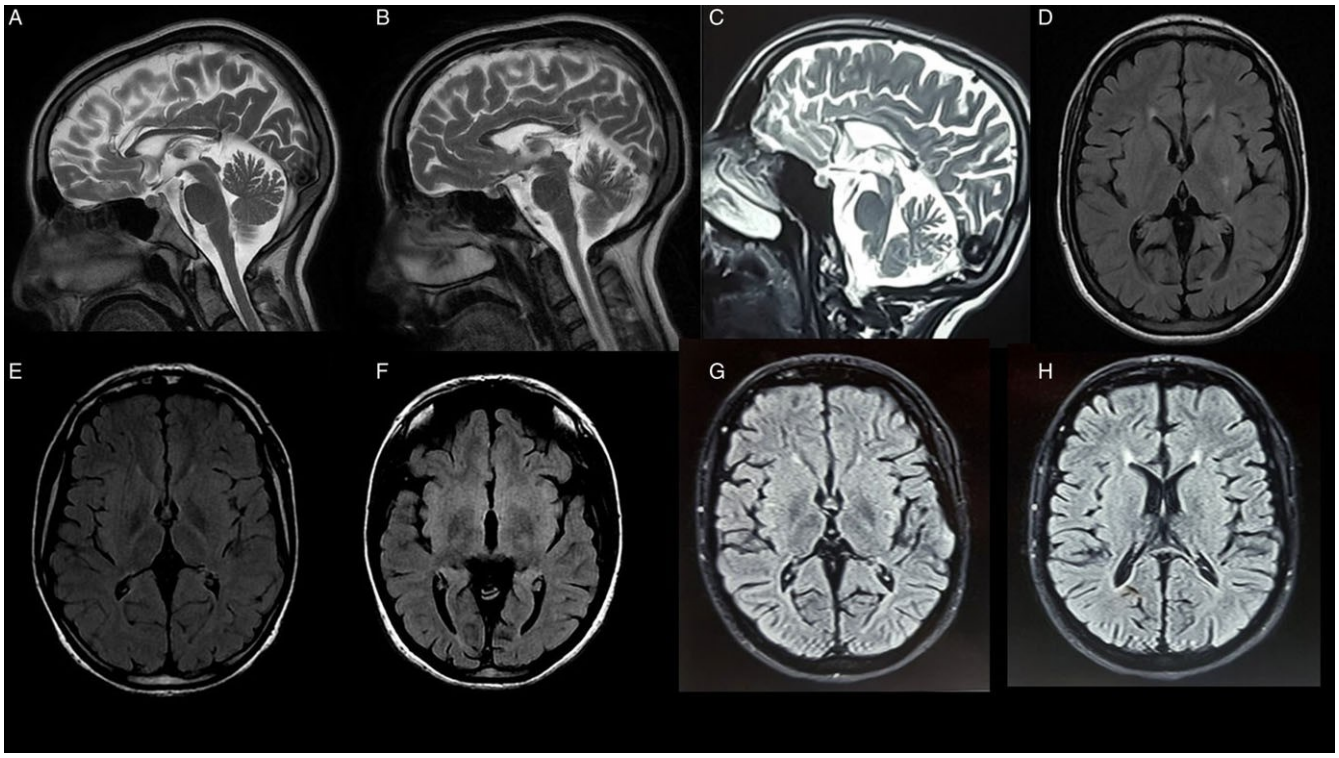

Figure 2. Brain MRI of cases II3 (A, D, E), II8 (B, F) and II9 (C, G, H) shows thin corpus callosum on sagittal T2 sequences (A, B, C), white matter hyperintensity around the frontal horns on FLAIR sequences (D, H) and normal basal ganglia (no evidence of iron accumulation) (E, F, G).

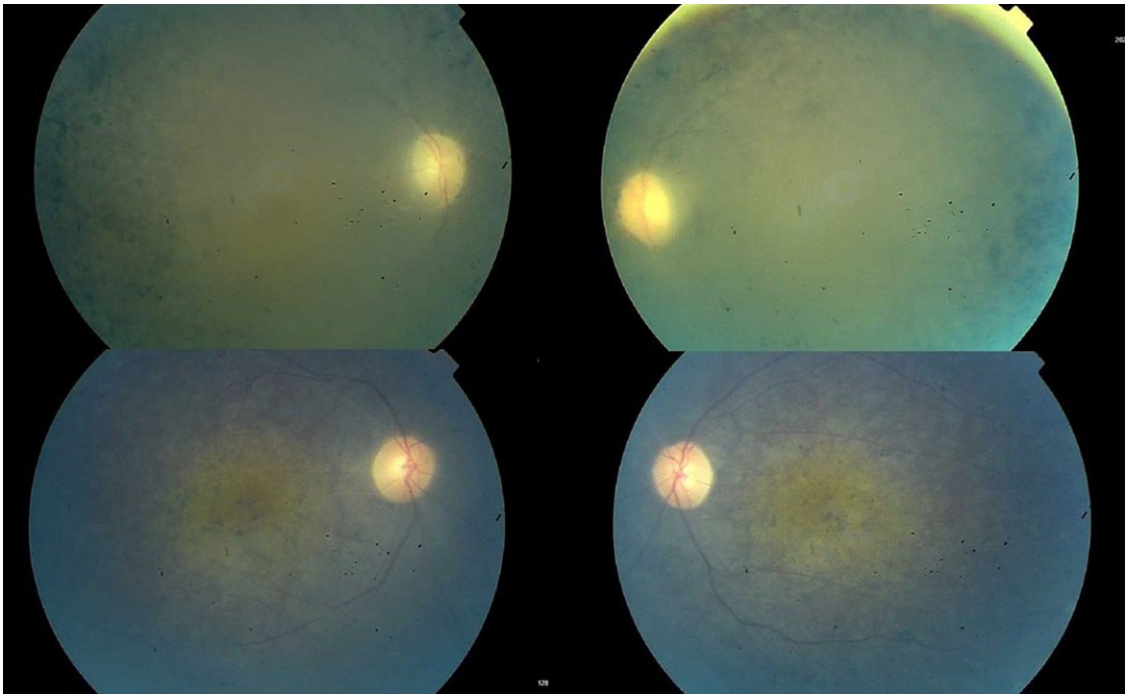

Figure 3. Fundus photos of cases II3 (upper row) and II9 (lower row) showing optic atrophy and retinal degeneration of the right and left eyes.

oromandibular dystonia, unintelligible speech, akinesia and rigidity, and spasticity of the lower limbs, dystonia of the limbs and trunk and spastic gait (Video 2). Like her sister, the renal function tests (Table 2) and abdominal ultrasound scan results were normal. Her sleep pattern was also similar to that of the proband. There was no evidence of myopathy or neuropathy. MRI showed mild cerebellar atrophy, atrophy of the corpus callosum and hyperintensity of the centrum semiovale and internal capsule.

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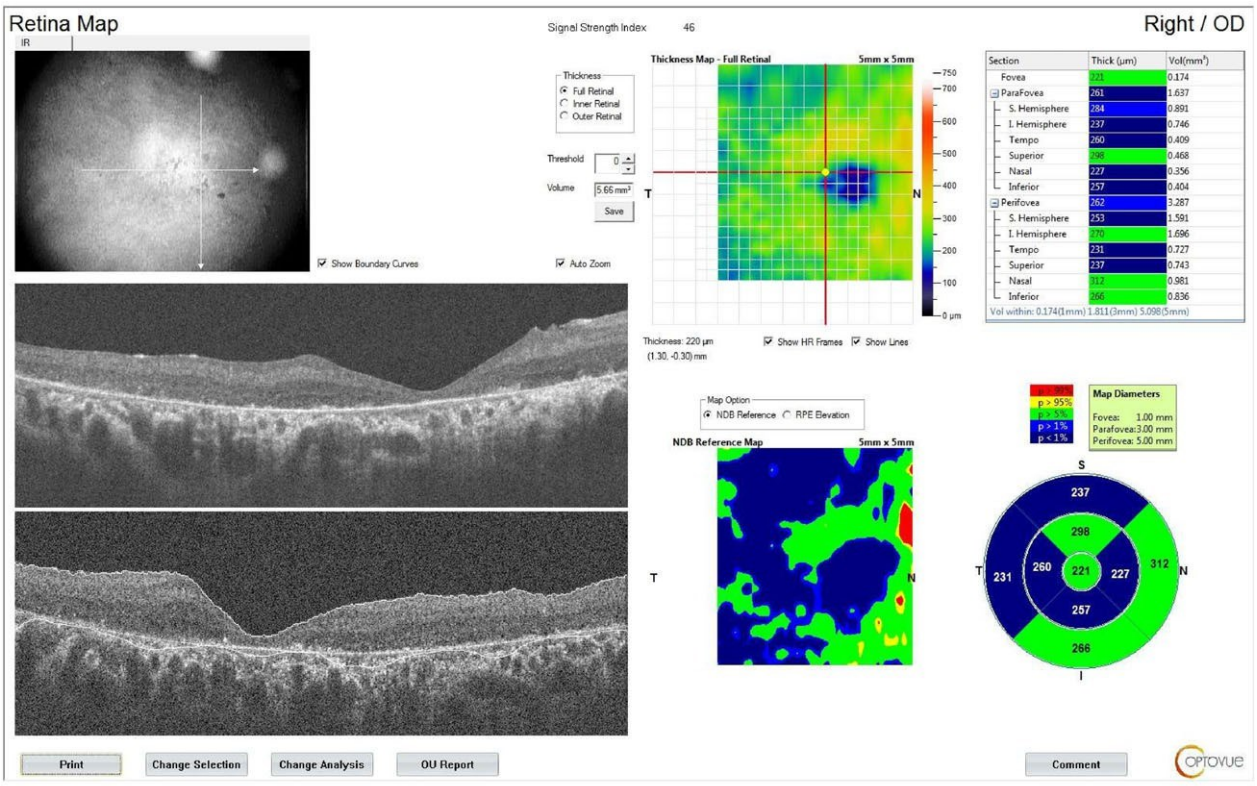

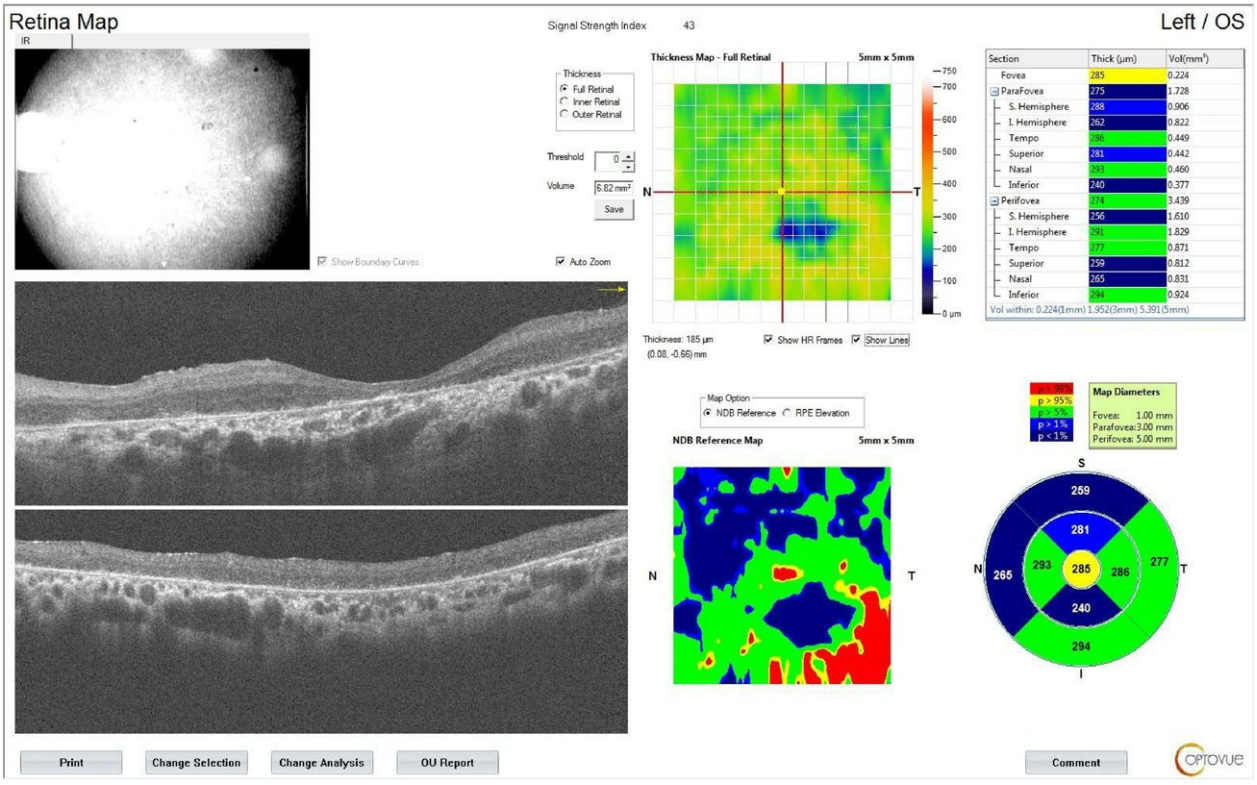

Figure 4. Optic coherence tomography (OCT) of case II9 showing evidence of retinal thickness changes in the inner and outer sectors of the macula in right and left eyes.

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Patient II8

The third affected sibling in this family (II8) was a 29-year-old female whose problems started at the age of 8, with cognitive decline, progressive visual disturbances and dysarthria. She had multiple episodes of generalized tonic–clonic seizures until she was 18 years old. Since she was seizure-free in recent years and does not receive any anti-epileptic medication at this point. Additional biochemical examinations revealed the high levels of serum gastrin, 383 pg/mL and iron deficiency anemia (consuming iron supplements since ~ 9 years) (Table 2). Her quality of life was better than that of the proband and II6, and she could walk unaided; however, her vision problems have made it difficult for her to walk. Positive findings on neurologic examination were RP, optic atrophy, oromandibular dystonia, hypokinesia, increased muscle stretch reflexes and spastic gait. Plantar reflexes were extensor bilaterally (Table 1 and Video 3). There was no evidence of myopathy or neuropathy. Abnormal findings on brain MRI were mild cerebellar atrophy and atrophy of the corpus callosum (Fig. 2B,F). SWI sequences showed no evidence of pathologic iron deposition. The renal function tests (Table 2) and abdominal ultrasound scan results were normal. Her sleep pattern was also similar to that of the proband.

Patient II9

The fourth patient in this family (II9) was a 27-year-old female whose problems started at the age of 13, with symptoms developing in a similar fashion to her other affected siblings, comprising visual abnormalities, cognitive decline, speech and swallowing disturbances, gait difficulty, the high levels of serum gastrin, > 1000 pg/mL and iron deficiency anemia (Table 2). She has been taking iron supplements since the age of nine. Her quality of life was similar to that of II8. Neurologic examination revealed RP and optic atrophy, pyramidal abnormalities (spasticity of limbs, increased deep tendon reflexes and Babinski signs) and a movement disorder manifesting dystonia of the jaw and limbs, hypokinesia and rigidity (Table 1). Neither neuropathy nor myopathy was evident. Her brain MRI was similar to that of her sisters (Fig. 2C,G,H).

Fundus examination by an ophthalmologist revealed bilateral optic atrophy and RP (Fig. 3). Optic coherence tomography showed evidence of retinal thickness changes in the inner and outer sectors of the macula in both eyes (Fig. 4). The renal function tests (Table 2) and abdominal ultrasound scan results, as well as the sleep pattern, were normal.

Exome sequencing

Whole-exome sequencing (WES) was performed on the DNA of the proband. WES data was analyzed based on previously reported workflows.[13] The candidate variant was PCR amplified and Sanger sequenced in the proband and her family members.

Results

A novel homozygous variant, c.362C > T:p. Thr121Met in *MCOLN1* (NM_020533.3), was identified. The variant was co-segregated with the disease status in the family (Fig. 1B) and predicted as likely pathogenic based on the American College of Medical Genetics and Genomics (ACMG) classification (rules PM1, PM2 and PP1). The minor allele frequency of the variant was 0.000028, and 0.000016 in 1000 genomes, and GenomAD, respectively. It was not found in a homozygous state in both databases and was also not detected among the exome data of the 1000 unrelated Iranian individuals (Iranome database; http://www.iranome.com/ and 200 in-house exomes).

Discussion

While MLIV is mainly characterized by ophthalmological abnormalities, developmental delay and hypoplastic corpus callosum,[11] the disease manifests variable expression.[12,14] The disease results from mutations in *MCOLN1*, which is a Ca2+/Fe2+ release channel in late endosomes and lysosomes.[15] Thus, mutations in this gene can cause the accumulation of excessive amounts of iron, which results in defects in endosomal/lysosomal trafficking, autophagy, lysosomal exocytosis dysregulation, mTORC1/TFEB signaling axis aberrations and heavy metal dyshomeostasis with reactive oxygen species formation.[15–17] Defects along each of these steps may help explain the heterogeneous phenotype observed in MLIV patients.[15] Although there are reports of iron accumulation in some cases,[7,18–20] our cases did not show evidence of iron accumulation on brain and other organs (Supplementary file 1).

Literature review also showed that MLIV cases share some relatively common features, including developmental delay, spasticity and impaired vision (4). As in our cases, there was the combination of cognitive disturbance, a movement disorder (dystonia, especially oromandibular dystonia, hypokinesia and rigidity), pyramidal signs (spasticity, increased deep tendon reflexes and Babinski signs) and RP (Table 1). However, there is variability in age at onset (AAO) and clinical heterogeneity in MLIV cases (Table 1). Based on these heterogeneities, Misko et al. have suggested that the natural history of MLIV consists of three stages: slow developmental gains in early life, plateauing with worsening hypertonicity and motor function and functional regression in early adolescence.[4] Also, they have mentioned that the majority of cases develop their symptoms at less than one year of age, ranging from 1.5 months to 8 years of age (mean age of 7.25 months)[4] (Table 1). In comparison, our cases also presented a three-stage history of MLIV, and like Misko's study, they clearly displayed neurodegenerative elements in addition to a static neurodevelopmental condition, but the mean AAO in our cases (8.25 +/−2.86 years) was higher than the median of reported cases.

The observation that warrants attention is that in Misko's investigation, a total of 18 out of 26 subjects displayed the presence of at least one c.406-2A > G allele, with 58% of them possessing Ashkenazi Jewish ancestry.[4] Maybe these issues make the spectrum of their symptoms more similar. Nevertheless, it is worth noting that a single patient (ID 1) with c.406-2A > G mutation exhibited a mild manifestation of the disease.[4] Also, our patients and other cases in Table 1, who carried different variants of *MCOLN1*, presented relatively similar features and disease history, despite the fact that a number of their symptoms have not been mentioned in detail.

Here, for the first time, we describe four Iranian MLIV siblings who carried a novel homozygous variant in the *MCOLN1* gene. In late childhood, our patients developed a progressive visual problem, RP, which is a rare symptom of MLIV. Thereafter, they developed mental decline, difficulty with school performance, dysarthria, dystonia, lower limb spasticity and gait disturbances. Additionally, patient II8 had multiple episodes of generalized tonic–clonic seizures. MLIV typically results in a very thin corpus callosum,[5] which is characteristic of our patients (Table 1). Overall, notwithstanding the fact that our patients exhibited a more advanced age of disease onset, the course of the disease appears to

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follow the same pattern as suggested by Misko et al.[4] Based on WES data, a novel variant of *MCOLN1* was detected, and MLIV disease was confirmed in this family (Fig. 1B). A later AAO in our cases may relate to the nature of the variant.

As is increasingly recognized in the field of neurogenetic disorders, the presentation of MLIV may overlap with a variety of other diseases, and genetic analysis is an important strategy to clarify the diagnosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.47.

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Narges Yazdi: 1C and 3A.
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