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ORIGINAL COMMUNICATION

Clinical and genetic features of patients suffering from CMT4J

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Abstract

Mutations in the *FIG4* gene have been identified in various diseases, including amyotrophic lateral sclerosis, Parkinson's disease, and Charcot–Marie–Tooth 4 J (CMT4J), with a wide range of phenotypic manifestations. We present eight cases of CMT4J patients carrying the p.Ile41Thr mutation of *FIG4*. The patients were categorized according to their phenotype. Six patients had a pure CMT; whereas, two patients had a CMT associated with parkinsonism. Three patients had an early onset and exhibited more severe forms of the disease. Three others experienced symptoms in their teenage years and had milder forms. Two patients had a late onset in adulthood. Four patients showed electrophysiological evidence of conduction blocks, typically associated with acquired neuropathies. Consequently, two of them received intravenous immunoglobulin treatment without a significant objective response. Interestingly, two heterozygous patients with the same mutations exhibited contrasting phenotypes, one having a severe early-onset form and the other experiencing a slow disease progression starting at the age of 49. Notably, although 7 out of 8 patients in this study were compound heterozygous for the p.Ile41Thr mutation, only one individual was found to be homozygous for this genetic variant and exhibited an early-onset, severe form of the disease. Additionally, one patient who developed the disease in his youth was also diagnosed with hereditary neuropathy with pressure palsies. Our findings provide insights into the CMT4J subtype by reporting on eight heterogeneous patient cases and highlight the potential for misdiagnosis when conduction blocks or asymmetrical nerve conduction study results are observed in patients with *FIG4* mutations.

Keywords Charcot · Marie · Tooth · FIG4 · CMT4J · Case report · Conduction blocks · Parkinsonism

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Abbreviations

ALS	Amyotrophic lateral sclerosis
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMAP	Compound motor action potential
CMT	Charcot–Marie–Tooth disease
CNS	Central nervous system
CSF	Cerebrospinal fluid
DML	Distal motor latency
DTR	Deep tendon reflexes
HNPP	Hereditary neuropathy with liability to pressure palsies
MRC	Medical Research Council
NCS	Nerve conduction study
NCV	Nerve conduction velocity
NGS	Next-generation sequencing
ONLS	Overall Neuropathy Limitations Scale
Plt	Pale tremor
WGS	Whole genome sequencing

Introduction

Charcot–Marie–Tooth disease (CMT) is the most prevalent inherited neuromuscular disorder, affecting approximately 1 in every 2500 individuals [1]. It is a complex condition involving over 100 genes and is characterized by motor and sensory deficiencies, as well as skeletal deformities. CMT can be categorized into four primary types: CMT1, which is a demyelinating form; CMT2, an axonal neuropathy; CMT3, a severe congenital hypomyelinating neuropathy; and CMT4, an autosomal recessive demyelinating neuropathy [2].

Among these types, CMT4J is caused by recessive mutations in the *FIG4* gene, which encodes phosphoinositide 5-phosphatase, that lead to both neuron loss and demyelination in the peripheral nervous system, with vacuolization indicative of endosome/lysosome trafficking defects [3].The first description of this mutation was provided by Chow et al. in 2007. They reported five heterozygous patients who carried at least one missense mutation p.Ile41Thr in exon 2 of the *FIG4* gene. All five patients exhibited an early-onset and severe form of the disease [3]. Subsequent studies have reported heterogeneous cases of both compound heterozygous and homozygous CMT4J patients, showcasing a range of clinical presentations from mild to severe forms, sometimes accompanied by central nervous system (CNS) defects and abnormal electrophysiological findings [3–10]. Furthermore, *FIG4* mutations have been linked to other disorders such as Yunis–Varòn syndrome (YVS) [11], which was first described in 1980, and early parkinsonism [12]. Several studies have taken disparate approaches to patient selection when investigating CMT disease. While some reports have exclusively focused on patients manifesting a "pure" CMT phenotype, others have included patients who exhibit CMT in conjunction with additional clinical presentations. For instance, certain patients were observed to have co-existing Parkinson's syndrome [12].

Additionally, autosomal dominant mutations of *FIG4* have previously been associated with severe forms of ALS known as ALS11 [15]. In a study of a European cohort of 200 ALS patients, whole genome sequencing (WGS) revealed that 3% of the patients carried a *FIG4* mutation, including members of one family and five sporadic cases [16]. *FIG4* mutations have been found to be associated with variable phenotypes of ALS and CMT4J [4, 13, 15–17].

Recent investigations have shown that *FIG4* mutations have a frequency of approximately 3 per 1000, depending on the populations being studied [16, 18]. The most common mutation, *FIG4-c.122 T>*C, p.Ile41Thr, has an allelic frequency below 1 in 500 in the Northern European population [19]. The *FIG4-c.122 T>*C variant is recognized as a hypomorphic allele that encodes an unstable protein. This characteristic explains the clinical stability observed in homozygous cases [20]. Seven out 8 of reported cases involve compound heterozygous individuals, 6 of whom possess both the *FIG4-c.122 T>*C mutation and an additional mutation introducing a premature stop codon, thereby resulting in a loss of function [11]. These latter cases are typically characterized as more severe and exhibit a rapid disease progression, as previously reported [12–14, 20, 21]. Functional and preclinical studies have demonstrated that restoring FIG4 expression could be a promising therapeutic avenue, warranting further investigation for potential clinical application in patients [3]. In anticipation of upcoming clinical trials, it is imperative to continue the identification and phenotypic-genotypic characterization of new patients.

In this report, we present eight cases of patients carrying the p.Ile41Thr mutation of *FIG4*. These patients developed CMT4J at different ages and exhibited diverse clinical manifestations.

Methodology

Eight patients with *FIG4* mutations associated with CMT4J were identified through the French network of reference centers for neuromuscular disorders (FILNEMUS). These patients were evaluated in specialized neuromuscular disorders centers that follow standardized procedures for patient follow-up and diagnosis. Genetic analyses, including a CMT panel screening of 116 genes known to be involved in CMT disease, were conducted for all patients.

Retrospective data collection was performed, encompassing information such as sex, age, age of onset of initial symptoms, clinical manifestations, disabilities, and various clinical scales and scores. The clinical scales and scores

included the Overall Neuropathy Limitations Scale (ONLS) for upper limbs (rated from 0 to 5), lower limbs (rated from 0 to 7), and total score (ranging from 0 to 12), the CMT Examination Score (CMTES, ranging from 0 to 28), the CMT Neuropathy Score (CMTNS, ranging from 0 to 36), and the Medical Research Council (MRC) score. Furthermore, Nerve Conduction Study (NCS) findings and available imaging results were also systematically collected. A familial genetic analysis was performed on four patients to delineate the mode of inheritance (P1, P2, P3, P4). The familial analysis could not be performed for the other patients (P5, P6, P7, P8).

Data collection was conducted in accordance with the local ethics committee and General Data Protection Regulation (GDPR). This study was registered with the Assistance-Publique Hôpitaux de Marseille (APHM, PADS23-183).

Results

The identified patients were categorized into two groups based on their clinical. We distinguished six patients who had a CMT "pure" (P1, P2, P3, P4, P5, P6) from two patients who had a CMT associated with parkinsonism. Table 1 provides detailed information regarding the characteristics of these patients. All the patients carried the p.Ile41Thr mutation. P2 was the only homozygous for this mutation. All the others were compound heterozygous. P1, P3, P5, P6, P7 and P8 carried a second mutation that induces the introduction of a premature translational stop signal thereby, resulting in a loss of protein function as previously described [11].

The familial genetic analysis performed on four patients (P1, P2, P3, P4) revealed that each mutation was maternally or paternally inherited, indicating biparental transmission of the mutations.

Patients with a pure CMT

Six patients had a "pure" CMT, five of whom were male patients with ages of 9 (P1), 19 (P2), 32 (P4), 34 (P5), and 49 (P6) years old and a female aged 30 (P3). Among them, P1 and P2 had an early onset, whereas P3, P4, P5 developed the disease in their early teenage years and P6 experienced disease onset during adulthood.

Patient P1 had a deceased maternal uncle with CMT, although limited information was available regarding his condition. Since birth, P1 displayed characteristics of a "floppy" child and had delayed motor development. He began sitting up at 18 months old and, at the age of 9, still required assistance with walking. A congenital nystagmus was observed during ophthalmological examination. Cerebral MRI results showed ventricular system dilatation, supra-tentorial ventricular system enlargement, visible Virchow–Robin spaces in the semi-oval centers, and an enlarged cistern. P1's mother reported an increasing frequency of falls as he grew older. He exhibited an ataxic gait with knee valgum and knee recurvatum, resulting in walking on the inner edge of his feet. Additional symptoms included kyphosis, scoliosis, dysarthria, facial symmetry with limited expression, difficulty swallowing, and absent lower limb tendon reflexes. However, his cognitive development was normal. Genetic analysis revealed a compound heterozygous mutation in the *FIG4* gene, (NM_014845) c.[122 T > C;1185del] p.[Ile41Thr;Ala396Leufs*3].

Patient P2 was capable of walking at his own pace but experienced fatigue and falls while running, attributed to foot lifting muscle deficiencies, until the age of 11. He suffered from back and leg pain in the evenings. Severe kyphosis and scoliosis (D8–D10) were observed, prompting considerations for arthrodesis. No cognitive issues were reported, but handwriting and drawing posed challenges. At 16, he exhibited an unstable and difficult gait with a steppage gait pattern, along with proprioceptive ataxia. Retraction of the lower limbs worsened, accompanied by cervical spine pain. A nerve conduction study (NCS) confirmed demyelinating neuropathy, with a right median nerve conduction velocity (NCV) of 3 m/s and a compound muscle action potential (CMAP) of 6.5 mV. Mild respiratory restrictive syndrome was recently reported. The MRC score was 4 + out of 5 for both upper and lower limbs. Genetic analysis revealed a homozygous *FIG4* mutation (c.122 T > C p.Ile41Thr, class III).

Patient P3 had normal motor development during infancy, and her parents were non-consanguineous. Until the age of 12, she actively participated in aerobic sports, including skiing. However, at 12 years old, her mother noticed high-arched feet. Over time, her physical activities became progressively limited, leading to the abandonment of skiing. At the age of 14, neurological examination revealed bilateral *pes cavus* with mild bilateral foot drop and a steppage gait pattern (Fig. 1A). Atrophy of foot muscles was observed, but there was no atrophy of calf muscles. Deep tendon reflexes (DTR) were preserved, except for Achilles reflexes. Manual muscle testing in the lower right limb resulted in an MRC muscle strength score of 3 out of 5 for foot eversion, foot dorsiflexion, and big toe dorsiflexion. The MRC score was 4 out of 5 on the left side. Superficial sensory examination yielded normal results, although the patient exhibited reduced pallesthesia in distal areas. Motor and sensory examinations of the upper limbs were normal, except for reduced DTRs.

Nerve conduction studies (Table 2) indicated predominantly demyelinating sensory–motor polyneuropathy, with increased distal motor latencies (DMLs) ranging between 6 and 7 ms. Nerve conduction velocities were reduced, and severe conduction blocks (> 50% decrease between proximal

Table 1 Patients' characteristics and *FIG4* mutations

	# Patient	Sex	Age (y)	Age at disease onset	Clinical manifestations	*FIG4* mutations	Segregation	References
''Pure" CMT	P1	male	9	3 months	Delayed gait acquisition, ataxia, osteotendinous areflexia, swallowing disorders, dysarthria, CNS involvement	c.122 T > C: p.(Ile41Thr) **c.1185del p.(Ala396Leufs*)**	Heterozygous compound	This report
	P2	male	19	childhood	Demyelinating distal motor impairment with leg amyotrophy, hollow feet and areflexia	c.122 T > C:p.(Ile41Thr) homozygous	Biallelic confirmed	Hu et al., 2018 [14]; Lafontaine et al., 2021 [18]
	P3	female	30	12 years	Pes cavus, difficulty walking, conduction blocks	c.122 T > C; p.(Ile41Thr) c.831_838del p.(Lys278Trpfs*6)	Heterozygous compound	Cottenie et al., 2013 [14]
	P4	male	32	8 years	Motor deficit and distal amyotrophy predominantly in the lower limbs. Osteotendinous areflexia, hypopallesthesia and hollow feet, conduction blocks	c.122 T > C:p.(Ile41Thr) c.289 + 4A > G	Heterozygous compound	This report
	P5	male	34	12 years	Diffuse areflexia, walking with two crutches, hyperdemyelinating profile, HNPP (*PMP22* deletion)	c.122 T > C; p.(Ile41Thr) c.2247dup; p.(Ser750Glnfs*10)	Untested parents	This report
	P6	male	49	43 years	Pes cavus, scoliosis, areflexia, tremors, ataxia, conduction blocks	c.122 T > C:p.(Ile41Thr) c.1688G > A:p.W563X*	Untested parents	This report
CMT associated with Parkinson	P7	female	68	49 years	Can walk one hour but with plantar foot pain, regular falls, left upper limb deficiency, conduction blocks and parkinsonism onset at 64	c.122 T > C:p.(Ile41Thr) **c.1185del p.(Ala396Leufs*3)**	Untested parents	This report
	P8	male	69	childhood	Demyelinating distal motor impairment with leg amyotrophy, parkinsonism onset at 45	c.122 T > C; p.(Ile41Thr) c.592C > T; p.(Gln198*)	Untested parents	Volodarsky et al., 2021 [21]

Bold values indicate the two highlighted patients share the same mutations but have opposite phenotypes

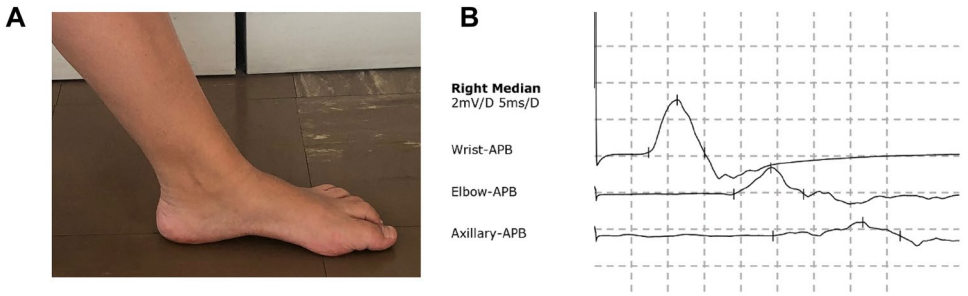

Fig. 1 Conduction block in a discreet form of CMT4J. In **A**, photography of the *pes cavus* of patient P3 who has a discreet form of CMT4J. In **B**, nerve conduction studies of patient P3, indicating conduction blocks/temporal dispersions in the right median nerve

Table 2 Electrophysiological findings for CIDP-like patients

Nerve	$Side_{location}$	Patient	DML	NCV	CMAP	AmpD%	FL	SNAP
Median	R_{wrist}	P3	7.39	20.9	2.90	50.3	55	NR
		P4	6.4	3	6.5			
		P6	6.3/5.6		7/9.6			
		P7	5.3		8.90			
	R_{elbow}	P3	21.8/21.5	19/20	1.44			
		P4	12	37	0.6			
		P6			1.8/1.1			
		P7			8.46			
	L_{wrist}	P3	7.92	17.7	2.10	88.6	49.7	4.1
		P6	5.9/8		7.3/2.5			
		P7	4.7					
	L_{elbow}	P3	32/29.1	11/14	0.24			
		P6	10.7	39	0.9/0.6			
		P7						
Ulnar	R_{wrist}	P3	4.04	17.5	3.50	55.1	55.2	3.0
		P4	11.4		2.4			
		P6	4.6/3.9		6.7/13.1			
		P7	3.3		8.13			
	$R_{below\ elbow}$	P3	27.5/19.8	15/20	1.57			
		P4	8.2	45	0			
		P6			1.7/2.8			
		P7			4.25			
	L_{wrist}	P3	3.65	19.5	5.30	71.9	50.3	9.5
		P6	4.3/4.4		8.3/10.5			
		P7	3.4		6.92			
	$L_{below\ elbow}$	P3	32.1/20.5	13/19	1.49			
		P6	9.1	38	1.5/2.5			
		P7			3.77			
Radial	R	P3	2.4/NR	50/NR	NR			
		P6			1/NR			
	L	P3			NR			
Tibialis	R_{ankle}	P3	4.35		0.40			
	L_{ankle}	P3	11.6		0.30			
Common peroneal	R_{ankle}	P3			NR			
	L_{ankle}	P3	20.8		0.11			
Sural	R	P3			NR			
	L	P3			NR			

CMAP compound muscle action potential (mV), *AmpD%* proximal/distal amplitude reduction of CMAP, *SNAP* sensory nerve action potential amplitude (μV), *DML* distal motor latency (ms), *MCV* motor conduction velocity (m/s), *FL* F-wave latency (ms), *NR* non-responsive

and distal CMAP) were observed in the right median nerve. There was a partial conduction block in the left ulnar nerve between the wrist and elbow (30% to 50% decrease between proximal and distal CMAP).

In her twenties, neurological examination showed no significant changes in the lower limbs compared to previous evaluations. However, weakness, distal paresthesia, and hypoesthesia were observed in the upper limbs. The patient had an ONLS score of 2 out of 12 (0/5 in upper limbs, 2/7 in lower limbs), and her CMTES was equal to 2 (CMTNS = 7). Further NCS revealed an increased severity and number of conduction blocks in both the median and ulnar nerves outside of entrapment sites (Table 2; Fig. 1B). Additionally, asymmetrical minimum F-wave latencies were observed in both nerves, with the left side exhibiting latencies over twice the normal values. Based on the NCS findings, the patient met the definite diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) established by the European Federation of Neurological Societies/Peripheral Nerve Society. Laboratory tests were normal, but cerebrospinal fluid (CSF) analysis showed elevated protein levels (71 mg/dL) with no presence of white blood cells or oligoclonal bands. Due to negative genetic results, electrophysiological findings, and increased CSF protein levels, a potential diagnosis of CIDP was considered. Intravenous immunoglobulin (IVIg) therapy was administered at 6-week intervals, with three courses given. Although the patient experienced a very mild subjective improvement, there were no significant changes observed during neurological examination. As a result, IVIg therapy was discontinued.

Genetic analysis revealed two mutations in the *FIG4* gene (NM_014845.6) c.[122 T > C;831_838del], p.[Ile41Thr;Lys278Trpfs*6], previously reported by Cottenie et al. in 2013 [13]. Segregation analysis demonstrated that the patient's mother carried one heterozygous mutation c.831_838del, p.Lys278Trpfs*6. These findings led to the conclusion that these trans-inherited mutations were responsible for the patient's disease.

Patient P4 began walking at 2 years old but frequently experienced falls. He exhibited thoracic and spinal deformities, as well as *pes cavus*. He could walk for up to one hour until the age of 15, with a bilateral steppage gait and ataxia. A nerve biopsy revealed myelin abnormalities. In his twenties, the patient could only walk short distances (maximum of 25 m) and eventually began using a wheelchair. Nerve conduction study results in 2012 confirmed demyelinating neuropathy (Table 2). Later in 2016, NCS showed a median NCV of 3 m/s and conduction blocks in the right median (wrist: 6.5 mV, elbow: 0.6 mV) and ulnar nerves (wrist: 2.4 mV, elbow: 0 mV). Muscle testing indicated symmetrical MRC scores of 4 for the deltoid, biceps, wrist extensor, and finger flexors, while finger extensors and pinch strength scored 3 out of 5. Lower limb MRC scores were 4 out of 5 for the gluteal muscle, psoas, hamstring muscle, and quadriceps, and 2 for the anterior tibialis. At this stage, the patient exhibited increased protein kinase C levels (800 UI/L). Sensitivity decreased in the upper limbs and was completely lost in the lower limbs, accompanied by severe neuropathic pain. Respiratory assessments revealed a restrictive syndrome along with a decrease in maximum expiratory pressure. The patient's CMTES was 16 (CMTNS = 22).

In 2017, genetic analysis revealed a compound heterozygous mutation in the *FIG4* gene (NM_014845): c.[122 T > C; c.289 + 4A > G] p. Ile41Thr;p.?]. A bioinformatic analysis, conducted using the MobiDetails platform (https://mobidetails.iurc.montp.inserm.fr/MD/), indicated that this particular mutation is predicted to disrupt mRNA splicing, which is a known causative factor in several diseases [23].

Patient P5, a 34-year-old male, experienced disease onset around the age of 12. He underwent surgery for scoliosis at that age, followed by ankle surgery. Nerve conduction study revealed a demyelinating neuropathy, while a biopsy displayed severe axonal loss. Ulnar and median NCVs were 6.8 and 7.7 m/s, respectively. Ulnar and median CMAP values were 0.8 and 2.2 mV. Severe amyotrophy was present in all four limbs, resulting in a CMTNS score of 20 and a total ONLS score of 7 (3 for upper limbs, 4 for lower limbs). The patient exhibited no grip and had difficulty walking, ultimately requiring two crutches by the age of 25. Diffuse areflexia was observed. At the age of 30, genetic analysis revealed a *PMP22* gene deletion associated with HNPP, as well as a compound heterozygous mutation in the *FIG4* gene: c.[122 T > C; 2247dup];p.[Ile41Thr;Ser750Glnfs*10].

Patient P6, aged 49, experienced initial symptoms at the age of 43, which included *pes cavus*, scoliosis, proprioceptive ataxia, absence of pallesthesia, and tremors. The patient had no reflexes. The initial genetic analysis yielded negative results, as did the biochemical investigations. Cerebrospinal fluid analysis revealed a protein level of 94 mg/dL. Blood samples tested negative for anti-gangliosides and anti-MAG antibodies, although there was a polyclonal increase in gamma globulin. Nerve conduction studies (Table 2) revealed several conduction blocks (> 50% decrease between proximal and distal CMAP) in both the right and left median and ulnar nerves, accompanied by the loss of sensitive signals. Based on these findings, there was a suspicion of CIDP, and IVIg therapy was initiated at 2 g/kg administered at 6-week intervals. However, after three courses of IVIg, there were no significant changes observed, particularly in the NCS results. As a result, IVIg therapy was discontinued. The clinical and electrophysiological status of the patient deteriorated over time, with decreased latencies and CMAP, persistent conduction blocks, and the radial nerve no longer responding in subsequent NCS evaluations. Symptoms such as hypoesthesia and paresthesia worsened and affected the lower limbs. The patient tested positive for anti-GM1 antibodies. Eventually, a compound heterozygous mutation in the FIG4 gene (NM_014845) was identified in 2018: c.[122 T > C; 1688G > A] p.[Ile41Thr; Trp563*].

Patients with a CMT associated with Parkinsonism

Two patients, one male and one female, respectively, aged 68 (P7) and 69 (P8) years old, were also diagnosed with Parkinsonism.

Patient P7 reported the onset of symptoms and sought medical attention at the age of 49, experiencing dysesthesia and neuropathic pain in the soles of her feet. Nerve conduction study revealed a median nerve NCV of 34 and 35 m/s. At the age of 50, she exhibited hollow feet, a slight deficit in lateral peroneal and toe flexion, and decreased vibratory sensitivity in all four extremities. By the age of 52, she required the use of a crutch and orthopedic shoes. At 59, her left Achilles tendon had retracted. Muscle testing scores indicated 3 + for the tibial anterior, 2 for the tibial posterior, and 2 out of 5 for the long peroneal muscle. At 64, she developed tremors in her left hand and akinesia, leading to a diagnosis of Parkinsonism. The assessment of her disabilities, particularly the ONLS, is biased due to an accident and the presence of Parkinsonism, resulting in scores of 2 in the upper limbs and 3 in the lower limbs. It is worth noting that this patient has a sister with an undiagnosed neuropathy and Parkinson's disease. Nerve conduction study revealed preserved NCVs for the median and ulnar nerves, as well as a mild conduction block in the ulnar nerve, despite the presence of Martin–Gruber anastomosis, with a CMAP of 8.13 mV at the wrist and 4.25 mV at the elbow (Table 2). A recent genetic analysis revealed a compound heterozygous mutation in the *FIG4* gene (NM_014845): c.[122 T > C;1185del] p.[Ile41Thr;Ala396Leufs*3].

Patient P8, aged 69, exhibited early disease onset and a severe phenotype (CMTNS = 21), characterized by distal amyotrophy and loss of reflexes. Nerve conduction study results showed a median NCV of 47.2 m/s and a CMAP of 3.9 mV. Walking assistance was required. Genetic analysis revealed a compound heterozygous mutation in the *FIG4* gene (NM_014845) c.[122 T > C;592C > T] p.[I41T;Gln198*]. At the age of 45, P8 developed early parkinsonism, further accentuating the severity of the disease.

Discussion

In the present report, we describe a cohort of eight patients diagnosed with CMT4J, each harboring distinct mutations in the *FIG4* gene. This includes one patient who is homozygous for the *FIG4*-Ile41Thr mutation and seven patients who are compound heterozygous for the same mutation. They were classified according to their phenotype, six patients had a ''pure'' CMT, whereas two patients had a CMT associated with a Parkinsonism.

Age of disease onset

Among these patients three had a disease onset in their childhood (P1, P2, P8), three others in their early teenage years (P3, P4, P5), and two others in their adulthood (P6, P7). It appears that patients who experienced symptoms in childhood tended to develop more severe forms of the disease compared to those who first manifested the condition during their teenage years or adulthood.

FIG4-Ile41Thr mutation frequency and associated disorders

The *FIG4*-Ile41Thr mutation, identified in all patients within our study cohort, represents the most prevalent genetic variant observed in CMT4J cases, who are predominantly compound heterozygous [13, 14]. This particular anomaly has also been identified in other diseases and is associated with a wide range of clinical manifestations [5, 21]. For instance, it has been detected in mild cases of autosomic dominant ALS within a European cohort that underwent WGS [16]. In a recent report, a patient with this mutation exhibited a slow disease progression over three years, sensory deficits, and no significant slowing of NCV, which is characteristic of peripheral demyelination seen in CMT4J. Brain atrophy, particularly in the frontoparietal region, was also observed [16]. On the other hand, a severe form of ALS associated with two heterozygous *FIG4* mutations, including the *FIG4*-Ile41Thr mutation and early onset has been documented.

In one study, a family carrying both *FIG4*-Ile41Thr and c.1949-10 T > G (intronic) mutations displayed CNS abnormalities leading to Parkinsonism and cognitive language impairment, but associated with a milder form of CMT [21]. However, another patient carrying both of these mutations exhibited a severe phenotype without CNS abnormalities. Generally, CNS deficits associated with *FIG4* mutations have been described as a continuum between CMT4J and YVS [12]. This continuum is characterized by a severe phenotype, significant disability, and cognitive impairments, with the majority of cases not being related to the *FIG4*-Ile41Thr mutation [8, 11, 12].

In our study, the most severe phenotype was observed in a patient (P1) with a heterozygous *FIG4*-Ile41Thr, Ala396Leu mutation, which was associated with the earliest disease onset and CNS involvement. Interestingly, according to a Greek study, the *FIG4*-Ile41Thr mutation, which is commonly associated with North Europeans, may not be exclusive to this population. In our case, the patient has North African descent [28].

Homozygous vs compound heterozygous mutations and variable phenotypes

Among the patients carrying a heterozygous mutation, there was a wide range of clinical manifestations and varying ages of onset. Notably, P1 and P7 shared the same mutations (c.[122 T > C;1185del] p.[Ile41Thr;Ala396Leufs*3]), but exhibited contrasting phenotypes. P1, the youngest affected patient, had the most severe form of the disease, while P7 experienced a later onset in her forties with a slow progression. Similarly, patient P3 in our study carried the same mutations (p.[Ile41Thr;Lys278Trp]) as patient S2 reported by Nicholson et al. (2011). However, while S2 developed the disease at the age of 5 and became wheelchair-bound at 20, P3 exhibited a milder and slowly progressing form of the disease.

The carrier of a homozygous *FIG4*-Ile41Thr mutation (P2) had one of the most severe phenotypes, characterized by progressive distal deficits that led to mobility loss before the age of 20. Lafontaine et al. described heterozygous patients with an early onset and rapidly progressing disease, while homozygous patients carrying the *FIG4*-Ile41Thr mutation showed clinical stability [17]. In a prior report, a 13-year-old female patient was described as carrying a compound heterozygous mutation in the *FIG4* gene, specifically *FIG4*-Ile41Thr/Phe98fsX38. The first mutation was maternally inherited, while the second originated from her asymptomatic father. Initially, her symptomatic mother was presumed to be homozygous for the mutation; however, subsequent Sanger sequencing revealed a deletion in exon 2. Remarkably, the patient also harbored a de novo *DMD* mutation, which served to exacerbate her clinical [6]. In contrast, our current study did not identify any additional mutations within the panel of genes analyzed for these patients. In 2020, Wright et al. reported four patients from unrelated families who were all homozygous for a *FIG4* missense variant (c.506A > C, p.Tyr169Ser), and exhibited features of both CMT4J and YVS [22]. Additionally, in another study, three homozygous patients carrying the *FIG4*-Ile41Thr mutation with early CMT4J onset and severely decreased NCV demonstrated preserved ambulation and no clinical progression of the disease over the years [17].

CMT4J and conduction blocks

Hereditary polyneuropathies are typically characterized by a slow or very slow progression, with consistent findings such as a homogeneous reduction of NCV or increased distal latencies without conduction blocks, particularly in demyelinating forms of CMT. On the other hand, the presence of patchy slowing of NCV or conduction blocks is highly indicative of an acquired inflammatory polyneuropathy, especially when accompanied by the typical pattern of albuminocytological dissociation in CSF [22]. It is worth noting that misdiagnosis between CMT and CIDP has been reported in various cases [24].

Previous descriptions of CMT4J have highlighted rapidly progressive asymmetrical weakness with minimal sensory symptoms, despite evidence of sensory involvement in electrophysiological and pathological studies. Electrophysiological studies have revealed severe demyelination with temporal dispersion and widespread denervation of proximal and distal muscles [4, 5, 17]. In our study, four patients (P3, P4, P6, and P7) exhibited conduction blocks and asymmetrical findings in NCS. Among them, two patients (P3 and P6) received IVIg treatment, but it was discontinued due to the lack of significant improvements. Conduction blocks have been observed in several CMT4J patients and have been associated with diverse clinical manifestations. Previous reports have described nine CMT4J patients with conduction blocks, each presenting different phenotypes. Some patients exhibited an early-onset and severe form of the disease, while others had a later onset and milder symptoms [14]. For instance, one report described a boy who first sought medical attention at the age of 13 and experienced rapid disease progression, becoming wheelchair-bound by the age of 22. Another patient, also followed since the age of 13, initially presented weakness and atrophy in the upper limbs, which worsened over time and extended to the lower limbs, resulting in quadriparesis with sensory symptoms and loss [13, 24]. Additionally, a patient with an onset at the age of 52 was initially misdiagnosed with CIDP due to the presence of conduction blocks. However, apart from worsening gait over the years, she exhibited a very mild form of the disease [9].

CMT4J and HNPP

In our study, we present a unique case of a patient with both genetically confirmed HNPP and CMT4J, the patient P5. This patient exhibited a hyperdemyelinating profile resulting from the coexistence of two demyelinating neuropathies. Remarkably, despite this double diagnosis, the patient retains the ability to walk, albeit with the assistance of two crutches. Further understanding of the patient's phenotype would necessitate long-term follow-up to assess disease progression and clinical outcomes.

CMT4J and Parkinsonism

In our cohort, we reported two patients who were also diagnosed with Parkinsonism. We observed that the compound heterozygous patient P7 experienced a late onset of CMT4J, whereas the compound heterozygous patient P8 had an early onset of CMT4J. The association of Parkinsonism with *FIG4* mutations and CMT4J has been previously reported. In a cohort of five CMT4J patients, three

individuals exhibited early Parkinsonism along with a late onset of CMT4J, including two siblings [12]. Another study described a 51-year-old woman who was initially diagnosed with distal motor and sensory neuropathy (dMSN) at the age of 14. Subsequently, she was diagnosed with CMT4J accompanied by early Parkinsonism attributed to heterozygous *FIG4* mutations (c.122 T > C, p.Ile41Thr; c.1447C > T, p.Arg483*) [24].

Phenotypic variability

Phenotypic variability is a hallmark of various CMT subtypes. Numerous cohorts have explored the complex relationships between phenotype–genotype correlations and the underlying factors contributing to this variability across different CMT subtypes [25, 26]. In the context of CMT4J, the presence of a broad spectrum of phenotypes have been discussed in previous studies, where patients were classified based on their disease onset age. For example, among 12 patients, 11 individuals had at least one *FIG4*-Ile41Thr mutation. One patient was homozygous for this mutation and exhibited a CMTES of 2 with an onset at the age of 9, while another patient had an associated Parkinson-like disorder [14]. Researches aimed at elucidating the mechanisms underlying phenotypic variability have suggested that additional variants in neuropathy-associated genes could contribute to the heterogeneous clinical expression of the disease [3, 5, 14]. Specifically, neuropathy genes have been found to harbor highly penetrant Mendelian variants (HPMVs) that interact genetically and exacerbate the phenotype. This supports the notion that the combinatorial effects of rare variants contribute to disease burden and variable expressivity [5]. In our study, as previously noted, no other mutations were identified within the gene panel analyzed for these patients.

The *FIG4*-Ile41Thr mutation is a hypomorphic variant that allows for partial protein function, potentially accounting for the milder symptoms observed in homozygous individuals. In contrast, mutations leading to a complete loss of protein function are the most frequent and generally result in more severe outcomes, as demonstrated in null pale tremor (plt) mice, which exhibited severe phenotypes and significant nerve degeneration [14, 22]. As mentioned above, a study reported a homozygous case for this variant, characterized by a disease onset at 9, authors found that the level of FIG4 was comparable in the homozygous case and the compound heterozygous cases, who had a later disease onset. They concluded that any compensation effect from Ile41Thr would be minimal [14]. Lafontaine et al. considered that this patient could be compound heterozygous as the familial analysis was not available, while they reported three unrelated homozygous cases for this variant who presented with milder forms of the disease [21]. Our confirmed homozygous patient (P2) manifested a severe phenotype, suggesting that additional factors may influence disease expressivity beyond the gene panel studied.

Unfortunately, only a few studies have focused on specific mutations to decipher the pathomechanisms of the disease which could help to understand the variability. Five of the observed variants here have never been reported elsewhere. Only the mutations of P3 and P8 were previously reported but only the patients' characteristics were discussed [13, 18].

Despite this high variability and the lack of studies, mutations in the *FIG4* gene remain the primary etiological factors for the disease [3, 4]. Recent preclinical studies utilizing an adenoviral vector to restore FIG4 expression in plt mice have demonstrated both high tolerability and efficacy. Other researchers performed cell and mice studies with some of the newly variants found. Indeed, they studied the fibroblasts of two compound heterozygous patients for the *FIG4* gene with the mutations Arg183X in exon 6 and Ile41Thr in exon 2. They concluded that the neurodegeneration observed in the disease was due to impaired trafficking of intracellular organelles because of obstruction by vacuoles and Ca^{2+} level increase. Thus, they have posited that calcium chelators could represent a promising therapeutic strategy [4]. Further investigations are still required to fully understand the pathogenic mechanisms of the disease and the factors influencing its severity.

The strength of our study rests in the identification of eight patients carrying ultra-rare mutations, each of whom was consistently monitored. This enabled us to collect key information regarding their conditions. However, due to the retrospective nature of our study, we encountered certain limitations, particularly the unavailability of family history for some patients and parental genetic data, which prevented us from effectively analyzing segregation profiles for all the patients.

Conclusion

This study provides valuable insights into the CMT4J subtype by reporting on eight patient cases. We categorized the patients according to their phenotype, we identified "pure" CMT vs. CMT associated with Parkinsonism and we observed that the patient with the earliest onset displayed the most severe phenotype. Notably, two patients received IVIg treatment due to a suspicion of CIDP. This highlights the challenge of relying solely on electrophysiological findings such as conduction blocks in NCS or asymmetrical NCS results as definitive markers for differentiating between CMT and acquired polyneuropathies. In cases of atypical forms or when patients initially receive a diagnosis of genetically non-confirmed CMT, it becomes necessary to supplement

electrophysiological analysis with additional biochemical, imaging, and genetic investigations.

Additionally, identifying asymptomatic relatives of probands who carry a single mutation in the *FIG4* gene, could be interesting, as their long-term follow-up assessments would help to ascertain the potential development of ALS.

Furthermore, the association of Parkinsonism with demyelinating neuropathies related to *FIG4* mutations suggests that testing for this genotype should be considered in the evaluation of patients presenting with Parkinsonism, particularly when early signs or symptoms of peripheral neuropathy are present. This underscores the importance of a comprehensive diagnostic work-up in such cases.

Author contributions SBD collected and analyzed the data, wrote and reviewed the manuscript. RJM, FF, AI, LS, SLL, MM, PV, TG, and JP followed patients, performed neurological examination, and reviewed the paper. VP and NBD performed the genetic analysis and reviewed the manuscript. SA was the principal investigator, designed and coordinated the project, performed neurological examination, analyzed the data, wrote and reviewed the paper. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest The authors report no disclosures relevant to the manuscript.

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