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A Novel Missense Mutation in *AIFM1* Results in Axonal Polyneuropathy and Misassembly of OXPHOS Complexes

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Abstract

Background and purpose—AIFM1 (apoptosis-inducing factor, mitochondrion-associated-1) in mitochondria has captured a great attention due to its well-described function in apoptosis. Mutations in *AIFM1* have resulted in multiple clinical phenotypes, including CMTX4. These syndromes usually involve multiple locations within the nervous system and/or multiple organs. This study describes a novel missense mutation in *AIFM1* and its associated peripheral nerve disease.

Methods—Patients with *AIFM1* mutation were characterized clinically, electrophysiologically, genetically and by MRI imaging. The fibroblasts were isolated from the patients to study mitochondrial OXPHOS complexes.

Results—We identified a family with a novel missense mutation (Phe210Leu) in *AIFM1* that developed an isolated late-onset axonal polyneuropathy in which the central nervous system and other organs were spared. Interestingly, this Phe210Leu mutation resulted in abnormal assembly of mitochondrial complex-I (CI) and III (CIII) and failed to disrupt AIFM1 binding with MIA40 in the patients' cells. Deficiency of either AIFM1 or MIA40 is known to impair the assembly of mitochondrial complex-I and IV. Yet, levels of both AIFM1 and MIA40 were unchanged.

Conclusions—Phe210Leu mutation in *AIFM1* induces an axonal polyneuropathy that might be contributed by the misassembly of mitochondrial CI and CIII. This misassembly appears to be independent of the traditional mechanism via AIFM1/MIA40 deficiency.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

List of all antibodies used in the study.

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Keywords

Charcot-Marie-Tooth disease type-X4; inherited neuropathy; apoptosis inducing factor mitochondrion-associated-1 (AIFM1); OXPHOS complex; peripheral nerve; axonal polyneuropathy; nerve conduction study; peripheral nerve MRI

Introduction

Charcot-Marie-Tooth disease (CMT) affects one out of 2,500 people. Most patients with CMT share many phenotypic features, including chronic sensory loss, muscle weakness and atrophy in distal limbs. Of 90 human genes associated with CMT, four genes are mapped to chromosome X (CMTX), including *apoptosis inducing factor mitochondrion associated-1* (*AIFM1*) at Xq26.1. Mutations in *AIFM1* cause axonal polyneuropathy in patients with X-linked Charcot-Marie-Tooth disease type-4 (CMTX4) [1].

AIFM1 encodes a 67kDa FAD-dependent NADH oxidase with a mitochondrial-specific targeting sequence (MLS) of 54 amino acids at its n-terminal. The remaining protein consists of the Inner Membrane Sorting Signal domain (55–128), two FAD domains (129–262, 401–480), a NADH binding domain (263–400) and a c-terminal domain (481–608) (Figure 1a). In response to apoptotic stimuli, AIFM1 cleaves off its n-terminal at residue 101 to become cytosolic AIFM1 and translocates into the nucleus resulting in DNA fragmentation and cell death [2]. Heat shock protein-70 (HSP70) binds AIFM1 at residues 150–288 in the cytosol preventing nuclear translocation, and thus inhibiting apoptosis [3].

Mitochondria execute their essential function - energy production - through the oxidative phosphorylation system (OXPHOS). OXPHOS is comprised of five protein complexes (CI – CV) in the inner mitochondrial membrane. OXPHOS couples the electron flow and proton translocation across the mitochondrial inner membrane to generate the electrochemical gradient that enables the production of ATP. In both cultured cells and mouse tissues, AIFM1 has been shown to interact with MIA40 (an oxidoreductase). Partial deficiency of AIFM1 (~80%) resulted in loss of MIA40 and misassembly of C1 and CIV leading to muscle atrophy, astrogliosis and progressive neurodegeneration in a mouse model [4].

In addition, mutations in human *AIFM1* have been associated with a wide spectrum of clinical phenotypes, including CMTX4 (Table 1; Figure 1a). In the vast majority of cases with *AIFM1* mutation, patients develop abnormalities in the central nervous system and/or other organs in addition to axonal polyneuropathy. However, in this study we report a family carrying a novel missense mutation in *AIFM1* that exhibits an isolated axonal polyneuropathy with misassembly of C1 and CIII.

Materials and Methods

Patients

The affected proband (0001) was initially evaluated at the Vanderbilt CMT Clinic. The proband, his affected brother (0100), and his unaffected sister (0102) were then evaluated at the Clinical Research Center of Vanderbilt University Medical Center (VUMC) (Figure 1b).

This study was approved by the local Institutional Review Board (IRB). A written consent was obtained from all participants. The proband's unaffected brother (0103) and his asymptomatic sister (0101) were consented and interviewed over the phone.

In addition to medical history and neurological examination, the CMT neuropathy score (CMTNS) [5] was obtained from patients 0001, 0100 and 0102. The electrophysiological portion of the score was omitted to produce the CMT Examination Score (CMTES). The electrophysiological data will be described separately. CMTES ranges from 0 to 28, with higher scores indicating an increase of disease severity.

Nerve Conduction Studies (NCS)

NCS data were acquired using conventional methods [6].

DNA Sequencing

Next Generation Sequencing—The proband's DNA was initially evaluated by targeted gene-panel next-generation sequencing, a service provided by Medical Neurogenetics, Atlanta, Georgia. The test sequenced 42 CMT-related genes and mitochondrial DNA as described [6].

Sanger Sequencing—Primers (5'-TCTGGACACTGGCAAACATC-3' and 5'-GCTTTCCCCAGAAAGACACA-3') were used to amplify a 491bp region of *AIFM1*. PCR products were then sequenced by GenHunter Corporation (Nashville, TN).

Human skin biopsy and fibroblast culture

Skin biopsies (2mm in diameter) were obtained from forearms of the proband (0001), his brother (0100) and his sister (0102). Fibroblasts were cultured from the biopsies as described [6] and harvested for biochemical studies.

Western blot and Co-immunoprecipitation (co-IP)

This method was modified from our published study [6]. In brief, human fibroblasts cells were lysed in immunoprecipitation buffer (Cat# 87788, Thermo scientific) and incubated with primary antibodies overnight at 4°C. Protein G agarose beads (Cat# 15920-010, Life technologies) were added for another 2 hour incubation at 4°C. Proteins were loaded into SDS-PAGE gels, transferred to a PVDF membrane, blotted with primary antibodies and secondary antibodies.

MRI and MTR Acquisition and Analysis

Acquisition of MRI images and MTR values of patients was carried out as described in a previously published study [7].

Antibodies—Please see them in the Supporting Information.

Results

Patients present with an axonal polyneuropathy with no symptoms from the central nervous system or other organs

Clinical phenotypes

Patient 0001: The proband is a 56-year-old man with a normal birth history. He was developmentally normal and denied any toe walking, tripping or ankle injury during childhood. At 14 years of age, he started to “walk like a duck” and “flip flopping” his feet. He was evaluated by a local neurologist who told him he might have a CMT. With a slow progression over decades, he now has severe ankle weakness requiring ankle braces to ambulate. He reports numbness from his mid-calf distally with, at times, severe burning pain. His hands are of weak grip and there is numbness in fingertips. After his initial visit to our clinic, the proband developed type-II diabetes about one year later.

On neurological examination, he had normal cranial nerve functions and intact cognitive functions. His ankle dorsal and plantar flexors were 0 and 2 on medical research council (MRC) scale respectively. The remaining muscle groups in legs and arms were 5 on MRC. Muscle atrophy was severe in distal legs but absent in hands and arms (Figure 1c). Sensation was intact to light touch, pinprick but decreased slightly at toes and was normal at ankles and knees. Deep tendon reflex was absent in ankle joints but present in other joints. His CMTES was 12.

Patient 0100: The proband’s brother is a 55-year-old man who had a normal birth/developmental history and excelled in track sports during his elementary school. He became symptomatic at 14 years of age and developed “floppy” feet and calf muscle cramps. He tripped himself many times with several ankle injuries. He uses a pair of high-edged boots to prevent future injury. He denied any sensory symptoms or history of diabetes, renal diseases or alcohol abuse. Neurological examination detected severe muscle weakness and atrophy in ankle dorsal/plantar flexors (0 on MRC) but 5 in other muscles. Sensory examination was normal. DTRs were absent in ankle joints but present in other joints. His CMT examination score (CMTES) was 6.

We evaluated his sister (0102) with neurological examination and NCS. The other sister (0101) and brother (0103) were not available for visit, but interviewed over the phone and their DNA samples shipped. All three were found to be asymptomatic.

Electrophysiological findings—Two affected patients, 0001 and 0100, were evaluated by NCS (Table 2). The findings were consistent with a predominantly motor axonal polyneuropathy due to the following reasons: (1) Sensory nerve action potential (SNAP) in legs was either normal or slightly decreased in amplitude in the two patients. Compound muscle action potential (CMAP) was absent in legs but normal in arms. In contrast, conduction velocities were normal or mildly reduced. (2) Needle EMG showed denervation in distal leg muscles. No myopathic motor unit action potentials were observed. Note that the NCS was performed prior to the diagnosis of diabetes in the proband.

MRI findings in the proband's sciatic nerve and thigh muscles—Physical findings in the patients suggest a length-dependent process of the peripheral neuropathy (Figure 1c; Table 2). While distal motor nerves in legs were severely affected and non-responsive in NCS, proximal nerves were difficult to be evaluated by conventional NCS. We have established a magnetic transfer ratio (MTR) technique that can quantify the proximal nerve pathology non-invasively [7]. We studied the proband using the MTR technique (Figure 2). Again, this study was done prior to his diagnosis of diabetes. As shown in Figure 2c, his sciatic nerve diameter was below the range of normal controls. His MTR value was at the borderline of the lower limit of normal controls. Thigh muscle volumes on the cross section appear to be preserved. There might be subtle changes of intramuscular architecture, which could be due to denervation. Together, these findings suggest an involvement of proximal nerves in the patient. As expected, the changes are mild in the proximal nerves while distal nerves are non-responsive in NCS. These features are in line with the length-dependent process in axonal polyneuropathy.

DNA analysis shows a missense mutation that changes a highly conserved phenylalanine to leucine in the first FAD domain of AIFM1.

The proband's DNA was initially sequenced by targeted gene-panel next-generation sequencing, a commercial diagnostic service provided by Medical Neurogenetics (Atlanta, GA). This technique was briefly described in the Method section. This test identified a hemizygous missense mutations, c.630C>G, in *AIFM1* on chromosome X. The mutation changed phenylalanine to leucine (Phe210Leu) in AIFM1. For the rest of the 42 CMT-related genes, no mutation was found. In addition, whole mitochondrial DNA was sequenced and revealed no mutation.

We verified the Phe210Leu missense mutation using Sanger sequencer in our laboratory (Figure 3, upper panel). Phe210Leu was only found in affected family members but absent in non-affected family members (0102, 0103). Heterozygous Phe210Leu mutation was also found in subject 0101. She was asymptomatic for polyneuropathy but considered as a carrier of the mutation. This co-segregation between Phe210Leu in *AIFM1* and affected individuals supported its pathogenic role of this disease. Furthermore, phenylalanine at the 210 residue of AIFM1 is highly conserved across species (Figure 3, lower panel).

The mutation was evaluated by two servers - PolyPhen-2 and SIFT. Both predicted that Phe210Leu is damaging. In addition, the Phe210Leu allele was absent in 107,784 chromosomes of control population in the ExAC database (<http://exac.broadinstitute.org/>).

Phe210Leu mutation misassembles CI and CIII in the absence of AIFM1 and MIA40 deficiency

To further evaluate the pathogenic role of the Phe210Leu mutation, we tested whether the mutation aberrantly affected the assembly of mitochondrial complexes (CI-V) since AIFM1 has been considered an assembly factor for mitochondrial complexes [4]. Lysates from human fibroblasts were analyzed by Western blot. It showed that CI and CIII levels were decreased by approximately 80% when compared to controls (Figure 4a).

Previous studies have demonstrated that deficiency of AIFM1 or MIA40 misassembles CI and CIV [4]. We thus evaluated levels of AIFM1 and MIA40 by Western blot in human fibroblasts. The levels were comparable between controls' and patients' fibroblasts (Figure 4a).

Taken together, these data suggest that the Phe210Leu mutation is sufficient to affect certain types of OXPHOS protein complexes independent of AIFM1/MIA40 deficiency.

Interaction between AIFM1 and MIA40 or between AIFM1 and HSP70 was not altered by the Phe210Leu mutation

AIFM1 is also known to bind with MIA40. The Phe210Leu mutation could disrupt this protein-protein interaction important in the assembly of mitochondrial complexes [4]. We cultured fibroblasts from the skin biopsies taken from the two affected patients (0001, 0100), a sibling with no Phe210Leu mutation (0102) and a healthy, unrelated control. A Co-IP experiment was performed with the protein extracts of these fibroblasts. This interaction was confirmed and was not altered in mutant cells (Figure 4b).

HSP70 is also known to bind AIFM1 at residues 150–288 in the cytosol. This interaction prevents AIFM1 from nuclear translocation, thereby inhibiting apoptosis [3]. The Phe210Leu mutation could also disrupt this protein-protein interaction. Co-IP experiment showed that the interaction between AIFM1 and HSP70 was not changed in patients with the Phe210Leu mutation (Figure 4b).

Discussion

Our study has identified a family afflicted by an inherited axonal polyneuropathy with motor axons predominantly damaged. This disease appears to be caused by a missense mutation (Phe210Leu) in *AIFM1*. This conclusion is supported by the following evidence: (1) The mutation was segregated in the affected individuals; (2) A polyneuropathy has been reported in other families with mutations in *AIFM1* (Table 1), although additional tissues were also affected in those families. In some cases, motor axons were predominantly affected, which may have been called distal spinal muscular atrophy (Table 1) [8]. (3). The Phe210Leu mutation changes a highly conserved amino acid. The mutation was not seen in the large cohort of control population (ExAC database); (4). Mutant AIFM1, not wild-type AIFM1, led the misassembly of C1 and CIII.

Mutations in *AIFM1* in previously reported families have resulted in diffuse pathologies in the nervous system and other organs, leading to severe neurological deficits in most cases (Table 1). These may include mental retardation, abnormal cortical development of cerebrum and myopathy. In contrast, the Phe210Leu mutation in this family causes an isolated polyneuropathy with motor axons predominantly affected. The patients had a late-onset, mild phenotype. The variable severities in all reported cases do not appear to have a clear association with mutations in specific domains of AIFM1 (Figure 1). For instance, Glu493Val mutation in C-terminal results in a phenotype with earlier onset and more severe neuropathy (Table 1) than that in our cases with a missense mutation in the first FAD domain which has well defined OXPHOS functions. However, severe phenotypes have been

associated with significant reduction of AIFM1 and/or MIA40 protein levels in human cells and rodent models (Table S1). In contrast, the Phe210Leu mutation neither alters the levels of AIFM1 and MIA40 nor the binding between them. Together, these observations suggest that, while the Phe210Leu mutation is sufficient to cause the misassembly of CI and CIII, the preserved level of AIFM1 is still able to exert other functions preventing our patients from a severe phenotype. Certain pleiotropic functions of AIFM1 may have not be affected by the Phe210Leu mutation, but would be affected if AIFM1 is severely deficient.

It is still unclear how exactly the Phe210Leu mutation misassembles CI and CIII. An elegant study has demonstrated that AIFM1 deficiency misassembles CI and CIV via its interaction with MIA40 and also results in MIA40 deficiency [4]. Because MIA40 is not deficient and binding between MIA40 and AIFM1 is still preserved in Phe210Leu cells, the misassembly of CI/CIII would not be achieved via the impaired interaction between AIFM1 and MIA40 or via MIA40 deficiency, but through a different mechanism. Therefore, findings in our study may have reached a conceptual advance. AIFM1/MIA40 deficiency is sufficient, but not necessary, in causing abnormal assembly of mitochondrial complexes. Certain mutations, like Phe210Leu, are sufficient to misassemble mitochondrial complexes, independent of AIFM1/MIA40 deficiency. We speculate that this effect of Phe210Leu in the misassembly of OXPHOS complexes might be achieved by impaired interactions between AIFM1 and other unidentified proteins in the OXPHOS system. Alternatively, mutant AIFM1 may misassemble CI/CIII by blocking or impairing MIA40's function, but, again, independent of MIA40 deficiency.

Notice that each complex of CI-V is comprised of multiple subunits. Our Western blot in Figure 4 only tested one subunit in each complex. Thus, the degree of reduction for the tested subunit does not necessarily reflect the degree of reduction of other subunits in the same complex. For this reason, other subunits in CIV could still be decreased in our patients.

Finally, our previous study has demonstrated that non-invasive MRI techniques can be used to define and quantify the pathological changes in myelin and axons of the peripheral nerves. [7]. While proximal nerves are difficult to be accessed by NCS or biopsy, this problem can be circumvented by using MRI. In this study, we were able to detect mild pathological changes in the proximal nerves.

In summary, we have identified a novel missense mutation in *AIFM1* that likely causes CMTX4 with isolated pathology in the motor neurons of peripheral nerve system. With preserved levels of AIFM1/MIA40 and binding between AIFM1 and MIA40, the Phe210Leu mutation still results in misassembly of mitochondrial OXPHOS complexes. This observation reinforces the critical role of AIFM1 in the formation and/or maintenance of OXPHOS complexes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(a) Functional domains and published pathogenic mutations in AIFM1. Shown are the Mitochondrial Localization Signal (MLS), Inner Membrane Sorting Signal (IMSS), Flavin Adenine Dinucleotide (FAD), Nicotinamide Adenine Dinucleotide (NADH) and c-terminal domains in AIFM1. (b) Family pedigree and length-dependent muscle atrophy in the proband. Arrow indicates the proband. Medical history and DNA was collected from subjects marked with numerical codes. Participants 0001, 0100, and 0102 were also examined clinically and electrophysiologically. Medical history and physical examination

were not available for members labelled with a question marker. Square = male; circle = female; shaded = clinically affected; half circle shaded = carrier but clinically unaffected by polyneuropathy; diagonal line = deceased. NT = not tested. (c) Severe muscle atrophy was seen in distal legs. However, the muscle bulk was well preserved in hands and arms.

Figure 2.

MRI study in the proband's proximal nerve. (a) Axial proton-density image from the mid-thigh of patient with CMTX4 (proband, 0001). The sciatic nerve is labeled via the red oval. The sciatic nerve diameter of the patient ($\text{mean} \pm \text{SEM} = 4.3 \pm 0.1 \text{ mm}$) was reduced relative to previously published values in controls ($\text{mean} \pm \text{SD} = 5.1 \pm 0.6$) [7]. (b) Corresponding MTR map from the same slice. (c) Mean MTR values versus age for controls and the patient with CMTX4. Note that MTR values were not dependent on age in controls ($\text{mean} \pm \text{SD} = 37.2 \pm 2.3$) [7] and MTR values in the patient with CMTX4 ($\text{mean} \pm \text{SEM} = 33.4 \pm 0.3 \text{ p.u.}$) were in the lower range of values observed in controls. (d) Corresponding axial proton-density slice and (e) MTR map from an age- and BMI-matched control (58 y.o. F, BMI = 31 kg/m²).

Figure 3.

Sanger sequencing: Upper panel: Original traces by Sanger sequencing are displayed for subject #0102 (unaffected sister) and #0001 (the proband). The mutated nucleotide (630 C>G) is indicated by a box. Lower panel: Sequence alignment shows that Phe210 (underlined) is conserved in all species listed.

Figure 4.

(a) Western blot analysis was performed in the fibroblasts of normal controls and fibroblasts from patients with the Phe210Leu mutation (0001 and 0100). The first control (49-year-old woman) was participant 0102 from this study. The 2nd control was from a 70-year-old man who was unrelated to this family. The percentages in parentheses are the ratios between patients and normal controls (normalized protein level in each patient / average of normalized protein levels from two normal controls). Western blot finding was replicated in a separate set of experiments. GAPDH was included as a loading control. Porin served as a

control of mitochondrial volume. (b) Cell lysates were immunoprecipitated with anti-AIFM1 antibody and the precipitated endogenous proteins were blotted with anti-HSP70, anti-MIA40 and anti-AIFM1 antibody. IgG was used as negative control. β -Tubulin served as a loading control.

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Table 1

Published phenotypes in patients with mutations in *AIFM1*

1 st Author	Y/N/P ¹	Journal	Mutation	Phenotype	
Ghezzi	2010/86/639	AJHG ²	Arg201Del	DD ⁹	encephalomyopathy
Berger	2011/104/517	MGM ³	Gly308Glu	DD	axonal S/M ¹⁰ polyneuropathy
Rinaldi	2012/91/1095	AJHG	Glu493Val	DD	cardiomyopathy
Ardissone	2015/26/2193	Neurology	Gly262Ser	DD	axonal S/M polyneuropathy
Kettwig	2015/21/12	Mito ⁴	Val243Leu	DD	axonal S/M polyneuropathy
Diodato	2016/24/463	EJHG ⁵	Gly338Glu	DD	axonal S/M polyneuropathy
Mierzewska	2017/91/30	Clin Genet ⁶	Asp237Gly	DD	axonal S/M polyneuropathy
			Leu344Phe		motor axonal neuropathy
			Arg422Trp		axonal S/M polyneuropathy
Zong	2015/52/523	JMG ⁷	Arg422Gln		axonal S/M polyneuropathy
			Arg451Gln		axonal S/M polyneuropathy
Morton	2017/3:a001560	CSHMCS ⁸	Gln479Arg	DD	encephalomyopathy

¹ year/volume/page;

² American Journal of Human Genetics;

³ Molecular Genetics and Metabolism;

⁴ Mitochondrion;

⁵ European Journal of Human Genetics;

⁶ Clinical Genetics;

⁷ Journal of Medical Genetics;

⁸ Cold Spring Harbor Molecular Case Studies;

⁹ developmental delay;

¹⁰ sensory/motor;

spinal muscular atrophy
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Electrophysiological findings

Table 2

Code	Sensory Nerve Conduction		Motor Nerve Conduction		
	Median	Median	Ulnar <i>DL(ms)/Amp(μv)/CV(m/s)</i> ¹	Peroneal	Tibial
		<i>DL(ms)/Amp(mv)/CV(m/s)</i>			
Norm ²	3.5/22.0/50 6.5/2.0/44	3.5/10.0/50 6.0/3.0/41	4.4/6.0/40	4.4/4.0/49	3.3/6.0/49
0001	3.3/20.0/42 3.4/12.8/54	2.5/16.0/57 nr	3.6/5.0/39 nr	4.5/9.2/51	
0100	4.2/20.0/42	3.8/23.0/48	4.5/8.0/42	4.4/9.5/54	
	3.4/10.9/58	nr	N/D		

¹ *DL(ms)/Amp(μv)/CV(m/s)* = distal latency (ms)/amplitude (mv)/conduction velocity (m/s). All numbers in each column were listed in this sequence. Letters in the parenthesis represent the units of the measurement;

² Norm = normative values. For DL, the listed numbers are the upper limit of normal. For Amp and CV, the listed numbers are the lower limit of normal.

³ nr = no response, N/D = not done.