BRAIN
LETTER TO THE EDITOR

Biallelic variants in the *COQ7* gene cause distal hereditary motor neuropathy in two Chinese families

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It was with great interest that we read the article published by Jacquier *et al.*[1] regarding autosomal recessive distal hereditary motor neuropathy (dHMN) caused by a pathogenic variant in the *COQ7* gene.[1] Using whole-exome sequencing (WES), the authors identified a homozygous variant, c.3G>T (p.Met1?) in the *COQ7* gene in three patients from a Portuguese family. Three patients in this family had onset of neuropathy, walking difficulties, and muscle weakness. Electrophysiological results revealed that two patients presented only pure motor axonal neuropathy impacting distal lower limbs. Apart from the symptoms of neuropathy, two patients had positive pyramidal signs. Further molecular analysis revealed a decrease in coenzyme Q10 level and corresponding increase in 6-demethoxy-coenzyme Q10 in the patient's fibroblast and blood plasma.

Here, we report two Chinese male dHMN patients carrying novel biallelic *COQ7* variants from two Charcot-Marie-Tooth disease cohorts in China (NCT04010188 and NCT04967716).[2] One splicing variant and three missense variants in the *COQ7* gene (NM_016138, chr17:19078921–19091417) were identified in two families from WES data. The patient from Family 1 had c.253-2A>T [chr16:19085241A>T(GRCh37)] and c.467T>A [chr16:19087142T>A(GRCh37)] compound heterozygous variants, and the patient from Family 2 had c.160C>T [chr16:19083336C>T(GRCh37)] and c.467T>G [chr16:19087142T>G(GRCh37)] compound heterozygous variants (Fig. 1A and B). The frequency of COQ7-related neuropathy in our cohorts was 0.238% (2/839). The patients and their parents signed written informed consents and the study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University [MRCTA, ECFAH of FMU (2019)192] and the Peking University Third Hospital (2019-005-02).

In Family 1, the proband was a 22-year-old male with a history of walking instability and frequent falls for 8 years. He presented slow progressive lower limbs distal muscle weakness and pes cavus. When he was 20 years old, orthopaedic surgery was performed on his left ankle, but the muscle weakness was not improved. The patient has had difficulty with long-distance walking; however, upper limb motor function was normal in daily life. Other family members did not have similar experiences. Neuromuscular examinations at the age of 22 showed distal muscle atrophy in the lower limbs, distal muscle weakness in all four limbs, and tendon reflexes were also active in the forelimbs (Fig. 1A and Table 1). Sensory examinations and pyramidal sign tests were normal (Table 1). Nerve conduction studies indicated that the compound muscle action potential of the ulnar nerve, peroneal nerve and tibialis nerve were decreased, and concentric needle electrode tests demonstrated neurogenic damage (Table 1). These results revealed a pure axonal motor neuropathy and normal sensory nerve conduction in all four limbs, corresponding to the diagnosis of dHMN. Muscle biopsy of biceps brachii revealed an absence of neurogenic and myogenic

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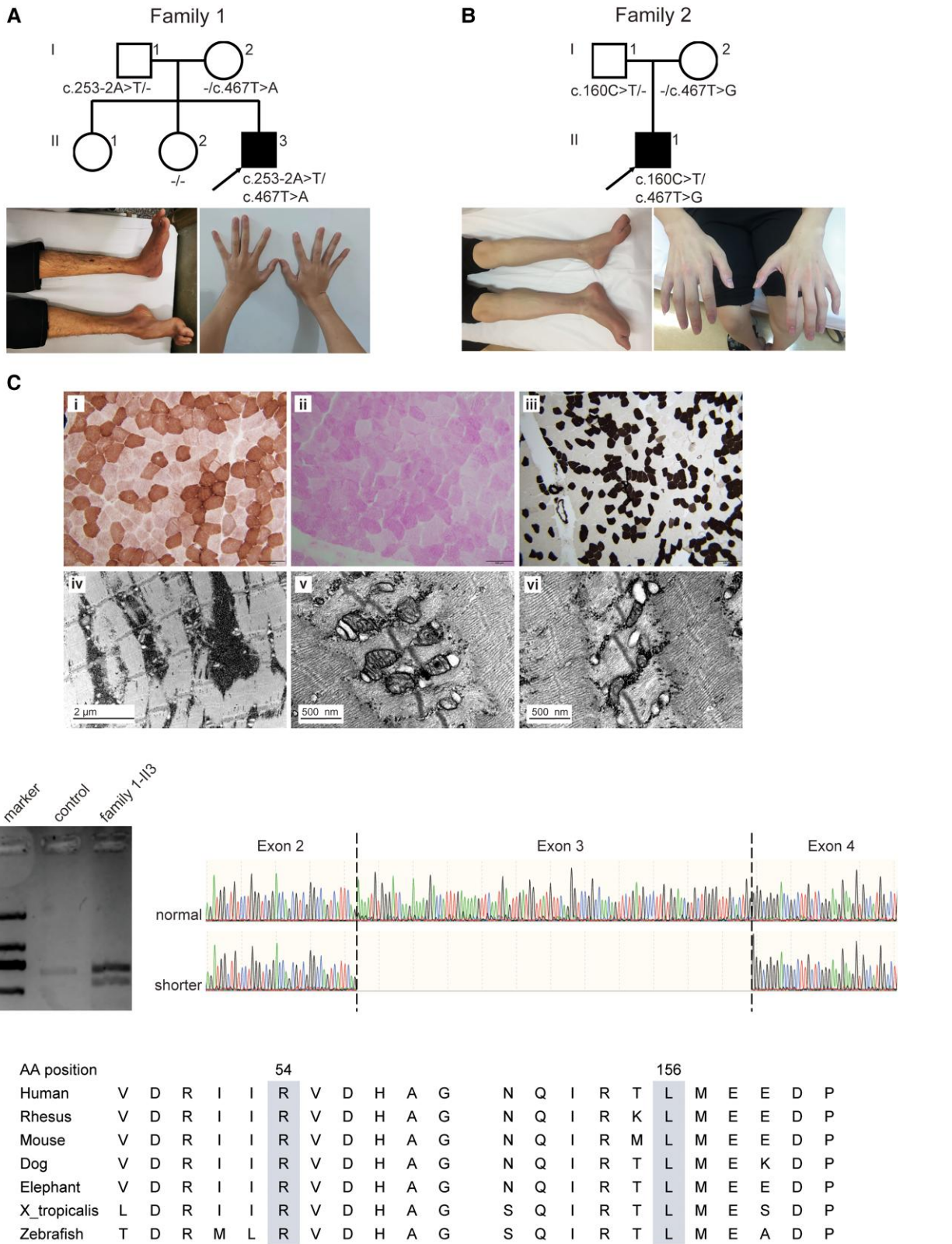

Figure 1 Two dHMN families with biallelic variants in the *COQ7* gene. (**A**) Pedigree and clinical manifestation of Family 1. (**B**) Pedigree and clinical manifestation of Family 2. (**C**) Muscular pathological feature of Family 1-II3. Under microscope, COX/SDH (**i**), PAS (**ii**), and ATP pH = 4.6 (**iii**) staining present no pathological changes. Under electron microscope, accumulation of glycogen (**iv**), and abnormal morphological mitochondria (**v** and **vi**) were found in myofibril. (**D**) The c.253-2A>T splicing variant led to shorter transcript of *COQ7*. (**E**) The conservation of the 54 and 156 residues throughout different species.

Table 1 Clinical features of patients carrying the COQ7 biallelic variants

	Family 1-II3	Family 2-II1
Gender	Male	Male
Age at onset, years	14	15
Limb weakness UL, MRC	Proximal: 5 Distal: 4+	Proximal: 5 Distal: 3
Limb weakness LL, MRC	Proximal: 5 Distal: 3	Proximal: 5 Distal: 3
Knee reflex	+++	+++
Pinprick sensation	–	–
Vibration sensation	–	–
Hoffman's sign	–	+
Babinski's sign	–	–
Pes cavus	+	+
Motor conduction	–	–
Median CMAP, mV	L: 13.0; R: 11.3	L: 3.1; R: 7.1
Median MCV, m/s	L: 57.7; R: 63.2	L: 53.3; R: 60.5
Ulnar CMAP, mV	L: 3.9; R: 4.5	L: 3.0; R: 2.5
Ulnar MCV, m/s	L: 50; R: 50	L: 63; R: 50.7
Peroneal CMAP, mV	L: absent; R: 0.3	L: 3.3; R: 0.8
Peroneal MCV, m/s	L: absent; R: absent	L: 45.3; R: 41.4
Tibialis CMAP, mV	L: 3.2; R: 2.3	L: 1.6; R: 1.8
Tibialis MCV, m/s	L: 42.4; R: 42.6	L: 44.8; R: 47.8
Sensory conduction		
Median SNAP, μV	L: 44; R: 34	L: 58.2; R: 51.8
Median SCV, m/s	L: 50.5; R: 50	L:54.0; R: 57.1
Ulnar SNAP, μV	L: 17; R: 19	L: 18.2; R: 12.1
Ulnar SCV, m/s	L: 50.3; R: 55.3	L:60.1; R:47.6
Sural SNAP, μV	L: 24; R: 16	L: 22.0; R: 29.7
Sural SCV, m/s	L: 46.4; R: 64.6	L: 61.6; R:60.4
Spontaneous activity		
Abductor digiti minimi	L: fib (+), pws (++); R: n	n
First dorsal interosseous	n	L: n; R: fib (+++), pws (+++)
Tibialis anterior	L: n; R: fib (++), pws (++)	L: fib (++), pws (++); R: n

Proximal upper limb (UL) Medical Research Council scale scores (edited) were evaluated by muscle strength of elbow flexion. Distal UL MRC were evaluated by muscle strength of thumb abduction and adduction. Proximal LL MRC were evaluated by muscle strength of hip flexion. Distal LL MRC were evaluated by ankle dorsiflexion and planter flexion. CMAP = compound muscle action potential; fib = fibrillantion potentials; L = left; LL = lower limbs; n = not done; pws = positive sharp waves; R = right.

damage (Fig. 1C). Under electron microscope, we found that accumulation of glycogen in myofibril and abnormal mitochondrial internal organization, coexisted with normal morphological mitochondrial internal organization (Fig. 1C).

In Family 2, the proband was a 19-year-old male with a history of muscle weakness in all four limbs for 4 years. He presented slowly, progressive distal muscle atrophy of his all four limbs and pes cavus. His parents did not have a similar experience. Neuromuscular examinations at the age of 19 showed distal muscle weakness and atrophy in all four limbs, and corresponding tendon reflexes active in four limbs (Fig. 1B and Table 1). The sensory examinations were normal (Table 1). Hoffman's sign and Rossolimo sign were positive (Table 1). The electrophysiological results revealed a pure axonal motor neuropathy, corresponding to the diagnosis of dHMN.

By analysis of WES data in patients and their parents, we identified four novel heterozygous variants in the *COQ7* gene (Fig. 1A and B and Supplementary Table 1). A co-segregation analysis by Sanger sequencing revealed that the probands harboured *COQ7* compound heterozygous variants. The four variants were not associated with genetic disease in the ClinVar database and the Human Gene Mutation Database (HGMD). The two variants in Family 1, c.253-2A>T and c.467T>A, were absent in the gnomAD database and the Westlake BioBank for Chinese (WBBC) (Supplementary Table 1). However, the two variants in Family 2, c.160C>T and c.467T>G, had a minimum allele frequency < 0.001. To confirm whether the c.253-2A>T variant impacted splicing, total RNA was isolated from patient's peripheral blood, and reverse transcribed into cDNA for subsequent amplification. Compared with healthy control, the amplification products showed a normal sized band and shorter sized band in the proband of Family 1. Sanger sequencing of the shorter band revealed that the splicing variant led to abnormal *COQ7* transcripts that loss of exon 3 (Fig. 1D). This abnormal transcript may therefore lead to unstable *COQ7* mRNA or protein. The residues impacted by missense variants are highly conserved across different species (Fig. 1E). COQ7 is a component of the COQ complex and is involved COQ10 biosynthesis. Recent studies found that COQ7 and COQ9 form a tetramer and soluble octamer, and coordinate subsequent synthesis steps toward producing COQ10.[3] We used DynaMut (https://biosig.lab.uq.edu.au/dynamut/prediction) to predict the three missense mutations on protein conformation, flexibility and stability.[4] By using DynaMut, the predicted ΔΔG of p.L156Q and p.L156R were −1.802 kcal/mol and −1.522 kcal/mol, respectively, which indicated that the mutant proteins were destabilizing in nature. However, the predicted ΔΔG of p.R54W was 1.639 kcal/mol, which therefore may not affect stability of the mutant proteins. The molecule flexibility of three missense variants were also predicted, to assist in determining binding affinity and specificity.[5] The predicted ΔΔSvib of p.R54W was −0.660 kcal/mol.K indicating a decrease in molecule flexibility. The predicted ΔΔSvib of p.L156Q and p.L156R were 0.743 kcal/mol.K and 0.088 kcal/mol.K, respectively, indicating an increase in molecule flexibility. Previous studies uncovered that COQ9 and COQ7 formed a soluble octamer that could assist in membrane association and participate in NADH electron-proton-electron donation mechanism. Therefore, we surmised that three missense variants may affect the COQ9:COQ7 complex in mitochondria.

In summary, our study reports two dHMN patients with *COQ7* compound heterozygous variants in two Chinese CMT cohorts, expanding the spectrum of causative variants as well as further confirming the pathogenicity of *COQ7* variants in dHMN. Our findings corroborate a previous study in *Brain* and confirm haploinsufficiency as an important mechanism in dHMN patients.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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