Broadening the phenotype of m.5703G>A mutation in mitochondrial tRNA^{Asn} gene from mitochondrial myopathy to myoclonic epilepsy with ragged red fibers syndrome

Jun Fu, Ming-Ming Ma, Mi Pang, Liang Yang, Gang Li, Jia Song, Jie-Wen Zhang

Department of Neurology, Henan Provincial People's Hospital, Zhengzhou, Henan 450003, China.

To the Editor: Mutations in mitochondrial DNA (mtDNA) cause mitochondrial diseases with multisystem involvement and variable clinical phenotypes. Myoclonic epilepsy with ragged red fiber (MERRF) syndrome is characterized by myoclonus, generalized epilepsy, cerebellar ataxia, and mitochondrial myopathy with ragged red fibers (RRFs). Other features include hearing impairment, psychiatric disorders, and dysarthria.[1] More than 20 heteroplasmic point mutations have been identified as responsible for MERRF, indicating the genetic heterogeneity of mitochondrial diseases. The m.8344A>G mutation in the mitochondrial tRNA^{Lys} (*MT-TK*) gene is the most common mutation and is responsible for approximately 80% of MERRF cases. Other MERRF-related mutations are relatively rare, but up to 10% of MERRF patients have no identifiable mutations. The m.5703G>A mutation in the mitochondrial tRNA^{Asn} (*MT-TN*) gene has previously been reported to cause mitochondrial myopathy (MM).[2,3] To the best of our knowledge, no association has been reported between MERRF syndrome and the m.5703G>A mutation. The present report describes a patient with typical MERRF syndrome carrying a heteroplastic m.5703G>A mutation and expands not only the genotypic spectrum of MERRF but also the phenotypic spectrum of the m.5703G>A mutation.

The patient was a 34-year-old Chinese man. He had experienced generalized tonic-clonic seizures once a year for 10 years, beginning at the age of 18. At the age of 23, he presented with prominent myoclonic seizures in his limbs, body, or head several times per day. The frequency of episodes was not well controlled by combination therapy of valproic acid and levetiracetam. At the age of 31, he developed muscle weakness and atrophy in all four limbs. He also felt fatigue and exercise intolerance. At the same time, fixation in bilateral eyes and mild right ptosis were noticed. He also showed weakness and atrophy in the masticatory and facial muscles, and mild dysarthria and dysphagia. At the age of 32, he complained of distal numbness in the lower limbs, which gradually progressed to the thighs. His gait was slightly unsteady. He also presented with mild hearing loss. No evidence of a positive family history was found.

On physical examination, the patient was underweight (height, 176 cm; weight, 42 kg). He demonstrated normal intelligence with mild dysarthria. Ophthalmoplegia was found with bilateral eye fixation and right ptosis. The masticatory and facial muscles were weak and atrophic. His muscle strength was grade 4/5 (Medical Research Council Score, grades 0–5) in all distal and proximal limbs with muscle atrophy. Ataxia (positive heel-to-shin, tandem gait test, and Romberg test) was noted. Vibration was decreased in the distal lower limbs with normal pinprick and touch sensation. Tendon reflexes were absent in all four limbs.

Laboratory tests revealed slightly elevated serum creatine kinase (CK, 613 U/L; laboratory reference, 50–310 U/L). The resting venous lactate, blood glucose, and thyroid hormone levels were within normal ranges. Electrocardiograph and echocardiogram results were normal. An audiogram revealed sensorineural hearing loss, particularly in the right ear. Fundoscopy revealed no retinal pigment degeneration, whereas monitoring of the visual evoked potential showed abnormality in the visual pathway. Electroencephalography (EEG) performed at the age of 25 years revealed a generalized spike-and-wave complex [Figure 1A]. Electromyography (EMG) indicated myogenic damage. Sensory axonal polyneuropathy was demonstrated by nerve conduction velocity study. Brain magnetic resonance imaging (MRI) revealed mild global cerebral atrophy. Muscle MRI revealed fatty infiltration predominantly in the posterior compartment of the thigh and calf muscles [Figure 1B].

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Correspondence to: Dr. Jie-Wen Zhang, Department of Neurology, Henan Provincial People's Hospital, No. 7, Weiwu Road, Zhengzhou, Henan 450003, China
E-Mail: zhangjiewen90@126.com

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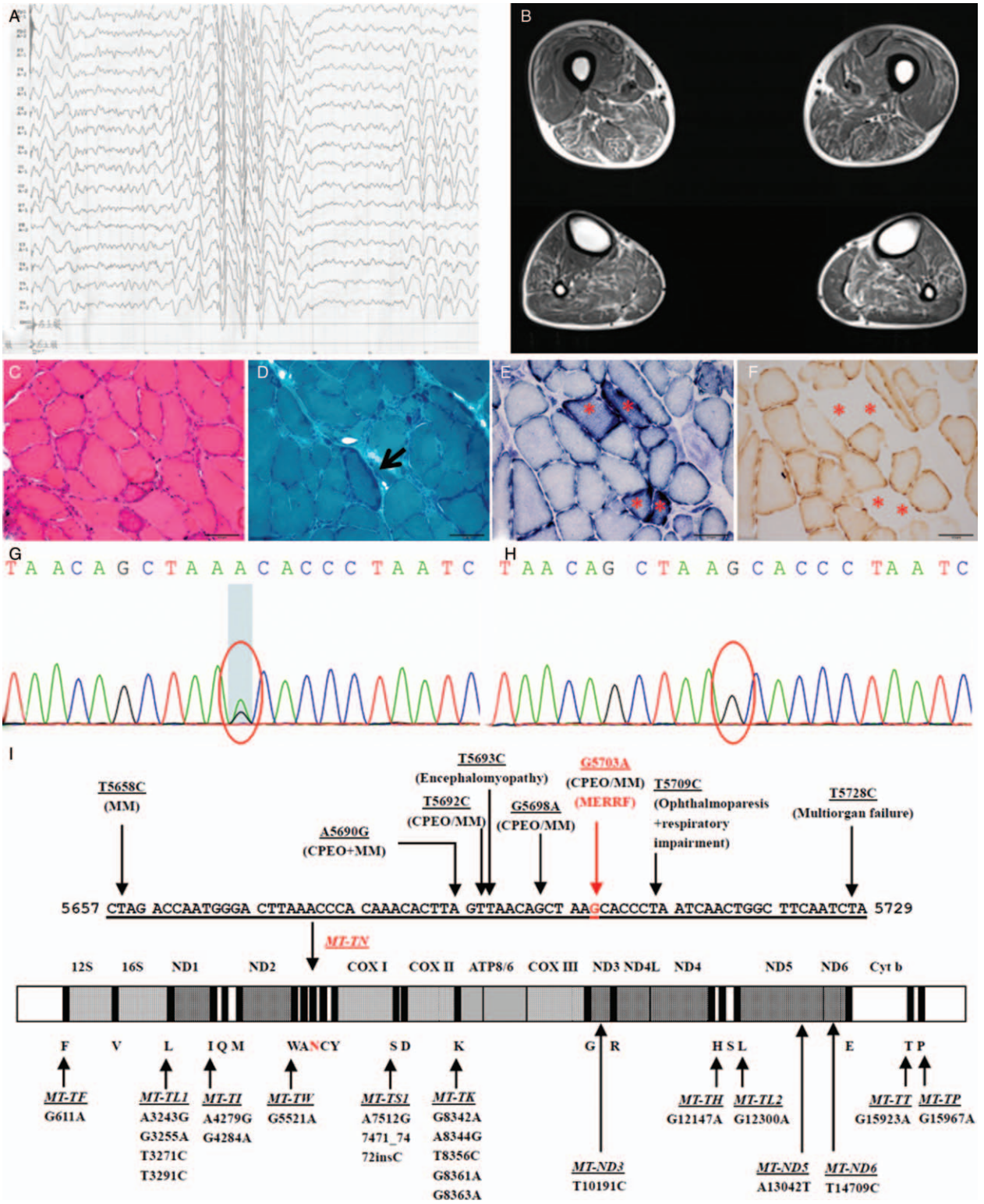

Figure 1: (A) Electroencephalography of the patient showed generalized spike-and-wave complexes. (B) Muscle magnetic resonance imaging revealed predominant posterior compartment involvement of fatty infiltration. (C) Muscle biopsy of hematoxylin and eosin showed a moderate variation in fiber size (original magnification ×200). (D) A ragged red fiber was observed on modified Gomori trichrome (arrow) (original magnification ×200). (E) Some ragged blue fibers were on succinate dehydrogenase (asterisk) (original magnification ×200). (F) Some cytochrome *c* oxidase (COX)-deficient fibers were on COX (asterisk) (original magnification ×200). (G) The m.5703G>A mutation was detected from blood of the patient, but not from his mother (H). (I) A linearized representation of mitochondrial DNA. The m.5703G>A identified in this study was shown in red.

On muscle biopsy, hematoxylin and eosin staining indicated a moderate variation in fiber size and mild endomysial fibrosis [Figure 1C]. Scattered RRFs were observed on modified Gomori trichrome staining [Figure 1D]. Some ragged blue fibers were found on succinate dehydrogenase staining without strongly succinate dehydrogenase-reactive vessels [Figure 1E]. Staining for cytochrome *c* oxidase (COX) activity revealed the presence of scattered COX-

deficient fibers [Figure 1F]. These results support the diagnosis of mitochondrial disease.

We conducted next-generation sequencing (NGS) of the whole mitochondrial genome as well as NGS of nuclear genes, including 681 muscular-disease-related genes and 1029 epilepsy-related genes, after obtaining informed consent from the patient. A m.5703G>A mutation in the *MT-TN* gene was identified in the patient's blood and muscle tissues with mutational ratios of 61% and 77%, respectively [Figure 1G], whereas this mutation was not detected in the blood of his mother [Figure 1H]. This mutation has previously been reported and confirmed as pathogenic in two patients with MM.[2,3] No other mitochondrial DNA or nuclear DNA variants were detected.

After a definite diagnosis was made, the patient stopped valproic acid, and was administered combination therapy of levetiracetam and clonazepam. The myoclonic seizures decreased after 1 month.

The present study reported a patient with myoclonus, episodes of generalized epilepsy, ataxia, and mitochondrial myopathy with RRFs, which are canonical features of MERRF syndrome. The initial symptom of the patient was generalized tonic-clonic seizures, followed by myoclonus confirmed by the presence of spike-and-wave complexes on EEG. The myoclonus and seizures were remarkable in this patient, lasting for more than 10 years before the involvement of other systems, resulting in a delayed diagnosis. Valproic acid is not recommended for myoclonic seizures with mitochondrial diseases, whereas levetiracetam in combination with clonazepam exert a favorable antimyoclonic effect on patients with MERRF.[4] The features of muscle weakness, exercise intolerance, mildly increased CK level, myopathic changes on EMG, and fatty infiltration on muscle MRI in this patient were suggestive of mitochondrial myopathy, which was confirmed by RRFs and COX-deficient fibers on muscle biopsy. Muscle MRI is rarely performed in MERRF patients, and our patient showed a predominant fatty infiltration of the posterior compartment muscles. The additional manifestations in this patient included external ophthalmoplegia, facial weakness, peripheral neuropathy, hearing impairment, dysarthria, and dysphagia, which are less common in MERRF.

The m.5703G>A mutation in the *MT-TN* gene had previously been reported in two patients.[2,3] The disease onset was early and the prominent clinical feature was pure myopathy, particularly in the extraocular muscles. The percentages of this mutation were 4% (blood) and 69% (muscle) in the first patient, and 48% (blood) and 80% (muscle) in the second patient. Our patient had apparent multisystem involvement from MM (chronic progressive external ophthalmoplegia [CPEO] and limb-girdle MM) to encephalopathy and peripheral neuropathy. The mutational ratio was similar to that of the two aforementioned patients in terms of muscle, but higher in terms of blood, which might indicate a relationship with his complex phenotype. Thus far, at least eight disease-related mutations in the *MT-TN* gene have been reported (https://www.mitomap.org/MITOMAP) [Figure 1I]. The most common phenotype is CPEO or limb-girdle MM, whereas encephalomyopathy is rare. The MERRF phenotype of our patient expanded the clinical spectrum of mutations in the *MT-TN* gene.

Thus far, more than 20 mutations have been identified as associated with MERRF [Figure 1I]. Although the m.8344A > G mutation in the *MT-TK* gene is the most common, novel mutations are increasingly being reported as causing MERRF.[5] Most mutations are located in the mitochondrial tRNA genes. The m.5703G>A mutation in our patient was the first mutation in the *MT-TN* gene to be reported as responsible for MERRF, and his clinical features were similar to those reported in patients with other mutations. The genetic heterogeneity in MERRF also highlights the value of NGS in the diagnosis of mitochondrial disorders.

In conclusion, this is the first report to describe the rare *MT-TN* m.5703G>A mutation in association with MERRF syndrome. It not only expands the genotypic spectrum of MERRF, but also broadens the phenotypic spectrum of the m.5703G>A mutation from MM to MERRF.

Declaration of the patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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