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Progressive myoclonus epilepsy without renal failure in a Chinese family with a novel mutation in *SCARB2* gene and literature review

Wo-Tu Tian[a,1], Xiao-Li Liu[a,b,1], Yang-Qi Xu[a], Xiao-Jun Huang[a], Hai-Yan Zhou[a], Ying Wang[a], Hui-Dong Tang[a], Sheng-Di Chen[a], Xing-Hua Luan[a,*], Li Cao[a,*]

[a] *Department of Neurology and Institute of Neurology, Rui Jin Hospital & Rui Jin Hospital North, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China*

[b] *Department of Neurology, Shanghai Fengxian District Central Hospital, Shanghai Jiao Tong University Affiliated Sixth People's Hospital South Campus, Shanghai, 201406, China*

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ABSTRACT

Purpose: To describe the clinical and genetic features of a Chinese progressive myoclonus epilepsy (PME) patient related with *SCARB2* mutation without renal impairment and review 27 *SCARB2*-related PME patients from 11 countries.

Methods: The patient was a 27-year-old man with progressive action myoclonus, ataxia, epilepsy, dysarthria and absence of cognitive deterioration. Renal functional test was normal. Electroencephalography (EEG) showed progressively slowed background activity and sporadic generalized spike-and-wave discharges. Electromyography (EMG) showed slowed motor and sensory nerve conduction velocities and distal motor latency delay accompanied by normal compound motor action potential (CMAP) and amplitudes of sensory nerve action potential (SNAP). The amplitude of cortical components of brainstem auditory-evoked potential (BAEP) was normal with slightly prolonged latencies. Generalized atrophy, ventricle enlargement and white matter degeneration was observed in brain magnetic resonance imaging (MRI). Open muscle biopsy and genetic analysis were performed. Two hundred healthy individuals were set for control. Quantitative real time PCR (qPCR), western blotting and immunofluorescence were carried out to evaluate the fate of the *SCARB2* mRNA and lysosomal-membrane type 2 (LIMP2) protein level.

Results: One homozygous mutation in *SCARB2* gene (c.1187 + 5G > T) was identified in the patient. Each of his parents carried a heterozygous variant. This mutation was not detected among the healthy controls and predicted to be damaging or disease causing by prediction tools. qPCR revealed a significantly lower level of *SCARB2* mRNA in peripheral blood cell of the proband compared with his parents and healthy control individuals. Muscle biopsy showed mild variation in fiber size. Western blotting and immunofluorescence detected an extremely weak signal of LIMP2 protein from skeletal muscle of the proband.

Conclusion: In this study, we identified a *SCARB2*-related PME patient with normal renal function and a novel homozygous splicing mutation. *SCARB2* gene should be analyzed in patients with progressive action myoclonus, epilepsy, peripheral neuropathy, without cognitive deterioration or renal failure.

1. Introduction

The progressive myoclonus epilepsies (PME) are a diverse group of genetic neurodegenerative diseases characterized by abnormal myoclonus, epileptic seizures and variable degrees of neurologic dysfunction, with debilitating evolution, resistance to treatment and poor prognosis [1,2]. Action myoclonus-renal failure syndrome (AMRF, OMIM 254900) is a rare autosomal recessive disorder with progressive myoclonus, dysarthria, ataxia, generalized seizure and absence of intellectual impairment. *SCARB2* has been confirmed as the causative gene

* Corresponding authors.
E-mail addresses: taat@sjtu.edu.cn (W.-T. Tian), 1127209141@sjtu.edu.cn (X.-L. Liu), xuyangqi4362186@sjtu.edu.cn (Y.-Q. Xu), shirley_xjh@hotmail.com (X.-J. Huang), zhaiyan.com@163.com (H.-Y. Zhou), wang-ying@medmail.com.cn (Y. Wang), thd10495@rjh.com.cn (H.-D. Tang), ruijincsd@126.com (S.-D. Chen), luanxinghua@bjmu.edu.cn (X.-H. Luan), caoli2000@yeah.net (L. Cao).

[1] These authors contributed equally to this work.

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of AMRF [3,4]. However, *SCARB2*-related PME is not always presenting with renal dysfunction. Thus, *SCARB2*-deficiency could be divided into two groups: PME with renal failure (AMRF) or without renal failure [5–8]. The syndrome is considered to be related to loss-of-function mutations in *SCARB2* which encodes lysosomal-membrane type 2 protein (LIMP2), a member of the CD36 scavenger receptor-like protein superfamily [9,10]. LIMP2 is a 478 amino acid transmembrane protein mainly expressed in lysosomes and late endosomes, which plays a critical role in β-glucocerebrosidase (β-GC) trafficking from the endoplasmic reticulum to the lysosome [10,11]. Mutations that impair LIMP2 interacting with β-GC or the biogenesis and maintenance of the lysosomal and endosomal compartment cause progressive myoclonus epilepsy. In the past two decades, 19 unrelated families with a recessive PME caused by *SCARB2* gene mutations have been described.

Here, we describe a Chinese PME patient with novel splicing mutation in intron 9 of *SCARB2*, characterized by progressive myoclonus, generalized seizures, ataxia, demyelinating polyneuropathy, without renal involvement or cognitive impairment.

2. Methods

2.1. Ethical approval

The Ethics Committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, approved the study. All participants provided written informed consent.

2.2. Patient

We identified a Han Chinese patient fulfilled the clinical diagnosis of PME. A family (Fig. 1A) with consanguineous history was included in this study. The patient and his family members were clinically examined.

2.3. Mutation analysis

Blood samples were taken from the proband and 3 family members. Unaffected individuals (n = 200) of matched geographic ancestry were also included as healthy controls. The protocols were all approved by the Rui Jin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine. Genomic DNA was extracted from 3 ml peripheral blood samples by a standard protocol using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Epilepsy panel was performed on genomic DNA from the patient. The sequence variant was further interpreted and classified according to the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines [12]. During this session, two neurogeneticists further analyzed the allele frequency (1000 g, ESP6500, dbSNP, ExAC-East Asian and 200 in-house ethnically matched healthy controls), pathogenicity prediction [Human Splicing Finder (http://www.umd.be/HSF3/index.html) and Mutationtaster (http://www.mutationtaster.org)], relation of the gene to disease, and inheritance pattern. Putative pathogenic variant was further confirmed by Sanger sequencing both the forward and reverse strands.

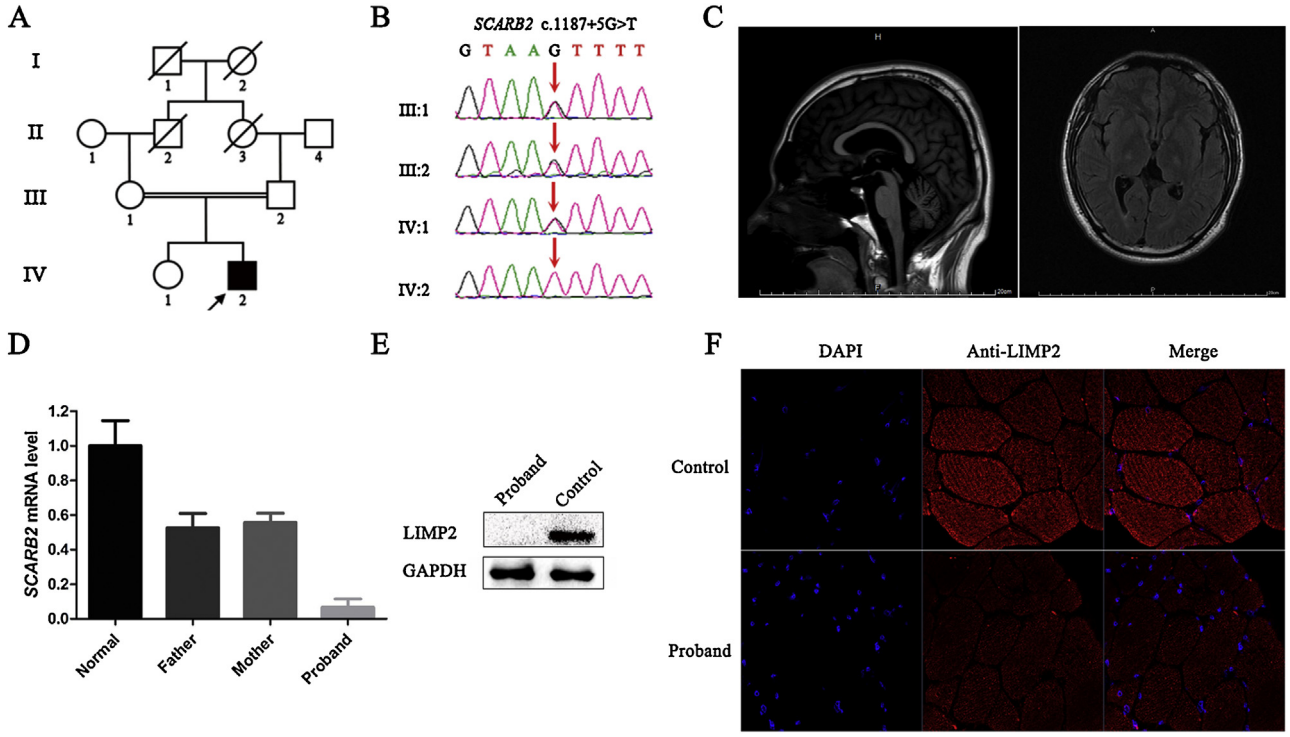

Fig. 1. A. The pedigree of a *SCARB2* family. B. The segreration of *SCARB2* c.1187 + 5G > T (IVS9 + 5G > T) was confirmed by Sanger sequencing showing the proband (IV:2) to be homozygous and his parents and sister (III:1, III:2 and IV:1) as heterozygous carriers. C. MRI revealed the proband with evident atrophy of bilateral cerebellum, brainstem, corpus callosum and hippocampus, ventrical enlargement, as well as mild degeneration of white matter around bilateral posterior ventricles. D. Relative *SCARB2* mRNA levels derived from blood samples of normal control, the proband and his parents. Bar plot indicated the statistical analysis (means ± S) of 3 experiments. T-test analysis demonstrated that mRNA levels in the proband were significantly lower than the controls (7.24%, $p < 0.01$). E. Detection of LIMP2 proteins of muscle tissues from the proband and normal control in western blotting showed mutant LIMP2 was significantly weaker than normal control group. F. Detection of LIMP2 protein in muscle frozen-section from normal control (top panel) and the proband (bottom panel) by immunofluorescence microscopy.