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Letter to the Editor

# Focal brain glucose hypermetabolism in myoclonus-dystonia syndrome caused by an epsilon-sarcoglycan gene mutation

## 1. Introduction

In vivo functional imaging investigating regional brain metabolism has greatly expanded our understanding of the pathophysiologies contributing dystonia and related disorders. Position emission tomography (PET) with 18-fluoro-2-deoxyglucose ($^{18}$FDG) in the resting state has been used in the pathophysiological characterization of several dystonia states [1]. Myoclonus-dystonia syndrome (MDS) is one of the dystonia-plus syndromes, characterized by a childhood onset of dystonia in the cervical and brachial

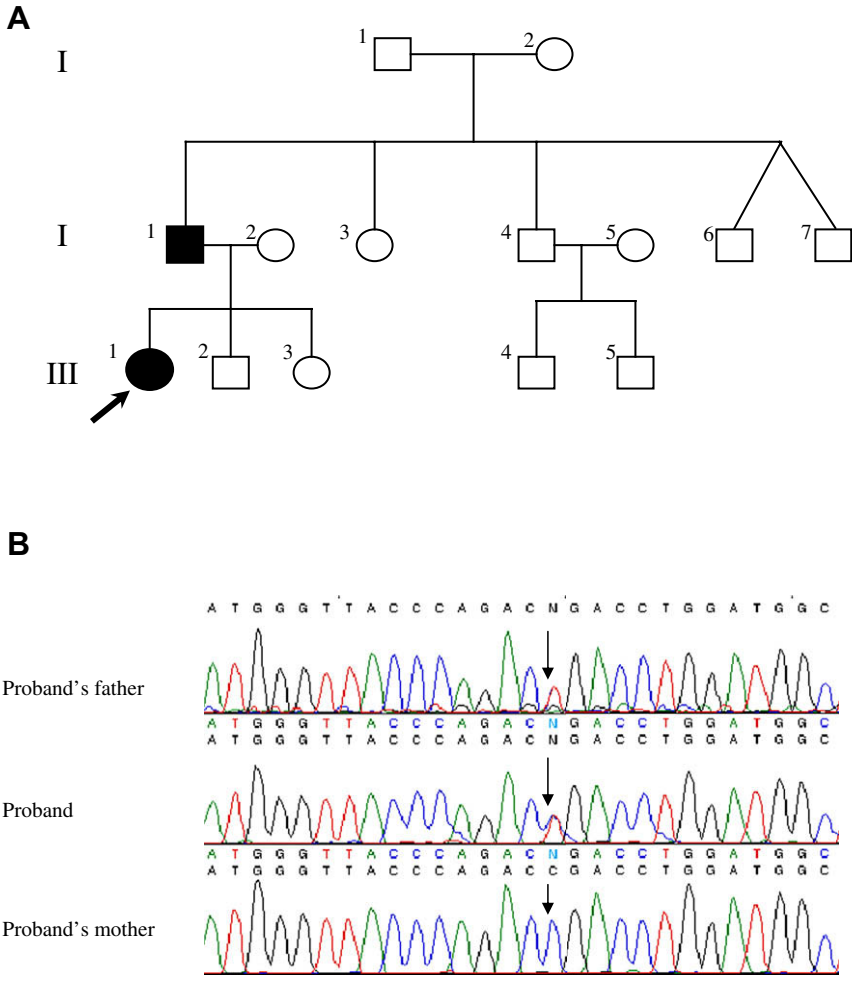


**Fig. 1.** (A) Family pedigree for the index patient (arrow) harboring a SGCE mutation. (B) Direct sequencing of the SGCE gene from the index patient and her parents. The position of the mutation in the cDNA sequence (NP_003910.1) was calculated based upon the position of the first methionine codon (ATG) of the open reading frame with the first "A" equal to +1.

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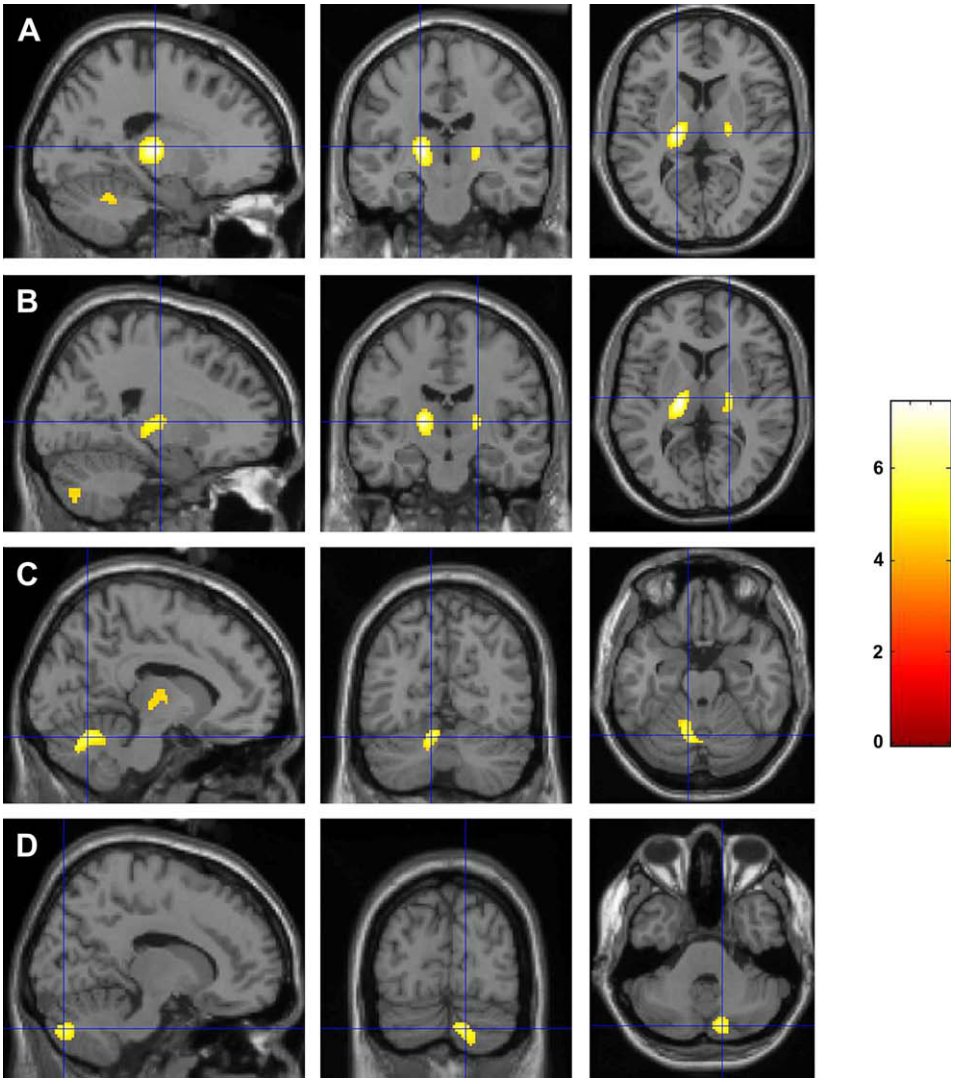


**Fig. 2.** Brain $^{18}$F-FDG PET imaging of the proband at the resting state demonstrates significant focal glucose hypermetabolism. (A, B) Hypermetabolic regions of the right and left thalamus, and (C, D) of the right and left cerebellum, respectively. Images of the patient were compared with those of age-matched healthy controls in a voxel-by-voxel basis using a 2-sample *t*-test. Voxels that were significantly different were projected onto the 3-dimensional rendered brain template provided by SPM99 for anatomical identification. Images included the height threshold $p < 0.001$ ($T = 4.30$), extent size threshold $p < 0.05$ (115 voxels), and were uncorrected for multiple comparisons.

regions, myoclonic jerks, and psychiatric symptoms [2]. MDS is an autosomal dominant disorder caused by mutations in ε-sarcoglycan (SGCE) located on chromosome 7q21 [3]. SGCE is widely expressed in different brain regions, including basal ganglia, thalamic nuclei, and cerebellum, but the function of ε-sarcoglycan remains largely unknown. SGCE gene mutation and MDS has been reported mostly in families of European descent, but is rarely identified in the Asian population. In the present study, we report $^{18}$FDG-PET findings in a Taiwanese family afflicted with MDS.

## 2. Methods

A Taiwanese family with a clinical phenotype that fulfilled the diagnostic criteria for MDS was identified. The index patient and her family members were given standard physical examinations by two neurologists (C.H.T. and M.J.L.). Informed consent was obtained and ethical approval was granted from our Institutional Review Board. All experiments were conducted in accordance with the World Medical Association's Declaration of Helsinki.

The entire coding region of SGCE, including the exon–intron junctions, was subjected to PCR-based direct sequencing using standard protocols. Primer sequences for all 12 exons were designed using Prime-It version 3 software from the Whitehead Institute (Boston, USA). The position of the mutation in the cDNA sequence (NP_003910.1) was calculated based upon the position of the first methionine codon (ATG) of the open reading frame with the first adenine nucleotide (A) equal to +1.

Brain $^{18}$F-FDG PET was performed on the index patient during a resting state. After the injection of 370 MBq (10 mCi) of $^{18}$F-FDG, transmission scan (GE Medical, USA) was obtained using a rotating Ge-68 pin source and images were reconstructed. Analysis was performed by the SPM99 program (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London, UK). Images of the patient were compared with those of age-matched healthy controls and the results were projected onto the 3-dimensional rendered brain template.

## 3. Results

The 26-year-old index patient visited our clinic and described insidious onset progressive postural abnormality involving her upper limbs and neck since childhood. The involuntary movements were aggravated by activity or anxiety, disrupting her daily life activities. Her father also suffered from childhood-onset twisting of the trunk and abnormal limb jerking (Fig. 1A), but the father's symptoms were milder. On physical examination, the index patient showed dystonia of cervical spine, upper trunk, and both brachial regions. Writer's cramp occurred during her writing tasks. She developed marked myoclonic jerks in her cervical and trunk

regions while walking or standing. The findings of brain MRI were unremarkable. Neuropsychological testing was normal. Psychiatric examination revealed chronic adjustment disorder with depression and anxiety. She received a therapeutic trial of levodopa up to 800 mg/day without improvement. Subsequent regimen of anticholinergics, clonazepan and baclofen, combined with botulinum toxin injections partially relieved her symptoms.

Direct sequencing of SGCE gene revealed a single nucleotide substitution, c.289C > T, in exon 3 in both the index patient and her father (Fig. 1B). This change caused a premature stop codon, p.R97X. The mutant allele was not found in her mother (Fig. 1B) or in 100 normal Taiwanese controls. Brain $^{18}$F-FDG PET images from the index patient at rest revealed focal brain regions of significant hypermetabolism in bilateral thalamic and cerebellar regions (Fig. 2). No area of hypometabolism was noted.

## 4. Discussion

Our study demonstrated focal brain glucose hypermetabolism in an Asian MDS patient with typical phenotype and a SGCE gene mutation. The myoclonic jerks affecting neck and trunk accompanied by marked dystonia of cervical and brachial regions, and a positive family history of the proband prompted our investigations to consider this dystonia-plus syndrome and subsequent genetic testing for SGCE gene mutations [2,3]. MDS is an autosomal dominant disorder with the phenomenon of maternal imprinting [3]. In this family, the mutant allele in the proband was derived from her father. A single normal allele from the mother was insufficient for the patient to sustain SGCE gene function, thereby leading to complete SGCE deficiency and manifestation of symptoms.

An abnormal pattern of brain regional glucose utilization has been demonstrated in cohort studies of DYT1 patients by $^{18}$FDG-PET. This specific metabolic topography, termed torsion dystonia-related pattern (TDRP), is characterized by hypermetabolism in putamen, globus pallidus, cerebellum, and supplementary motor areas [1]. The TDRP was also detected in cohort of DYT6 patients, but was not found in patients with dopa-responsive dystonia (DRD). DRD patients revealed another distinct pattern of brain glucose metabolism on $^{18}$FDG-PET [1]. Currently, no $^{18}$FDG-PET study in an MDS cohort has been reported. Our study revealed significant hypermetabolism in both ventrolateral thalamus and bilateral spinocerebellar regions in the patient, suggesting MDS cohort may also show a distinct metabolic topography by $^{18}$FDG-PET. A controlled study utilizing $^{18}$F-FDG PET on post-hypoxic myoclonus patients revealed significant increase in glucose metabolism in bilateral ventrolateral thalamus in these patients, which appears to be in part comparable to our findings [4]. Furthermore, there is additional supporting evidences from a functional MRI study revealing specific activations within thalamus and dentate nucleus in a 5 year-old girl with genetically confirmed MDS [5].

In conclusion, our study suggested that MDS with a SGCE gene mutation may exhibit a unique brain metabolic pattern via $^{18}$FDG-PET imaging. Further study on a larger MDS cohorts should provide a more definitive answer. This disease-related neuroimaging pattern could provide a useful tool for further investigations of the pathophysiological mechanisms underlying MDS.

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Chun-Hwei Tai
*Department of Neurology, College of Medicine and University Hospital, National Taiwan University, No. 7, Chong-Shan South Road, 100 Taipei, Taiwan*

Ruoh-Fan Yen
*Department of Nuclear Medicine, College of Medicine and University Hospital, National Taiwan University, Taipei, Taiwan*

Chin-Hsien Lin
*Department of Neurology, College of Medicine and University Hospital, National Taiwan University, No. 7, Chong-Shan South Road, 100 Taipei, Taiwan*

Kuo-Yang Yen
*Department of Nuclear Medicine and the PET Center, China Medical University Hospital, Taichung, Taiwan*

Ping-Keung Yip
*Neurological Institute, Cardinal Tien Hospital, Xindian, Taiwan*

Ruey-Meei Wu
Ming-Jen Lee*
*Department of Neurology, College of Medicine and University Hospital, National Taiwan University, No. 7, Chong-Shan South Road, 100 Taipei, Taiwan*
* Corresponding author. Tel.: +886 2 2356 2144; fax: +886 2 2341 8395.
*E-mail address:* mjlee@ntu.edu.tw (M.-J. Lee)

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