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Peripheral Blood mRNA Profiling of SGCE and TOR1A in Myoclonus-Dystonia Syndrome: A Genetic Expression Study

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Graphical Abstract

This study examined peripheral blood samples from patients with myoclonus–dystonia and healthy controls to profile mRNA expression of *SGCE* and *TOR1A*. Using real-time PCR, we identified significant overexpression of both genes in patients compared to controls, with a clear positive correlation between their expression levels. These findings indicate that *SGCE* and *TOR1A* expression changes may act as molecular biomarkers to distinguish affected patients from healthy subjects.

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Abstract: Myoclonus-Dystonia (M-D) is a rare autosomal-dominant movement disorder characterized by myoclonic jerks and dystonic symptoms. Myoclonus-Dystonia has been linked to mutations affecting the epsilon-sarcoglycan (SGCE, DYT11) gene. The syndrome has also been associated with mutations in the TOR1A (DYT1) gene. Herein we propose for the first time a link between the mRNA expression levels of SGCE and TOR1A. The main aim of this study was to detect the SGCE and TOR1A mRNA levels in peripheral blood of M-D patients and to explore the correlation between their mRNA levels. We have demonstrated that SGCE mRNA was highly expressed in peripheral blood of M-D patients compared to healthy controls (P = 0.04). We also observed that TOR1A mRNA levels were markedly higher in M-D patients than in healthy controls (P = 0.009). Furthermore, we have demonstrated a significant positive correlation between the SGCE and TOR1A mRNA levels in M-D patients (r = 0.659, p = 0.01). These findings suggest that the analysis of SGCE and TOR1A mRNA levels in peripheral blood could serve as a potential molecular biomarker for distinguishing M-D patients from healthy controls.

Keywords: Myoclonus-Dystonia, SGCE, TOR1A, Biomarker.

Introduction

Myoclonus-Dystonia (M-D), one of the combined dystonia syndromes, is a rare hereditary movement disorder clinically characterized by the presence of both myoclonus (rapid, involuntary jerks) and dystonia (muscle contractions that cause abnormal postures), which affect mainly the upper part of the body; lower limbs are occasionally involved [1]. Symptom onset is usually in the first two decades of life [2–5]. The disorder manifests with a range of symptoms that vary in severity, including tremors, bradykinesia and psychiatric abnormalities [6–7]. The vast majority of familial cases of M-D are linked to mutations in the SGCE gene. Inheritance follows an autosomal-dominant pattern with reduced penetrance on maternal transmission as a result of imprinting of the maternal allele [8]. Epsilon-sarcoglycan (SGCE, DYT11) is the major M-D gene located on chromosome 7q21-q31 and encodes the ε-sarcoglycan protein, a transmembrane glycoprotein within the dystrophin-glycoprotein complex (DGC) [9–11]. The DGC is composed of a number of transmembrane proteins that bind the cytoskeleton to the extracellular matrix in adult muscle fibres [12]. SGCE protein is found in striated and smooth muscle, heart and lung. In the brain, ε-sarcoglycan is strongly expressed in the midbrain monoaminergic neurons, cerebellar Purkinje cells, hippocampus and cortex [13]. The precise function of SGCE protein in the brain remains unknown [4,12,13]. Mutations of the SGCE gene are detected in about 30–50% of M-D cases; most are believed to cause a loss of function through frameshift and protein truncation before the transmembrane domain [9]. The pathophysiology of M-D is therefore not entirely clear [4]. Earlier reports indicated that M-D could also be linked to mutations in the TOR1A gene (DYT1), sometimes in combination with SGCE mutations [14–16].

Early-onset generalized torsion dystonia is a dominantly inherited movement disorder caused by a 3-bp deletion (ΔGAG) in the TOR1A gene that results in a loss of a glutamic acid residue (ΔE) in the carboxy-terminal region of the encoded protein torsinA [17]. This protein is a member of the AAA+ (ATPases associated with various cellular activities) superfamily of ATPases with an unknown biological function. This group of chaperone proteins is involved in protein folding, assembly of protein complexes, and transport of cargo in cells. TorsinA is localized in the contiguous lumen of the endoplasmic reticulum (ER) and nuclear envelope (NE) [17]. Previous studies revealed an association between TorsinA and SGCE protein, suggesting that TorsinA contributes to the quality control of SGCE [13,15,18]. In addition, since mRNA is translated into protein, one might presume that there is some correlation between the level of mRNA and that of protein. The present study aimed to detect the mRNA expression levels of SGCE and TorsinA in the peripheral blood of M-D patients and to explore the correlation between their mRNA levels.

Methods

Patients and samples

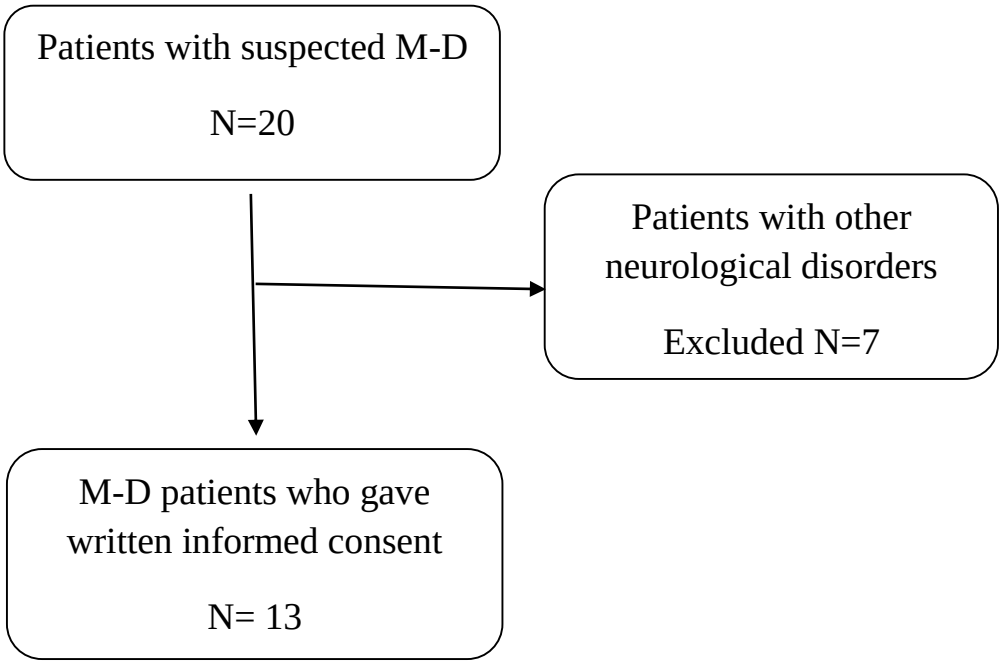
Patients and healthy control subjects were recruited at the Neurology Department of CHU IBN ROCHD (Casablanca, Morocco). All patients went through standardized neurological examinations performed by a movement disorder specialist and were diagnosed according to previously published diagnostic criteria. Psychiatric diagnoses were also made. The exclusion criteria were patients who had other neurological deficits or abnormal findings on electroencephalogram (EEG). After the neurological examination, 13 patients were included in the study. Table 1 shows clinical details of each patient. Our study also included 13 healthy control subjects who had no history of movement disorder. Figure 1 shows patient and control flow charts. Written informed consent was obtained from each patient. This study was approved by the Ethics Committee for Biomedical Research of the Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Casablanca, Morocco, under reference number 21/15. Peripheral blood samples were obtained from all patients and healthy controls. PBMCs were isolated by standard density centrifugation using Ficoll-Paque PLUS.

Table 1. Clinical features of M-D patients.

Case/sex	Age at onset (years)	Age at examination	Myoclonus distribution	Dystonia distribution	Alcohol sensitivity	Additional features
1/M	10	27	UL / C	UL / C / T	Yes	Depression
2/M	12	21	UL / C / Cr	UL / C / Wc	NK	OCD
3/M	12	20	UL / C	UL / C / Wc	NK	–
4/M	25	29	UL / C	Wc / N / T	Yes	Anxiety, Depression
5/F	7	25	UL / C / Cr	UL / C / Wc	NK	OCD
6/F	27	41	UL / C	C	NK	–
7/M	7	14	UL / C / Cr	UL / C / Wc	NK	–
8/M	15	18	UL / LL / C / T	UL / C / Wc	NK	–
9/M	Childhood	23	UL / LL / C / T	UL / LL / C	NK	–
10/M	3	17	UL / C	UL / LL / C / Wc	NK	–
11/M	Childhood	20	UL / C	UL	NK	–
12/M	Childhood	26	UL / C	C	NK	Anxiety
13/M	16	57	UL / C / N	UL / C / Wc	NK	OCD

UL = upper limbs; LL = lower limbs; C = cervical; Cr = cranial; N = neck; T = trunk; Wc = writer's cramp; NK = not known; OCD = obsessive–compulsive disorder.

M-D patients flow chart



Healthy controls flow chart

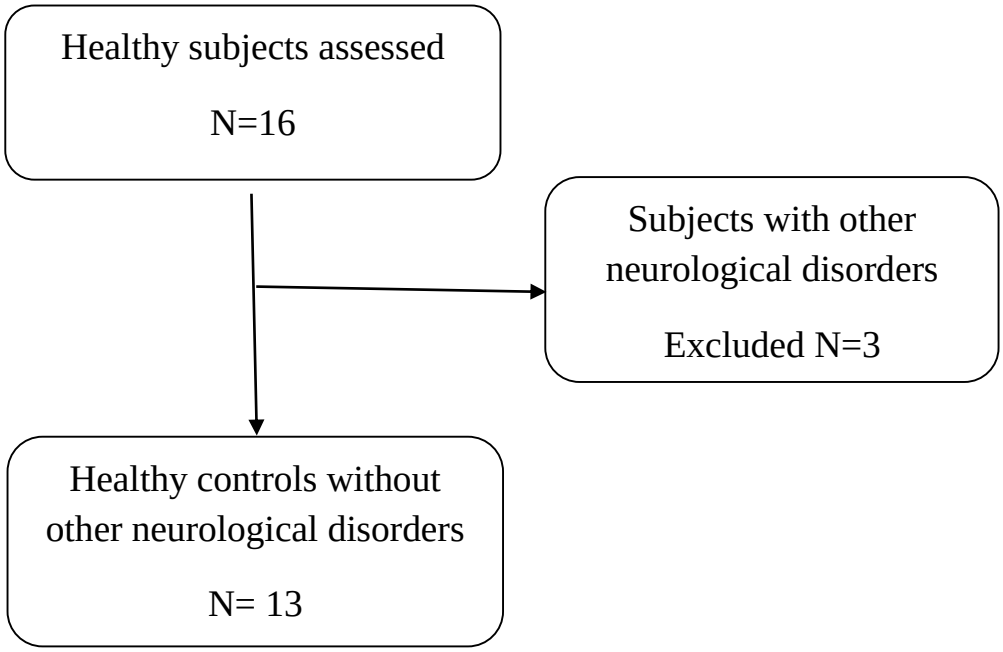


Figure 1. Flow charts of patients and controls

RNA Extraction and Reverse Transcription

Total ribonucleic acid RNA was extracted from PBMCs using TRIzol® Reagent (Invitrogen) according to the manufacturer's instructions. The quality and quantity of total RNA were determined by measuring the absorbance at 260–280 nm (ratio 1.8–2.1) using a spectrophotometer (GE Healthcare, UK), and stored at -80°C prior to analysis. The total RNA was reverse transcribed into cDNA using Random Hexamer (Invitrogen, 300 µg/µl) as a primer for denaturation, then the reverse transcription with: 10 nM dNTP (Invitrogen), DTT (0.1 M), recombinant RNasin, 5× first strand buffer, and SuperScript III RT (Invitrogen).

Quantitative analysis by Real-Time Polymerase Chain Reaction (RT-PCR)

To detect the mRNA expression levels of SGCE, TOR1A genes, and the housekeeping gene (β-ACTIN), quantitative PCR (qPCR) was carried out in duplicate using SYBR Green PCR Master Mix on the Applied Biosystems 7500 Fast Real-Time PCR System. Primers were designed as shown in Table 2. We analysed the relative quantification of SGCE and TOR1A mRNA expression levels using the comparative Ct method (2-ΔCt method) with β-ACTIN as the internal **control**

Table 2. Primers used for quantitative real-time PCR

Gene	Primer	Sequence (5'→3')
β-actin	Forward	5′-AGAGATGGCCACGGCTGCTT-3′
β-actin	Reverse	5′-ATTTGCGGTGGACGATGGAG-3′
SGCE	Forward	5′-ATGCAAACACCAGACATCCA-3′
SGCE	Reverse	5′-ACAGGGTGGAACACAGGAAG-3′
TOR1A	Forward	5′-TGGCCTTGTGTGTGTGTTTT-3′
TOR1A	Reverse	5′-CTTGGAGAGGCTGTTTCAGG-3′

Statistical Analysis

Statistical analysis was performed using SPSS software version 15.0.1 (Chicago, IL). Student's t-test and one-way ANOVA were applied to compare expression levels of SGCE and TOR1A mRNA among controls and M-D patients. Correlation between the SGCE and TOR1A mRNA levels was determined by Pearson's correlation coefficient. A criterion of p-value < 0.05 was considered significant [* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$].

Results

Measurement of SGCE gene mRNA expression levels:

The results showed that M-D patients exhibited an overexpression of the SGCE gene compared to the control cases (**Figure 2**, $p = 0.04$).

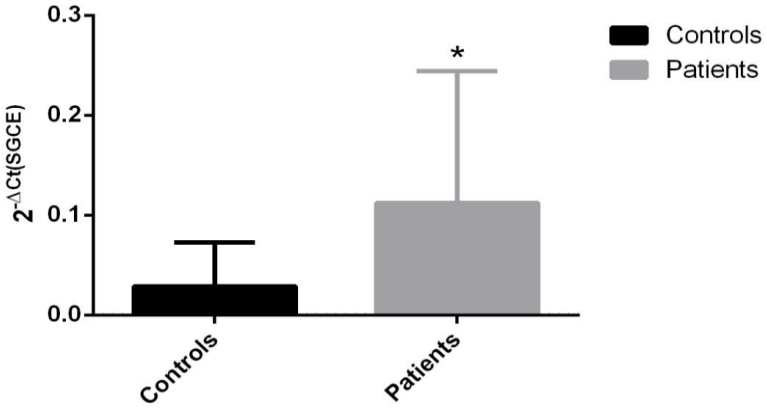


Figure 2. SGCE mRNA expression levels in peripheral blood of M-D patients and controls were determined using the quantitative RT-PCR.

Based on these data, it can be inferred that the overexpression of SGCE mRNA observed in M-D patients is correlated with the mutational load. A comparison was made between carriers of mutations and those without mutations.

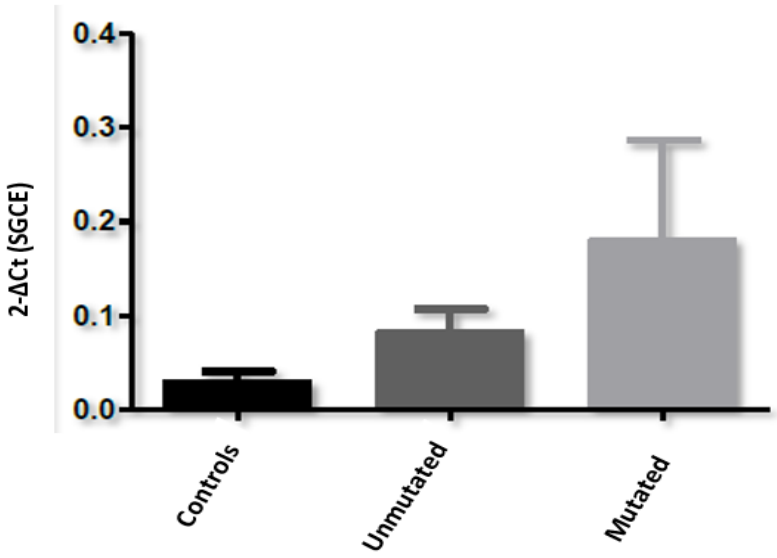
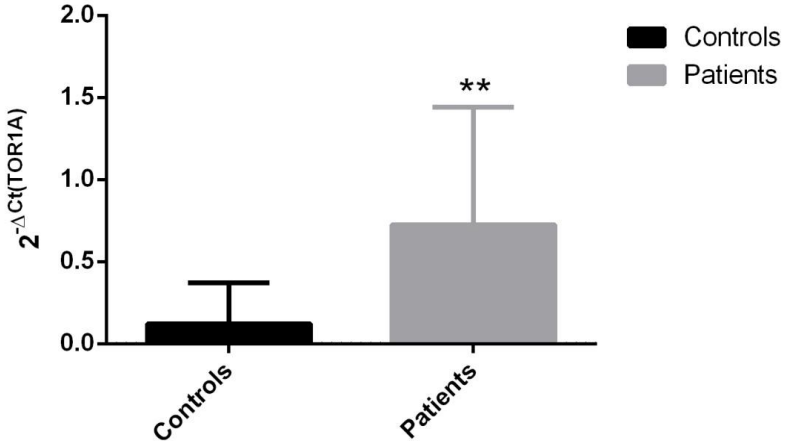


Figure 3. Comparison of SGCE Gene Expression Levels Between Mutated, Unmutated, and Healthy Controls

Our data showed higher SGCE mRNA levels in M-D patients carrying mutations compared to patients without mutations and control cases. A slight increase in mRNA levels was observed in patients without mutations compared with control cases. Comparison between the three groups highlighted a difference in their mRNA levels (Figure 3), but whether this difference is statistically significant remains unclear.

Measurement of TOR1A gene mRNA expression levels

As shown in Figure 4, overexpression of TOR1A mRNA was observed in M-D patients compared to their healthy counterparts (p = 0.009).



gure 4. mRNA expression levels of TOR1A in the peripheral blood of M-D patients and controls were determined using the quantitative RT-PCR (p = 0.009).

*A significant difference of SGCE and TOR1A mRNA expression levels was noticed respectively at *p < 0.05; **p < 0.01.*

The abnormal expression of the TOR1A gene could be related to the M-D phenotype. It is hypothesized that variations in the regulatory regions of the TOR1A gene may be associated with the development of the disease.

Comparison of SGCE and TorsinA mRNA levels in M-D patients

By comparing the expression levels of the two target genes, the result showed a lower expression rate of the SGCE gene compared to the TOR1A gene (Figure 5, p = 0.006).

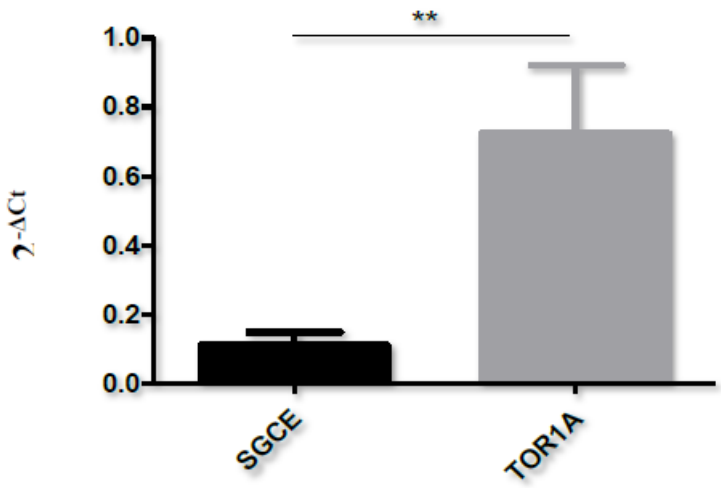


Figure 5. Comparison of SGCE and TOR1A gene expression levels.

Previous studies have revealed an association between TOR1A and SGCE. Since mRNA is translated into protein, it can be inferred that there is a correlation between mRNA levels and protein levels. To assess the association between SGCE and TOR1A, a correlation test was used.

Correlation analysis between SGCE and TOR1A mRNA levels in M-D patients

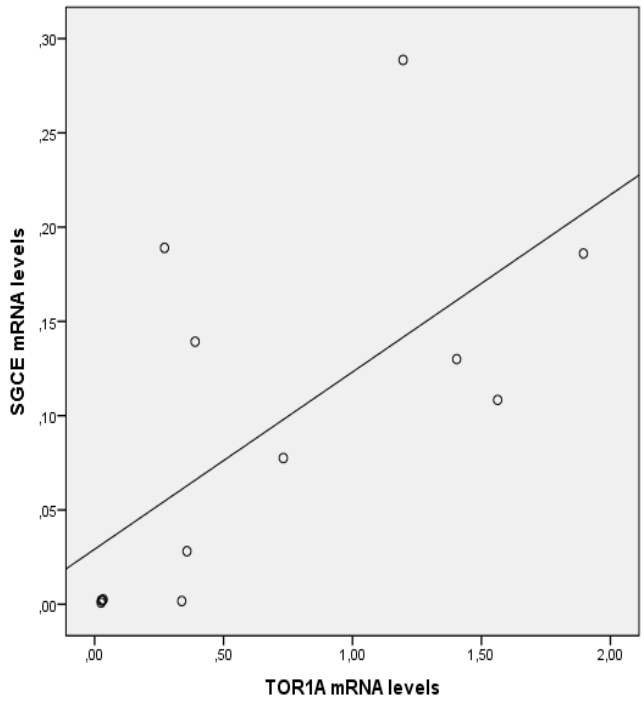


Figure 6. Correlation between SGCE and TOR1A mRNA expression levels in peripheral blood of M-D patients, determined using Pearson's correlation analysis (r = 0.659, p = 0.01).

In M-D patients, a significant positive correlation was found between SGCE and TOR1A mRNA levels in peripheral blood according to Pearson's correlation test (Figure 6, r = 0.659, p = 0.01)

Discussion

Although it is known that mutations in the SGCE gene cause M-D [9], the precise pathophysiology remains incompletely understood [4]. Three isoforms of SGCE have been reported, with exon 11b being the major brain-specific isoform, predominantly expressed in the cerebral cortex, cerebellum, and hippocampus [19]. The protein ε-sarcoglycan, a member of the transmembrane protein family, is localized to the plasma membrane in neurons, muscle, and transfected cells [20]. In the presence of missense mutations, ε-sarcoglycan fails to traffic to the plasma membrane and is retained intracellularly, polyubiquitinated, and degraded by the proteasome [13,20]. Previous studies have demonstrated that TorsinA, encoded by the TOR1A gene, forms a stable complex with mutant forms of ε-sarcoglycan, promotes its degradation, and plays a role in its quality control [13,17,18,21]. In this context, we propose for the first time a link between SGCE and TOR1A mRNA expression levels in patients with M-D.

Our results revealed significant overexpression of SGCE mRNA in M-D patients compared with controls ($p = 0.04$), suggesting that SGCE expression is altered in the context of M-D. This finding supports previous research linking SGCE expression levels to the pathogenesis of the disease. We observed higher SGCE mRNA levels in mutation carriers, which were significantly greater than in patients without mutations and in controls. This suggests that the mutational load may correlate with the overexpression of SGCE mRNA. A slight increase in mRNA levels was also observed in patients without mutations compared to controls, indicating possible subtle alterations in gene expression in this group. Despite these variations, the comparison between the three groups revealed a significant difference in SGCE mRNA levels (Figure 24), but whether this difference is statistically significant remains obscure and requires further investigation**.**

The elevated SGCE mRNA levels in M-D patients raise the possibility of overexpression of ε-sarcoglycan protein in key brain structures involved in motor function. Such overexpression may contribute to the pathophysiology of M-D by altering normal protein folding and trafficking processes. In this context, we hypothesize that mutations in SGCE lead to the retention of misfolded proteins within the endoplasmic reticulum (ER), where they are polyubiquitinated and degraded by the proteasome. This misfolding may be exacerbated in the presence of TorsinA, a protein known to organize the ER and the nuclear envelope. TorsinA may play a critical role in the quality control of SGCE in the ER, further supporting the idea of a functional interaction between the two proteins. The binding of TorsinA to mutant SGCE and its role in promoting its degradation have been well documented [13,15,18], and our findings of a significant correlation between the mRNA levels of SGCE and TOR1A ($r = 0.659$, $p = 0.01$) lend support to this interaction at the gene expression level.

Furthermore, the comparison of the expression levels of SGCE and TOR1A revealed lower expression of SGCE compared to TOR1A (Figure 27, $p = 0.006$), suggesting differential regulation of these two genes in the context of M-D. This result may imply that, although both genes are involved in the pathogenesis of M-D, their expression is not entirely coordinated. It is noteworthy that the relationship between SGCE and TOR1A expression could have implications for understanding the broader molecular mechanisms underlying the disease.

Based on these findings, we suggest that the overexpression of SGCE and the correlated expression of TOR1A may be indicative of a pathological process in M-D patients. This raises the possibility that the analysis of SGCE and TOR1A mRNA levels in peripheral blood could serve as a potential molecular biomarker for distinguishing M-D patients from healthy controls. Continual mutation testing of SGCE and TOR1A in M-D patients will be crucial in further elucidating the molecular basis of these expression changes and their relationship to disease progression.

Conflicts of interest

The authors declare no conflict of interest.

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