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Confirmation of a Causal Role for *SHQ1* Variants in Early Infantile-Onset Recessive Dystonia

An overarching goal of genetics research in dystonia is the definition of converging molecular pathways, allowing grouping of patients according to disease biology rather than phenomenology.[1] This may improve the development of stratification schemes and contribute to the transition from empiric selection of treatments to etiology-directed therapeutics. One downstream mechanistic effect shared by different mutant dystonia-associated gene products includes the perturbation of translational control.[1] For example, abnormalities in eIF2α-signaling, induced by mutations in *EIF2AK2* or *PRKRA*, are considered to result in aberrant protein synthesis via translation-initiation impairments.[2] Most recently, Sleiman and colleagues have introduced a new player in translational defect-mediated dystonia, *SHQ1*[3]; the gene encodes a component of the H/ACA–ribonucleoprotein complex, responsible for the modification of various RNA species, including those that regulate protein synthesis in the ribosome.[4] Although two *SHQ1*-mutated families with dystonia have been described,[3] the gene–phenotype relationship has not yet been firmly established.[5]

We have prioritized compound heterozygous *SHQ1* variants, c.523G>T (p.Asp175Tyr) and c.828_831del (p.Asp277Serfs*27), in whole-exome sequencing data of a female study proband with infantile-onset dystonia (Table 1); these variants remained of uncertain significance during initial analysis (August 2021).[6] Eventually, bioinformatics pipeline-based (re-) assessment of latest literature/ClinVar data revealed that our candidate *SHQ1* variants were identical to mutations observed in one of the families reported by Sleiman and colleagues.[3] These published carriers of c.523G>T/c.828_831del developed dystonia before the age 6 months, with diurnal fluctuations and partial response to levodopa.[3] Similarly, our proband manifested dystonia in her first months of life, and the disorder was levodopa responsive. Her motor milestones were delayed. Over time, movement abnormalities evolved into a more complex pattern, and she experienced a generalized tonic–clonic seizure at age 14 years. On recent examination, she displayed a mixed hyperkinetic disorder characterized by dystonia, myoclonus, and chorea affecting the limbs, trunk, and facial region (Video S1). There was worsening of hyperkinesia in the evening, cognitive impairment, and truncal hypotonia, leading to an initially suspected diagnosis of *ADCY5*-related dyskinesia.[1] All routine diagnostic studies were unrevealing except for an isolated moderate decrease in HVA levels in cerebrospinal fluid.

Recurrence of c.523G>T/c.828_831del in two separate dystonia-affected families provides strong evidence for pathogenicity of these variants. Moreover, c.828_831del has been detected in combination with another *SHQ1* mutation in a third family[3] (Table 1). Observing the same set of compound-heterozygous alleles in two nonrelated pedigrees is an uncommon finding and could be explained by the population frequency of the variants. Notably, both c.523G > T and c.828_831del are very rare but observed in an appreciable number of gnomAD controls (Table 1); c.523G>T is even found in 1 gnomAD individual in the homozygous state, indicating that it could represent a hypomorphic allele.[3] We expect that *SHQ1*-associated dystonia is underdiagnosed and may have been ignored in some exome-sequenced cases analyzed using standard filter settings (often removing variants present in homozygous controls).[7]

Our report provides replication for the involvement of *SHQ1* in autosomal recessive early-onset dystonia, which appears to be a more complex and progressive movement disorder. *SHQ1* should be added to the compendium of dystonia-associated genes involved in translational control, expanding our understanding of common molecular themes in dystonia pathogenesis.

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Data Availability Statement

Full data set available from the corresponding author upon request.

Key Words: dystonia; infantile-onset movement disorder; *SHQ1*; translational control

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TABLE 1 *Comparison of clinical features of affected individuals with biallelic* SHQ1 *variants*

	Present family Affected child	Family 2, Sleiman et al Individual 3	Family 2, Sleiman et al Individual 4	Family 1, Sleiman et al Individual 1	Family 1, Sleiman et al Individual 2
SHQ1 variants RefSeq transcript: NM_018130.3	c.523G>T (p.Asp175Tyr); c.828_831del (p.Asp277Serfs*27)	c.523G>T (p.Asp175Tyr); c.828_831del (p.Asp277Serfs*27)	c.523G>T (p.Asp175Tyr); c.828_831del (p.Asp277Serfs*27)	c.874G>A (p.Glu292Lys); c.828_831del (p.Asp277Serfs*27)	c.874G>A (p.Glu292Lys); c.828_831del (p.Asp277Serfs*27)
Variant CADD scores	31; 33	31; 33	31; 33	32; 33	32; 33
Zygosity	Compound heterozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous
Allele frequency (gnomAD)	108/282666 (1 homozygote); 188/282496 (no homozygotes)	108/282666 (1 homozygote); 188/282496 (no homozygotes)	108/282666 (1 homozygote); 188/282496 (no homozygotes)	1/249960 (no homozygotes); 188/282496 (no homozygotes)	1/249960 (no homozygotes); 188/282496 (no homozygotes)
Sex	Female	Male	Male	Female	Female
Age (most recent examination)	17 years	10 years	8 years	10 years (deceased)	11 years
Family history	Negative (2 unaffected sibling)	Positive (2 affected siblings)	Positive (2 affected siblings)	Positive (2 affected siblings)	Positive (2 affected siblings)
Dystonia	Yes	Yes	Yes	Yes	Yes
Dystonia age at onset/ disease course	<6 months/slowly progressive	<6 months/nonprogressive	<6 months/nonprogressive	<6 months/progressive	<6 months/progressive
Accompanying movement disorder(s)	Choreatic and myoclonic elements	No	No	Chorea, athetosis, ballism	Chorea, athetosis, ballism
Developmental delay/ cognitive impairment	Yes	No	No	Yes	Yes
Hypotonia	Yes	No	No	Yes	Yes
Epileptic activity	Yes (1 generalized tonic–clonic seizure)	No	No	Yes	Yes
Behavioral issues	Not reported	No	No	Yes	Yes
Brain MRI	Normal	Normal	Normal	Cerebellar atrophy	Normal
CSF analysis results	HVA: 277 nmol/L (normal: 300–1000 nmol/L) 5-HIAA: 239 nmol/l (normal: 200–600 nmol/l)	HVA: 0.32 nmol/L (normal: 0.49–0.66 nmol/L) 5-HIAA: 0.26 nmol/L (normal: 0.19–0.30 nmol/L)	NA	HVA: 174 nmol/L (normal: 233–928 nmol/L) 5-HIAA: 105 nmol/L (normal: 74–345 nmol/L)	HVA: 194 nmol/L (normal: 294–1115 nmol/L) 5-HIAA: 172 nmol/L (normal: 129–520 nmol/L)
Levodopa response	Yes (partial, worsening of dyskinesia)	Yes (partial, worsening of dyskinesia)	Yes (partial)	No	Yes (partial)

CADD, combined annotation dependent depletion; MRI; magnetic resonance imaging; CSF, cerebrospinal fluid; NA, not available.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.