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A novel *SUCLA2* mutation presenting as a complex childhood movement disorder

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Abstract

SUCLA2 defects have been associated with mtDNA depletion and the triad of hypotonia, dystonia/Leigh-like syndrome, and deafness. A 9-year-old Brazilian boy of consanguineous parents presented with psychomotor delay, deafness, myopathy, ataxia, and chorea. Despite the prominent movement disorder, brain MRI was normal while ¹H-MRS showed lactate peaks in the cerebral cortex and lateral ventricles. Decreased biochemical activities of mitochondrial respiratory chain enzymes containing mtDNA-encoded subunits and mtDNA depletion were observed in muscle and fibroblasts. A novel homozygous mutation in *SUCLA2*, the first one in the ligase CoA domain of the protein, was identified. Escalating doses of CoQ₁₀ up to 2000 mg daily were associated with improvement of muscle weakness and stabilization of the disease course. Our findings indicate the importance of screening for mitochondrial dysfunction in patients with complex movement disorders without brain MRI lesions and further investigation for potential secondary CoQ₁₀ deficiency in patients with *SUCLA2* mutations.

Keywords

SUCLA2; Coenzyme Q10; movement disorders; Brain MRI

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AUTHOR CONTRIBUTION

CG carried out experiments and data analysis, drafted the manuscript; JGG contributed to histology experiments and cared for the patient; SSC contributed to genetic study; SK contributed to biochemical experiments; AN contributed to biochemical experiments; CMQ supervised experimental plan and edited the manuscript; MH designed the study, evaluated the patient, directed and supervised experimental procedures and edited the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

Informed consent for anonymous publication of the patient's clinical features, videotape and analyses of DNA and muscle tissue were obtained under a Columbia University Institutional Review Board-approved protocol.

Introduction

Mitochondrial DNA depletion syndrome (MDS) comprises a group of clinically and genetically heterogeneous disorders with reduction of mitochondrial DNA (mtDNA) copy number in tissues, leading to decreased synthesis of mitochondrial respiratory chain complexes (RC)¹. Mutations in 10 nuclear genes have been identified as causes of MDS (*TK2*, *DGUOK*, *POLG*, *MPV17*, *RRM2B*, *SUCLA2*, *SUCLG1*, *MGME1*, *C10orf2*, and *FBXL4*) mainly encoding protein involved directly at the DNA replication fork or in the metabolism of deoxynucleotide triphosphate precursors pools for mtDNA replication^{2, 3}.

SUCLA2 and *SUCLG1* genes encode the β and α subunits of succinyl-CoA synthase, which interacts with the mitochondrial nucleoside diphosphate kinase, an enzyme required for the mitochondrial deoxynucleotide salvage pathway⁴. Homozygous mutations in *SUCLA2* were first identified in two cousins from a consanguineous Israeli-Muslim family with an autosomal recessive mitochondrial encephalomyopathy, severe mtDNA depletion in muscle (32%) and defects in the activities of complex I and IV of the respiratory chain⁵. In addition, sixteen patients from Faroes Island and eight Caucasian have been described^{6–9} with the clinical triad hypotonia, dystonia/Leigh-like syndrome, and deafness, and the metabolic profile of methylmalonic aciduria caused by *SUCLA2* deficiency.

Here, we report a novel mutation in *SUCLA2* in a Brazilian child with deafness, myopathy, and a complex movement disorder characterized by chorea and ataxia.

Case summary

A 9-year-old boy of consanguineous parents with mixed ethnic backgrounds (Portuguese and indigenous Brazilian), presented with early onset chorea, ataxia, and myopathy. He was after an uneventful 36 week pregnancy. There was no family history of neurodegenerative disorders. At age 11 months, he was noted to have delays in motor and language development, which progressed to marked hypotonia, ataxic gait, and frequent falls at age 18 months. After an acute febrile illness at 22 months of age, he became wheelchair-bound. Audiometry revealed 80% hearing loss and, despite the use of hearing aids, he never acquired the ability to talk. He developed chorea and migraine headaches with nausea and vomiting. Signs and symptoms of systemic involvement were also noted with growth retardation, gastrointestinal reflux, as well as incontinence of stool and urine.

At age 4, because of the combination of myopathy and ataxia, he was suspected of having CoQ₁₀ deficiency and supplementation was started at 300 mg daily. Response to treatment was promptly evident: 2 weeks later, he regained the ability to hold his head up, to sit unassisted, and to crawl with difficulty.

At the latest clinical evaluation at age 9 years, he was taking CoQ₁₀ 2,000 mg daily and L-carnitine 1,200 mg daily, thiamine 100 mg daily, and biotin 10 mg daily. Relative to the examination three years prior, choreic and ataxic movements appeared stable while improvement in muscle weakness was evident (Video 1). He was able to walk without support and communicate with sign language. Brain MRIs were normal at ages 3, 6, and 9

years-old, but brain ¹H-MRS revealed lactate peaks in the cerebral cortex and lateral ventricles (Figure 1 A–E).

Metabolic tests showed elevated fasting venous lactate (57.7 mg/dl, nl 4.5–14.4) and CSF (29 mg/dl, nl 9–16) and normal plasma and urine amino acids; while urine organic acid profiles showed variable increases of lactic acid and 3-hydroxy-isovaleric acid and 3-methylglutaconic acid.

Quadriceps muscle biopsy showed ragged-red fibers (RRF), hyperactivity of NADH and succinate dehydrogenase, type I fiber predominance, and lipid droplets (Figure 1F–H). Respiratory chain enzyme activities in muscle showed markedly decreased activities of succinate-cytochrome c reductase (II+III) (4% of control mean normalized to citrate synthase, a marker of mitochondrial mass), cytochrome c oxidase (IV) (12%) and NADH-dehydrogenase-cytochrome c reductase (I+III) (19%). In contrast, the patient's cultured skin fibroblasts showed partial deficits of complexes II+III (49%) and IV (75%). Thus, the defects in respiratory chain activities in muscle, but not in fibroblasts fulfill Walker major diagnostic criterion (<20% activity of control mean) for mitochondrial disease¹⁰.

Quantitation of mtDNA by real-time PCR revealed 16% residual mtDNA in muscle and 63% in fibroblasts relative to normal controls (Supplemental Table 1).

High-density genome-wide SNP genotyping by hybridization of total genomic DNA extracted from patient fibroblasts on Human 660w-quad BeadChips (Illumina Inc.) was performed and SNP data were analyzed using BeadStudio v3 (Illumina Inc.). Twelve chromosomal loci revealed homozygosity in the patient and genes known or predicted to encode mitochondrial proteins were studied by Sanger sequence.

A novel homozygous variation c.1276C>T (p.Arg407Trp) in *SUCLA2* was identified in a high conserved amino acid residue, localized in the ligase CoA domain of the protein. The missense change was predicted to be “probably damaging” by Polyphen (<http://genetics.bwh.harvard.edu/pph/>), was heterozygous in both parents, and absent in dbSPN137 database and in the DNA from 100 healthy individuals tested by sequencing.

Discussion

Inborn errors of metabolism comprise a heterogeneous group of disorders often presenting with complex clinical syndromes characterized by psychomotor retardation, pyramidal signs, epilepsy, and movement disorders. Childhood-onset movement disorders such as ataxia and dystonia have been frequently described in mitochondrial disorders and are often due to Leigh or Leigh-like lesions in basal ganglia or cerebellar atrophy.

Here, we present describe the first patient with a *SUCLA2* defect, presenting with psychomotor retardation, ataxia, chorea, myopathy, and deafness. Despite the complex movement disorder, no brain lesions were identified MRI scans, while abnormal lactic acid peaks were present in both the cerebral cortex and ventricles. Defects in *SUCLA2* have been associated with muscle mtDNA depletion and severe progressive mitochondrial encephalomyopathy with psychomotor retardation, feeding problems, hearing loss, speech delay and Leigh-like brain lesions and occasional additional manifestations (Table 1).

Normal brain MRIs have been described in only two patients with early childhood onset and devastating disease courses.

In patients with *SUCLA2* defects, metabolic assessments have shown elevations of citric acid intermediates, L-leucine metabolites, lactic acid that are considered important markers for the genetic diagnosis^{8, 11}. The metabolic profile in our patient together with those of reported cases^{9, 12} demonstrated variable abnormalities of intermediate metabolites, but lactic acidosis was more consistently detected in both plasma and brain MRIs. Our report underscores the importance of screening for mitochondrial dysfunction using brain MRS in patients with complex movement disorder without brain MRI lesions.

We confirmed the presence of severe mtDNA depletion in muscle of *SUCLA2* mutant patients, and also found reduction of mtDNA copy number in fibroblasts, a peculiar finding in dividing cells, that has been described in only two out of 24 patients¹³. The pathogenic pathway linking *SUCLA2* defects and mtDNA maintenance is still unknown. Loss of interaction between succinyl-CoA synthase and mitochondrial nucleoside diphosphate kinase, followed by secondary deficiency of the mitochondrial deoxyribonucleotide diphosphate phosphorylation have been postulated to impair mitochondrial DNA synthesis^{5, 14}.

Therapeutic strategies in mitochondrial disorders include supportive or disease modifying treatment. Early nutritional support in the first months of life delayed the disease progression in 3 children with *SUCLA2* mutations from Faroe Island. In our patient coenzyme Q₁₀ supplementation appeared to improve muscle weakness and stabilized the clinical course of the disease.

Our report contributes to expand the spectrum of *SUCLA2* mutations adding a milder phenotype in which ataxia and chorea were the main debilitating and severe symptoms. Although the limited number of patients reported does not allow genotype-phenotype correlation, the mutation in the ligase CoA domain may explain the milder phenotype observed in our patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Panel A-C: Axial, sagittal and coronal T2-weighted brain MRI images showing normal gray and white matter; Panel D: spectral metabolites of brain MRS showing lactate peak. Panel E-H: cytochrome *c* oxidase (COX) (E), modified Gomori trichrome (F), oil-red-oil (G) and hematoxylin and eosin (H) stains of muscle biopsy showing lipid droplets and ragged fibers.

Table 1 –Genotype-phenotype correlation of patients with *SUCLA2* mutations.

Mutation	Ethnic origin	Clinical Symptoms	Brain MRI	Metabolic findings	N	References
c.308C>A (p.Ala103Asp)	Italian	Spastic-dystonic tetraparesis, hearing loss, ptosis and progressive external ophthalmoplegia	Leigh-like lesions + cerebellar atrophy	↑Plasma and CSF lactic acid ↑Plasma carnitine short chain esters	2	Lamperti, 2013
c.352G>A (p.Gly118Arg)	Italian	Dystonia, deafness, and severe psychomotor delay	Leigh-like lesions + cerebral atrophy	↑Plasma and CSF lactic acid ↑Urinary methylmalonic acid ↑Plasma and urinary carnitine esters ↑Urinary citric acid cycle intermediates	1	Carrozzo, 2007
c.534+1G>A	Faroe Island	Neonatal onset of encephalopathy with/without other signs/symptoms (external ophthalmoplegia, seizures, polyneuropathy, cardiomyopathy, renal tubular dysfunction)	Leigh syndrome/ Leigh-like lesions	↑Urinary methylmalonic, 3-methylglutaconic and 3-hydroxyisovaleric acids ↑Plasma and CSF lactic acid ↑Urinary carnitine esters	16	Ostergard, 2007 Carrozzo, 2007 Morava, 2009
c.751G>A (p.Asp251Asn)	Iranian	Severe generalized dystonia, severe psychomotor delay, severe hypotonia, hearing loss, failure to thrive	Leigh-like lesions	↑Plasma lactic acid ↑Plasma succinylcarnitine	2	Jaberi, 2013
c.789_802+29delinsATAAA	Muslim	Severe psychomotor retardation, generalized seizures, hearing loss, microcytic anemia	Leigh syndrome	Not reported	2	Elpeleg, 2005
c.850C>T (p.Arg284Cys)	Italian	Dystonia, hearing loss, severe hypotonia and developmental delay	Leigh-like lesions + cerebral atrophy	↑Plasma and CSF lactic acid ↑Urinary methylmalonic acid ↑Plasma and urinary carnitine esters ↑Urinary citric acid cycle intermediates	3	Carrozzo, 2007
c.1276 C >T (p. Arg407Trp)	Brazilian	Hearing loss, myopathy, chorea, dystonia	Normal	↑Plasma and CSF lactic acid ↑Urinary 3-hydroxyisovaleric and 3-methylglutaconic acids	1	Current report