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# *SDHAF1* Gene Mutation Causing Succinate Dehydrogenase Deficiency, a Treatable Neurometabolic Disorder: A Case Series

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**Abstract**

**Background:** Succinate dehydrogenase (SDH) deficiency is a rare autosomal recessive neurometabolic disorder that causes brain involvement, cardiomyopathy, and/or exercise intolerance.

**Case Presentation:** Here, we report three families who had children with developmental regression, signal changes in brain white matter in MRI, which suspected to leukodystrophy, and elevated level of succinate peak in brain MRS. Due to lack of seizure and normal intellectual abilities, the primary diagnosis was SDH deficiency. Whole Exome sequencing was performed in all patients and three novel variants in *SDHAF1* gene were found. After treatment, they showed significant responses in clinical and then in neuroimaging findings. In genetic study, SDH deficiency was confirmed in all three patients. Here, we discuss clinical courses, para clinic studies, treatment and follow up of each patients.

**Conclusion:** According to our findings, SDH deficiency as a treatable neurometabolic disorder should be considered, in any patients with arrest of developmental milestones and regression, accompanied by hyperintensity in white matter.

**Keywords:** *SDHAF1* gene, Succinate Dehydrogenase Deficiency; Neurometabolic Disorder; Mitochondrial Dysfunction

## Introduction

The onset and range of phenotypic expression of mitochondrial dysfunction is diverse, with onset from neonatal to seventh decade of life. The range of dysfunction is heterogeneous, ranging from single organ to multisystem involvement.

Succinate dehydrogenase (SDH) plays an important role in the mitochondria. Any severe deficiency of this enzyme was regarded as being incompatible with life, previously. Inherited SDH deficiency is a rare autosomal recessive neuro metabolic disorder that cause encephalomyopathy in children [1]. Symptoms may include brain involvement, cardiomyopathy, and/or exercise intolerance.

In a study, one hundred eight muscle biopsies were evaluated from patients with suspected mitochondrial myopathies. Qualitative histochemical analysis and quantitative biochemical analyses of respiratory-chain enzymes showed that Fifty-two patients had defects in respiratory-chain complexes. Of these patients, 12 (23%) had partial deficiencies in succinate dehydrogenase activity [2].

The authors report three children with succinate dehydrogenase deficiency.

## Case Presentation

### Case 1

A 15 month-old girl, presented with developmental regression. She was born from relative parents with no family history of neurological disorder. She had normal developmental milestones

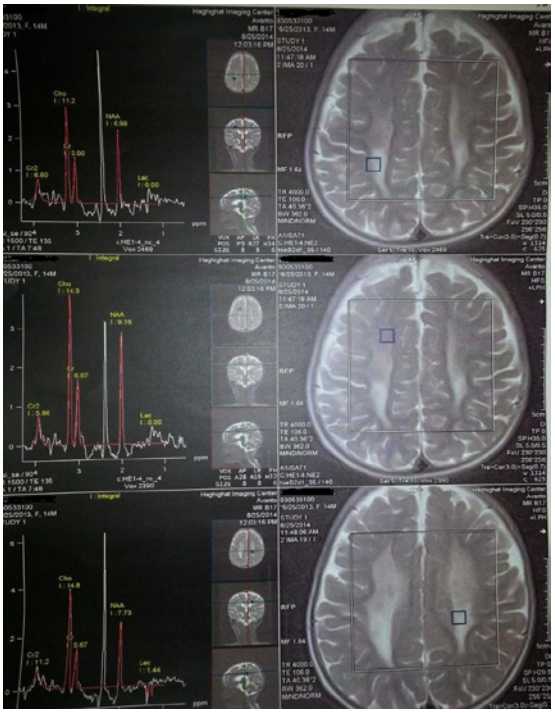

**Figure 1:** MRS of the case number1 shows remarkable Succinate peak in this patient.




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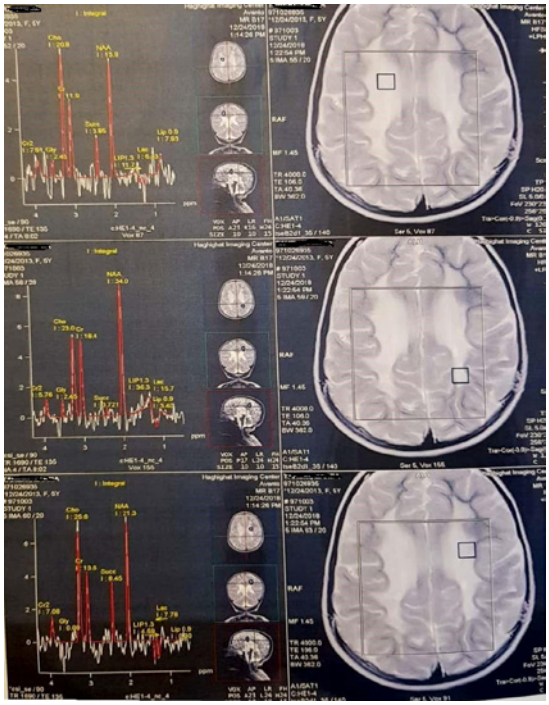


**Figure 2:** MRS of the case number 1 after treatment shows remarkable decrease in Succinate peak.

until 14 months old, so that she was able to walk and talking was normal for aging. Gradually, she lost ability of sitting, walking, talking and even neck holding. She had no episode of seizure in history. In physical examination, she was alert, but agitated. The patient's tone was spastic, but Deep Tendon Reflexes (DTR) was normal. Ammonia, lactate, metabolic screening and Arylsulfatase were normal. Magnetic Resonans Imaging (MRI) showed leukodystrophy pattern. In Magnetic Resonans Spectroscopy (MRS), high succinate peak at 2.4 parts per million (ppm) was detected. So, treatment with vitamin Thiamin, Riboflavin, Co-enzyme Q10, L-carnitine and Biotin was started. After 3 months, agitation was resolved and she was able to hold her neck, and had rolling from supine to prone position and vice versa, but she had dystonic movements. She recognized some parts of her body. After 6 months of treatment, abnormal movements was improved. She recognized some objects and walked by her mother's help. Still, lower limbs were spastic and scissoring. We started occupational therapy. After 9 months, eye contact was good. She sometimes, had tremor when she got excited. 13 month after treatment, she was able to sit for five minutes and told 5-6 words. After 25 months, her cognition and talking was improved and she was able to stand with help (Figure 1 and 2).

## Case 2

A 31 month-old girl presented with arrest of developmental milestones and then regression. She was the product of consanguineous marriage (parents were first cousin) and there was history of developmental delay in her father. Sitting was at age 7 months old. At age 15 months, she was able to stand and walk with help and told 5-6 words.

After that, she lost these abilities up to age 18 month. There was

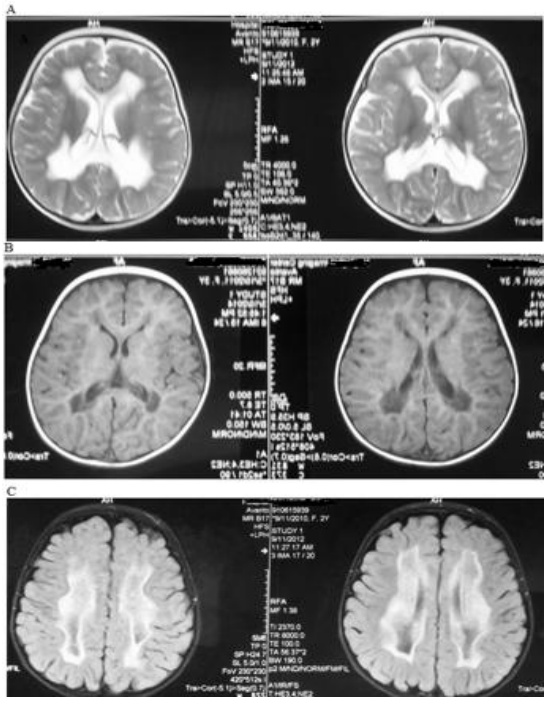


**Figure 3:** A) T2 weighted axial brain MRI in case number 2 shows diffuse white matter hyperintensity in both hemisphere; B) T1 weighted shows hypointensity in periventricular white matter; C) Axial T2 weighted brain MRI after one year of treatment.

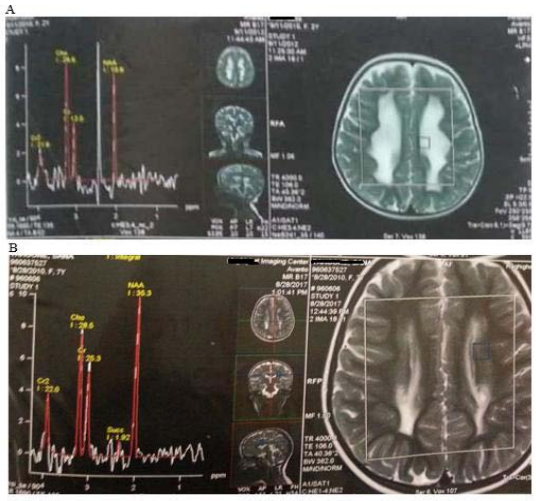


**Figure 4:** A) Brain MRS of the case number 2, shows the peak of Succinate in 2.4ppm; B) MRS of the same patient, after treatment shows remarkable decreasing the Succinate peak in this patient.

not history of seizure. In physical examination, she was alert. The patient's tone was spastic and DTR was increased. Ammonia, HPLC for detection of ammonia and other metabolic studies showed normal results. MRI revealed signal changes in white matter as hyperintensity in T2 and hypointensity in T1, with necrotic areas. MRS indicated high succinate peak at 2.4ppm. Then, she was admitted and underwent intravenous corticosteroid therapy continued with oral corticosteroid. She also, received vitamin Thiamin, Riboflavin, Co-enzyme Q10, L-carnitine and Biotin. 2 months after treatment, she

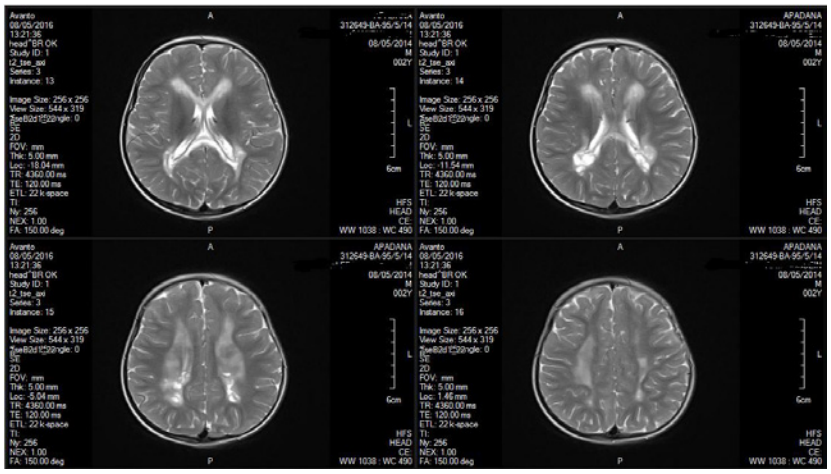


**Figure 5:** Axial brain MRI shows high signal changes in both periventricular white matter.

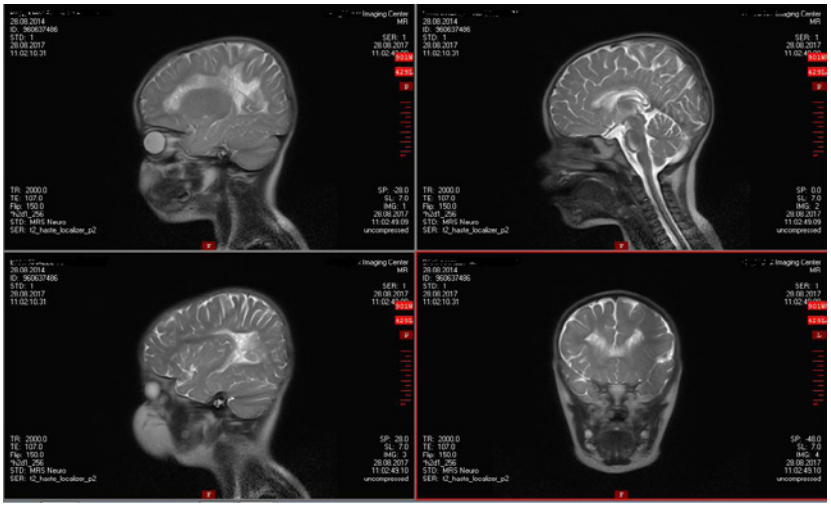


**Figure 6:** Sagittal view of the same patient.

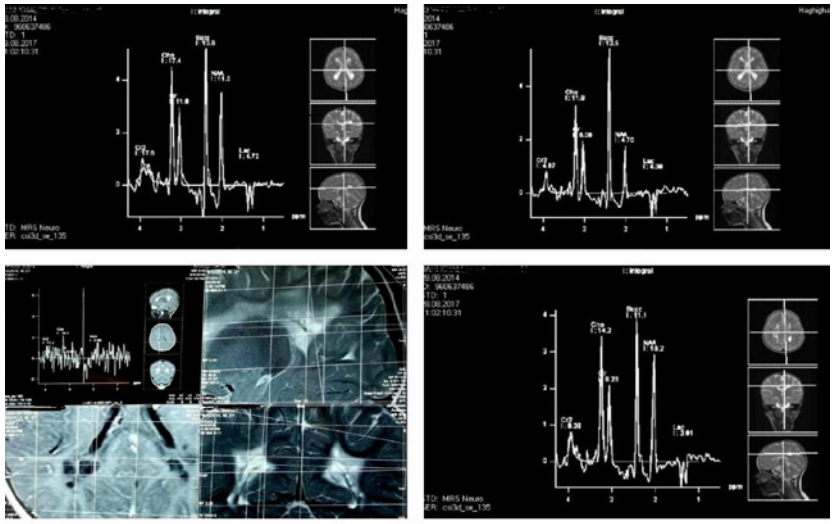
got ability of siting, crawling and talking respectively. In follow up, after 11 months of treatment, she was able to make sentences. She could stand independently and walked with help. We referred her to rehabilitation center for occupational therapy to facilitate walking. After 20 months, she was able to walk by herself, but with inversion in left foot, so she was underwent correctional surgery. After 40 months of treatment, MRS showed decrease of succinate peak. After 6 years of treatment, MRI showed significant improvement of hyperintensity in white matter. After 7 years of therapy, she has walking and running independently, she is student of primary school and learning is in within normal limits (Figure 3 and 4).

### Case 3

A 3 year-old boy presented with ataxia after age of one year. In history, parents were cousin and there wasn't any neurological disorder in his family. He was developmentally normal until first year. At age 1.5 years, he had history of fever and admission. After that, he showed gait disorder (Tip toe walking). Then he lost his balance gradually and at age 2 years old, had falling attack during walking. He had speech disorder, too. In physical examination, he was alert. Weakness and increased Deep Tendon Reflexes (DTR) were detected. Serum lactate and urine organic acids were in normal limits. Brain MRI showed diffuse hypersignal intensity in white matter of both hemisphere. MRS showed high succinate peak at 2.4ppm. Therefore, treatment was started with high dose of vitamin Riboflavin, Co-enzyme Q10, L-carnitine, Biotin and Prednisolone 0.5mg/kg/day. After a month, his walking improved significantly. After 6 months of treatment, spasticity was resolved, DTR went to normal range and speech was acceptable for aging. After treatment, MRI showed decrease in signal intensity in white matter and MRS revealed decrease in peak of succinate in 2.4ppm (Figure 5-7).

## Materials and Methods

The blood samples were collected and genomic DNA was isolated using the QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's protocol. Whole Exome Sequencing (WES) was initially performed on the probands sample for all exons of protein-coding genes as well as adjacent nucleotide regions. In brief, the whole-exome library was prepared using the Agilent SureSelect Library Prep Kit high 20X end-to-end coverage



| Metabolite | Pos./ppm | Integral | Ratio |
|---|---|---|---|
| NAA | 1.95 | 2.69 | 1.00 |
| Cr | 3.06 | 0.00 | 0.00 |
| Cho | 3.28 | 10.14 | 3.77 |
| Cr2 | 3.90 | 11.18 | 4.16 |

**Figure 7:** Brain MRS of the same patient shows the peak of Succinate in 2.4ppm.

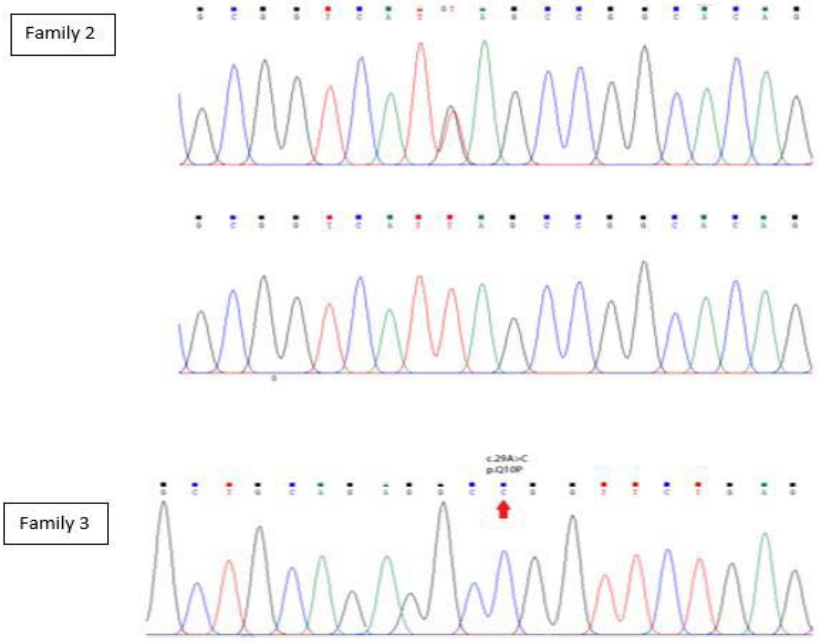



**Figure 8:** Genotype analysis of proband by Sanger sequencing in family 2 revealed homozygous variant c.3G>A. Her mother was heterozygous for this variant. In family 3 the proband is homozygous for c.29A>C variant.

of targeted exonic regions from 20,000 genes. The Agilent SureSelect Human All Exon v6 Kit (Agilent Technologies, Santa Clara, CA) was used to enrich all production of the hybridization library. Sequencing was performed on Illumina HiSeq4000 Sequencer (about 100 million reads with paired-end sequencing, read length of 101bp and coverage of 100X).Test platform examined>95% of the targeted regions with sensitivity above 99%.Variations were called and annotated using ANNOVAR software tool and in-house codes. After the

**Table 1:** Data of three prediction tools for two missense variants in family 2 and 3.

| Variant | CADD score | SIFT | DANN score | ACMG classification |
|---|---|---|---|---|
| c.3G>A p.Met1Ile | 25.5 | Damaging | 0.997 | Pathogenic |
| c.29A>C p.Gln10Pro | 27 | Damaging | 0.995 | VUS |

CADD: Combined Annotation Dependent Depletion, SIFT: Sorting Intolerant From Tolerant, DANN: deep neural network, ACMG: American College of Medical Genetics and Genomics

sequencing reads passed from the filters, the reads were aligned to the human reference genome (University of California Santa Cruz hg19; genome.ucsc.edu), ExAC databases, EVS (Exome Variant Server) and an in-house database of 500 exomes. In order to identify pathogenic mutation, variants evaluated by various bioinformatics databases and softwares including PolyPhen, SIFT, Mutation Taster and CADD [3]. Furthermore, the allele frequency of each variant in normal population was acquired dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and 1000 Genomes (http://www.1000genomes.org/). Sanger sequencing of variants detected by WES, was performed on genomic DNA in affected and suspected members of the family. Oligonucleotide primers were designed using the Primer 3 program (primer3.ut.ee). The regions containing the suspected variants were amplified by standard polymerase chain reaction (PCR) analysis for encompassing the exon and intronic boundaries of *SDHAF1* gene. Products were purified and sequenced on the ABI 3500X automated sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA).

## Results

Family 1: In this family a large homozygous deletion (about 550bp) was found. This variant causes deletion of exon 1 of *SDHAF1* gene.

Family 2: In affected member of family 2 a homozygous pathogenic variant (c.3G>T, p.Met1Ile) in SDHAF1 (NM_001042631.2) gene was found. The parents are heterozygous for this variant.

Family 3: In this pedigree the patient is homozygous for variant c.29A>C, p.Gln10Pro in SDHAF1 gene (Figure 8 and Table 1).

Her mother was heterozygous for this variant. In family 3 the proband is homozygous for c.29A>C variant.

## Discussion

Inherited SDH deficiency is a rare autosomal recessive neuro metabolic disorder that cause brain involvement, cardiomyopathy, and/or exercise intolerance. There are few studies that reported SDH deficiency. Here, the authors report three children with clinical courses and neurological imaging compatible with succinate dehydrogenase deficiency, confirmed by genetic study.

In all three patients, Developmental milestones were in normal limits, but they all regressed. Furthermore, in physical examination, they were alert, fix and follow were in normal limits therefore these patients had regression mostly in motor development and cognition was less involved. MRI showed signal changes similar to leukodystrophia, but they were alert with no history of seizure and all evaluation in the field of leukodystrophia was negative. So, leukodystrophia was under question. Thereafter, we performed MRS that showed a high metabolite peak in 2.4ppm, thus we found this should be succinate peak. After diagnosis, treatment was started with Thiamin, Riboflavin, Biotin, coenzyme Q10, L-Carnitine. Corticosteroid was used during acute phase in two patients, in order to subside inflammation and brain edema. Also, Genetic study was done for confirmation of all diagnosis and all results were positive.

Occupational therapy was useful for decrease of spasm. After treatment, all patients improved in different aspects of developmental milestones. Movement was the first ability that was improved. Then, speech and cognition had promotion, respectively.

## Conclusion

According to our findings, SDH deficiency as a treatable neurometabolic disorder should be considered, in any patients with arrest of developmental milestones and regression, accompanied by hyperintensity in white matter (as similar as leukodystrophia). As the outcomes depends on early diagnosis, early suspicion and treatment can improve prognosis.

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