A NOVEL *SUCLA2* MUTATION IN A PORTUGUESE PATIENT

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INTRODUCTION

Succinyl CoA synthase is a mitochondrial matrix enzyme that catalyzes the reversible synthesis of succinate and ATP or GTP from succinyl-CoA and ADP in the tricarboxylic acid cycle (TCA). This enzyme is made up of two subunits, α and β, encoded by *SUCLG1* and *SUCLA2*, respectively (Figure 1) [1].

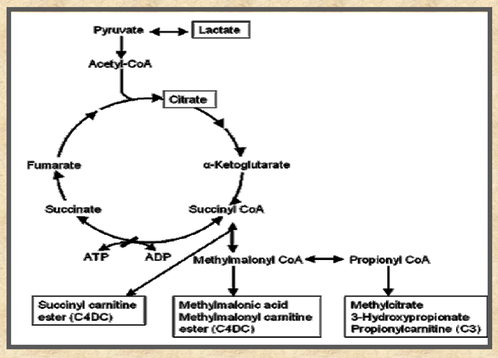

Figure 1. Relevant metabolic pathways illustrating the metabolic effects of ADP-forming succinyl-CoA synthetase deficiency.

The clinical features of patients with mutations in *SUCLA2* include early childhood hypotonia, developmental delay, and almost invariably, progressive dystonia and sensorineural deafness. Mutations in *SUCLA2* and *SUCLG1* cause an encephalomyopathic form of infantile mtDNA depletion syndrome[2].

A useful diagnostic clue in succinyl CoA synthase disorders is a "mildly" elevated urinary methylmalonic acid (MMA), and presence of TCA intermediates.

To date, few patients with *SUCLG1* mutations have been reported, whereas mutations in *SUCLA2* have been reported in 20 patients [3]. We here present an additional patient with a novel *SUCLA2* mutation.

PATIENTS AND METHODS

We report a 17-month-old-boy, who presented severe muscular hypotonia, failure to thrive, developmental delay, weight loss during a gastroenteritis crises, dysmorphisms and muscular atrophy.

A biochemical investigation disclosed hyperlactacidemia together with moderate excretion of MMA and elevated C4-dicarboxylic carnitine (C4DC).

Sequencing analysis of *SUCLA2* and *SUCLG1,* mitochondrial DNA quantification and western blot was performed in patient's fibroblasts, using standard methods.

RESULTS

Mutation analysis of *SUCLA2* revealed a novel homozygous c.985A>G mutation in exon 8 (p.M329V) (Figure 2A). The involvement of SUCLA2 was confirmed by western blot analysis, which showed some residual amount of SUCLA2 protein in patient's fibroblasts (Figure 2B). The patient also presented a moderate mitochondrial DNA depletion in fibroblasts (40% of aged-matched controls). This missense mutation affects an amino acid that is highly conserved in different species and was not found in controls. The analysis by bioinformatics tools also confirmed a pathogenic mutation (Figure 3). Altogether, these findings indicate that the identified mutation is pathogenic and responsible for this disorder.

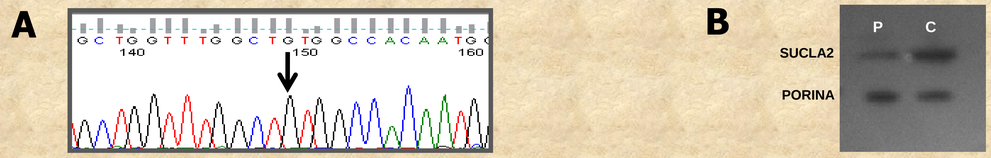

Figure 2. Identification of a novel *SUCLA2* mutation . **A)** Patient's *SUCLA2* sequence with the p.M329V mutation; **B)** Western-blot analysis of patient's fibroblasts (p) and a control subject (C).

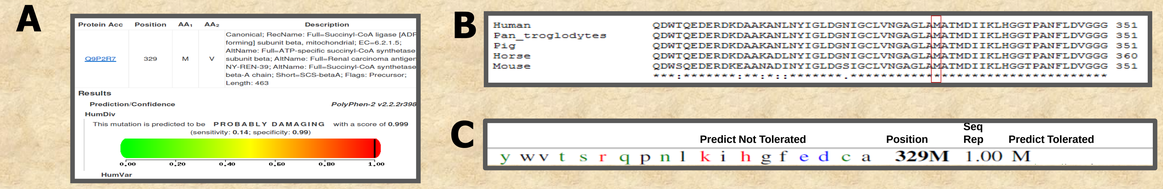

Figure 3. Analysis by bioinformatics tools of a *SUCLA2* mutation: p.M329V. **A)** PolyPhen-2 prediction of functional effects of human variations; **B)** ClustalW aligments; **C)** Sift predictions.

DISCUSSION / CONCLUSION

The clinical and biochemical phenotype of our patient is strikingly similar to other reported patients with *SUCLA2* mutations [1]. In addition, the mildly elevated levels of MMA and C4DC raised the suspicion of this disease, which was confirmed by the identification of a novel mutation in *SUCLA2.* In agreement with this results, western blot showed some residual amount of SUCLA2 protein and a moderate reduction of mitochondrial DNA copy number was found in patient's fibroblasts.

Our study contributed to expand the spectrum of patients with *SUCLA2* mutations, and will be important for an accurate genetic counseling and a prenatal diagnosis to the affected family.

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