A NOVEL MISSENSE MUTATION IN *SUCLA2* ASSOCIATED WITH MILD METHYLMALONIC ACIDURIA

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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].

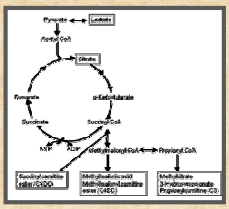

Figure 1. Relevant metabolic pathways illustrating the metabolic effects of ADP-forming succinyl-CoA synthetase deficiency.

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

Sequencing analysis of *SUCLA2* and *SUCLG1* was performed using standard methods.

RESULTS

Mutation analysis of *SUCLA2* revealed a homozygous c.985A>G mutation in exon 8 (p.M329V) (Figure 2). 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.

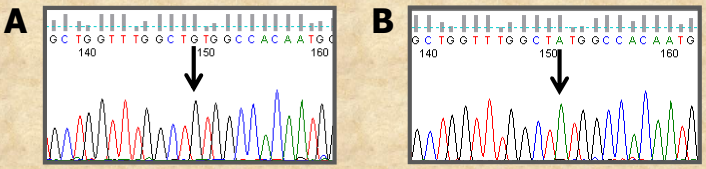

Figure 2. Sequence analysis of part of *SUCLA2* gene. **A)** Patient's sequence with p.M329V mutation; **B)** Normal control sequence.

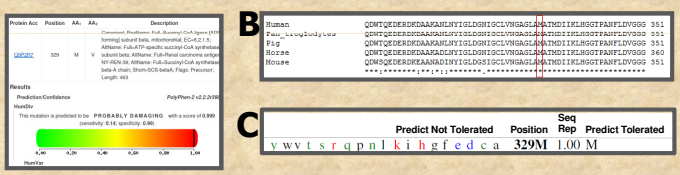

Figure 3. Analysis by bioinformatics tools of p.M329V **A)** PolyPhen-2 prediction of functional effects of human variations; **B)** ClustalW aligments; **C)** Sift predictions.

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 methylmalonate and C4DC raised the suspicion of this disease, which was confirmed by the identification of a novel mutation in *SUCLA2*.

Further studies will be perform to determine mitochondrial DNA depletion in muscle tissue, and the expected reduced amounts of SUCLA2 protein, by Western-blot.

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.

REFERENCES

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