A novel ACAD9 mutation causes severe myopathy and cardiomyopathy in an affected family

Allegorico L.[1],Lombardi L.[1],Sampaolo S.[1], Limongelli G[2]., Esposito T.[3], Napolitano F[3]., Lamantea E.[4], Garavaglia B.[4], Di Iorio G[1].

[1]Department of Neurology - Second University of Naples, [2]Department of Cardiology - Second University of Naples, [3] Institute of Genetic and Byophisics – CNR Naples, [4] Molecular Neurogenetics – Fondazione IRCCS Istituto Neurologico Carlo Besta-Milan

Background

Acil-CoA-dehydrogenase-9 (ACAD9) has a critical role in complex I of the mitochondrial respiratory chain, and is mainly expressed in the brain, in skeletal and cardiac muscle, in liver and kidneys. Both homozygous and heterozygous mutations may cause hypertrophic cardiomyopathy, encephalopathy and myopathy with lactic acidosis.

Methods and Materials

A 13 year old boy (IV2) was admitted to our Department, with complaints of muscle weakness, easy fatiguability, and cramps; this condition, present since birth, had slowly progressed during the patient's life. His parents were first cousins, and his father (III2) had been followed in our Department for mitochondrial myopathy. Over the years, the father had developed respiratory failure and non obstructive hypertrophic cardiomyopathy (NHCM), with sudden cardiac death at the age of 43. The patient also had a 10 year old brother (IV3), who was healthy at the time of observation. His medical history was otherwise unremarkable, except for hyperCKemia.

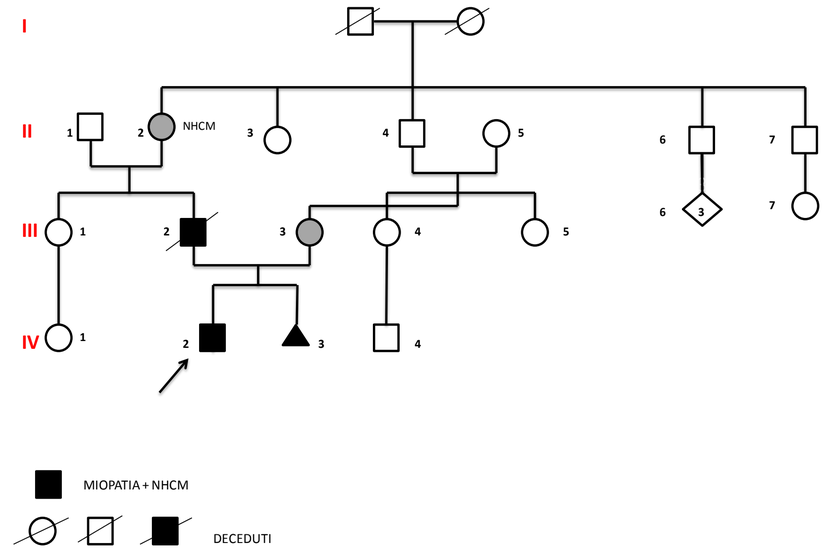
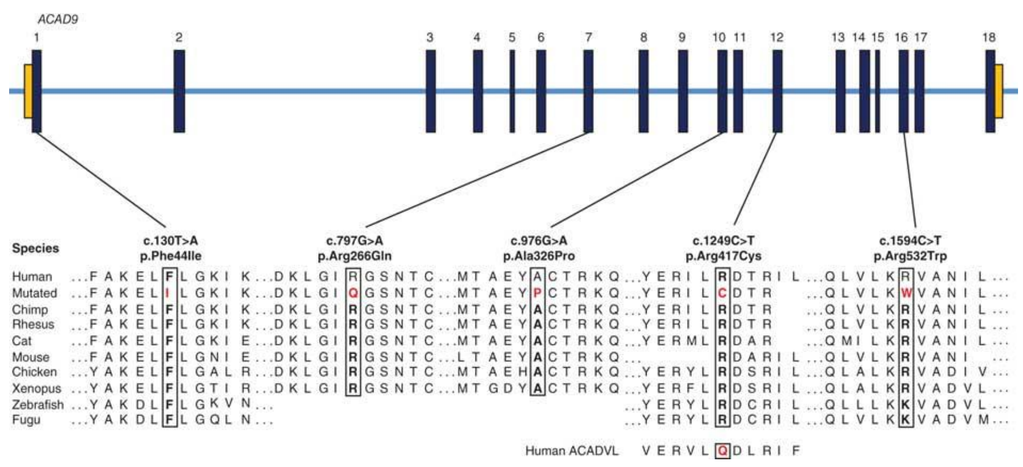


Fig. 1. *Mutation analysis of the entire gene of ACAD9 on chromosome 3q26 revealed only a very rare c.1240C>T genetic variant in exon 12, leading to p. Ar414Cys aminoacid substition in homozygousity in the proband and his younger brother, and in heterozygousity in his parents.*

Results

An echocardiogram showed NHCM, with reduced systolic function, asymmetric hypertrophy of the left ventricle, hypokinesia of the inferior wall and hypertrabeculation of the apex. A muscle biopsy showed a predominance of type I fibers, with high caliber variability and numerous subsarcolemmal aggregates (*ragged red fibres*). Mutation analysis of the ACAD9 gene was performed in the patient, in his brother and in both parents; it led to the identification of a novel c.1240C>T genetic variant in exon 12, with p. Ar414Cys aminoacid substitution; both sons were homozygous for this mutation, while the parents were heterozygous. Notably, during our follow-up, the patient's younger brother had developed dyspnea, post-exercise nausea and vomit, and hyperCKemia. Given that riboflavin is a precursor of the flavin-adenin-dinucleotide cofactor that is essential for ACAD enzyme activity and stability, both brothers were prescribed riboflavine supplements, with good response.

ACAD-9 GENE



Discussion and Conclusions

This is the first time that a c.1240>T Arg414 Cys mutation has been described. The history of this family lead us to hypothesize a causal link between this mutation and the described condition of severe progressive myopathy and cardiomyopathy, with high intrafamilial variability. Remarkably, the father, who was heterozygous, only became symptomatic in the fourth decade, while the sons, both homozygous, have shown signs of disease in childhood; the mother remains asymptomatic to this day. Further studies are needed in order to discern what other factors (environmental, nutritional, endocrinological, etc) may influence the expression of this condition.

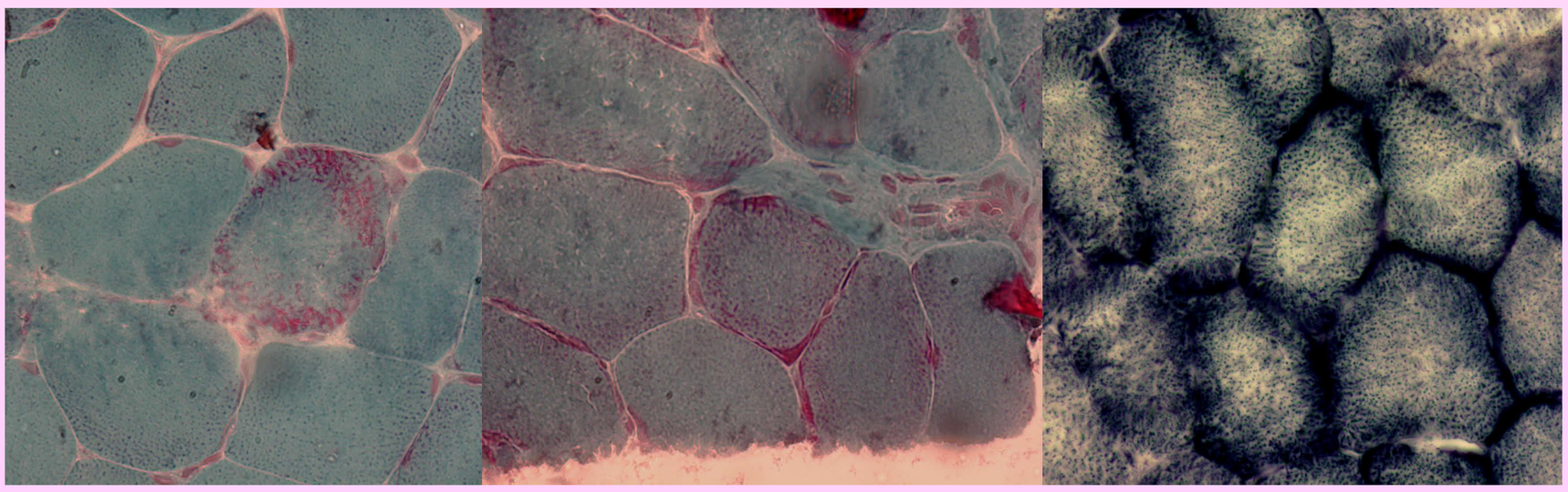


Fig. 3. *Histology and histochemistry of quadriceps muscle biopsy revealed a myopathic pattern characterized by consistent variability of muscle fibers calibers with scattered atrophic and several hyperthrophic fibers in addition to a predominance of type I fibers; marked subsarcolemmal accumulation of Gomori Trichrome, SDH and NADH positive material was seen in ragged red fibres. These findings are suggestive of mitochondrial myopathy.*

References. *Schiff M, Haberberger B, Xia C et al. Complex I assembly function and fatty acid oxidation enzyme activity of ACAD9 both contribute to disease severity in ACAD9 deficiency. Human Molecular Genetics. 2015; 24:3238-3247 Brunel-Guitton C, Levtova A and Sasarman F. Mitochondrial Disease and Cardiomyopathies. Canadian Journal of Cardiology. 2015; 31:1360-1376*

Sin XLVII CONGRESSO NAZIONALE 22-25 OTTOBRE 2016 – VENEZIA

WebPoster