Metabolomics analysis highlight the involvement of muscle energetic metabolism in ALS pathophysiology

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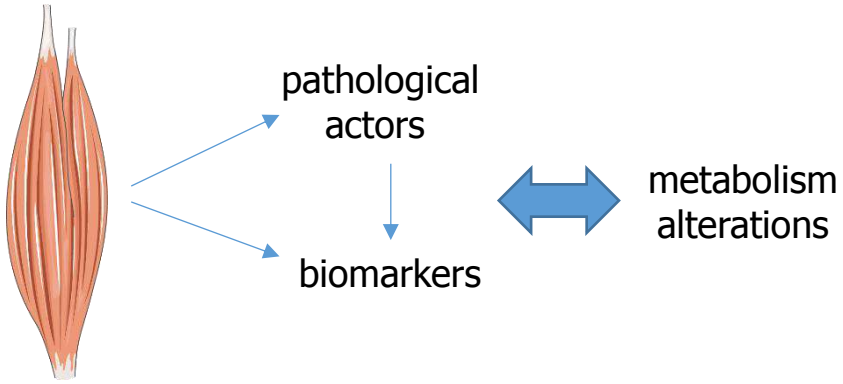
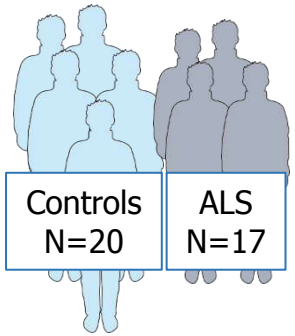
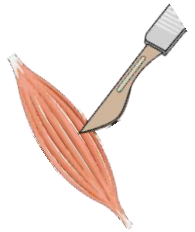


To investigate the metabolism and the mitochondrial function of the skeletal muscle.

Clinical trial identifier: NCT02670226





Deltoid biopsy

Data	Controls	ALS	p
Age	56.9 ± 19.2	65.9 ± 9.9	0.0793
Sex (men)	8/20 (40%)	8/17 (47%)	0.746*
Weight (kg)	69.4 ± 13.6	64.2 ± 15.8	0.299
BMI (kg/m^2)	24.9 ± 3.8	23.5 ± 4.0	0.3024
Age at onset (years)	-	65.0 ± 9.5	
Disease duration (from onset; months)	-	11.1 ± 6.8	
Diagnosis delay (from onset; months)	-	9.3 ± 4.7	
Spinal onset	-	64.7%	
FVC at diagnosis (%)	-	98.0+-7.1	
ALSFRS-r at diagnosis		34.7 ± 7.2	

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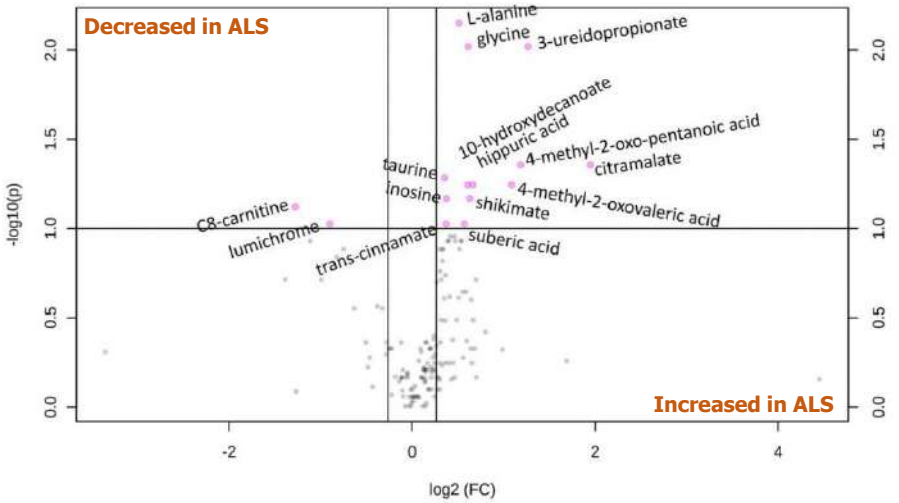
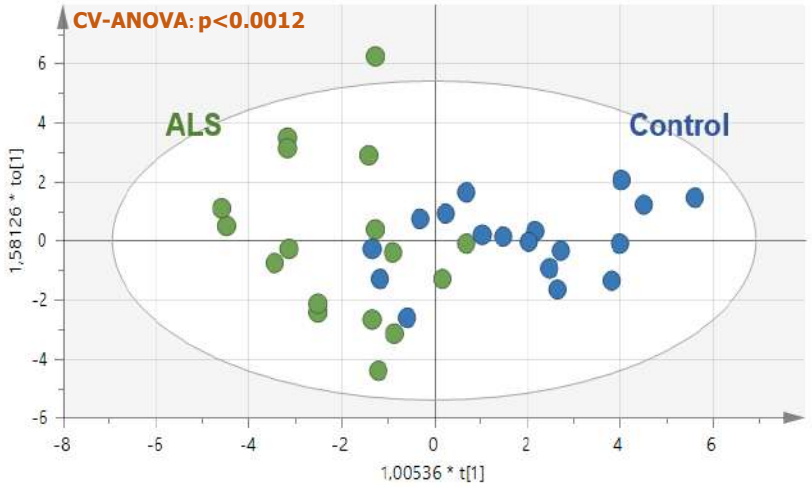


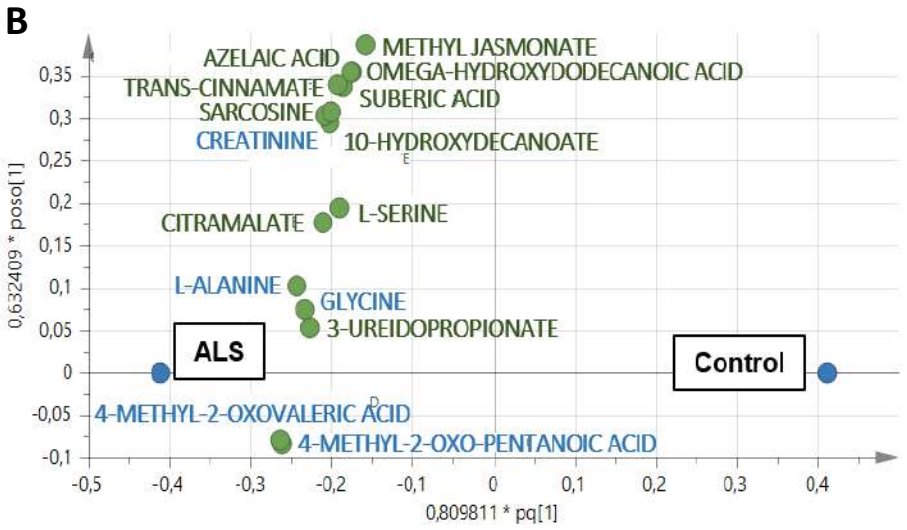
Different metabolites between ALS and controls muscle. Univariate volcano plot analysis performed with MetaboAnalyst 5.0.

A



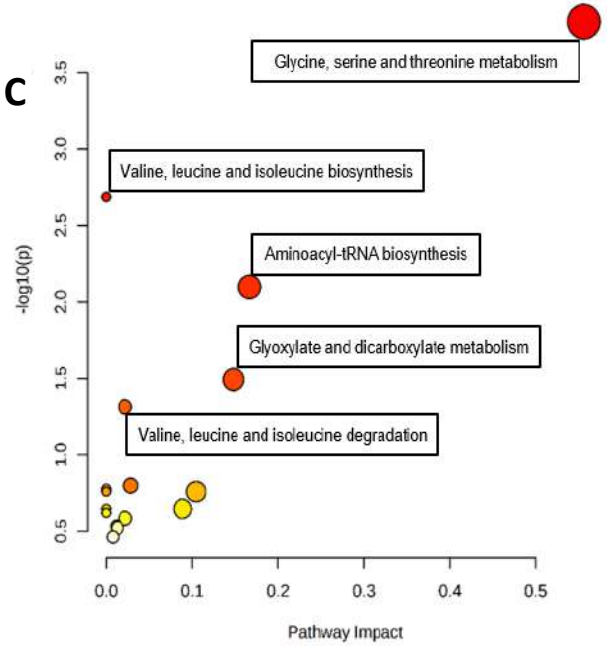
OPLS-DA model, with R2X=0.76, R2Y=0.555, Q2=0.446

B



Metabolites with VIP score >1

C



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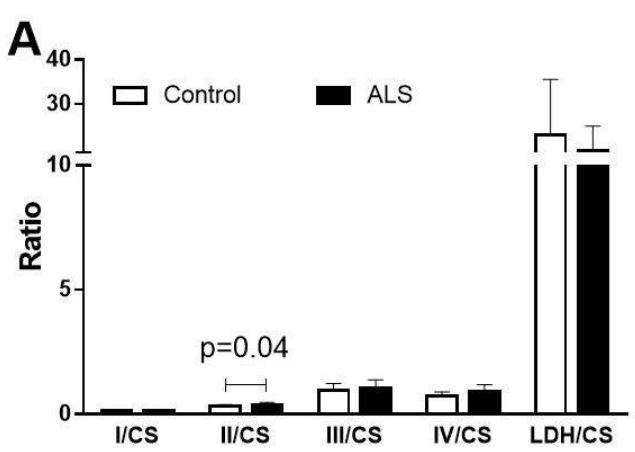
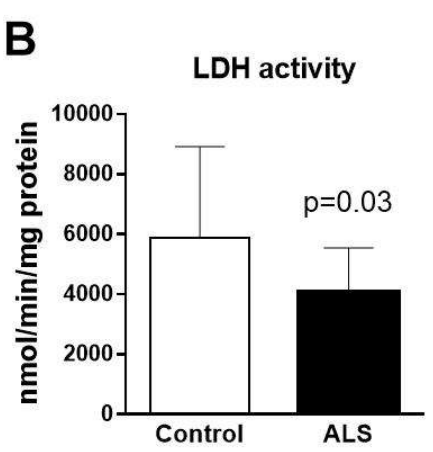
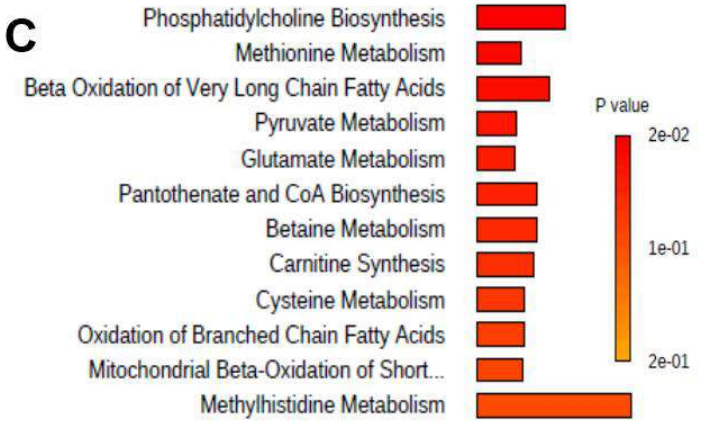
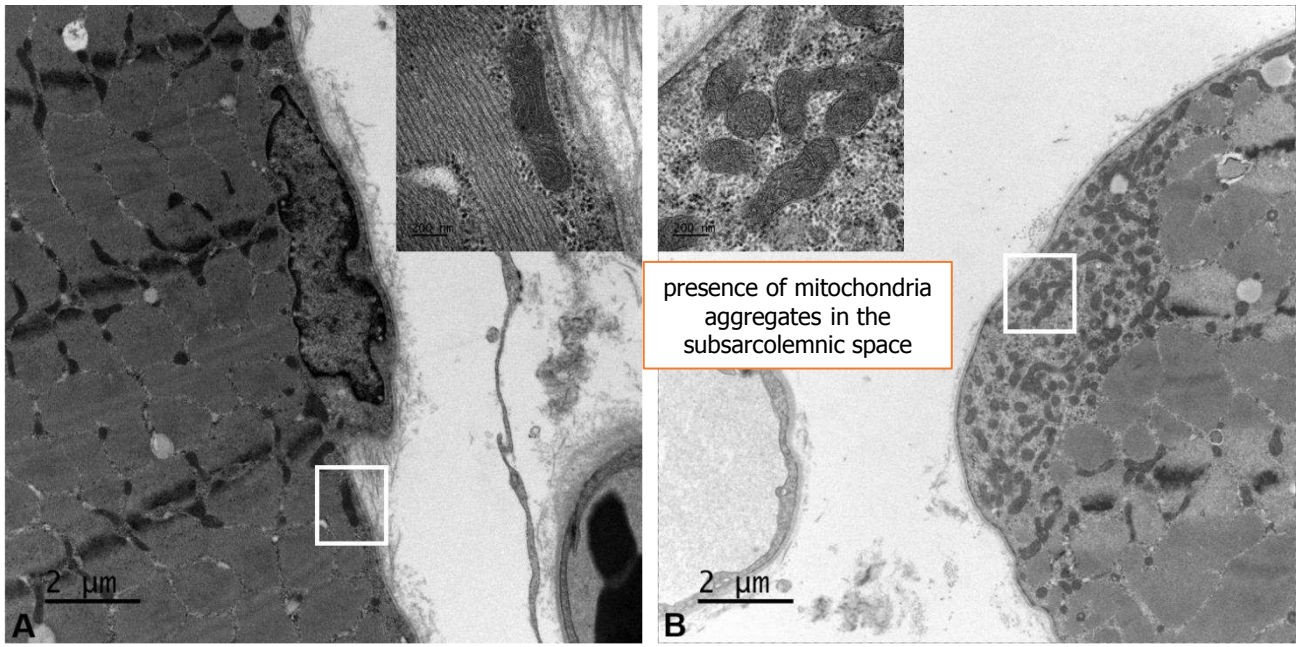
Mitochondrial enzymatic activity in the muscle of ALS patients and controls.
Results are shown as median±SD.
Data was analyzed using the Mann-Whitney statistical test.







Ultrastructural alterations in muscle mitochondria from ALS patients compared to control subjects.



Univariate and multivariate analysis regarding metabolites levels in muscle and survival in ALS patients (p values).

	Univariate	Multivariate
C8-Carnitine	0.0202	
C10-Carnitine	0.0476	0.0476
C14-Carnitine	0.0054	
Lauroylcarnitine	0.0027	

Conclusions:

- ✓ We showed, for the first time, metabolic alterations in muscle that correlate with pathological findings, namely mitochondria dysfunction.
- ✓ The dysfunction in the muscular energetic metabolism in the early stages of ALS disease was observed through a multi-parametric exploration of metabolism at the time of diagnosis.
- ✓ Our findings strengthen the theory of key muscle dysfunction in the pathology of ALS, through the description of new metabolic actors.