



**UNIVERSITÀ DI MILANO**  
**“CENTRO DINO FERRARI”**

PER LA DIAGNOSI E LA TERAPIA DELLE MALATTIE  
NEUROMUSCOLARI E NEURODEGENERATIVE

**FONDAZIONE IRCCS CA' GRANDA**  
**OSPEDALE MAGGIORE – POLICLINICO**

FONDAZIONE DI RICOVERO E CURA A CARATTERE  
SCIENTIFICO DI NATURA PUBBLICA



Milan, July 20, 2010

**Muscle mitochondrial dysfunction plays a role in the pathogenesis of**  
**Amyotrophic Lateral Sclerosis**

Researchers of the “**Dino Ferrari Center**, “ Laboratories at the Foundation Ospedale Maggiore Policlinico and Istituto Auxologico Italiano, Department of Neurological Sciences, University of Milan, Milan, Italy, led by Dr. Maurizio Moggio, Prof. Giacomo Comi and Prof. Vincenzo Silani, in collaboration with Prof. Salvatore Di Mauro , Department of Neurology, Columbia University Medical Center, New York, NY, have identified variable degree of respiratory chain impairment in muscle biopsy of about 50% of mainly sporadic **Amyotrophic lateral sclerosis** (ALS patients). This large cohort of patients allowed to establish that defects of cytochrome c oxidase and other respiratory chain complexes occur along the clinical progression of ALS, therefore energy production failure is likely to contribute to the clinical deterioration in patients and may be one of the therapeutic targets to halt disease progression. The study also informs that a consistent degree of biochemical heterogeneity exists among sporadic ALS patients, as far as respiratory chain activity is considered- This finding correlates with a considerable degree of genetic heterogeneity observed in the familial counterpart of the disease.

These data have been published in the July issue of **Archives of Neurology** . (2010 Jul;67(7):849-54.: **Mitochondrial respiratory chain dysfunction in muscle from patients with amyotrophic lateral sclerosis**. Crugnola V, Lamperti C, Lucchini V, Ronchi D, Peverelli L, Prella A, Sciacco M, Bordoni A, Fassone E, Fortunato F, Corti S, Silani V, Bresolin N, Di Mauro S, Comi GP, Moggio M.

Amyotrophic lateral sclerosis (ALS) is a major cause of neurological disability and its pathogenesis remains elusive despite a multitude of studies. Although defects of the mitochondrial respiratory chain have been described in several ALS patients, their pathogenic significance was unclear.

To review systematically the muscle biopsy specimens from patients with typical sporadic ALS to search for possible mitochondrial oxidative impairment, the histochemistry for succinate dehydrogenase and cytochrome c oxidase, the biochemistry of respiratory chain complexes as well as the mitochondrial DNA genome and the sequence analysis of genes relevant to mtDNA stability, were retrospectively analysed.

Fifty patients with typical sporadic ALS (mean age, 55 years). were assessed for clear muscle mitochondrial dysfunction assessed through histochemical and biochemical muscle analysis.

The histochemical data showed cytochrome c oxidase (COX)-negative fibers in 46% patients. Based on COX histochemical activity, patients fell into 4 groups: 27 had normal COX activity; and 8 had mild (2-4 COX-negative fibers of 100 fibers), 8 had moderate (5-10 COX-negative fibers of 100), and 7 had severe (>10 COX-negative fibers of 100) COX deficiency. Spectrophotometric measurement of respiratory chain activities showed that 3 patients with severe histochemical COX deficiency also showed combined enzyme defects. In 1 patient, COX deficiency worsened in a second biopsy taken 9 months after the first. Among the patients with severe COX deficiency, one had a new mutation in the SOD1 gene, another a mutation in the TARDBP gene, and a third patient with biochemically confirmed COX deficiency had multiple mitochondrial DNA deletions detectable by Southern blot analysis.

The data confirmed that the histochemical finding of COX-negative fibers is common in skeletal muscle from patients with sporadic ALS. We did not find a correlation between severity of the oxidative defect and age of the patients or duration of the disease. However, the only patient who underwent a second muscle biopsy did show a correlation between severity of symptoms and worsening of the respiratory chain defect. In 7 patients, the oxidative defect was severe enough to support the hypothesis that mitochondrial dysfunction must play a role in the pathogenesis of the disease.