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Nogo Provides a Molecular Marker for Diagnosis of Amyotrophic Lateral Sclerosis

Luc Dupuis,* Jose-Luis Gonzalez de Aguilar,* Franck di Scala,* Frédérique Rene,* Marc de Tapia,* Pierre-François Pradat,† Lucette Lacomblez,† Danielle Seihlan,‡ Rabinder Prinjha,§ Frank S. Walsh,§ Vincent Meininger,† and Jean-Philippe Loeffler*

**Laboratoire de Signalisations Moléculaires et Neurodégénérescence, EA 3433, Faculté de Médecine, Université Louis Pasteur, 11 rue Humann, 67085 Strasbourg Cedex, France; †Service de Neurologie and ‡Service de Neuropathologie, Hôpital de la Pitié Salpêtriere, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France; and §Neurodegeneration Department, Neurology CEDD, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, United Kingdom*

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Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder characterized by the selective degeneration of upper and lower motor neurons. The lack of a molecular diagnostic marker is of increasing concern in view of the therapeutic strategies in development. Using an unbiased subtractive suppressive hybridization screen we have identified a clone encoding the neurite outgrowth inhibitor Nogo and shown that its isoforms display a characteristic altered expression in ALS. This was first confirmed by analyzing Nogo isoform expression in a transgenic ALS model at early asymptomatic stages where we found increased levels of Nogo-A and decreased Nogo-C and importantly, not following experimentally induced denervation. Furthermore, we confirmed these changes in both post-mortem and biopsy samples from diagnosed ALS patients but not control patients. Thus, the alteration in Nogo expression pattern, common to sporadic and familial ALS, represents a potential diagnosis tool and points strongly to Nogo having a central role in disease.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the progressive and selective loss of motor neurons in the spinal cord, brainstem, and motor cortex. Clinical features include limb weakness with muscle atrophy and a progressive involvement of respiratory muscles leading to death within 3 to 5 years after the onset (Brooks, 1994). Several mechanisms have been postulated to explain motor neuron degeneration, including oxidative stress, glutamate excitotoxicity and apoptosis, which suggest that the disease is multifactorial in origin (Eisen, 1995). However, the precise molecular mechanisms responsible for the selective loss of motor neurons remain obscure. Five to 10% of ALS cases are dominantly inherited, and genetic linkage studies revealed that 20% of these are associated with point mutations in the gene encoding cytosolic Cu/Zn superoxide dismutase (SOD1) (Rosen *et al.,* 1993), a free radical scavenging enzyme that protects cells against oxidative stress (Fridovich, 1986). It has been demonstrated that the deleterious mechanism of these mutations is related to a gain of function (Brown, 1995). The identification of such mutations has allowed the production of transgenic mice that develop neurological disorders characteristic of ALS (Gurney *et al.,* 1994; Ripps *et al.,* 1995; Wong *et al.,* 1995).

In man, sporadic and familial ALS are clinically and pathologically similar, suggesting a common pathogenesis (Ince *et al.,* 1998). No treatment has yet proved to stop the course of the disease. However, it has been

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