

**PW 7:
SMA and ALS – Clinical
and genetic findings**

PW7-077	<p><u>MOLECULAR GENETICS OF SPINAL MUSCULAR ATROPHY: CONTRIBUTION OF THE NAIP GENE TO CLINICAL SEVERITY</u> SIFI Y¹, SIFI K², BESTANDJI K¹, BOULEFKHAD A¹, ABADI N², BENLATRECHE C², HAMRI A¹ (1) Service de Neurologie CHU Benbadis, Constantine, ALGERIA. (2) Laboratoire de Génétique et Biologie Moléculaire, Constantine, ALGERIA.</p>
To contact the author:: sifimina@yahoo.fr.	<p>Introduction: Spinal muscular atrophy (SMA) is one of the most common autosomal recessive disorders, characterized by degeneration of anterior horn cells in the spinal cord, and leads to progressive muscular weakness and atrophy. In the present study, to elucidate the correlation between genotype and clinical severity in SMA patients, we analyzed the molecular genetic features of 57 Algerian patients with SMA, from 38 unrelated</p> <p>Patients and methods: All patients fulfilled the diagnostic criteria of SMA as defined by the International SMA Consortium. Deletions of exons 7 and 8 of the SMN gene were analysed by an enzyme digestion assay as described by van der Steege and al. NAIP gene analysis was performed by PCR amplification of exon 4 and 5 as described by Roy et al.</p> <p>Results and Discussion : The patients were classified into SMA type-I (09 patients), type-II (11 patients), and type-III (37 patients). 37 of the 57 SMA patients (64,9%), were homozygous for deletion of SMN1 exon 7 and 8 (13 type I, 10 type II and 14 type III). We did not find any correlation between the <i>SMN1</i> deletion and clinical severity of SMA. NAIP exon 4 and 5 was deleted in 16 of 57 SMA patients (09 type I, 05 type II, 02 type III).</p> <p>In all patients with a deletion of NAIP exon 4 and 5, there was also a deletion of SMN1 exon 7. Frequency of NAIP deletions was significantly higher in type I patients than in type II or III patients. 07 type I patients died or required artificial respiratory before the age of 6 months, among these seven patients, 5 lacked the NAIP gene.</p> <p>Conclusion: Deletion of the NAIP gene is closely related to the clinical severity of SMA, while the deletion of <i>SMN1</i> does not correlate with clinical severity.</p>

PW7-078	<p><u>GENETIC VARIANTS IN VITAMIN D RECEPTOR AND RISK FOR CHILDHOOD SPINAL MUSCULAR ATROPHY</u> STAVARACHI M¹, APOSTOL P¹, CIMPONERIU D¹, TOMA M¹, BUTOIANU N², BURLOIU C², CRAIU D², MAGUREANU S², GAVRILA L¹ (1) University of Bucharest, Institute of Genetics, Bucharest, ROMANIA. (2) "Al.Obregia" Hospital, Bucharest, ROMANIA.</p>
To contact the author:: monica.stavarachi@gmail.com.	<p>Vitamin D is a steroid hormone known for its key roles in calcium homeostasis, proliferation and apoptosis. Previous studies have also reported the association of vitamin D deficiency with muscle weakness and neuromuscular dysfunction. The vitamin D action is mediated by its receptor (VDR) which is a candidate locus for different diseases.</p> <p>We hypothesise that VDR start codon polymorphism (Fok I) is associated with risk for childhood spinal muscular atrophy (SMA) disease.</p> <p>In order to test this, we conducted a case-control study with 65 clinically diagnosed SMA patients (26 SMA I, 21 SMA II, 18 SMA III) and 65 healthy subjects. After the informed consent was obtained, DNA was extracted from peripheral blood, using a commercial kit. Molecular diagnosis for SMA patients and Fok I genotypes analysis (PCR-RFLP) were performed for all the subjects.</p> <p>The distribution of VDR Fok I genotypes was in compliance with Hardy-Weinberg equilibrium, for SMA ($\chi^2 = 0.09$) and control ($\chi^2 = 1.28$) lots. We observed that the frequency of FF genotype was higher in SMA patients than in controls (47,7% vs. 30,7%). O.R._{FF} (2.5, C.I. 95%, 1.0014<O.R.<4.2028, DF=1, p=0.0481) suggests a significantly association between FF genotype and SMA. The calculated risk for F allele was more reduced (O.R.=1.5424, C.I.=95%, 0.9276<O.R.<2.5646).</p> <p>To our knowledge, this is the first report about relationship between a VDR gene polymorphism (Fok I) and SMA. Studies with an increased statistical power will be assessed to confirm the correlation between the VDR gene polymorphism and SMA disease.</p>

PW7-079	<p><u>MOLECULAR DIAGNOSIS OF PROXIMAL SPINAL MUSCULAR ATROPHY IN ALGERIA. ANALYSIS OF 300 PATIENTS.</u> BENHASSINE T¹, HAMADOUCHE T¹, ASSAMI S², MAKRI S³, CHAOUCH M⁴, TAZIR M²</p> <p>(1) Laboratory of Molecular Biology, Pasteur Institute of Algeria, Algiers, ALGERIA. (2) Department of Neurology, CHU Mustapha Bacha, Algiers, ALGERIA. (3) Department of Neurology, EHS Ali Ait Idir, Algiers, ALGERIA. (4) Department of Neurology, CHU Ben Aknoun, Algiers, ALGERIA.</p>
To contact the author:: trakibenhassine@hotmail.com.	<p>Proximal spinal muscular atrophy (SMA) are a group of motor neuropathies characterized by the degeneration of spinal motoneurons leading to muscular paralysis with muscular atrophy. They are the second most fatal autosomal recessive disease, with an incidence of approximately 1 in 10,000. Childhood SMA is divided into three types (I to III) according to age of onset and severity of the disease, while type IV concerns adult-onset SMA. SMA is caused by mutations in the survival motor neuron 1 (SMN1) gene, with more than 90% of patients having a homozygous deletion of exon 7 in this gene.</p> <p>The aim of this work was to explore Algerian patients for whom a clinical diagnosis of spinal muscular atrophy has been suspected.</p> <p>300 patients have been tested by PCR-based methods, all for the detection of the homozygous deletion of exon 7 of SMN1, while some of them have been investigated for the presence of gene conversion events affecting exons 7 and 8 of this gene.</p> <p>Molecular results showed that about 70% of the patients had the homozygous deletion of exon 7 of SMN1, thus establishing a precise genetic diagnosis for these patients.</p> <p>All the SMA patients clinically suspected type I had this deleterious mutation, while those of type II and III displayed it in approximately 50-60% of the cases. For type IV, we could detect this mutation in only 10% of the patients. The search for gene conversion events affecting exons 7 and 8 of SMN1 allowed us to identify 3% patients with this molecular alteration. The relative low frequency of SMN1 exon 7 homozygously deleted patients suggests that other types of mutations could affect this gene, or that other genes could be involved in the non-deleted patients, or more probably that clinical diagnosis of SMA could be overestimated by the clinicians.</p>

PW7-080	<p><u>THE LACK OF ASSOCIATION BETWEEN RENIN-ANGIOTENSIN SYSTEM POLYMORPHISMS AND SMA SEVERITY</u> APOSTOL P¹, CIMPONERIU D¹, STAVARACHI M¹, BUTOIANU N², MINCIU I², BURLOIU C², TOMA M¹, MAGUREANU S², GAVRILA L¹ (1) Institute of Genetics, University of Bucharest, Bucharest, ROMANIA. (2) Department of Pediatrics Neurology "Alexandru Obregia" Hospital, Bucharest, ROMANIA.</p>
To contact the author:: apostol_pompilia@yahoo.com.	<p>Background Skeletal muscle dysfunction is the main clinical feature in patients with different types of spinal muscular atrophy (SMA). We consider that improper muscle irrigation could accelerate the progression of muscular dysfunction in these patients. However, we have no knowledge about studies regarding the association between polymorphisms in RAS system and SMA. The aim of this study was to test the association between ACE ID and AT1R A1166C polymorphism and SMA severity. Material and methods: this study has encompassed 69 SMA patients, classified by <i>ISMAC</i> criteria, and 100 controls. The blood samples were obtained from Bucharest pediatric hospital (patients) and from healthy voluntaries (control group). Patients were selected after informed consent obtaining and confirmation of SMA by molecular diagnosis (homozygous deletion of exon 7 and 8 in SMN1 gene). Patients and controls were matched for sex and ethnicity. The ACE ID and ATR1 A1166C genotypes were established in all samples by PCR and PCR-RFLP methods. Chi square test were used for comparisons between lots and a $p < 0.05$ was considered significant. Results and discussion. The distribution of genotypes in both lots is in concordance with Hardy-Weinberg equilibrium ($\chi^2=0,62$ for SMA lot and $\chi^2=2,17$ for control lot). The frequency of genotypes and alleles in patients and control lot are similar (ACE D: 57% versus 57% and ATR1 A: 75% versus 73%). We observed that 14,5% of patients and 11% of controls are homozygous for ACE DD and ATR1 AA. However, the potential association between combination of these polymorphisms and SMA severity must be reevaluated in a much powerful studies. In conclusion, our study indicated a lack of association between individual polymorphisms in ACE and ATR1 genes and SMA severity. To obtain more precisely data, a larger number of SMA patients will need to be examined in the future.</p>

PW7-081	<p><u>COMPENSATORY MECHANISMS DURING GAIT IN RESPONSE TO MUSCLE WEAKNESS IN SPINAL MUSCULAR ATROPHY, TYPE III</u> PRAŽNIKAR A¹, KRAJNIK J², OLEŃSEK O², MATJAŠIČ Z², TOMŠIČ I², KLEMEN A², EYMARD B³, ZUPAN A² (1) University clinical centre, Department of Neurology, Ljubljana, SLOVENIA. (2) Rehabilitation Institute, Ljubljana, SLOVENIA. (3) Institut de Myologie, PITIE-SALPETRIERE Groupement hospitalier universitaire, Paris, FRANCE.</p>
To contact the author:: ales.praznikar@kclj.si.	<p>Neuromuscular disorders are heterogeneous group of diseases of motor unit with muscular weakness as the predominant clinical sign. One of the most frequent complaint patients have are difficulties in gait.</p> <p>Spinal muscular atrophy (SMA) types I, II, and III is a hereditary disease that causes mostly symmetric and predominantly proximal weakness (specifically psoas quadriceps, triceps) and wasting of the voluntary muscles. Most patients with SMA III experience slow loss of function over time that is difficult to measure. Clinical data on gait in patients with SMA III are scarce.</p> <p>We asked ourselves whether we can determine characteristic compensatory mechanisms in pathologically disturbed gait in patients with SMA III.</p> <p>For that purpose, we used isokinetic dynamometry and clinical gait analysis (kinematic, kinetic and EMG data) in 7 patients with SMA III and 10 healthy subjects (control group).</p> <p>The results show that patients with SMA III negotiate gait problems by:</p> <ol style="list-style-type: none"> 1. reducing mechanical output requirements of weakened muscles (lower gait velocity, shorter step length, decrease in swing time); 2. minimizing external moments produced by ground reaction force (GRF) on the knee and hip by: <ul style="list-style-type: none"> • stronger activity of plantar flexors which controls centre of pressure during loading response and midstance to facilitate minimization of external flexion moment acting on the knee and hip; • anterior rotation of pelvis which facilitates rapid hip extension to secure GRF in front of the knee and behind the hip; • prolonged activity of contralateral hip abductors which decreases weight acceptance. <p>We conclude that the most important muscle groups enabling efficient compensation of diminished strength of knee and hip muscles are ankle plantarflexors, hip rotators and hip abductors, which might have direct application in rehabilitation programs. We also propose clinical gait analysis as a method for functional evaluation and measuring the progression of the disease.</p>

PW7-082	<p><u>RESULTS OF THE MULTINATIONAL SPINAL MUSCULAR ATROPHY PARENT SURVEY</u> FINKEL R¹, BERTINI E² (1) The Children's Hospital of Philadelphia, Philadelphia, USA. (2) Hospital Bambino Gesù, Rome, ITALY.</p>
To contact the author:: finkel@email.chop.edu.	<p>Hypothesis: Parental surveys in pediatric neuromuscular disorders provide useful data when considering clinically meaningful responses to treatment, generating standard of care guidelines and in designing effective clinical trials.</p> <p>Design/Methods: We constructed a 70-question survey for parents of children with Spinal Muscular Atrophy (SMA). Only patient de-identified data was collected. The IRB-approved survey was posted on a website in English, Spanish, Italian, German and French and was publicized by several SMA and neuromuscular advocacy groups.</p> <p>Results: 972 responses were collected in 2006-07. Respondents are parents/caregivers of children with SMA Type-I 33%, Type-II 46% and Type-III 17%. 82% are now alive. Examples of responses (%):</p> <ol style="list-style-type: none"> 1. SMN1 deletion confirmation of diagnosis=87 2. Parental Carrier testing : Type-I=53, II=46, III=37 3. Supportive of newborn screening=76 4. Care provided to child significantly affected by parents' finances=35 5. Caregiver burden is increased for Type I=Type-II, slightly less so for Type-III 6. Type-IIs who lost sitting (46) , Type-IIIs who lost walking (46) 6. Gastrostomy tube: Type-I=68, II=17, III=2 7. Scoliosis surgery: Type-I=8, II=22, III=18 8. Participation in a clinical trial (CT)=21 (71% would do so again, 54% had no opportunity) 9. Important factors for deciding to participate in a CT: safety (82), supportive animal model data (63), physician recommendation (53) 10. Expectations of participating in Phase 2 CT: not made worse (54), stabilizes course (40), cures SMA (20) 11. Obstacles to participation in a CT: missing work (32), transportation (35), childcare (28) 12. Would participate in a CT with a placebo arm = 77 (42% for > 6 months) 13. Best resource for information on SMA = advocacy group websites and conferences (70) <p>Conclusions/Relevance: This multinational SMA survey is an effective means of gathering data on diagnostic and treatment aspects of SMA and of parental opinions on clinical trial design.</p>

PW7-083	<p><u>SPINAL MUSCULAR ATROPHY TYPE 3 WITH CARDIOMYOPATHY: A CASE REPORT</u> AMAROF K¹, INAMO J², SARRAZIN E¹, DESCHAMPS R¹, SMADJA D³, BELLANCE R¹ (1) CERCA - CHU P. Zobda-Quitman, Fort de France, FRANCE. (2) Service de Cardiologie - CHU P. Zobda-Quitman, Fort de France, FRANCE. (3) Service de Neurologie - CHU P. Zobda-Quitman, Fort de France, FRANCE.</p>
	<p>Spinal muscular atrophy (SMA) is a recessive disorder characterized by degeneration of motor neurons in the anterior horn cells of the spinal cord and the brainstem, and with, clinically progressive weakness and hypotonia. The most common SMA is caused by deletion of the survival motor neuron 1 gene (SMN1), located on chromosome 5q13. The most serious complications are restrictive lung disease, dysphagia and orthopaedic deformities. Cardiac involvement is rare and mainly secondary to the chronic respiratory insufficiency. We report a rare case of Kugelberg-Welander disease (SMA type 3) with cardiomyopathy.</p> <p>This 17-year-old boy presented since the age of 3 nocturnal cramps, and then developed difficulty to walk and climb stairs. Neurological examination revealed fasciculation, proximal and distal deficit of lower limbs, with mild muscular atrophy. Muscle biopsy and electromyography confirmed neurogenic muscular degeneration and homozygous deletion of SMN1 gene was found. He complaint of mild dyspnoea and respiratory exploration revealed minimal restrictive syndrome. Electrocardiography was unremarkable but echocardiography showed diffuse hypokinetic cardiomyopathy with left ventricular ejection fraction significantly decreased. We review the relevant literature and argue that patients with Kugelberg-Welander disease should be evaluated systematically for cardiac disease.</p>

PW7-084	<p><u>FIRST CLINICAL EXPERIENCE OF PROXIMAL SPINAL MUSCULAR ATROPHY PATIENTS TREATMENT WITH VALPROIC ACID PREPARATIONS IN RUSSIA</u> BARANOV VS¹, VAKHARLOVSKY VG¹, KOMANTZEV V², MALYSHEVA OV¹, KISELEV AV¹ (1) Ott's Instit Obstetr & Gynecol RAMS, St Petersburg, RUSSIA. (2) Human Brain Institute RAMS, St.Petersburg, RUSSIA.</p>
<p>To contact the author:: baranov@vb2475.spb.edu.</p>	<p>The results of prolonged valproic acid (VA) treatment of 13 patients affected with proximal spinal muscular atrophy (SMA) are summarized. Positive clinical response was registered in 10 out of 13 SMA patients. Some minor clinical progress was registered in only 1 out of 2 SMA-1 patients with severe early manifestation of disease. Out of the rest 11 SMA-2 patients drastic clinical improvements were registered in only 2 subjects, who had got the ability to walk without extra assistance. Moderate improvements in some muscles contractions and normalization in electromyography were observed in 7 SMA patients ,while only definite clinical stabilization was obvious in the rest 2 SMA patients under present study. Common neurological examination failed to reveal any positive clinical manifestation in the latter group. .Thus positive outcome of VA treatment are rather variable in SNA patients. The success of VA treatment depends on the age of manifestation onset as well as the severity of locomotion defects, before treatment. VA-treatment of SMA-2 patients seems to be mostly beneficial provided if it is started before 4 years age when many muscles are still operative and thus many motor neurons still remain alive Further progress in SMA therapy could be attributed to precise estimation of SMN-2 genes counts, evaluation of primary RNA transcript doses for SMN2 genes as well as monitoring of neurotrophic protein –smn-protein levels during all courses of the treatment with VA preparations</p>

PW7-085	<p><u>DNAJB2, A CO-CHAPERONE INVOLVED IN THE UBIQUITIN PROTEASOME PATHWAY IS MUTATED IN A RARE DISTAL HEREDITARY MOTOR NEURONOPATHY WITH AUTOSOMAL RECESSIVE INHERITANCE</u></p> <p>BLUMEN SC¹, ISRAELI D³, ROBIN V², ASTORD S³, BARKATS M³, VIGNAUD L³, PORTE F¹, ACHIRON A¹, CARASSO RL¹, GUREVICH M¹, BRAVERMAN I¹, BLUMEN N¹, VIOLLET L²</p> <p>(1) Hillel Yaffe Medical Center, Neurology Department, Hadera, ISRAEL. (2) Hôpital Necker Enfants Malades, Génétique Médicale, INSERM U781, Paris, FRANCE. (3) Genethon, CNRS FRE 3087,, Evry, FRANCE.</p>
To contact the author:: viollet@necker.fr.	<p>Distal hereditary motor neuronopathies form a heterogeneous group of rare inherited lower motor neuron disorders. Autosomal recessive inheritance has been reported in six subtypes (dHMN III, IV, VI, Jerash type). We studied a large inbred Israeli family of Moroccan ancestry composed of three affected and eight non-affected sibilings. The disease was characterized by early adult onset and predominance of paralyses in the distal part of lower limbs. By homozygosity mapping strategy, we localized the disease gene in a 6,2 cM genetic interval on chromosome 2q35-2q36.1. In this region, we identified a homozygous point mutation in the sequence of gene DNAJB2. The mutation cosegregated with the disease in the family and was absent in 200 DNA controls.</p> <p>DNAJB2, or Heath Shock Protein DNAJ like 1(HSJ1), belongs to the DNAJ/HSP40 co-chaperone family. DNAJ/HSP40 are ATP-dependent positive regulators of HSP70 chaperon proteins, acting in the folding of protein substrates. Two main isoforms (DNAJB2-V1/HSJ1a and DNAJB2-V2/HSJb) are highly expressed in brain and spinal cord. Previous functional studies showed that DNAJB2 is involved in the ubiquitylation and the sorting of misfolded proteins to the ubiquitin proteasome system (UPS). The mutation reported here is responsible for an abnormal splicing of the DNAJB2 transcripts, causing retention of intron 4 and leading to a premature stop codon. Western blot analysis on patient's fibroblasts revealed a severe reduction of DNAJB2-V2 and the absence of DNAJB2-V1.</p> <p>Altered co-chaperone activity has been reported in many neurodegenerative diseases, including hereditary motor neuropathies (dHMNI and II) and animal models of motoneuron degeneration (Wobbler mouse). Recent studies highlighted the role of DNAJB2 in the reduction of intraneuronal aggregates in a cellular model of neurodegenerative disease (polyglutamine expansion) by increasing protein ubiquitylation and targeting to the UPS. Further functional studies will be required to understand the consequences of DNAJB2 defect on motor neuron degeneration process.</p>

PW7-086	<p><u>PROGRESSION OF CORTICAL AND SPINAL DYSFUNCTIONS OVER TIME IN AMYOTROPHIC LATERAL SCLEROSIS</u> ATTARIAN S¹, POUGET J¹, SCHMIED A² (1) CHU La Timone, Marseille, FRANCE. (2) CNRS, P3M, Marseille, FRANCE.</p>
To contact the author:: sattarian@ap-hm.fr.	<p>In view of the conflicting results about the links between lower and upper motor neurons (LMN, UMN) dysfunction in amyotrophic lateral sclerosis (ALS), our objective was to correlate their changes over time. Single motor units (MUs) were characterized by their macro-MU potentials, twitches, and excitatory responses to transcranial magnetic stimulation (TMS). Ten ALS patients were studied 2 to 4 times and their data was subdivided into epochs corresponding to mean disease duration of 12 (58 MUs), 20 (60 MUs), 32 (50 MUs), 43 (40 MUs) and 168 months (55 MUs). The MU size increased and the contractile effectiveness and the excitatory response rates decreased significantly with time. The contractile effectiveness of MUs producing normal excitatory responses decreased with time, whereas, a gradual loss of excitatory responses was observed among MUs with normal electromechanical properties.</p> <p>Since no correlation was found between UMN and LMN dysfunction, we conclude that UMN and LMN probably degenerate independently in ALS.</p>

PW7-087

MOTOR NEURON DISEASE IN A PATIENT WITH INFLAMMATORY BOWEL DISEASE

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INTRODUCTION

Inflammatory Bowel Disease (IBD) presents many neurological complications. Up to 3% of patients with IBD have neurological involvement (Thromboembolic phenomena, myelopathy, myopathy, multiple sclerosis and various neuropathies). Just one case of motor neuron disease (MND) has been previously reported. We present a case of MND in a young patient with IBD.

CASE REPORT

A 33 years old male diagnosed of Ulcerative Colitis at 20 years age and in treatment with mesalazine and folic acid was referred to consultation. He referred weakness in right arm a year ago and then progress to the left arm and both legs. He has no familial history of MND. In physical examination he has muscular wasting in deltoids and first dorsal interosseous, fasciculation were seen in biceps, deltoids, and quadriceps muscles and it was observed weakness in arms and legs, hiperreflexia with ankle clonus, and extensor plantar response.

Blood tests were normal except for elevation of eritrosedimentation. B12 vitamin and folic acid were normal; VDRL and HIV serology were negative. CSF showed normal cell account with protein concentration of 0.75 mg/dL without oligoclonal bands. Central nervous MRI was normal. EMG revealed fasciculation and fibrillation in muscles of legs and arms, with normal conduction velocity and without block of conduction.

EVOLUTION

The patient received treatment with intravenous immunoglobulin 0,4 g/kg/day during 5 days, for four times without any response. The patient continues to deteriorate with severe difficulties to walk but without bulbar symptoms.

DISCUSSION

The physiopathology of MND is not well understood. Several factors (inflammatory, oxidative stress, apoptosis, excitotoxicity...) have been implicated. The precocious age of beginning of the disease and the co-existence of both diseases suggest that they share a common pathological basis. We discuss the possible relation between the two diseases.

PW7-088	<p>REGULATION OF RAS-RELATED ASSOCIATED WITH DIABETES IN AMYOTROPHIC LATERAL SCLEROSIS MUSCLE HALTER B¹, GONZALEZ DE AGUILAR JL¹, FRICKER B¹, RENE F¹, DEROIDE N², PETRI S³, ECHANIZ-LAGUNA A², DENGLER R³, LOEFFLER JP¹ (1) Inserm, U692, Laboratoire de Signalisations Moléculaires et Neurodégénérescence, Université Louis Pasteur, Faculté de Médecine, Strasbourg, FRANCE. (2) Département de Neurologie, Hôpital Civil de Strasbourg, Strasbourg, FRANCE. (3) Department of Neurology and Clinical Neurophysiology, Medical School of Hannover, Hannover, GERMANY.</p>
	<p>Amyotrophic lateral sclerosis (ALS) is a fatal adult-onset neuromuscular disease characterized by selective degeneration of upper and lower motor neurons, progressive muscle wasting, and paralysis. Some familial cases are caused by missense mutations in the gene encoding Cu/Zn-superoxide dismutase (SOD1), a free radical-scavenging enzyme that protects cells against oxidative stress. Because it is thought that the first motor symptoms result from premature damage to the distal part of the motor unit, we recently analysed gene expression in skeletal muscle of mutant SOD1 (G86R) mice using a high-density oligonucleotide microarray approach. One of the strongest regulations detected concerned Ras-related associated with diabetes (Rad), a small GTPase of the Ras superfamily. In the present study, we analyzed the expression of Rad during the course of the disease in G86R mice and related this expression to the presence of denervation and oxidative stress at early stages of the muscle pathology in ALS. Our findings indicate that the increase in muscle Rad expression is early and age-dependent, occurs within adult muscle fibers, and is also present in patients with sporadic ALS. We also show that Rad is not only stimulated by muscle denervation but also in response to an ischemia/reperfusion stress, which generates high levels of reactive oxygen species. Interestingly, both Rad up-regulation and increase amounts of reactive oxygen species were detected early in asymptomatic G86R mice, before the onset of denervation. Therefore, these findings provide evidence for the early oxidative stress mechanisms affecting muscle in ALS.</p>