

[P01.038] Association between the Survival Motor Neuron Genotype and the Phenotype of Sporadic Motor Neuron Diseases

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OBJECTIVE: To investigate whether survival motor neuron (SMN) genotypes leading to decreased expression of the SMN protein are associated with increased susceptibility or poor prognosis in patients with amyotrophic lateral sclerosis (ALS) or lower motor neuron disease (LMND) **BACKGROUND:** Adult-onset sporadic ALS or LMND is believed to be multifactorial in origin with modifying genes affecting the clinical expression. Childhood-onset spinal muscular atrophy (SMA) is an autosomal recessive disorder of motor neurons, caused by mutations of the survival motor neuron (*SMN*) gene. The *SMN* gene exists in two highly homologous varieties: *SMN1*, the causative gene and *SMN2*, the phenotype modifier gene. Several studies investigated the association between *SMN* genotypes and sporadic MND, but produced conflicting results. **DESIGN/METHODS:** Quantitative PCR analysis for both *SMN1* and *SMN2* genes was performed in 243 ALS patients, 80 LMND (47 with generalised and 33 patients with non-generalised forms) patients, and 175 controls. A meta-analysis of all available data was performed. **RESULTS:** In ALS, we found that a heterozygous deletion of *SMN1* increased the susceptibility (OR = 4.1, 95%-CI = 1.2-14.3, p = 0.02), which was confirmed in the meta-analysis (OR = 5.2, 95%-CI = 2.5-10.7, p < 0.001). The absence of *SMN2* was independently associated with poorer survival in ALS (HR = 2.0, 95%-CI = 1.1-3.8, p = 0.03). In addition, *SMN2* copy numbers were correlated with survival in ALS suggesting a dose-effect relationship (HR = 0.8, 95%-CI = 0.6-0.9, p < 0.05). In LMND, a heterozygous deletion of *SMN1* increased the susceptibility in the generalised forms (OR = 5.6, 95%-CI = 1.2-25.9, p = 0.03). Although a non-significant overrepresentation of an absence of *SMN2* was found in our patients with generalised LMND (OR = 2.2, 95%-CI = 0.9-5.3, p = 0.07), the meta-analysis revealed that an absence of *SMN2* was significantly associated with generalised LMND (OR = 5.1, 95%-CI = 2.9-9.2, p < 0.001). Absence of *SMN2* was overrepresented in patients with LMND with a rapidly progressive disease course (OR = 3.7, 95%-CI = 1.3-10.8, p < 0.02). **CONCLUSIONS:** We conclude that *SMN1* is a susceptibility gene and *SMN2* a phenotype-modifying gene in patients with ALS and generalised LMND.

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