invasive ventilation). Maintenance of and improvement in a patient's quality of life are important factors in the management of ALS, especially in patients who have started TIV. The current literature on music therapy for ALS is poor, and there are no reports on music therapy for patients with TIV.

Objective: To investigate the effects of music therapy on the quality of life of patients with ALS.

Patients and Methods/Material and Methods: Fifty-one patients with ALS (35 men and 16 women), including 37 with TIV and 7 in the totally locked-in state, were exposed to music therapy. One to three music therapists visited the patients' homes and played instruments and sang songs at the patients' requests. During the session, the therapist and patient talked about the songs and any related memories. One session lasted between 45 minutes and 1 hour. Each patient received one to eight sessions at a frequency of once per month. After the sessions were over, patients and their families noted their impressions of music therapy.

Results: A total of 266 sessions (average 5.2 sessions per person) were held. 95.2% of patients and 93.8% of families answered that the music therapy was good.

Conclusion: Music therapy is not only pleasant and restorative for patients with ALS and their families, but it can also support their power to live with the disease and improve their quality of life.

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SHIFT 4 - MOTOR NEURON DISEASE
Copy number variations in sporadic amyotrophic lateral sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) is a fetal neurodegenerative disorder characterized by the selective loss of motor neurons in the brain and spinal cord. Although the molecular mechanisms underlying ALS pathogenesis remain unclear, recent studies have suggested that genetic risk factors are implicated in susceptibility to both familial and sporadic forms of the disease. In addition to single nucleotide variants and small insertion/deletions, structural changes such as copy number variations (CNVs) contribute to human diseases including ALS. However, the accurate detection of CNVs remains challenging.

Objective: The aim of this study was to examine CNVs in known ALS-related genes in sporadic patients with ALS.

Patients and Methods/Material and Methods: Whole-exome sequencing of thirteen sporadic ALS patients was performed using amplicon-based next-generation sequencing. Then, we performed CNV analysis of previously reported ALS-related genes using a hidden Markov model based algorithm.

Results: Four sporadic ALS patients carried CNVs that were not detected in 176 control subjects in *ALS2*, *OPTN*, *SPG11*, *SQSTM1*, *CHMP2B*, and *PCSK6*. We found multiple CNVs in two cases.

Conclusion: Our findings imply that CNVs in familial ALS-related genes are implicated in sporadic ALS. Furthermore, additive effects of multiple CNVs may play an important role in ALS pathogenesis.

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SHIFT 4 - MOTOR NEURON DISEASE
Loss of function mutant of ter94, Drosophila VCP, partially enhanced motor neuron degeneration induced by knockdown of TBPH, Drosophila TDP-43

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Background: In amyotrophic lateral sclerosis (ALS), TAR DNA-binding protein-43 (TDP-43) is a pathological hallmark. Loss of nuclear TDP-43 functions likely contributes to neurodegeneration. *TBPH* is the *Drosophila* ortholog of human *TDP-43*. In human disease, mutations in *Valosin containing protein* (*VCP*) have been associated with neurodegenerative disease, including ALS. *Ter94* is the *Drosophila* ortholog of human *VCP*. Here, we searched genetic interaction between *TBPH* and *ter94*.

Objective: To find genetic interaction of *TBPH* and *ter94*, we cross the loss-of-function allele of *ter94* with *TBPH*-knockdown phenotypes in flies.

Patients and Methods/Material and Methods: To elucidate the effects of *TBPH*-knockdown and *ter94* on motor function of the fly, we investigated the life span, climbing assays and the morphology of motoneuron presynaptic terminals at neuromuscular junctions (NMJs).

Results: Fly models with neuron-specific *TBPH*-knockdown presented deficient locomotive behaviors, reduced life span and anatomical defects in presynaptic terminals of motoneurons at NMJs in third instar larvae. The loss-of-function allele of *ter94* enhanced the locomotive dysfunction induced by *TBPH*-knockdown until day14 (n = 100, *P* < 0.001). Life spans and morphology of NMJ were not changed.

Conclusion: Neuron-specific *TBPH*-knockdown flies developed locomotive deficits, life span reduction and anatomical defects in motoneurons at NMJs. Loss of function ter94 mutant enhanced these phenotypes during young age. We next search the candidate of improving the effect of *TBPH*. This data may support to find the candidate of improving TDP-43-related ALS.

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SHIFT 4 - MOTOR NEURON DISEASE
The association between education, rurality and mining - Agricultural occupation with mortality by amyotrophic lateral sclerosis in Chile: A time serie analysis of 24 years

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Background: This is the first study investigating the association of contextual variables and mortality by amyotrophic lateral sclerosis (ALS) in Latin America.

Objective: To determine the association of contextual variables and mortality rates by ALS in Chile over the last 24 years.

Patients and Methods/Material and Methods: A 24 years (1990-2013) time-series analysis over 696 strata was performed including sex, age, education and 29 geographical areas. Deaths were extracted from the national registry, while contextual exposure variables were estimated by each stratum, using data from a national representative socioeconomic characterization survey (biennial from 1990 to 2013). Variables included were percentage of people of the strata (1) living in rural zone, (2) agricultural occupation, (3) mining occupation, and (4) belonging to an ethnic group. Multilevel Poisson regression analysis was performed and relative mortality rate ratios (RR) were reported. Interaction terms were explored.

Results: The general trend showed a mild increase of ALS mortality rate over time (Figure). Females presented almost 30% lower risk than men in mortality by ALS, while aging was strongly associated to higher risk (Table). Lower education showed an important association with the risk of death by ALS, although the interaction terms analysis pointed out that the gradient of effect diminished across the years. Rurality also presented a strong association to a higher mortality, independent of other variable. Although mining and agricultural occupation were related to mortality by ALS, their effects were confounded by age and education respectively.

Table. Association between contextual exposure variables and mortality rates by ALS in Chile 1990-2013.

	Univariate		Multivariate (3)	
	RR	CI	RR	CI
Sex	0,8	[0,69-0,82]	0,7	[0,60-0,74]
Age 1 (<20 y)	1,00	-	1,0	-
Age 2 (20-34 y)	15,3	[10,2-23,0]	14,9	[9,9-22,4]
Age 3 (35-50 y)	64,5	[43,6-95,9]	60,5	[40,6-90,2]
Age 4 (<50 y)	135,5	[91,2-201,3]	124,5	[83,3-186,1]
Education 2 (<12 y)	1,0	-	1,0	-
Education 1 (9-12 y)	1,5	[1,3-1,7]	1,0	[0,9-1,2]
Education 0 (0<9 y)	4,5	[4,0-5,2]	1,2	[1,1-1,5]
Rurality	30,3	[18,9-48,6]	2,9	[1,3-6,5]
Agricultural	20,0	[14,1-28,4]	0,8	[0,4-1,5]
Mining	0,05	[0,01-0,2]	3,6	[0,7-18,2]
Ethnicity	0,22	[0,08-0,6]	1,3	[0,4-3,8]
Year	1,03	[1,02-1,03]	1,01	[1,01-1,02]

Figure:
Mortality rates by ALS in Chile 1990-2013
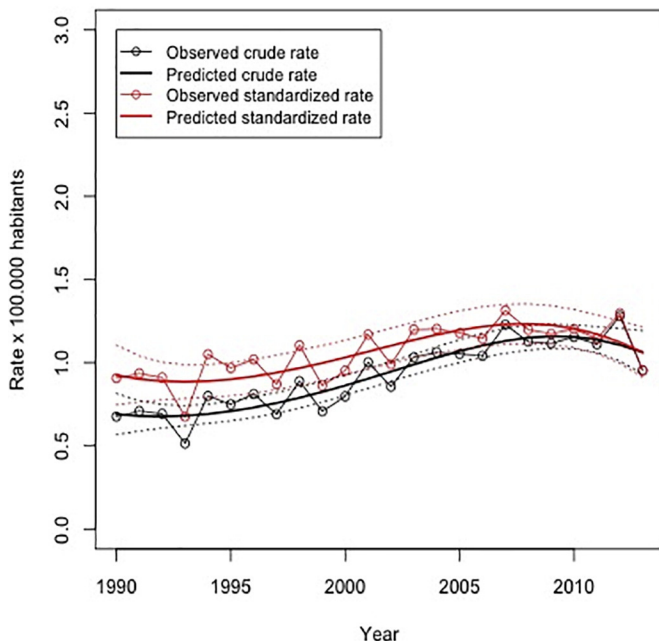
Conclusion: In Chile, education and rurality were the main factors associated with an increased risk of mortality by ALS.

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SHIFT 4 - MOTOR NEURON DISEASE
Characteristics of cognitive features in ALS using the addenbrooke's cognitive examination revised (ACE-R)

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Background: ALS is now known to involve a range of cognitive impairments, there are limited studies characterizing cognitive deficits in the Japanese ALS population.

Objective: We aimed to characterize the cognitive features of Japanese ALS patients and show factors that influence cognitive decline.

Patients and Methods/Material and Methods: We applied ACE-R which has a potential for evaluating five cognitive domains including orientation/attention, memory, verbal fluency, language and visuo-spatial ability. 131 ALS patients (64 females; mean age:65.48 ± 9.56; mean education:12.95 ± 2.27) and 151 age-, gender- and education-matched controls were enrolled. We excluded ALS-FTD patients. The prevalence of cognitive decline was defined as a score less than 5%tile of the controls' mean on the score.

Results: The prevalence of cognitive decline in total score was 44.3%. The most frequent cognitive deficit domain were orientation/attention and language (33.6%) followed by verbal fluency (30.5%), memory (29.8%), and visuospatial ability (21.4%). The prevalence of cognitive decline in multiple domains was 38.9%. In each item, the most frequent cognitive decline was three words recall (48.9%), followed by comprehension (46.6%), name and address recall (40.5%), animals and objects naming (38.2%). Using cluster analysis, ALS patients were classified into three groups based on ACE-R score (ACE-R≥89, 73≤ACE-R<89, ACE-R≤72). Among 3 groups, there was no difference in onset types and disease duration. ALS with normal cognition was significantly younger (p<0.001) and had higher education than other groups (p=0.001). Moderate decline group showed mild frontotemporal dysfunction and severe decline group showed widespread but particularly memory impairment.

Conclusion: ALS patients frequently show frontotemporal dominant cognitive decline closely associated age at examination.

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SHIFT 4 - MOTOR NEURON DISEASE
A clinical overview of lathyrism

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