controls. A significant difference in the total number of variants in ALS-associated genes was not observed. Further, PCA clustering analysis did not suggest an observable difference in genetic variance between C9orf72-positive patients and unknown cause patients, nor between ethnicity, gender, or site of disease onset groups.

Discussion: The oligogenic hypothesis could help to explain why certain genes have been statistically associated with ALS, but that single mutations are often not sufficient to cause the disease in all mutation carriers. However, because we did not observe a significantly increased burden of mutations within the ALS genes, it is unlikely that the disease is caused by carrying multiple mutations in these genes at once. It may be that there remain several genes yet to be associated with ALS that will explain the disease in these unknown-cause patients.

Conclusion: Our evidence does not support the oligogenic hypothesis in ALS.

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GEN-31 Genetic testing of sporadic ALS patients reveals pathogenetic mutations in non-ALS genes

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Keywords: ALS, next-generation sequencing, neurodegenerative panel

Background: The rise of next-generation sequencing (NGS), allowing fast and cheap massive-parallel DNA sequencing, in genetic testing has revolutionized the approach to diagnosis in neurodegenerative diseases. The traditional approach, which considered different neurodegenerative diseases as separated conditions, mainly associated to groups of known canonical genes, has been overturned by the advent of multiple genes and exomes panels. Increasing evidence supports the existence of a close relationship between genetic profiles of different neurodegenerative diseases, further reinforcing the hypothesis of a co-morbidity between these disorders.

Materials and methods: In this study, DNA extracted from blood of 63 sporadic ALS patients has been sequenced with a newly-defined customized 'neurodegenerative panel' (SureSelect, Agilent), containing classical ALS genes such as *SOD1*, *TARDBP* and *FUS*, together with Parkinsonian genes such as *PINK1* and *LRRK2*, and genes involved in different neuropathies (eg Charcot-Marie-Tooth, Hereditary spastic paraplegia), for a total of 103 genes. DNA-seq was performed using an Illumina MiSeq sequencer and data analysis was performed according to the best practices described for these applications to identify single nucleotide variants and small insertions/deletions. Pathogenic and likely pathogenic mutations have been confirmed via Sanger sequencing.

Results: For six patients, mutations in classical ALS genes have been identified. Three patients have mutations in the *SOD1* gene, Two with p.G147S and one p.G93D, one in *FUS* gene p.G302A and two brothers with mutation in *VCP* gene (p.R191Q). Surprisingly, likely pathogenetic mutations in non-canonical ALS genes such as *PINK1*, *LRRK2*, *BAG3* and *PDYN* were also found. These genes have not been reported to be associated to ALS, but associated to Parkinson's disease and Spinocerebellar Ataxia 23. Two ALS cases have a very rare nucleotide substitution in LRRK2: rs141252946 and p.E1011D, and one presents a mutation in *BAG3* gene p.R71W and one in PDYN E192V.

Conclusion: These findings support the hypothesis of the existence of a comorbidity between neurodegenerative diseases and strongly highlight the importance of wide genetic screenings on genes not yet associated to the studied disease. It is clear that the old genotype-phenotype view is quite simplistic and the approach to the disease must be changed.

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GEN-32 The identification of genetic modifiers in the motor neuron diseases ALS and SMA

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Keywords: genetic modifiers, SMA, C. elegans

Background: Understanding genetic modifiers of motor neuron disease can provide insight into the mechanisms underlying these disorders. Increasing evidence suggests that common pathways are perturbed across motor neuron diseases and therefore identified genetic modifiers could have an effect across multiple diseases. Plastin 3 (PLS3) is a known genetic modifier of spinal muscular atrophy (SMA) and while implicated as a possible cross-disease modifier, it has yet to be tested.