Amyotrophic lateral sclerosis: disease or syndrome?

https://neurodegenerationresearch.eu/survey/amyotrophic-lateral-sclerosis-disease-or-syndrome/

Name of Fellow

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Institution
Funder

ZonMw

Contact information of fellow
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The Netherlands

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Amyotrophic lateral sclerosis: disease or syndrome?

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ZonMw

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The project/programme is most relevant to:

Motor neurone diseases

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Research Abstract

Amyotrophic Lateral Sclerosis is usually described as a progressive disorder of upper- and lower motor neurons leading to muscle weakness and death due to respiratory failure on average 3

years
after the onset of symptoms. In clinical practice, however, we experience a large variability in the clinical expression of the disease. An important gap in our knowledge of ALS pathophysiology is whether motor neurons in ALS die from a complex interaction between multiple factors or from the
manifestation of a unique cause. In other words, is ALS one disease or just a phenotype of a large
number of diseases with many causes? Filling this gap in knowledge may have important consequences for molecular diagnostic and therapeutic strategies in ALS and possibly other complex/neurodegenerative diseases. My working hypothesis is that ALS should be considered either
as a collection of single, unique rare diseases or a diagnostic continuum in which ALS can be subclassified
according to the relative contribution of genetic, environmental/lifestyle and phenotypic factors. I propose to establish the largest population-based case-control study of >2500 incident ALS
patients and >5000 controls to determine phenotypic variability, genetic/environmental/lifestyle susceptibility and disease-modifying factors. I plan to discover additional ALS associated genes by
applying (1) whole genome sequencing techniques in genetically unexplained familial ALS patients,
and (2) a novel study design that, using imputation approaches, can then take advantage of discovered
variants from whole genome sequence data from a subset of ALS patients, to infer untyped rare variants in the in my laboratory available datasets from previous GWAS. By using sophisticated exploratory cluster techniques, where multiple data modalities (phenotypic, neuroimaging, environmental/lifestyle, genetic) serve as input, subgroups will be identified. The results of this VICI
research line may yield new insights in pathways underlying ALS and give leads for improved treatment of patients suffering from ALS.

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