Identification of ALS associated genes using whole genome sequencing

https://www.neurodegenerationresearch.eu/survey/identification-of-als-associated-genes-using-whole-genome-sequencing/

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Country

USA

Title of project or programme

Identification of ALS associated genes using whole genome sequencing

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15/07/2011

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Familial Amyotrophic Lateral Sclerosis, whole genome, Amyotrophic Lateral Sclerosis, genetic element, genome sequencing

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a lethal adult-

onset neurodegenerative disease caused by the selective loss of motor neurons. Although most ALS cases are sporadic in nature (SALS), ~10% are familial (FALS). Unfortunately, one-third of the underlying genetic causes of FALS still remain to be explained. Recently, we have developed a methodology to identify causal mutations by using exome sequencing results of index familial cases (i.e. one affected member per family) in an unbiased case-control rare variant analysis. Through the analysis of over 600 FALS samples, we successfully identified a novel gene associated with familial ALS, TUBA4A, encoding the Tubulin, Alpha 4A protein, further emphasizes a strong role for cytoskeletal defects in ALS. Although our approach to identify novel ALS genes was successful with exome data, it did have limitations. These included an inability to analyze approximately half of all coding genes, copy number variants, (CNVs), and non-coding regions such as miRNAs, lincRNAs, promoter regions and other non-coding elements. As demonstrated by the ENCODE project and others in recent years, these genetic components have been increasing shown to be of vital importance in cellular regulation and human disease. Here we propose to expand our study by whole genome sequencing this familial ALS sample cohort. The Specific Aims of this proposal are: (1.) Discovery of Novel Genetic Elements Associated with Familial ALS. Over 600 index familial ALS samples will be whole genome sequenced. Control samples will include a minimum of 7,500 whole genomes to be sequenced by the international Project Mine consortium. The genomes will be subject to rare variant and CNV analysis of coding and non-coding regions to identify novel genetic elements associated FALS. (2.) Validation / Characterization of Novel Genetic Elements Associated with Familial ALS. Top candidate genetic elements will be further evaluated by targeted sequencing of an independent replication cohort of >300 FALS and ~10,000 controls. Furthermore, we will examine the association of these genetic elements within a panel of up to 15,000 SALS cases. Lastly, we will prioritize variants present with FALS- associated genes likely to have a functional impact through predictive software, allele frequency comparisons and testing proper segregation within affected family members. (3.) Functional Analysis of Novel Genetic Elements Associated with Familial ALS. The consequences of identified alteration will be evaluated based on their predicted functional impact. The pathogenic effect of the coding mutations will be evaluated in Drosophila and yeast models. Non-coding changes will be evaluated for their effect on gene expression, regulation and/or splicing patterns depending on the nature of the genetic element. We are confident that the proposed project will lead to the discovery of one or more novel genetic elements contributing to ALS increasing our knowledge of the pathways contributing to this devastating disease and open new avenues of research including the development of new therapeutic targets.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is an adult-onset, rapidly progressive and ultimately fatal neurodegenerative disease caused by the selective loss of motor neurons. The overall goal of this proposal is to identify novel genes associated with familial ALS through whole genome sequencing of patients. This information will facilitate our understanding how such defects lead to disease and reveal therapeutic targets to extend the lifespan of patients.

Further information available at:

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Investments > €500k

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United States of America

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