Development of an information-rich assay for C9ORF72 as a test for ALS and FTD

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Contact information of lead PI
Country

USA

Title of project or programme

Development of an information-rich assay for C9ORF72 as a test for ALS and FTD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,265,825.69

Start date of award

01/07/2014

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Motor neurone diseases

Keywords

C9orf72, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Chromosomes, Human, Pair 9, Proliferating Cell Nuclear Antigen

Research Abstract

Project Summary The long term goal of this project is to develop, validate, and commercialize

an assay for improved analysis of C9orf72, a gene on chromosome 9 that is linked to frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Expansion of a guanine and cytosine rich hexanucleotide repeat (GGGGCC) in the non-coding region of C9orf72 is associated with 39% of familial ALS. The expansion also appears in 25% of familial frontotemporal dementia (FTD) cases, as well as 7% of sporadic ALS and 6% of sporadic FTD. The C9orf72 region is difficult to size accurately because most expansions in affected individuals are >700 repeats in length. Currently testing typically relies on “homebrew” PCR-based assays for accurate sizing of < 35 repeats, or, separately, Southern blot analysis for crude sizing of >35 repeats. We have developed a solution to enable high throughput, reliable, sensitive, and accurate sizing of the repeat region for both short (< 35 repeats) up to 145 repeats, and long expansions (146 to at least ~800 repeats) in a reflex assay. The proposed assay offers a solution to these technical challenges based on the repeat-primed assay platform (AmplideX® FMR1 PCR) that Asuragen has developed and successfully commercialized for fragile X syndrome, a CGG triplet repeat disorder. We will continue to leverage >6 years of experience in optimizing high performance diagnostic assays for GC- rich repeat sequences to develop an accurate and robust diagnostic test for C9orf72. Funding for this Phase II will support the efforts necessary to complete the development of the test. The specific aims of this proposal are: Aim 1. Integrate a novel engineered PCR polymerase system to achieve extreme processivity and reliable amplification of >800 hexanucleotide repeats. Aim 2. Develop and integrate a set of controls and standards in an optimized workflow that supports C9orf72 testing. Aim 3. Develop a data analysis pipeline and reporting tools within a user-friendly application that allows rapid and accurate identification C9orf72 repeat number. Aim 4. Evaluate an assay system that integrates the workflow and controls (Aims 1 and 2) with the analysis software (Aim 3). Validate the integrated system with cell lines and retrospective clinical samples. The development of an improved, information-rich assay for C9orf72 will be useful as a screening and diagnostic test for ALS and FTD as well as a clinical research tool to identify intermediate and/or expanded repeat sizes that are potentially relevant to other forms of age-onset neurodegeneration. In addition, this assay can further the understanding of known and novel genotype-phenotype associations and enable opportunities for targeted therapeutics and clinical trials.

Lay Summary

Project Narrative We are developing a test to improve diagnosis and screening for genetic alterations that are linked to neurodegenerative diseases. Alterations in the gene, C9ORF72, are associated with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The test will be useful as a clinical research tool to support opportunities for emerging therapeutic options.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias, Motor neurone diseases

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