Association of ALS to gene-environment mediated changes in HDL proteins

https://www.neurodegenerationresearch.eu/survey/association-of-als-to-gene-environment-mediated-changes-in-hdl-proteins/

Principal Investigators

SIDDIQUE, TEEPU

Institution

NORTHWESTERN UNIVERSITY AT CHICAGO

Contact information of lead PI
Country

USA

Title of project or programme

Association of ALS to gene-environment mediated changes in HDL proteins

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,456,997.25

Start date of award

01/02/2013

Total duration of award in years

2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

High Density Lipoproteins, Amyotrophic Lateral Sclerosis, aryldialkylphosphatase, particle, rodent genome

Research Abstract
DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) or Lou Gehrig

disease is a fatal neurodegenerative disease that primarily affects mid-life and older adults. There are two forms of disease, familial (FALS) and sporadic (SALS), respectively comprising 10% and 90% of cases, respectively. The genetic causes of FALS have been linked to mutations in several genes such as superoxide dismutase, TDP-43, FUS, optineurin, ubiquilin 2 and C9ORF72. The etiology of SALS, however, remains elusive. A few years ago our laboratory found that there were polymorphisms in genes for enzymes called paraoxonases that were associated with SALS. These enzymes detoxify certain pesticides and toxic agents, and thus became the first environmentally related genes linked to ALS. Further studies of the paraoxonases and apolipoprotein L1 in the plasma indicate that their levels are significantly elevated in SALS patients. These proteins are found on specific high density lipoprotein (HDL) particles that have several functions including lipid and cholesterol transport and protecting lipoproteins from deleterious oxidation. Similar particles are also found in the cerebrospinal flui (CSF). Thus, in this proposal we further characterize the protein composition of selected HDL species in the plasma and CSF of SALS patients using high throughput technologies. We can now, for the first, time determine how certain HDL proteins change in a neurodegenerative disease and if they are linked to the disease process. We will also determine whether the genes for HDL-associated proteins contain variants that are associated with risk of SALS and whether these changes are related to alterations in HDL protein levels. Mechanisms of the deleterious effects of these changes will be studied in cell culture and genetically engineered mice. Results from this work will open paths to therapies to rescue potential dysfunctional HDL found not only in neurodegenerative disease such as ALS but also in more common cardiovascular and metabolic diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) or Lou Gehrig disease is a fatal neurodegenerative disease that primarily affects mid-life and older adults. The genetic causes of ALS have been linked to mutations in several genes, but the origins of sporadic ALS remains elusive. One clue to a potential environmental link to ALS came from our studies of the genes of the enzymes known as paraoxonases that detoxify insecticides and other agents and also protect certain fat particles in blood called HDL (“”good”” cholesterol containing particles) and LDL (bad cholesterol containing particles) from deleterious oxidation events. Specific genetic variants in the genes of these enzymes in SALS patients are associated with disease. We began studies of these proteins in blood and cerebrospinal fluid. Paraoxonase levels are higher in the plasma of SALS patients compared to controls suggesting there are links to protein function and disease. Moreover, another HDL particle protein, ApoL1 is also elevated in the plasma of SALS patients. Thus, we will further study levels of these proteins in the blood and cerebrospinal fluid, investigate genetic variants that may confer risk of ALS, and carry out studies in cell culture and genetically modified animals to study how these proteins may contribute to ALS.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A