Identification of novel genetic risk factors for sporadic ALS by whole genome sequencing discordant identical twins

Investigator: Michael A. van Es, Utrecht, The Netherlands

Grant : 150 000€

Project duration: two years

Sporadic ALS (SALS) is considered to be a complex disease caused by environmental and genetic factors. Studies have estimated that the genetic contribution to SALS is large (~60%) and therefore, unraveling the genetics of ALS is essential to understanding the underlying pathophysiology. Although progress has been made, the genetics of SALS remain poorly understood. The aim of this study is to identify novel genetic risk factors for ALS by using a novel study design. There are monozygotic twins of which one has ALS and the other does not (discordant twins). The obvious question is why? We hypothesize that is due to a single (epi)genetic difference between the monozygotic twins. If one were able to find such a difference this would directly constitute the discovery of a novel risk gene for ALS. We therefore propose to identify (epi)genetic differences between discordant monozygotic twins, by analyzing the entire genome (complete DNA code) and comparing their DNA code using novel techniques and computer algorithms. Differences in DNA code will be validated in independent experiments using different techniques. Differences found between the DNA of the twins, will then be tested in other ALS patients and compared to healthy control subjects in order to confirm that the identified DNA variants are indeed risk factors for ALS. In order to include as many discordant monozygotic twins as possible, we have established a European twin database to which 11 centers from across Europe have contributed.

European ALS twin database: **PJ Shaw (**Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, UK), **M de Carvelho** (University of Lisbon Medical School, Santa Maria Hospital, Lisbon, Portugal), **PM Andersen** (Umeå University Hospital, Umeå, Sweden), **K Talbot** (University of Oxford, Nuffield Department of Clinical Neurosciences & John Radcliffe Hospital, Oxford, UK), **M Kuzma-Kozakiewicz** (University of Warsaw, Poland), **A Chio** (Neurological Institute, Catholic University and I.CO.M.M. Association for ALS Research, Rome, Italy) **M Weber** (Kantonspital, St Gallen, Switzerland), **V Silani** (Istituto Neurologico Carlo Besta, Milano, Italy) **O Hardiman** (Beaumont Hospital & Trinity College Dublin, Ireland), **AC Ludolph** (University of Ulm, Ulm, Germany) and **W Robberecht** (University of Leuven, Leuven, Belgium).

In total DNA samples from 25 discordant monozygotic twins have been collected and DNA from 410 FALS cases, 5,000 SALS cases and >8,000 healthy controls is available for confirmation experiments.
The proposed strategy is novel, but supported by sound logic and recent studies have provided proof of principle. This study could be a highly effective way to indentify novel risk genes for SALS.

The research will be conducted in Utrecht, within the neurology department. The project group holds extensive experience and expertise in analyzing large data sets in the field complex genetics. The project group is further capable of designing software and algorithms to analyze data, such variable threshold test designed association testing in studies dealing with rare variants.

Michael A. van Es is a neurology resident and a researcher in the laboratory for experimental neurology at the University Medical Center Utrecht, Netherlands

His five major contribution to publications are:

(1) van Es MA, *et al*. *Angiogenin* variants in Parkinson's disease and amyotrophic lateral sclerosis. **Annals of Neurology** (in press).

(2) van Es MA, van den Berg LH. Alzheimer's disease beyond *APOE*. **Nat Genet** (2009).

(3) van Es MA, *et al*. Genome-wide association study identifies 19p13.3 (*UNC13A*) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. **Nat Gen** (2009).

(4) van Es MA, *et al*. Genetic variation in *DPP6* is associated with susceptibility to amyotrophic lateral sclerosis. **Nat Genet (**2008).

(5) van Es MA, *et al*. *ITPR2* as a susceptibility gene in sporadic amyotrophic lateral sclerosis: a genome-wide association study. **Lancet Neurol** (2007).