ESMI
European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative

Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3) is worldwide the most common autosomal dominantly inherited ataxia disorder. It is caused by expansion of polyglutamine encoding CAG repeats in the *ATXN3* gene. The encoded abnormally elongated protein encoded by *ATXN3*, ataxin-3, is considered to be the major cause of the disease. Consequently, gene silencing therapy approaches are highly promising. They are currently being developed by a number of pharmaceutical companies and will be tested in clinical trials within the near future. The principal goal of ESMI is to increase trial readiness by (1) setting up a longitudinal SCA3 cohort, (2) bringing together data from existing cohorts and (3) developing novel outcome markers.

The new longitudinal ESMI cohort comprises > 250 mutation carriers including > 50 pre-ataxic individuals and 100 matched controls. We are currently completing the 1st year follow-up visits and have already performed around 50 2nd year follow-up visits. The ESMI cohort is the largest and best characterized SCA3 cohort worldwide. More importantly, it is the first cohort that did systematic biosampling using standardized protocols. These materials allowed developing and validating new fluid biomarkers. Serum and plasma neurofilament light protein (NfL), a blood marker of axonal degeneration, was found to be strongly elevated in SCA3 patients compared to controls. Concentrations increased with age, repeat length and disease severity. Concentrations were also increased in pre-ataxic individuals indicating that neurodegeneration in SCA3 starts before the onset of ataxia.

We further developed a highly sensitive assay to measure the concentration of mutant ataxin-3 in body fluids. Mutant ataxin-3 was present in CSF and plasma of pre-ataxic and ataxic SCA3 mutation carriers, but not detectable in materials from healthy controls. Concentrations increased with disease severity. This assay will be extremely useful for therapeutic development, as it can serve as a target engagement biomarker in gene silencing trials. The ESMI cohort includes an MRI substudy. So far, we have obtained > 100 scans, which are currently being analysed with a particular focus on studying early impairment of white matter integrity. In an international effort that included 12 study sites worldwide we brought together > 320 existing MRI scans from ataxic and pre-ataxic SCA3 mutation carriers. Using a fully automated segmentation and volumetry pipeline, we identified a number of anatomical regions that undergo volume loss in SCA3.

Our results show a sequential order of atrophy development starting more than one decade before ataxia onset. In the pre-ataxia stage, atrophy affects the spinal cord, lower brainstem, cerebellar white matter and pallidum. In the cerebellar grey matter, first alterations occur in the motor-related anterior part, while other parts of the cerebellum lose volume only after onset of ataxia.
The clinical, biomarker and MRI data obtained in the ESMI project have allowed to develop a biomarker-based model of disease evolution in SCA3 that conceives the pre-ataxia stage and the ataxia stage as the graded manifestation of one disease process. According to this model, mutant ataxin-3 is constantly accumulating in the central nervous system of SCA3 mutation carriers. This initiates a clinically silent process of neurodegeneration which is detectable by the increase of neurodegeneration markers in blood and by volume loss in extracerebellar brain structures. The onset of cerebellar tissue loss roughly coincides with that of clinically manifest ataxia.