SCA Global

Concept for a worldwide platform for clinical research in spinocerebellar ataxias (SCAs)

Thomas Klockgether

February 2018

Background

The spinocerebellar ataxias (SCAs) are a group of autosomal dominantly inherited progressive ataxia disorders. More than 40 genetically different SCAs have been defined. The most common - SCA1, SCA2, SCA3 and SCA6, which together affect more than half of all families with a history of SCA - are caused by translated CAG repeat expansion mutations that code for an elongated polyglutamine tract within the respective proteins. Other SCAs are caused by non-repeat or by non-translated repeat mutations that affect a variety of different genes.

SCAs have a worldwide distribution, however with variable prevalence rates reported across the world. Despite the large heterogeneity of the various SCAs, people with SCA and their families are facing similar problems. Once started, ataxia takes a relentlessly progressive course leading to disability and often premature death. Ataxia is frequently accompanied by non-ataxia symptoms which considerably impact quality of life. Currently, there is no cure for any SCA. In fact, there are not even symptomatic medical treatments so that management of SCA patients has to rely on physical and speech therapy.

The need for a global initiative

Although a number of large longitudinal cohort studies, such as EUROSCA, RISCA, SPATAX or CRC-SCA provided valuable information on the disease characteristics and natural history of the common polyglutamine SCAs, there remain major knowledge gaps that preclude further progress towards development of effective therapies. Specifically, it is not known whether the longitudinal clinical data that have been obtained in European and North American cohorts are representative for patients from other world regions. Furthermore, the clinical characteristics of the less prevalent SCAs caused by non-repeat mutations remain largely undefined. There is also insufficient knowledge how the diseases impact on everyday life of affected people and their families. A major obstacle on the way towards successful therapeutic trials is the lack of validated biomarkers. The few biomarker studies that have been completed focussed on imaging and included only small patient numbers. Biochemical markers that will be of critical importance in future trials are completely lacking.

Currently, many clinical investigators worldwide are addressing these issues, but due to a lack of a common research infrastructure, clinical research in SCAs often remains fragmented. The JPND-funded ESMI and the NIH-U01 projects are first examples of international collaboration, and may thus serve as a starting point for more intense, global collaboration.

To deal with these multiple challenges, we present the concept of **SCA Global**, a worldwide initiative for clinical research in SCAs. SCA Global is conceived as a flexible and open research platform, with which we wish to pursue the following goals:

- To better understand the manifestation, evolution and impact of the various SCAs
- To develop and validate biomarkers which can be used in future interventional trials
- To facilitate access to people with SCAs who are willing to participate in clinical trials

Harmonization and standardization

As there are many researchers worldwide who are collecting data and materials of SCAs, but do not collaborate, there is an urgent need to define a common clinical assessment program, a standard imaging protocol and standards for biomaterial sampling and storage. The leading clinical investigators worldwide as well as ataxia lay organizations need to be involved in the standardization process. The goal will be to achieve the highest possible level of conformity and standardization but, on the other hand, to ensure continuity, wherever possible, to allow joint analysis of existing and newly acquired data.

Education and training

To ensure highest data quality, a training and education program will be implemented. The program includes the correct use of clinical scales, appropriate application of questionnaires and self-assessment tools, correct performance and quality control of imaging as well as standardized handling and storage of biomaterials. Training sessions will be offered at international meetings. In addition, we are currently developing an online training tool for clinical assessment that will be made available to all participants of SCA Global.

Database

Ideally, the core resource of SCA Global would be a worldwide registry of SCA patients and family members that enables collection of standardized longitudinal clinical data, provides information about available imaging data and biomaterials, and allows to identify patients who are willing to participate in trials.

In the framework of the ESMI project, we built the **SCA Registry**, a secure web-based data capture system and database which was developed by 2mt Software GmbH (Ulm, Germany). The SCA Registry contains all data of the EUROSCA and RISCA study as well as of the ongoing ESMI project. Currently, we are importing data from the CRC-SCA study and the international SPATAX database. The SCA Registry was devised with the intention to make it available to clinical investigators worldwide. It can be accessed through the internet, is easy to use, and encompasses the entire spectrum of SCAs.

Although, the existing SCA Registry will be an extremely valuable resource of SCA Global, use of this database is not a requirement for participation in SCA Global. If investigators are using functional and secure own databases, they will have the opportunity to continue their own database, provided that they follow the agreed common protocols and are willing to share data.

Website

A second essential resource that needs to be created is a website that provides comprehensive information about SCAs including current news on scientific developments and ongoing studies for people with SCAs and for health professionals. As additional instruments that will be specifically devised to facilitate enrollment in clinical trials we will create a trial finder and provide a trial site registry. The internal area of the website will provide access to assessment protocols and training material.

Participation, governance and institutional framework

Participants of SCA Global include lay organizations and clinical investigators representing study sites. The endorsement of the project by the people with SCA is essential. Lay organizations will therefore have an important role in SCA Global and will be represented in all panels. They will be encouraged to use SCA Global as a platform to promote studies that emphasize the patient view and investigate the everyday consequences of being affected by SCA. There will be no limitations for participation of clinical investigators and clinical sites provided that they have expertise documented by a dedicated clinical program involving an appropriate number of patients and by research experience.

To enable SCA Global, we will agree on a transparent and democratic governance structure that includes affected people and clinical investigators. Written regulations will guarantee that all investigators have full and unlimited access to their own data and materials, and that decisions about use of data and materials of more than one investigator or the entire consortium are only made in a transparent way by the appropriate democratically legitimized panel. To facilitate exchange of data and materials, SCA Global participants will agree on lean, research friendly administrative processes including common consent forms and standardized data and material transfer agreements.