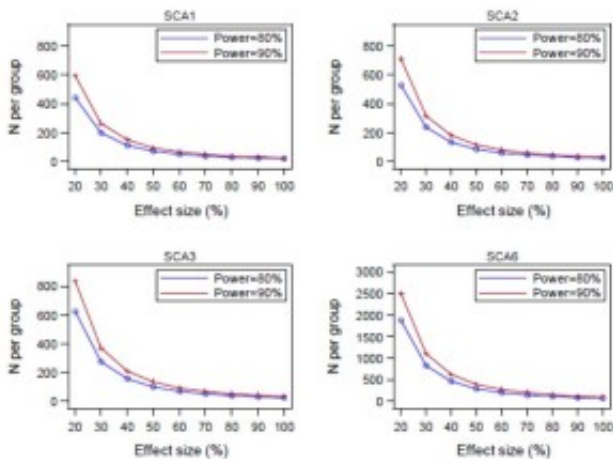


## Natural history of spinocerebellar ataxias

The spinocerebellar ataxias (SCAs) are autosomal, dominantly inherited progressive ataxia disorders. More than 35 genetically different SCAs have been defined. The most common, SCA1, SCA2, SCA3, and SCA6, which together affect more than half of all families with dominantly inherited ataxia, are caused by translated CAG repeat expansions, a specific type of mutation that results in the formation of abnormal proteins that contain elongated polyglutamine tracts. Clinically, they are characterised by progressive unsteadiness of gait and stance, impaired coordination of limb movements, slurred speech and abnormal eye movements. These symptoms are the result of cerebellar degeneration that is typically accompanied by degeneration of other parts of the central and peripheral nervous system in SCA1, SCA2, and SCA3, but not in SCA6. In SCA1, SCA2, and SCA3, ataxia typically manifests in the fourth decade, whereas the onset of ataxia in SCA6 is approximately 20 years later. In all four genotypes, ataxia leads to severe disability and often premature death.

Currently, there is no cure for SCAs. However, as the mechanisms causing these diseases are increasingly better understood, potential treatments for SCAs are being developed. To enable future clinical trials, there is a need to characterise the natural history of SCAs by assessing the functional decline in each type and to identify factors that determine disease progression. To address these issues we initiated in 2005 the EUROSCA natural history study, a European multicentre longitudinal cohort study of 526 patients with SCA1, SCA2, SCA3 or SCA6. We assessed participants with the Scale for the Assessment and Rating of Ataxia (SARA) which measures the severity of ataxia, and the Inventory of Non-Ataxia Signs (INAS) which allows to estimate the non-cerebellar involvement in these diseases.



Sample size calculation

Of the 526 patients enrolled, 462 who had at least one follow-up visit were analysed. These patients had a median number of 5 study visits and a median observation time of 49 months. Patients with a longer disease duration, more severe ataxia and stronger non-cerebellar involvement at baseline had a higher risk to drop out of the study. In all four genotypes, the severity of ataxia increased linearly. The increase was greatest in SCA1 followed by SCA2 and SCA3, between which progression rate did not differ, and SCA6. In contrast, the INAS score reflecting non-cerebellar involvement reached a plateau in SCA1, SCA2, and SCA3. In SCA6, the INAS score was lower and increased linearly, but more slowly than in SCA1, SCA2, and SCA3. Factors that predicted faster progression of ataxia were older age at inclusion and longer repeat expansions in SCA1, lower age at onset and lower baseline SARA score in SCA2, and lower baseline SARA score in SCA6. In SCA3, we did not identify factors that influenced progression of ataxia. Lower age of onset was a predictor of a faster increase of non-cerebellar involvement in SCA1, SCA2, and female SCA3 patients. In SCA1, SCA2, and SCA6, a lower INAS score was associated with a faster increase of this score. Sample size calculation showed that a 1-year interventional trial with 142 SCA1, 172 SCA2, 202 SCA3, or 602 SCA6 patients would be able to detect a 50% reduction in progression of the SARA score in the respective genotype.

Our analysis of the EUROSCA cohort allows new insights into the evolution of SCA1, SCA2, SCA3, and SCA6 based on a follow-up period that exceeds those of previous studies. The data provide useful information for the design of interventional trials in these disorders.

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## Publication

[Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study.](#)

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*Lancet Neurol.* 2015 Sep 11