**Staging of Brain Degeneration in Spinocerebellar Ataxia Types 2 and 3: MRI Analysis from ENIGMA-Ataxia**

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**Introduction**

Spinocerebellar ataxias (SCAs) are rare genetic disorders that result in loss of motor coordination due to progressive atrophy preferentially targeting the spinal cord, cerebellum, and brainstem. Historically, neuroimaging studies of SCAs have relied on relatively small samples due to their rarity, limiting statistical power, generalisability, and characterisation of inter-individual variability. The ENIGMA-Ataxia working group addresses these limitations by aggregating MRI data from SCA cohorts worldwide to perform large-scale, well-powered inference of brain atrophy in these rare diseases.

**Methods**

Structural MRI, demographic, and clinical data were collected from 14 global partner sites and two partner consortia. The final dataset contained 128 SCA2 subjects with 110 age- and sex-matched healthy controls; and 339 SCA3 subjects with 276 controls. Whole-brain assessments of regional brain volume changes in the SCA2 and SCA3 cohorts were undertaken relative to the control groups. Stratified analyses were then undertaken in five subgroups defined by ataxia severity.

**Results**

In both SCA2 and SCA3, the earliest and largest magnitude of atrophy occurred in the cerebellar white matter (WM) and brainstem, especially the pons. Many key white matter tracts linking the spine, cerebellum, and cerebrum were also heavily affected. Atrophy was also evident throughout the cerebellar grey matter (GM) in both diseases, although lower in intensity compared to the WM.

Substantial differences between SCA2 and SCA3 were observed in the stratified WM analysis. In SCA2, WM atrophy is first evident in the cerebellar WM and pons in the pre-ataxic stage, progressively expanding over worsening disease stages to encompass the cerebellar-cerebral pathways. By contrast, in SCA3, the WM atrophy also begins in the cerebellum and brainstem, and becomes more severe in these areas, but does not progressively expand with disease severity. Meanwhile, GM loss in both SCA2 and SCA3 progressively encompassed the entire cerebellum; cerebral involvement was sparse in both diseases.

**Conclusions**

This study represents the first results from a long-term project to better characterize and understand common SCA disorders. We have found that, while the principal involvement of the cerebellum and brainstem is unsurprisingly common to both disorders, the progression and pattern varied considerably between them.