Genetic architecture of MRI-derived cervical spinal cord morphology reveals sensory-motor axis and systemic disease biomarkers

Zhuopin Sun, Jiru Han, Zachary F Gerring, Victoria E. Jackson, Oneil G Bhalala, Gustavo M Jarola, Ian H. Harding, Thiago J.R. Rezende, Melanie Bahlo

The spinal cord is critical to motor, sensory, autonomic function, and increasingly implicated in neurological disease and human health, yet its genetic architecture remains largely unexplored. We performed the first large-scale phenotyping of the upper cervical spinal cord (C1-C3) structure using brain magnetic resonance imaging from over 40,000 UK Biobank participants, extracting shape metrics including cross-sectional area, diameters, and eccentricity using an AI-based protocol. We identified a total of 179 independent genome-wide significant variants, with cervical spinal cord morphology showing moderate to high SNP-based heritability (0.16 to 0.42). We also uncovered sex-specific genetic signals, highlighting potential biological sex differences in spinal cord development. In addition, spinal cord structure was associated with a wide range of neurological, metabolic, and systemic conditions, such as multiple sclerosis, neuropathies, diabetes, and attention-deficit/hyperactivity disorder. PRS were constructed for the remainder of the UKBB and tested for trait association, validating many of the findings with the AI-derived MRI spinal cord metrics. These findings establish the cervical spinal cord as a genetically informative and health relevant structure, offering new opportunities to study its role in disease mechanisms and human health.