iAXON-Brazil-HSP network: building a trial-ready national cohort for hereditary spastic paraplegias in the Global South

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Hereditary spastic paraplegias (HSPs) are a heterogeneous group of genetic neurodegenerative disorders comprising more than 90 subtypes that share a core phenotype of progressive lower limb weakness and spasticity due to length-dependent degeneration of the corticospinal tract.[1] Clinical severity, age of onset, and longitudinal progression are highly variable, with the most frequent subtypes typically following a very slowly progressive course.[2,3]

A therapeutic shift is underway in monogenic diseases, with recent regulatory approvals of disease-modifying therapies for motor neuron disorders such as spinal muscular atrophy and amyotrophic lateral sclerosis.[4,5] For HSP, an upper motor neuron disease, therapeutic development remains at an early stage, including recent N-of-1 trials using gene therapy[6] and antisense oligonucleotides.[7] Despite these advances, the natural history and pathophysiology of many HSP subtypes remain incompletely understood, largely due to the rarity of the condition and its marked heterogeneity. To mitigate these challenges, standardized evaluation protocols and centralized biorepositories have been developed, and dedicated trial-ready research networks have been established to advance HSP research in both Europe (ClinicalTrials.gov identifier: NCT03981276) and the United States.[8]

Brazil has historically contributed to collaborative and multicentric HSP research, which enabled the creation of the Inherited AXOnopathies translational research Network—Hereditary Spastic Paraplegias Brazil (iAXON-Brazil-HSP). The Network was designed to characterize the natural history of HSPs; identify fluid, neuroimaging, and digital biomarkers; validate clinical outcome assessments (COAs); and establish a national registry and biorepository within a trial-readiness framework in a population from the Global South (Fig. 1) that has been historically underrepresented in translational and clinical research.

The iAXON-Brazil-HSP Network is a multicenter, longitudinal study with a planned duration of at least five years and annual follow-up assessments. A case–control design is implemented within the biomarker subproject, with controls recruited at baseline. Clinical and genetic data are collected through a shared database using a standardized Case Report Form (CRF). Detailed information regarding the Network's governance, operational planning, and core procedures, including the CRF, is provided in the Appendix.

The Network currently comprises seven centers distributed across four Brazilian regions. Between April 2024 and December 2025, 155 patients and 29 controls were enrolled, forming an initial cohort suitable for preliminary analyses. Continued expansion is expected over the next few years, with the goal of enrolling at least 300 patients by 2027. Since 2024, Network projects have received approximately BRL 2,000,000 (USD 357,000) from national and regional public funding agencies, covering overlapping periods between December 2024 and December 2028. These grants support longitudinal phenotyping, genomic studies, and translational initiatives. Notably, all funding obtained up to submission derives from Brazilian governmental sources, representing a significant national investment in rare disease research.

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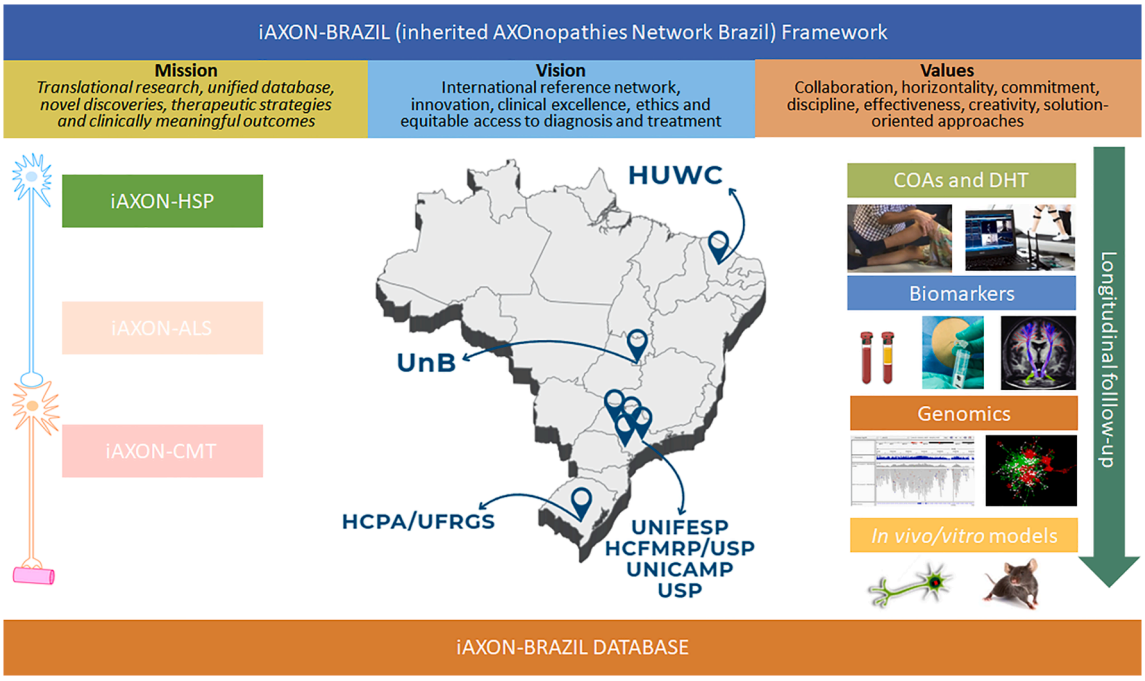

Fig. 1: **iAXON-Brazil-HSP framework and geographic distribution of participating centers.** The iAXON-HSP cores are highlighted, as the present project refers exclusively to this branch of the collaboration. Acronyms displayed on the map correspond to the institutional names of each participating site within the network. ALS, amyotrophic lateral sclerosis; CMT, Charcot–Marie–Tooth disease; COAs, clinical outcome assessments; DHTs, Digital Health Technologies; HSP, hereditary spastic paraplegia.

The establishment of a Brazilian HSP network addresses important global disparities in neurogenetic research. Although HSPs affect individuals across continents and ethnicities, most data on genetics, natural history, and experimental models originate from high-income countries in the Global North.[1,2,8] As observed in other neurogenetic conditions, Latin American populations remain underrepresented in genomic research. This underrepresentation is particularly concerning given the marked genetic diversity of Latin American populations, which differ substantially from European and North American cohorts and may harbor region-specific variants or subtypes.[9]

Despite Brazil's strong academic and healthcare institutions, socioeconomic inequities limit access to specialized care for a significant portion of the population. Although governmental efforts to strengthen rare disease policies have intensified in recent years, structural limitations persist. A recent publication in The Lancet Regional Health—Americas emphasized the importance of national registries and coordinated research strategies to overcome such barriers in Latin America.[10] In this context, iAXON-Brazil-HSP provides a structured framework to enhance awareness, standardize evaluations, and foster integration between research and public health systems.

Beyond infrastructure, the Network has rapidly positioned itself among the largest coordinated HSP initiatives worldwide. Public funding supports not only longitudinal clinical characterization but also genomic and translational projects aimed at identifying novel subtypes and generating preclinical data for advanced therapies (Fig. 1). These efforts demonstrate that countries in the Global South can generate high-impact research and contribute meaningfully to therapeutic development in rare diseases.

The network's initial sample size already exceeds that of most single-center studies,[3] preliminarily demonstrating the feasibility of recruiting substantial cohorts, with greater potential for biomarker characterization, validation of sensitive clinical outcome assessments (COAs), and implementation of digital health technologies. Collectively, these advances position Brazil as a developer, rather than merely a participant, in future global HSP clinical trials. The collaborative model developed within the iAXON-Brazil-HSP framework may also serve as a template for other rare neurogenetic disorders, underscoring the value of integrated, multidisciplinary, and nationally coordinated research strategies in the Global South.

Contributors

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AI use statement

English language revision and Supplementary Figures S2–S4 were performed with the assistance of an artificial intelligence language model developed by OpenAI (GPT-5.2).

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

All authors reported no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2026.101455.

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