CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

The Spastic Paraplegia–Centers of Excellence Research Network (SP-CERN)

Clinical Trial Readiness for Hereditary Spastic Paraplegia

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Neurol Genet 2025;11:e200249. doi:10.1212/NXG.0000000000200249

Abstract

Objectives

The primary objective of this paper was to present the establishment of the Spastic Paraplegia–Centers of Excellence Research Network (SP-CERN) aimed at promoting clinical trial readiness for hereditary spastic paraplegia (HSP). SP-CERN is unique in its approach to addressing the diagnostic and therapeutic challenges associated with HSP through a large-scale, collaborative effort.

Methods

Participants with HSP are identified through multicenter collaborations across 11 institutions in the United States. SP-CERN systematically collects longitudinal clinical data, biospecimens, and wearable device data from patients. Data are stored in a centralized REDCap database, facilitating shared access for analysis. Patients are evaluated using standardized assessment tools for motor function, biomarkers, and digital outcome measures.

Results

SP-CERN has established a biorepository, centralized data collection methods, and standardized clinical assessments. It is conducting natural history studies for all HSP subtypes, enabling the validation of biomarkers and development of gene-based therapies.

Discussion

SP-CERN's collaborative approach bridges gaps in clinical care and research for HSP by improving diagnostic capabilities and promoting clinical trial readiness. This initiative represents a framework for rare disease research, accelerating the development of novel therapies and improving patient outcomes through standardized, multi-institutional collaboration.

Spastic Paraplegia–Centers of Excellence Research Network

Neurodegenerative disorders are largely untreatable[1] and cause significant personal health and societal burden.[1] Recent advances in molecular understanding of conditions with strong genetic causality are yielding remarkable progress in therapy development.[2] For example, improved gene vector delivery methods and the emergence of platform technologies for DNA and RNA

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manipulation have enabled the introduction of gene-specific and variant-specific treatments for several monogenic diseases, including spinal muscular atrophy, giant axonal neuropathy, amino acid decarboxylase deficiency, and forms of amyotrophic lateral sclerosis.[2-6] A logical extension of this spectrum of neurogenetic disorders is hereditary spastic paraplegia (HSP).[7,8]

HSP encompasses more than 80 rare monogenic disorders and collectively constitutes the most common cause of inherited spasticity worldwide, with an estimated combined prevalence of 5–10 cases per 100,000 individuals.[7,8] Dysfunction particularly affecting the distal ends of corticospinal tract axons underlies functional motor disabilities, not only for the most common type of HSP, hereditary spastic paraplegia type 4 (SPG4), but also for several other subtypes.[9,10] Nearly all our specific understanding of HSP pathophysiology has arisen from identifying causative genes and reliably classifying pathogenic variants.[11] Despite remarkable advances in next-generation sequencing, however, approximately 30%–40% of patients with HSP still do not receive a genetic diagnosis.[12] This underscores the need for additional diagnostic methods, including in-depth sequencing and other innovative approaches.[12-16] Recent improvements in long-read genome sequencing are likely to uncover new HSP loci that remain inaccessible to short-read analyses. There are an increasing number of prominent examples of noncoding or highly homologous genomic loci that explain diseases leading to a length-dependent distal axonal degeneration.[17,18]

Another area of considerable interest is the identification of genetic modifying factors. Recent studies on SPG4 have uncovered the first such loci, with more anticipated due to the remarkable phenotypic variability observed in many HSP genes.[19-22] Drawing from the successes of the past decade, genetic studies must adopt multicenter approaches, embrace data sharing, and standardize analysis pipelines to bridge the diagnostic gap and deepen our understanding of the underlying genetic mechanisms of these diseases.

In the United States, investigators working independently or in small scale collaborations have made seminal contributions to our knowledge of HSPs, including the description of cross-sectional clinical data, discovery of novel genetic causes, development of animal models, and elucidation of the molecular biology of HSP-associated proteins.[21,23-28] This scientific foundation paves the way for the development of clinical trials for HSP, necessitating a new level of interinstitutional collaboration for subject recruitment, natural history studies, and standardized assessment methods.

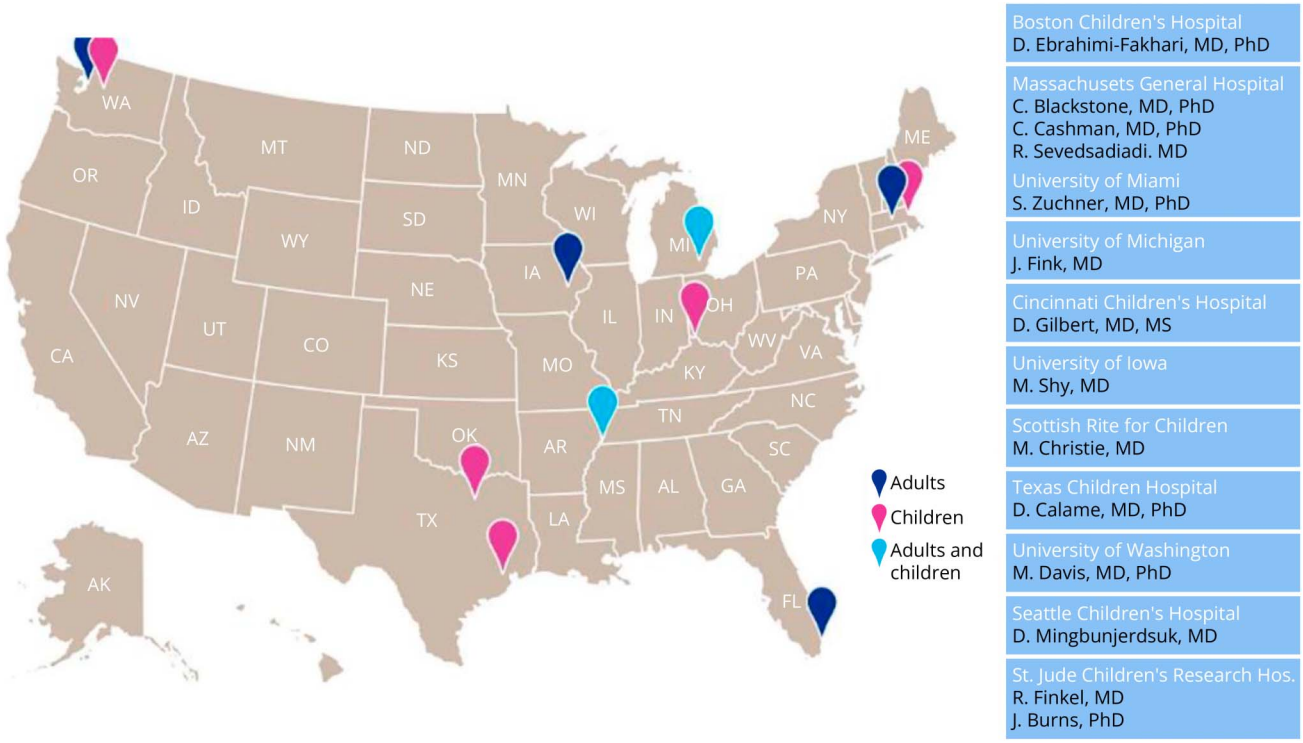
To address this need, we recently established the Spastic Paraplegia–Centers of Excellence Research Network (SP-CERN). The goals of SP-CERN are to support the systematic and rational development of disease-modifying treatments. SP-CERN aims to (1) conduct natural history studies of HSP subtypes, (2) establish and validate biomarkers as well as patient-reported and clinician-reported and digital outcome measures, (3) elucidate the molecular pathophysiology of HSP and develop rational therapeutic targets, and (4) conduct adequately powered clinical trials. These objectives are achievable with existing technology, but only through a large-scale consortium of investigators working collaboratively.

Systematically conducting natural history studies for major subtypes of HSP in accordance with regulatory agency guidance are invaluable for establishing therapeutic trial readiness. This is a challenging endeavor, considering there are more than 80 genetic etiologies of HSP identified to date, some of which are extremely rare, and each requires longitudinal evaluation. Currently, no approved therapies exist for HSP that halt or slow disease progression. Given that the delivery of therapeutic cargo to motor neurons has been successful in other motor neuron diseases, gene-based therapies for HSP are not only feasible but are already in development for SPG50, a rare childhood-onset form of HSP.[9,27,29-31]

SP-CERN uses standardized assessment methods, a centralized database, shared biobanking, and the capacity to recruit adult and pediatric participants at centers throughout the United States (Figure). Standardized retrieval and storage of longitudinal clinical data from patients and caregivers is facilitated by a shared central REDCap database.[32,33] This model draws on the experiences of the International Registry and Natural History Study for Early-Onset HSP (ClinicalTrials.gov Identifier: NCT04712812), the TREAT-HSP network (ClinicalTrials.gov Identifier: NCT03981276), and the RDCRN-Inherited Neuropathy Consortium (ClinicalTrials.gov Identifier: NCT01193075). A biorepository is being developed to bank materials, including blood, serum, RNA, DNA, and other biospecimens. To characterize and validate digital surrogates of gait and balance, SP-CERN will leverage wearable devices to monitor activity and movements. Two specific subgoals have been defined: (1) to characterize habitual inactivity in patients with HSP using a wearable sensor device at home and (2) to validate wearable inertial sensors that measure gait and balance in young children with HSP, assessing their sensitivity and responsiveness during established timed motor function tests. This initiative aims to understand the real-world physical activity of individuals with different HSP subtypes and the effect of disease progression on habitual inactivity, with the intention of implementing these outcome measures as digital biomarkers in clinical trials.

HSP is a group of genetically heterogeneous conditions, making genomic data aggregation and the development of analytical tools, including in silico prediction models and high-throughput functional assays, crucial for improving the classification of Variants of Uncertain Significance. To achieve this, we will use the GENESIS database, which already contains sharable genome-level data from more than 2,000 patients with HSP.[34] Standardized data and sample collections will greatly accelerate progress and serve as a reliable resource for future sponsored clinical trials.

Figure Overview of the Spastic Paraplegia–Centers of Excellence Research Network



Multidisciplinary teams at 11 institutions across the United States support the initial phase of the Spastic Paraplegia–Centers of Excellence Research Network (SP-CERN). The institution and site investigators are indicated. Centers for children and young adults with HSP are indicated in magenta. Centers for adults with HSP are indicated in blue. For more information, visit spcern.childrenshospital.org.

Collaborative research into HSP is essential for establishing comprehensive programs that advance diagnostic progress and clinical trial readiness, ultimately supporting the development of novel therapeutic approaches. Challenges in HSP research, as in many rare disease investigations, include a geographically dispersed and small patient population, lack of diversity limiting generalizability, limited availability of disease experts, a lack of harmonization among existing research protocols, and diverging requirements from individual Institutional Review Board (IRB) protocols. These challenges highlight the urgent need for a consortium and international collaboration within the scientific community. Supported by seed funding, SP-CERN has assembled a team of experts who have significantly contributed to the clinical and molecular understanding of HSP.[9,16,22,24-28,35-46] During the initial 2-year period, SP-CERN has created a shared IRB protocol, finalized reliance agreements with collaborative sites, built a REDCap database, and established clinician-reported and patient-reported outcome measures. Over a 2-year pilot phase, SP-CERN aims to enroll 100 patients with childhood-onset and adult-onset HSP. Following this period, the consortium will be prepared for additional collaborators to join as we work to enhance clinical trial readiness. Efforts are also underway to harmonize HSP research methods in the United States with those in Europe, Asia, South America, and Oceania, thereby accelerating global HSP research. An International Liaison Committee will coordinate international collaborative initiatives. Data collection will be standardized through a shared study protocol, established CROMs and PROMs, and the uniform structure of the REDCap database. Recognizing the essential role of patient perspectives in guiding research, SP-CERN will continue to collaborate closely with patient advocacy groups (PAGs) to assist in identifying participants for enrollment in SP-CERN, particularly for rare forms of HSP, and to maintain focus on issues important to the patient community. Patient participation will be ensured through the involvement of PAGs in administrative committees and their attendance at monthly SP-CERN meetings. This will facilitate the inclusion of patients' perspectives and raise awareness of the needs within the patient communities. The backbone of SP-CERN is an administrative unit, which consists of 5 groups: (1) a central administrative core; (2) an internal advisory board; (3) an external advisory committee; (4) the international liaison, diversity liaison, and clinical trials committee; and (5) a working group for gene-based therapies. These groups will collaborate to maximize the quality and productivity of SP-CERN.

In summary, SP-CERN aims to establish critical research infrastructure for collaborative, high-quality research on HSP in the United States and internationally, with the goal of developing frameworks for the advancement of novel therapies for HSP and the progression of rare disease research more broadly.[43,47]

Acknowledgment

The authors thank their patients and their families for supporting research and education on hereditary spastic paraplegia.

Author Contributions

L. Schierbaum: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. V. Quiroz: drafting/revision of the manuscript for content, including medical writing for content. K. Yang: drafting/revision of the manuscript for content, including medical writing for content. J. Rong: drafting/revision of the manuscript for content, including medical writing for content. N. Battaglia: drafting/revision of the manuscript for content, including medical writing for content. U. Zubair: drafting/revision of the manuscript for content, including medical writing for content. M. Christie: drafting/revision of the manuscript for content, including medical writing for content. marie davis: drafting/revision of the manuscript for content, including medical writing for content. D. Calame: drafting/revision of the manuscript for content, including medical writing for content. M.C. Danzi: drafting/revision of the manuscript for content, including medical writing for content. R.S. Finkel: drafting/revision of the manuscript for content, including medical writing for content. J. Burns: drafting/revision of the manuscript for content, including medical writing for content. D.L. Gilbert: drafting/revision of the manuscript for content, including medical writing for content. D. Mingbunjerdsuk: drafting/revision of the manuscript for content, including medical writing for content. G. Pruitt: drafting/revision of the manuscript for content, including medical writing for content. N. Pruitt: drafting/revision of the manuscript for content, including medical writing for content. J. Cobb: drafting/revision of the manuscript for content, including medical writing for content. R. Sadjadi: drafting/revision of the manuscript for content, including medical writing for content. C.R. Cashman: drafting/revision of the manuscript for content, including medical writing for content. C. Blackstone: drafting/revision of the manuscript for content, including medical writing for content. J.K. Fink: drafting/revision of the manuscript for content, including medical writing for content. M.E. Shy: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Zuchner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D. Ebrahimi-Fakhari: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The SP-CERN Pilot Study is supported by the Spastic Paraplegia Foundation.

Disclosure

L. Schierbaum was supported by a fellowship from the German Research Foundation (536105452). V. Quiroz reports a fellowship from the Movement Disorders Society—Pan America Section. C. Cashman was supported by the Johns Hopkins Merkin Peripheral Neuropathy and Nerve Regeneration Center and American Neuromuscular Foundation. J.K. Fink gratefully acknowledges support from the Paul and Lois Katzman Family and the Gao Hai-Feng family. D. Ebrahimi-Fakhari has received research funding from the NIH/NINDS, CureAP4 Foundation, CureSPG50 Foundation, Spastic Paraplegia Foundation, Tom Wahlig Foundation, Un raggio di Sole per Martina, Manton Center for Orphan Disease Research, BCH Office of Faculty Development, and BCH Translational Research Program and Astellas Pharmaceuticals. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* September 26, 2024. Accepted in final form January 21, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Alexandra Durr, MD, PhD.

References

1. Van Schependom J, D'Haeseleer M. Advances in neurodegenerative diseases. *J Clin Med*. 2023;12(5):1709. doi:10.3390/jcm12051709
2. Sun J, Roy S. Gene-based therapies for neurodegenerative diseases. *Nat Neurosci*. 2021;24(3):297-311. doi:10.1038/s41593-020-00778-1
3. Pena SA, Iyengar R, Eshraghi RS, et al. Gene therapy for neurological disorders: challenges and recent advancements. *J Drug Target*. 2020;28(2):111-128. doi:10.1080/1061186X.2019.1630415
4. Bharucha-Goebel DX, Todd JJ, Saade D, et al. Intrathecal gene therapy for giant axonal neuropathy. *N Engl J Med*. 2024;390(12):1092-1104. doi:10.1056/NEJMoa2307952
5. Pearson TS, Gupta N, San Sebastian W, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons. *Nat Commun*. 2021;12(1):4251. doi:10.1038/s41467-021-24524-8
6. Roubertie A, Opladen T, Brennenstuhl H, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency: requirements for safe application and knowledge-generating follow-up. *J Inherit Metab Dis*. 2024;47(3):463-475. doi:10.1002/jimd.12649
7. Murala S, Nagarajan E, Bollu PC. Hereditary spastic paraplegia. *Neurol Sci*. 2021;42(3):883-894. doi:10.1007/s10072-020-04981-7
8. Martinuzzi A, Blackstone C, O'Kane CJ, Stevanin G. Editorial: hereditary spastic paraplegias: at the crossroads of molecular pathways and clinical options. *Front Neurosci*. 2021;15:708642. doi:10.3389/fnins.2021.708642
9. Blackstone C. Importance of genetic testing for childhood-onset hereditary spastic paraplegia. *Dev Med Child Neurol*. 2023;65(3):307-308. doi:10.1111/dmcn.15416
10. Meyyazhagan A, Orlacchio A. Hereditary spastic paraplegia: an update. *Int J Mol Sci*. 2022;23(3):1697. doi:10.3390/ijms23031697
11. Lallemant-Dudek P, Durr A. Clinical and genetic update of hereditary spastic paraparesis. *Rev Neurol (Paris)*. 2021;177(5):550-556. doi:10.1016/j.neurol.2020.07.001
12. Shi Y, Wang A, Chen B, et al. Clinical features and genetic spectrum of patients with clinically suspected hereditary progressive spastic paraplegia. *Front Neurol*. 2022;13:872927. doi:10.3389/fneur.2022.872927
13. Ho NJ, Chen X, Lei Y, Gu S. Decoding hereditary spastic paraplegia pathogenicity through transcriptomic profiling. *Zool Res*. 2023;44(3):650-662. doi:10.24272/j.issn.2095-8137.2022.281
14. Saputra L, Kumar KR. Challenges and controversies in the genetic diagnosis of hereditary spastic paraplegia. *Curr Neurol Neurosci Rep*. 2021;21(4):15. doi:10.1007/s11910-021-01099-x

15. Bis-Brewer DM, Zuchner S. Perspectives on the genomics of HSP beyond mendelian inheritance. *Front Neurol*. 2018;9:958. doi:10.3389/fneur.2018.00958
16. Fink JK, Heiman-Patterson T, Bird T, et al. Hereditary spastic paraplegia: advances in genetic research. Hereditary Spastic Paraplegia Working group. *Neurology*. 1996; 46(6):1507-1514. doi:10.1212/wnl.46.6.1507
17. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011;72(2):245-256. doi:10.1016/j.neuron.2011.09.011
18. Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. *Nat Genet*. 2019;51(4):649-658. doi: 10.1038/s41588-019-0372-4
19. Parodi L, Fenu S, Barbier M, et al. Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. *Brain*. 2018;141(12):3331-3342. doi: 10.1093/brain/awy285
20. Lallemant-Dudek PM, Parodi LP, Coarelli GM, et al. Individual perception of environmental factors that influence lower limbs spasticity in inherited spastic paraparesis. *Ann Phys Rehabil Med*. 2023;66(6):101732. doi:10.1016/j.rehab.2023.101732
21. Mo A, Saffari A, Kellner M, et al. Early-onset and severe complex hereditary spastic paraplegia caused by de novo variants in SPAST. *Mov Disord*. 2022;37(12): 2440-2446. doi:10.1002/mds.29225
22. Akçakaya NH, Özeş Ak B, Gonzalez MA, Züchner S, Battaloğlu E, Parman Y. Clinical and genetic aspects of hereditary spastic paraplegia in patients from Turkey. *Neurol Neurochir Pol*. 2020;54(2):176-184. doi:10.5603/PJNNS.a2020.0026
23. Siow SF, Yeow D, Rudaks LI, et al. Outcome measures and biomarkers for clinical trials in hereditary spastic paraplegia: a scoping review. *Genes (Basel)*. 2023;14(9): 1756. doi:10.3390/genes14091756
24. Fink JK, Rainier S. Hereditary spastic paraplegia: spastin phenotype and function. *Arch Neurol*. 2004;61(6):830-833. doi:10.1001/archneur.61.6.830
25. Alecu JE, Ohmi Y, Bhuiyan RH, et al. Functional validation of novel variants in B4GALNT1 associated with early-onset complex hereditary spastic paraplegia with impaired ganglioside synthesis. *Am J Med Genet A*. 2022;188(9):2590-2598. doi:10.1002/ajmg.a.62880
26. Alecu JE, Saffari A, Jordan C, Srivastava S, Blackstone C, Ebrahimi-Fakhari D. De novo variants cause complex symptoms in HSP-ATL1 (SPG3A) and uncover genotype-phenotype correlations. *Hum Mol Genet*. 2023;32(1):93-103. doi:10.1093/hmg/ddac182
27. Behne R, Teinert J, Wimmer M, et al. Adaptor protein complex 4 deficiency: a paradigm of childhood-onset hereditary spastic paraplegia caused by defective protein trafficking. *Hum Mol Genet*. 2020;29(2):320-334. doi:10.1093/hmg/ddz310
28. Blackstone C. Converging cellular themes for the hereditary spastic paraplegias. *Curr Opin Neurobiol*. 2018;51:139-146. doi:10.1016/j.conb.2018.04.025
29. Davies AK, Alecu JE, Ziegler M, et al. AP-4-mediated axonal transport controls endocannabinoid production in neurons. *Nat Commun*. 2022;13(1):1058. doi: 10.1038/s41467-022-28609-w
30. Saffari A, Brechmann B, Böger C, et al. High-content screening identifies a small molecule that restores AP-4-dependent protein trafficking in neuronal models of AP-4-associated hereditary spastic paraplegia. *Nat Commun*. 2024;15(1):584. doi: 10.1038/s41467-023-44264-1
31. Byrne DJ, Garcia-Pardo ME, Cole NB, et al. Liver X receptor-agonist treatment rescues degeneration in a Drosophila model of hereditary spastic paraplegia. *Acta Neuropathol Commun*. 2022;10(1):40. doi:10.1186/s40478-022-01343-6
32. Paul A Harris RT, Thielke Robert, Payne Jonathon, Gonzalez Nathaniel, Conde JoseG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
33. Harris PA, Taylor R, Minor BL, et al.; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
34. Gonzalez M, Falk MJ, Gai X, Postrel R, Schule R, Zuchner S. Innovative genomic collaboration using the GENESIS (GEM.app) platform. *Hum Mutat*. 2015;36(10): 950-956. doi:10.1002/humu.22836
35. Ebrahimi-Fakhari D, Saffari A, Pearl PL. Childhood-onset hereditary spastic paraplegia and its treatable mimics. *Mol Genet Metab*. 2022;137(4):436-444. doi:10.1016/j.ymgme.2021.06.006
36. Saffari A, Kellner M, Jordan C, et al. The clinical and molecular spectrum of ZFYVE26-associated hereditary spastic paraplegia: SPG15. *Brain*. 2023;146(5): 2003-2015. doi:10.1093/brain/awac391
37. Blackstone C. Cellular pathways of hereditary spastic paraplegia. *Annu Rev Neurosci*. 2012;35:25-47. doi:10.1146/annurev-neuro-062111-150400
38. Zuchner S. The genetics of hereditary spastic paraplegia and implications for drug therapy. *Expert Opin Pharmacother*. 2007;8(10):1433-1439. doi:10.1517/14656566.8.10.1433
39. Zuchner S, Kail ME, Nance MA, et al. A new locus for dominant hereditary spastic paraplegia maps to chromosome 2p12. *Neurogenetics*. 2006;7(2):127-129. doi: 10.1007/s10048-006-0029-1
40. Zuchner S, Wang G, Tran-Viet KN, et al. Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31. *Am J Hum Genet*. 2006; 79(2):365-369. doi:10.1086/505361
41. Jerath NU, Grider T, Shy ME. Progressive lower extremity weakness and axonal sensorimotor polyneuropathy from a mutation in KIF5A (c.611G>A;p.Arg204Gln). *Case Rep Genet*. 2015;2015:496053. doi:10.1155/2015/496053
42. Minnerop M, Kurzwelly D, Wagner H, et al. Hypomorphic mutations in POLR3A are a frequent cause of sporadic and recessive spastic ataxia. *Brain*. 2017;140(6): 1561-1578. doi:10.1093/brain/awx095
43. Reilly MM, Herrmann DN, Pareyson D, et al. Trials for slowly progressive neurogenetic diseases need surrogate endpoints. *Ann Neurol*. 2023;93(5):906-910. doi: 10.1002/ana.26633
44. Beecroft SJ, McLean CA, Delatycki MB, et al. Expanding the phenotypic spectrum associated with mutations of DYNC1H1. *Neuromuscul Disord*. 2017;27(7):607-615. doi:10.1016/j.nmd.2017.04.011
45. Krumm L, Pozner T, Zagha N, et al. Neuroinflammatory disease signatures in SPG11-related hereditary spastic paraplegia patients. *Acta Neuropathol*. 2024;147(1):28. doi: 10.1007/s00401-023-02675-w
46. Calame DG, Herman I, Maroofian R, et al. Biallelic variants in the ectonucleotidase ENTPD1 cause a complex neurodevelopmental disorder with intellectual disability, distinct white matter abnormalities, and spastic paraplegia. *Ann Neurol*. 2022;92(2): 304-321. doi:10.1002/ana.26381
47. Trummer B, Haubenberger D, Blackstone C. Clinical trial designs and measures in hereditary spastic paraplegias. *Front Neurol*. 2018;9:1017. doi:10.3389/fneur.2018.01017