

Hereditary spastic paraplegia: Novel insights into the pathogenesis and management

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Wireko Andrew Awuah¹ , Joecelyn Kirani Tan², Anastasiia D Shkodina³, Tomas Ferreira⁴, Favour Tope Adebuseye¹ , Adele Mazzoleni⁵, Jack Wellington⁶, Lian David⁷, Ellie Chilcott⁶, Helen Huang⁸, Toufik Abdul-Rahman¹, Vallabh Shet⁹, Oday Atallah¹⁰, Jacob Kalmanovich¹¹, Riaz Jiffry⁸ , Divine Elizabeth Madhu⁶, Kateryna Sikora¹, Oleksii Kmyta¹ and Mykhailo Yu Delva³

Abstract

Hereditary spastic paraplegia is a genetically heterogeneous neurodegenerative disorder characterised primarily by muscle stiffness in the lower limbs. Neurodegenerative disorders are conditions that result from cellular and metabolic abnormalities, many of which have strong genetic ties. While ageing is a known contributor to these changes, certain neurodegenerative disorders can manifest early in life, progressively affecting a person's quality of life. Hereditary spastic paraplegia is one such condition that can appear in individuals of any age. In hereditary spastic paraplegia, a distinctive feature is the degeneration of long nerve fibres in the corticospinal tract of the lower limbs. This degeneration is linked to various cellular and metabolic processes, including mitochondrial dysfunction, remodelling of the endoplasmic reticulum membrane, autophagy, abnormal myelination processes and alterations in lipid metabolism. Additionally, hereditary spastic paraplegia affects processes like endosome membrane trafficking, oxidative stress and mitochondrial DNA polymorphisms. Disease-causing genetic loci and associated genes influence the progression and severity of hereditary spastic paraplegia, potentially affecting various cellular and metabolic functions. Although hereditary spastic paraplegia does not reduce a person's lifespan, it significantly impairs their quality of life as they age, particularly with more severe symptoms. Regrettably, there are currently no treatments available to halt or reverse the pathological progression of hereditary spastic paraplegia. This review aims to explore the metabolic mechanisms underlying the pathophysiology of hereditary spastic paraplegia, emphasising the interactions of various genes identified in recent network studies. By comprehending these associations, targeted molecular therapies that address these biochemical processes can be developed to enhance treatment strategies for hereditary spastic paraplegia and guide clinical practice effectively.

Keywords

Hereditary spastic hyperplasia, genetics, neurodegeneration, metabolism

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¹Sumy State University, Sumy, Ukraine

²Faculty of Medicine, University of St. Andrews, St. Andrews, Scotland, UK

³Department of Neurological Diseases, Poltava State Medical University, Poltava, Ukraine

⁴Department of Clinical Neurosciences, School of Clinical Medicine, University of Cambridge, Cambridge, UK

⁵Barts and the London School of Medicine and Dentistry, London, UK

⁶Cardiff University School of Medicine, Cardiff University, Wales, UK

⁷Norwich Medical School, University of East Anglia, Norwich, UK

⁸Royal College of Surgeons in Ireland, University of Medicine and Health Sciences, Dublin, Ireland

⁹Faculty of Medicine, Bangalore Medical College and Research Institute, Karnataka, India

¹⁰Department of Neurosurgery, Hannover Medical School, Hannover, Germany

¹¹Drexel University College of Medicine, Philadelphia, PA, USA

Corresponding author:

Wireko Andrew Awuah, Sumy State University, 2, Rymyskogo-Korsakova Street, Sumy 40007, Ukraine.

Email: andyvans36@yahoo.com

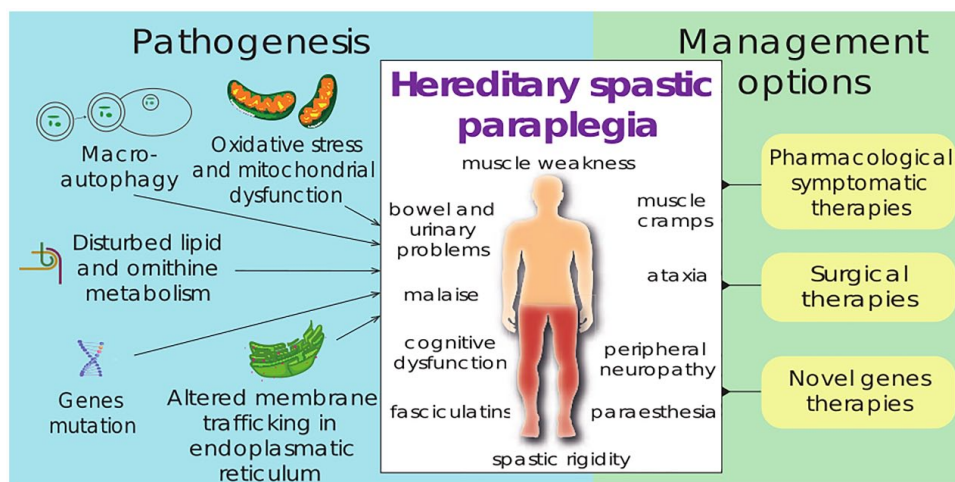


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Graphical abstract



Introduction

Hereditary spastic paraplegia (HSP) constitutes a diverse group of rare neurological disorders, typically arising from single-gene defects, with a global incidence rate of 3.6 per 100,000 individuals.¹ HSP is characterised by spasticity and paralysis in the lower limbs, resulting from developmental and neurodegenerative abnormalities in lower limb neurons.² Approximately 80 genes have been associated with HSP, including *SPG3A*, *SPG4* and *SPG11*, which are prominent spastic paraplegia genes.^{2,3}

Among the dominant HSP types (AD-HSP), *SPG4* is identified as the most prevalent, accounting for 40%–45% of familial cases.³ The second most common form of AD-HSP, *SPG3A*, is caused by mutations in the *ATL1*, estimated to contribute to about 7% of AD-HSP cases.⁴ The autosomal recessive HSP type *SPG11* is prevalent, affecting 18% of HSP patients globally, with the majority of cases found in Northern Africa and Western Asia.¹ Nevertheless, there is geographical variation in the prevalence of different HSP types, with *SPG4* being the dominant form in German ethnic groups.⁵

The pathogenesis of HSP involves a complex network of physiological processes, including membrane transport, endoplasmic reticulum (ER) shaping, mitochondrial functionality, DNA repair, autophagy, lipid metabolism and myelination.¹ Recent studies have also highlighted the potential roles of mitochondrial DNA (mtDNA) polymorphisms and abnormalities in endosome membrane trafficking and oxidative stress in the onset of the disease. HSP symptoms can manifest at any age, from infancy to late adulthood, with varying rates of progression and impairment.^{1,2} The most common genetic mutations and pathogenic pathways are illustrated in Figure 1.

Clinically, HSP is categorised into two distinct groups: pure and complicated HSP, distinguished by the symptoms exhibited by patients.⁶ Pure HSP typically presents with

lower limb stiffness and urinary urgency, whereas complicated HSP is associated with a broader spectrum of symptoms, including signs of both upper and lower motor neuron dysfunction, such as fasciculations and increased spasticity.¹

In addition to primary neurological manifestations, HSP can lead to various secondary symptoms, encompassing paraesthesia, rigidity, scoliosis, malaise and muscle cramps and extending to cognitive dysfunction, ataxia and peripheral neuropathy.¹ The clinical picture is further complicated by the variability in symptom severity and age-related exacerbations that impact mobility and, consequently, the quality of life of affected individuals.

Recent advancements in artificial intelligence and machine learning have provided the means to utilise network analysis tools for the stratifying disease features in HSP, offering novel approaches to enhance our understanding of HSP subtypes.⁷ By employing bioinformatics tools alongside molecular studies, this approach has revealed shared biological processes among clusters of HSP patients. Although further research is required to replicate and validate these findings, they suggest that patients can be grouped into distinct aetiological categories, based on molecular features that characterising HSP in each case. This implies that there may be more molecular interactions at play in the initiation and development of HSP than currently known.⁷ By categorising patients with common molecular processes and comprehending all the mechanisms contributing to HSP development, this approach may pave the way for the development of precision medicine tools to improve patients' quality of life.

Nevertheless, therapeutic options for HSP are presently limited, with no available disease-modifying interventions capable of reversing or slowing down disease progression. This review aims to explore the genetic basis of HSP, investigating the intricate relationships within interactome networks to unveil the metabolic mechanisms crucial to its

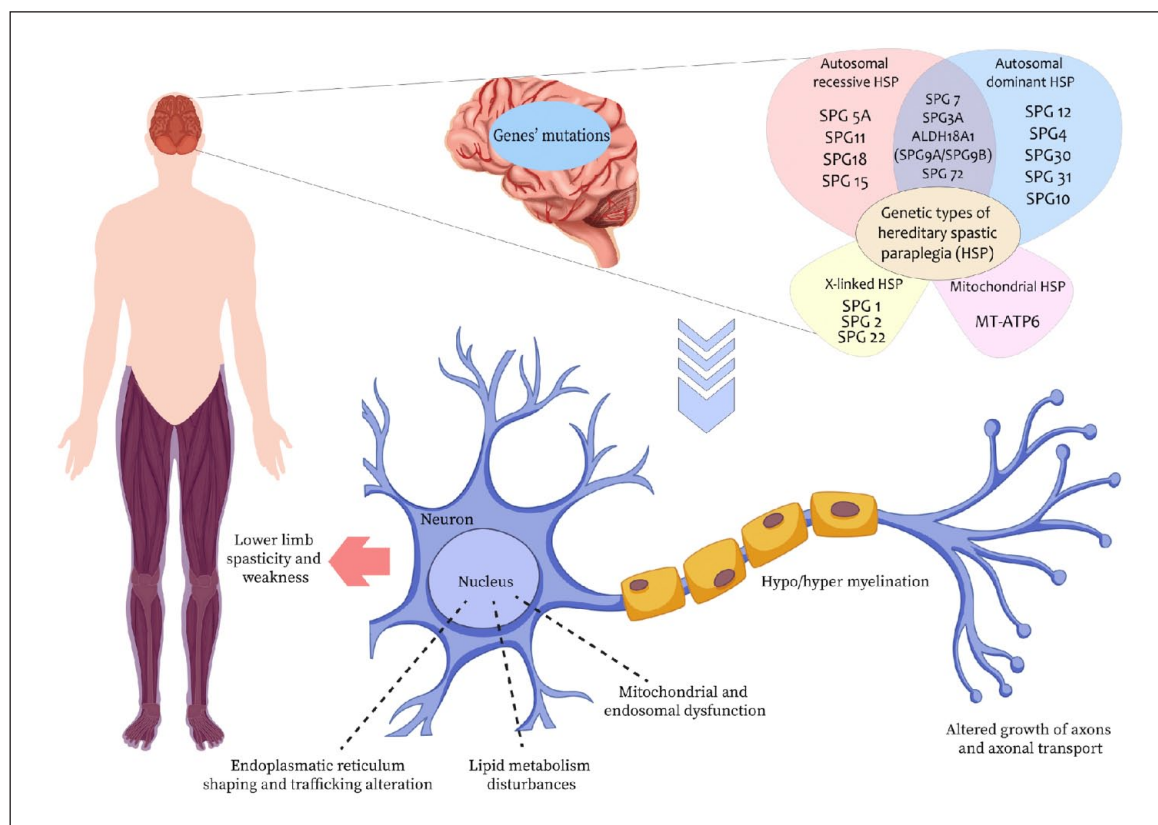


Figure 1. Common genetic mutations and pathogenesis pathways in HSP. The diagram depicts the most common genetic mutations associated with HSP, as well as the pathogenesis pathways that contribute to the disease. The genetic loci for HSP are classified based on the mode of inheritance, and the figure highlights the common pathways that lead to HSP.

pathophysiology. Understanding these associations may pave the way for targeted molecular therapy of various metabolic pathways, enabling the development of more effective HSP treatment algorithms and guiding valuable therapeutic strategies in clinical practice.

Methodology

This narrative review on the pathogenesis and management of HSP employed a rigorous methodology to ensure a comprehensive exploration of the topic. The inclusion criteria encompassed studies of various designs, including observational studies, case-control investigations, cohort studies and randomised controlled trials. Furthermore, the review considered studies involving both paediatric and adult populations, as well as those addressing all types of HSP. There was no set time frame for study inclusions, although we prioritised recently published papers to reflect on current advances on the topic. The literature search was conducted through prominent databases, including Scopus, MEDLINE, EMBASE and the Cochrane Library. The search was characterised by the use of precise search terms, such as ‘HSP’, ‘management’, ‘treatment’ and ‘pathogenesis’. Additionally,

a manual search was performed to identify references from recently published reviews. It is important to note that stand-alone abstracts and unpublished studies were excluded from the review.

Through this comprehensive and methodical approach, the review aspires to offer a high-quality academic assessment, presenting novel insights into the pathogenesis and management of HSP. This will facilitate a thorough synthesis of pertinent findings and contribute to a deeper understanding of this complex condition. A summary of the methodology is provided in Table 1 for reference.

Comprehensive overview of HSP pathophysiology

Oxidative stress and mitochondrial dysfunction

Oxidative stress and mitochondrial dysfunction are central to the pathogenesis of HSP. Neurons have a high energy demand to maintain their resting membrane potential and support axonal transport, especially in long axons. Therefore, the proper functioning and organised distribution of mitochondria within neurons are crucial.⁸

Table 1. Summary of methodology for pathogenesis and management of HSP.

Methodology steps	Description
Literature search	Scopus, MEDLINE, EMBASE and the Cochrane Library
Inclusion criteria	Full-text articles published in the English language were selected, with no specific time frame A diverse range of study designs, comprising observational studies, case-control investigations, cohort studies, cross-sectional analyses and randomised controlled trials Studies involving paediatric and adult populations Studies addressing all subtypes of HSP
Exclusion criteria	Stand-alone abstracts and unpublished studies
Search terms	Precise terms such as 'Hereditary spastic paraplegia', 'management', 'treatment' and 'pathogenesis' were employed
Additional search	A manual search was systematically undertaken to identify references pertaining to recently published reviews
Sample size requirement	No strict sample size requirement

One key aetiological element in HSP pathogenesis is the absence of the paraplegin/*AFG3L2* complex in the inner mitochondrial membrane. This complex not only prevents neuronal degeneration but also sustains the oxidative phosphorylation pathway, responsible for generating adenosine triphosphate (ATP).⁹ In *SPG7* patients with loss-of-function mutations in this complex, cells become more vulnerable to oxidative stress, leading to increased sensitivity to reactive oxygen species and reduced mitochondrial ATP production.^{9,10} This can further impair neuronal function and contribute to the onset of HSP.

Disruption of mitochondrial fission–fusion dynamics can lead to morphological, mobility, and spatial distribution changes in mitochondria.⁸ This results in impaired mitochondrial axonal transport, leading to deficiencies in oxidative phosphorylation, apoptosis, deletion mutations in mtDNA, and ultimately axonal degeneration.⁸ Several HSP subtypes, including *SPG15*, *SPG48* and *SPG31*, have been linked to impaired mitochondrial dynamics.^{11,12} Meanwhile, *SPG7* and *SPG61* are associated with mitochondrial morphology and network disruptions.¹³ Notably, the *SPG7* gene encoding paraplegin, a protein found in the inner mitochondrial membrane, and the *SPG13* gene encoding heat shock protein-60, a mitochondrial chaperone, are both related to mitochondrial dysfunction and spastic paraplegia.¹⁴ Mutations in mitochondrial fusion–fission genes have also been reported in various HSP types, including dynamin-related protein 1 (*DRP1*), optic atrophy gene 1 and mitofusin-1 and -2 (*Mfn1* and *Mfn2*).^{15,16}

Mitophagy is another crucial process in the regulation of mitochondrial dynamics and function within axons.¹⁷ Disruption of mitophagy can lead to the formation of abnormal mitochondrial networks and subsequent axonal degeneration.¹⁷ HSP subtypes such as *SPG11*, *SPG15* and *SPG48* result from autosomal recessive mutations in the genes *SPG11*, *ZFYVE26* and *AP5Z1*, encoding spatacsin, SPASTIZIN and AP5Z1, respectively.¹⁸ These genes hold promise for the discovery of new therapeutic targets for these HSP subtypes. Recent research has shown that inhibiting the

overexpression of *DRP1*, a mediator of mitochondrial fission, can reverse axonal defects observed in neurons of *SPG15* and *SPG48*-HSP subtypes.⁸

Finally, the accumulation of mitochondria within axons, lack of ATP and disruption of the neuronal cytoskeleton can result in axonal swelling, leading to various neurological disorders, including HSP.^{11,12}

Metabolic processes influencing HSP

Disturbed ER function and HSP. Disrupted ER function is a significant contributor to the pathogenesis of HSP. The ER is essential for proper lipid synthesis and metabolism and facilitates intracellular communication by generating microdomains in plasma membranes.¹⁹ Neurodegenerative processes have been linked to ER and lysosomal malfunction, where sphingolipids are produced and degraded. Sphingolipids are crucial for normal neuronal structure and functionality.¹⁹ Patients with a missense mutation in fatty acid-2-hydroxylase, the enzyme responsible for sphingolipid production, are at risk of developing complex HSP.²⁰ Additionally, deficiencies in proteins like Receptor Expression-Enhancing Protein 1 (REEP1), which play a vital role in shaping the tubular ER network, can lead to shorter corticospinal axons and rapid declines in motor function tests, indicative of early onset HSP.²¹

The spastin gene, typically involved in conventional microtubule production and cellular stability, has a strong association with HSP development.²² Recent research has shown that spastin dysfunction leads to the accumulation of lipid droplets (LDs) within neuronal cells.²² While more research is needed to fully understand these novel findings, it is plausible to hypothesise that HSP pathogenesis may involve an alternative mechanism of abnormal LD accumulation and metabolism in addition to the well-known spastin gene dysfunction.²³

Moreover, three distinct mutations – frameshift, whole-gene deletion and single missense mutations – within the reticulon 2 (*RTN2*) gene have been associated with aberrant

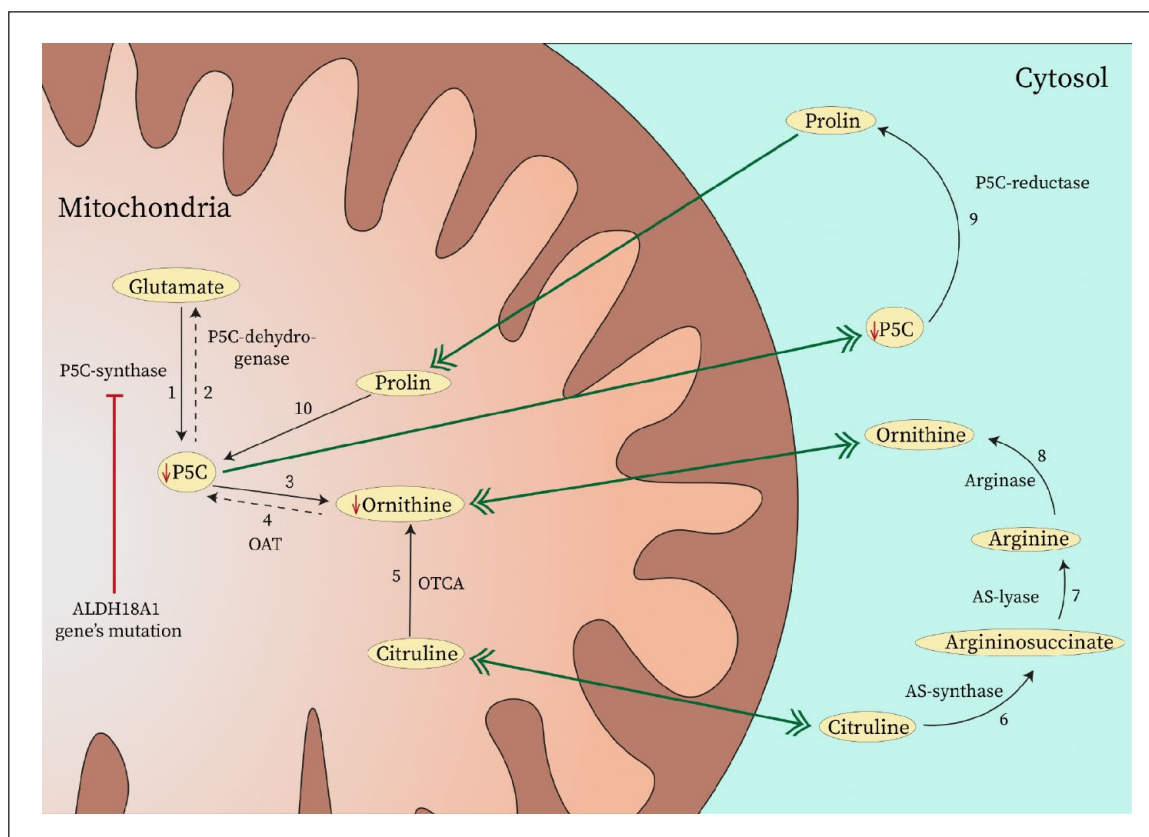


Figure 2. The ornithine metabolic cycle and its association with lipid metabolism in relation to HSP.

P5C: pyrroline-5-carboxylate; OAT: ornithine aminotransferase; OTCA: ornithine transcarbamylase; AS: argininosuccinate.

ER morphogenesis in *SPG12*.²⁴ *RTN2* encodes a member of the reticulon family, which serves as prototypic ER-shaping proteins in families afflicted by *SPG12*. The truncated *RTN2* protein is believed to act through a haploinsufficiency mechanism, although the possibility of a toxic gain of function in the cytosol or nucleus remains.²⁴ The interaction between *RTN2* and spastin is contingent on a hydrophobic region within spastin, a region involved in ER localisation and projected to form a curvature-inducing/sensing hairpin loop domain.²⁴ These findings collectively suggest the involvement of a reticulon protein in axonopathy as part of a network of interactions among HSP proteins engaged in ER shaping. This supports the prevailing hypothesis that ER dysfunction constitutes a pathogenic mechanism in HSP.

Ornithine metabolism and HSP. The ornithine and HSP genes are illustrative instances of metabolic pathways that exhibit multiple links with lipid metabolism.²⁵ Ornithine, a non-essential amino acid found in the urea cycle, is recognised for its pivotal role in various metabolic processes. Dysregulation of ornithine metabolism has been associated with several diseases, including leukaemia, hyperammonemia, neuroblastoma and neurodegenerative syndromes like HSP.²⁵

Mutations in the *ALDH18A1* gene, which participates in the ornithine pathway, have been correlated with the pathogenesis of HSP.²⁵ The *ALDH18A1* gene encodes the *P5CS* enzyme, which catalyses the initial step in the biosynthesis of proline and ornithine.^{25,26} This enzyme converts gamma-glutamyl phosphate into gamma-glutamyl semialdehyde, which subsequently undergoes spontaneous degradation to P5C. Located in the inner mitochondrial membrane, P5C can then be further metabolised into proline or, through the urea cycle, into ornithine, citrulline and ultimately arginine, with the assistance of the P5C reductase (*PYCR1*) enzyme (Figure 2).^{25,26} Consequently, low levels of plasma ornithine are a matter of concern for individuals with HSP.

HSP resulting from *ALDH18A1* gene mutations can manifest as either a simple autosomal recessive or complex autosomal dominant condition. Patients from autosomal dominant families consistently exhibit low to extremely low plasma citrulline levels, along with less consistently reduced plasma levels of ornithine, arginine and proline, regardless of the specific protein domain affected by the mutation.²⁵ Notably, patients with autosomal dominant HSP linked to *ALDH18A1* mutations may derive substantial benefits from long-term citrulline supplementation, a therapeutic approach

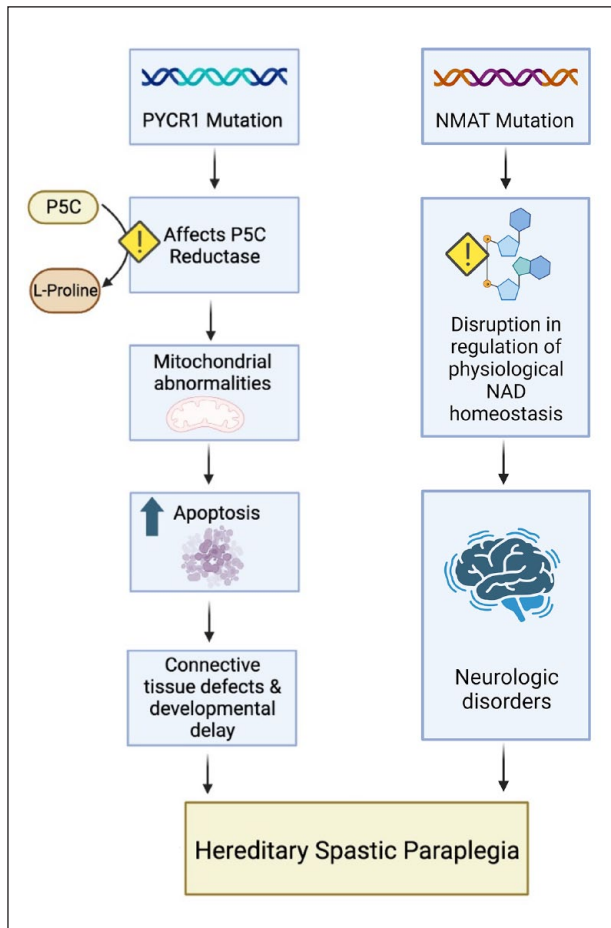


Figure 3. Lesser known mechanisms in HSP.
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that has demonstrated success in patients with inborn metabolic disorders affecting the urea cycle, either directly or indirectly, such as ornithine transcarbamylase deficiency or lysinuric protein intolerance.

Lesser known mechanisms in HSP

Spastic paralysis is a frequently observed phenotype in various rare mutations affecting interconnected pathways related to glutamate and urea cycle metabolism, as well as mitochondrial degeneration.²⁷ Notable examples of such mutations involve *PYCR1* and *NMNAT1* genes, which are associated with cutis laxa and the nicotinamide adenine dinucleotide (NAD) biosynthetic network, respectively.²⁷ A comprehensive examination of the underlying pathology associated with these mutations can provide valuable insights into our comprehension of HSP (Figure 3).

***PYCR1* mutations.** *PYCR1* mutations have been implicated in an autosomal recessive neurocutaneous syndrome associated with a range of clinical manifestations, including mental retardation, cutis laxa, joint hyperlaxity, progeroid

dysmorphism, growth retardation, microcephaly and corpus callosum dysgenesis. These mutations are also believed to play a role in neurodegeneration within the mitochondria.²⁸

The *PYCR1* gene encodes the enzyme *P5C* reductase, which is responsible for the final step in proline biosynthesis, converting *P5C* into L-proline.²⁸ Notably, although proline plasma levels remain normal in individuals with *PYCR1* mutations, they exhibit mitochondrial abnormalities characterised by increased apoptosis during oxidative stress, resulting in the development of cutis laxa with progeroid changes.²⁸

It is worth noting that mutations in the *PYCR1* gene, as well as *P5CS* deficiency associated with the ornithine cycle, share common features, including connective tissue defects and developmental delays. Both enzymes are situated in the inner membrane of mitochondria.^{27,28}

***NMNAT1* mutations.** The Nicotinamide mononucleotide adenylyltransferase enzyme plays a crucial role as a co-substrate for a group of enzymes within the NAD biosynthetic network. Recent evidence from whole-exome sequencing indicates a potential link between a variant in *NMNAT1* and HSP.²⁹ This association was observed in two affected siblings diagnosed with HSP, where a homozygous variant (Glu257Lys) in *NMNAT1*, the most prevalent variant in patients with *LCA9*, displayed clinical manifestations completely consistent with pure HSP.²⁹ Notably, this study represents the first report of *NMNAT1* mutations contributing to neurological disorders by disrupting the regulation of physiological NAD homeostasis. To validate this hypothesis, further rigorous and large-scale clinical trials are imperative.

Cellular transport mechanisms and HSP

Malfunction in axonal transport represent an additional pathophysiological process associated with specific subtypes of HSP.¹² Axonal transport plays a vital role in various essential functions, encompassing the regulation of axon composition, the preservation of axonal function, and the support of neurogenesis.¹² This process relies on motor proteins, including kinesin for anterograde transport, which facilitates the movement of ribonucleic acids (RNAs), proteins, lipids and mitochondria towards axon terminals and growth cones. In contrast, retrograde transport is orchestrated by dynein motor proteins, responsible for transporting trophic factors and misfolded proteins back to the soma for degradation.³⁰

Kinesin heavy chain 5A (*KHC5A*) is a pivotal anterograde motor protein belonging to the kinesin family that is responsible for transporting neurofilaments and vesicles to growth cones and synapses.³¹ It also plays a regulatory role in cargo transport within dendrites and is involved in processes such as exocytosis and endocytosis. The *KHC5A* protein is encoded by the *KIF5A* gene, which has been found to be mutated not only in *SPG10* but also in other neurodegenerative diseases, including Charcot–Marie–Tooth (CMT) disease Type 2 and amyotrophic lateral sclerosis (ALS).³¹ These

mutations predominantly manifest as missense changes and tend to cluster in the gene's N-terminal motor domain, as indicated by comprehensive genome-wide analyses. A similar anterograde protein, the Kinesin Family Member 1A protein (*KIF1A*), encoded by the *KIF1A* gene, is responsible for the transport of membranous organelles along the axon.³¹ Notably, Klebe et al.³² employed targeted next-generation sequencing to establish that mutations in the *KIF1A* gene underlie the development of *SPG30*.

KIF1A gene mutations have also been associated with other neurological conditions, including hereditary sensory neuropathy type IIC and nonsyndromic intellectual disability.³³ On the other hand, the *SPAST* gene, mutated in the most prevalent form of autosomal dominant HSP, *SPG4*, encodes for spastin, a protein pivotal in regulating microtubule dynamics and arrays.^{34,35} As the normal functioning of kinesin and dynein motor proteins relies heavily on microtubule activity, any dysregulation stemming from mutant spastin proteins can lead to defective axonal transport.³⁶ Another analogous protein, Spartin, encoded by the *SPART* gene, is also associated with microtubule dynamics, in addition to its involvement in endosomal trafficking, and has been implicated in *SPG20*, also known as Troyer syndrome.³⁷

Distinctively, *SPG33* is a subtype of HSP resulting from mutations in the *ZFYVE27* gene, which encodes for protrudin. Protrudin is a protein localised to the ER and plays a role in the outgrowth of neurites.¹⁸ *SPG33* stands out as its causative protein, protrudin, interacts with proteins associated with several other spastic paraplegias. It forms connections with both *SPG4* and atlastin-1 (*SPG3A*), while also interacting with the *KIF5* proteins (*SPG10*).¹⁸

Membrane trafficking in ER networks. HSP-associated genes have been identified to play pivotal roles as modifiers and regulators of the ER network, impacting protein secretion and calcium sequestration.³⁸ The ER, a membrane-bound organelle, participates in a multitude of cellular processes and, most notably, plays a critical role in expanding axonal membranes to facilitate postsynaptic signalling pathways.³⁸ Mutations that disrupt ER shaping and function contribute not only to the phenotypic spectrum of HSP but also to various other neurodegenerative conditions, including Alzheimer's disease (AD), CMT, Parkinson's disease (PD) and ALS.³⁸

Genetically, HSP can be inherited in different modes, including autosomal dominant, autosomal recessive, X-linked or mitochondrial. However, the most prevalent form of HSP is autosomal dominant HSP, affecting 75%–80% of HSP patients.³⁹ Dysregulation in the tubular ER network can largely be attributed to three main genes: *SPG3A/ATL1*, *SPG4/SPAST* and *SPG31/REEP1*, accounting for approximately 50% of HSP cases.⁴⁰ Heterozygous mutations in the *ATL1* gene result in *SPG3A* AD-HSP. *ATL1* encodes the GTPase atlastin, which interacts with spastin.⁴¹ Atlastin-1 is instrumental in shaping the ER morphology by catalysing the fusion of membrane tubules, forming three-way

junctions.⁴² Mutations in this gene culminate in the abnormal morphogenesis of the ER and Golgi, thereby impacting axon development and maintenance, ultimately contributing to HSP.⁴³ The *SPAST* gene encodes for spastin, which is part of the ATPases Associated with the diverse cellular Activities (AAA) family. Spastin plays a crucial role in mediating microtubule stability, and its loss has been shown to result in defective synaptic growth and neurotransmission in vivo in *Drosophila*.^{44,45} This highlights spastin as a potential therapeutic target for HSP treatment.

Mutations in the *REEP1* gene are another well-recognised cause of *SPG31* AD-HSP.⁴⁶ Previous studies yielded conflicting data regarding the localisation of *REEP1*, with both the ER and mitochondria being suggested. However, an in vitro study clarified that *REEP1* is localised in the ER-mitochondria interface. Pathological *REEP1* mutations disrupt ER-mitochondria interactions, leading to growth defects and neuronal degeneration, which can be attributed to the inability to maintain healthy long axons in HSP.⁴⁷ Within the ER, *REEP1* forms protein complexes with both atlastin-1 and spastin, necessitating the presence of hydrophobic hairpin domains in these proteins.⁴⁷ Further in vitro research highlighted the role of REEP proteins, particularly those with extended C-terminal domains (REEP1–4), in ER shaping and their involvement in interactions between ER tubules and the microtubule cytoskeleton.⁴⁷ Notably, an *SPG31* mutation in *REEP1* without a C-terminal domain was found to fail to interact with the ER membrane in corticospinal neurons, potentially contributing to the pathogenesis of HSP.⁴⁷

The *BSCL2* gene, also known as the Berardinelli–Seip congenital lipodystrophy gene, encodes the ER protein seipin. Mutant seipins in *BSCL2*-associated HSP have been found to accumulate in the ER, triggering the upregulation of ER-stress-mediated molecules, which, in turn, induce apoptosis. This mechanism provides insight into the degeneration observed in HSP.⁴⁸

The ER is co-localised by protrudin, a membrane protein involved in polarised vesicular trafficking in neurons.⁴⁹ In vitro studies demonstrated that the forced expression of protrudin promotes the formation and stabilisation of the ER tubular network. Conversely, mutant protrudin cells exhibited greater susceptibility to ER stress, potentially contributing to the pathogenesis of HSP.⁴⁹

Vesicular trafficking of lysosomes. Lysosomes are dynamic organelles enclosed by a single membrane, displaying significant heterogeneity in terms of size, location, shape, enzyme composition and substrates within cells. These organelles house a multitude of integral and peripheral membrane proteins, including transporters and ion channels.^{50–52} The acidic environment of the lysosomal lumen, with a pH typically ranging from 4.5 to 5.5, is primarily maintained by the lysosomal multi-subunit V-ATPase. In this low-pH setting, over 50 intralysosomal hydrolases become activated,

enabling the breakdown of macromolecules like proteins, nucleic acids, lipids and carbohydrates.^{52–54}

Lysosomes play a crucial role in importing and degrading various substances, including endocytic materials like small molecules and cell surface proteins, phagocytosis of larger particles such as inflammatory cells and exogenous bacteria, and autophagy of cytoplasmic components like damaged mitochondria, ER and other lysosomes.^{52–54} These organelles act as cellular waste disposal sites, recycling the by-products of lysosomal digestion for cellular maintenance.

Lysosomal dysfunction is clinically implicated in various human disorders, including lysosomal storage diseases such as Tay–Sachs disease and neurodegenerative diseases like ALS and HSP.^{55,56} In HSP, genes like the kinesin family member 5A gene (*KIF5A*) and protrudin play essential roles in vesicular trafficking and ER-lysosome interactions, respectively, contributing to the pathogenesis of the disease.^{57,58} Additionally, lysosomal proteins such as *VPS35* (vacuolar protein sorting 35 orthologs), a component of the Retromer complex that sorts endosomal products, have been associated with HSP.⁵⁹

The absence of components of the Wiskott–Aldrich syndrome protein and SCAR homologue 1 (WASH-1) complex, which interacts with endosomes, as well as the absence of FAM21 and actin-capping proteins responsible for regulating actin dynamics, can result in increased tubulation of early endosomes. This change may be due to the lack of actin-mediated forces needed for the separation of tubular transport intermediates from endosomes. This alteration affects the transport of early endosomal compartments and is particularly relevant in the case of corticospinal neurons, which have exceptionally long axons and are more susceptible to reductions in functional WASH. This susceptibility could be a contributing factor in HSP.⁶⁰

Furthermore, endosomal membrane trafficking in HSP is associated with specific proteins, including *KIAA0415* (*SPG48*), spatacsin (*SPG11*) and spastizin/*FYVE-CENT* (*SPG15*). Clinical similarities between *SPG11* and *SPG15* are noted, including their presentation as juvenile parkinsonism and a connection with the thin corpus callosum. The interaction of spastizin and spatacsin with the *SPG48* protein *KIAA0415* suggests a link between HSP and DNA repair.⁶¹

Macro-autophagy

Autophagy is a fundamental cellular process that enables cells to respond effectively to potential disruptions, safeguarding the cellular environment from organelles and misfolded proteins that could compromise internal balance.⁶² Macro-autophagy, a central aspect of autophagy, involves the sequestration of cytoplasmic components into double-membrane vesicles known as autophagosomes, which subsequently merge with lysosomes to form autolysosomes.⁶² This pivotal cellular process is indispensable for normal cell function, and any defects in autophagy have far-reaching implications,

particularly in the context of neurodegenerative conditions like HSP.⁶³ The malfunction of the autophagic pathway, in conjunction with endolysosomal processes, has been associated with 24 gene mutations linked to HSP, signifying its pivotal role in the pathogenesis of HSP (Figure 4).⁶³

The autophagosome. In the process of autophagosome biogenesis, malfunctioning proteins serve as attractants for autophagy-related (ATG) proteins, initiating the creation of phagophore assembly site (PAS) and ultimately giving rise to the formation of a phagophore.⁶⁴ This sequence is then succeeded by nucleation and elongation phases, culminating in the generation of an autophagosome that encapsulates intracellular material.

Within this process, ATG protein 9A (*ATG9A*) plays a crucial role. *ATG9A*, a transmembrane protein, is indispensable for the assembly of autophagosomes. During autophagy, *ATG9A* is transported to the PAS by vesicle transport mechanisms and takes on the pivotal role of overseeing the regulation and elongation of the phagophore (Figure 4).⁶⁴

Adaptor protein deficiency syndromes, the Kinesin family and autosome-lysosome fusion in HSP. Adaptor Protein Complex 4 (AP-4) is a complex predominantly associated with the trans-Golgi network (TGN). Depletion of this complex has been linked to HSP and has direct consequences on *ATG9A*, including its mislocalisation and retention at the TGN rather than reaching the PAS).⁶⁵ Mutations in *AP-4* have been identified in severe neurodevelopmental forms of HSP, specifically *SPG47*, *SPG50*, *SPG51* and *SPG52*, collectively known as AP-4 deficiency syndromes.⁶⁶

Another pivotal player in the *ATG9A* trafficking process is *KIF1A*, a member of the Kinesin-3 family. *ATG9A* is typically located at the PAS and axon terminals.³² Pathological variations in *KIF1A* have been associated with impaired transport of ATG-9 to neurites and are linked to both autosomal recessive and dominant forms of HSP, including *SGP30*.³²

Furthermore, several other genes in the Kinesin family have been implicated in HSP. Mutations in *KIF5A*, which encodes the heavy chain of kinesin-1, are known to disrupt axonal transport, particularly affecting neuronal microtubule motors. This disruption is associated with *SPG10*-HSP.⁶⁷ These kinesin motors play essential roles in the fusion of autophagosomes with lysosomes, and their differential intracellular locations necessitate trafficking.⁶⁷ Another protein involved in the union of autophagosomes and lysosomes is Light Chain 3 (LC3), a member of the ATG8 protein family, which recruits interacting partners to initiate transport, tethering, and fusion, including the Homotypic Fusion and Vacuole Protein Sorting Tethering Complex (HOPS).⁶⁸

Additionally, the Tectonin Beta-Propeller Repeat Containing 2 (*TECPR2*) protein is associated with pathways involving ATG8 and the HOPS complex family. Mutations in the *TECPR2* gene have been linked to *SPG49*-HSP. A

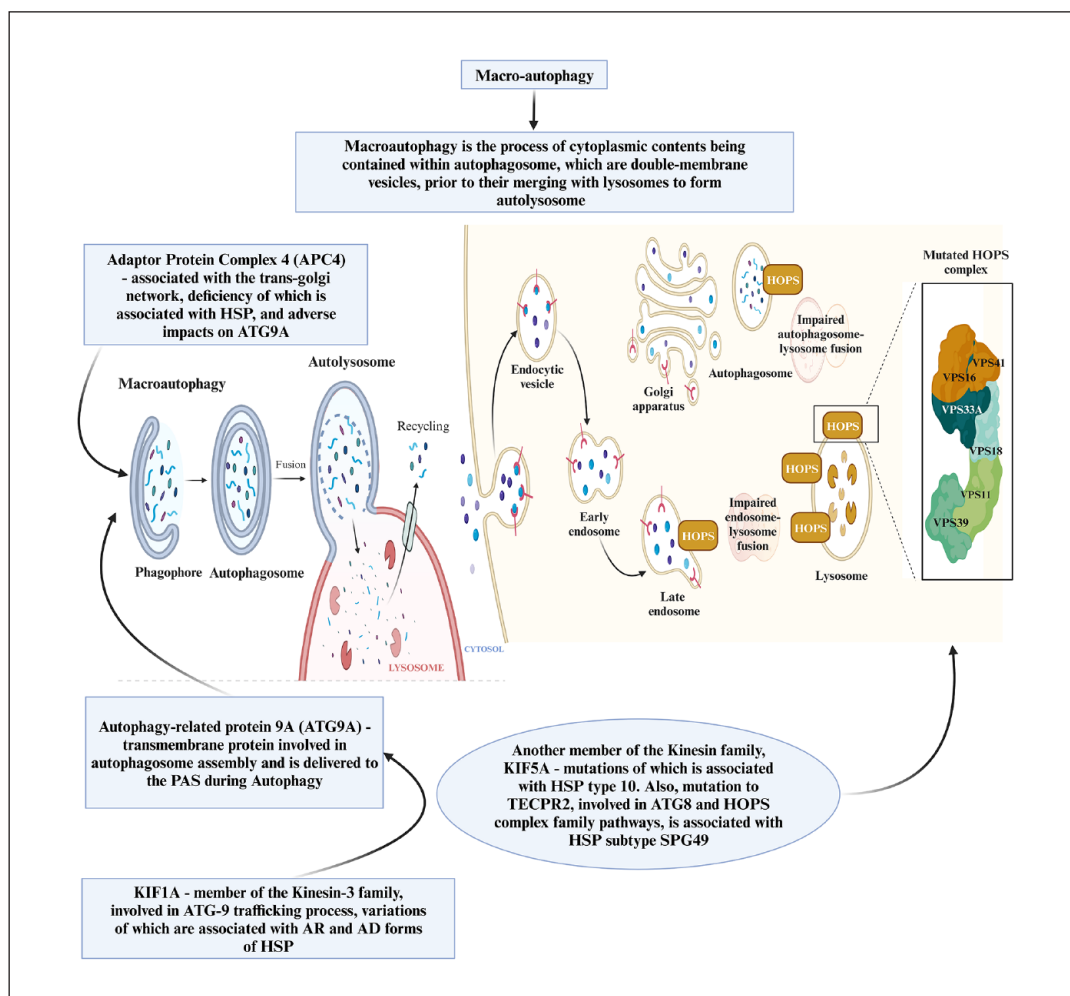


Figure 4. Macro-autophagy.

Source: Created with Biorender.com.

study examining fibroblasts from an HSP patient revealed defects in autophagy associated with *TECPR2* mutations.⁶⁹ It is suggested that *TECPR2* regulates autophagosome-lysosome tethering and fusion by interacting with LC3 and HOPS (Figure 4).⁷⁰

Impaired lysosomal storage and HSP. *ATP13A2* is an enzyme closely associated with lysosomal transport and *SPG78*-HSP. This enzyme belongs to the P5-type transport ATPase family and plays a pivotal role in lysosomal function. Individuals with *ATP13A2* mutations often exhibit an abnormal accumulation of lysosomal and autophagosome structures, resulting in impaired lysosomal storage. This disruption leads to a defect in the clearance of damaged mitochondria and hinders the degradation of intracellular protein aggregates.⁷⁰

Once autophagosomes have tethered to lysosomes to form autolysosomes, the internal materials contained within are subjected to degradation. The final step in autophagic pathways is the recycling of lysosomal

components, which facilitates the formation of new lysosomes during reformation.⁷⁰

Multiple proteins linked to HSP are known to play roles in the process of lysosomal reformation, including spatacsin (*SPG11*), spastizin (*SPG15*), *AP5Z1* (*SPG48*) and the AP-4 complex. *AP5Z1* is a part of the adaptor protein complex 5 (AP-5) and is closely associated with both spatacsin and spastizin.⁷¹ Mutations in *AP5Z1* can result in the loss of AP-5 protein function, leading to abnormal storage of lysosomal materials (Figure 4).⁷²

Myelination disruptions and HSP

PLP1. The *PLP1* gene encodes proteolipid protein 1. Mutations in the *PLP1* gene itself or in its distal enhancers have been identified as contributing factors to HSP and specifically as causative factors for with *SPG2* being one of the specific manifestations linked to these mutations.^{73–75} Notably, a microdeletion at the Xq22.2 region, which contains one of the distal enhancers of the *PLP1* gene, has been found

to lead to *SPG2*-HSP.⁷³ When these distal enhancers are absent or impaired, the transcription of *PLP1* in oligodendrocytes can be suppressed. This transcriptional suppression can limit the ability of the gene to maintain myelin, contributing to the development of the *SPG2* phenotype.⁷³

LICAM. The *LICAM* gene is responsible for encoding myelin proteins, which play a crucial role as they are expressed on oligodendrocytes that provide vital support to motor neurons.⁷⁶ When mutations occur in the *LICAM* gene, it results in a deficiency of myelin proteins in neurons.⁷⁶ Notably, in the axons of neurons expressing the Trk-fused gene (TFG) mutation (p.R106C), there is a reduction in the levels of cell surface *LICAM* when compared to controls. This observation supports the idea that the transport of *LICAM* to the cell surface is compromised in these conditions.^{77,78} These findings underscore the significance of effective membrane trafficking in the early secretory pathway, especially in the context of the long corticospinal motor neurons that degenerate in cases of HSPs. Such efficient trafficking is essential for maintaining neuronal homeostasis.⁷⁷

Intersecting genes and metabolic pathways in diseases related to HSP

Familial ALS

Familial ALS (fALS) is a rapidly progressing neurodegenerative disease that leads to paralysis.⁷⁹ Multiple genes, including *BSCL2*, *ERLIN1*, *ERLIN2*, *SPG11* and more, are thought to contribute to fALS. Differentiating between HSP and fALS can be challenging as each of these genes interacts with the metabolic pathways associated with both conditions.⁸⁰

Seipin is a protein encoded by the *BSCL2* gene. Seipin is highly prevalent in the brain, particularly in spinal motor neurons and cortical neurons in the frontal lobes. It is a membrane protein found in the ER of various cell types and is believed to be involved in the formation of LDs.⁸¹ In fALS, this gene and its variants, such as *P.N88S*, *P.S90L* and *P.S90W*,⁸² exhibit a harmful gain-of-function mutation. This mutation results in the misfolding of Seipin protein, leading to its accumulation in the ER, causing neurotoxicity and ultimately resulting in neurodegeneration. Studies suggest that *BSCL2* mutations can lead to a wide range of manifestations involving both upper and lower motor neurons, as well as peripheral motor axons. Patients with the *P.N88S* mutation may have a shorter disease course than patients with the *P.S90L* mutation.⁸¹

The *ERLIN1* gene codes for an ER protein known as ER lipid raft-associated protein 1. *ERLIN1* forms a ring-shaped complex with *ERLIN 2* to create the *ERLIN1-2* complex. This complex is involved in the ER-associated degradation (ERAD) pathway, which is activated when the ER is under stress. The ERAD pathway identifies misfolded proteins,

ubiquitinates them and transports them for degradation via a proteasome or autophagosome. Although limited to case series analyses, *ERLIN1* mutations have been shown to correlate with *SPG62*, a pure subtype of HSP that specifically impairs upper motor neurons and causes focal deficits.⁸³ Given that *ERLIN2* participates in the ERAD pathway of inositol 1,4,5-triphosphate (IP3), which is important for ubiquitination and the control of cellular cholesterol homeostasis,⁸⁴ further investigation into this connection is warranted, as the genetic spectrum of the disease may be broader than initially reported.

The *SPG11* gene, responsible for the development of spastic paraplegia and the most prevalent subtype of HSP, is inherited in an autosomal recessive manner. It codes for a protein called Spastacsin, whose exact function is yet to be fully understood.⁸⁵ This genetic mutation typically results in progressive spasticity, neuropathy, cognitive impairment and a thin corpus callosum observed on MRI. The role of Spastacsin may also be involved in weight gain and management, but its complete range of functions remains unclear.⁸⁵ Exome sequencing has shown that heterozygous deletions may lead to missense and nonsense mutations, with premature stop codons in the *SPG11* gene. Such mutations are prominently expressed across various brain regions, leading to nonsense, insertional and deletional mutations, resulting in frame shifts and loss of functionality.⁸⁶ This is particularly relevant because it has been associated with corpus callosum thinning, dementia symptoms and overall grey matter impoverishment.⁸⁵ Additionally, reduced volumetric size has been reported in various brain regions, such as the thalamus, accumbens nucleus, substantia nigra, amygdala and red nucleus.⁸⁵ Notably, clinical studies have shown that the spectrum attributed to *SPG11* mutations is broader than previously documented, with patients afflicted by autosomal recessive juvenile ALS (ARJALS) exhibiting extended periods of survival.⁸⁷ Therefore, conducting a comprehensive analysis of *SPG11* mutations in additional families with motor neuron disorders showing similar clinical manifestations is essential.⁸⁷ Consequently, further research into the mechanisms causing neurodegeneration associated with *SPG11* functionality is warranted.⁸⁶

Monogenic PD/parkinsonism

Parkinsonism represents a group of neurological disorders characterised by symptoms such as rigidity, tremors and slowed movement.⁸⁸ A significant study of *SPG11*, one of the largest cohort studies on the subject, revealed that 60% of participants responded to levodopa (L-Dopa) treatment, and one in six *SPG11* individuals exhibited parkinsonian features, suggesting a strong connection between parkinsonism and *SPG11*.⁸⁹ Research in this area has shed light on the crucial role of *SPG11* in the existence and functionality of neurons.⁸⁹ Specific *SPG11* mutations have been shown to harm dopaminergic neurons, suggesting that these mutations

might lead to early-onset parkinsonism.⁹⁰ Furthermore, the analysis of HSP patients presenting with parkinsonism-like symptoms has revealed various additional variants in genes such as *SPG7*, *FA2H* and the *ZFYVE26/SPG15* complex HSP genes.⁹⁰ Patients with *SPG7* often exhibit symptoms of Parkinsonism.⁹¹ Regardless of the number of mutant alleles, the type of variation, or the status of patient or carrier, pathogenic variants of *SPG7* impact mtDNA homeostasis. Consequently, *SPG7* plays a role in promoting mtDNA maintenance, and variations in this gene may result in parkinsonism due to anomalies in mtDNA.⁹¹ Intriguingly, the study mentioned found that a genetic cause of parkinsonism was not identified in more than half of the included patients, hinting at the possible involvement of as-yet-identified genes in this condition.⁹⁰

The *ATP13A2* gene encodes a P5-type transport ATPase protein found in lysosomes.⁹² While its specific binding partners are not yet known, *ATP13A2* expression has been associated with neuronal protection by preventing the accumulation of manganese.^{70,92} Loss of *ATP13A2* function can lead to mitochondrial and lysosomal dysfunction in neuronal groups, contributing to the development of neurological diseases such as HSP and parkinsonism.⁷⁰ Whole-exome sequencing and homozygosity mapping have revealed a homozygous p.Thr512Ile (c.1535C 4T) mutation in *ATP13A2*, which has been associated with Kufor-Rakeb syndrome, an autosomal recessive form of juvenile-onset parkinsonism. This research underscores the connection between *ATP13A2*, parkinsonism and HSP.⁷⁰ Routine screening of patients with complex HSP for *ATP13A2* mutations may prove beneficial in clinical practice.

The *UCHL1* gene, also known as the *PARK5* gene, codes for ubiquitin carboxyl-terminal esterase L1, which is a deubiquitinating enzyme involved in hydrolysing ubiquitin in the ubiquitin-proteasome pathway. *UCHL1* is highly expressed in neuronal, neuroendocrine and podocyte cells, where it helps maintain ubiquitin stability, a crucial factor in brain functionality.⁹³ Meta-analyses of the *UCHL1S18Y* variant and its association with PD have demonstrated a significantly increased risk of sporadic PD in individuals with the AA genotype of this gene variant.⁹⁴

Hereditary neuropathy

Hereditary neuropathies encompass a class of inherited diseases affecting the peripheral nervous system. One such condition is CMT, characterised by symptoms such as symmetrical, length-dependent motor neuropathy, muscle weakness, paraesthesia and foot deformities. Typically, CMT manifests in childhood and progresses slowly. There are clinical and genetic similarities between CMT and other distal hereditary motor neuropathies (dHMNs).⁹² Genes associated with dHMNs, including the *COQ7* variant, have also been linked to HSP.⁹⁵

CMT type 2 is primarily caused by mutations in the *BSCL2* gene. Exome sequencing studies have identified *BSCL2* mutations in individuals clinically suspected of having CMT type 2. For example, among 47 Japanese CMT patients, 5 had heterozygous *BSCL2* mutations. Notably, *p.N88T* and *p.S141A* mutations were observed in three cases. Patients with *p.N88T* exhibited a severe clinical presentation that began at an early age (1.5 years) and included vocal cord paralysis, distinguishing it from previous findings.⁹⁶ *P.S141A* is considered a unique and uncommon variation associated with CMT demyelinating neuropathy.⁹⁶ However, further cases are needed to confirm the pathogenic significance of *p.S141A* and *p.N88T* in CMT. In another study, three of 206 Chinese patients with CMT had *BSCL2* mutations (*p.S154W*, *p.S154L*, *p.A437P* and *p.A282V*). Variants of the *BSCL2* gene have also been implicated in dHMNs. In Taiwan, 76 CMT type 2 patients with dHMNs were found to carry two *BSCL2* variants: *p.S90L* (in a CMT family) and *p.R96H* (in a sporadic dHMN case).⁹⁷

Methionyl-tRNA synthetase, also known as *MARS1*, is an enzyme responsible for charging tRNAs with their corresponding amino acids, a crucial step in protein synthesis.^{97,98} Mutations in *MARS1* have been linked to the aberrant production of neurofilaments within axons.⁹⁹ Although *MARS1* has been suggested as a potential gene associated with a subtype of CMT disease, the evidence is limited to exome sequencing analysis of a single family with CMT, necessitating further investigation into the potential role of *MARS1* mutations, particularly in cases of axonal CMT.^{100,101}

REEP1, encoded by the *REEP1* gene, is a protein expressed in neurons throughout the brain and spinal cord, localised in both the ER and mitochondria. It is believed to play a role in developing the tubular network structure of the ER, regulating its size and protein processing capacity, and enhancing G-protein coupled receptor (GPCR) activity.¹⁰² The HSP phenotype has been associated with *REEP1*. Interestingly, intellectual disability and behavioural problems have been linked to factors outside of *REEP1* in HSP patients, such as *SPAST*-HSP missense mutations.^{102,103} Additionally, the *SPG31* gene has been correlated with *REEP1*, with *REEP1* recently identified as the causative gene for dHMN type 5.¹⁰⁴

The *ALS5/SPG11/KIAA1840* gene has emerged as the causative factor behind a diverse array of clinical presentations, encompassing autosomal recessive HSP, ARJALS and autosomal recessive axonal CMT2 (ARCMT2). Notably, no significant large deletions or duplications have been associated with the *ALS5/SPG11/KIAA1840* gene, and haematological and biochemical profiles appear unremarkable.¹⁰⁵ However, it is linked to the loss of myelinated fibres, resulting in motor and sensory axonal neuropathy, with a more pronounced impact on the lower limbs and characterised by low amplitudes of compound motor and sensory nerve action potentials.¹⁰⁵ As such, it is imperative to consider genetic

screening of the *ALS5/SPG11/KIAA1840* gene not only in patients exhibiting symptoms of autosomal recessive HSP with thin corpus callosum and ARJALS but also in cases of ARCMT2.¹⁰⁵

Given the intricate and heterogeneous nature of these neurodegenerative conditions, next-generation sequencing techniques stand as the most effective diagnostic tools for identifying the genetic underpinnings in patients presenting with myelopathy or neuropathy, whether through targeted sequencing panel approaches or whole-genome sequencing.¹⁰⁵

Cerebellar ataxia

Ataxia is a clinical manifestation characterised by issues such as speech difficulties, abnormal gait, loss of voluntary muscle control and uncoordinated ocular movements. Cerebellar ataxia patients often exhibit symptoms like tremors, overshooting movements, impaired articulation and poor balance. Importantly, these ataxia-related features share common pathogenic mechanisms with HSP.¹⁰⁶

CAPN1. The Calpain-1 (*CAPN1*) gene encodes calcium-activated neutral proteases known as calpains. *CAPN1* is believed to contribute to essential neural processes and functional pathways that are common to both the corticospinal and cerebellar tracts.¹⁰⁷ Its involvement has been associated with *SPG76*, a condition characterised by cerebellar ataxia, further underscoring the connection between cerebellar ataxia and HSP.^{107,108}

KIF1A. The *KIF1A* gene codes for a motor protein responsible for transporting membrane-bound organelles along axonal microtubules. Mutations in *KIF1A* have been linked to autosomal recessive *SPG30* and, in some cases, are associated with cerebellar ataxia. Additionally, hereditary sensory neuropathy and mental retardation type 9 (autosomal dominant) have been observed in connection with *KIF1A* mutations.^{109,110} Notably, an estimated number of 61 *KIF1A* mutations have been reported, and certain missense variants have been associated with cerebellar atrophy and ataxia.^{110,111}

Spastic ataxia of Charlevoix–Saguenay. Spastic Ataxia of Charlevoix–Saguenay (SACS), also known as Sacsin, encodes the sacsin protein highly expressed in the central nervous system. It plays a crucial role in recruiting Hsp70 chaperone proteins that help regulate the effects of ataxia-related proteins, such as amazon-1.^{112,113} Whole-exome sequencing studies have identified various SACS variants and their associations with changes in protein function and resultant phenotypes. For instance, gene variants *p.Y508C* and *L.456V* have been linked to infantile-onset spinocerebellar ataxia.¹¹⁴

VPS13D. Vacuolar Protein Sorting 13 Homolog D (*VPS13D*) codes for a protein involved in lipid transport between organelle membranes and is thought to play a role in

mitochondrial clearance, contributing to overall cell health, mitochondrial size and homeostasis.¹¹⁵ Dysfunctions in the *VPS13D* gene have been reported in patients with autosomal recessive cerebellar ataxia. In some cases, individuals with *VPS13D* mutations have displayed adult-onset cerebellar ataxia, macrosaccadic intrusions, pyramidal tract signs and neuropathy.¹¹⁶ In other instances, *VPS13D* mutations were found in individuals with pure HSP or complex HSP, with variations in the age of onset and symptom complexity associated with the nature of the mutations.^{117,118}

ERAD pathway. The ER plays a pivotal role in the regulation of cellular calcium levels. Two distinct classes of calcium release channels, inositol IP3 and ryanodine receptors, are instrumental in mediating this regulation. GPCRs on the plasma membrane activate IP3 receptors located in the ER membrane, leading to the efflux of calcium from the ER into the cytoplasm.¹¹⁹ Dysregulation of this mechanism has been implicated in the pathophysiology of several neurodegenerative diseases, including HSP, spinocerebellar ataxias and Huntington's disease. The ERAD pathway is responsible for the degradation of active IP3 receptors. Compromised functioning of the ERAD pathway may also contribute to the development of neurodegenerative disorders.¹¹⁹

The intersecting genes and metabolic pathways in diseases related to HSP have been summarised in Table 2.

Current and emerging therapeutic targets and management strategies

This review covers both pharmacological therapies and non-pharmacological therapies for HSP management.

Pharmacological therapies

Intrathecal baclofen therapy. Baclofen is a selective GABA-B receptor agonist and is frequently used for the treatment of spasticity.¹²⁰ It can be administered orally or intrathecally by the surgical implantation of a specialised pump. A more recent retrospective investigation of intrathecal baclofen (ITB) device implantation in seven patients with HSP revealed significant improvements in the Reflex Scale and spasticity according to the modified Ashworth Scale, as well as improvements in the modified Rankin Scale.¹²⁰ Long-term implantation observed improvement in spasticity for 2–3 years, followed by a stable phase of ambulatory and other mobility functions for 4–5 years. Additionally, there was no reported adverse events (Table 3).¹²⁰

Levodopa. L-Dopa, an amino acid precursor to dopamine commonly used to manage PD symptoms, has been explored for its potential in HSP treatment. Historically, the evidence for L-Dopa in HSP has been largely based on case studies, offering limited-quality data.^{121,122} Although case studies have reported positive outcomes with L-Dopa treatment in

Table 2. Summary of intersecting genes and metabolic pathways in diseases related to hereditary spastic paraplegia.

Diseases related to HSP	Intersecting genes and metabolic pathways
Familial amyotrophic lateral sclerosis. ^{81–87}	<i>BSCL2</i> (P.N88S, P.S90L and P.S90W variants), <i>ERLIN1</i> , <i>ERLIN2</i> , <i>SPG11</i> genes interact with the metabolic pathways associated with both HSP and fALS
Monogenic Parkinson's disease/parkinsonism ^{89–94}	Strong link between <i>SPG11</i> -HSP, and parkinsonism Probable link between <i>SPG7</i> -HSP and parkinsonism, through anomalies in mitochondrial DNA due to dysfunction in <i>SPG7</i> , which promotes mitochondrial DNA maintenance Probable link between <i>ATP13A2</i> gene and HSP and Parkinsonism <i>UCHL1S18Y</i> variant increases the risk of sporadic Parkinson's disease
Hereditary neuropathy ^{92,95–97,99–105}	<i>COQ7</i> gene variant, which is related to dHMNs, is associated with HSP <i>BSCL2</i> (p.N88S, and p.S141A variants) Probable link between CMT and <i>MARS1</i> mutation, leading to aberrant production of neurofilaments intrinsic to axons Link between <i>REEP1</i> gene, <i>SPG31</i> -HSP and dHMN type 5 <i>ALS5/SPG11/KIAA1840</i> genes are causative for HSP, ARJALS and ARCMT2
Cerebellar ataxia ^{106–108,110,111,113–119}	Intersecting genes between cerebellar ataxia and HSP include <i>CAPN1</i> gene, <i>KIF1A</i> gene, <i>SACS</i> gene and <i>VPS13D</i> gene Compromised ERAD pathway, and dysregulation in the mechanism involving IP3, ryanodine receptors

HSP: hereditary spastic paraplegia; fALS: familial amyotrophic lateral sclerosis; SPG: spastic paraplegia; dHMN: distal hereditary motor neuropathy; DNA: deoxyribonucleic acid; CMT: Charcot–Marie–Tooth disease; ARJALS: autosomal recessive juvenile amyotrophic lateral sclerosis; ARCMT2: autosomal recessive axonal Charcot–Marie–Tooth disease type 2; ERAD: ER-associated degradation; IP3: 1,4,5-triphosphate.

Table 3. Summary table of the effects of pharmacological treatments on hereditary spastic paraplegia.

Author (s), year	Drug	Action	Studied effect in HSP
Pucks-Faes et al. ¹²⁰	Intrathecal baclofen injections	Agonist of the beta subunit of the GABA receptors is administered intrathecally through surgical implantation of a specialised pump	Significant improvements in the Reflex Scale and spasticity according to the modified Ashworth Scale. Improvements in the modified Rankin Scale. Improvement in spasticity for 2–3 years, followed by a stable phase of ambulatory and other mobility functions for 4–5 years. No reported adverse events
Faber et al. ⁸⁹	L-Dopa	Amino acid precursor to dopamine	RCT demonstrated no significant improvement for SPG11 HSP-related parkinsonism
Diniz de Lima et al. ¹²³	Botulinum toxin type A injection	Inhibits neuromuscular function by binding presynaptically to cholinergic nerve terminals and lowering acetylcholine release	Reduction in the adductor tone, with transient and tolerable adverse events. No functional improvement observed
Bellofatto et al. ¹²¹	Dalfampridine (4-aminopyridine)	Targets the nervous system directly, and blocks the voltage-gated potassium channels to improve action potential conduction in demyelinated axons	General improvement in motor function as measured by gait analysis, TWT, the 6 MWT. Decreased weariness on the MFIS. Perceived improvement in emotional stability. Greater concentration when doing specified activities
Marelli et al. ¹²⁴	Cholesterol-lowering drugs (atorvastatin)	Reduction in plasma 27-OHC	Significant reduction in total serum bile acids associated with a relative decrease of ursodeoxycholic and lithocholic acids compared to deoxycholic acid., for SPG5-related HSP
Sardina et al. ¹²⁵	Pharmacological interventions inhibiting neddylation-mediated degradation in neurons	Inhibits neddylation-mediated degradation in neurons	Inhibition of neddylation processes effectively restores spastin levels and subsequently rescue neurite cells in spastin mouse model of HSP and patient-derived cells. Promising potential as a therapeutic target for addressing SPG4-HSP

HSP: hereditary spastic paraplegia; GABA: Gamma-aminobutyric acid; SPG: spastic paraplegia; MAS: MAS modified Ashworth scale; SPRS: spastic paraplegia rating scale, MFIS: modified fatigue impact scale, 6 MWT: 6-meter walk test; *CYP7B1*: oxysterol-7-hydroxylase; L-Dopa: Levodopa; MSWS-12: 12-item multiple sclerosis walking scale; TWT: time up and go test; 27-OHC: 27-hydroxycholesterol.

HSP patients, an RCT conducted on individuals with *SPG11* HSP-related parkinsonism did not show significant improvements in the cohort.⁸⁹ This disparity highlights the need for more comprehensive research to unravel the complex mechanisms underlying parkinsonism in HSP. For instance, the ineffectiveness of L-Dopa treatment might be attributed to extreme postsynaptic disruption, suggesting that further studies are warranted (Table 3).

Botulinum toxin injection. Botulinum toxin functions by inhibiting neuromuscular activity, binding to cholinergic nerve terminals, and reducing acetylcholine release. In a double-blind, randomised, placebo-controlled crossover trial (SPASTOX Trial), 55 HSP patients received either botulinum toxin type A (BoNT-A) injections or saline injections.¹²³ The results indicated that BoNT-A effectively reduced adductor tone, with transient and tolerable adverse events. However, it did not lead to significant functional improvements (Table 3).¹²³

Dalfampridine (4-aminopyridine). Dalfampridine, an oral medication given at a dose of 10 mg twice daily for 15 days, yielded significant results in trials. It is a voltage-dependent potassium channel blocker designed to enhance walking ability in patients.¹²¹ A study involving six patients showed a general improvement in motor function, as assessed through gait analysis, the time up and go test (TWT), the 6-meter walk test (6 MWT) and reduced fatigue based on the Modified Fatigue Impact Scale (MFIS). Patients also reported enhanced concentration during specific activities and perceived improvements in emotional stability.¹²¹ Nevertheless, since these studies were uncontrolled, further controlled research is essential to provide stronger evidence regarding the safety and efficacy of dalfampridine for HSP patients (Table 3).

Cholesterol-lowering drugs. *SPG5*-HSP is caused by recessive mutations in the gene for oxysterol-7-hydroxylase (*CYP7B1*), resulting in the accumulation of neurotoxic oxysterols.¹²⁴ Cholesterol-lowering drugs, such as atorvastatin, have shown some potential in managing this subtype of HSP. A study involving 14 HSP patients revealed that treatment with atorvastatin led to a moderate reduction in plasma 27-hydroxycholesterol (27-OHC) levels, along with a significant decrease in total serum bile acids. This was associated with a relative decrease in ursodeoxycholic and lithocholic acids when compared to deoxycholic acid levels (Table 3).¹²⁴

Drugs inhibiting neddylation process. As previously elucidated, the diminished function of spastin has been associated with the pathogenesis of HSP. Investigations conducted in a spastin mouse model of HSP and utilising patient-derived cells have unveiled that the overexpression of Homeodomain Interacting Protein Kinase 2 (*HIPK2*) or inhibition of neddylation processes can effectively restore spastin levels and subsequently rescue neurite cells.¹²⁵ These insightful

observations present the intriguing prospect of employing pharmacological interventions to inhibit neddylation-mediated degradation in neurons, thereby unearthing a novel and promising therapeutic target for addressing *SPG4*-HSP (Table 3).¹²⁵

Non-pharmacological therapies

Transcranial and direct current stimulation. Research into transcranial and direct current stimulation as potential treatments for HSP has been undertaken to alleviate symptoms and enhance patients' quality of life. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that involves modulating neural networks by applying magnetic pulses.¹²⁶ Two RCTs have explored the use of rTMS. Although one trial, involving eight patients, showed improvements in lower limb spasticity, secondary outcomes such as lower limb motor function and short-term quality of life improvements did not significantly differ between treatment and control groups.¹²⁷ In the other trial, leg muscle strength improved, but spasticity in distal leg muscles did not significantly change.¹²⁶ Although there was speculation that rTMS could be paired with gait training to achieve greater functional improvements, an RCT on gait-adaptability training for HSP patients did not show significant benefits.¹²⁸ Notably, an RCT on transcutaneous spinal direct current stimulation (tsDCS), a non-invasive method for modulating spinal cord function, demonstrated reductions in spasticity and is proposed as a complementary strategy for patients not responding to alternative treatments (Table 4).¹²⁹

Selective dorsal rhizotomy. Selective dorsal rhizotomy (SDR) is a surgical procedure commonly used to manage spastic cerebral palsy, aiming to reduce spasticity and enhance ambulatory function. It has also been explored for HSP patients.¹³⁰ In a study by Park et al.,¹³⁰ 37 HSP patients, with *SPG4* and *SPG3A* being the most common genetic mutations, underwent SDR. The procedure successfully eliminated spasticity in almost 90% of the patients, enabling them to regain independence. Approximately 16% of the patients experienced an improvement in ambulatory function, regaining their ability to walk independently. Although complications are rare, they can include spinal fluid leaks, mild lower limb numbness, and functional decline necessitating the use of a wheelchair (Table 4).¹³⁰

Disease modifying therapies and biomarkers. Currently, there are no available disease modifying therapies (DMTs) for HSP. However, certain subtypes may present opportunities for the development of interventions. For example, *SPG5*, characterised by a loss-of-function mutation leading to the accumulation of 25- and 27-hydroxycholesterol, which can cross the blood-brain barrier and disrupt neurons, has been a focus of study. The injection of *CYP7B1* mRNA has been explored as a potential treatment option.¹³¹ This strategy has

Table 4. Summary table of the effects of non-pharmacological interventions on hereditary spastic paraplegia.

Author, Year	Intervention	Action	Studied effect in HSP
Bastani et al. ¹²⁷ , Antczac et al. ¹²⁶	Repetitive transcranial magnetic stimulation	Non-invasive modulation of the neural network by the application of magnetic pulses	Limited improvements in lower limb spasticity and leg muscles strength
Ardolino et al. ¹²⁹	Spinal direct current stimulation	Non-invasive modulation of spinal cord function, possibly through modulating GABA(a)ergic intracortical networks and interhemispheric balance	Improvement in spasticity levels of participants, and proposed as a complementary treatment option
Park et al. ¹³⁰	Selective dorsal rhizotomy	Surgical intervention entails the selective severing of sensory nerve fibres, typically those contributing to the induction of spasticity	Almost 90% of the patients experienced successful removal of spasticity and ability to regain independence. 16% of the patients experienced improvement in ambulatory function and regained independence in walking. Complications, although rare, include spinal fluid leak, mild lower limb numbness and functional decline requiring wheelchair
Hauser et al. ¹³¹	<i>CYP7B1</i> mRNA injection	Injections containing <i>CYP7B1</i> mRNA facilitates the conversion of 25- and 27-hydroxycholesterol and mitigates the accumulation of neurotoxic lipids	Positive results in animal studies of HSP, <i>SPG5</i> in particular, leading to lowered 25- and 27-hydroxycholesterol levels in mice liver and brain
Costamagna et al. ¹³⁴	Human NMJ generated from patient-derived iPSC	The NMJ model was created to produce lower motor neurons and myotubes, thereby preserving the genetic characteristics of the HSP patient donors	Promising potential in the exploration of novel treatment options for rescuing axonal defects and diverse cellular processes, including membrane trafficking intracellular motility and protein degradation in HSP

HSP: hereditary spastic paraplegia; SPG: spastic paraplegia, MAS: MAS modified Ashworth scale; SPRS: spastic paraplegia rating scale; MFIS: modified fatigue impact scale; 6 MWT: 6-meter walk test; *CYP7B1*: oxysterol-7-hydroxylase; iPSC: induced pluripotent stem cells; NMJ: neuromuscular junction.

demonstrated a reduction in the accumulation of neurotoxic agents in mouse liver and brain. Given the potential for targeting this enzyme through lipid-lowering therapies,¹³² it is conceivable that DMTs may be identified along this route in the future (Table 4).¹³¹

Novel stem cells. The use of patient-derived induced pluripotent stem cells (iPSCs) has been investigated for various neurological and motor disorders, including spinal muscular dystrophy and ALS. However, HSP, characterised by more widespread axonal degeneration that extends beyond the corticospinal tract, may limit the potential application of iPSCs, as described in the literature.¹³³ Human neuromuscular junctions (NMJs) generated from iPSCs obtained from five HSP patients have shown promise. These NMJs create lower motor neurons and myotubes while maintaining the genetic background of HSP patient donors.¹³⁴ The NMJ model has displayed potential in exploring novel treatment options for addressing axonal defects and various cellular processes, including membrane trafficking, intracellular motility and protein degradation in HSP (Table 4).¹³⁴

Limitations of study

This comprehensive review employs a methodologically rigorous approach to elucidate various facets of HSP, offering

valuable insights into its underlying mechanisms, genetic determinants and the current landscape of treatment options, including those under active investigation. Nevertheless, it is essential to acknowledge certain inherent limitations.

Firstly, the literature search strategy encompassed a diverse array of reputable databases, including Scopus, MEDLINE, EMBASE and the Cochrane Library. Despite the diligence in this process, it is possible that some pertinent studies on the subject may have inadvertently been omitted, as no search methodology can claim absolute exhaustiveness. Secondly, a notable limitation lies in the review's exclusive focus on English-language literature. While this approach ensured the inclusion of a substantial body of relevant research, it may have unintentionally excluded valuable insights presented in non-English publications. This linguistic bias introduced by the language restriction warrants consideration, as it may have implications for the comprehensiveness of the review. Furthermore, the review process itself may introduce certain biases. For instance, the selection of specific keywords for the search query may inadvertently exclude relevant literature that employs differing terminology, thereby potentially affecting the scope of the review. Interpretive bias, stemming from the subjective judgement involved in synthesising and analysing the selected literature, is an additional limitation. Lastly, it is worth noting that some studies are small-scale with limited

sample sizes, limiting the generalisability of the findings across the population.

Conclusion and prospects

Due to the heterogeneous clinical nature of HSP, early diagnoses and subsequent management becomes challenging. Although genetics-based management has shown progress for some neurological disorders, HSP lags behind due to its genetic diversity, complex disease processes, range of subtypes and slower disease onset. Moreover, screening and scoring systems, such as the 6- and 10-min walk test alongside the TWT used to assess fatigue and quality of life, may be beneficial in HSP. To advance our understanding and treatment of this neuromuscular condition, extensive research is required, which should involve international collaboration and RCTs conducted on substantial population cohorts. These efforts are particularly critical when considering the administration of combination medications. Furthermore, there is a pressing need for the identification of biomarkers and distinctive mechanisms that can differentiate HSP from other neurological disorders presenting similar clinical symptoms. Additionally, research should focus on the development of promising pharmacological and non-pharmacological treatments, striving to strike a balance between treatment efficacy and the mitigation of adverse effects when addressing HSP symptoms.

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Author contributions

Conceptualisation: W.A.A. and H.H. Data Curation: W.A.A., J.K.T., A.D.S., T.F., F.T.A., A.M., J.W., L.D., E.C. and H.H. Writing – Original draft: W.A.A., J.K.T., A.D.S., T.F., F.T.A., A.M., J.W., L.D., E.C., H.H., T.A.R., V.S., O.A., J.K., R.J. and D.E.M. Writing – Second draft: W.A.A., J.K.T., A.D.S., T.F., F.T.A., A.M., J.W., L.D., E.C., H.H., T.A.R., V.S., O.A., J.K., R.J., D.E.M., K.S., O.K. and M.Y.D. Review and Editing: W.A.A., J.K.T., A.D.S., H.H., O.A. and M.Y.D. Visualisation: V.S. and A.D.S. Approval of final manuscript: All authors.

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ORCID iDs

Wireko Andrew Awuah  <https://orcid.org/0000-0003-2380-2949>

Favour Tope Adebuseye  <https://orcid.org/0000-0001-5362-3920>

Riaz Jiffry  <https://orcid.org/0000-0001-7479-3224>

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