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Abstract:

Introduction

Hereditary spastic paraplegias (HSPs) are heterogeneous neurodegenerative disorders characterized by progressive lower limb weakness and spasticity as core symptoms of the degeneration of the cortico-spinal motor neurons. Even after exclusion of infectious and toxic mimickers of these disorders, the definitive diagnosis remains tricky, mainly in sporadic forms, as there is significant overlap with other disorders. Since their first description, various attempts failed to reach an appropriate classification. This was due to the constant expansion of the clinical spectrum of these diseases and the discovery of new genes, a significant number of them was involved in overlapping diseases.

Areas covered

In this perspective review, extensive literature study was conducted on the historical progress of HSP research. We also revised the previous and the current classifications of HSP and the closely related neurogenetic disorders and analysed the areas of overlap.

Expert opinion/commentary

There is undeniable need for objective case definition and reclassification of all neurogenetic disorders including HSPs, a prerequisite to improve patient follow-up, biomarker identification and develop therapeutics. The challenge is to understand why mutations can give rise to multiple phenotypic presentations along this spectrum of diseases in which the corticospinal tract is affected.

TEXT

Hereditary spastic paraplegias (HSPs) consist of a group of neurodegenerative disorders which are characterized by progressive lower limb weakness and spasticity as the core clinical features [1].

Historically, HSP has been classified as pure (uncomplicated) or complex (complicated), according to the absence or presence of additional neurological and non-neurological features. The disease can be inherited as autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), or through mitochondrial/maternal transmission (Table 1).

Even after excluding, in sporadic cases, toxic or infectious causes and compression of the spinal cord, overlaps with other neurological disorders characterized by spastic paraplegia/quadriplegia can lead to challenging diagnostic difficulties. This is also true for familial forms with the surge of newly identified causative genes consequent to the emergence of next-generation sequencing (NGS)-based techniques that have recently extended, to unexpected level, the phenotypic and genetic heterogeneity of HSPs.

History of spastic neurogenetic disorders

It is important to go back to the history of HSP and the evolution of its definition and classification over time in order to understand the dimensions of HSP. This will help to identify the clinical and functional links between all the overlapping neurogenetic disorders that present with a pyramidal syndrome as all or part of their phenotypic spectrum.

HSP was first described by the German neurologist Adolph Strümpell in 1883 and was characterized more extensively by the French physician Maurice Lorrain in 1888. Indeed, HSP is still sometimes referred to as Strumpell–Lorrain disease. The new era of genetics prompted A. E. Harding to suggest a classification of hereditary ataxias (HAs) and HSPs in 1983 [1]. In this classification, HSP was distinguished into pure and complicated HSP and each was further

divided into subtypes based on the mode of inheritance in the case of pure HSP and on clinical syndrome presentation in the case of complicated forms. It is worth mentioning that many of the syndromes included in Harding's complicated forms have now been reclassified as subtypes of other overlapping syndromes. Examples include Sjögren–Larsson syndrome (SLS), now classified as leukodystrophy [2], and AR spastic ataxia of Charlevoix–Saguenay (ARSACS) [3], often considered within the classification of ataxic syndromes. Other subclasses were broadly described as could be predicted in that era when modern genetic studies were just starting [1].

Only five loci and one gene had been described by 1996 [4]. By 1999, 12 loci, including six AD loci and two XL genes had been linked to HSP [5]. Progress with the human genome sequence project (publication of the draft genome in 2001 and completion of the sequence in 2004) heralded a new era of medical and genetic research, and neurogenetic research was no exception [6,7]. By 2003, 20 loci and nine genes involved in HSP had been identified [8]. The advent of NGS technologies in the late 2000s [9,10] has resulted in the identification of an even larger number of genes especially since 2010 with more than 60 or 80 genes implicated, according to the classifications [11].

A continuum of spastic neurogenetic disorders

Neurodegeneration can now be considered a continuum of disorders. This concept is illustrated by the following two features in HSP.

First, mutations in one gene give multiple neurogenetic diseases. Mutations in multiple spastic paraplegia (SPG) genes can account not only for HSP but also for other phenotypes where spasticity is not always present among the core phenotypic features. A good example is SPG39, due to mutations in *PNPLA6*, initially identified in pure HSP patients but the phenotype was further extended to spastic ataxia, including not only Gordon Holmes ataxia but also Boucher

Neuhauser syndrome, which does not include spasticity (Figure 1) [12]. This is also the case across the wide spectrum of motor neuron diseases (MND), in which mutations in *KIAA1840* (SPG11) and *ERLIN1* (SPG62) can account for amyotrophic lateral sclerosis (ALS) in addition to HSP [13-17], and *ERLIN2* (SPG18) regarding primary lateral sclerosis (PLS) and HSP [18,19]. The reverse situation is also true: mutations in *ALS2*, a major cause of ALS, are also found in HSP families [20]. Moreover, mutations in *HSPD1* (SPG13) or *FA2H* (SPG35) are associated with a range of phenotypes going from adult onset HSP to early onset leukodystrophy [21-25]. SPG7 mutations are also leading to late-onset cerebellar ataxia, adult-onset spastic ataxia or isolated optic neuropathy with no other neurological sign [26]. Finally, two mitochondrial genes provide clear examples of genes that present with phenotypic alleles: *MT-ATP6* and *MT-CO3*. *MT-ATP6* has recently been related to HSP [27]. Previously, *MT-ATP6* was linked to Leigh syndrome, Leber hereditary optic neuropathy (LHON) and NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome [28-30]. *MT-CO3* gene has been linked to HSP but with a Leigh syndrome-like lesion in the brain [31]. This phenotypic diversity can also extend to non CNS disorders as shown by mutations in *SPG17* that are found in patients with HSP, encephalopathy, neuropathy and amyotrophy (Silver syndrome) and patients with Berardinelli-Seip congenital lipodystrophy [32-38]. The nature of the mutations provides here phenotype-genotype correlations. Another example illustrating the clinical overlap with other diseases is SPG9. The identification of mutations in the causative gene (*ALDH18A1*) and the study of the proposed protein function provided the first demonstration of the involvement of the amino acid metabolic pathway in HSP [39,40], which was considered as a differential diagnosis of HSP, as is the case with other genes/proteins such as *ARG1* related to the urea cycle [41,42] or other genes related to lipid metabolism (e.g.: *GBA2*/SPG46, *DDHD2*/SPG54, *CYP7B1*/SPG5, *B4GALNT1*/SPG26, etc) [43]. *ALDH18A1* was initially reported to be involved in a neurocutaneous disorder with recessive inheritance associating *cutis laxa*, cataract and

neurodevelopmental delay without spasticity [44], but it was associated later with pure HSP [39] and more recently with complex HSP, particularly associating cerebellar manifestations and further expanding its phenotype [45]. Mutations in *ALDH18A1* are also an example of the limitations of the classifications distinguishing HSP according to the mode of transmission, as AR and AD inheritance with the neurocutaneous syndrome or the HSP phenotype have both been identified, adding to the immense complexity of these disorders. Indeed, multiple inheritance patterns have now been associated with multiple HSP genes, including *SPG7* [26, 46], *SPG58* [17, 47], SPG9*/ALDH18A1* [39, 40], *SPG72* [48], *SPG18/ERLIN2* [18] and it would not be surprising if other genes are added to this list and if oligogenism/digenism were to account, in the future, for a significant proportion of HSP cases. These recently characterized novel clinico-genetic forms implicating lipid or amino acid metabolism raise the question of whether or not metabolic spastic disorders (previously classified as non HSP conditions (e.g., *ARG1*) should now be reclassified as HSP or if, more likely, a larger revision of the nosology of neurological conditions needs to be undertaken.

Second, mutations in a causative gene can be associated with neurological signs that are the major clinical features of overlapping diseases. This phenomenon is sometimes inseparable from the above observation about one gene presenting with multiple allelic disorders. For example, hereditary ataxias (HA) and HSP represent the two extremes of the spectrum of spinocerebellar neurodegenerative disorders. HAs can sometimes be difficult to differentiate clinically from HSPs as cerebellar manifestations are present as part of their clinical presentation in more than 30 clinico-genetic SPG entities (Figure 2). The reverse is also frequent. This is well illustrated with mutations in *GBA2* published either in patients with ataxia and pyramidal syndrome or in patients with HSP with ataxia [43,49]. Many HSP subtypes present with peripheral neuropathy (e.g.: SPG5A, SPG11, SPG17, SPG30, SPG31, SPG57, SPG70 and rarely, SPG3A) and there are genes that can account for multiple phenotypes. Along

this continuum of disorders affecting the first and second motor neuron are genes like *SPG11* (HSP, ALS and Charcot-Marie-Tooth disease), *ALS2* (PLS, ALS, HSP) or *BICD2* (HSP, spinal muscular atrophy) [11]. Another example is leukodystrophy, a non-neurodegenerative group of disorders. Although leukodystrophy is classified as a differential diagnosis of HSP that should be excluded in the early steps of clinico-genetic investigations, white matter abnormalities are described as a complicating feature for at least 28 HSP subtypes, making the distinction between these differential diagnoses a real challenge. Consequently, there are numerous causative genes that are located in the overlap zone, with related clinical scenarios. Examples of genes located in overlap zones are illustrated in Figure 2. These genes are classified as being related to HSP, HA, leukodystrophy, neurodegeneration with brain iron accumulation (NBIA), parkinsonism, PLS and ALS, cerebral palsy spastic quadriplegia (CPSQ), hereditary dystonia, mental retardation, peripheral neuropathy (PN) and even some inborn errors of metabolism (IEM) or neuro-development disorders. Clearly not all the above-mentioned categories are neurodegenerative, as exemplified by some of the overlapping metabolic disorders: e.g., leukodystrophy and IEM.

All these observations following the explosion of results from NGS techniques suggest that clinico-genetic classifications are imperfect and a new classification combining the clinical, genetic and cellular pathogenic mechanisms may provide a sound option that could be used to stratify the patients for future treatment strategies [50].

Therapeutic options.

There is no curative treatment for HSP yet, and only few symptomatic treatments are available for the disease. The existing options include physiotherapy, surgical intervention and pharmacological treatments (e.g.: antispastic drugs, botulinum toxin). Elucidation of the underlying pathogenic mechanisms is still required to develop more effective therapeutic

agents and reveal potential biomarkers for their evaluation in clinical trials. The putative functions of the known HSP proteins [51], mainly involved in the intracellular trafficking, lipid metabolism and mitochondrial functions together with the analysis of animal and cellular models, including neurons derived from human induced pluripotent stem cells (hiPSC), have highlighted potential targets of interest. The interplay between the mitochondrion compartment, the microtubule cytoskeleton and the tubular endoplasmic reticulum seem critical in HSP pathogenesis [52, 53]. Preclinical trials in SPG4 knockout flies indicated that drugs that destabilize microtubules might have therapeutic interest [54, 55]. Another trial on hiPSC derived from SPG4 patients showed full response to lentiviral overexpression of spastin isoforms with reversion of the observed neuritic impairments [56]. In addition, intramuscular viral delivery of paraplegin (*SPG7*) partially rescued the peripheral axonopathy occurring in the *SPG7*-deficient mouse model [57].

In view of therapeutics in the long term, there are very few available biomarkers. Brain magnetic resonance imaging is probably the most sensitive in complex forms. The recent involvement of metabolic genes/proteins in the pathogenesis in neurodegenerative disorders confers an additional outstanding value of being amenable to potential therapeutic interventional measures. Their accumulating metabolites can be used as biomarkers to monitor the disease progression and the response to treatment in clinical trials. Magnetic resonance spectroscopy has been used to detect accumulations of metabolites in the brain as in the case of *DDHD2* [58]. 27-OH cholesterol in SPG5 patients was found to accumulate in blood and cerebrospinal fluid but its reversion to normal values through the use of statins was only possible in the blood under the treatment window used [59,60].

Hormones, like testosterone in SPG46 male patients [43], or biochemical dosages such as amino-acid levels in *ALDH18A1*-mutated patients [39] are also potential biomarkers in specific forms. Finally, gangliosides in the brain of patients mutated in *SPG11* can be considered as

pathological hallmarks of the most frequent form of recessive spastic paraplegia but their relevance as biomarkers has not been established yet, although acting on their level in zebrafish Spg11 models improved their motor phenotype [61]. The lack of large cohorts of patients here is an issue facing biomarker discovery/validation and shows the need for large continental registries.

Expert commentary: A new nosology and objective case definition of HSP: a timely issue

As already indicated, HSPs share multiple overlap zones with other neurogenetic disorders, with or without pyramidal features as the core phenotype. Consequently, the concept of neurodegeneration as a continuum of disorders is now gaining strength based on the huge amount of knowledge obtained over the past ten years and the rapidly expanding numbers of HSPs and overlapping disorder subtypes regularly being discovered.

This first raises the fundamental question of specificity of the lesions and why sometimes the same mutation can be associated with different clinical presentations and even different diseases along the continuum of disorders. It also highlights the question about the involvement of modifiers, as in SPG4, and their probable role in this complexity. Indeed, most of the time, there is no clear phenotype-genotype correlation as shown for *SPG39*/*PNPLA6* mutations [12].

The second aspect of these observations is related to the clinical practice. There is now an urgent need for a new nosology with a wider umbrella that includes all closely related neurological disorders. This has recently given rise to a number of reviews highlighting these overlaps [11, 62, 63] and suggesting reclassification [50] or even expert case definition and classification of some of these entities (leukodystrophies and leukoencephalopathies) [64].

There is a definite need for improved and more objective case definition in order to minimize subjectivity in diagnosis, especially with regard to the overlap zones, and to decrease technical

diagnostic difficulties arising from a lack of sufficient expertise in the rapidly growing field of neurogenetics. The validation of variant pathogenicity is often a bottleneck in reaching high diagnosis yield, calling then for the development of dedicated validation assays as developed for mutations in *CYP2U1* [65]. The problem is further amplified when the setting does not provide the necessary multi-systemic medical neurogenetic centers with suitably equipped facilities and the required expertise for a neurogenetic workup in developing countries. If we consider that many of these communities have high levels of consanguinity with predominant AR patterns of inheritance and with a high chance of private new genes being discovered, the importance of guidelines and classification to facilitate proper phenotypic stratification at minimal cost is clearly apparent. This point has been highlighted by the high number of genes discovered through international collaborations between teams with high-level facilities and specialists from developing countries [17].

A simple and practical working frame for neurogenetic disorders will increase the chance of faster discovery rates for genes and a better understanding of the physiopathological background and emergence of new phenotypes. Guidelines for reporting pathologic variants and their associated phenotypes and clear curation and validation strategies are also required to avoid reporting false positive mutations and their consequences in classification of neurogenetic disorders. Indeed, the biological effect of the ZFYVE27 mutation is still debated on SPG33 [66]. This calls for the necessary validation of the biological effect of mutations in new genes, even when dealing with expanding phenotypes of known genes, either through functional assays [65] or through multiple cases observation. All these measures will have major repercussions on our understanding of these disorders. Collaborative efforts, particularly in large registries and phenotype/genotype correlations, and knowledge sharing at international level are one solution to achieve progress with these complex disorders.

Five-year view

In an optimized classification of neurogenetic disorders the disease identifier will likely include the name of the mutated gene, the main phenotype (HSP, HA, Complex HSP, complex HA, etc) and the inheritance mode or zygosity of the mutation. Branching based on cellular pathogenetic mechanisms can be added within each phenotype or in parallel to be included when therapeutic options are to be considered. This will make more feasible the formation of large cohorts of patients mutated in a given gene if dedicated databases are promoted by reference centers in the field, a prerequisite for natural history studies, biomarker validation and therapeutic trials in rare disorders, as done recently in the case of SPG5 [59,60].

Key issues

- Hereditary spastic paraplegias are heterogeneous disorders with phenotypic overlap with other neurogenetic conditions.
- Genes mutated in spastic paraplegias are those found mainly in HSP patients (>60) and those mutated in other neurogenetic conditions for which spasticity can occasionally occur as the major clinical presentation.
- Diagnosis is complicated by the occurrence of multiple inheritance modes associated to a given gene, sometimes with the same mutations.
- The lack of phenotype-genotype correlations and of validated biomarkers in most cases is a challenge for future therapeutic opportunities.

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** : of considerable interest

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Figure legends

Figure 1. Schematic illustration of the phenomenon of causative HSP genes that can be mutated and that can account for other diseases with overlapping signs, including peripheral neuropathies, ataxias and extra pyramidal syndromes.

Mutations in *BSCL2* can account for Charcot Marie Tooth 4D neuropathy and SPG17; *KIF1A*, for hereditary autonomic neuropathy and SPG30; *REEP1*, for hereditary motor neuropathy 5B and SPG31; *PNPLA6*, for SPG39 and Boucher Neuhauser ataxia. *SACS* mutations are associated to spastic ataxia phenotypes but pure forms of ataxia or HSP can be found. *SPG7* can be mutated in cases with optic neuropathy, SPG7 and late-onset ataxia.

Figure 2. Diagram showing the overlap zone between several spastic neurogenetic disorders: evidence for the need of new nosology and objective case definition.

Genes mutated in mixed phenotypes that include spasticity are shown, regardless they are in the HSP classification or in the classification of overlapping diseases.

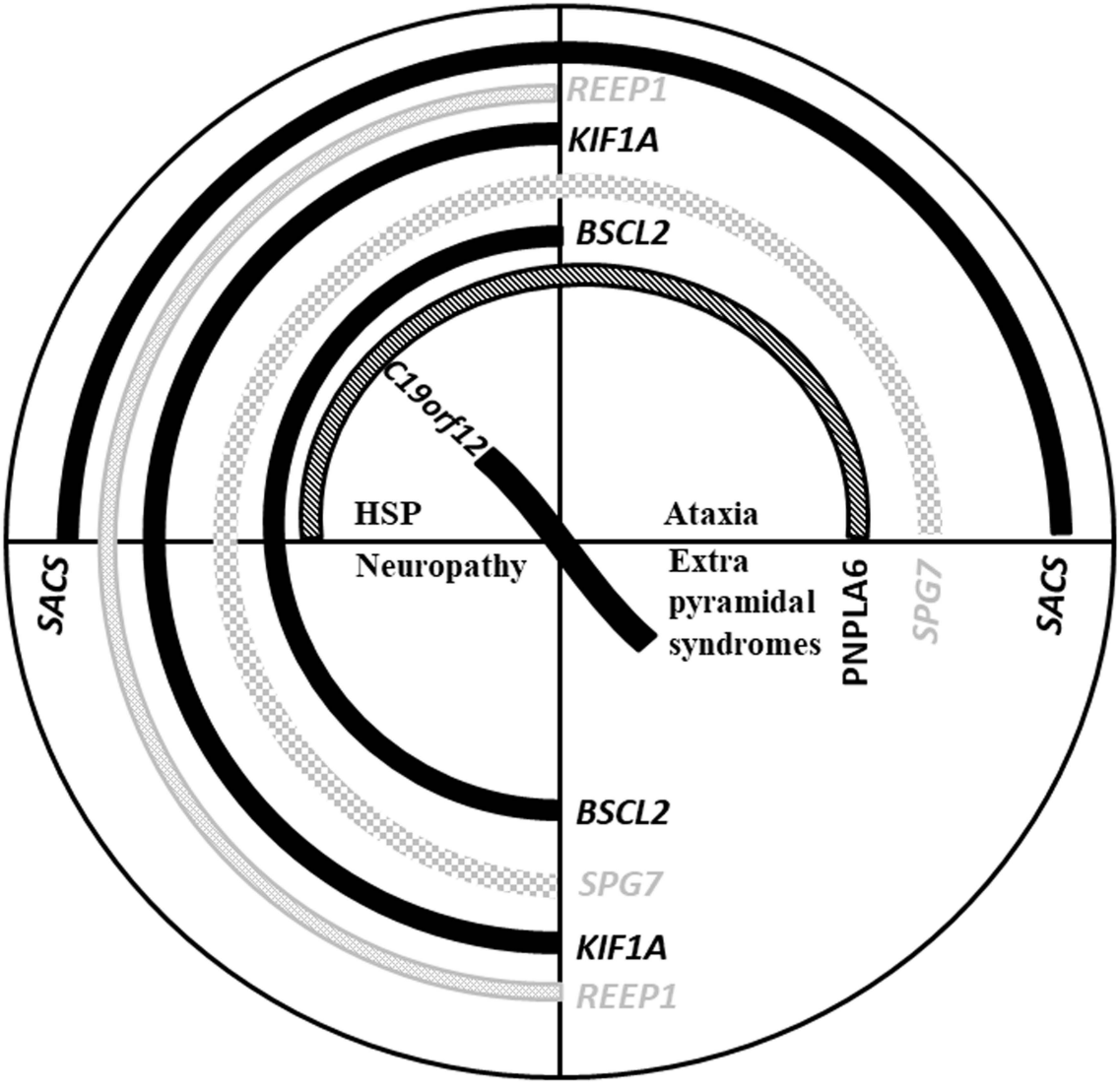
HSP: hereditary spastic paraplegia; PLS: primary lateral sclerosis; ALS: amyotrophic lateral sclerosis; PN: peripheral neuropathy; CPSQ: cerebral palsy spastic quadriplegia; NBIA: neurodegeneration with brain iron accumulation; PD: Parkinson disease; WMH: white matter hypersignals.

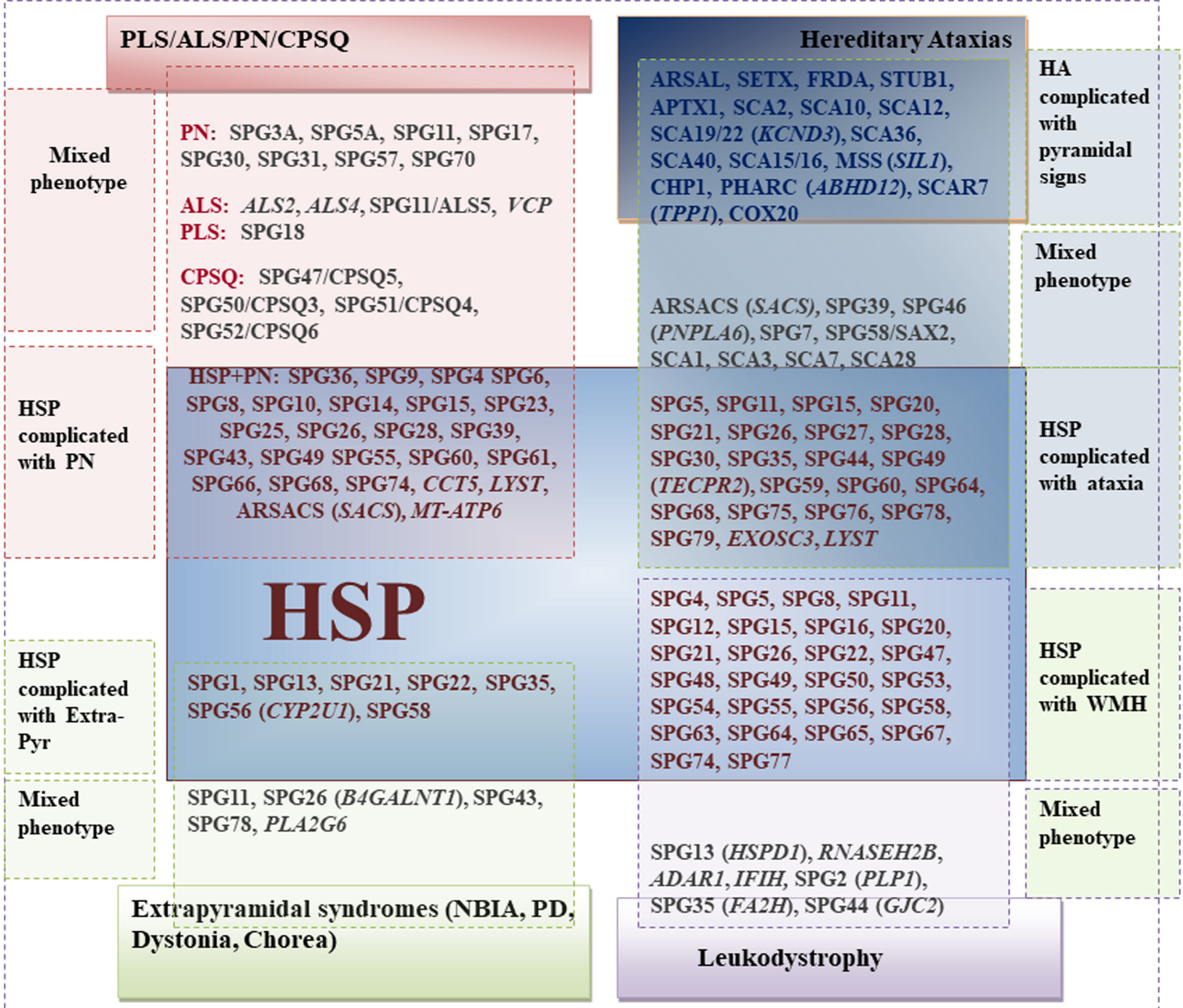
Clinical summary	No. of HSP forms	HSP forms
CLASSICAL HSP with predominant pyramidal syndrome		
Pure HSP	**15**	**AD: SPG4, SPG6, SPG31, SPG33, SPG38, SPG12, SPG19, SPG40, SPG41, SPG42, SPG73** **AR: SPG62, SPG71, SPG24, SPG15, SPG11, SPG77** **Other genes: AR; *ADAR1*, *IFIH1*, *RNASEH2B*** **Mixed; SPG30, *SPG72*, XL; *SPG34***
Complicated HSP	**33**	**AD: SPG4 *SPG8, SP*G10,SPG13, SPG17, SPG31 SPG36, SPG4, SPG6, SPG33, SPG38** **Other genes: VCP** **AR: SPG5, SPG11,SPG14, SPG15, SPG18, SPG20, SPG21, SPG23, SPG27, SPG28, SPG35, SPG44, SPG45, SPG53, SPG54, SPG55, SPG56, SPG57, SPG59, SPG60, SPG61, SPG64, SPG65, SPG66, SPG68, SPG69, SPG70, SPG74, SPG75, SPG25, SPG39, SPG48, SPG63,SPG67,SPG32, SPG76** **Other genes: CCT5, FAM134B, LYST, EXOSC3** **XL: SPG1, SPG16** **Mito: MT-TI, MT-CO3, MT-ATP6** **Mixed: SPG3A, SPG7, SPG30** **Other genes: *BICD2***
Atypical forms (pyramidal syndrome not always prominent)		

Spastic ataxia (equal burden)/ hereditary ataxia	**1**	**AR: SPG39, SPG46, ARSACS, SPG79** **AD: SPG7, SPG58**
Upper or lower motor neuron diseases (ALS or CMT-like)	**1**	**AR: SPG11, SPG62**
HSP (secondary to metabolic disorder)	**1**	**AR: SPG5A, SPG77** **Mixed: SPG9**
Cerebral Palsy-like	**4**	**AR: SPG47, SPG50, SPG51, SPG52**
Complex presentation with pyramidal signs	**3**	**AD: SPG29** (gene not known but phenotype suggests probable metabolic pathway involvement) **AR: SPG49(*TECPR2*), SPG56** **XL: SPG22**
NBIA / Leukodystrophy	**3**	**AR: SPG43, SPG44, SPG78** **XL: SPG2**

Table 1. Clinical classification of various clinico-genetic HSP forms.

CMT: Charcot-Marie-Tooth neuropathy; HSP: hereditary spastic paraplegia; amyotrophic lateral sclerosis; NBIA: neurodegeneration with brain iron accumulation. **AD=autosomal dominant, AR= autosomal recessive, XL=X linked, Mito = Mitochondrion, Mixed=mixed inheritance: AD/AR**


REEP1
KIF1A
BSCL2
C19orf12
HSP
Neuropathy
Ataxia
Extra
pyramidal
syndromes
SACS
PNPLA6
SPG7
SACS
BSCL2
SPG7
KIF1A
REEP1


PLS/ALS/PN/CPSQ
Hereditary Ataxias
Mixed phenotype
PN: SPG3A, SPG5A, SPG11, SPG17, SPG30, SPG31, SPG57, SPG70
ALS: ALS2, ALS4, SPG11/ALS5, VCP
PLS: SPG18
CPSQ: SPG47/CPSQ5, SPG50/CPSQ3, SPG51/CPSQ4, SPG52/CPSQ6
ARSAL, SETX, FRDA, STUB1, APTX1, SCA2, SCA10, SCA12, SCA19/22 (KCND3), SCA36, SCA40, SCA15/16, MSS (SIL1), CHP1, PHARC (ABHD12), SCAR7 (TPP1), COX20
HA complicated with pyramidal signs
Mixed phenotype
ARSACS (SACS), SPG39, SPG46 (PNPLA6), SPG7, SPG58/SAX2, SCA1, SCA3, SCA7, SCA28
HSP complicated with PN
HSP+PN: SPG36, SPG9, SPG4 SPG6, SPG8, SPG10, SPG14, SPG15, SPG23, SPG25, SPG26, SPG28, SPG39, SPG43, SPG49 SPG55, SPG60, SPG61, SPG66, SPG68, SPG74, CCT5, LYST, ARSACS (SACS), MT-ATP6
SPG5, SPG11, SPG15, SPG20, SPG21, SPG26, SPG27, SPG28, SPG30, SPG35, SPG44, SPG49 (TECPR2), SPG59, SPG60, SPG64, SPG68, SPG75, SPG76, SPG78, SPG79, EXOSC3, LYST
HSP complicated with ataxia
HSP
HSP complicated with Extra-Pyr
SPG1, SPG13, SPG21, SPG22, SPG35, SPG56 (CYP2U1), SPG58
SPG4, SPG5, SPG8, SPG11, SPG12, SPG15, SPG16, SPG20, SPG21, SPG26, SPG22, SPG47, SPG48, SPG49, SPG50, SPG53, SPG54, SPG55, SPG56, SPG58, SPG63, SPG64, SPG65, SPG67, SPG74, SPG77
HSP complicated with WMH
Mixed phenotype
SPG11, SPG26 (B4GALNT1), SPG43, SPG78, PLA2G6
SPG13 (HSPD1), RNASEH2B, ADAR1, IFIH, SPG2 (PLP1), SPG35 (FA2H), SPG44 (GJC2)
Mixed phenotype
Extrapyramidal syndromes (NBIA, PD, Dystonia, Chorea)
Leukodystrophy