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Overcoming the Divide Between Ataxias and Spastic Paraplegias: Shared Phenotypes, Genes, and Pathways

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Abstract

Autosomal-dominant spinocerebellar ataxias, autosomal-recessive spinocerebellar ataxias, and hereditary spastic paraplegias have traditionally been designated in separate clinicogenetic disease classifications. This classification system still largely frames clinical thinking and genetic workup in clinical practice. Yet, with the advent of next-generation sequencing, phenotypically unbiased studies have revealed the limitations of this classification system. Various genes (eg, *SPG7, SYNE1, PNPLA6*) traditionally rooted in either the ataxia or hereditary spastic paraplegia classification system have now been shown to cause ataxia on the one end of the disease continuum and hereditary spastic paraplegia on the other. Other genes such as *GBA2* and *KIF1C* were almost simultaneously published as both a hereditary spastic paraplegia and an ataxia gene. The variability and fluidity of observed phenotypes along the ataxia-spasticity spectrum warrants a rethinking of the traditional classification system. We propose to replace this divisive diagnosis-driven ataxia and hereditary spastic paraplegia classification system by a descriptive, unbiased approach of *modular phenotyping*. This approach is also open to expansion of the phenotype beyond ataxia and spasticity, which often occur as part of broader multisystem neuronal dysfunction. The concept of a continuous ataxia-spasticity disease spectrum is further supported by ataxias and hereditary spastic paraplegias sharing not only overlapping phenotypes and underlying genes, but also common cellular pathways and disease mechanisms. This suggests a shared vulnerability of cerebellar and corticospinal neurons for common pathophysiological processes. It might be this *mechanistic* overlap that drives their *clinical* overlap. A mechanistically inspired classification system will help to pave the way for mechanism-based strategies for drug development.

Keywords

spinocerebellar ataxia; recessive ataxia; hereditary spastic paraplegia; genetics; classification; pathway; molecular

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Supporting Data

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Hereditary spinocerebellar ataxias and hereditary spastic paraplegias (HSPs) each define a genetically heterogeneous group of rare degenerative disorders characterized by progressive degeneration of the cerebellar Purkinje cells and spinocerebellar tracts (ataxias) and corticospinal tracts (HSPs), respectively. They were traditionally designated in separate clinicogenetic disease classifications, according to the predominant disease phenotype on first gene locus description and to the mode of inheritance:

1. Neurodegenerative diseases first conceptualized as *autosomal-dominant spinocerebellar ataxias* (*SCAs*) were classified in the SCA classification, which entails 43 SCA subtypes to date.[1]
2. Neurodegenerative diseases first described as *autosomal-recessive spinocerebellar ataxias* (*SCARs*) were classified in the SCAR classification, comprising 24 subtypes.[1] This SCAR classification is partly paralleled and duplicated, yet with different numbers, by another autosomal-recessive cerebellar ataxia (ARCA) classification, the ARCA classification.[1]
3. Neurodegenerative diseases first reported with *spastic paraplegia* were classified in the spastic paraplegia gene (SPG) classification irrespective of mode of inheritance. Seventy-eight distinct SPG loci are currently reported by OMIM.[1]
4. A small number of genes presenting with combined ataxia and spasticity were somewhat arbitrarily also categorized as *spastic ataxia* genes (SPAX/SAX). The 7 loci listed in these classifications are mostly duplicate entries also contained in either the HSP or ataxia classification systems.

Each of these classification systems bears in itself the same problems known from similar classification systems of other movement disorders (for a broader discussion, see the analysis by the International Parkinson and Movement Disorder Society Task Force[2]). These include (1) erroneously assigned loci, (2) duplicated loci, (3) missing symbols or loci, and (4) unconfirmed loci and genes.[2] For example, some recessive ataxias are not contained in the SCAR or the ARCA list (eg, Friedreich's ataxia or AOA1), and some recessive ataxias are listed only in one of them (eg, AOA2 only in SCAR classification). Moreover, some dominant ataxias can also be inherited in a recessive manner and vice versa (*GRID2*,[3] *AFG3L2*,[4] *SPTBN2*[5]), making it difficult to designate them as either on the SCA or the SCAR/ARCA list (or both). Most important, the systematic value of each of these classification systems is also very limited. Numbers in the SCA/ARCA/SCAR/SPG lists are assigned in the order in which the disease was identified (initially by linkage analysis and more recently by gene discovery). Yet these numbers do not carry any systematic information in themselves that might help to facilitate clinical diagnostics, to understand the disease etiology, or to devise treatment strategies.

In addition to these shortcomings, each of these classification systems carries in itself the classification systems for ataxias and HSPs that also bear a particular limitation when seen together. They suggest a conceptual and classificatory divide between ataxias and HSPs, when in fact there exists a large phenotypic, genetic, and pathophysiological overlap. This intersection between ataxias and HSPs has been increasingly acknowledged throughout the last decade,[6] but its appreciation was notably facilitated by recent next-generation

sequencing (NGS) studies. Classic clinical and genetic strategies were largely constrained by preexisting clinical conceptions, classifications, and diagnostic workflows, leading to confirmation bias in genotype-phenotype correlation studies. In contrast, NGS has facilitated gene discoveries and phenotypic classifications unbiased from prior clinical and diagnostic preconceptions. This development has led to further weakening and even partial removal of the defined boundaries between ataxias and HSPs. As we show here, recent NGS and related genomic studies have demonstrated

1. a rapidly increasing number of both *novel* genes and *long-established* "ataxia genes" and "HSP genes," causing a phenotypic spectrum ranging from ataxia to HSP as 2 extremes on a continuous spectrum;
2. shared pathways and mechanisms between ataxias and HSPs.

We thus argue to move on from the linkage-inspired divisive classifications system of largely distinct ataxias and HSP categories toward a more *modular understanding of phenotypes* that reflects the increasingly complex relationship between genotype, neuronal system damage, and phenotypic expression. The frequent co-occurrence of ataxia and spasticity might thereby be driven by shared vulnerability of corticospinal tract axons and cerebellar circuits toward disturbances of the same molecular pathways (for graphical overview of the main hypothesis and concept proposed here, see Fig. 1). A mechanistically inspired classification system will prioritize research on shared pathways and pave the way for mechanism-based strategies for drug development.

Discovering the Phenotypic and Genetic Spectrum From the Extremes

Discovery of an increasing number of genes causing both prominent cerebellar and predominantly pyramidal phenotypes over the past few years has raised awareness of the substantial overlap between these 2 disease classifications. Thereby, the "divide" was closed from both sides: classical "HSP genes" were discovered to cause ataxia as well as classical "ataxia genes" were recognized to result in HSP phenotypes.

For genes discovered in the pre-NGS era, it commonly took years (and, in some cases, the phenotypically unbiased screening approaches enabled by NGS application) to overcome the preconception of the predominant phenotype associated with a gene. *SPG7*, identified as a cause of HSP in 1998,[7] was not systematically considered a cause of predominant (and even pure) cerebellar ataxia until 15 years later.[8] Yet, within the past 2 years, it has been appreciated as one of the most common causes of autosomal-recessive cerebellar ataxia,[9,10] and the cerebellar features may be even more pronounced than spasticity in some cohorts.[10] Mutations in *PNPLA6* were identified as a cause of autosomal-recessive HSP complicated by motor axonal neuropathy in 2008, leading to the designation SPG39.[11] However, it was not before 2014 that mutations in *PNPLA6* were also appreciated as a cause of predominant cerebellar ataxia,[12,13] and it has now been shown that *PNPLA6* mutations can even cause pure cerebellar ataxia.[14] In light of these observations of patients with predominant or pure cerebellar disease, the terms "SPG7" and "SPG39" reflect the historical meaning at best — and appear to be misnomers for these patients and phenotypes. The fatty acid 2-hydroxylase gene (*FA2H*) is even part of multiple classification systems. After initially being discovered

as the causative gene for leukodystrophy associated with spastic paraparesis and dystonia,[15] it was published 2 years later as a novel HSP gene (*SPG35*),[16] only to be recognized to cause a novel form of neurodegeneration with brain iron accumulation (NBIA) termed FAHN — *FA2H*-associated neurodegeneration — a few months later.[17] Not until recently, the substantial cerebellar ataxia present in many patients with *FA2H* mutations was systematically recognized.[18,19]

Likewise, HSP phenotypes were often recognized belatedly for "traditional" ataxia genes. Recessive mutations in *SYNE1* were identified as a cause of cerebellar ataxia in 2007[20] and consequently designated ARCA1 and SCAR8. For almost a decade mutations in *SYNE1* were thought to cause a slowly progressive, largely pure cerebellar ataxia,[21,22] before it was realized in 2016 that they are in fact causative for a broad pleiotropic phenotypic spectrum, with corticospinal tract damage and even predominant complicated HSP presentations among the most frequent features.[23,24] Recessive mutations in *PLA2G6* were found in 2006 to cause, among others, a childhood-onset ataxia cluster (termed infantile neuroaxonal dystrophy).[25] Although concomitant corticospinal tract features have already been described in several reports in recent years, it was not until recently that complicated HSP has been acknowledged as one of the main phenotypic presentations of *PLA2G6* (Ozes et al, submitted). Biallelic *STUB1* mutations were first published as a cause of recessive ataxia (eg, as part of a Gordon Holmes syndrome).[26,27] Later studies then revealed that corticospinal tract damage is a frequent concomitant feature[28] and sometimes even is predominate in the clinical presentation.[29] Examples can also be found for recently identified *autosomal-dominant* disease genes. Dominant mutations in *KCNA2* were first reported as a cause of (early-onset) cerebellar ataxia in 2015,[30,31] before it was shown in 2016 that dominant *KCNA2* mutations can also cause HSP phenotypes,[32] with both phenotypes occurring on a phenotypic continuum.

NGS has sped up not only disease gene discovery but also the time span from disease gene discovery until a broadened phenotypic spectrum can be appreciated. In some cases, this has led to the almost simultaneous "discovery" of one and the same gene as a novel ataxia gene and an HSP gene. Autosomal-recessive mutations in the nonlysosomal glucosylceramidase gene *GBA2*, for example, were designated SPG46 because of the predominant lower-limb spasticity noted by the European team of researchers.[33] In the same journal issue, however, *GBA2* was published as a novel gene for "cerebellar ataxia with spasticity" because of the initial disease manifestation as cerebellar ataxia in this independent patient cohort.[34] Similarly, *KIF1C* mutations were discovered to cause autosomal-recessive HSP complicated by ataxia features, termed SPG58.[35] At the same time, however, it was discovered that *KIF1C* mutations can also cause predominant cerebellar ataxia (with variable spasticity of the lower limbs).[36]

These recent examples underscore the value of unbiased screening approaches enabled by NGS technology that — when combined with a modular phenotyping approach — enable rapid and comprehensive delineation of phenotypic spectra associated with Mendelian disease genes. Moreover, they illustrate that cerebellar and pyramidal disease manifestations commonly cooccur and can vary considerably in predominance and phenotypic expression along a continuous spectrum. This variable phenotypic presentation therefore does not

justify the classification of these ataxia-spasticity spectrum genes as SPG versus SCA/SCAR/ARCA genes. The distinct SPG-versus-SCA/SCAR/ARCA classification system fails to capture this inherent phenotypic fluidity, rendering it in part arbitrary, and is therefore of limited systematic value for clinic and research.

Large Common Genetic Basis of Ataxias and HSPs

The aforementioned examples of ataxia-spasticity spectrum (ASS) genes are part of a larger, rapidly growing list of genes causing ataxia and HSP on a phenotypic continuum. Based on review of the literature and our own experience with whole-exome sequencing (WES) and whole-genome sequencing of large cohorts of cases with ataxia and/or HSP, we have compiled an extendable list of 69 genes that we consider relevant in the differential diagnosis of ASS disease (Table 1). We included only genes the phenotypic descriptions of which included both ataxia and spasticity (rather than merely pyramidal signs) in subjects from at least 2 different families (rather than merely single cases). The majority of these ASS genes cause autosomal-recessive disease (n = 49), but autosomal-dominant (n = 16) and X-linked recessive (n = 3) modes of inheritance also occur. For mutations in *AFG3L2*, autosomal-recessive (SCAR5) and autosomal-dominant (SCA28) modes of inheritance have been established. Notably, only 29 genes (42%) are part of either of the HSP or ataxia classification systems mentioned above (SCA/SCAR/ARCA/SPG). Consequently, even combining disease genes contained in either of the HSP or ataxia classifications is insufficient to capture the relevant disease genes for the ASS. The implications for clinical and genetic diagnostic practice are apparent: NGS-based approaches to test for mutations in ataxia genes (“ataxia panels”) need to also comprise HSP genes and vice versa to do the overlapping disease spectra justice; in addition, both ataxia and HSP gene panels should be expanded to cover not only the relevant genes “by classification,” but need to go beyond classification systems to cover also genes not included in any of the classification systems.

Common Pathophysiological Pathways and Mechanisms in Ataxias and HSPs

Under the surface of the seemingly disparate clinical syndromic and diagnostic classifications between ataxias and HSPs lurk not only shared allelic genes, but also common mechanisms and pathways. In this respect, the overlap between ataxias and HSPs resembles the well-established gene and pathway overlap between amyotrohic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Like HSP and ataxias, these 2 conditions have long been considered clinically disparate syndromes. Yet, over the past decade, we have increasingly recognized that they co-occur within families and even within individuals and largely share the same genes. Consequently, ALS and FTD are now usually studied jointly as a disease spectrum. Overcoming the diagnostic divide between ALS and FTD and focusing on shared pathways instead have led to identification of major shared mechanism hubs. For example, dysfunctional nuclear-cytoplasmic transport has emerged as a common mechanistic denominator uniting not only the different clinical conditions, but also various ALS/FTD genes like *C9orf72, FUS*, and *TARDPB*.[37-39]

Similarly, HSP and ataxias, which share a substantial number of genes, might also be connected on a functional level via shared cellular pathways and pathomechanisms. A protein-protein interaction network using known ASS genes as seeds (Table 1, n = 63, here excluding the dominant repeat ataxias) reveals that the proteins encoded by these genes share a multitude of physical interactions and form several highly connected "protein communities" that are visualized by different colors shown in Figure 2. Functional annotation of these genes using GO terms and subsequent gene set enrichment analysis highlight functional clusters that are enriched in these proteins (Fig. 3, Supplementary Table). The 3 major functional clusters are: (1) lipid metabolic processes, (2) acid metabolic processes, and (3) cytoskeleton or dendritic intracellular transport processes. These 3 clusters represent only a small subset of molecular pathways known to be involved in HSPs or cerebellar ataxias individually. This supports the hypothesis that pathways affected in ASS reflect shared selective vulnerabilities of corticospinal and cerebellar neurons. The *clinical* overlap of ASS spectrum diseases might thus be driven by underlying *mechanistic* overlaps (for an illustration of the relation between genetic, pathway, and clinical overlaps, see Fig. 1).

Some exemplary clusters of shared or interacting pathways underlying ASS diseases are:

- *Phospholipid metabolism*, including the genes *PNPLA6*,[12,40,41] *PLA2G6, DDHD1* (SPG 28), *DDHD2* (SPG54[42]), *CYP2U1* (SPG49), and *ABHD12*[43] (for further overview, see references [40] and [44]).
- *Sphingolipid metabolism*, including the genes *FA2H*,[15] *GBA2*,[33,45] *GALC, HEXA, ASA, PSAP*, and *GLB1*.
- *Autophagy-lysosomal activity*, including the genes *SPG15*, *SPG11*,[46,47] *ATP13A2* (SPG78),[48,49] *NPC1*, and *NPC2* disease.[50-55]

Toward a Mechanism-Based Classification of Ataxia-Spasticity Spectrum Diseases

As our concepts of cellular pathways involved in ASS diseases grow, a mechanism-based classification system of the ASS comes into reach. Classification of genetically defined disorders by shared affected pathways rather than the perceived predominant phenotype will allow overcoming the classic SCA/SCAR/ARCA and HSP/SPG divide and appreciation of a more systematic, pathophysiological perspective. Other than the resolution of multiple inconsistencies of the traditional classification system which we have detailed above, a mechanistically inspired classification system of ASS diseases offers key advantages in therapeutic respects. Such a classification system will prioritize research on shared pathways and might pave the way for mechanism-based strategies for drug development. Hypothetically, compounds targeting dysfunctional pathways rather than single genes have the potential to address groups of genetically defined diseases rather than single ataxia or HSP subtypes (for graphical illustration of this idea, see label "causal treatment strategies targeting pathways" in Fig. 1). For example, one class of drugs might target ASS diseases with abnormal cholesterol processing and cholesterol sequestration such as *CYP7B1* (SPG5), *NPC1, NPC2*, or *SERAC1* by exploiting cholesterol-depleting agents.[56] Another

class of drugs might aim at ASS diseases with defective autophagy-lysosomal activity (eg, *SPG11, ZFYVE26, ATP13A2*), using an autophagy inducer.[56] A mechanism-based disease classification might thus facilitate the translation of the giant genetic progress rendered possible by NGS over the past 5 years into first targeted molecular therapies.

Conclusions for Clinical Practice

In conclusion, we suggest to give up the classificatory divide between ataxias and HSPs in favor of a concept of a clinical, genetic, and pathophysiological ASS. From this inclusive rather than discriminatory approach, a number of advantages can be inferred for current clinical practice:

1. *Increased precision of phenotypic description and improved efficiency of diagnostic workup*. Early discriminatory classification of patients into fixed diagnostic categories potentially introduces bias into the clinical and diagnostic workup. We suggest taking a modular approach to phenotyping that allows the appreciation of nuanced individual phenotypic expression along the spectrum of ataxia and spasticity. This descriptive, unbiased approach of *modular phenotyping* would also be open to expansion of the phenotype beyond ataxia and HSP, as ataxia and spasticity often occur not in isolation, but as part of multisystem neuronal dysfunction. It thus allows for a more comprehensive, dynamic and systematic perspective than the traditional SCA/SCAR/ARCA and HSP/SPG classifications. Avoidance of narrow-minded ataxia and HSP clinical engrams will ultimately facilitate diagnosis in so-far unexplained complex neurodegenerative disease.

2. *Individualized treatment*. Following the idea of individualized medicine, modular phenotyping allows for individualized clinical treatment and management according to each individual's particular phenotypic spectrum (rather than by the overall clinical diagnosis or SPG/SCA/ARCA classification) (for a graphic illustration of the role of symptomatic treatment according to individual phenotype, see Figure 1). For example, patients with a major ataxia component due to *PNPLA6* or *SPG7* mutations will be clinically managed according to their individual ataxia, receiving, for example, physiotherapy exercises specifically targeting ataxia dysfunctions,[57,58] even if these genes are traditionally grouped in the HSP/SPG classification (SPG39 and SPG7, respectively). Vice versa, patients with pronounced spasticity because of *SYNE1* or *STUB1* mutations will be clinically managed according to their spasticity, receiving, for example, antispastic drugs, even if these genes are traditionally grouped in ARCA classifications.

3. *Efficient diagnostic testing*. Given the variability of phenotypes across the ASS and the sheer number of ASS genes, genetic testing on a gene-by-gene basis or relying on small gene panels is inefficient and mostly obsolete. Instead, genetic testing needs to resort to large gene panels or WES covering all ASS genes. Single-gene testing in ataxia spasticity spectrum diseases should be largely reserved for a few exceptions, for example, genotyping the FRDA repeat in

patients with afferent ataxia and pyramidal tract damage without major cerebellar atrophy, or the *SACS* gene in patients with the characteristic hypointense pontine stripes on T2-MRI imaging.[59]

4. *Aggregated ASS gene panels and gene lists*. In NGS diagnostics, the design of separate ataxia and HSP NGS gene panels and of separate ataxia and HSP gene lists, respectively, for WES analyses is not productive. NGS gene panels and lists need to aggregate *all* ASS genes.

Limitations and Future Challenges

The proposed approach of modular phenotyping bears several limitations. Patients might prefer to have a clear-cut clinical label for their disease (eg, HSP or spinocerebellar ataxia) rather than an open and dynamic broad descriptive phenotypic description of the individually affected neurological systems. A clear label might yet be given the name of the underlying gene and/or the pathway cluster. However, sporadic ASS patients without monogenic disease causation or obvious hit in one of the pathway clusters will escape classification by the proposed pathway-driven classification system.

The suggested pathway-driven classification is also limited by it requiring the affected cellular pathways to be known. For the large majority of ASS diseases, however, the pathway implications of the respective disease genes have yet to be identified. Future basic research now has to move on from NGS genetics to functional pathway explorations, both for each specific ASS gene and for possible shared pathway hubs, identifying in particular those pathway hubs that might be druggable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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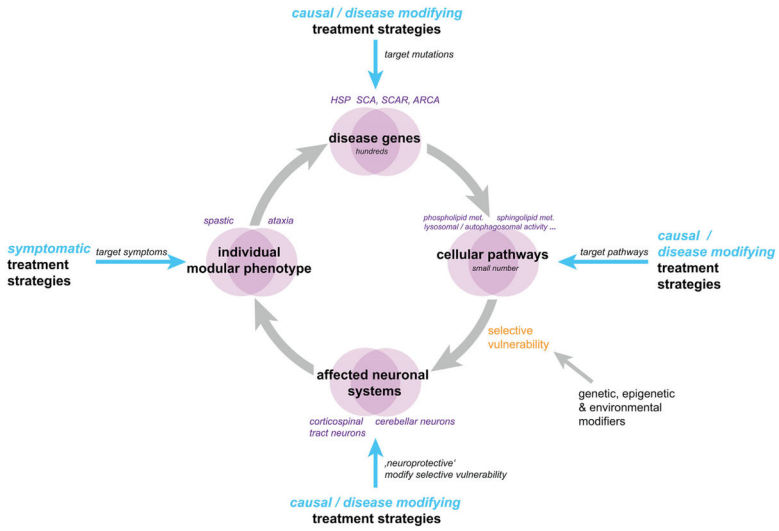

FIG. 1.

From clinical diagnosis to modular phenotyping and underlying shared genes and pathways in ataxia-spasticity spectrum diseases. Ataxias and HSPs have traditionally been designated in separate clinicogenetic disease classifications, depending on the first phenotypic descriptions and pattern of inheritance, namely, either in autosomal-dominant spinocerebellar ataxias (SCAs) and autosomal-recessive spinocerebellar ataxias (SCARs) or hereditary spastic paraplegias (HSPs/SPGs). However, the molecular etiologies of these 2 disease groups overlap greatly, based on manifold shared disease genes (top). Moreover, proteins encoded by HSP and ataxia genes closely interact physically as well as functionally. The heterogeneous genetic etiology of HSPs and ataxias thus converges into a small number of cellular pathways that are dysregulated in both diseases (right). Selective vulnerability of specific neuronal cell types that can be modified by additional genetic, epigenetic and environmental factors ultimately determines which neuronal systems and circuits will be affected by the pathway dysfunction (bottom). In ataxia-spasticity spectrum diseases, cerebellar and corticospinal tract neurons share selective vulnerabilities. The individual phenotypic expression (left) is a result of the pattern of neuronal system affection. It is essential to appreciate these 4 aspects, not only to understand an individual's disease, but also to use all therapeutic routes, whether they be symptomatic or causal/disease modifying. Pathway-based treatment approaches are hereby particularly promising, as (1) they offer the potential to cure, not only to modify the disease condition, with the (2) pathway-based etiologies partly converging from the vastly heterogeneous genetic etiology. Targeting dysfunctional pathways rather than single genes or disease conditions thus has the potential to address whole groups of genetically defined ASS diseases. [Color figure can be viewed at wileyonlinelibrary.com]

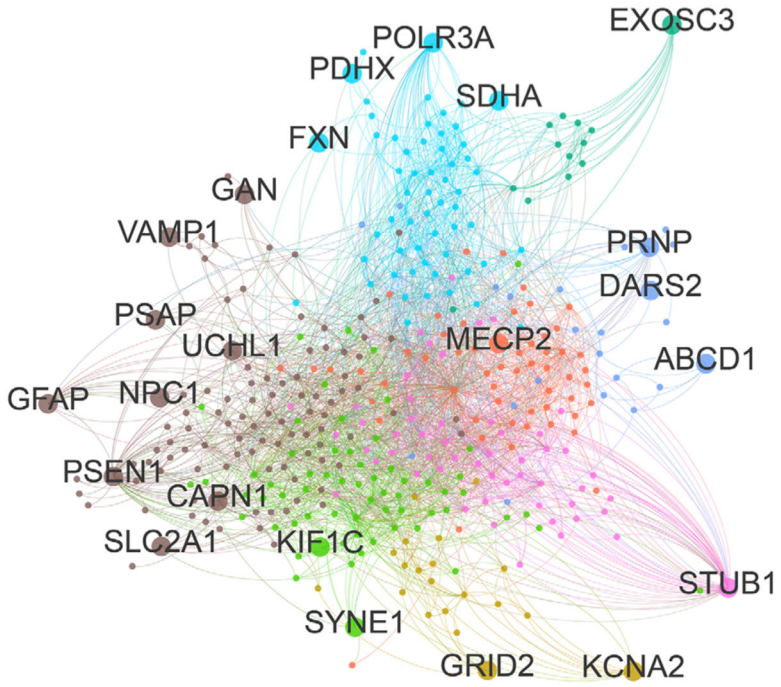

FIG. 2.

Protein-protein-interaction network for ataxia-HSP spectrum disease genes. To generate a protein-protein-interaction (PPI) network, interactors (iteration 1) of 63 spastic ataxia genes listed in Table 1 were extracted using the iRefScape plugin in Cytoscape v2.8.3.[60-62] Autosomal-dominant repeat-expansion genes were removed from the seed list, as their binding properties appear to be largely shaped by their polyglutamine tracts rather than the properties of the wild-type protein. The PPI network was then imported into Gephi v0.9.1 and filtered, whereby nonhuman interactions, predicted interactions, interactions based solely on high-throughput experiments, self-loops, and nodes with a degree < 2 were removed, retaining only nodes that were maximum 1 degree removed from the input spastic ataxia seed genes. The resulting network contained 389 nodes and 2582 undirected edges. We then applied the Louvain method to detect communities, neighborhoods of highly connected nodes. A total of 8 communities were detected, represented by differently colored nodes and edges in the figure. Ataxia-spasticity spectrum seed genes are represented by larger dots and labeled with the respective gene name. [Color figure can be viewed at wileyonlinelibrary.com]

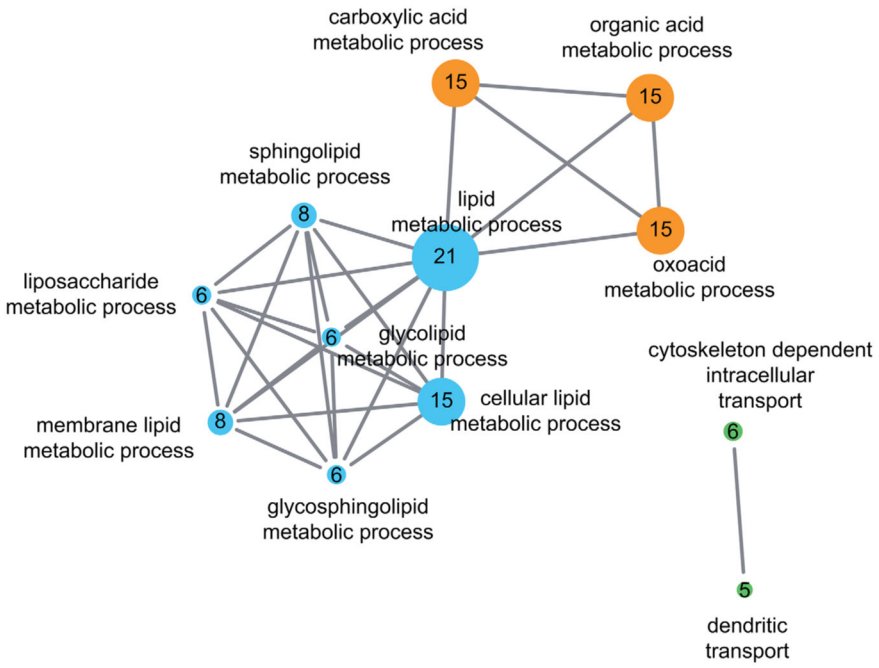

FIG. 3.

Pathway enrichment map of ataxia-HSP spectrum gene sets. Gene-set enrichment analysis reveals several functional clusters associated with ataxia-spasticity spectrum genes. To generate the pathway, enrichment map spastic ataxia genes (Table 1, n = 63 genes; dominant repeat genes excluded) were uploaded to DAVID Bioinformatics Resources 6.8[63,64] and annotated with gene ontology terms (GOTERM_BP_FAT, GOTERM_MF_FAT).[65] The fully annotated gene list is provided in the Supplementary Table. A gene enrichment map was then generated using the Enrichment Map plugin[66] in Cytoscape v3.2 with the following parameters: P cutoff, 0.0001; FDR Q cutoff, 0.05; similarity cutoff overlap, 0.4. Three major enrichment clusters can be appreciated: (1) lipid metabolic processes (blue), (2) acid metabolic processes (orange), and (3) cytoskeleton or dendritic intracellular transport processes (green). Each major network contains several subnetworks highlighting a specific cellular process underlying ataxia-spasticity spectrum disease. The size of the nodes reflects the number of ataxia-spasticity spectrum genes represented in the respective functional cluster; the number of genes is also indicated by the number in each of the nodes. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1.

Genes causing ataxia and HSP (ataxia-HSP spectrum disease genes)

Gene	Locus	Protein name (UniProt)	Inheritance	OMIM	Remarks	Key references
ABCD1		ATP-binding cassette subfamily D member 1	XR	#300100	Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN); increased very long-chain fatty acids in plasma	67
ABHD12		Monoacylglycerol lipase ABHD12	AR	#612674	Peripheral neuropathy, hearing loss, retinitis pigmentosa, cataract (PHARC)	43
AFG3L2	SPAX5 (AR), SCA28 (AD)	AFG3-like protein 2	AR/AD	#614487	Catalytic subunit of the m-AAA protease (like paraplegin/SPG7); ophthalmoparesis, slow saccades, ptosis	4
ARSA		Arylsulfatase A	AR	#250100	Metachromatic leukodystrophy (MLD): reduced arylsulfatase A activity in leukocytes	68
ATN1		Atrophin-1	AD	#125370	Dentatorubral-pallidolysian atrophy (DRPLA); CAG trinucleotide expansion; myoclonic epilepsy, dementia, ataxia, and choreoathetosis; rare outside Japan	69
ATP13A2	SPG78	Probable cation-transporting ATPase 13A2	AR	#606693	Juvenile parkinsonism, vertical gaze palsy, cognitive deficits	70
ATXN1	SCA1	Ataxin-1	AD	#164400	CAG trinucleotide expansion	71
ATXN2	SCA2	Ataxin-2	AD	#183090	CAG trinucleotide expansion; slow horizontal saccades	72
ATXN3	SCA3	Ataxin-3	AD	#109150	CAG trinucleotide expansion; Machado-Joseph disease; frequent SCA in central Europe	73
ATXN8/ATXN8OS	SCA8	Ataxin-8; putative protein ATXN8OS	AD	#608768	Expanded CTG trinucleotide repeat in ATXN8OS gene and complementary CAG repeat in ATXN8 gene	74
AUH		Methylglutaconyl-CoA hydratase, mitochondrial	AR	#250950	3-Methylglutaconic aciduria type 1 (MCGA1): elevated levels of 3-methylglutaconic acid (3-MGA), 3-methylglutaric acid (3-MG) and 3-hydroxyisovaleric acid (3-HIVA) in urine; cognitive deficits	75
CAPN1	SPG76	Calpain-1 catalytic subunit	AR	#616907	Upper limb involvement, foot deformities, dysarthria	76
CYP27A1		Sterol 26-hydroxylase, mitochondrial	AR	#213700	Cerebrotendinous xynthomatosis (CTX): juvenile cataract, lipid deposits i.a. in brain, lungs, and Achilles tendons, chronic diarrhea, early atherosclerosis, elevated levels of cholestanol in plasma	77,78
CYP7B1	SPG5	25-Hydroxycholesterol 7-alpha-hydroxylase	AR	#270800	Afferent ataxia due to dorsal column dysfunction, elevated levels of 27-hydroxycholesterol, 25-hydroxycholesterol, and cholestanoic acid in plasma and CSF	79,80
DARS2		Aspartate-tRNA ligase, mitochondrial	AR	#611105	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL)	81
EXOSC3	PCH1B	Exosome complex component RRP40	AR	#614678	Pontocerebellar hypoplasia, type 1B	82
FA2H	SPG35	Fatty acid 2-hydroxylase	AR	#612319	Spastic paraplegia, leukodystrophy, and/or brain iron deposition	18,19
FXN		Frataxin	AR	#229300	Friedreich ataxia (FRDA); predominant afferent ataxia with pyramidal tract signs	83
GALC		Galactocerebrosidase	AR	#245200	Krabbe disease: infantile forms with extreme irritability, spasticity, and developmental delay; late-adult forms: spasticity, ataxia; reduced GALC enzyme activity	84
GAN		Gigaxonin	AR	#256850	Giant axonal neuropathy (GAN1); infantile form: kinky hair and unique posture of legs	85
GBA2	SPG46	Nonlysosomal glucosylceramidase	AR	#614409	Mental impairment, cataracts, cerebral, cerebellar, and corpus callosum atrophy	33
GFAP		Glial fibrillary acidic protein	AD	#203450	Alexander disease; infantile form: leukoencephalopathy with macrocephaly, seizures, and psychomotor retardation; adult form: bulbar signs and spasticity, more slowly progressive	86
GJC2	SPG44, HLD2	Gap junction gamma-2 protein	AR	#613206, #608804	Hypomyelinating leukodystrophy; Pelizaeus-Merzbacher-like disease (PMLD)	87

Gene	Locus	Protein name (UniProt)	Inheritance	OMIM	Remarks	Key references
GLB1		Beta-galactosidase	AR	#230500, #230600, #230650	GM1-gangliosidosis, type I-III (GLB1); mucopolysaccharidosis type IVB (Morquio syndrome B); reduced beta-galactosidase-1 enzyme activity	88
GLRX5		Glutaredoxin-related protein 5, mitochondrial	AR	#616859	Increased serum glycine; leukodystrophy and/or lesions in the upper spinal cord	89
GRID2	SCAR18	Glutamate receptor ionotropic, delta-2	AR	#616204	Early-onset cerebellar ataxia, intellectual disability; occasional or persistent tonic upgaze	90
HEXA		Beta-hexosaminidase subunit alpha	AR	#272800	Tay-Sachs disease/GM2-gangliosidosis; infantile: developmental retardation, followed by paresis, cognitive decline, and blindness; adult: lower motor neuron damage, psychosis, dementia; reduced hexosamindase A enzyme activity	91
KCNA2		Potassium voltage-gated channel subfamily A member 2	AD	#616366	Early infantile epileptic encephalopathy; ataxia, spasticity; often de novo	30,32
KCND3	SCA19	Potassium voltage-gated channel subfamily D member 3	AD	#607346	Allelic with Brugada syndrome 9	92
KIF1A	SPG30, HSN2C	Kinesin-like protein KIF1A	AR	#610357, #614213	Allelic with autosomal-dominant mental retardation 9 (MRD9)	93
KIF1C	SPG58, SPAX2	Kinesin-like protein KIF1C	AR	#611302	Cerebellar ataxia and variable spasticity of the lower limbs in first 2 decades of life	36,94
MARS2	SPAX3	Methionine-tRNA ligase, mitochondrial	AR	#611390	Often deletions or duplications; decreased activity of mitochondrial complexes I and IV	95
MECP2		Methyl-CpG-binding protein 2	XR	#312750	Atypical Rett syndrome	96
MMADHC		Methylmalonic aciduria and homocystinuria type D protein, mitochondrial	AR	#277410	Homocystinuria and/or methylmalonic aciduria; usually additional complicating features like developmental delay	97
MTPAP	SPAX4	Poly(A) RNA polymerase, mitochondrial	AR	#613672	Childhood-onset cerebellar ataxia, spastic paraparesis, dysarthria, and optic atrophy	98
NPC1		Niemann-Pick C1 protein	AR	#257220	Niemann-Pick disease, type C1/D; infantile: often accompanying neurovisceral phenotype; juvenile and adult: often vertical supranuclear gaze palsy or cognitive decline	55,99
NPC2		Epididymal secretory protein E1	AR	#607625	Niemann-Pick disease, type C2; infantile: often accompanying neurovisceral phenotype; juvenile and adult: often vertical supranuclear gaze palsy or cognitive decline	55,99
OPA1		Dynamin-like 120-kDa protein, mitochondrial	AD	#125250	Optic atrophy plus syndrome, in particular, in cases of biallelic OPA1 mutations	100,101
OPA3		Optic atrophy 3 protein	AR	#258501	Optic atrophy plus syndrome, 3-methylglutaconic aciduria, type III	102
PDHX		Pyruvate dehydrogenase protein X component, mitochondrial	AR	#245349	Lacticacidemia from PDX1 deficiency; often additional mental retardation, delayed psychomotor development and/or seizures	103
PEX16		Peroxisomal membrane protein PEX16	AR	#614877	Peroxisome biogenesis disorder 8B; white matter abnormalities; increased VLCFA	104
PLA2G6	NBIA2A	85/88-kDa calcium-independent phospholipase A2	AR	#256600, #610217	Infantile neuroaxonal dystrophy 1 (INAD); neurodegeneration with brain iron accumulation 2B (NBIA2B), autosomal recessive Parkinson's disease 14 (PARK14)	105,106
PLP1	SCA2	Myelin proteolipid protein	XR	#312920, #312080	Pelizaeus-Merzbacher disease (PMD); X-linked recessive hypomyelinative leukodystrophy (HLD1)	107
PNPLA6	SPG39	Neuropathy target esterase	AR	#612020, #215470, #275400, #245800	Boucher-Neuhauser syndrome, Gordon Holmes syndrome; Oliver-McFarlane syndrome, Laurence-Moon syndrome	12
POLR3A	HLD7	DNA-directed RNA polymerase III subunit RPC1	AR	#607694	Hypomyelinating leukodystrophy 7 (HLD7) with or without oligodontia and/or hypogonadotropic hypogonadism	108,109
POLR3B	HLD8	DNA-directed RNA polymerase III subunit RPC2	AR	#614381	Hypomyelinating leukodystrophy 8 (HLD8) with or without oligodontia and/or hypogonadotropic hypogonadism, but leukodystrophy might also be missing	110
PRNP		Major prion protein	AD	#137440	Familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler disease (GSD), fatal familial insomnia (FFI), but also complicated HSP	111,112

Gene	Locus	Protein name (UniProt)	Inheritance	OMIM	Remarks	Key references
PSAP		Prosaposin	AR	#249900	Metachromatic leukodystrophy from SAP-b deficiency; atypical Krabbe disease; atypical Gaucher disease	113
PSEN1		Presenilin-1	AD	#607822	Early-onset Alzheimer's disease, sometimes complicated by spastic paraparesis and/or ataxia	114
SACS	SPAX6	Sacsin	AR	#270550	Autosomal-recessive spastic ataxia Charlevoix-Saguenay (ARSACS), early-onset ataxia with spastic paraparesis and axonal-demyelinating sensorimotor neuropathy; hypointense pontine stripes on T2-MRI	59,115
SCN8A		Sodium channel protein type 8 subunit alpha	AD	#614306	Early infantile epileptic encephalopathy 13 (EIEE13)	116
SDHA		Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	AR	#252011	Mitochondrial complex II deficiency	117
SETX	SCAR1	Probable helicase senataxin	AR	#606002	AD mutations in SETX are associated with ALS4 (#602433); AR mutations with early-onset ataxia with elevated alpha-fetoprotein	118
SLC17A5		Sialin	AR	#604369, #269920	Sialic acid storage disorder	119
SLC25A15		Mitochondrial ornithine transporter 1	AR	#238970	Hyperornithinemia-hyperammonemiahomocitrullinemia syndrome	120
SLC2A1	DYT9	Solute carrier family 2, facilitated glucose transporter member 1	AD	#612126	GLUT1 deficiency syndrome 1 (GLUT1); DYT9	121
SPG11	SPG11	Spatacsin	AR	#604360	cHSP with thin corpus callosum; juvenile-onset amyotrophic lateral sclerosis-5	122
ZFYVE26	SPG15	Zinc finger FYVE domain-containing protein 26	AR	#270700	cHSP with variable mental retardation, hearing and visual defects, and thin corpus callosum	123
SPG7	SPG7	Paraplegin	AR	#607259	Variable spasticity and cerebellar ataxia	7
SPR		Sepiapterin reductase	AR	#612716	Dopa-responsive dystonia because of sepiapterin reductase deficiency	124
STUB1	SCAR16	E3 ubiquitin-protein ligase CHIP	AR	#615768	Spasticity and ataxia can be part of a broader multisystemic neurodegeneration, including hypogonadotropic hypogonadism, and cognitive decline	29,125
SYNE1	SCAR8	Nesprin-1	AR	#610743	Cerebellar ataxia and variable spasticity and further multisystemic neurologic damage	23,24
TBP	SCA17	TATA box-binding protein	AD	#607136	CAG repeat expansion; Huntington's disease-like 4; ataxia, pyramidal and extrapyramidal signs, cognitive impairments, psychosis, and seizures	126
TTC19		Tetratricopeptide repeat protein 19, mitochondrial	AR	#615157	Mitochondrial complex III deficiency nuclear type 2 (MC3DN2); sometimes abnormal signals putamen, caudate, and brain stem on T2-MRI	127
TTPA		Alpha-tocopherol transfer protein	AR	#277460	Ataxia with isolated vitamin E deficiency	128
TUBB4A	HLD6, DYT4	Tubulin beta-4A chain	AD	#612438, #128101	Hypomyelinating leukodystrophy (HLD6); autosomal-dominant dystonia-4 (DYT4)	129
UCHL1	PARK5	Ubiquitin carboxyl-terminal hydrolase isozyme L1	AR	#615491	Childhood-onset neurodegeneration with optic atrophy	130
VAMP1	SPAX1	Vesicle-associated membrane protein 1	AD	#108600	Newfoundland families	131
VWA3B	SCAR22	von Willebrand factor A domain-containing protein 3B	AR	#616948	Intellectual disability associated with adult-onset cerebellar ataxia and spasticity	132

List of genes causing ataxia-spasticity spectrum disease; we anticipate this list to grow considerably in the future (ie, dynamic, extendable list). The selection contains only genes whose phenotypic descriptions include both manifest ataxia and spasticity (rather than merely pyramidal signs) in subjects from at least 2 different families (rather than merely single cases).

OMIM, Online Mendelian Inheritance in Man; AD, autosomal-dominant; AR, autosomal-recessive; XR, x-chromosomal recessive.