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HEREDITARY SPASTIC PARAPLEGIA: PATHOGENESIS AND PATHOPHYSIOLOGY

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Abstract

- Hereditary spastic paraplegias constitute a larger group of disorders than expected.
- Autosomal dominant types are mainly composed of SPAST, Atlastin (SPG3A) and REEP1 mutations. Genetic testing is suggested mainly for these genes.
- The most common autosomal recessive type is SPG11, hereditary spastic paraplegia with thin corpus callosum, but SPG15 shares the same clinical features with SPG11. Genetic testing should be done for both if thin corpus callosum is present in patients.

How different genes with many different biological functions, including axonal transport, mitochondrial functions, fatty acid and cholesterol pathways and DNA repair defects, cause hereditary spastic paraplegia is still unknown.

The major pathological finding of hereditary spastic paraplegia is the degeneration of axons of the pyramidal tract and dorsal column pathways. The axons of the corticospinal tract are the longest in the nervous system, and degeneration of the crossed pyramidal tracts increases toward terminal portions, maximally at the lumbar spinal cord; it may be considered that a "dying back" axonopathy occurs toward the cell body. Demyelination and gliosis can occur with axonal loss. Spinocerebellar tract involvement is seen in 50% of cases. Peripheral nerves, dorsal roots, and dorsal ganglia are generally normal. Anterior horn cells are also usually normal, but sometimes loss of anterior horn cells is also reported (Schwarz and Liu 1956; Behan and Maia 1974; Harding 1981; 1993; McDermott 2000). Knowledge about the molecular and genetic basis of pathogenic mechanisms of hereditary spastic paraplegia continually increases. Because of recently defined loci and genes, a common underlying pathology, "defective intracellular trafficking," has been proposed.

SPG1 results from mutations in *LICAM*, which is one of a subgroup of integral membrane glycoproteins belonging to a large class of immunoglobulin superfamily cellular adhesion molecules that mediate cell-to-cell adhesion at the cell surface. They guide neurite outgrowth during development, neuronal cell migration,

axon bundling, synaptogenesis, myelination, and neuronal cell survival, and they have a long-term effect on signal transduction pathways (Kenwrick et al 2000). Gene locus is Xq28. This adhesion molecule is required for normal development of the corticospinal tract. In patients with altered *LICAM* function, pyramids were found to be absent or reduced in size, and spastic paraplegia is a common finding (Yamasaki et al 1995). *LICAM* mutations can also cause X-linked hydrocephalus, MASA syndrome (mental retardation, aphasia, shuffling gait, adducted thumbs), and agenesis of corpus callosum. Because there is interfamilial and intrafamilial variability with this mutation, Fransen and colleagues refer to the syndrome as CRASH syndrome (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus) (Fransen et al 1995).

SPG2 can give rise to both pure and complicated types of hereditary spastic paraplegia. Gene map locus is Xq22, and it results from the mutations in proteolipid protein. This locus is the same with the Pelizaeus-Merzbacher disease; therefore, SPG2 and Pelizaeus-Merzbacher disease are allelic disorders at the same locus (Saugier-Verber et al 1994). High number of mutations have been reported in PLP related disorders. In 60-70 % of patients gene duplications of variable size and in 15 - 20 % intragenic lesions

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are present. Clinical severity is independent of the size of the duplication in most of the patients and peripheral neuropathy never occurs in patients with PLP1 gene duplications (Grossi et al 2011). A novel missense mutation was found in an autopsy case of an 67 year old SPG2 patient who was the oldest age of onset at 35 years of age (Suzuki 2011). Proteolipid protein is the primary constituent of myelin, and it has 2 isoforms, namely proteolipid protein and DM20. Altered proteolipid protein structures are thought to compromise oligodendrocyte function. Experimental studies in knockout animals that do not express any proteolipid protein have shown that these animals have normal CNS function with normal life expectancy, but they have axonal swelling and degeneration due to impaired axonal transport (Griffiths et al 1998). These data may help to understand that proteolipid protein mutation causes a dysfunction in local support of oligodendroglia for myelinated axons because its absence does not cause dysmyelination as in Pelizaeus-Merzbacher disease (Casari and Rugarli 2001).

SPG16 is another X-linked hereditary spastic paraplegia that causes both pure and complicated forms of the disease. Its gene locus is Xq11.2. Motor aphasia, reduced vision, mild mental retardation, and bowel and bladder dysfunction are the symptoms of the complicated form (Fink 2002).

Some families with X-linked pedigrees do not show linkage to the known loci. In 2002, Starling and colleagues reported a large Brazilian family with pure hereditary spastic paraplegia showing linkage to the proteolipid protein locus, but no mutation could be found. They suggested that their results may show either a fourth X-linked gene with close proximity to proteolipid protein or a novel mutation in the noncoding regions of the proteolipid protein gene (Starling et al 2002).

Autosomal dominant hereditary spastic paraplegia has 18 known loci, most of which lead to a pure form. SPG8 (8q23-q24), SPG10 (12q13), SPG6 (15q11.1), SPG12 (19q13), SPG19 (9q33-q34), SPG37 (8p21.1-q13.3), and SPG41 cause pure hereditary spastic paraplegia. SPG9 (10q23.3-q24.2) is spastic paraplegia associated

with cataracts, gastroesophageal reflux, and motor neuropathy. SPG10 (12q13) usually causes pure spastic paraplegia, but sometimes it can be complicated with distal atrophy (Fink 2002; 2003a). SPG29 is a complicated autosomal dominant form associated with sensorineural hearing impairment and vomiting due to hiatal hernia. Most of the patients had hyperbilirubinemia without kernicterus in the neonatal period (Orlacchio et al 2005).

SPG4 is the most frequent form of autosomal dominant spastic paraplegia and accounts for 45% of all autosomal dominant kindreds (Fink et al 1996). It is mapped to chromosome 2p22-p21, which encodes a protein named spastin. There are more than 150 SPG4 mutations, including point mutations, small insertions, and deletions; most reported families have a unique mutation (de Bot et al 2010; Magariello et al 2010). Usually, age of onset is in adulthood and genetic anticipation can occur with SPAST mutations, but a novel de novo mutation has been found to cause an infantile onset disease in a family in which most members were diagnosed with diplegic cerebral palsy (Blair et al 2007). Some mutations like multi-exonic *SPG4* duplication lead to a more severe and early onset disease in males (Mitne-Neto et al 2007), and another mutation in an Italian family caused a reduced penetrance of disease (Aridon et al 2007). Two polymorphisms were defined in SPG4 gene, S44L and P45Q, causing a phenotype modifier effect associated with early onset of disease (Svenson et al 2005). Although SPG4 is accepted as an uncomplicated form of hereditary spastic paraplegia, in some families with mental retardation, auditory impairment, thin corpus callosum, and cerebellar atrophy, a new mutation of SPG4 has been detected (Orlacchio et al 2004). Families with dementia, dysplastic corpus callosum, and a family (with 4 generations) with cerebellar ataxia, dysarthria, unipolar depression, epilepsy, migraine, and cognitive impairment were also found to have mutations in *SPG4* gene (McMonagle et al 2004; Nielsen et al 2004; Alber et al 2005). In a large series of 151 Dutch patients, swallowing difficulties and dysarthria were present in 2 patients, and tremor (not men-

tioned earlier) was present in 10% of *SPAST* patients (de Bot et al 2010). Cognitive impairment is a well-known feature of *SPG4*; in *SPG4* patients with normal MRI, magnetic resonance spectroscopy showed metabolic abnormalities in the motor cortex of those with age-related verbal learning and memory reduction (Erichsen et al 2009a).

By phenotypic expansion of *SPG4*, it is suggested that not only the length of the axon but also modifying factors play a role in the pathogenesis of *SPG4* (Fink 2004). Proukakis and colleagues have found the frequency of *SPG4* mutations in pure autosomal dominant disease to be 33.3% (Proukakis et al 2003). With the introduction of multiplex ligation-dependent probe amplification, families with strong linkages to *SPG4* but negative for *SPAST* mutations were screened, and aberrant profiles representing partial deletions were identified. The frequency of these deletions was estimated at 11%, raising the overall involvement of *SPAST* in autosomal dominant hereditary spastic paraplegia to over 50% (Beetz et al 2006). Males were reported more than females suggesting that penetrance or severity of disease caused by *SPAST* mutations may be sex dependent (Proukakis et al 2011). Screening for *SPAST* mutations seems to be the first step for families with autosomal dominant hereditary spastic paraplegia.

Spastin is a member of group of proteins known as AAA proteins (ATPases associated with diverse cellular activities) (Hazan et al 1999). These proteins have several functions in protein degradation, trafficking, and organelle biogenesis. It is shown that spastin works in microtubule dynamics. Spastin interacts transiently with microtubules, and its microtubule binding ability comes from the AAA homologous region that provides the structural framework for microtubule interaction (Errico et al 2002). It was shown that endogenous spastin is located at the centrosome and mitotic spindle poles, and it persists throughout the cell cycle supporting its role in microtubule dynamics (Svenson et al 2005). Wild-type spastin promotes microtubule disassembly in transfected cells, and this property is decreased with mutant spastin, so

spastin is described as microtubule severing protein. This property is closely related with katanin in sequence and function. Katanin is another microtubule severing protein that regulates axon growth and generates short microtubules that can be efficiently transported and remodeled. Studies have shown that, like katanin, spastin promotes the formation of microtubule networks that are essential for axon outgrowth, and reduced spastin function severely impairs motor axon outgrowth (Wood et al 2006).

Altered microtubule dynamics may also result in abnormal mitochondrial distribution within the axon, which may lead a defective oxidative phosphorylation (Fink 2004). By discovery of endosomal proteins as binding partners for spastin, it has been suggested that, besides microtubule regulation function, spastin may also be involved in membrane trafficking events (Sanderson et al 2006). Spastin has been shown to affect axonal transport. Mutant spastin was found to perturb both anterograde and retrograde transport in mice (Kasher et al 2009).

SPG3A is another autosomal dominant hereditary spastic paraplegia that results from mutations in the atlastin gene and constitutes 10% of autosomal hereditary spastic paraplegias (Fink et al 1996). It is the most common type in patients with onset before age 10 years (Namekawa et al 2006). Novel mutations in this gene showed that it can lead to both an early-onset and an adult-onset disease. Dalpozzo and colleagues reported a novel mutation in the atlastin gene that caused spastic paraparesis in infancy, resembling cerebral palsy, with upper limb amyotrophy (Dalpozzo et al 2003). De novo occurrence of atlastin mutation has been reported in very early-onset disease, and investigation of de novo mutations might be considered in patients with cerebral palsy for which no other cause is identified (Rainier et al 2006). *SPG4* and *SPG3A* mutations together cause 50% of dominantly inherited hereditary spastic paraplegias. Genetic penetrance in these diseases is high, so prenatal testing is commercially available for these 2 kinds of hereditary spastic paraplegias (Hazan et al 1999; Fink 2003b). Atlastin has been discovered in a large family with HSN type

1 and HSN1 and SPG3A are allelic disorders (Guelly et al 2011). Atlastin is a member of the dynamin family of large GTPases that play essential roles in vesicle trafficking events important for neurotransmission and action of neurotrophic factors. Dynamins take place in vesicle formation and liberation in both endocytic and secretory pathways and have been implicated in the maintenance and distribution of the mitochondria (Zhao et al 2001; Fink 2002). Atlastin has been found in high concentration in vesicular structures of growth cones, implicating a possible role in axonal development other than trafficking (Zhu et al 2006). Three forms of atlastin have been discovered; atlastin-1 is mostly found in brain whereas -2 and -3 are localized to endoplasmic reticulum and found mostly in other tissues. In contrast to previous suggestions about their roles in vesicular trafficking, they are thought to function in both endoplasmic reticulum and Golgi morphogenesis. Morphologically abnormal Golgi and endoplasmic reticulum are reported to interfere with proper distribution or polarity of long corticospinal tract motor neurons (Rismanchi et al 2008).

SPG6 is caused by *NIPA1* gene mutations. The disease is an adolescent- or adult-onset form of a typical slowly progressive uncomplicated hereditary spastic paraplegia. However idiopathic generalized epilepsy and peripheral neuropathy have been described in families with SPG6 (Svenstrup et al 2011, Du et al 2011). The function of this gene is not yet known, but it is widely expressed in the central nervous system, and it is suggested that *NIPA1* encodes a membrane protein. Patients totally lacking this gene (non imprinted in Prader-Willi and Angelman loci) do not develop hereditary spastic paraplegia, so *NIPA1* is said to act through "dominant negative" gain of function (Fink 2003a; Rainier et al 2003). In a Chinese family with SPG6 mutations, severe spinal cord atrophy, especially in the cervical and upper thoracic cord, was found as a specific symptom for SPG6 (Liu et al 2008). Recently, it was discovered that atlastin-1 and *NIPA1* are direct partners with coexpression to support axonal maintenance. Mutations in one of the proteins caused protein sequestration

either in golgi complex or endoplasmic reticulum. Also, in cultured rat cortical neurons axonal and dendritic sprouting was reduced, showing the common biochemical pathway that atlastin and *NIPA1* shared (Botzolakis et al 2011).

SPG8 is a severe, pure autosomal dominant hereditary spastic paraplegia on chromosome 8p24.13. Strumpellin protein of *KIAA0196* gene is mutated in SPG8. The exact function of this protein is still unknown, but motor-axon-outgrowth impairment is suggested (Valdmanis et al 2007). Strumpellin mutations are loss-of-function mutations and cause reduction in axonal outgrowth in human neuroblastoma cells. Strumpellin was identified as a novel valosin-containing, protein binding partner (Clemen et al 2010). Valosin-containing protein mutations cause autosomal dominant inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. Also, strumpellin was identified in pathological aggregates of myofibrillar myopathies and a Huntington disease mouse model and adds to the complexity of pathogenesis of hereditary spastic paraplegias (Clemen et al 2010).

SPG9 is a complicated dominant type of hereditary spastic paraplegia linked to 10q23.3-q24.2 with bilateral cataracts and gastroesophageal reflux with persistent vomiting amyotrophy (Panza et al 2008).

A mutation in a kinesin heavy chain gene, *KIF5A*, results in chromosome 12q-linked autosomal dominant hereditary spastic paraplegia, SPG10 (Reid et al 2002). It is thought to be a rare form of disease at least in Europe; only 3% of patients were found to have SPG10 in European autosomal dominant hereditary spastic paraplegia families in one report (Schule et al 2008). In another report by Goizet in 2009, *SPG10* mutations were found in 10% of patients with complicated autosomal dominant disease. Patients had variable complex features, such as peripheral neuropathy, severe limb amyotrophy (Silver syndrome-like), mental impairment, parkinsonism, and retinitis pigmentosa (Goizet et al 2009a). A single *KIF5A* mutation was found in an Italian patient with CMT2 (Crimella et al 2011). Mutations can cause both early- and adult-onset

disease (Blair et al 2006). Kinesin is part of a protein motor complex that functions in the microtubule transport system in both anterograde and retrograde direction. Kinesin mutation studies support a defect in microtubule-mediated trafficking, which leads to axonal degeneration (Crosby and Proukakis 2002).

Heat shock protein 60, also known as "chaperonin 60," is encoded by *HSPD1* gene. It is a mitochondrial chaperone and has been identified in uncomplicated autosomal dominant form SPG13. Chaperones are the phenotype modulators. Hsp60 is part of a mitochondrial complex that regulates correct protein folding in mitochondria (Hansen et al 2002; Reid 2003). SPG13 is a rare cause of hereditary spastic paraplegia, but new information shows the importance of this mitochondrial chaperone protein. A newly described *HSP60* polymorphism p.[Gly563Ala] was found in a spastin mutation-positive family suggesting that this polymorphism may result in earlier onset of phenotype (Hewamadduma et al 2008). Also p.[Ser44Leu] polymorphism of spastin has been shown to have a phenotype modifier effect. Interactions between different genes of hereditary spastic paraplegia open new gateways to the pathogenetic mechanisms.

A new disorder caused by a missense mutation (D29G) in HSP60, termed MitCHAP60, was defined in an Israeli Bedouin kindred with hypomyelinating leukodystrophy. The patient was negative for *PLP1* and connexin 47 mutations, and inheritance was autosomal recessive (Magen et al 2008).

Silver syndrome, SPG17 (11q12-q14), is an autosomal dominant hereditary spastic paraplegia associated with amyotrophy of hand muscles and weakness of small muscles. Although there is genetic heterogeneity in this locus, *BSCL2* gene, seipin mutations were shown both in Silver syndrome and distal hereditary motor neuropathy type V (Windpassinger 2004). It is the gene of Berardinelli-Seip congenital lipodystrophy Type 2. Two heterozygous missense mutations resulting in amino acid substitutions N88S and S90L were shown in Silver syndrome and distal hereditary motor neuropathy type V. It is an integral

membrane protein of the endoplasmic reticulum, and mutations cause aggregate formation leading to neurodegeneration (Windpassinger et al 2004). Seipin is expressed widely in central nervous system, spinal cord, pituitary gland, and testis. Mutations result in proteins that are improperly folded and cause accumulation of some kind of inclusion bodies in endoplasmic reticulum (leading to activation of unfolded protein response pathway) and induce endoplasmic reticulum stress-mediated cell death. Because of a large group of both upper and lower motor neuron diseases caused by N88S and S90L mutations associated with endoplasmic reticulum stress, Ito and colleagues suggested seipin-related diseases be collectively called "seipinopathies" (Ito et al 2008; Ito and Suzuki 2009).

Investigation of 2 Italian families with characteristics of Silver syndrome resulted in a novel locus at 4p16-p15 (SPG38) for Silver syndrome and a new mutation of SPG4 (Orlacchio et al 2008). Among the 15 members of the family with a mutation in SPG4, all presented with cardinal features of Silver syndrome, and 14 presented with temporal lobe epilepsy and cognitive dysfunctions; this was the first report of a family with temporal lobe epilepsy in hereditary spastic paraplegia. Silver syndrome also shows genetic heterogeneity like SPG4, and the relation with SPG4 demonstrates that HSP genes might interact with each other.

SPG31 is defined in 2 Caucasian families with pure hereditary spastic paraplegia. The causative protein is receptor expression-enhancing protein 1 (*REEP1*), which is related with odorant receptors in mouse tissue and promotes their expression in various brain tissues. It is located in mitochondria. Hereditary spastic paraplegia caused by REEP1 mutations is suggested to be the third most common type after spastin and atlastin mutations (Zuchner et al 2006). In a study composed of 535 hereditary spastic paraplegia patients, overall mutation rate for *REEP1* mutations was 3%. When the study group was narrowed to only pure hereditary spastic paraplegia, the mutation rate was 8%. So it is suggested that SPG31 is a relatively frequent type, and genetic

testing should be done for REEP1 as well (Beetz et al 2008; McCorquodale et al 2011). Patients showed pure-type hereditary spastic paraplegia with bimodal pattern of onset of age--either before 20 years of age or after 30. A 5-year-old patient with slowly progressive disease has been reported with a multiexonic deletion in REEP1 gene (Battini et al 2011). With availability of genetic testing, complicated phenotypes are also described. Peripheral neuropathy, spastic tetraparesis, and pseudobulbar palsy have been found in 2 patients with *REEP1* mutations (Hewamaduma et al 2009). In a Chinese family with a novel mutation in the *REEP1* gene, clinical features and electrophysiological studies showed pure phenotype, but MRI revealed atrophy of the thoracic spinal cord (Liu et al 2009).

SPG33 is another pure type of hereditary spastic paraplegia in which the causative mutation is in zinc finger FYVE domain-containing protein 27 (ZFYVE27). It is an intracellular protein with close interaction with spastin through its microtubule interacting and trafficking motif.

Mutations severely affect the interaction with spastin (Mannan et al 2006).

SPG36 is on 12q23-24 and is complicated by peripheral neuropathy (Schule et al 2009). SPG37 is a "pure" autosomal dominant hereditary spastic paraplegia on chromosome 8p21.1-q13.3 (Hanein et al 2007). A causative gene is not yet defined for SPG36 and SPG37.

SPG41 is a pure form described in a Chinese family and linked to 11p14.1-p11.2 (Zhao et al 2008).

SPG42 is caused by a mutation in the gene for acetyl-CoA transporter (SLC33A1), which is on 3q24-q26 (Lin et al 2008). It is suggested that this is a loss-of-function mutation important in the outgrowth and maintenance of the motor neuron axons.

A family with progressive spastic paraparesis and dystonia was linked to 2q24-2q31 and suggested to be a new locus for autosomal dominant hereditary spastic paraplegia (Gilbert et al 2009). Causative gene and disease name according to genome database is not yet clear.

Table1

Autosomal Dominant Hereditary Spastic Paraplegias

Genotype	Locus	Type	Gene
SPG3A	14q11-21	Pure	Atlastin
SPG4	2p21-p22	Pure	SPAST (Spastin)
SPG6	15q11.1	Pure	NIPA1
SPG8	8q23-q24	Pure	KIA0196 (Strumpellin)
SPG9	10q23.3-q24.2	Complicated	
SPG10	12q13	Pure or complicated	KIF5A
SPG12	19q13	Pure	
SPG13	2q24-34	Pure	HSPD1 (Hsp60)
SPG17	11q12-14	Complicated	BSCL2 (Seipin)
SPG19	9q33-q34	Pure	
SPG29	1p31.1-1p21.1	Complicated	
SPG31	2p12	Pure or complicated	REEP1
SPG33	10q24.2	Pure	ZFYVE27
SPG36	12q23-24	Complicated	
SPG37	8p21.1-q13.3	Pure	
SPG38	4p16-p15	Complicated	
SPG41	11p14.1-p11.2	Pure	
SPG42	3q24-q26	Pure	SLC33A1 (Acetyl coA transporter)

In autosomal recessive hereditary spastic paraplegia, the first gene identified was paraplegin. It is an uncommon cause of hereditary spastic paraplegias. Approximately 1.5% to 4% of recessive and sporadic cases of spastic paraplegia have mutations in the SPG7 gene (on chromo-

some 16q 24.3). It can either cause a pure or a complicated form of disease with dysarthria, dysphagia, optic disc pallor, axonal neuropathy, cerebellar atrophy, and cerebral atrophy. Even if the clinical picture shows a pure form, cranial imaging may show cerebellar atrophy (Elleuch et

al 2006). A novel SPG7 mutation has been defined in 6 members of a family with supranuclear palsy, cerebellar syndrome, and cognitive impairment. Diffusion tensor imaging studies have shown bilateral disturbance of white matter integrity in corticospinal tracts, frontal lobes, and midbrain, widening the different brain systems involved in hereditary spastic paraplegias (Warnecke et al 2007). Paraplegin is the product of SPG7 gene. It is a member of AAA proteins and located in mitochondria. Mitochondrial AAA proteins have chaperone-like activity, and they have a role in the activation of respiratory chain complexes; furthermore, they function in protein quality control by binding unfolded peptides and ensuring the specificity of the proteins (Leonhard 1999; Casari and Rugarli 2001). Although muscle involvement is unexpected in hereditary spastic paraplegia, the original family in which the paraplegin mutation was identified had muscle biopsies resembling the mitochondrial diseases with ragged-red fibers, with intense succinate dehydrogenase-stained areas and cytochrome oxidase negative fibers. But the other families having paraplegin mutation did not show these types of changes in their muscles. A study from the UK showed that in 2 patients with SPG7 mutation, although muscle biopsies did not show any histological phosphorylation defect histologically, biochemical studies showed a reduction in citrate-synthase corrected complex I and complex II/III activities in muscle samples and complex I activity in cultured myoblasts, which may suggest a respiratory chain defect in pathogenesis of the disease (Wilkinson et al 2004). Location of paraplegin was shown in the inner mitochondrial membrane along with its binding partner. This complex is lacking in mutated cells, and they show diminished activity of complex-I of the respiratory chain leading to increased susceptibility to oxidative stress. Paraplegin shows both proteolytic and chaperone-like activities (Atorino et al 2003; Lindholm et al 2004). Mutations can lead to a dysfunction of mitochondria causing an accumulation of misfolded proteins within the mitochondrial matrix. Although all tissues may have this impaired quality control and poor proof-reading, the

longest tract with high energy requirements, corticospinal tract axons, might show this kind of mitochondrial neurodegeneration (Casari and Rugarli 2001). Experimental studies in SPG7^{-/-} mice have shown an interesting finding: enlarged and structurally abnormal mitochondria accumulated in the synaptic terminals of long motor axons, not shorter axons and glial cells. Dynamic changes in the structure of the mitochondria seem to affect the axonal transport of mitochondria. Normally, old axons are replaced by newer ones in the axons by dyneins and kinesins retrogradely. Abnormal mitochondria might be less efficiently transported at the distal parts of very long axons, which may contribute to the axonal degeneration (Rugarli and Langer 2006). This process of neurodegeneration is blocked by intramuscular injection of adenoassociated viral vector that encodes paraplegin to the hind limb muscles of SPG7^{-/-} mice. After injection, transportation of the vector along the axons leads synthesis of new paraplegin, which is correctly imported into mitochondria and reduces number of swollen axons (Pirozzi et al 2006).

A family with slowly progressive disease of onset around 30 years of age showed a mutation in mitochondrial ATP6 gene. Patients had additional mitochondrial disease features like diabetes, cardiomyopathy, supraventricular tachycardia, and cerebellar symptoms. The disease was inherited maternally. Authors concluded that maternal inheritance pattern was the first time reported for hereditary spastic paraplegia (Verny et al 2011). (No designation as SPG is reported.)

SPG5 causes uncomplicated disease, and it was the first autosomal recessive locus mapped in 1994 in a group of Tunisian families. Muscle biopsies of a family linked to 8q11.1-q21.2 did not show oxidative phosphorylation system defects, suggesting that gene probably was not coding for a mitochondrial protein (Wilkinson et al 2003). Locus was narrowed down to 8q12.3, and a mutation in cytochrome P450-7B1 (CYP7B1) was found to cause SPG5. CYP7B1 is involved in an alternative pathway for cholesterol degradation in the liver, and because cholesterol cannot cross the brain-blood barrier and

is produced locally in brain, CYP7B1 provides the primary means of modification of dehydroepiandrosterone neurosteroids in brain (Tsaousidou et al 2008). Mutations in this alternative pathway might cause neurosteroid toxicity because of increased oxysterol levels or because impaired DHEA-related neurosteroids lose neuroprotection function. This interesting finding brings a new insight into hereditary spastic paraplegia because defective lipid metabolism might be one of the underlying pathogenic causes and might identify a new therapeutic strategy. Mutations in CYP7B1 are found in patients with both pure and complex clinical features (Goizet et al 2009b). The frequency of mutations in autosomal recessive families was 7.3% and 3.3% in sporadic pure spastic paraplegias (Goizet et al 2009b). Age of onset ranges from early childhood to the fifth decade. Cerebellar signs, distal amyotrophy, and white matter hyperintensities are common in patients with complex phenotype (Biancheri et al 2009; Criscuolo et al 2009; Goizet et al 2009b). Although patients presented with pure clinics, MRI investigations showed variable lesions like diffuse cerebral atrophy, punctate hyperintensities in white matter and cerebellum and enlargement of the fourth ventricle. One patient had autoimmune hepatitis, and it is not clear if mutation pathogenesis has a role in hepatic disorder (Goizet et al 2009b). With newly defined features, it is hard to say SGP5 is a pure type.

SPG11 is linked to chromosome 15q13-15 and causes complicated spastic paraplegia characterized by slowly progressive spastic paraparesis, mental retardation, and thin corpus callosum. Sometimes upper extremity weakness, dysarthria, and nystagmus can be seen. The locus of SPG11 has been refined to 2.93 cM with a maximum lod score of 11.84 at marker D15S659 (Olmez et al 2006), and the causative gene KIAA1840 (also known as FLJ21439) has been found (Stevanin et al 2006). A product of the gene is spatacin, which has a subcellular localization expressed in all tissues associated with mitochondria and endoplasmic reticulum, but not with Golgi structures or cytoskeleton. The function of spatacin is not yet known, but it

may be involved in gene expression, or, like many other hereditary spastic paraplegia proteins, it may be involved in cellular trafficking events (Stevanin et al 2007b; Paisan-Ruiz et al 2008a).

SPG11 is the most common form of autosomal recessive hereditary spastic paraplegia worldwide from China to Europe (Lee et al 2008; Paisan-Ruiz et al 2008a; Stevanin et al 2008). In 76 patients, mutation frequency was 41% in those who presented with thin corpus callosum and 4.5% in those without thin corpus callosum. Another study showed that overall frequency of SPG11 was 14% and 42% in patients with thin corpus callosum (Schule et al 2009b). It is highly found in patients without thin corpus callosum in both familial and nonfamilial cases (Crimella et al 2009). Additional features include lower motor degeneration with wasting and slight ocular cerebellar signs with long duration; on MRI, white matter changes and cortical (especially frontal) atrophy may be seen in addition to thin corpus callosum (Stevanin et al 2008). Extent of corpus callosum thinning and cerebellar atrophy might be correlated with disease severity (Rajakulendran 2011). Clinical heterogeneity is common in this form, and although onset is in the first and second decades, a female athlete was reported to have first symptoms at 27 years of age and had a mild course (Paisan-Ruiz et al 2008b).

Thin corpus callosum is not specific for SPG11. A locus for autosomal recessive hereditary spastic paraplegia with thin corpus callosum and epilepsy (SPG18) has been described at 8p12-p11.21 in two Omani families. Corpus callosum was reported to be subtotally agenetic with dysmorphic lateral ventricles in one of the families (Al-Yahyaee et al 2006).

Two patients with early-onset parkinsonism with resting tremor, akinesia, and rigidity who were initially responsive to levodopa developed progressive spastic paraparesis in the second decade. Their mutation analysis showed a mutation in SPG11, indicating that juvenile parkinsonism may also be related to SPG11 (Anheim et al 2009).

Spatacin is also related to autosomal reces-

sive juvenile amyotrophic lateral sclerosis (Orlacchio et al 2010). According to El-Escorial criterion from Italy, Brazil, Canada, Japan, and Turkey, spatacsin mutations were present in 10 of 25 families with definite autosomal recessive juvenile amyotrophic lateral sclerosis. SPG11 and ALS5 share the same chromosomal segment, and mutations found in ALS5 patients extended the spectrum of spatacsin-causative diseases (Orlacchio et al 2010).

SPG15 is linked to 14q22-24 (Kjellin syndrome) and causes complicated spastic paraplegia associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration. Genetic heterogeneity is also evident in this form of hereditary spastic paraplegia. Families with signs of cerebellar dysfunction, axonal neuropathy, mental decline, and even thin corpus callosum, but not the other signs of Kjellin syndrome, were linked to SPG15 (Elleuch 2007). Disease is caused by a mutation in zinc finger protein called spastizin encoded ZFYVE26 (Hanein et al 2008). It is widely distributed in human tissues and in rat embryos and colocalized with endoplasmic reticulum and endosomes, suggesting a possible role in trafficking (Hanein et al 2008). Newly published reports showed that patients with thin corpus callosum and mental decline have mutations in ZFYVE26/SPG15; this mutation is found in roughly 5% of patients with SPG11 in Italy (Denora et al 2009). However, patients with a clinical phenotype of Kjellin syndrome with central retinal degeneration also showed mutations in SPG11 (Orlen et al 2009). Orlen and her colleagues reported that central retinal degeneration, unreported in SPG11 before, is also a feature of SPG11 and that it develops later in the course of the disease and should be overlooked in SPG11 patients. SPG11 and SPG15 make most of the autosomal recessive hereditary spastic paraplegias, and after reports with clinical overlap, genetic testing is required for both in autosomal recessive patterns. EFNS guidelines suggest molecular testing for both SPG11 and SPG15 when thin corpus callosum with an autosomal recessive inheritance pattern is present, and molecular diagnosis for SPG7 is suggested if

cerebellar features are positive (Gasser et al 2010).

SPG14 is linked to 3q 27-28 and causes complicated spastic paraplegia with mental retardation and distal motor neuropathy.

SPG18 is a complicated form of HSP described in a large Saudi family and associated with ERLIN2 mutations which is a component of endoplasmic reticulum associated degradation pathway and it is localized to ER (Alazami 2011).

SPG23 is mapped to chromosome 1q24-q32. It is associated with prematurely aged facial appearance, hypopigmentation, microcephaly, and cognitive impairment (Blumen et al 2003). The product of the gene has not yet been identified. SPG24 is a pure autosomal recessive form linked to chromosome 13q14 (Hodgkinson et al 2002). SPG25 is complicated with disc hernia and linked to 6q23.3-q24.1 (Zortea et al 2002). In SPG26, wasting of small muscles of hands and feet and mild intellectual impairment occurs (Wilkinson et al 2005). SPG27 is linked to 10q22.1-10q24.1, which overlaps the locus of SPG9. It is not known whether it is a new locus or an allelic disorder with different mode of inheritance (Meijer et al 2004), but a new family different than SPG9 with early onset spastic paraparesis, mental retardation, sensorimotor neuropathy, cerebellar syndrome, and dysmorphic face in one child has reduced the SPG27 locus, suggesting that it is a new type (Ribai et al 2006). SPG28 is mapped to 14q21.3-q22.3 with pure characteristics (Bouslam et al 2005).

SPG30 is linked to chromosome 2q37.3 and caused by a mutation in the motor domain of KIF1A; a protein functions in anterograde axonal transportation. Erlich et al has discovered the gene in a pure Palestinian HSP family however patients reported in 2006 showed progressive spastic paraparesis, neuropathy, cerebellar signs like ataxia, dysarthria, and nystagmus, and cerebellar atrophy on cranial imaging studies (Erlich et al 2011, Klebe et al 2006). Together with SPG7, SPG21, and SPG27, SPG30 shows that cerebellar atrophy might not be an infrequent sign in hereditary spastic paraplegias and should not be overlooked even in patients with the pure form of the disease (Klebe et al 2006).

SPG32 is a new locus at 14q12-q21 with mild mental retardation, brainstem dysraphia, cerebellar atrophy, and corpus callosum thinning. It is an early-onset type of disease with very slow progression, and a marked feature is malformation of the pons in SPG32 (Stevanin et al 2007a).

SPG35 is defined in an Omani family, and it is linked to 16q21-q23.1. Clinical features were complicated with seizures, dysarthria, and intellectual disability. MRI was normal (Dick et al 2008). In another Omani family linked to the same locus, patients had ophthalmoplegia, optic atrophy, and dystonic upper limb movements with cognitive decline (Dick et al 2010). Hyperintense lesions in cerebral and cerebellar white matter, cerebral and cerebellar atrophy, in addition to brainstem atrophy were detected on MRI. Mutation analysis of both families showed homozygous mutations in fatty acid-2 hydroxylase gene (FA2H) (Dick et al 2010). A familial type of leukodystrophy and neurodegeneration with brain iron accumulation (NBIA) are also caused by FA2H mutations (Kruer et al 2010).

Like other motor neuron diseases like amyotrophic lateral sclerosis, causative mutation of SPG39 supported the role of neurotoxic substances in motor neuron disorders. Organophosphate compound-induced delayed neuropathy occurring after exposure to toxic substances may cause ataxia, weakness, muscle fasciculation, and flaccid paralysis followed by progressive spastic paraplegia (Rainier et al 2008; Chang and Wu 2009). It causes degeneration of the longest axons of nervous system and involves neuropathy target esterase protein. In a family with clinical features resembling either Troyer syndrome or organophosphate compound-induced delayed neuropathy, Rainier and her colleagues demonstrated a mutation in neuropathy target esterase protein, and it is designated as SPG39. They suggested that polymorphisms of neuropathy target esterase may play a role in motor neuron disorders like amyotrophic lateral sclerosis, even in the absence of exposure to toxic substances (Rainier et al 2008). NTE protein is found mainly in the large neurons of the central nervous system and regulates phospholipid metabolism. Lethality in knockout mice

suggested its role in embryonic survival (Chang and Wu 2010).

SPG43 was described in 2 sisters with hereditary spastic paraplegia and distal amyotrophy. Its mapped to 19p13.11-q12 (Meilleur et al 2010).

SPG45 is linked to 10q24.3-q25.1 and is complicated with mental retardation and ocular abnormalities like myopia, hyperopia, optic atrophy, and nystagmus (Dursun et al 2009).

SPG46 is a new type with thin corpus callosum and mental impairment. In addition to spastic paraplegia, thin corpus callosum, and mental impairment, patients all have congenital cataract and cerebellar ataxia (Boukhris et al 2010). SPG46 is linked to 9p21.2-q21.12 and is the first autosomal recessive type found on chromosome 9.

SPG47 is also associated with thin corpus callosum. It is described in two siblings from an Arabic consanguineous family with slowly progressive spastic paraparesis, mental retardation, seizures, thin corpus callosum and periventricular white matter abnormalities on 1p13.2-1p12 (Blumkin et al 2011).

SPG48 is caused by a mutation in the KIAA0415/SPG48 gene. It encodes a helicase involved in DNA double strand break repair pathway. Interestingly, patients were screened for other HSP mutations and were negative for SPG11 and SPG15 (Slabicki et al 2010). In addition to different metabolic pathways involved in pathogenesis of hereditary spastic paraplegias, DNA repair defects also show the complexity of etiology in this large group of disorders.

Another type of autosomal recessive hereditary spastic paraplegia is infantile-onset spastic paraplegia, which is allelic to the condition reported as juvenile amyotrophic lateral sclerosis. This type presents with infantile onset severe spastic paraparesis with progression to tetraplegia and anarthria during the early teenage years; dysphagia and slow eye movements develop in the second decade. Eymard-Pierre and colleagues reported that this type of hereditary spastic paraplegia is associated with alsin mutation (Eymard-Pierre et al 2002). Alsin is thought to have guanine nucleotide exchange factor

activities. Guanine nucleotide exchange factors are known to associate with the GDP-bound form of GTPases. They are thought to have function in GTP binding and dissociation, thus, activating the GTPases. Alsin might have a key function in regulating these guanine nucleotide exchange factors and, thus, a role in many functions of endocytic trafficking, microtubule organization, and signaling cascades as well as neuronal development (Eymard-Pierre et al 2002). It has been shown that alsin has a role also in neurodegeneration by enhancing apoptosis, and a missense mutation of alsin is cytotoxic

(Panzeri et al 2006).

Many alsin mRNA transcripts were found in various tissues when Als2 knockout mice were examined. It is suggested that different isoforms produced by different types of mutations are responsible for phenotypes of alsin mutations (Gros-Louis et al 2008). Recently, a new mutation caused by maternal uniparental heterodisomy with partial isodisomy of chromosome 2 was detected in an infantile ascending hereditary spastic paraplegia patient, extending the necessity of genetic testing in patients without consanguinity (Herzfeld et al 2009).

Table 2

Autosomal Recessive Hereditary Spastic Paraplegias

Genotype	Locus	Type	Gene
SPG5	8q11.1-q21.2	Pure or complicated	CYP7B1
SPG7	16q24.3	Pure or complicated	Paraplegin
SPG11	15q13-15	Pure or complicated	KIAA1840 (spatacsin)
SPG14	3q27-28	Complicated	
SPG15	14q22-24	Complicated	ZFYVE26 (spastizin)
SPG18	8p12-p11.21	Complicated	Erlin2
SPG20	13q12.3	Complicated	Spartin
SPG21	15q22.31	Complicated	Masparidin
SPG23	1q24-q32	Complicated	
SPG24	13q14	Pure	
SPG25	6q23.3-q24.1	Complicated	
SPG26	12p11.1	Complicated	
SPG27	10q22.1-24.1	Pure	
SPG28	14q21.3-q22.3	Pure	
SPG30	2q37.3	Complicated	KIF1A
SPG32	14q12-q21	Complicated	
SPG35	16q21-q23.1	Complicated	FA2H (fatty acid 2-hydroxylase)
SPG39	19p13.3	Complicated	PNPLA6 (neuropathy target esterase)
SPG43	19p13.11-q12	Complicated	
SPG45	10q24.3-q25.1	Complicated	
SPG46	9p21.2-q21.12	Complicated	
SPG47	1p13.2-1p12	Complicated	KIAA0415
SPG48	7p22.1	Complicated	KIAA0415

Troyer syndrome, one of the syndromic forms of hereditary spastic paraplegia (SPG20), is caused by a mutation in spartin, located on chromosome 13q12.3. Troyer syndrome is associated with dysarthria and distal amyotrophy and is seen with high frequency in the Old Order Amish population; however, it has been detected in 2 Omani families also (Manzini et al 2010). Spartin is thought to have an important role in intracellular protein trafficking and trafficking through the endocytic pathway (between plasma mem-

branes and trans-Golgi network), like spastin molecule by its microtubule-interacting and trafficking molecules domain and through an interaction with Eps15 protein (Crosby and Proukakis 2002; Robay et al 2006). Studies have shown its subcellular location and localized it to mitochondria. Spartin with its plant-related senescence domain, associates with cardiolipin, a major mitochondrial phospholipid. Spartin knock-out mice and spartin depleted cells have depolarized mitochondrial membrane and

reduced mitochondrial calcium influx (Joshi and Bakowska 2011). Mutant protein loses its mitochondrial localization. Lu and colleagues suggest that, in addition to defective trafficking events, mitochondrial dysfunction may also be involved in the pathogenesis of Troyer syndrome (Lu et al 2006). However, in cultured fibroblasts and lymphoblasts derived from affected individuals, no spartin protein could be detected, and it was suggested that Troyer syndrome results from complete loss of spartin protein (Bakowska et al 2008). Manzini and colleagues showed that in vitro SPG20 expression is highest and more specific to limbs, face, and forebrain during early morphogenesis, supporting the phenotypic congenital abnormalities seen in Troyer syndrome (Manzini et al 2010).

Mast syndrome is a complicated form of hereditary spastic paraplegia that is also seen in high frequency in the Old Order Amish. It is usually a disease of early adulthood and is associated with slow progression to dementia, cerebellar and extrapyramidal signs, thin corpus callosum, and white matter abnormalities. Childhood-onset diseases with hypoplastic corpus callosum have been defined in Caucasian patients (Brockmann et al 2005). It was mapped to 15q22.31, and the gene encodes a protein named maspardin (Mast syndrome, spastic paraplegia, autosomal recessive with dementia). Exact function of maspardin is not yet clear. It may be involved in sorting or trafficking of molecules between the endosomal/trans-Golgi network (Simpson et al 2003). Hanna and Blackstone showed that mas-

pardin localizes to cytoplasm and membranes, supporting a functional role in the trans-Golgi network/endosomal pathway. It interacts with aldehyde dehydrogenase ALDH16A1 as a binding partner in this network. How mutations cause neurodegeneration is unknown, but mutations in aldehyde dehydrogenase ALDH3A2 result in Sjögren-Larsson syndrome, which is characterized by spastic paraparesis and ichthyosis; this shows the importance of aldehyde dehydrogenases in the pathogenesis of neurologic diseases (Hanna and Blackstone 2009).

Autosomal recessive Spastic ataxia of Charlevoix-Saguenay (ARSACS) was defined in French Canada in the Charlevoix-Saguenay region of Quebec and is associated with progressive spasticity, dysarthria, truncal ataxia, late-onset deep sensory disturbances, and characteristic retinal myelinated fiber thickening. The gene has been mapped to chromosome 13q11-12, and it encodes sarsin. Although rare outside the Charlevoix-Saguenay region of Quebec, mutations in this gene have been identified in Tunisian, Turkish, Italian, and Japanese families. Sarsin has a DnaJ domain resembling Hsp40 and is thought to have chaperone-mediated actions in protein folding (El-Euch-Fayache et al 2003; Grieco et al 2004; Ogawa et al 2004; Richter et al 2004). A novel locus mapped to chromosome 17p13, SAX2, was defined in a group of families that was not linked to ARSACS locus (Bousslam et al 2007). ARSAL and dominant SAX1 are also defined for spastic ataxias, but genes are not defined yet.

Table 3

Clinical Signs of Syndromic Forms of Hereditary Spastic Paraplegias

Troyer syndrome	Dysarthria, distal amyotrophy, mental retardation, and short stature
Kjellin syndrome	Pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration
Charlevoix-Saguenay syndrome	Progressive spasticity, dysarthria, truncal ataxia, late-onset deep sensory disturbances, and characteristic retinal myelinated fiber thickening
Silver syndrome	Amyotrophy of small hand muscles, involvement of shoulder girdle at later stages
Mast syndrome	Slowly progressing disease, early adulthood onset, dementia, cerebellar and extrapyramidal signs, thin corpus callosum, and white matter abnormalities

All this molecular and genetic research may result in a common insight by providing a link between so many different clinical and genetic forms. However, progress in genetics, such as findings of defective cholesterol metabolism in SPG5 or interaction of hereditary spastic paraplegia genes like silver syndrome and SPG4, and finally DNA repair defects, amplifies the mys-

tery. Although we still do not know whether all types share a common biochemical basis, the underlying mechanisms seem to be mainly related to trafficking to the axonal transport or mitochondrial dysfunction. Because these are the longest axons, they need much more energy, and degeneration may result from inadequate supply of the needed energy.

НАСЛЕДСТВЕННАЯ СПАСТИЧЕСКАЯ ПАРАПЛЕГИЯ: ПАТОГЕНЕЗ И ПАТОФИЗИОЛОГИЯ

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