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AP-4-Associated Hereditary Spastic Paraplegia

Synonyms: Adaptor Protein Complex 4 Deficiency (AP-4 Deficiency), AP-4-Associated HSP, AP-4 Deficiency Syndrome

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Summary

Clinical characteristics

AP-4-associated hereditary spastic paraplegia (HSP), also known as AP-4 deficiency syndrome, is a group of neurodegenerative disorders characterized by a progressive, complex spastic paraplegia with onset typically in infancy or early childhood. Early-onset hypotonia evolves into progressive lower-extremity spasticity. The majority of children become nonambulatory and usually wheelchair bound. Over time spasticity progresses to involve the upper extremities, resulting in a spastic tetraplegia. Associated complications include dysphagia, contractures, foot deformities, dysregulation of bladder and bowel function, and a pseudobulbar affect. About 50% of affected individuals have seizures. Postnatal microcephaly (usually in the -2SD to -3SD range) is common. All have developmental delay. Speech development is significantly impaired and many affected individuals remain nonverbal. Intellectual disability in older children is usually moderate to severe.

Diagnosis/testing

The diagnosis of AP-4-associated HSP is established in a proband by identification of biallelic pathogenic variants in one of four genes: *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1*.

Management

Treatment of manifestations: Management by an interdisciplinary team (including a neurologist, clinical geneticist, developmental specialist, orthopedic surgeon/physiatrist, physical therapist, occupational therapist, and a speech and language pathologist) to address spasticity/weakness, secondary musculoskeletal findings, developmental delay and intellectual disability, seizures, and swallowing and feeding difficulties.

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Surveillance: Evaluation every six to 12 months by an interdisciplinary team to assess disease progression and to maximize ambulation and communication skills while reducing the effect of other manifestations (e.g., musculoskeletal complications, dysphagia / feeding difficulties, and seizures).

Genetic counseling

AP-4-associated HSP is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the AP-4-associated HSP-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

AP-4-Associated Hereditary Spastic Paraplegia: Included Disorders [1]
• *AP4B1*-related AP-4 deficiency (SPG47) • *AP4E1*-related AP-4 deficiency (SPG51) • *AP4M1*-related AP-4 deficiency (SPG50) • *AP4S1*-related AP-4 deficiency (SPG52)

1. Genetic loci for HSP are designated "SPG" (for "*s*pastic *p*araplegia") followed by a number indicating the order of their discovery [Fink 2013].

Diagnosis

Formal diagnostic criteria for AP-4-associated hereditary spastic paraplegia (HSP) have not been established.

Suggestive Findings

AP-4-associated HSP **should be suspected** in individuals with the following clinical findings and characteristic brain imaging findings [Verkerk et al 2009, Abou Jamra et al 2011, Moreno-De-Luca et al 2011, Ebrahimi-Fakhari et al 2018].

Clinical Findings

Characteristic findings:

- Progressive spastic paraplegia with progression to tetraplegia in the later stages (94%, 58/62) *
- Early-onset developmental delay (100%, 68/68) *
  - Delayed motor milestones (100%, 54/54) *
  - Failure to achieve or loss of independent ambulation (93%, 41/44) *
  - Impaired or absent speech development (98%, 51/52) *
- Neonatal/infantile hypotonia (usually mild) (100%, 41/41) *
- Postnatal microcephaly (77%, 47/61) (usually in -2SD to -3SD range) *
- Early-onset seizures including frequent febrile seizures (42%, 25/59) *

Less frequent findings:

- Short statue (65%, 17/26) *
- Nonspecific dysmorphic facial features (82%, 41/50) *
- Episodes of stereotypic laughter [Ebrahimi-Fakhari et al 2018]
- Foot deformities (i.e., clubfoot)

Brain Imaging Findings

Characteristic findings:

- Thinning of the corpus callosum (with prominent thinning of the posterior parts) (88%, 37/42) *
- Delayed myelination and nonspecific loss of the periventricular white matter (69%, 29/42) *
- Ex-vacuo ventriculomegaly, often with prominent enlargement of the posterior horns of the lateral ventricles (60%, 24/40) *

Less frequent findings:

- Cortical atrophy and cerebellar atrophy
- Brain iron accumulation [Vill et al 2017, Roubertie et al 2018]

* Data from the International Registry and Natural History Study of Adaptor-Protein 4-Related Hereditary Spastic Paraplegia (updated 5-20-18)

Establishing the Diagnosis

The diagnosis of AP-4-associated HSP **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in one of four genes: *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1* (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance (or identification of one known pathogenic variant and one variant of uncertain significance) in any of the genes listed in Table 1 does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (typically exome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Developmental delay / intellectual disability, spasticity, epilepsy, or microcephaly multigene panels that include *AP4B1*, *AP4E1*, *AP4M1*, *AP4S1*, and other genes of interest (see Differential Diagnosis) are most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of AP-4-associated HSP, some panels for developmental delay / intellectual disability and/or spasticity and/or epilepsy and/or microcephaly may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is the best option when the clinician cannot determine which multigene panel best fits the affected individual's clinical findings. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in AP-4 Associated Hereditary Spastic Paraplegia

Gene [1, 2]	Proportion of AP-4 Deficiency Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method [3]	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
AP4B1	~40% (32/80 probands)	100% (25/25 probands)	None reported
AP4E1	~14% (11/80 probands)	70% (7/10 probands)	30% (3/10 probands)
AP4M1	~31% (25/80 probands)	100% (22/22 probands)	None reported
AP4S1	~15% (12/80 probands)	100% (11/11 probands)	None reported

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. International Registry and Natural History Study of Adaptor-Protein 4-Related HSP (updated 5-20-18)
4. See Molecular Genetics for information on allelic variants detected in this gene.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

AP-4-associated hereditary spastic paraplegia (HSP) is characterized by complex spastic paraplegia in all affected individuals reported to date. Onset is usually before age one year. Infants manifest hypotonia, microcephaly, and delayed developmental milestones; some also have seizures. The early-childhood hypotonia evolves into progressive lower-extremity weakness and spasticity with pyramidal signs (plantar extension and hyperreflexia). Over time children often become nonambulatory and ultimately require mobility aids / wheelchairs. Spasticity progresses to involve the upper extremities, resulting in spastic tetraplegia.

Associated complications include dysphagia, contractures secondary to progressive spasticity, foot deformities, and dysregulation of bladder and bowel function.

Microcephaly becomes evident in infancy in the majority and is often in the -2 SD to -3 SD range.

Developmental delay is universal. Delayed motor milestones are often the presenting manifestation:

- Rolling (mean age: 6.5 months)
- Sitting (mean age: 10.2 months)
- Crawling (mean age: 22.8 months)

Only a subset of children achieve independent walking (mean age: 33.5 months), a skill that is often lost as the disease progresses [Data from the International Registry and Natural History Study of AP-4-Related HSP; updated 5-20-18].

Speech and language development is significantly impaired and many affected individuals remain nonverbal. Intellectual disability in older children is usually moderate to severe.

Seizures often occur in the first two years of life; about 50% of individuals with AP-4-associated HSP have a diagnosis of epilepsy. Seizure types include focal-onset seizures (often with secondary generalization) as well as

primary generalized seizures. Status epilepticus has been reported in a significant subset of patients. About 50% of affected individuals, including individuals with and without epilepsy, have seizures in the setting of fever. In general, seizures become less frequent with age and are often well controlled with standard anti-seizure medication.

Episodes of stereotypic laughter, perhaps indicating a pseudobulbar affect, are a characteristic finding in a subset of individuals [Ebrahimi-Fakhari et al 2018].

Less frequent clinical manifestations include short stature, nonspecific dysmorphic facial features, optic nerve atrophy, dystonia, and ataxia.

To date, uncomplicated hereditary spastic paraplegia, a pure spastic paraplegia without other neurologic manifestations, has not been reported in individuals with AP-4 deficiency.

Prognosis. Natural history data are not currently available. The oldest reported individuals are young adults.

Phenotype Correlations by Gene

AP-4-associated HSP is caused by biallelic loss-of-function variants in one of the four genes that encode subunits of the AP-4 complex (β4, ε, μ4, σ4). Because loss of any one subunit renders the entire complex nonfunctional, biallelic loss-of-function variants in any one of the four genes cause the same molecular defect – loss of AP-4 complex function – and the same phenotype.

Brain iron accumulation has been reported in one family with *AP4M1*-related AP-4 deficiency syndrome [Roubertie et al 2018] and one individual with *AP4S1*-related AP-4 deficiency syndrome [Vill et al 2017]. Given the rarity of this finding and a potential age bias, it is unknown if brain iron accumulation is a feature of AP-4-associated HSP regardless of cause.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported for any of the four genes known to cause AP-4-associated HSP (*AP4B1*, *AP4E1*, *AP4M1*, *AP4S1*).

Nomenclature

Table 2. Other Terms Used to Refer to AP-4-Associated Hereditary Spastic Paraplegia Subtypes

Subtype	Terms
AP4B1-related AP-4 deficiency syndrome	• Hereditary spastic paraplegia type 47 • Spastic paraplegia type 47 (SPG47 [1]) • *AP4B1*-related hereditary spastic paraplegia (HSP-AP4B1)
AP4E1-related AP-4 deficiency syndrome	• Hereditary spastic paraplegia type 51 • Spastic paraplegia type 51 (SPG51) • *AP4E1*-related hereditary spastic paraplegia (HSP-AP4E1)
AP4M1-related AP-4 deficiency syndrome	• Hereditary spastic paraplegia type 50 • Spastic paraplegia type 50 (SPG50) • *AP4M1*-related hereditary spastic paraplegia (HSP-AP4M1)
AP4S1-related AP-4 deficiency syndrome	• Hereditary spastic paraplegia type 52 • Spastic paraplegia type 52 (SPG52) • *AP4S1*-related hereditary spastic paraplegia (HSP-AP4S1)

1. Genetic loci for HSP are designated "SPG" (for "*s*pastic *p*araplegia") followed by a number indicating the order of their discovery [Fink 2013].

Recommendations for the nomenclature of genetic movement disorders, including AP-4-associated HSP, have been published [Marras et al 2016].

Prevalence

AP-4-associated HSP is rare. To date about 80 individuals are known; all have been included in the International Registry and Natural History Study of AP-4-Related Hereditary Spastic Paraplegia (updated 5-20-18).

Families with AP-4-associated HSP have been reported from North America, Europe, the Middle East, and the Indian subcontinent. *

About two thirds of individuals with AP-4-associated HSP have consanguineous parents; * however, this could be the result of ascertainment bias, as initial reports have mainly focused on families from countries with high rates of consanguinity [Verkerk et al 2009, Abou Jamra et al 2011, Moreno-De-Luca et al 2011]. More recently, AP-4-associated HSP has been reported in populations with low rates of consanguinity [Ebrahimi-Fakhari et al 2018].

* International Registry and Natural History Study of AP-4-Related HSP

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *AP4B1*, *AP4S1*, or *AP4M1*.

Heterozygous variants in *AP4E1* have been described in individuals with persistent stuttering [Raza et al 2015].

Differential Diagnosis

Many of the initial manifestations of AP-4-associated HSP are nonspecific and may resemble other disorders characterized by spasticity, developmental delay / intellectual disability, and a thin corpus callosum. Many children with AP-4-associated HSP are diagnosed with cerebral palsy before genetic testing is obtained.

Table 3 summarizes the features that distinguish the disorders most likely considered in the differential diagnosis from AP-4-associated HSP.

Table 3. Distinguishing Clinical Features of Hereditary Disorders to Consider in the Differential Diagnosis of AP-4-Associated HSP

Gene(s) [1] (Locus/Disorder)	MOI	Distinguishing Clinical Features of the Differential Diagnosis Disorder
AMPD2 (SPG63)	AR	• Central visual impairment • Cerebellar hypoplasia/atrophy
ARSI (SPG66)	AR	Peripheral neuropathy
MTRFR (formerly *C12orf65*) (SPG55)	AR	• Optic atrophy • Motor sensory neuropathy
CYP2U1 (SPG56)	AR	Basal ganglia calcification
DDHD2 (SPG54)	AR	Optic-nerve hypoplasia is more common.
FA2H (SPG35; fatty acid hydroxylase-associated neurodegeneration)	AR	• Later onset • Brain iron accumulation is more common.

Table 3. continued from previous page.

Gene(s) [1] (Locus/Disorder)	MOI	Distinguishing Clinical Features of the Differential Diagnosis Disorder
GBA2 (SPG46)	AR	• Congenital cataracts • Hearing loss • Neuropathy
GJC2 (SPG44)	AR	Later onset
L1CAM (SPG1; L1 syndrome)	XL	Adducted thumbs
NT5C2 (SPG45 [SPG65])	AR	Optic atrophy is more common.
PGAP1 (SPG67)	AR	Tremor
RUSC2 (*RUSC2*-associated ID; OMIM 617773)	AR	Described in 1 family only
SPG11 (spastic paraplegia 11)	AR	• Later onset • Distal amyotrophy • Pigmentary retinopathy • Ataxia • Parkinsonism • Ears of the lynx sign on MRI
SPG21 (SPG21)	AR	• Onset in young adulthood • Cerebellar signs
TECPR2 (SPG49; see *TECPR2*-Related Hereditary Sensory Neuropathy with Intellectual Disability.)	AR	• Autonomic sensory neuropathy • Apneas / chronic respiratory disease • Dysmorphism
ZFR (SPG71)	AR	Described in 1 individual only
ZFYVE26 (spastic paraplegia 15)	AR	• Later onset • Pigmentary retinopathy • Neuropathy • Parkinsonism

Note: See Hereditary Spastic Paraplegia Overview for a general discussion of this phenotype.
AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; SPG = spastic paraplegia; XL = X-linked
1. Genes are in alphabetic order.

Other hereditary disorders to consider in the differential diagnosis of AP-4-associated HSP include the leukodystrophies and certain inborn errors of metabolism (particularly important are treatable conditions such as dopa-responsive dystonia (see GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with AP-4-associated hereditary spastic paraplegia (HSP), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with AP-4-Associated HSP

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	• To assess visual acuity • To perform fundoscopic exam for evidence of optic atrophy
Neurologic	Neurologic eval	To incl brain MRI. Consider EEG if seizures are a concern.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.
Pulmonary	Pulmonary eval	To incl eval of aspiration risk & secretion mgmt
Genitourinary	Neuro-urologic eval	To incl urodynamic testing
Musculoskeletal	Orthopedics / physiatry / PT & OT eval	To incl PT/OT eval & assessment for mobility, activities of daily living, contractures, scoliosis, & foot deformities
	Referral to pediatric pain specialist	For those w/pain due to deforming joint contractures
Miscellaneous/ Other	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support & resources	• Community or online resources (e.g., Parent to Parent) • Social work involvement for parental support • Home nursing referral if needed
	Referral to palliative care	When deemed appropriate by family & health care providers

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

At present, no treatment prevents, halts, or reverses neuronal degeneration in AP-4-associated HSP. Treatment is directed at reducing symptoms and preventing secondary complications.

Table 5. Treatment of Manifestations in Individuals with AP-4-Associated HSP

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties & growth failure	• Nutritional supplementation • G-tube feeds	• Referral to nutritionist • Gastrostomy feeding ↓ aspiration risk / provides a reliable route for medication / can improve nutritional status.
Dysphagia	G-tube feeds	Dysphagia-assoc aspiration may → recurrent aspiration pneumonia.
Sialorrhea	• Anticholinergic drugs • Botulinum toxin injections • Surgery	Mgmt by an interdisciplinary aerodigestive team
Aspiration	• Management of secretions • G-tube feeds	
Pulmonary complications	• Minimize aspiration risk (see above) • Pulmonary toilet	• Aspiration, pulmonary infections, restrictive lung disease secondary to scoliosis & spasticity • Referral to pulmonologist

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Bowel dysfunction, chronic constipation, gastroesophageal reflux	• Stool softeners, prokinetics, osmotic agents, or laxatives as needed • Proton pump inhibitors, histamine receptor antagonists, or antacids as needed • Consideration of fundoplication in refractory cases	Referral to gastroenterologist
Delayed speech development	Speech & language therapy	See Developmental Delay / Intellectual Disability Management Issues.
Delayed motor development	PT & OT	
Spasticity/ Weakness/ Hypotonia	• PT • Antispastic medications such as oral or intrathecal baclofen • Botulinum toxin injections • Surgical treatment	• Progression of contractures, scoliosis, & foot deformities may be delayed w/regular physiotherapy & antispastic medications. • Consider need for positioning and mobility devices. • Monitor skin integrity.
Musculoskeletal	Contractures	PT; referral to orthopedic surgery
	Scoliosis	
	Foot deformities	PT; ankle-foot orthoses; referral to orthopedic surgery
Urinary urgency	Anticholinergic drugs	Referral to urologist
Epilepsy	Standard anti-seizure medication	Most patients respond to standard anti-seizure therapy. [1]
Osteopenia	Vitamin D & calcium supplementation	
Routine health care	Standard immunizations per local guidelines	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources & support. • Ensure care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment for need of palliative care involvement &/or home nursing

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory-impairment specialists. In the US, early intervention is a federally funded program available in all states; it provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, and/or

cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; however, for children too medically unstable to attend, home-based services are provided.

Ages 5-21 years. IEP services:

- In the US, an IEP based on the individual's level of function should be developed by the local public school district and will dictate specially designed instruction/related services.
- IEP services will be reviewed annually to determine if any changes are needed.
- Special education law requires that children participating in an IEP be in the least restrictive environment at school and included in general education as much as possible, when and where appropriate.
- Vision consultants should be a part of the child's IEP team to support access to academic material if the child has visual impairment.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material.
- As a child enters adolescence, an educational transition plan should be discussed and incorporated into the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

Discussion about transition plans including financial and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral-motor dysfunction should be reassessed in regular intervals and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Feeds can be thickened or chilled to minimize feeding problems; when severe feeding dysfunction is present, a gastrostomy tube may be necessary. Assuming that the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist, can be helpful to improve coordination or sensory-related feeding issues.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in this area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

Patients should be evaluated periodically (i.e., every 6-12 months) by an interdisciplinary team that includes a neurologist, clinical geneticist, developmental specialist, orthopedic surgeon/physiatrist, physical therapist, occupational therapist, and speech and language pathologist to assess disease progression, maximize ambulation and communication skills, and reduce other manifestations (Table 6).

Table 6. Recommended Surveillance for Individuals with AP-4 Associated Hereditary Spastic Paraplegia

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval for visual acuity & need for support services for the visually impaired	As needed
Gastrointestinal/ Feeding	• Aspiration risk & nutritional status • Monitor for constipation & bowel dysfunction.	
Pulmonary	Monitor for aspiration & pulmonary complications.	
Genitourinary	Urodynamic testing	
Musculoskeletal	• PT/OT eval; assess for contractures, scoliosis, & foot deformities. • Hip/spine x-rays	Annually; more frequently if needed
Neurologic	• Monitor & treat spasticity. • Monitor those w/seizures as clinically indicated.	
Miscellaneous/ Other	Monitor developmental progress & educational/family needs.	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

AP-4-associated hereditary spastic paraplegia (HSP) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with AP-4-associated HSP are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *AP4B1*, *AP4E1*, *AP4M1*, or *AP4S1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Cure AP-4, Inc.**

  24R Pleasant Street

  Unit 2

Newburyport MA 01950
Email: info@cureap4.org
www.cureap4.org

- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  www.hspersunite.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Tom Wahlig-Foundation**
  Tom Wahlig Stiftung
  Germany
  www.hsp-info.de/en/foundation.htm
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  sp-foundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. AP-4-Associated Hereditary Spastic Paraplegia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AP4B1	1p13.2	AP-4 complex subunit beta-1		AP4B1	AP4B1
AP4E1	15q21.2	AP-4 complex subunit epsilon-1		AP4E1	AP4E1
AP4M1	7q22.1	AP-4 complex subunit mu-1	AP4M1 database	AP4M1	AP4M1
AP4S1	14q12	AP-4 complex subunit sigma-1		AP4S1	AP4S1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for AP-4-Associated Hereditary Spastic Paraplegia (View All in OMIM)

602296	ADAPTOR-RELATED PROTEIN COMPLEX 4, MU-1 SUBUNIT; AP4M1

Table B. continued from previous page.

607243	ADAPTOR-RELATED PROTEIN COMPLEX 4, SIGMA-1 SUBUNIT; AP4S1
607244	ADAPTOR-RELATED PROTEIN COMPLEX 4, EPSILON-1 SUBUNIT; AP4E1
607245	ADAPTOR-RELATED PROTEIN COMPLEX 4, BETA-1 SUBUNIT; AP4B1
612936	SPASTIC PARAPLEGIA 50, AUTOSOMAL RECESSIVE; SPG50
613744	SPASTIC PARAPLEGIA 51, AUTOSOMAL RECESSIVE; SPG51
614066	SPASTIC PARAPLEGIA 47, AUTOSOMAL RECESSIVE; SPG47
614067	SPASTIC PARAPLEGIA 52, AUTOSOMAL RECESSIVE; SPG52

Molecular Pathogenesis

AP-4-associated hereditary spastic paraplegia (HSP) is caused by biallelic pathogenic variants in one of four genes (*AP4B1*, *AP4E1*, *AP4M1*, *AP4S1*) that encode subunits of the AP4 complex (β4, ε, μ4, σ4, respectively). Loss of any one subunit renders the entire heterotetrameric complex nonfunctional; hence, loss-of-function variants in any one of the four genes cause the same cellular outcome – loss of AP-4 complex function [Hirst et al 2013, Frazier et al 2016]. Reduction or loss of the mutated subunit causes a reduction in the whole cell level of the other subunits as they are no longer able to be incorporated into a stable complex, and so are degraded by the cell. Evolutionary studies also support the obligate nature of the AP-4 complex because organisms either have all four AP-4 HSP-related genes or none at all [Hirst et al 2013].

The AP-4 complex is ubiquitously expressed in human tissues, including in the central nervous system [Hirst et al 2013]. At steady state, AP-4 localizes at the subcellular level to the *trans*-Golgi network (TGN), where it functions in the sorting of transmembrane cargo proteins into transport vesicles for TGN export. In AP-4-deficient cells these cargo proteins will be missorted and so will become mislocalized in the cell, likely affecting their function. A number of proteins have been suggested to be AP-4 cargo proteins. Evidence has emerged supporting a role for AP-4 in the post-Golgi trafficking of the autophagy protein ATG9A (see BioRxiv) [Mattera et al 2017, Davies et al 2018, De Pace et al 2018].

AP4B1

Gene structure. The predominant *AP4B1* transcript NM_006594.4 consists of 11 exons. Alternatively spliced transcript variant that encode different isoforms are known.

See Table A, **Gene** for a detailed summary of gene, transcript, and protein information.

Normal gene product. The NM_006594.4 transcript encodes the AP-4 complex subunit beta-1 (also known as β4) predicted to be 739 amino acids in length (NP_006585.2) [Dell'Angelica et al 1999, Hirst et al 1999]. The sequence of β4 is strongly conserved through evolution with orthologs in mammals and other vertebrates. β4 assembles into protein complex AP-4 (see Molecular Pathogenesis). β4 domains include one involved in the assembly of the AP-4 complex, and a second that binds an accessory protein for AP-4 known as tepsin [Frazier et al 2016].

Abnormal gene product. Most *AP4B1* pathogenic variants identified to date predict truncation and/or destabilization of the protein, suggesting that pathogenicity results from loss of function of the β4 protein [Ebrahimi-Fakhari et al 2018].

AP4E1

Gene structure. The *AP4E1* transcript NM_007347.4 consists of 21 exons. Alternatively spliced transcript variants that encode different isoforms are known.

See Table A, **Gene** for a detailed summary of gene and protein information.

Normal gene product. The NM_007347.4 transcript encodes the AP-4 complex subunit epsilon-1 (also known as ε) predicted to be 1,137-amino acids in length (NP_031373.2) [Dell'Angelica et al 1999, Hirst et al 1999]. The sequence of ε is strongly conserved through evolution with orthologs in mammals and other vertebrates. ε assembles into protein complex AP-4 (see Molecular Pathogenesis). ε domains include one involved in the assembly of the AP-4 complex, and a second shown to bind an AP-4 accessory protein known as tepsin [Mattera et al 2015].

Abnormal gene product. Most *AP4E1* pathogenic variants identified to date predict truncation and/or destabilization of the protein, suggesting that pathogenicity results from loss of function of the ε protein [Abou Jamra et al 2011].

AP4M1

Gene structure. The *AP4M1* transcript NM_004722.3 has 15 exons. There are multiple splice variants.

See Table A, **Gene** for a detailed summary of gene and protein information.

Normal gene product. The transcript NM_004722.3 encodes AP-4 complex subunit mu-1 (also known as μ4) predicted to be 453 amino acids in length (NP_004713.2) [Dell'Angelica et al 1999, Hirst et al 1999]. The sequence of μ4 is strongly conserved through evolution with orthologs in mammals and other vertebrates. μ4 assembles into protein complex AP-4 (see Molecular Pathogenesis). The μ4 domains include one that is involved in the assembly of the AP-4 complex, and a protein-protein interaction module known as a Mu homology domain that in adaptor protein complexes binds to linear sorting motifs in transmembrane cargo proteins.

Abnormal gene product. Most *AP4M1* pathogenic variants identified to date predict truncation and/or destabilization of the protein, suggesting that pathogenicity results from loss of function of the μ4 protein [Verkerk et al 2009].

AP4S1

Gene structure. *AP4S1* consists of six exons. There are multiple alternative splice variants encoding different protein isoforms.

See Table A, **Gene** for a detailed summary of gene and protein information.

Normal gene product. The NM_007077.4 transcript encodes AP-4 complex subunit sigma-1 (also known as σ4) predicted to be 159 amino acids in length (NP_009008.2) [Dell'Angelica et al 1999, Hirst et al 1999]. The sequence of σ4 is strongly conserved through evolution with orthologs in mammalians and other vertebrates. σ4 assembles into a protein complex, named AP-4 (see Molecular Pathogenesis). σ4 has a 1-142 amino acid region that is involved in the assembly of the AP-4 complex.

Abnormal gene product. Most *AP4S1* pathogenic variants identified to date predict truncation and/or destabilization of the protein, suggesting that pathogenicity results from loss of function of the σ4 protein [Abou Jamra et al 2011, Hardies et al 2015].

Chapter Notes

Author Notes

Please visit:

www.CureSPG47.org to learn about ongoing research on AP-4-associated hereditary spastic paraplegia. Current research includes an International Registry and Natural History Study that is open for enrollment.

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