

# AP-4-Associated Hereditary Spastic Paraplegia



**Boston Children's Hospital**  
Until every child is well™

# What is AP-4-HSP?

AP-4-Associated Hereditary Spastic Paraplegia (AP-4-HSP) is a group of **neurodegenerative** disorders that affect the nervous system, the brain and the spinal cord. It's also called:

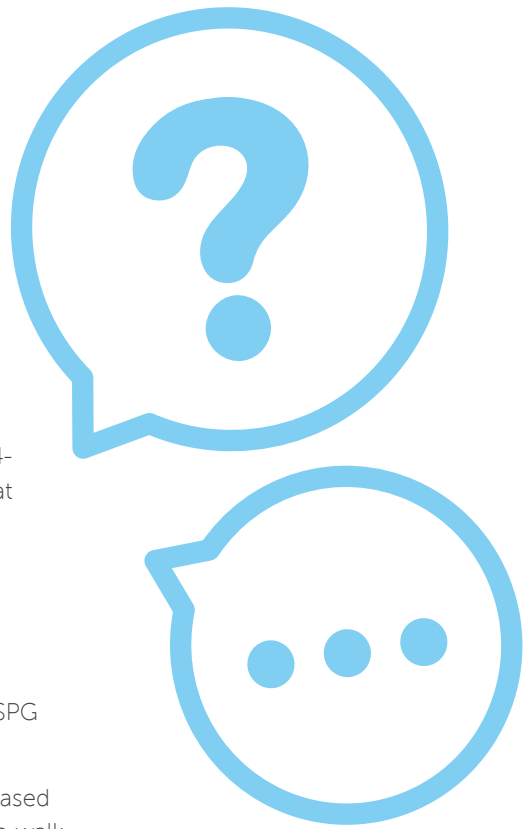
- AP-4 deficiency syndrome
- Adaptor protein complex 4 (AP-4) deficiency
- Hereditary spastic paraplegia 47, 50, 51, 52, or SPG 47, 50, 51, 52

Many children with AP-4-HSP have **spasticity** (increased tone) in their arms and legs. Most lose their ability to walk and need to use a wheelchair.

## What are the signs and symptoms of AP-4-HSP?

Many of the early signs of AP-4-HSP look like other disorders. This means that children may be misdiagnosed with cerebral palsy, for example.

Many babies with AP-4-HSP have **hypotonia** (muscles that are weaker than normal, also called **low muscle tone**) at birth. Your baby may feel limp and like a rag doll in your arms. Most children develop **hypertonia** (tighter and stiffer muscles, also called **high muscle tone**). All patients develop **spasticity** (when muscle tone increases, limiting range of motion.)



As children grow, other signs are:

1. A small head (also known as **microcephaly**)
2. Developmental delay and intellectual impairment
3. Problems with speech
4. Seizures
5. Short **stature** (height)
6. **Dystonia** (involuntary movements or abnormal postures)
7. **Ataxia** (trouble with balance and coordination)

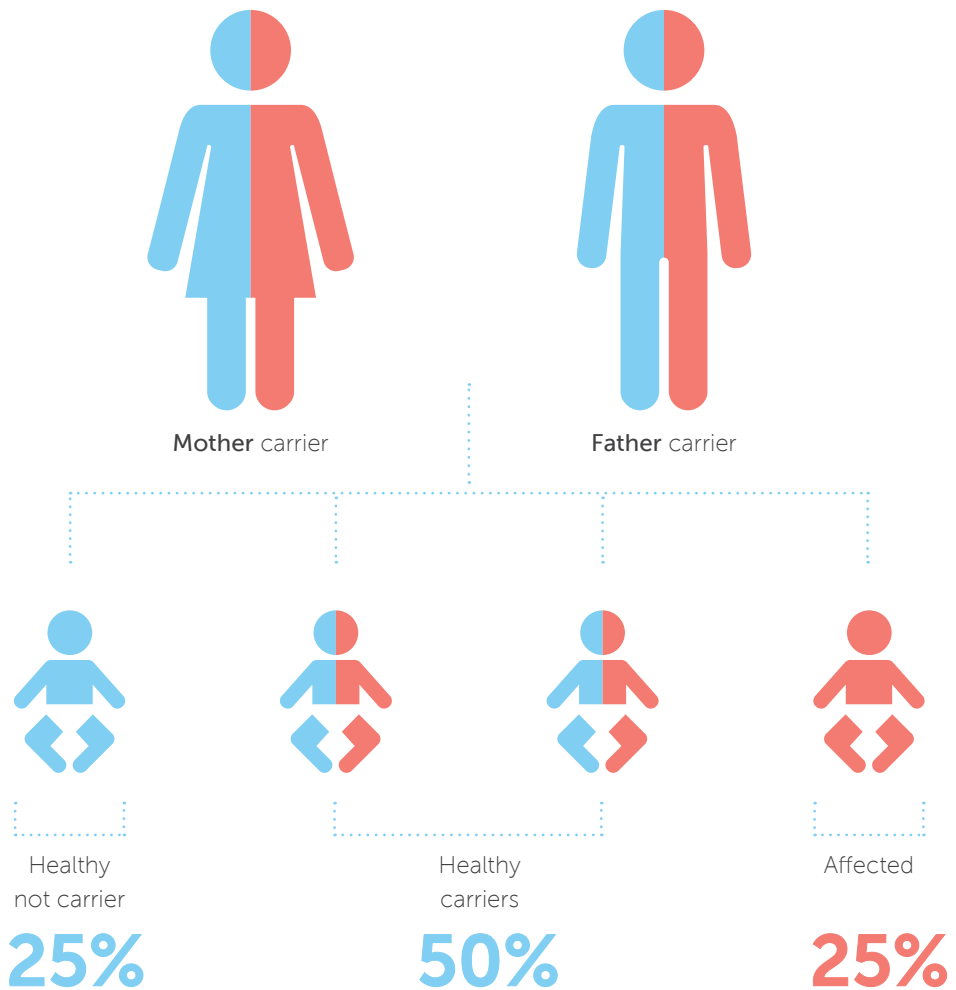
Some children with AP-4-HSP may also have differences in how their face looks:

- High palate (the roof of the mouth is too high or narrow)
- Wide bridge of the nose
- Bulbous (large and round) nose
- Wide mouth
- **Protruding** (sticking out) tongue
- **Short philtrum** (the groove between the bottom of the nose and top of the lips)
- Narrow forehead
- Flat feet or club feet

## What causes AP-4-HSP?

AP-4-HSP is an **inherited disorder** (passed from parent to child). It is caused by genes that have a **mutation** (a "broken" gene that does not work the right way). These genes are called AP4B1, AP4M1, AP4E1 and AP4S1.

Mutations that cause AP-4-HSP are inherited as follows:



## What are the kinds of AP-4-HSP?

Children who get AP-4-HSP can have 1 of 4 different kinds of the disorder:

- AP4B1-related HSP or SPG47
- AP4M1-related HSP or SPG50
- AP4E1-related HSP or SPG51
- AP4S1-related HSP or SPG52

## Who does ASP-4-HSP affect most?

AP-4-HSP affects boys and girls of ethnic groups from around the world. It's not known exactly how many people have AP-4-HSP.

## How is ASP-4-HSP diagnosed?

Symptoms of AP-4-HSP can make it look like other disorders or conditions. Your child's doctor may need to do more testing to find out for sure whether your child has AP-4-HSP.

This may include:

- **Magnetic resonance imaging (MRI)**  
Detailed pictures of the brain are taken to see if there are problems with the brain or spinal cord.
- **Genetic testing**  
This is the most accurate way to diagnose AP-4-HSP. A doctor takes a blood sample from your child and/or a swab from your child's cheek.

## How is AP-4-HSP treated?

There is no specific treatment for AP-4-HSP right now. But there are many services to help treat your child's symptoms.

Ages  
0–3  
years

We recommend an Early Intervention program. This program connects your child to occupational, physical, speech and feeding therapies. It also connects you with mental health services, special educators and specialists in **sensory** (how your child sees, hears, touches and so on) issues.

Ages  
3–5  
years

We recommend that your child goes to preschool in your local public school district. Your child will have an evaluation before being placed in a classroom to figure out what services and therapies they'll need. An individualized education plan (IEP) is developed for children who qualify based on their motor, language, social and/or cognitive delay(s). The Early Intervention program usually helps with this transition.

Ages  
5–21  
years

An IEP based on your child's level of ability should be put together by your local public school district. It will include instructions and related services that are needed for your child. It's a good idea to start talking about plans for getting your child ready to be an adult, including financial and medical arrangements, when your child is around 12 years old. Developmental pediatricians can offer help with **transitioning** (changing) to adulthood.

## What therapies will my child need?

### Physical therapy to help with gross motor skills

Physical therapy helps your child's **gross motor skills** (their large muscle movement, like walking or lifting things) and their mobility (how well they can move overall). Your child's therapist may use durable medical equipment (DME) and positioning devices (like wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

### Feeding and swallowing therapy to help with oral-motor skills

Your child's care team should check your child's **oral-motor** (muscles used for talking, chewing, swallowing) ability regularly. Feeding evaluations and/or swallowing studies should be done to check on choking or gagging during feeds, poor weight gain, frequent respiratory illnesses and/or not wanting to eat that is not explained by another reason.

### Occupational therapy to help with fine motor skills

Occupational therapy helps with **fine motor skills** (small muscle movement, like writing or picking things up with fingers) that affect movements that are part of feeding, grooming, dressing and typing.

### Speech therapy to help with communication skills

Speech therapy can help build a vocabulary or alternative means of communication. Think about getting your child evaluated for alternative communication tools (like [Augmentative and Alternative Communication](#)) for children with expressive language challenges.



# Specialists Your Child Will See

Your child may see some or all of the specialists listed here:

- Neurologist
- Speech therapist
- Physical therapist
- Occupational therapist
- Ophthalmologist (if needed)







## Drug screening

Dr. Darius Ebrahimi-Fakhari at Boston Children's is setting up a drug screening test on **fibroblasts** (cells from connective tissue in the body) taken from AP-4-HSP patients. The test begins with taking skin cells from the person with AP-4 HSP and also from the parent of the same gender. [iPSC stem cells](#) are grown from these skin cells and then studied in a lab.

The goal of the project is to test whether some compounds which are FDA-approved for other diseases might be helpful for people with AP-4-HSP. This research could someday help pinpoint a treatment that could help people with all 4 forms of this disorder.

## Gene therapy

The organization Cure AP-4 has asked Dr. Mimoun Azzouz of the University of Sheffield (UK) to come up with an AP4B1 [gene therapy](#) plan. Cure AP-4 will also support Dr. Steven Gray of the University of Texas Southwestern Medical Center in working on a plan for AP4M1 using a method called gene therapy. With gene therapy a patient's AP-4 genes stay in place and a good, working copy of the gene is added to the cell. This may be a way to help patients with AP-4-HSP in the future.

# AP-4 HSP Reading List

## Published Studies

Abdollahpour, H., Alawi, M., Kortüm, F., Beckstette, M., Seemanova, E., Komárek, V., ... Kutsche, K. (2014). An AP4B1 frameshift mutation in siblings with intellectual disability and spastic tetraplegia further delineates the AP-4 deficiency syndrome. *European Journal of Human Genetics*, 23(2), 256–259. doi: 10.1038/ejhg.2014.73.

Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535153/>

Ebrahimi-Fakhari, D. (2018, December 13). AP-4-Associated Hereditary Spastic Paraplegia. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK535153/>.

Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535153/>

Ebrahimi-Fakhari, D., Cheng, C., Dies, K., Diplock, A., Pier, D. B., Ryan, C. S., ... Bennett, J. T. (2017). Clinical and genetic characterization of AP4B1-associated SPG47. *American Journal of Medical Genetics Part A*, 176(2), 311–318. doi: 10.1002/ajmg.a.38561

Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29193663>

Ebrahimi-Fakhari, D. (2017). Congenital Disorders of Autophagy: What a Pediatric Neurologist Should Know. *Neuropediatrics*, 49(01), 018–025. doi: 10.1055/s-0037-1608652

Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29112993>

Tüysüz, B., Bilguvar, K., Koçer, N., Yalçinkaya, C., Çağlayan, O., Gül, E., ... Günel, M. (2014). Autosomal recessive spastic tetraplegia caused by AP4M1 and AP4B1 gene mutation: Expansion of the facial and neuroimaging features. *American Journal of Medical Genetics Part A*, 164(7), 1677–1685. doi: 10.1002/ajmg.a.36514.

Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/ajmg.a.36514>

Verkerk, A. J., Schot, R., Dumée, B., Schellekens, K., Swagemakers, S., Bertoli-Avella, A. M., ... Mancini, G. M. (n.d.). Mutation in the AP4M1 Gene Provides a Model for Neuroaxonal Injury in Cerebral Palsy. *The American Journal of Human Genetics*, 85(1), 40–52. doi: 10.1016/j.ajhg.2009.06.004.

Available from: [https://www.cell.com/ajhg/fulltext/S0002-9297\(09\)00240-7](https://www.cell.com/ajhg/fulltext/S0002-9297(09)00240-7)

# AP-4 Resources

## AP-4 Community

### Cure AP-4

24R Pleasant St, Unit 2

Newburyport, MA 01950

Website: <http://cureap4.org>

E-mail: [info@cureap4.org](mailto:info@cureap4.org)

WhatsApp group : <https://chat.whatsapp.com/5jzYxKCI9xfDqJqErp9puN>

Facebook: [@CureAP4](https://www.facebook.com/CureAP4)

» [@AP-4-associated HSP Support Group: AP4B1, AP4M1, AP4E1, AP4S1 \(SPG47,50, 51, 52\)](#)

Twitter: [@CureAP4](https://twitter.com/CureAP4)

Instagram: [@CureAP4](https://www.instagram.com/CureAP4)

## Organizations

### Cerebral Palsy Alliance Research Foundation

404 5th Avenue, Level 3

New York, NY 10018

Phone: (646) 340 1209

Website: <https://cparf.org/>

### Cerebral Palsy Research Network

Paul Gross

University of Utah

Williams Building

295 Chipeta Way, Room: 1N455

Salt Lake City, UT 84108

Phone: (402) 302-CPRN (2776)

Website: <https://cprn.org/>

Email: [paul@cprn.org](mailto:paul@cprn.org)

### Genetic and Rare Diseases (GARD) Information Center

PO Box 8126

Gaithersburg, MD 20898-8126

Phone: (301) 251-4925

Toll-free: (888) 205-2311

Website: <http://rarediseases.info.nih.gov/GARD/>

### National Organization for Rare Disorders (NORD)

Website: <https://rarediseases.org/rare-diseases/ap-4-associated-hereditary-spastic-paraplegia/>

### Tom Wahlig Foundation

Veghestrasse 22

Münster, 48149 Germany

Phone: +49 (0) 251-20 07 91 20

Email: [pressea@hsp-info.de](mailto:pressea@hsp-info.de)

Website: <http://www.hsp-info.de>

### Spastic Paraplegia Foundation

1605 Goularte Place

Fremont, CA 94539-7241 USA

Toll-free: (877) 773-4483

Website: <https://rarediseases.org/organizations/spastic-paraplegia-foundation/>

Email: [information@sp-foundation.org](mailto:information@sp-foundation.org)

# Questions to ask your health care provider

Learning that your child has been diagnosed with AP-4-HSP can be scary. It can also be confusing since this is such a rare disorder. The best thing you can do is learn as much about this condition as possible. This can feel like a big challenge while you are still getting used to the news.

That is why we recommend the following list of questions for you and your doctor to discuss:

What does an AP-4-HSP diagnosis mean?

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How do you expect my child's condition to change?

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What do you expect my child's daily life to be like?

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What are some common complications connected to AP-4-HSP?

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Who will be the members of my child's medical team?

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What might happen as part of my child's treatment plan—both now and in the future?

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Could my child be helped by physical therapy, speech therapy and/or behavioral therapy?  
What happens as part of these treatments?

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Could mechanical aids and devices (like a motorized wheelchair or computerized communication device) help my child?

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If so, how do we get these devices?

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Who will teach us how to use them?

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Will medications be used to treat my child's AP-4-HSP or help cut down on how serious any complications may be? If so, what medications might be prescribed?

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How will these medications be given?

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What are the most common side effects connected to these medications?

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Who should I contact if my child has serious side effects?

Department of Neurology, 300 Longwood Avenue,

Fegan, 11th Floor

Boston, Massachusetts 02115

Phone number: 617-355-6388

Could my child be helped by orthopedic surgery or neurosurgery? Why or why not?

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Would you recommend an experimental treatment for my child?

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How can I learn more about research on AP-4-HSP?

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I plan on having more children. Is there a risk that this could happen again?

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## Next appointment

Date: \_\_\_\_\_

This Family Education sheet was created using content from NORD: [National Organization for Rare Disorders](#), created by Dr. Darius Ebrahimi-Fakhari.









# *Family Education Guide*