



## Giant axonal neuropathy

Giant axonal neuropathy is an inherited condition characterized by abnormally large and dysfunctional axons called giant axons. Axons are specialized extensions of nerve cells (neurons) that transmit nerve impulses. Symptoms of the disorder first become apparent in the peripheral nervous system, in which long axons connect the brain and spinal cord (central nervous system) to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound. However, axons in the central nervous system are affected as well.

The signs and symptoms of giant axonal neuropathy generally begin in early childhood and get worse over time. Most affected individuals first have problems with walking. Later they may lose sensation, strength, and reflexes in their limbs; experience difficulty coordinating movements (ataxia); and require wheelchair assistance. Visual and hearing problems may also occur. Many individuals with this condition have extremely kinky hair as compared to others in their family.

Giant axonal neuropathy can also impact the autonomic nervous system, which controls involuntary body processes. Affected individuals may experience problems with the release of urine (neurogenic bladder), constipation, heat intolerance, and reduction in or loss of the ability to sweat.

As the disorder worsens, paralysis, seizures, and a gradual decline in mental function (dementia) can also occur. Most people with giant axonal neuropathy do not survive past their twenties.

### Frequency

Giant axonal neuropathy is a very rare disorder; only about 50 affected families have been described in the medical literature. The condition is thought to be under-diagnosed because its early symptoms resemble those of other, more common disorders affecting the peripheral nervous system, such as Charcot-Marie-Tooth disease.

### Genetic Changes

Giant axonal neuropathy is caused by mutations in the *GAN* gene, which provides instructions for making a protein called gigaxonin. Gigaxonin is part of the ubiquitin-proteasome system, which is a process that identifies and gets rid of excess or damaged proteins within cells. In particular, gigaxonin plays a role in the breakdown of neurofilaments, which comprise the structural framework that establishes the size and shape of axons.

The *GAN* gene mutations that have been identified in people with giant axonal neuropathy result in an unstable gigaxonin protein that breaks down more easily than normal, resulting in much less gigaxonin in cells. In neurons without enough functional gigaxonin, neurofilaments that would otherwise have been broken down by the ubiquitin-proteasome system accumulate. The neurofilaments become densely packed in the giant axons of people with giant axonal neuropathy. These giant axons do not transmit signals properly and eventually deteriorate, resulting in the death of neurons. The loss of nerve cells leads to problems with walking and sensation in people with giant axonal neuropathy.

### **Inheritance Pattern**

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

### **Other Names for This Condition**

- *GAN*
- giant axonal disease

### **Diagnosis & Management**

#### Genetic Testing

- Genetic Testing Registry: Giant axonal neuropathy  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1850386/>

#### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

## **Additional Information & Resources**

### MedlinePlus

- Health Topic: Peripheral Nerve Disorders  
<https://medlineplus.gov/peripheralnervedisorders.html>

### Genetic and Rare Diseases Information Center

- Giant axonal neuropathy  
<https://rarediseases.info.nih.gov/diseases/6500/giant-axonal-neuropathy>

### Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Hereditary Neuropathies Information Page  
<https://www.ninds.nih.gov/Disorders/All-Disorders/Hereditary-Neuropathies-Information-Page>

### Educational Resources

- Disease InfoSearch: Giant Axonal Neuropathy  
<http://www.diseaseinfosearch.org/Giant+Axonal+Neuropathy/3042>
- MalaCards: giant axonal neuropathy  
[http://www.malacards.org/card/giant\\_axonal\\_neuropathy](http://www.malacards.org/card/giant_axonal_neuropathy)
- Neuromuscular Disease Center, Washington University  
<http://neuromuscular.wustl.edu/time/child.html#gan>
- Orphanet: Giant axonal neuropathy  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=643](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=643)

### Patient Support and Advocacy Resources

- Child Neurology Foundation  
<http://www.childneurologyfoundation.org/>
- Hannah's Hope Fund  
<http://www.hannahshopefund.org/>
- National Organization for Rare Disorders (NORD)  
<https://rarediseases.org/rare-diseases/giant-axonal-neuropathy/>
- The Foundation for Peripheral Neuropathy  
<https://www.foundationforpn.org/>

### GeneReviews

- Giant Axonal Neuropathy  
<https://www.ncbi.nlm.nih.gov/books/NBK1136>

## ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22giant+axonal+neuropathy%22>

## Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28giant+axonal+neuropathy%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2520+days%22%5Bdp%5D>

## OMIM

- GIANT AXONAL NEUROPATHY 1, AUTOSOMAL RECESSIVE  
<http://omim.org/entry/256850>

## **Sources for This Summary**

- Boizot A, Talmat-Amar Y, Morrogh D, Kuntz NL, Halbert C, Chabrol B, Houlden H, Stojkovic T, Schulman BA, Rautenstrauss B, Bomont P. The instability of the BTB-KELCH protein Gigaxonin causes Giant Axonal Neuropathy and constitutes a new penetrant and specific diagnostic test. *Acta Neuropathol Commun.* 2014 Apr 24;2:47. doi: 10.1186/2051-5960-2-47.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/24758703>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234992/>
- Bomont P, Cavalier L, Blondeau F, Ben Hamida C, Belal S, Tazir M, Demir E, Topaloglu H, Korinthenberg R, Tüysüz B, Landrieu P, Hentati F, Koenig M. The gene encoding gigaxonin, a new member of the cytoskeletal BTB/kelch repeat family, is mutated in giant axonal neuropathy. *Nat Genet.* 2000 Nov;26(3):370-4.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/11062483>
- Hentati F, Hentati E, Amouri R. Giant axonal neuropathy. *Handb Clin Neurol.* 2013;115:933-8. doi: 10.1016/B978-0-444-52902-2.00052-7. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23931822>
- Incecik F, Herguner OM, Ceylaner S, Zorludemir S, Altunbasak S. Giant axonal disease: Report of eight cases. *Brain Dev.* 2015 Sep;37(8):803-7. doi: 10.1016/j.braindev.2014.12.002. Epub 2014 Dec 19.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25533284>
- Johnson-Kerner BL, Garcia Diaz A, Ekins S, Wichterle H. Kelch Domain of Gigaxonin Interacts with Intermediate Filament Proteins Affected in Giant Axonal Neuropathy. *PLoS One.* 2015 Oct 13; 10(10):e0140157. doi: 10.1371/journal.pone.0140157. eCollection 2015.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/26460568>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604155/>
- Johnson-Kerner BL, Roth L, Greene JP, Wichterle H, Sproule DM. Giant axonal neuropathy: An updated perspective on its pathology and pathogenesis. *Muscle Nerve.* 2014 Oct;50(4):467-76. doi: 10.1002/mus.24321. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/24947478>
- Kamate M, Ramakrishna S, Kambali S, Mahadevan A. Giant axonal neuropathy: a rare inherited neuropathy with simple clinical clues. *BMJ Case Rep.* 2014 Sep 12;2014. pii: bcr2014204481. doi: 10.1136/bcr-2014-204481.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25216920>

- Kuhlenbäumer G, Timmerman V, Bomont P. Giant Axonal Neuropathy. 2003 Jan 9 [updated 2014 Oct 9]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1136/>  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20301315>
- Mussche S, De Paepe B, Smet J, Devreese K, Lissens W, Rasic VM, Murnane M, Devreese B, Van Coster R. Proteomic analysis in giant axonal neuropathy: new insights into disease mechanisms. *Muscle Nerve*. 2012 Aug;46(2):246-56. doi: 10.1002/mus.23306.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22806374>
- Neuromuscular Disease Center, Washington University  
<http://neuromuscular.wustl.edu/time/child.html#gan>
- Vijaykumar K, Bindu PS, Taly AB, Mahadevan A, Bharath RD, Gayathri N, Nagappa M, Sinha S. Giant axonal neuropathy. *J Child Neurol*. 2015 Jun;30(7):912-5. doi: 10.1177/0883073814547721. Epub 2014 Sep 11.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25213662>
- Yiu EM, Ryan MM. Genetic axonal neuropathies and neuronopathies of pre-natal and infantile onset. *J Peripher Nerv Syst*. 2012 Sep;17(3):285-300. doi: 10.1111/j.1529-8027.2012.00412.x. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22971091>

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