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# Giant Axonal Neuropathy

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## Summary

**Disease characteristics.** Giant axonal neuropathy (GAN) is characterized by a severe early-onset peripheral motor and sensory neuropathy, central nervous system involvement (mental retardation, seizures, cerebellar signs, and pyramidal tract signs), and characteristic tightly curled hair. Most individuals become wheelchair dependent in the second decade of life and eventually bedridden with severe polyneuropathy, ataxia, and dementia. Death usually occurs in the third decade.

**Diagnosis/testing.** The diagnosis of GAN is established by clinical findings including nerve conduction velocity (NCV), brain MRI, and peripheral nerve biopsy. The pathologic hallmark is so-called giant axons caused by the accumulation of neurofilaments. GAN is caused by mutations in the gene *GAN*, encoding the protein gigaxonin. *GAN* is the only gene currently known to be associated with GAN; however, evidence exists for genetic heterogeneity. Molecular genetic testing of the *GAN* gene is available on a research basis only.

**Management.** *Treatment of manifestations:* A team including (pediatric) neurologists, orthopedic surgeons, physiotherapists, psychologists, and speech and occupational therapists is recommended; goals are to optimize intellectual and physical development through speech therapy to improve communication, occupational therapy to maximize independence in activities of daily living, physiotherapy to preserve mobility as long as possible, and early intervention and special education; orthopedic surgery as needed for foot deformities; ophthalmologic treatment as needed for diplopia. *Prevention of secondary complications:* for wheelchair-bound or bedridden individuals, prophylaxis and frequent examination for decubitus ulcers. *Surveillance:* at least yearly reassessment of intellectual abilities, peripheral neuropathy, ataxia, spasticity, and cranial nerve dysfunction.

**Genetic counseling.** GAN 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 an at-risk individual is known to be unaffected, the chance of his/her being a carrier is 2/3. Individuals with GAN usually do not reproduce. Prenatal testing may be available through laboratories offering custom prenatal testing if the disease-causing mutations in a family are known.

# Diagnosis

## Clinical Diagnosis

Giant axonal neuropathy (GAN) is characterized by the following:

- Severe early-onset peripheral motor and sensory neuropathy
- Tightly curled lackluster hair that differs markedly from that of the parents
- Central nervous system involvement including mental retardation, cerebellar signs (ataxia, nystagmus, dysarthria), and pyramidal tract signs

Nerve conduction studies often show normal to moderately reduced nerve conduction velocity (NCV) but severely reduced compound motor action potentials and absent sensory nerve action potentials.

Auditory brain stem evoked responses, visual evoked responses, and somatosensory evoked responses are often abnormal.

EEG often shows increased slow wave activity.

MRI of the brain often demonstrates white matter abnormalities in the form of high signals on T2 sequences in the anterior and posterior periventricular regions as well as the cerebellar white matter [Demir et al 2005].

MRI and magnetic resonance spectroscopy (MRS) in an 11-year-old revealed evidence for significant demyelination and glial proliferation in the white matter, but no neuroaxonal loss [Alkan et al 2003]. MRS of another individual revealed signs of damage or loss of axons accompanied by acute demyelination in the white matter, and generalized proliferation of glial cells in both gray and white matter [Brockmann et al 2003].

## Testing

Peripheral nerve biopsy demonstrates giant axons (distorted nerve fibers with large axonal swellings) caused by intermediate filament pathology and reduction of microtubules. These swellings start at the node of Ranvier and are caused by densely packed bundles of neurofilaments. The myelinated nerve fiber density is reduced, indicating progressive axonal loss. Segmental demyelination and remyelination and onion-bulb formation by multiple Schwann cell processes suggest Schwann cell dysfunction.

Giant axons are also observed in the cerebral cortex and other parts of the brain.

Microscopic examination of unstained hair shows abnormal variation in shaft diameter and twisting (pili torti) similar to the abnormality seen in Menkes disease (OMIM 309400) (see ATP7A-Related Copper Transport Disorders. The hair in GAN also shows longitudinal grooves on scanning electron microscopy.

Skin fibroblasts from persons with GAN may show accumulation of intermediate filaments forming whorls on electron microscopic examination, but it is not known whether all persons with GAN show this abnormality. Skin biopsy is not a well-established diagnostic test for GAN [Demir et al 2005].

### Molecular Genetic Testing

*GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the* GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

*any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

**Molecular Genetic Testing—Gene.** *GAN*, encoding the protein gaxonin, is the only gene known to be associated with giant axonal neuropathy.

**Other loci.** Genetic heterogeneity has been reported in one Algerian family; however, compared to giant axonal neuropathy caused by *GAN* mutations, the disease onset was, on average, somewhat later (age 4-10 years), the course milder, and the characteristic hair abnormalities absent [Tazir et al 2002].

**Research testing**

- **Sequence analysis.** Using sequence analysis, Bomont et al (2000) identified point mutations in 12 of 15 (80%) families analyzed. The three remaining families were homozygous for genetic markers in the *GAN* region, indicating that the failure to find a mutation most likely resulted from limitations of the testing methodology rather than genetic heterogeneity. Mutations in these families may be located in regions of the gene that were not sequenced (e.g., introns) or may be of a type not detectable by sequence analysis (e.g., larger deletions, duplications, splice site mutations).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Giant Axonal Neuropathy

| Test Method | Mutations Detected | Mutation Detection Frequency [1] | Test Availability |
|---|---|---|---|
| Sequence analysis | Exonic *GAN* point mutations | 70%-90% | Research only |
| Unknown | Other *GAN* mutations | 10%-30% | |

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

### Genetically Related (Allelic) Disorders

No other phenotypes are known to be caused by mutations in the *GAN* gene.

## Clinical Description

### Natural History

Giant axonal neuropathy (GAN) is a neurodegenerative disorder affecting both the peripheral and central nervous systems. GAN is classified within the hereditary motor and sensory neuropathies.

GAN typically presents in early childhood before age five years and progresses to death, usually by early adulthood. Individuals present with a motor and sensory peripheral neuropathy that may also involve the cranial nerves, resulting in facial weakness, optic atrophy, and ophthalmoplegia. Tendon reflexes are often absent; Babinski's sign may be present as a result of CNS involvement.

The majority of affected individuals show signs of CNS involvement including mental retardation, cerebellar signs (ataxia, nystagmus, dysarthria), epileptic seizures, and signs of pyramidal tract damage.

Most affected individuals have characteristic tightly curled lackluster hair, unlike that of their parents.

Most individuals become wheelchair dependent in the second decade of life and die in the third decade. They eventually become bedridden with severe polyneuropathy, ataxia, and dementia. Death results from secondary complications, such as pneumonia.

### Genotype-Phenotype Correlations

GAN-associated gigaxonin mutations are scattered over the whole gene, and clear correlations between specific mutations and particular phenotypic characteristics have not been reported.

### Prevalence

GAN is a very rare disorder; the true prevalence is not known.

## Differential Diagnosis

*For current information on availability of genetic testing for disorders included in this section, see* GeneTests Laboratory Directory. —ED.

Severe early-onset autosomal recessive **hereditary neuropathies** (i.e., those classified as Charcot-Marie-Tooth hereditary neuropathy type 4 [CMT4]) may be considered in the differential diagnosis of giant axonal neuropathy (GAN), especialy in the (rare) absence of both the characteristic hair abnormaliities and prominent CNS abnormalities. (In the past the term Dejerine-Sottas syndrome was used to designate severe childhood-onset genetic neuropathies of any inheritance; the term is no longer in general use [see CMT overview].)

CMT4 is a genetically heterogeneous disorder inherited in an autosomal recessive manner. Five types caused by mutations in six genes are recognized:

- **CMT4A** (OMIM 214400) comprises a peripheral neuropathy typically affecting the lower extremities earlier and more severely than the upper extremities. As the neuropathy progresses, the distal upper extremities also become severely affected. Even proximal muscles can become weak. The age at onset ranges from infancy to early childhood. In most cases the disease progression causes disabilities within the first or second decade of life. The neuropathy can be either of the demyelinating type with reduced NCVs or the axonal type with normal NCVs. Vocal cord paresis is common. The disease is caused by mutations in the ganglioside-induced differentiation-associated protein 1 gene *(GDAP1*).
- **CMT4B** (OMIM 601382, 604563), characterized by myelin outfoldings seen on nerve biopsy, is caused by mutations in either the myotubularin-related protein 2 gene *MTMR2* (CMT4B1) or the *MTMR13* gene (CMT4B2).
- **CMT4C** (OMIM 608206), a demyelinating neuropathy with onset in the first or second decade associated with scoliosis and respiratory compromise, is caused by mutations in the SH3 domain and tetratricopeptide repeats-containing protein 2 gene *(SH3TC2*).
- **CMT4E** (OMIM 605253) has been described in a few families with autosomal recessive severe congenital hypomyelinating neuropathy and is caused by mutations in the early growth response protein 2 gene *(EGR2*).
- **CMT4F** (OMIM 605725) is a severe demyelinating neuropathy caused by mutations in the periaxin gene *(PRX*).

Several **toxic substances** (e.g., n-hexane and acrylamide) cause a mixed axonal and demyelinating peripheral neuropathy with axonal swelling. Toxicity from n-hexane can result from occupational exposure or, rarely, from recreational gasoline vapor inhalation [Chang et

al 1998]. However, chronic exposure to these toxic substances is extremely unlikely in children around the age of onset of GAN.

**Menkes disease** (OMIM 309400) is a rare X-linked recessive disorder with prominent CNS involvement and hair changes resembling those of GAN. Menkes disease is a disorder of copper transport caused by mutations in the copper-transporting ATPase gene *(ATP7A*). Serum copper concentration and serum ceruloplasmin concentration are low. Infants with classic Menkes disease appear healthy until age two to three months, when loss of developmental milestones, hypotonia, seizures, and failure to thrive occur. The diagnosis is usually suspected when infants exhibit typical neurologic changes and concomitant characteristic changes of the hair (short, sparse, coarse, twisted, often lightly pigmented). Temperature instability and hypoglycemia may be present in the neonatal period. Death usually occurs by age three years.

**Infantile neuroaxonal dystrophy** (INAD, or Seitelberger disease) (OMIM 256600) is an infantile-onset disease of the CNS and peripheral nervous system with neurologic symptoms resembling GAN but without the characteristic hair changes of GAN. A characteristic pathologic feature is the presence of axonal spheroids made of vesiculotubular structures, tubular membranous material with clefts; these axonal spheroids are found in both the CNS and the peripheral nervous system, including the cutaneous or conjunctival nerve twigs. Recently mutations in a phospholipase A2 gene *(PLA2G6*) were demonstrated in persons with INAD [Morgan et al 2006]. The study, however, did not find mutations in *PLA2G6* in all affected individuals tested, suggesting either incomplete detection of mutations or genetic heterogeneity.

**Arylsulfatase A deficiency** (ARSA, or metachromatic leukodystrophy [MLD]) (OMIM 250100) is a disorder of impaired breakdown of sulfatides that occur throughout the body but are found in greatest abundance in nervous tissue, kidneys, and testes. Onset ranges from late infancy to adulthood.

- **Late-infantile MLD.** Onset is between ages one and two years. Typical presenting signs include clumsiness, frequent falls, toe walking, and slurred speech. Weakness and hypotonia are observed initially. Later signs include inability to stand, difficulty speaking, deterioration of mental function, increased muscle tone, pain in the arms and legs, generalized or partial seizures, compromised vision and hearing, and peripheral neuropathy. The final stages include tonic spasms, decerebrate posturing with rigidly extended extremities, feeding by gastrostomy tube, blindness, and general unawareness of surroundings. Expected life span is about 3.5 years after onset of symptoms but can be up to ten or more years with current treatment approaches.
- **Juvenile MLD.** Onset is between age four years and sexual maturity (age 12 to 14 years). Initial manifestations include decline in school performance and emergence of behavioral problems, followed by clumsiness, gait problems, slurred speech, incontinence, and bizarre behaviors. Seizures, more commonly partial seizures, may occur. Expected life span is ten to 20 or more years after diagnosis.
- **Adult MLD.** Onset occurs after sexual maturity; therefore, it would not be confused with GAN.

MLD is suspected in individuals with progressive neurologic dysfunction and MRI evidence of a leukodystrophy. *ARSA* is the only gene associated with the disorder. MLD is suggested by ARSA enzyme activity in leukocytes that is less than 10% of normal controls using the Baum-type assay. The diagnosis is confirmed by one or more of the following additional tests:

- Molecular genetic testing of the *ARSA* gene
- Urinary excretion of sulfatides

- Finding of metachromatic lipid deposits in nervous system tissue

MLD is inherited in an autosomal recessive manner.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with giant axonal neuropathy (GAN), the following evaluations are recommended:

- Assessment of development/cognitive abilities to establish the extent of disease and monitor progression or attempted intervention
- Clinical and electrophysiologic (sensory and motor NCVs, electromyography) examination of the peripheral motor and sensory nervous system (including assessment of the function of cranial nerves) to establish the diagnosis and monitor progression
- Neuroophthalmologic examination to look for nystagmus resulting from cerebellar dysfunction or strabismus caused by involvement of cranial nerves III, IV, or VI
- EEG, somatosensory and motor evoked potentials, and brain MRI to establish the diagnosis and determine the degree of CNS involvement

### Treatment of Manifestations

Treatment is symptomatic and often involves a team including (pediatric) neurologists, orthopedic surgeons, physiotherapists, psychologists, and speech and occupational therapists. Major goals are to optimize intellectual and physical development and, later in life, to slow the inevitable deterioration of these capacities.

Note: Early intellectual development is nearly normal in many children, enabling them to attend a normal school initially; however, significant intellectual impairment usually occurs before the second decade of life.

Treatment includes the following:

- Speech and occupational therapy to improve communication and activities of daily living
- Early intervention and special education directed to the individual's disability. Frequent reassessment is needed because of the progressive nature of the disorder. Special education often becomes necessary between ages five and 12 years.
- Physiotherapy (typically for distal weakness, ataxia, and spasticity) to preserve mobility as long as possible
- Orthopedic surgery as required for foot deformities (Note, however, that most affected individuals become wheelchair bound between ages ten and 20 years for other reasons.)
- Appropriate ophthalmologic treatment (e.g., surgery or glasses), especially if diplopia occurs

### Prevention of Secondary Complications

Wheelchair-bound or bedridden individuals require frequent examination for decubitus ulcers and appropriate prophylaxis.

### Surveillance

The following should be monitored in persons with GAN:

- Intellectual development/deterioration
- Progression of the peripheral neuropathy, ataxia, spasticity, and cranial nerve dysfunction

The frequency of the monitoring should depend on disease progression; at least yearly evaluation is recommended.

### Testing 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 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.

### Other

**Genetics clinics**, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

**Support groups** have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the* GeneTests Clinic Directory.

### Mode of Inheritance

Giant axonal neuropathy (GAN) is inherited in an autosomal recessive manner.

### Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes are asymptomatic.

**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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband.** No individuals with GAN are known to have reproduced.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier.

### Carrier Detection

Carrier testing is not clinically available.

### Related Genetic Counseling Issues

**Family planning.** The optimal time for determination of genetic risk is before pregnancy.

**DNA banking.** DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly important in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

### Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of GAN are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified. For laboratories offering custom prenatal testing, see Testing.

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

## Molecular Genetics

*Information in the Molecular Genetics tables is current as of initial posting or most recent update.* —ED.

Table A. Molecular Genetics of Giant Axonal Neuropathy

| Gene Symbol | Chromosomal Locus | Protein Name |
|---|---|---|
| *GAN* | 16q24.1 | Gigaxonin |

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Giant Axonal Neuropathy

| | |
|---|---|
| 256850 | GIANT AXONAL NEUROPATHY 1; GAN1 |
| 605379 | GAN GENE; GAN |

Table C. Genomic Databases for Giant Axonal Neuropathy

| Gene Symbol | Locus Specific | Entrez Gene | HGMD |
|---|---|---|---|
| *GAN* | GAN | 8139 (MIM No. 605379) | GAN |

For a description of the genomic databases listed, click here.

## Molecular Genetic Pathogenesis

Axonal loss, reduced numbers of microtubules, and disorganized neurofilaments are three major pathologic findings that must be explained by models of the molecular genetic pathogenesis of giant axonal neuropathy (GAN). Gigaxonin binds to microtubule-associated protein 1B light chain (MAP1B-LC), microtubule-associated protein 8 (MAP8), and tubulin-binding cofactor B (TBCB) and controls their ubiquitin-mediated degradation [Allen et al 2005, Ding et al 2006]. This degradation is inhibited in gigaxonin-deficient mice, leading to accumulation of MAP1B, MAP8, TBCB, and most likely other as-yet-unidentified proteins. MAP1B-LC and MAP accumulation is toxic to neurons, leading to neuronal death. Overexpression of TBCB destabilizes microtubules, possibly accounting for the reduced number of microtubules found in affected individuals and gigaxonin-deficient mice. The pathomechanism causing the disorganized neurofilament network remains to be elucidated.

**Normal allelic variants:** The *GAN* cDNA is 4677 nt long with an open reading frame of 1791 nt encoding a protein of 597 amino acids [Bomont et al 2000]. *GAN* is organized in 11 exons. Bomont et al (2000) described two polymorphisms within the coding sequence (see Table 2).

Table 2. Polymorphisms in the *GAN* Coding Sequence

| Exon | Nucleotide Change [1] | Amino Acid Change | Approximate Frequency |
|---|---|---|---|
| 4 | 806G>A | p.Arg269Glu | 30% |
| 8 | 1293C>T | p.Tyr431Tyr (none) | 35% |

1. With reference to the cDNA sequence GenBank Accession number: AF291673

**Pathologic allelic variants:** Putative causative mutations in the *GAN* gene (Table 3) were first reported by Bomont et al (2000) and later by Kuhlenbäumer et al (2002),Bomont et al (2003),Bruno et al (2004),Demir et al (2005), and others.

All currently known *GAN* mutations are listed in the Mutation Database of Inherited Peripheral Neuropathies [Nelis et al 1999]. (See Genomic Databases table above.)

**Normal gene product:** *GAN* encodes the ubiquitously expressed protein gigaxonin. Gene and protein sequence analysis indicates that gigaxonin is a novel and distinct member of the BTB/kelch superfamily [Timmerman et al 2000]. The kelch domain or repeat found in gigaxonin predicts a conserved tertiary structure called a beta-propeller that is important for protein-protein interaction. BTB (**b**road-complex, **t**ramtrack and **b**ric a brac domain) mediates in the dimerization of the kelch domains [Bomont et al 2000]. The kelch-repeat superfamily contains mainly intracellular proteins that are involved in many aspects of the cell function, including association with the actin cytoskeleton, coordination of cell morphology and growth, cytoplasmic sequestration of transcription factors, and contribution to viral pathogenesis [Adams et al 2000].

Gigaxonin is expressed in a wide variety of neuronal cell types; confocal microscopy studies revealed that a proportion of the protein localizes to the Golgi and endoplasmic reticulum [Cullen et al 2004]. Gigaxonin interacts via its C-terminal kelch domains with microtubule-associated protein 1B (MAP1B-LC), microtubule-associated protein 8 (MAP8), and tubulin-folding cofactor B (TBCB), and via its N-terminal BTB domain with ubiquitin-activating enzyme E1 (UBE1). In the presence of gigaxonin, the C-terminally bound proteins are directed toward ubiquitin-mediated degradation [Allen et al 2005, Ding et al 2006].

**Abnormal gene product:** *GAN* disease-causing mutations (resulting in gigaxonin deficiency) are distributed over the entire gene. Gigaxonin deficiency impedes ubiquitin-mediated protein degradation of MAP1B-LC, MAP8, TBCB, and possibly of other unidentified proteins.

## Resources

*GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search* GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

**Muscular Dystrophy Association-Canada**
2345 Yonge St Suite 900
Toronto M4P 2E5
Canada
**Phone:** 1-800-MUSCLE-8 (1-800-687-2538)
**Fax:** 416-488-7523
**Email:** info@muscle.ca
Giant Axonal Neuropathy

**National Library of Medicine Genetics Home Reference**
Giant Axonal Neuropathy

**Child Neurology Foundation**
1821 University Avenue West Suite N-169
St. Paul Minnesota 55104
**Phone:** 651-645-4244
**Fax:** 651-645-4349
**Email:** cnf@childneurologyfoundation.org
www.childneurologyfoundation.org

## References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

### Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

### Literature Cited

Adams J, Kelso R, Cooley L. The kelch repeat superfamily of proteins: propellers of cell function. Trends Cell Biol. 2000;10:17–24. [PubMed: 10603472]

Alkan A, Kutlu R, Sigirci A, Baysal T, Altinok T, Yakinci C. Giant axonal neuropathy: MRS findings. J Neuroimaging. 2003;13:371–5. [PubMed: 14569833]

Allen E, Ding J, Wang W, Pramanik S, Chou J, Yau V, Yang Y. Gigaxonin-controlled degradation of MAP1B light chain is critical to neuronal survival. Nature. 2005;438:224–8. [PubMed: 16227972]

Bomont P, Ioos C, Yalcinkaya C, Korinthenberg R, Vallat JM, Assami S, Munnich A, Chabrol B, Kurlemann G, Tazir M, Koenig M. Identification of seven novel mutations in the GAN gene. Hum Mutat. 2003;21:446. [PubMed: 12655563]

Bomont P, Cavalier L, Blondeau F, Ben Hamida C, Belal S, Tazir M, Demir E, Topaloglu H, Korinthenberg R, Tuysuz 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;26:370–4. [PubMed: 11062483]

Brockmann K, Pouwels PJ, Dechent P, Flanigan KM, Frahm J, Hanefeld F. Cerebral proton magnetic resonance spectroscopy of a patient with giant axonal neuropathy. Brain Dev. 2003;25:45–50. [PubMed: 12536033]

Bruno C, Bertini E, Federico A, Tonoli E, Lispi ML, Cassandrini D, Pedemonte M, Santorelli FM, Filocamo M, Dotti MT, Schenone A, Malandrini A, Minetti C. Clinical and molecular findings in patients with giant axonal neuropathy (GAN). Neurology. 2004;62:13–6. [PubMed: 14718689]

Chang AP, England JD, Garcia CA, Sumner AJ. Focal conduction block in n-hexane polyneuropathy. Muscle Nerve. 1998;21:964–9. [PubMed: 9626263]

Cullen VC, Brownlees J, Banner S, Anderton BH, Leigh PN, Shaw CE, Miller CC. Gigaxonin is associated with the Golgi and dimerises via its BTB domain. Neuroreport. 2004;15:873–6. [PubMed: 15073534]

Demir E, Bomont P, Erdem S, Cavalier L, Demirci M, Kose G, Muftuoglu S, Cakar AN, Tan E, Aysun S, Topcu M, Guicheney P, Koenig M, Topaloglu H. Giant axonal neuropathy: clinical and genetic study in six cases. J Neurol Neurosurg Psychiatry. 2005;76:825–32. [PubMed: 15897506]

Ding J, Allen E, Wang W, Valle A, Wu C, Nardine T, Cui B, Yi J, Taylor A, Jeon NL, Chu S, So Y, Vogel H, Tolwani R, Mobley W, Yang Y. Gene targeting of GAN in mouse causes a toxic accumulation of microtubule-associated protein 8 and impaired retrograde axonal transport. Hum Mol Genet. 2006;15:1451–63. [PubMed: 16565160]

Kuhlenbaumer G, Young P, Oberwittler C, Hunermund G, Schirmacher A, Domschke K, Ringelstein B, Stogbauer F. Giant axonal neuropathy (GAN): case report and two novel mutations in the gigaxonin gene. Neurology. 2002;58:1273–6. [PubMed: 11971098]

Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, Cangul H, Coryell J, Canham N, Nardocci N, Zorzi G, Pasha S, Rodriguez D, Desguerre I, Mubaidin A, Bertini E, Trembath RC, Simonati A, Schanen C, Johnson CA, Levinson B, Woods CG, Wilmot B, Kramer P, Gitschier J, Maher ER, Hayflick SJ. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet. 2006;38:752–4. [PubMed: 16783378]

Nelis E, Haites N, Van Broeckhoven C. Mutations in the peripheral myelin genes and associated genes in inherited peripheral neuropathies. Hum Mutat. 1999;13:11–28. [PubMed: 9888385]

Tazir M, Vallat JM, Bomont P, Zemmouri R, Sindou P, Assami S, Nouioua S, Hammadouche T, Grid D, Koenig M. Genetic heterogeneity in giant axonal neuropathy: an Algerian family not linked to chromosome 16q24.1. Neuromuscul Disord. 2002;12:849–52. [PubMed: 12398836]

Timmerman V, De Jonghe P, Van Broeckhoven C. Of giant axons and curly hair. Nat Genet. 2000;26:254–5. [PubMed: 11062452]

## Suggested Readings

Bomont P, Cavalier L, Blondeau F, Ben Hamida C, Belal S, Tazir M, Demir E, Topaloglu H, Korinthenberg R, Tuysuz 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;26:370–4. [PubMed: 11062483]

Timmerman V, De Jonghe P, Van Broeckhoven C. Of giant axons and curly hair. Nat Genet. 2000;26:254–5. [PubMed: 11062452]

Yang Y, Allen E, Ding J, Wang W. Giant axonal neuropathy. Cell Mol Life Sci. 2007;64:601–9. [PubMed: 17256086]

## Chapter Notes

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