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GAN-Related Neurodegeneration

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Summary

Clinical characteristics

GAN-related neurodegeneration comprises a phenotypic continuum ranging from severe (sometimes called classic giant axonal neuropathy) to milder pure early-onset peripheral motor and sensory neuropathies. The classic giant axonal neuropathy phenotype typically manifests as an infantile-onset neurodegenerative disorder, starting as a severe peripheral motor and sensory neuropathy and evolving into central nervous system impairment (intellectual disability, seizures, cerebellar signs, and pyramidal tract signs). Most affected 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. At the milder end of the spectrum are predominantly motor and sensory neuropathies (with little to no CNS involvement) that overlap with the axonal form of Charcot-Marie-Tooth neuropathies.

Diagnosis/testing

The diagnosis of *GAN*-related neuropathy is established in a proband with suggestive findings and biallelic *GAN* pathogenic variants identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive care is focused on managing the clinical findings of the individual, and often involves a team including neurologists, orthopedic surgeons, physiotherapists, occupational and physical therapists, psychologists, and speech-language pathologists. Major goals are to optimize intellectual and physical development.

Surveillance: Surveillance is individualized to monitor response to ongoing interventions and identify new manifestations.

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Genetic counseling

GAN-related neuropathy is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GAN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *GAN* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *GAN*-related neurodegeneration have been published.

Suggestive Findings

***GAN*-related neurodegeneration should be suspected** in individuals with the following clinical, electrophysiologic, and brain imaging findings, and family history.

Clinical findings

- Early-onset peripheral motor and sensory neuropathy (in all individuals)
- Variable findings typically observed in classic giant axonal neuropathy:
  - Infantile- to early childhood-onset CNS involvement that may include developmental delay / intellectual disability, cerebellar signs (ataxia, oculomotor involvement, nystagmus, dysarthria), and/or pyramidal tract signs (i.e., spasticity)
  - Kinky hair. Tightly curled lackluster hair that differs markedly from that of the parents. In individuals with milder phenotypes the hair tends to be mildly curly rather than frizzled or kinky [Bharucha-Goebel et al 2021].

Electrophysiologic findings

- Nerve conduction studies often show normal to moderately reduced nerve conduction velocity 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

Brain imaging

- **Classic giant axonal neuropathy.** In early stages of classic GAN, brain MRI shows hyperintense signal in the cerebellar white matter surrounding the dentate nucleus [Bharucha-Goebel et al 2021]. As the condition advances, high signals on T_2- weighted sequences in the anterior and posterior periventricular regions as well as in the cerebellar white matter are often seen [Demir et al 2005, Echaniz-Laguna et al 2020, Bharucha-Goebel et al 2021].

  Brain MRI and magnetic resonance spectroscopy (MRS) reveal evidence of significant demyelination and glial proliferation in the white matter, but no neuroaxonal loss [Brenner et al 2008, Ravishankar et al 2009].

- **Intermediate phenotype.** MRI shows mild and diffuse T_2-weighted signal abnormalities in the posterior limb of the internal capsule and periventricular white matter. Infratentorial signal abnormalities are observed in the dentate nucleus and middle cerebellar peduncle [Abu-Rashid et al 2013].

- **Milder phenotypes.** Brain MRI findings vary from normal in most individuals to signs of mild cerebral and cerebellar atrophy [Zemmouri et al 2000, Aharoni et al 2016, Koichihara et al 2016, Bharucha-Goebel et al 2021].

Milder phenotypes of *GAN*-related neurodegeneration could be considered in individuals with early-onset peripheral motor and sensory neuropathy where work up for Charcot-Marie-Tooth disorders has proved inconclusive.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *GAN*-related neurodegeneration **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *GAN* identified by molecular genetic testing (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 *GAN* variants of uncertain significance (or identification of one known *GAN* pathogenic variant and one *GAN* variant of uncertain significance) does not establish or rule out a diagnosis of *GAN*-related neuropathy.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (Option 1), whereas genomic testing does not (Option 2).

Option 1

Single-gene testing. In individuals with suggestive findings of *GAN*-related neurodegeneration, sequence analysis of *GAN* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A neuropathy multigene panel that includes *GAN* and other genes of interest (see Differential Diagnosis) is 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 *GAN*-Related Neurodegeneration

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GAN	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	~10% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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

GAN-related neurodegeneration, caused by biallelic *GAN* pathogenic variants, encompasses a phenotypic continuum ranging from classic giant axonal neuropathy (GAN) – a neurodegenerative disorder affecting both the peripheral and central nervous systems at the severe end – to milder phenotypes with early-onset peripheral motor and sensory neuropathy with or without other findings. These phenotypes do not necessarily run true in families; in one family, phenotypes in family members with the same biallelic *GAN* pathogenic variants ranged from classic giant axonal neuropathy to milder peripheral neuropathy presentations [Tazir et al 2009].

To date, approximately 50 families have been identified with biallelic *GAN* pathogenic variants [Ben Hamida et al 1990, Zemmouri et al 2000, Kuhlenbäumer et al 2002, Abu-Rashid et al 2013, Koichihara et al 2016, Aharoni et al 2016, Hoebeke et al 2018, Didonna & Opal 2019, Echaniz-Laguna et al 2020, Bharucha-Goebel et al 2021].

Table 2 outlines the findings of classic giant axonal neuropathy, the first described phenotype, which is now known to be at the severe end of the *GAN*-related neurodegeneration phenotypic continuum.

Table 2. Select Features of Severe *GAN*-Related Neurodegeneration

Feature		Severe *GAN*-Related Neurodegeneration (Classic Giant Axonal Neuropathy)
Motor neuropathy		+++
Sensory neuropathy		+++
Cranial nerve involvement	**Optic nerve**	+
	Facial nerve	+
	Extraocular muscles	+
Hearing loss		+
Pyramidal tract involvement		Masked by neuropathy
Cerebellar involvement		++
Dysarthria		++
Dysphagia		++

Table 2. continued from previous page.

Feature	Severe *GAN*-Related Neurodegeneration (Classic Giant Axonal Neuropathy)
Seizures	+
Intellectual disability	+
Cognitive decline	++
Kinky hair	++
Scoliosis	+

+++ = always present; ++ = often present; + = rare

Classic Giant Axonal Neuropathy

Neurologic findings. Classic giant axonal neuropathy, the phenotype first recognized in the *GAN*-related neurodegeneration spectrum, starts as severe peripheral motor and sensory neuropathy before age five years and evolves into central nervous system (CNS) impairment (intellectual disability, seizures, cerebellar signs, and pyramidal tract signs).

The motor and sensory peripheral neuropathy may also involve the cranial nerves, resulting in facial weakness, optic atrophy, and ophthalmoplegia. Tendon reflexes are often absent; Babinski sign may be present as a result of CNS involvement.

The majority of affected individuals show signs of CNS involvement including intellectual disability, cerebellar signs (ataxia, nystagmus, and dysarthria), epileptic seizures, and pyramidal tract signs (i.e., spasticity). Early intellectual development is nearly normal in many affected children, enabling them to attend a normal school initially; however, significant intellectual impairment usually occurs before the second decade of life.

Most affected individuals become wheelchair dependent in the second decade of life and eventually bedridden with severe polyneuropathy, ataxia, and dementia. In those with the most severe manifestations, death usually occurs in the third decade, typically the result of secondary complications such as respiratory failure.

Hair. Most individuals with classic giant axonal neuropathy have characteristic tightly curled lackluster hair that differs markedly from that of their parents. Microscopic examination of unstained hair shows abnormal variation in shaft diameter and twisting (*pili torti*) similar to the abnormality seen in Menkes disease; it can also show longitudinal grooves on scanning electron microscopy [Kennerson et al 2010, Kaler 2011, Yi et al 2012].

Milder *GAN*-Related Neurodegeneration Phenotypes

Milder phenotypes have been reported with later age of onset, extended survival, or modest CNS deterioration with pathology reminiscent of Charcot-Marie-Tooth axonal disorders, sometimes referred to as axonal CMT (plus) syndrome [Ben Hamida et al 1990, Zemmouri et al 2000, Aharoni et al 2016, Hoebeke et al 2018, Bharucha-Goebel et al 2021].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported for *GAN*-related neurodegeneration. Famiy members with the same pathogenic variant who had different clinical phenotypes have been reported [Tazir et al 2009].

Nomenclature

The term "axonal CMT (plus) syndrome" may be used to refer to predominantly motor and sensory neuropathy phenotypes (with little to no CNS involvement) that overlap with axonal forms of Charcot-Marie-Tooth neuropathy [Bharucha-Goebel et al 2021].

Prevalence

To date, about 50 families with *GAN*-related neurodegeneration have been reported worldwide. The actual prevalence is not known.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GAN*.

Differential Diagnosis

Hereditary Disorders in the Differential Diagnosis of Classic Giant Axonal Neuropathy

At onset, classic giant axonal neuropathy (GAN) presents with features (e.g., neuropathic deficits, giant axons, and neurofilament aggregation) similar to those associated with several severe, early-onset hereditary motor and sensory neuropathies [Lescouzères & Bomont 2020]. These neuropathies and other disorders of interest in the differential diagnosis of classic GAN are summarized in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Classic Giant Axonal Neuropathy

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/classic GAN	Distinguishing from classic GAN
ARSA	Late-infantile metachromatic leukodystrophy (MLD) (See Arylsulfatase A Deficiency.) [1]	AR	Age at onset: <30 mos; typically presents w/ weakness, hypotonia, clumsiness, frequent falls, toe walking, & dysarthria; later signs incl spasticity, pain, seizures, & compromised vision & hearing. Final stage is assoc w/tonic spasms, decerebrate posturing, & general unawareness of surroundings.	Progressive CNS demyelination; no hair abnormalities
ATP7A	Classic Menkes disease (See *ATP7A* Copper Transport Disorders.)	XL	Prominent CNS involvement & hair changes similar to GAN. Infants appear healthy until age 2-3 mos, when loss of developmental milestones, hypotonia, seizures, failure to thrive, & concomitant characteristic hair changes (short, sparse, coarse, twisted, often lightly pigmented) occur. Death usually by age 3 yrs.	Hypopigmentation of the hair; wormian bones, metaphyseal spurring of long bones, & rib fractures

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/classic GAN	Distinguishing from classic GAN
DCAF8	Severe early-onset HMSN [2, 3, 4]	AD	Cardiomyopathy	No hair abnormalities; no prominent CNS involvement
EGR2	Severe early-onset HMSN (See CMT Overview.)	AR	Severe congenital hypomyelinating neuropathy	
GDAP1	Severe early-onset HMSN (See *GDAP1*-HMSN.)	AR	Peripheral neuropathy typically affecting lower extremities earlier & more severely than upper extremities; onset from infancy to early childhood. Neuropathy is demyelinating or axonal; vocal cord paresis is common.	
NEFL	Severe early-onset HMSN [4] (See CMT Overview.)	AD AR		
PLA2G6	Classic infantile neuroaxonal dystrophy (INAD)	AR	Infantile-onset disease of CNS & PNS w/ neurologic symptoms resembling GAN. Characteristic pathologic feature: axonal spheroids made of vesiculotubular structures (tubular membranous material w/clefts) in both CNS & PNS (incl the cutaneous or conjunctival nerve twigs)	No hair abnormalities
SBF2	Severe early-onset HMSN (See CMT Overview.)	AR	Myelin outfoldings seen on nerve biopsy	No hair abnormalities; no prominent CNS involvement
SH3TC2	Severe early-onset HMSN [2, 4] (See *SH3TC2*-HMSN.)	AR	Demyelinating neuropathy; early-onset severe spine deformities. Typically presents w/scoliosis or kyphoscoliosis at age 2-10 yrs.	
TRIM2	Severe early-onset HMSN [4] (OMIM 615490)	AR	Vocal cord paresis & respiratory insufficiency	

AD = autosomal dominant; AR = autosomal recessive; CMT = Charcot-Marie-Tooth (neuropathy); CNS = central nervous system; DiffDx = differential diagnosis; GAN = giant axonal neuropathy; HMSN = hereditary motor and sensory neuropathy; MOI = mode of inheritance; PNS = peripheral nervous system; XL = X-linked

1. Arylsulfatase A deficiency 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.

2. 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.

3. Klein et al [2014]

4. Lescouzères & Bomont [2020]

Differential Diagnosis of Milder *GAN*-Related Neurodegeneration Phenotypes

Milder *GAN*-related neurodegeneration phenotypes overlap with Charcot-Marie-Tooth (CMT) hereditary neuropathy and should be considered in the broader differential diagnosis of CMT. More than 80 different genes are associated with CMT (see Causes of Charcot-Marie-Tooth Hereditary Neuropathy) with a subset of these associated with giant axons, even more closely mimicking *GAN*-related neurodegeneration [Fabrizi et al 2004, Azzedine et al 2006, Ylikallio et al 2013, Klein et al 2014].

Management

No clinical practice guidelines for *GAN*-related neurodegeneration have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GAN*-related neurodegeneration, 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 *GAN*-Related Neurodegeneration

System/Concern	Evaluation	Comment
Extent of neurologic involvement	Complete neurologic exam	
	Assess LMN dysfunction: weakness, amyotrophy, sensory loss.	• Assessment to incl cranial nerve dysfunction (See **Ophthalmologic involvement** in this table.) • Consider motor & sensory NCV to document a sensorimotor axonal pattern of neuropathy.
	Assess UMN dysfunction: spasticity, Babinski signs, hyperreflexia.	
	Assess cerebellar motor dysfunction: gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit.	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1, 2]
	EEG & brain MRI (if not previously performed) if seizures are a concern	
Motor disability & ADL	Orthopedics / physical medicine & rehab / PT / OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
ID / Cognitive decline	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Dysarthria	Assessment by speech-language pathologist	
Feeding difficulty	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in patients w/dysphagia &/or aspiration risk.
Ophthalmologic involvement	Complete eye exam	To assess: • Extraocular movement (re cranial nerve involvement & strabismus) • For evidence of optic atrophy: best corrected visual acuity, color vision, visual fields, visual evoked potentials, OCT, fundus exam • Need for visual aids
	Neuroophthalmologic exam (if not performed as part of eye exam above)	• Nystagmus (caused by cerebellar dysfunction) • Strabismus (caused by involvement of cranial nerves III, IV &/or VI)

Table 4. continued from previous page.

Auditory nerve involvement	Exam by audiologist	
Genetic counseling	By genetics professionals [3]	To inform patients & their families re nature, MOI, & implications of *GAN*-related neuropathy in order to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADL = activities of daily living; ID = intellectual disability; LMN = lower motor neuron; MOI = mode of inheritance; OCT = optical coherence tomography; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron
1. SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Co-operative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale
2. Bürk & Sival [2018]
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care is focused on managing the clinical findings of the individual, and often involves a team including (pediatric) neurologists, orthopedic surgeons, physiotherapists, occupational and physical therapists, psychologists, and speech-language pathologists. Major goals are to optimize intellectual and physical development.

Table 5. Treatment of Manifestations in Individuals with *GAN*-Related Neurodegeneration

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Cognitive decline	See Developmental Delay / Intellectual Disability Management Issues.	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Motor disability & ADL	Physical medicine & rehab / PT / OT eval	• Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), dressing (e.g., dressing hooks). • PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function • OT to optimize ADL • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) See also CMT Hereditary Neuropathy Overview.
	Orthopedics	Surgery as required for foot deformities in those who are ambulatory
Poor weight gain / FTT	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Dysarthria / Language delay		By speech-language pathologist	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Eye involvement	**Optic atrophy**	Correction of refractive errors	• Evaluate for visual aids. • Community vision services through Early Intervention or School District
	Diplopia	Surgery	

ADL = activities of daily living; ASM = anti-seizure medication; FTT = failure to thrive; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for 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 that 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, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - When relevant, vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - 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. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating,

assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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.

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 the 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

Surveillance is individualized and involves monitoring response to ongoing interventions and identifying new manifestations. Surveillance may involve some or all of the recommendations in Table 6.

Table 6. Recommended Surveillance at Each Visit for Individuals with *GAN*-Related Neurodegeneration

System/Concern	Evaluation
Development / Cognitive decline	Monitor developmental progress & educational needs. [1]
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess progression of peripheral neuropathy, ataxia, spasticity, & cranial nerve dysfunction.
Motor disability & ADL	Physical medicine, OT/PT assessment of mobility, self-help skills
Wheelchair-bound or bedridden persons	Examine for bedsores & decubitus ulcers.
Dysarthria / Language delay	Speech-language pathology assessment
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake
Optic atrophy	• Eye exam (visual acuity, color vision testing, slit lamp exam for cataracts, fundoscopy, visual fields) • Evaluate effectiveness of low-vision aids.

OT = occupational therapist; PT = physical therapist
1. Frequent reassessment is needed because of the progressive nature of the disorder. Special education often becomes necessary between ages five and 12 years.

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

GAN-related neurodegeneration is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are typically heterozygotes (i.e., carriers of one *GAN* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GAN* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent:
  - And the child has compound heterozygous *GAN* pathogenic variants, the child may have one inherited variant and one *de novo* pathogenic variant [Shi et al 2020].
  - And the child appears to have homozygous *GAN* pathogenic variants, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy for chromosome 16 [Miyatake et al 2015].
- Heterozygotes are clinically asymptomatic but can display mild axonal neuropathy, as revealed by moderate reduction of nerve action potential amplitudes [Demir et al 2005].

Sibs of a proband

- If both parents are known to be heterozygous for a *GAN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Significant intrafamilial clinical variability has been reported in *GAN*-related neurodegeneration. In one family, phenotypes in family members with the same biallelic *GAN* pathogenic variants ranged from classic giant axonal neuropathy to milder peripheral neuropathy presentations [Tazir et al 2009].
- If the proband has *GAN*-related neurodegeneration as the result of uniparental isodisomy, only one parent is heterozygous for a *GAN* pathogenic variant, and neither parent has a chromosome rearrangement, each sib of an affected individual has at conception a 50% chance of being a clinically asymptomatic carrier and an approximately 50% chance of being unaffected and not a carrier; the risk to sibs of a proband of being affected is unknown but is presumed to be less than 1%.

Offspring of a proband

- Individuals with classic giant axonal neuropathy are not known to reproduce.
- The offspring of an individual with a milder *GAN*-related neurodegeneration phenotype are obligate heterozygotes (carriers) for a pathogenic variant in *GAN*.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for a *GAN* pathogenic variant, the parent's family members are at risk of being carriers.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GAN* pathogenic variants in the family.

Note: Some clinically asymptomatic heterozygotes can show mild axonal neuropathy, as revealed by moderate reduction of nerve action potential amplitudes [Demir et al 2005].

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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 *GAN* 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.

- **Hannah's Hope Fund for Giant Axonal Neuropathy**
  19 Blue Jay Way
  Rexford NY 12148
  Phone: 518-383-9053
  Email: lorisames@yahoo.com
  www.hannahshopefund.org

- **MedlinePlus**
  Giant Axonal Neuropathy

- **Association CMT France**
  France
  Phone: 820 077 540; 2 47 27 96 41
  www.cmt-france.org

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682
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- **Child Neurology Foundation**
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- **Hereditary Neuropathy Foundation**
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  www.hnf-cure.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. GAN-Related Neurodegeneration: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GAN	16q23.2	Gigaxonin	GAN homepage - Leiden Muscular Dystrophy pages	GAN	GAN

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 GAN-Related Neurodegeneration (View All in OMIM)

256850	GIANT AXONAL NEUROPATHY 1, AUTOSOMAL RECESSIVE; GAN1
605379	GIGAXONIN; GAN

Molecular Pathogenesis

GAN encodes gigaxonin, a BTB-Kelch protein [Adams et al 2000]. Gigaxonin controls the turnover of specific proteins by targeting them to the proteasome for degradation. While all the substrates have yet to be identified, a key substrate, cytoskeletal intermediate filaments, which include neurofilaments (NFs), have been found to accumulate in neurons and glial fibrillary acidic protein (GFAP) in glial cells [Opal & Goldman 2013, Israeli et al 2016, Didonna & Opal 2019]. Accumulation of these proteins impairs mitochondrial bioenergetics, organelle motility, and cell survival [Israeli et al 2016]. Although gigaxonin also interacts with three proteins involved in microtubule (MT) homeostasis and dynamics (the MT-associated proteins MAP1B and MAP1S, and the tubulin chaperone TBCB) [Ding et al 2002, Allen et al 2005, Wang et al 2005, Ding et al 2006, Cleveland et al 2009], studies suggest that they do not play an important role in *GAN*-related neurodegeneration. More recent evidence suggests that GAN controls the levels of Atg16L involved in autophagy [Scrivo et al 2019].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

An overview of current work in the lab and contact information can be found on our website.

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Revision History

- 14 October 2021 (bp) Comprehensive update posted live
- 9 October 2014 (me) Comprehensive update posted live
- 21 June 2012 (me) Comprehensive update posted live
- 11 August 2009 (cd) Revision: sequence analysis available clinically
- 2 July 2007 (me) Comprehensive update posted live
- 28 February 2005 (me) Comprehensive update posted live
- 9 January 2003 (me) Review posted live
- 5 August 2002 (vt) Original submission

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