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NKX6-2-Related Disorder

Synonyms: *NKX6-2*-Related Spastic Ataxia with Hypomyelination, SPAX8

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Summary

Clinical characteristics

NKX6-2-related disorder is characterized by a spectrum of progressive neurologic manifestations resulting from diffuse central nervous system hypomyelination. At the severe end of the spectrum is neonatal-onset nystagmus, severe spastic tetraplegia with joint contractures and scoliosis, and visual and hearing impairment, all of which rapidly progress resulting in death in early childhood. At the milder end of the spectrum is normal achievement of early motor milestones in the first year of life followed by slowly progressive complex spastic ataxia with pyramidal findings (spasticity with increased muscle tone and difficulty with gait and fine motor coordination) and cerebellar findings (nystagmus, extraocular movement disorder, dysarthria, titubation, and ataxia) with loss of developmental milestones. To date *NKX6-2*-related disorder has been reported in 25 individuals from 13 families.

Diagnosis/testing

The diagnosis of *NKX6-2*-related disorder is established in a proband with typical clinical and neuroimaging findings and biallelic pathogenic variants in *NKX6*-2 identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and typically involves a multidisciplinary team of specialists in the areas of developmental pediatrics, neurology, pediatric rehabilitation, orthopedics, PT/OT, social work, nutrition, pulmonary/sleep medicine, ophthalmology, audiology, and palliative care.

Surveillance: Sleep studies for evidence of apnea. Routine assessment of: nutritional status and safety of oral intake; development; progression of spasticity and contractures.

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Genetic counseling

NKX6-2-related disorder is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *NKX6-2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

NKX6-2-related disorder **should be suspected** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Onset between birth and age five years of either spasticity or hypotonia with rapid progression to spasticity (typically manifesting as spastic quadriplegia in those with early onset)
- Motor delay or developmental delay in those with a more severe phenotype
- Nystagmus
- Visual impairment manifest in severely affected children as loss of visual fixation and ocular pursuit and in older individuals as severe limitation of eye movements
- Hearing impairment
- Ataxia
- Dystonia particularly involving the upper limbs

Brain MRI findings

- **Neonatal/childhood-onset disease.** Diffuse and severe hypomyelination of subcortical and deep white matter including the external capsules; globi pallidi; thalami; and peridentate, mesencephalon, pons, and cerebellum as early as age nine months. T_2-weighted and FLAIR signal are diffusely increased in the white matter with corresponding iso- to hyperintense signal on T_1-weighted images (see Figure 1).
- **Later-onset disease.** The same findings as in neonatal/childhood-onset disease plus cerebellar atrophy and diffuse spinal cord volume loss with abnormal T_2-weighted hyperintensity of the ventral and dorsal horn cells

Establishing the Diagnosis

The diagnosis of *NKX6-2*-related disorder **is established** in a proband with typical clinical and neuroimaging findings and biallelic pathogenic (or likely pathogenic) variants in *NKX6-2* 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 *NKX6-2* variants of uncertain significance (or of one known *NKX6-2* pathogenic variant and one *NKX6-2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted testing** (multigene panel) or **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

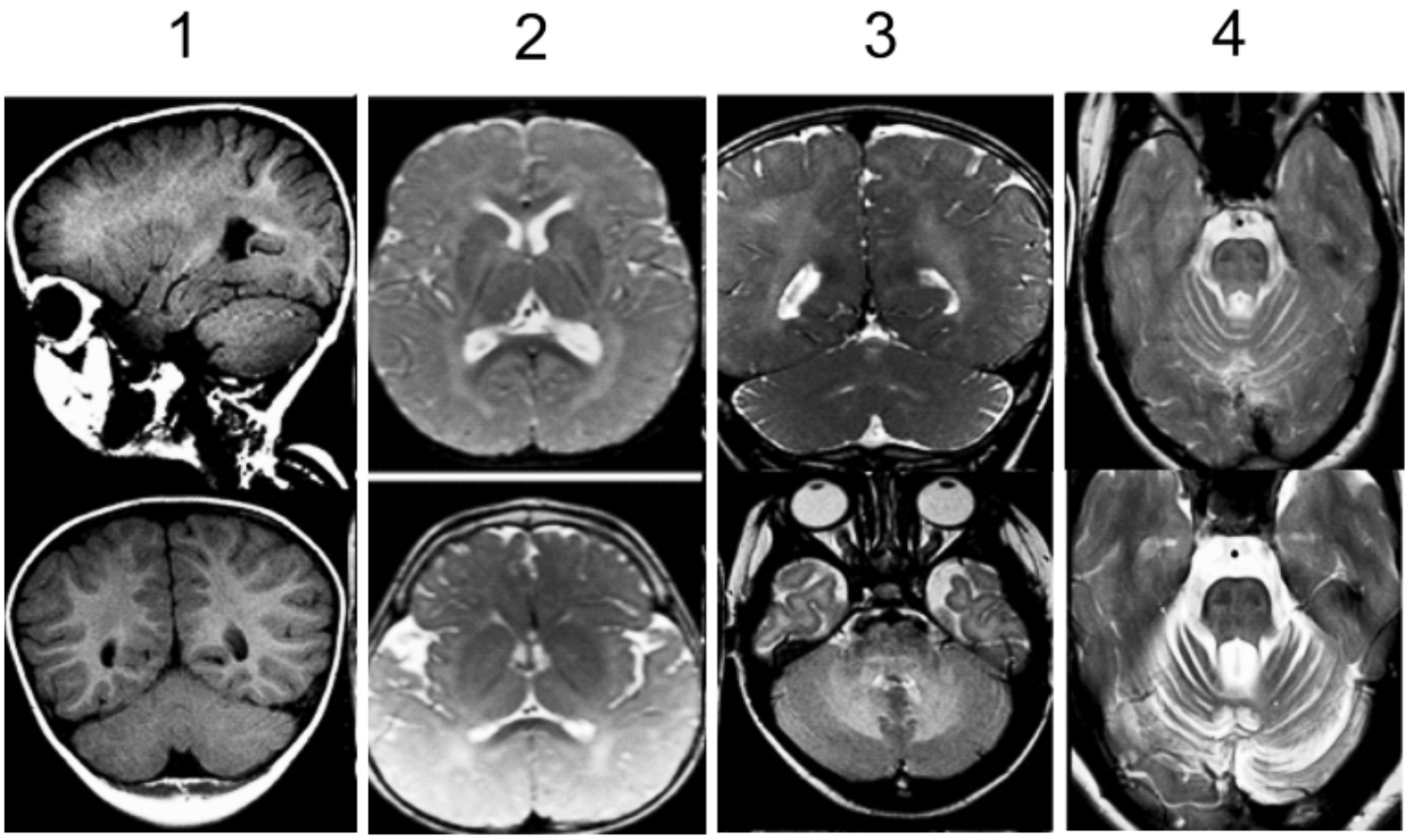

Figure 1. T_1-weighted and T_2-weighted MRIs in *NKX6-2*-related disorder

Column 1. Normal to hyperintense T_1-weighted white matter signal suggestive of hypomyelination observed in areas corresponding to the T_2-weighted hyperintense signal change (column 2) involving the subcortical and deep white matter, external capsules, and globi pallidi and thalami

Column 3. Diffuse cerebellar white matter T_2-weighted hyperintense signal change including the peridentate white matter with relative preservation of cerebellar volume

Column 4. Predominantly diffuse pontine T_2-weighted hyperintense signal change and cerebellar volume loss

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with ataxia and/or spasticity are more likely to be diagnosed using genomic testing (Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of *NKX6-2*-related disorder, use of a **multigene panel** is recommended.

An ataxia, spastic paraparesis, or hypomyelinating leukodystrophy multigene panel that includes *NKX6-2* 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*. Of note, given the rarity of *NKX6-2*-related spastic ataxia with hypomyelination, some panels for ataxia and/or spasticity

may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by ataxia and/or spasticity with hypomyelination on brain MRI, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

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 *NKX6-2*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
NKX6-2	Sequence analysis [3]	13/13 families [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown (no data available)

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. Anazi et al [2017], Chelban et al [2017], Dorboz et al [2017], Baldi et al [2018]
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

NKX6-2-related disorder is characterized by a spectrum of progressive neurologic manifestations resulting from diffuse central nervous system hypomyelination. To date *NKX6-2*-related disorder has been reported in 25 individuals from 13 families [Anazi et al 2017, Chelban et al 2017, Dorboz et al 2017, Baldi et al 2018].

At the severe end of the spectrum is neonatal-onset nystagmus, severe spastic tetraplegia with joint contractures and scoliosis, and visual and hearing impairment, all of which rapidly progress resulting in death in early childhood. At the milder end of the spectrum is normal achievement of motor milestones in the first year of life followed by slowly progressive complex spastic ataxia with pyramidal findings (spasticity with increased muscle tone and difficulty with gait and fine motor coordination), cerebellar findings (nystagmus, extraocular movement disorder, dysarthria, titubation, and ataxia), and loss of developmental milestones.

Affected individuals are born at term following uneventful pregnancy and delivery.

Nystagmus is usually the first manifestation and has been reported as early as age three months. Other ocular features include loss of visual fixation and ocular pursuit, reduced upgaze, and limited voluntary eye movements [Chelban et al 2017, Dorboz et al 2017, Baldi et al 2018].

Pyramidal syndrome, characterized by increased muscle tone in the lower extremities, hyperreflexia, and positive Babinski sign, has been present in all affected individuals reported to date. Some children with neonatal onset presented with hypotonia that progressed to spasticity within a few months [Dorboz et al 2017, Baldi et al 2018].

Extrapyramidal syndrome can be associated with *NKX6-2*-related disorders and most frequently presents with cervical and/or limb dystonia that can lead to development of joint contractures.

Cerebellar syndrome develops during later infancy and is characterized by dysarthria, titubation, and truncal and limb ataxia. Complications such as dysphagia lead to recurrent aspirations and the need for gastrostomy feedings in more advanced stages [Dorboz et al 2017, Baldi et al 2018]. Not all children develop a cerebellar syndrome.

Walking and mobility vary. Children with neonatal onset and severe disease never achieve ambulation [Dorboz et al 2017, Baldi et al 2018]. At the milder end of the spectrum affected individuals achieve early motor milestones (sitting independently) but are not able to walk well or run. Mobility aids are used during childhood, and disease progression typically leads to wheelchair dependence in the second decade of life [Chelban et al 2017].

Cognitive function varies greatly. Severe developmental language and motor delay with arrested speech development was reported in children at the severe end of the spectrum [Anazi et al 2017, Dorboz et al 2017, Baldi et al 2018]. In contrast, some individuals have mild intellectual disability, and one individual has normal cognitive function and has completed a university degree [Chelban et al 2017]. However, in some instances cognitive function is difficult to assess fully due to severe motor impairment.

Seizures have been reported in some individuals. The motor phenotype can vary from severe [Anazi et al 2017] to mild. Clinically evident tonic seizures, secondary generalized seizures, and focal seizures have been confirmed on electroencephalography [Author, personal observation].

The following additional features have been reported:

- Failure to achieve head control
- Hearing impairment
- Recurrent apnea, with some children developing respiratory failure that leads to early death
- Congenital abnormalities including congenital heart disease and undescended testes

Neurophysiologic studies

- Normal electromyogram and nerve conduction studies [Chelban et al 2017]

  Delayed visual evoked potentials [Dorboz et al 2017]

- Absent somatosensory evoked potentials
- On EEG, loss of age-based background activity and absent anterior-posterior gradient of background activity and multifocal epileptic discharges [Author, personal observation]

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been associated with biallelic *NKX6-2* pathogenic variants.

Of note, biallelic pathogenic variants in the homeobox domain (c.487C>G, c.606delinsTA, c.565G>T, c.599G>A, c.589C>T, c.608G>A, c.196delC) are associated with a severe phenotype including early onset (i.e., soon after birth), severe psychomotor developmental delay, widespread hypomyelination on MRI, and rapid disease progression leading in some instances to death in the first years of life [Anazi et al 2017, Chelban et al 2017, Dorboz et al 2017, Baldi et al 2018].

Prevalence

Prevalence is not known. To date, 25 affected individuals from 13 families of different ethnic backgrounds (northern European, Arab, North African, Asian) have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic pathogenic variants in *NKX6-2*.

Differential Diagnosis

Hypomyelinating leukodystrophies and spastic ataxias (particularly when associated with hypomyelination) should be considered in the differential diagnosis of *NKX6-2* related disorder. See Table 2.

Table 2. Movement Disorders to Consider in the Differential Diagnosis of *NKX6-2*-Related Disorder

Disorder	Gene(s)	MOI	Overlapping Clinical Features				Distinguishing Clinical Features
			Onset	Movement disorder	Brain MRI	Other	
Pelizaeus-Merzbacher disease (PMD) (See *PLP1* Disorders.)	*PLP1*	XL	Infancy or early childhood	Pyramidal, extrapyramidal, & cerebellar	Diffuse hypomyelination; cerebellar atrophy	Early-onset nystagmus	Null *PLP1* variants are assoc w/mild demyelinating neuropathy & reduced levels of N-acetyl aspartate in cerebral white matter.
Pelizaeus-Merzbacher-like disease 1 (PMLD1)	*GJC2*	AR	Early childhood	Pyramidal, extrapyramidal, & cerebellar	Diffuse hypomyelination	• Very similar to *NKX6-2*-related disorder • DD & speech delay • Preservation of cognition	In PMLD1: • Thinning of the corpus callosum in some • No cerebellar atrophy on MRI
POLR3-related leukodystrophy	*POLR3A* *POLR3B* *POLR1C*	AR	Early childhood	Pyramidal, extrapyramidal, & cerebellar	Diffuse hypomyelination		In POLR3-related leukodystrophy: • Abnormal dentition • Hypogonadotropic hypogonadism

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Overlapping Clinical Features				Distinguishing Clinical Features
			Onset	Movement disorder	Brain MRI	Other	
Hypomyelination w/atrophy of basal ganglia & cerebellum (H-ABC) (See *TUBB4A*-Related Leukodystrophy.)	*TUBB4A*	AD	Infancy or childhood	Pyramidal & cerebellar	Diffuse cerebral hypomyelination	Motor DD	In H-ABC: • Abnormalities of basal ganglia, esp atrophy (a classic sign) • Aphonia or "whispering" dysphonia may be a feature. [1]
Salla disease (See Free Sialic Acid Storage Disorders.)	*SLC17A5*	AR	Birth	Pyramidal & extrapyramidal	Hypomyelination	• Psychomotor retardation • Seizures	In severe form of Salla disease: • Severe DD • Coarse facial features • Hepatosplenomegaly • Cardiomegaly • Death usually in early childhood

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; XL = X-linked
1. TUBB4A pathogenic variant c.4C>G causes the adult-onset disorder laryngeal dysphonia or whispering dysphonia (also known as DYT4 dystonia), with normal MRI.

See Hereditary Ataxia Overview and Hereditary Spastic Paraplegia Overview.

See Spastic Ataxia: OMIM Phenotypic Series and Hypomyelinating Leukodystrophy: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NKX6-2*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of *NKX6-2*-Related Disorder

System/Concern	Evaluation	Comment
Constitutional	Height, weight, head circumference	Assess for evidence of failure to thrive.
Eyes	Ophthalmologic eval	Assess for: • ↓ vision; • Abnormal ocular movement.
Hearing	Audiologic eval	Assess for hearing loss.
Cardiovascular	Consideration of echocardiogram	To screen for congenital heart defects

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Respiratory	Assessment of : • Airway • Pulmonary function • Secretion management	Sleep study to assess for apnea
Gastrointestinal	Assessment (esp in later stages of disease) of: • Swallowing • Feeding • Nutritional status	Determine safety of oral vs gastrostomy feeding.
Musculoskeletal	Referral to specialist in pediatric pain mgmt	For those who have pain due to deforming joint contractures
	Referral to rehab specialist	To evaluate mobility & ability to perform activities of daily living
Genitourinary	Physical exam for cryptorchidism in males	Refer males w/cryptorchidism to urologist.
Neurologic	Referral to pediatric neurologist	Assess for evidence of spasticity &/or seizure activity.
Miscellaneous/ Other	Consultation w/clinical geneticist or genetic counselor	
	Developmental assessment	Evaluate the following: • Motor skills • Speech/language • General cognitive skills • Vocational skills
	Referral to palliative care specialist	When deemed appropriate by family & care providers
	Family support & resources	• Community or online resources (e.g., Parent to Parent) • Social work involvement for parental support • Home nursing referral if needed

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *NKX6-2*-Related Spastic Ataxia with Hypomyelination

Manifestation/ Concern	Treatment	Considerations/Other
Eyes	Standard treatment per ophthalmology review	Community vision services through early intervention or school district
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Congenital heart defect	Standard treatment per cardiologist	
Respiratory insufficiency	Standard treatment per respiratory review; consider assisted ventilation as appropriate.	• Airway & pulmonary assessment for evidence of ↓ pulmonary function or poor secretion mgmt • Sleep study
Dysphagia / Inadequate nutrition	Nasogastric or gastrostomy tube may be required.	Maintain a low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs &/or symptoms of dysphagia.
Cryptorchidism	Standard treatment per urologist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	• PT (incl stretching) to avoid contractures & falls • Trial of pharmaceutical agents (e.g., baclofen or tizanidine) as recommended by rehab specialist	• Assess for evidence of spasticity. • Consider need for positioning & mobility devices, disability parking placard.
Seizures	Anti-seizure medication	Typically difficult to control [1]
Family/ Community	• Appropriate social work involvement to connect families w/local resources, respite, & support • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	• Ongoing assessment for need of palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

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

Developmental Delay / Intellectual Disability Management Issues

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

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

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; however, home-based services are provided for children too medically unstable to attend.

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

- **IEP services** are for those who require specially designed instruction / related services.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - 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 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 years.

- **504 plan services** can be considered for those who require accommodations or modifications including front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, enlarged text, and other accommodations.
- **Developmental Disabilities Administration** (DDA) enrollment is recommended. DDA is a public agency in the US that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Prevention of Secondary Complications

The following additional recommendations are based on the leukodystrophies consensus [Van Haren et al 2015]:

- Frequent repositioning and skin care to avoid skin sores in affected individuals who are not mobile
- Yearly flu vaccination
- Vitamin D supplementation (to prevent osteoporosis)

Surveillance

Table 5. Recommended Surveillance for Individuals with *NKX6-2*-Related Disorder

System/Concern	Evaluation	Frequency
Eyes	Visual acuity & eye movement	At each visit
Hearing	Formal audiology assessment	As required
Respiratory	Sleep studies recommended if signs of apnea	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal/ Feeding	Measurement of growth parameters	At each visit
	Eval of nutritional status & safety of oral intake	
Neurologic	Assessment of developmental progress	
	Assessment for progression of spasticity & contractures w/annual hip & spine x-ray	
	EEG	If concerns for new seizure activity or progression of seizures

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

NKX6-2-related disorder is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *NKX6-2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

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

Offspring of a proband. To date, individuals with *NKX6-2*-related disorder are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *NKX6-2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *NKX6-2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *NKX6-2* pathogenic variants have been identified in an affected family member, prenatal 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.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  sp-foundation.org
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020

Fax: 763-553-0167

Email: naf@ataxia.org

www.ataxia.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. NKX6-2-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
NKX6-2	10q26.3	Homeobox protein Nkx-6.2	NKX6-2	NKX6-2

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 NKX6-2-Related Disorder (View All in OMIM)

605955	NK6 HOMEOBOX 2; NKX6-2
617560	SPASTIC ATAXIA 8, AUTOSOMAL RECESSIVE, WITH HYPOMYELINATING LEUKODYSTROPHY; SPAX8

Gene structure. *NKX6-2* (NM_177400.2) has three exons and encodes a protein of 277 amino acids (NP_796374.1).

Pathogenic variants. Known pathogenic variants are listed in Table 6.

Table 6. *NKX6-2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.121A>T	p.Lys41Ter	NM_177400.2 NP_796374.1
c.196delC	p.Arg66GlyfsTer122	
c.487C>G	p.Leu163Val	
c.565G>T	p.Glu189Ter	
c.589C>T	p.Gln197Ter	
c.599G>A	p.Arg200Gln	
c.606delinsTA	p.Lys202Asnfs? [1]	
c.608G>A	p.Trp203Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. ? = The predicted consequence of a frame-shifting variant changes Lys202 to Asn, but the new reading frame does not encounter a new translation termination (stop) codon.

Normal gene product. *NKX6-2* is a recently identified member of the human homeobox gene family, which has more than 330 loci comprising 255 genes and 78 likely pseudogenes [Zhong & Holland 2011]. All homeobox family members share a sequence of 180 base pairs encoding a string of 60 self-folding amino acids [Gehring

1993] recognized as the homeodomain that acts as a transcription factor. NKX6-2 comprises 277 amino acids and has one functional domain – the homeobox (residues 151-204 of NP_796374.1).

Abnormal gene product. Truncating variants can be located throughout *NKX6-2* and lead to disease through a loss-of-function mechanism. All reported pathogenic missense variants affect the major functional domain of NKX6-2, the homeobox. It is likely that disruption of the highly conserved homeobox sequence also disrupts DNA binding.

Chapter Notes

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