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SLC6A1-Related Neurodevelopmental Disorder

Synonyms: *SLC6A1*-Related Disorder, SLC6A1 Deficiency Disorder

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Summary

Clinical characteristics

SLC6A1-related neurodevelopmental disorder (*SLC6A1*-NDD) is characterized by mild-to-severe developmental delay and/or intellectual disability, hypotonia, epilepsy, movement disorders (e.g., tremor, stereotypies, ataxia), and neurobehavioral and/or psychiatric manifestations (e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder, aggression, anxiety, and/or sleep disturbances). Language skills, particularly expressive language, are often more significantly affected than motor development. Developmental regression has been reported. Gastrointestinal manifestations (e.g., constipation, diarrhea) are also common.

Diagnosis/testing

The diagnosis of *SLC6A1*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SLC6A1* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; anti-seizure medications are often needed to control seizures; behavioral strategies and/or neuropharmacologic interventions for psychiatric, behavioral, and/or sleep disorders; standard treatments for bowel dysfunction; family support and care coordination.

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Surveillance: Assess at each visit developmental and behavioral issues, new seizures and/or changes in seizures, movement disorders, constipation or diarrhea, and family needs.

Agents/circumstances to avoid: Individuals with *SLC6A1*-NDD have intolerable behavioral side effects with levetiracetam at higher rates than reported in the general population. If behavioral side effects are experienced with levetiracetam, alternative anti-seizure medications should be considered.

Genetic counseling

SLC6A1-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with *SLC6A1*-NDD inherited a pathogenic variant from a heterozygous parent. Each child of an individual with *SLC6A1*-NDD has a 50% chance of inheriting the pathogenic variant. Once the *SLC6A1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

SLC6A1-related neurodevelopmental disorder (*SLC6A1*-NDD) **should be considered** in individuals with the following clinical findings.

Clinical findings

- Mild-to-severe developmental delay (DD) and/or intellectual disability (ID)
- Generalized hypotonia of infancy
- Epilepsy including absence or atypical absence seizures, epilepsy with myoclonic-atonic seizures, generalized tonic-clonic seizures
- Movement disorders such as tremor, stereotypies, and ataxia
- Autism spectrum disorder, attention-deficit/hyperactivity disorder, aggression, anxiety, and/or sleep disturbances

Family history. Because *SLC6A1*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Occasionally, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *SLC6A1*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *SLC6A1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" 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 variant" in this section is understood to include any likely pathogenic variant. (2) Identification of a heterozygous *SLC6A1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with DD or an older individual with ID may begin with chromosomal microarray analysis (CMA); however, this is unlikely to identify an individual with *SLC6A1*-NDD. Most individuals with *SLC6A1*-NDD have small *SLC6A1* single-nucleotide variants or indels that can be identified on a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *SLC6A1*) is rarely useful and typically NOT recommended.

- **An epilepsy multigene panel** that includes *SLC6A1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an epilepsy multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing epilepsy whereas some multigene panels may not. **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 *SLC6A1*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SLC6A1	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [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

SLC6A1-related neurodevelopmental disorder (*SLC6A1*-NDD) is characterized by developmental delay, epilepsy, autism spectrum disorder, and attention-deficit/hyperactivity disorder. Many individuals also have hypotonia, intermittent tremor or ataxia, and sleep disturbances [Johannesen et al 2018, Goodspeed et al 2020, Bain et al 2022]. To date, more than 100 individuals have been identified with a pathogenic variant in *SLC6A1* [Goodspeed et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *SLC6A1*-Related Neurodevelopmental Disorder

Feature	% of Persons w/Feature	Comment
Developmental delay	>90%	Mild to severe

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Hypotonia	60%	Low muscle tone in infancy is common & improves w/age.
Intellectual disability	35%	Mild to severe
Seizures	85%	Absence & atypical absence, myoclonic, & atonic seizures are most prevalent. Some persons have intractable epilepsy.
Movement disorders	40%	Intermittent tremor w/fine motor tasks & ataxia are most common.
ASD	30%	Rigidity, repetitive speech patterns & behaviors, sensory sensitivity, & sensory-seeking behaviors are most common.
ADHD	15%	Hyperactive, inattentive, or combined type

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

Developmental delay (DD) is the most prevalent clinical feature, but it can vary from mild to severe among affected individuals. Many children with *SLC6A1*-NDD come to medical attention with hypotonia and delayed motor and language milestones within the first year of life (range: 3 months to 2 years).

Hypotonia is typically mild to moderate. Individuals typically sit by age nine months (range: 5-13 months) and walk by age 19 months (range: 11-33 months).

Language development is often more delayed than motor development. Children with *SLC6A1*-NDD often babble around age 14 months (range: 6-36 months), say their first word by age 25 months (range: 10-52 months), and use phrased speech by age 34 months (range: 23-54 months). Some individuals, however, never use words or phrases, and receptive communication is often better than expressive communication [Bain et al 2022].

Some children with *SLC6A1*-NDD have developmental regression that is either episodic, with recovery of skills, or followed by a plateau in development [Goodspeed et al 2020]. Regression may involve a loss of language skills, impairment in motor skills, or loss of social and adaptive skills. Factors that contribute to developmental regression are not currently known.

Intellectual disability (ID). Approximately one third of individuals will have ID; severity varies from mild to severe. Many of those who do not meet the criteria for ID will have a specific learning disorder such as dyslexia or dysgraphia [Johannesen et al 2018, Goodspeed et al 2020, Bain et al 2022].

Other neurodevelopmental manifestations. Approximately one third of individuals have autism spectrum disorder, and 10%-20% have attention-deficit/hyperactivity disorder. Children are often described as being interested in their peers, but struggle to maintain friendships and have restricted interests, repetitive speech or behavior patterns, and sensory-seeking or avoidant behaviors.

Epilepsy. Several seizure phenotypes have been reported in individuals with *SLC6A1*-NDD:

- **Early-onset absence epilepsy / childhood absence epilepsy.** Absence and atypical absence seizures are the most prevalent seizure semiology in individuals with *SLC6A1*-NDD. EEG features include 2-4 Hz spike and wave discharges, exacerbated by hyperventilation, and intermittent rhythmic delta activity, especially in the occipital region. Staring spells present across a broad age range, from age four to 60 months, though not all staring events will have an ictal EEG correlate in this disorder.
- **Myoclonic and atonic seizures (including Doose syndrome).** Myoclonic seizures are typically noted around age two years, but atonic events can be seen as early as age 12 months [Carvill et al 2015].
- **Developmental and epileptic encephalopathy (DEE).** Some individuals with more severe developmental delay may be classified as DEE. These individuals often have generalized or multifocal independent spike-wave discharges and background slowing on EEG and may meet criteria for Lennox-Gastaut syndrome.

- **Focal epilepsy.** Fewer than 10% of individuals with *SLC6A1*-NDD have focal-onset seizures with focal epileptiform discharges on EEG.

Movement disorders. Approximately half of individuals with *SLC6A1*-NDD have abnormal movements. These are often described as tremors of the upper extremities with fine motor activities or lower-extremity tremor with activity. Ataxic gait patterns with impaired balance have been reported in some children. Many also have motor stereotypies, including a tendency to clench their fists, stiffen their arms, and stare at their hands in infancy.

Behavioral issues are common in individuals with *SLC6A1*-NDD and likely have a significant contribution to the burden of disease. Aggression and irritability have been reported, often described as yelling or screaming and hitting themselves or caretakers. Repetitive behaviors and speech can sometimes be interpreted as a manifestation of anxiety. Sleep disturbances are also common and described as difficulty falling asleep or staying asleep. Challenging behaviors often increase in intensity when strict bedtime routines are not maintained.

Gastrointestinal issues. Some individuals with *SLC6A1*-NDD have abnormal bowel habits, but these can vary between constipation and chronic diarrhea. Many with autism spectrum disorder also have restrictive eating habits.

Other

- **Growth.** Abnormalities of growth (short stature) or head circumference are rare [Mermer et al 2022].
- **Neuroimaging.** Individuals with *SLC6A1*-NDD do not have distinctive features on brain imaging. Nonspecific white matter changes or other incidental findings such as arachnoid cysts have been identified.
- **Facial features.** No consistent dysmorphic features have been identified. If present, dysmorphic features are nonspecific.
- **Psychiatric features.** A small number of adults with an *SLC6A1* pathogenic variant have been diagnosed with schizophrenia [Goodspeed et al 2020].

Prognosis. It is unknown whether life expectancy in individuals with *SLC6A1*-NDD is reduced. Some individuals inherited an *SLC6A1* pathogenic variant from a parent with a variable phenotype (e.g., epilepsy, learning disability, behavior disorder) [Johannesen et al 2018], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified to date. However, ongoing studies suggest that the level of GAT-1 function (see Molecular Genetics) may correlate with disease severity, such that those with lower residual GAT-1 function have the most severe manifestations of *SLC6A1*-NDD [Mermer et al 2022].

Penetrance

Penetrance appears to be incomplete [Poliquin et al 2021].

Prevalence

SLC6A1-NDD is rare. Fewer than 500 individuals have been reported worldwide, with an estimated incidence of 2.65 in 100,000 births [López-Rivera et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC6A1*.

Differential Diagnosis

The phenotypic features associated with *SLC6A1*-related neurodevelopmental disorder (*SLC6A1*-NDD) are not sufficiently specific to diagnose this condition clinically; all disorders with intellectual disability and/or seizures without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series:

- Autosomal Dominant Intellectual Developmental Disorder
- Autosomal Recessive Intellectual Developmental Disorder
- Nonsyndromic X-Linked Intellectual Developmental Disorder
- Syndromic X-Linked Intellectual Developmental Disorder
- Developmental and Epileptic Encephalopathy

SLC6A1-NDD shares phenotypic similarities, including developmental delay, epilepsy, and autism spectrum disorder, with the disorders listed in Table 3. In particular, Rett syndrome may be considered in individuals with developmental regression, and Angelman syndrome may be considered in those with intermittent rhythmic delta activity on their EEG. Finally, sodium channelopathies (*SCN1A*, *SCN2A*, *SCN8A*) and $GABA_A$ receptor-related epilepsies (*GABRA1*, *GABRB2*, *GABRB3*, *GABRG2*) also have a broad phenotypic spectrum that includes epilepsy, developmental delay, and autism spectrum disorder.

Table 3. Selected Genes of Interest in the Differential Diagnosis of *SLC6A1*-Related Neurodevelopmental Disorder

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
GABRA1 *GABRB2* *GABRB3* *GABRG2*	$GABA_A$ receptor-related epilepsies (OMIM 137160, 600232, 137192, 137164)	AD	Generalized epilepsy w/or w/o NDD. Some individuals have ASD, behavioral issues, or movement disorders. EEGs can have variable findings ranging from normal to abnormal w/focal or generalized spike-wave discharges, hypsarrhythmia, or burst-suppression pattern. Fever-related seizures are common. Eye abnormalities, incl nystagmus, can be seen.	Persons w/*SLC6A1*-NDD are unlikely to have hypsarrhythmia or burst-suppression pattern on EEG & may be more likely to have NDD.
MECP2	Rett syndrome (See *MECP2* Disorders.)	XL	Progressive NDD primarily affecting females characterized by apparently normal psychomotor development in 1st 6-18 mos of life, followed by short period of developmental stagnation, then rapid regression in language & motor skills, followed by long-term stability. During rapid regression phase, repetitive, stereotypic hand movements replace purposeful hand use. Additional findings incl seizures & acquired microcephaly.	Persons w/Rett syndrome typically have more severe DD/ID than those w/*SLC6A1*-NDD.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
SCN1A *SCN2A* *SCN8A*	Sodium channelopathies (See, e.g., *SCN1A* Seizure Disorders and *SCN8A*-Related Epilepsy w/ Encephalopathy.)	AD	Epilepsy, ASD, & DD. Seizures are often exacerbated by heat & persons are prone to status epilepticus. May have encephalopathic features on EEG consistent w/DEE or LGS. Seizure onset is typically w/in 1st yr of life, & there is ↑ risk of SUDEP.	Generalized tonic-clonic seizures & heat sensitivity are less prevalent in *SLC6A1*-NDD than in most sodium channel disorders.
UBE3A [1]	Angelman syndrome (AS)	See footnote 2.	Severe DD/ID, severe speech impairment, gait ataxia &/or tremulousness of limbs, & unique behavior w/apparently happy demeanor that incl frequent laughing, smiling, & excitability. Microcephaly & seizures are common. DDs are first noted at ~6 mos; however, unique clinical features of AS do not become manifest until >1 yr of age.	Persons w/AS typically have more severe DD/ID than those w/*SLC6A1*-NDD; however, EEG abnormalities can be similar.

AD = autosomal dominant; ASD = autism spectrum disorder; DD = developmental delay; DEE = developmental and epileptic encephalopathy; ID = intellectual disability; LGS = Lennox-Gastaut syndrome; MOI = mode of inheritance; NDD = neurodevelopmental disorder; SUDEP = sudden unexpected death in epilepsy; XL = X-linked

1. Angelman syndrome (AS) is associated with deficient expression or function of the maternally inherited *UBE3A* allele.

2. Individuals with AS typically represent simplex cases and have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk.

Management

No clinical practice guidelines for *SLC6A1*-related neurodevelopmental disorder (*SLC6A1*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SLC6A1*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SLC6A1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Consider brain MRI if neurologic exam is abnormal, if there is developmental regression, or if there are seizures. • Consider EEG if seizures are a concern. • Consider referral to a movement disorder specialist for severe tremor &/or ataxia.
Movement disorder / Ataxia	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)

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl findings suggestive of ASD, ADHD, aggression, anxiety, &/or sleep disturbances
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of nutritional status • Assess for chronic constipation or diarrhea.
Hearing	Audiologic eval	Assess for hearing impairment in those w/language delay. [1]
Genetic counseling	By genetics professionals [2]	• To inform affected persons & their families re nature, MOI, & implications of *SLC6A1*-NDD to facilitate medical & personal decision making • For an online portal to aid in variant eval, click here.
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Hearing impairment has not been reported in individuals with *SLC6A1*-NDD; however, hearing assessment is recommended in all individuals with language delay.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *SLC6A1*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	• Most persons w/*SLC6A1*-related seizures have generalized seizures. • ASM managed by experienced neurologist should be considered.	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/ caregivers [1]
Psychiatric/ Behavioral	• Standard mgmt using behavioral strategies & neuropharmacologic interventions • Stimulants could be considered for mgmt of ADHD. • Risperidone or aripiprazole are FDA-approved medications for irritability & aggression assoc w/ ASD.	
Sleep disorder	• Standard mgmt using behavioral strategies & neuropharmacologic interventions • Treatments for sleep may incl sleep hygiene, melatonin, clonidine, or trazodone.	
Bowel dysfunction	Standard treatments for constipation & diarrhea	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = anti-seizure medication
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 US; 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.
  - 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.

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.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician or neurodevelopmental disabilities neurologist may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 6 are recommended.

Table 6. Recommended Surveillance for Individuals with *SLC6A1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Development	• Monitor developmental progress & educational needs. • Physical medicine & OT/PT assessment of mobility & self-help skills	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Psychiatric/ Behavioral	Behavioral assessment for findings suggestive of ASD, ADHD, aggression, self-injury, anxiety, &/or sleep disturbances	
Gastrointestinal	Monitor for constipation or diarrhea.	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Given the high prevalence of challenging behaviors in individuals with *SLC6A1*-NDD, levetiracetam should be used with caution. Individuals with *SLC6A1*-NDD have intolerable behavioral side effects with levetiracetam at higher rates than reported in the general population.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

There are therapies for *SLC6A1*-NDD in development. To date, one clinical trial is assessing the safety and efficacy of 4-phenylbutyrate in individuals with *SLC6A1*-NDD (NCT04937062).

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.

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

SLC6A1-related neurodevelopmental disorder (*SLC6A1*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- The majority of individuals reported to date with *SLC6A1*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo SLC6A1* pathogenic variant [Goodspeed et al 2020].

- Rarely, individuals diagnosed with *SLC6A1*-NDD inherited an *SLC6A1* pathogenic variant from a heterozygous parent. Phenotypic variability may be observed in these families, such as a heterozygous parent who experienced learning disabilities.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * A parent with somatic and germline mosaicism for an *SLC6A1* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with *SLC6A1*-NDD may appear to be negative because of reduced penetrance or failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Affected sibs often display similar phenotypes although clinical variability may be observed between heterozygous family members.
- If the *SLC6A1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *SLC6A1*-NDD has a 50% chance of inheriting the *SLC6A1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SLC6A1* pathogenic variant, the parent's family members may be at risk.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC6A1* pathogenic variant has 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.

- **SLC6A1 Connect**
  Phone: 303-907-8038
  Email: afreed@SLC6A1Connect.org
  www.slc6a1connect.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  epilepsy.ca
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  vor.net
- **Simons Searchlight Registry**
  SLC6A1

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. SLC6A1-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

SLC6A1	3p25.3	Sodium- and chloride-dependent GABA transporter 1	SLC6A1	SLC6A1

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 SLC6A1-Related Neurodevelopmental Disorder (View All in OMIM)

137165	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, GABA), MEMBER 1; SLC6A1
616421	MYOCLONIC-ATONIC EPILEPSY; MAE

Molecular Pathogenesis

SLC6A1 encodes the sodium- and chloride-dependent GABA transporter 1 (GAT-1), which is responsible for the reuptake of GABA into presynaptic neurons and glia. GABA is the principal inhibitory neurotransmitter that counterbalances neuronal excitation in the brain. The exact mechanism of molecular pathology is not yet fully understood; however, it is known that disruption of this inhibitory balance can result in seizures [Carvill et al 2015, Goodspeed et al 2020].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Dr Goodspeed and Dr Johannesen are actively involved in clinical research regarding individuals with *SLC6A1*-related neurodevelopmental disorder (*SLC6A1*-NDD). They would be happy to communicate with persons who have any questions regarding the diagnosis of *SLC6A1*-NDD or other considerations.

Contact Dr Lal, Dr Goodspeed, Dr Johannesen, or Dr Kang to inquire about review of *SLC6A1* variants of uncertain significance.

Acknowledgments

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- 9 February 2023 (sw) Review posted live
- 15 October 2018 (kg) Original submission

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