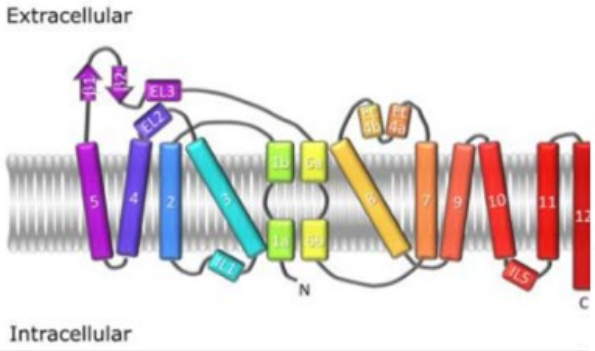
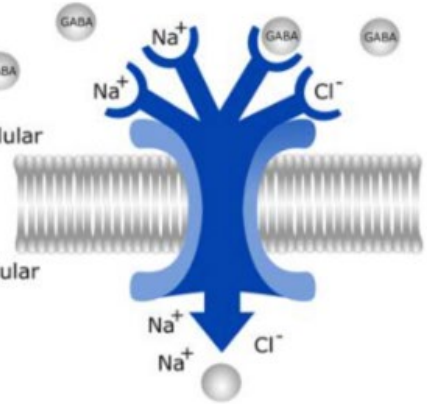
SLC6A1-Related Neurodevelopmental Disorder

ICD-10-CM Code Request

The *SLC6A1* Gene

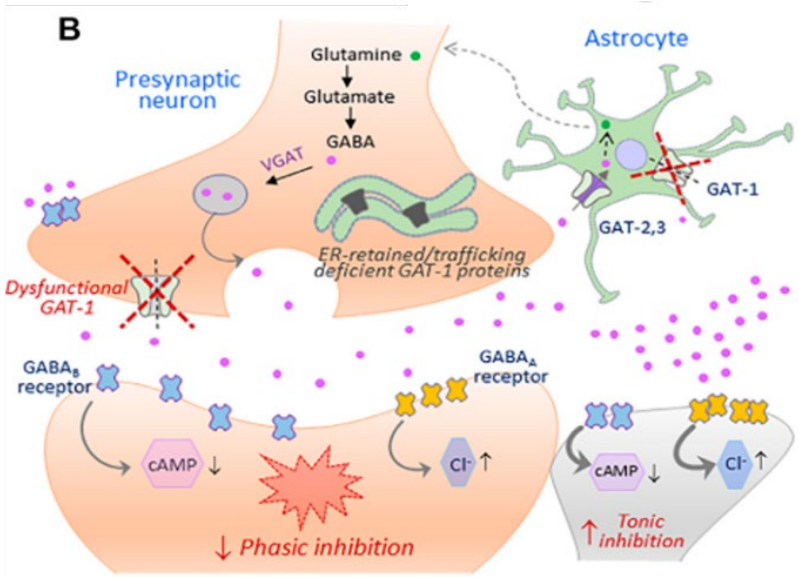
- Encodes GABA Transporter Type 1 on Chromosome 3
- Single chain transporter with 12 transmembrane domains
- Na-Cl-GABA Transporter





Johannesen et al, Epilepsia, 2018; Bragina *et al.,* 2008; Conti et al., 2011
Goodspeed & Perez-Palma, et al, Brain Comm, 2020

The *SLC6A1* Gene



Putative effects of GAT-1 pathogenic variants

- Na-Cl-GABA Transporter responsible for reuptake of GABA from the synaptic cleft to lower extracellular GABA concentration
- Expressed in GABAergic neurons and astrocytes in the cerebellum, basal ganglia, interpeduncular nucleus, and hippocampus
- Role in excitatory/inhibitory balance and GABA recycling

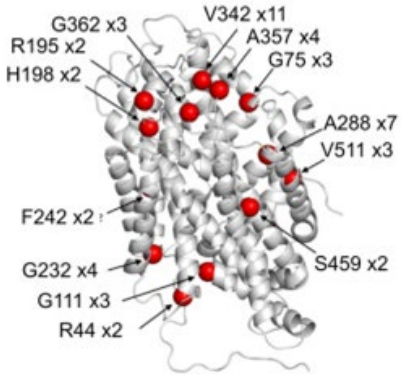
Johannesen et al, Epilepsia, 2018; Bragina *et al.,* 2008; Conti et al., 2011
Goodspeed & Perez-Palma, et al, Brain Comm, 2020; Fischer et al., Frontiers, 2022

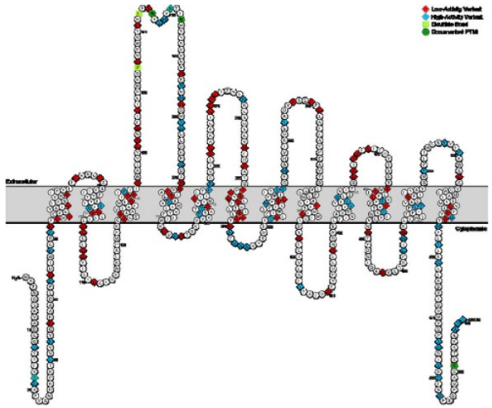
SLC6A1-NDD

Patients have a monoallelic, loss of function variant in *SLC6A1*

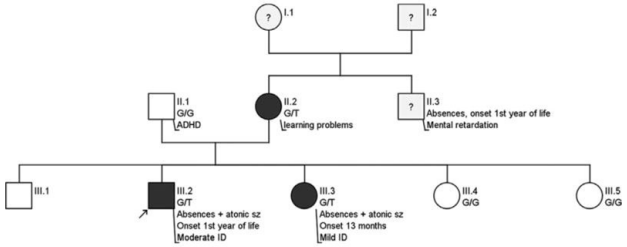
Most are de novo, but some variants are inherited in an AD pattern, with variable expressivity

Variants are identified across the length of the gene

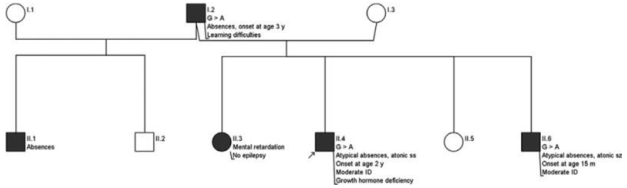




Family 1. Gly232Val



Family 2. Val342Met



Johannesen et al, Epilepsia, 2018; Goodspeed & Perez-Palma, et al, Brain Comm, 2020

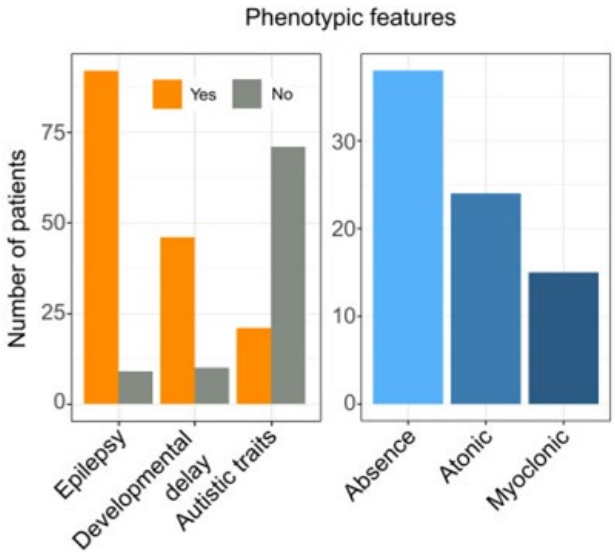
SLC6A1—NDD

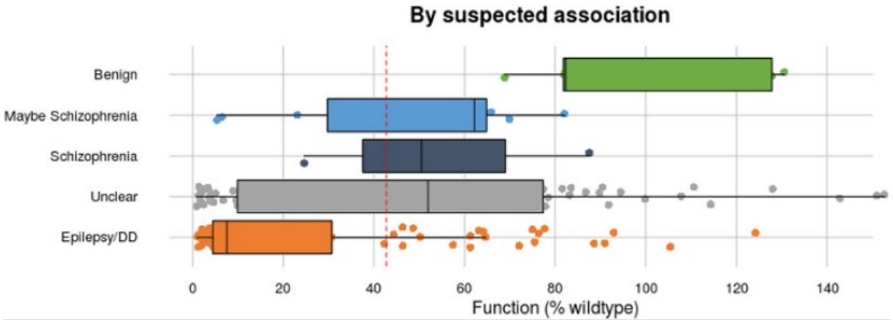
Estimated Incidence: 2.65 per 100,000 births

Core Clinical Characteristics

1. Developmental Delay
2. Epilepsy
3. Autism Spectrum Disorder

Reduced residual GAT1 activity correlates with the developmental and epileptic phenotypes



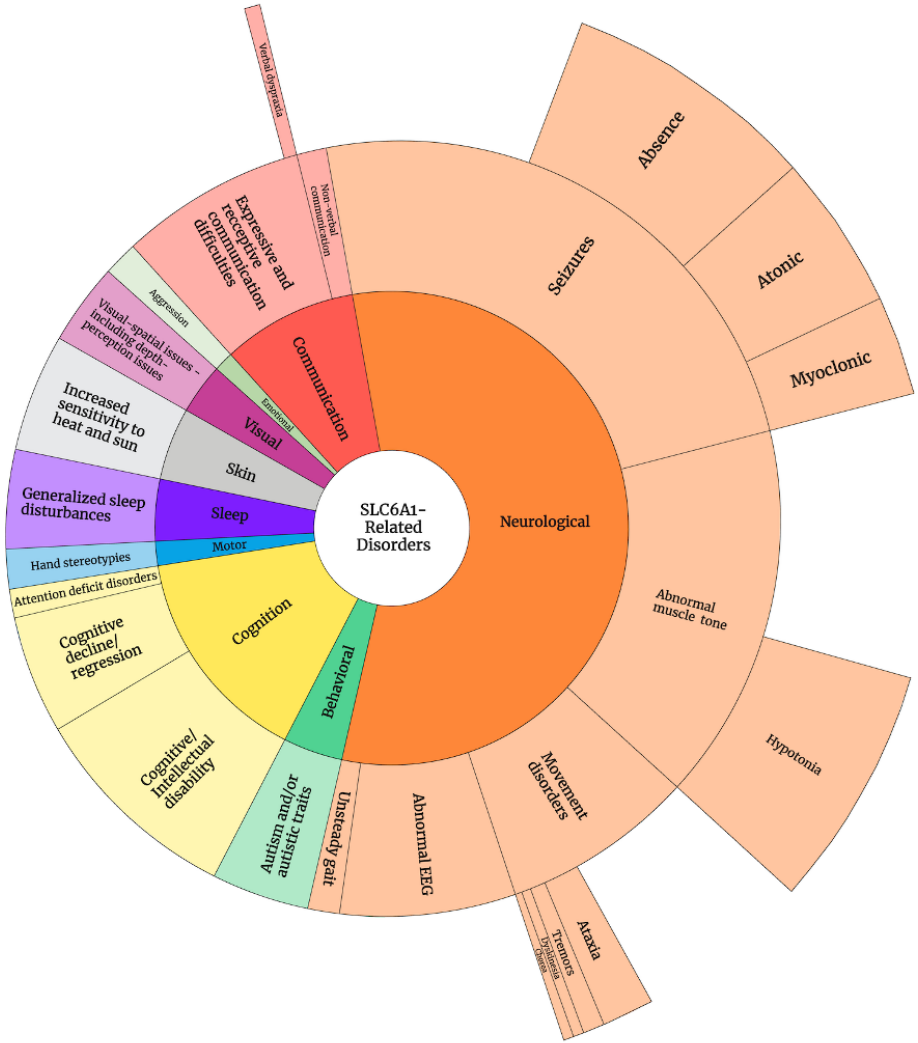


Goodspeed & Perez-Palma, et al, Brain Comm, 2020

SLC6A1—NDD (cont,)

Other Clinical Features

- Cognitive impairment
- Language impairment
- Behavioral problems
- Hypotonia
- Movement disorder
- Sleep disorder
- Visual perception problems

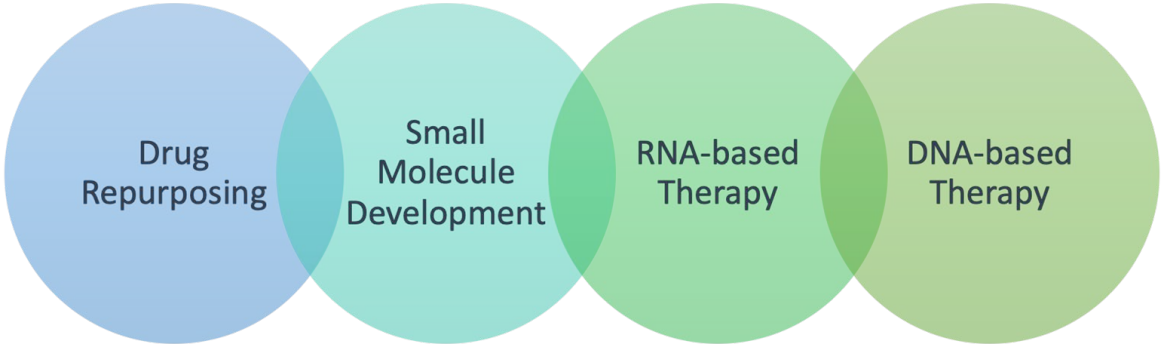


Goodspeed et al, Frontiers, 2023

An SLC6A1-NDD Code Provides an Opportunity to Improve Care

- Improve seizure medication recommendation
  - Tiagabine is an approved anti-seizure medication that is a GAT1 antagonist and should not be used for SLC6A1.
  - Myoclonic atonic seizures and atypical absence seizures can be difficult to detect clinically. A higher index of suspicion with a dedicated ICD-10 code could improve outcomes.
- Faster referral for occupation and physical therapy
  - Patients often suffer from balance and coordination abilities requiring coordinated therapy
- Faster referral for speech therapy language
  - Patients often suffer from communication impairment and should be evaluated for an augmentative assistive communication device
- Improved evaluation and management of comorbid symptoms
  - Patients often display sleep and behavioral disorders, including autism, ADHD, and sleep disorders.
  - Patients should be screened for comorbidities and managed symptomatically with behavioral interventions or medication to reduce disease burden.

SLC6A1-NDD Research



Multiple treatments specifically for SLC6A1-NDD are currently in development. Some have received rare pediatric disease and orphan drug designations from the U.S. FDA and orphan drug designation from the European Commission.

A drug repurposing clinical trial is ongoing – NCT04937062: Phenylbutyrate for STXBP1 Encephalopathy and SLC6A1 Neurodevelopmental Disorder

A unique ICD-10-CM code is required to identify patients who will benefit from these treatments; some are only applicable for patients with variants in the *SLC6A1* gene

These designations indicate that the FDA and EMA consider SLC6A1-NDD a separate indication that cannot be grouped with others in ICD coding.

A Unique Code Can Capture the Disorder

With a unique code:

- We can specify the specific disorder
- We can specify the relevant gene (*SLC6A1*)
- We can capture the multisystem effects of SLC6A1-NDD
- We can track mortality in this disease

This leads to:

- Positive impact on medical care
- Improvement of appropriate surveillance, therapies, treatments, and care team
- Consistent records; multiple and codes for the same patient
- Creates unity between clinical care, insurance authorization and research studies, which depend on ICD-10 codes
- Decreased time to diagnosis

Summary

- There is no current ICD-10-CM code with the specificity and meaning of “SLC6A1-related Neurodevelopmental Disorder”

- With a code, patient care improvements include:
  - Ability to automatically flag inappropriate prescriptions and treatments
  - Ability to determine qualification for novel treatments
  - Ability to alert or authorize language, physical, occupational, and behavioral therapies
  - Ability to alert families about implications for family planning