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GNAI1-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

GNAI1-related neurodevelopmental disorder (*GNAI1*-NDD) is characterized by mild-to-profound developmental delay and intellectual disability, hypotonia, neurobehavioral and/or psychiatric manifestations, and epilepsy. The neurobehavioral and/or psychiatric manifestations include features of autism spectrum disorder such as stereotypic behaviors (hand flapping, head banging, hand wringing, repetitive noises, teeth grinding, mouthing behaviors), sensory sensitivities, and poor eye contact. Temper tantrums, anxiety, agitation, aggression, and attention-deficit/hyperactivity disorder are also reported. Seizure onset typically occurs within the first six months of life; seizure types include absence, generalized tonic-clonic, and focal-onset impaired awareness. Additional common features include scoliosis, hip dysplasia, feeding difficulties or obesity with insatiable appetite, constipation, and strabismus.

Diagnosis/testing

The diagnosis of *GNAI1*-NDD is established in a proband with characteristic clinical features and a heterozygous pathogenic variant in *GNAI1* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational services; standard epilepsy treatment with anti-seizure medications by an experienced neurologist; physical medicine and rehabilitation, physical therapy, and occupational therapy to include stretching to help avoid contractures and falls; feeding therapy with gastrostomy tube placement as needed; standard treatments for constipation and strabismus; social work support and care coordination as needed.

Surveillance: At each visit, assess developmental progress, educational needs, mobility and self-help skills, growth, nutrition, and family needs, as well as for new seizures or changes in seizures, scoliosis, and

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constipation; behavioral assessment for autistic features, anxiety, attention-deficit/hyperactivity disorder, and aggressive or self-injurious behaviors as needed.

Genetic counseling

GNAI1-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the *GNAI1* pathogenic variant identified in the proband is not identified in either parent, the recurrence risk to sibs is estimated to be 1%-8% because of the possibility of parental germline mosaicism. Once the *GNAI1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

GNAI1-related neurodevelopmental disorder (*GNAI1*-NDD) **should be considered** in probands with the following clinical and brain MRI findings and family history.

Clinical findings

- Mild-to-profound developmental delay
- Hypotonia
- Mild-to-profound intellectual disability
- Neurobehavioral/psychiatric manifestations (autism spectrum disorder, temper tantrums, anxiety, agitation, aggression, and attention-deficit/hyperactivity disorder)
- Epilepsy (absence, generalized tonic-clonic, focal-onset impaired awareness)

Brain MRI findings

- Atrophy (global)
- Delayed myelination
- Choroid plexus cysts

Family history. Because *GNAI1*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

Establishing the Diagnosis

The diagnosis of *GNAI1*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GNAI1* 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 can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GNAI1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with exome sequencing. Other options include use of a multigene panel or genome. Note: Single-gene testing (sequence analysis of *GNAI1*) is rarely useful and typically NOT recommended. Chromosomal microarray analysis may not be a useful first-line test because, to date, no large pathogenic deletions/duplications have been identified in individuals with *GNAI1*-NDD.

- **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 intellectual disability multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, 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.

- **An intellectual disability or epilepsy multigene panel** that includes *GNAI1* and other genes of interest (see Differential Diagnosis) may be considered 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 *GNAI1*-NDD, some panels for intellectual disability and/or epilepsy 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.

Table 1. Molecular Genetic Testing Used in *GNAI1*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
GNAI1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4, 6]

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Muir et al [2021], Wayhelova et al [2022], and 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. To date, no large intragenic deletions/duplications have been reported in individuals with *GNAI1*-NDD.

Clinical Characteristics

Clinical Description

GNAI1-related neurodevelopmental disorder (*GNAI1*-NDD) is characterized by mild-to-profound developmental delay and intellectual disability, hypotonia, neurobehavioral and/or psychiatric manifestations, and epilepsy. To date, at least 26 individuals have been identified with a pathogenic variant in *GNAI1* [Deciphering Developmental Disorders Study 2017, Muir et al 2021, Wayhelova et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports. An additional

approximately eight individuals with a *GNAI1* pathogenic variant have also been reported as part of large cohort studies without phenotypic details [Kosmicki et al 2017, Lim et al 2017, Turner et al 2019, Kaplanis et al 2020, Satterstrom et al 2020, Zhou et al 2022].

Table 2. Select Features of *GNAI1*-Related Neurodevelopmental Disorder

Feature	Proportion of Persons w/Feature	Comment
Developmental delay	26/26	Mild to profound
Hypotonia	22/23	
Intellectual disability	19/19 [1]	Mild to profound
Neurobehavioral/psychiatric manifestations	19/24	Autism, aggression, temper tantrums, hypersensitivity, hand stereotypies
Epilepsy	17/23	Absence, generalized tonic-clonic, focal-onset impaired awareness
Abnormal brain MRI	10/22	Global atrophy, delayed myelination, choroid plexus cysts

Based on Muir et al [2021], Wayhelova et al [2022]
1. One individual with *GNAI1*-related neurodevelopmental disorder who was mosaic for a *GNAI1* pathogenic variant did not have intellectual disability [Muir et al 2021].

Developmental delay has been apparent for all reported individuals with *GNAI1*-NDD. Developmental delays can range from mild to profound, and the majority of individuals have hypotonia. Sitting and walking milestones are often delayed (20/23 and 21/25, respectively), and some individuals have not or do not achieve sitting or walking (5/23 and 9/25, respectively). Speech can be significantly impaired; many individuals use only a few sounds or words, and ~64% (16/25) of individuals reported remain nonverbal. In general, expressive language skills are more impaired than receptive skills.

Intellectual disability. All individuals with *GNAI1*-NDD due to a germline variant have intellectual disability ranging from mild to profound (mild/moderate: n=6; severe/profound: n=13). One affected individual who was mosaic for a *GNAI1* pathogenic variant did not have intellectual disability [Muir et al 2021].

Autism and other neurobehavioral/psychiatric manifestations. Approximately 80% of reported individuals had one of several neurobehavioral or psychiatric manifestations, including autism spectrum disorder (7/21). Common reported neurobehavioral and psychiatric features include stereotypic behaviors (hand flapping, head banging, hand wringing, repetitive noises, teeth grinding, mouthing behaviors), sensory sensitivities, poor eye contact, temper tantrums, anxiety, agitation, aggression, hyperactivity, and attention-deficit/hyperactivity disorder.

Epilepsy. About 74% of individuals with *GNAI1*-NDD have had seizures. Age at seizure onset and seizure types are variable. Use of and response to anti-seizure medications (ASMs) is also variable. Some individuals have intractable epilepsy despite multiple ASMs, while others have seizures that resolve [Muir et al 2021].

- **Seizure onset** typically occurs within the first six months of life (median age of onset is five months), although the earliest seizure onset noted was at 36 hours of life, and the oldest reported onset to date is seven years.
- **Seizure types** that are most common include absence, generalized tonic-clonic, and focal-onset impaired awareness (~5 individuals each). Some seizures are nocturnal.
- **Electroencephalography (EEG)** may show slowing, multifocal activity, other epileptic abnormalities, and encephalopathy. There are no specific EEG findings suggestive of *GNAI1*-related NDD.

Neuroimaging. About half of individuals have abnormal brain MRI imaging. The most common abnormal findings include global atrophy with progressive volume loss, delayed myelination, and choroid plexus cysts.

Musculoskeletal features. Scoliosis has been reported in six individuals. Hip dysplasia was reported in four individuals, with at least two requiring osteotomy.

Feeding. Feeding difficulties can be present, requiring modified diets (e.g., liquid diet) and/or gastrostomy tube feedings. Obesity and insatiable appetite have also been observed (n=7).

Gastrointestinal issues. Some individuals have constipation.

Ophthalmologic involvement. Strabismus has occurred in a few individuals but does not appear to be common.

Facial features. If present, dysmorphic features are nonspecific in individuals with *GNAI1*-NDD.

Prognosis. Information about progression and/or regression of neurologic findings is not known. It is also unknown whether life span in individuals with *GNAI1*-NDD is abnormal; all individuals reported thus far have been children and adolescents. One reported individual is alive at age 18 years [Muir et al 2021], 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.

Prevalence

Fewer than 30 individuals have been reported to have *GNAI1*-NDD. Two large studies provide estimates of the prevalence (0.6 in 100,000) [Gillentine et al 2022] and incidence (1.3 in 100,000) [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 *GNAI1*.

Differential Diagnosis

The phenotypic features associated with *GNAI1*-related neurodevelopmental disorder are not sufficient to diagnose this condition clinically; all disorders with intellectual disability and epilepsy without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with:

- 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

Management

No clinical practice guidelines for *GNAI1*-related neurodevelopmental disorder (*GNAI1*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GNAI1*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *GNAI1*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ASD, anxiety, agitation, aggression, &/or ADHD
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Musculoskeletal	Physical medicine & rehab / PT & OT eval / orthopedics	To incl assessment of: • Gross motor & fine motor skills • Scoliosis • Hip dysplasia • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	• Evaluate height & weight. • Gastroenterology / nutrition / feeding team eval • Assess for constipation.	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval to assess for strabismus	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *GNAI1*-NDD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine 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; *GNAI1*-NDD = *GNAI1*-related neurodevelopmental disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. 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 4).

Table 4. *GNAI1*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral manifestations	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	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]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Feeding issues	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation	
Eyes	Standard treatment of strabismus per ophthalmologist	
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.

ASM = anti-seizure medication; 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.
  - Vision 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 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.

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.

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.

Neurobehavioral/Psychiatric 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 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 summarized in Table 5 are recommended.

Table 5. *GNAI1*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurobehavioral/ Psychiatric	Assess for ASD, anxiety, ADHD, & aggressive or self-injurious behavior.	As needed
Neurologic	• Assess for new seizures. • Monitor those w/known seizures as clinically indicated.	At each visit
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Assess for scoliosis.	
Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	
Gastrointestinal	Monitor for constipation.	
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).	
Transition to adult care	Develop realistic plans for adult life (see American Epilepsy Society Transitions from Pediatric Epilepsy to Adult Epilepsy Care).	Starting by age ~10 yrs

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

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

GNAI1-related neurodevelopmental disorder (*GNAI1*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *GNAI1*-NDD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo* heterozygous or mosaic *GNAI1* pathogenic variant [Muir et al 2021].
- A proband with *GNAI1*-NDD may have the disorder as the result of a pathogenic variant inherited from a parent with germline or somatic and germline mosaicism. In one family reported to date, the proband inherited a *GNAI1* pathogenic variant from a parent who was determined to be mosaic (6% minor allele fraction in DNA extracted from leukocytes) [Muir et al 2021].
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and to inform recurrence risk assessment.
- 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 a *GNAI1* pathogenic variant may theoretically be mildly/minimally affected.

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 known to have the *GNAI1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *GNAI1* 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%-8% because of the possibility of parental germline mosaicism [Myers et al 2018, Muir et al 2021].

Offspring of a proband. Each child of an individual with *GNAI1*-NDD has a 50% chance of inheriting the *GNAI1* pathogenic variant. (There are no reports of individuals with *GNAI1*-NDD who have reproduced; however, many are not yet of reproductive age.)

Other family members. Given that all probands with *GNAI1*-NDD reported to date have the disorder as the result of a *GNAI1* pathogenic variant that occurred *de novo* in the proband or in a mosaic parent, the risk to other family members is presumed to be low.

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 *GNAI1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing is possible. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo GNAI1* pathogenic variant. There is, however, a recurrence risk (~1%-8%) to sibs based on the possibility of parental germline mosaicism [Myers et al 2018, Muir et al 2021]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic 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.

- **American Epilepsy Society**
  aesnet.org
- **Autism Society**
  Phone: 800-328-8476
  Email: info@autism-society.org
  autismsociety.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Child Neurology Foundation**
  Phone: 888-417-3435
  Email: programs@childneurologyfoundation.org
  childneurologyfoundation.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
- **Simons Searchlight Registry**

Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.

Phone: 855-329-5638

Fax: 570-214-7327

Email: coordinator@simonssearchlight.org

simonssearchlight.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. GNAI1-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
GNAI1	7q21.11	Guanine nucleotide-binding protein G(i) subunit alpha-1	GNAI1	GNAI1

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 GNAI1-Related Neurodevelopmental Disorder (View All in OMIM)

139310	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-INHIBITING ACTIVITY POLYPEPTIDE 1; GNAI1
619854	NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, IMPAIRED SPEECH, AND BEHAVIORAL ABNORMALITIES; NEDHISB

Molecular Pathogenesis

GNAI1 encodes guanine nucleotide-binding protein G(i) subunit alpha-1 (Gαi1), which is an inhibitory subunit of G protein complex that can bind GDP and GTP [Neves et al 2002]. When bound to GDP, it forms an inactive heterotrimer with beta (β) and gamma (γ) G protein subunits. Once a G protein-coupled receptor (GPCR) is activated, GDP is exchanged for GTP, causing the α subunit to dissociate from the βγ complex, so that each subunit (α and βγ) is active and can act on downstream signaling pathways [Oldham & Hamm 2008]. Several genes encoding G protein subunits have been implicated in neurodevelopmental disorders and epilepsy [Petrovski et al 2016, Feng et al 2017, Nakamura et al 2013] (see also *GNB1* Encephalopathy).

Gαi1 couples negatively to adenylyl cyclase (AC) to inhibit the production of cyclic adenosine monophosphate (cAMP) with downstream impact on the MAPK/ERK pathway, while their G protein βγ partners mediate the Akt-mTOR and other pathways, which are important in regulation of cell proliferation and growth [Cao et al 2009, Marshall et al 2018].

To date, at least 17 pathogenic variants in *GNAI1* have been identified, including 13 missense variants, three small in-frame deletions of one to four amino acids, and one variant predicted to cause a frameshift that would not be expected to undergo nonsense-mediated decay based on its location. Six missense variants and one coding deletion are recurrent in more than one unrelated individual, and most missense and in-frame deletion variants (10/16) impact residues in the GDP/GTP binding pocket.

Mechanism of disease causation. To date, the impact of reported pathogenic variants on protein function (gain vs loss of function) is not known. Although *GNAI1* is predicted to be intolerant to loss-of-function variants [Muir et al 2021], *de novo* disease-causing truncating variants in *GNAI1* have not yet been identified.

Chapter Notes

Author Notes

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Dr Mefford (heather.mefford@stjude.org) and her team are actively involved in clinical and translational research regarding *GNAI1*-related neurodevelopmental disorder (*GNAI1*-NDD). They would be happy to communicate with persons who have any questions regarding diagnosis of *GNAI1*-NDD or other considerations, such as *GNAI1* variants of uncertain significance.

Revision History

- 1 August 2024 (sw) Review posted live
- 8 September 2023 (hm) Original submission

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