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GNB5-Related Neurodevelopmental Disorder

Synonyms: Intellectual Developmental Disorder with Cardiac Arrhythmia (IDDCA) Syndrome, Language Delay and ADHD / Cognitive Impairment with or without Cardiac Arrhythmia (LADCI)

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Summary

Clinical characteristics

GNB5-related neurodevelopmental disorder (*GNB5*-NDD) is characterized by a spectrum of neurodevelopmental phenotypes that range from severe-to-profound intellectual disability (ID; 31/41 reported individuals), to mild-to-moderate ID (5/41), to normal intellect with severe language disorder (5/41, one extended family). A unique and specific feature of *GNB5*-NDD – regardless of neurodevelopmental phenotype – is nearly universal bradycardia caused by sinoatrial node dysfunction (sick sinus syndrome). Most individuals with severe and profound ID have a developmental and epileptic encephalopathy with focal seizures or epileptic spasms, as well as visual impairment (central or retinal) with nystagmus, difficulty feeding, and gastroesophageal reflux disease. The risk of early mortality is increased.

Diagnosis/testing

The diagnosis of *GNB5*-NDD is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *GNB5* identified by molecular genetic testing.

Management

Treatment of manifestations: Management by multidisciplinary specialists including a general pediatrician, developmental pediatrician, pediatric neurologist, speech-language pathologist, orthopedist, physical medicine

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and rehabilitation specialist, physical therapist, occupational therapist, pediatric ophthalmologist, and pediatric cardiologist is recommended.

Surveillance: Routine follow up by multidisciplinary care providers based on individual needs and circumstances.

Agents/circumstances to avoid: Use parasympathomimetics with extreme caution because of the potential to cause asystole. It is best to avoid other drugs that can potentiate bradycardia, particularly beta blockers.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of at-risk neonates (if prenatal testing was not performed) in order to identify as early as possible those who warrant developmental assessment (and monitoring) and evaluation by a pediatric cardiologist.

Genetic counseling

GNB5-NDD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GNB5* pathogenic variant, each sib of an affected individual has at conception 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 *GNB5* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

This chapter reviews the entire spectrum of neurodevelopmental and arrhythmia phenotypes associated with biallelic *GNB5* pathogenic variants and addresses medically actionable manifestations across the entire phenotypic spectrum for which an individual with a molecular diagnosis of *GNB5*-NDD (regardless of the clinical findings that prompted molecular genetic testing) should be evaluated.

Diagnosis

No consensus clinical diagnostic criteria for *GNB5*-related neurodevelopmental disorder (*GNB5*-NDD) have been published.

Suggestive Findings

GNB5-NDD **should be suspected** in the following two age groups:

- **Infants younger than age six months** with two or more of the following clinical findings:
  - Developmental delay
  - Bradycardia due to sinoatrial node dysfunction (sick sinus syndrome)
  - Hypotonia
  - Visual impairment with nystagmus
  - Seizures (focal seizures, epileptic spasms)
- **Individuals older than age six months** typically with both of the following:
  - Developmental delay / intellectual disability and severe language delay. One exception appears to be an extended family in which severe language delay is not accompanied by intellectual deficits [Shamseldin et al 2016].
  - Bradycardia due to sinoatrial node dysfunction (sick sinus syndrome)

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

Establishing the Diagnosis

The diagnosis of *GNB5*-NDD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *GNB5* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *GNB5* variants of uncertain significance (or identification of one known *GNB5* pathogenic variant and one *GNB5* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *GNB5*-NDD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

An intellectual disability or epilepsy multigene panel that includes *GNB5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *GNB5*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Detectable by Method
GNB5	Sequence analysis [4]	~100% [5]
	Gene-targeted deletion/duplication analysis [6]	~0% [5]

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. One additional individual with homozygous contiguous gene deletions (not included in these calculations) has been reported (see Genetically Related Disorders).
4. 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.
5. Lodder et al [2016], Shamseldin et al [2016], Turkdogan et al [2017], Malerba et al [2018], Vernon et al [2018], Poke et al [2019], Mai et al [2020], Tang et al [2020], Yazdani et al [2020], De Nittis et al [2021]
6. 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

GNB5-related neurodevelopmental disorder (*GNB5*-NDD) is characterized by a spectrum of neurodevelopmental phenotypes that range from severe-to-profound intellectual disability (ID; 31/41 individuals, ~75%), to mild-to-moderate ID (5/41 individuals, ~12%), to normal intellect with severe language disorder (5/41 individuals, from one family, ~12%; see Neurodevelopmental Disorder, **Impaired language development without ID**). A unique and specific feature of *GNB5*-NDD – regardless of neurodevelopmental phenotype – is nearly universal bradycardia caused by sinoatrial node dysfunction (sick sinus syndrome). Most individuals with severe and profound ID have a developmental and epileptic encephalopathy with focal seizures or epileptic spasms, as well as visual impairment (central or retinal) with nystagmus, difficulty feeding, and gastroesophageal reflux disease. The risk of early mortality is increased.

To date, 41 individuals with biallelic *GNB5* pathogenic variants have been identified [Lodder et al 2016, Shamseldin et al 2016, Turkdogan et al 2017, Malerba et al 2018, Vernon et al 2018, Poke et al 2019, Mai et al 2020, Tang et al 2020, Yazdani et al 2020, De Nittis et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports (see Table 2).

Table 2. *GNB5*-Related Neurodevelopmental Disorder: Summary of Select Features

Feature		# of Persons with Feature [1]	Comment
Neurodevelopmental disorder	Severe/profound DD/ID	31/41	
	Mild/moderate DD/ID	5/41	
	Severe language disorder w/o ID	5/41 [2]	
Other neurodevelopmental features	Hypotonia	31/35	Hyporeflexia is common; contractures may develop.
	ASD or ADHD	7/41	
Sinus node dysfunction		27/28	Typically presents w/ bradycardia

Table 2. continued from previous page.

Feature		# of Persons with Feature [1]	Comment
Other features only in individuals w/severe/profound DD/ID	Epilepsy	25/31	
	Nystagmus	25/27	
	Retinopathy	10/16	Confirmed w/ERG
	GERD	14/24	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; ERG = electroretinogram; GERD = gastroesophageal reflux disease; ID = intellectual disability

1. Number of persons with feature out of number of persons assessed for feature

2. Five members of a single family [Shamseldin et al 2016]; see detailed information below in **Impaired language development without ID**.

Neurodevelopmental Disorder

Cognitive outcome is variable. Severe-to-profound ID is seen in ~75%, mild-to-moderate ID in ~12%, and normal intellect with a severe language disorder in ~12% (one family).

Severe-to-profound ID. Children who manifest developmental abnormalities in the first months of life eventually have severe or profound ID. They are often nonambulatory and nonverbal. Developmental regression is rare [Yazdani et al 2020]. Of the children who developed epilepsy, all were delayed before seizure onset. Two children required enteral tube feeding [Poke et al 2019, Yazdani et al 2020].

Mild-to-moderate ID. In the five children reported with mild-to-moderate ID, language development was more affected than motor skills.

Of the three individuals reported by Lodder et al [2016], two sibs (ages 8 and 13 years) were nonverbal, and the younger sib was noted to have impaired fine motor skills; the third individual (age 23 years) had mild ID with no information on verbal skills.

Malerba et al [2018] reported a girl age 2.5 years with a developmental quotient of 50-55; she used sign language and had 12 spoken words. She was reported to be social, curious, and interactive with a high activity level and short attention span.

De Nittis et al [2021] reported a girl age seven years who walked at 31 months and was nonverbal, but used sign language and was considered to have mild ID (a formal neuropsychological assessment was not performed). She was enrolled in a special education class.

Impaired language development without ID. One extended family is reported with five affected children (ages 3-10 years) from three sibships. Children were reported to have normal cognitive function despite severe receptive and expressive language abnormalities [Shamseldin et al 2016]. Two children (ages 5 and 10 years) had IQs of 80 and 110 (Wechsler Intelligence Scale for Children). Two children (ages 3 and 9 years) did not have formal cognitive assessments but clinical assessment was consistent with normal intelligence. Data was lacking for the fifth child. Three of the children had fine motor delay that was less severe than their language problems.

Other Neurodevelopmental Features

Hypotonia and hyporeflexia are common initially and are near universal in children with severe or profound ID. Hypertonia, spasticity, and joint contractures develop in a minority. At least one individual required surgery for hamstring contractures [Author, personal observation].

Attention-deficit/hyperactivity disorder (ADHD) was reported in 3/5 children with language delay but normal IQ; ADHD as assessed by DSM-IV criteria was either hyperactive or inattentive [Shamseldin et al 2016]. Autism or autistic traits were reported in 4/32 with severe-to-profound ID [Turkdogan et al 2017, De Nittis et al 2021].

Sinus Node Dysfunction

The presence or absence of cardiac involvement does not correlate with the level of developmental impairment.

Bradycardia due to sinus node dysfunction (sick sinus syndrome), the most common arrhythmia, may present with cyanosis or apnea, or be asymptomatic and incidentally picked up on EKG. Bradycardia may be identified prenatally [Malerba et al 2018]. In some instances bradycardia was more pronounced during sleep [Lodder et al 2016, Mai et al 2020]. The bradycardia can be extreme, with periods of asystole.

Animal models suggest that *GNB5* is crucial for parasympathetic control of heart rate but not sympathetic control. Hence, heart rates at rest may be very slow (commonly <25 beats per minute), but with preserved positive chronotropic response at times of stress or excitement to rates greater than 150 beats per minute [Lodder et al 2016].

Other arrhythmias rarely reported [Lodder et al 2016, Tang et al 2020]:

- AV block (2 individuals)
- Atrial tachycardia (1 individual)
- Atrial fibrillation (1 individual)
- Sinus tachycardia (1 individual)

Six children had a pacemaker inserted; four had profound ID and two had mild-to-moderate ID [Lodder et al 2016, Malerba et al 2018, Vernon et al 2018, Yazdani et al 2020]. Only two had symptomatic bradycardia [Lodder et al 2016]; however, one child without definite cardiac symptoms was noted to have improved balance and fewer falls after pacemaker insertion [Malerba et al 2018]. The other four had pacemakers inserted due to the length and/or frequency of cardiac pauses on monitoring. When one child's depleted pacemaker battery was not replaced, no adverse cardiac events occurred in the ensuing five years [Yazdani et al 2020].

Epilepsy

Twenty-six individuals had a developmental and epileptic encephalopathy, presenting with developmental delay prior to seizure onset [Lodder et al 2016, Turkdogan et al 2017, Poke et al 2019, Mai et al 2020, Sciacca et al 2020, Tang et al 2020, Yazdani et al 2020, De Nittis et al 2021].

The median age at seizure onset was six months (range: 1 week to 3 years).

In the 16 individuals for whom detailed seizure semiology (i.e., seizure type) was provided, the first seizure type was epileptic spasms in seven, focal motor seizures in seven, and tonic-clonic seizures in two. The most common seizure type overall was epileptic spasms (onset age: 2 months to 3 years), which can occur either at seizure presentation or later.

While EEGs may be normal in the first weeks of life, by age three to six months there is burst suppression or hypsarrhythmia, and by age three years multifocal discharges with background slowing [Poke et al 2019].

Visual Impairment

Visual impairment is common in children with severe-to-profound ID; it has not been reported in children with mild ID.

Nystagmus affects nearly all children with severe-to-profound ID. Both upbeat nystagmus [Vernon et al 2018] and horizontal nystagmus [Mai et al 2020, De Nittis et al 2021] is described. While some children with

nystagmus may have retinopathy or cortical visual impairment [Yazdani et al 2020], others have no retinal disease [De Nittis et al 2021] and normal visual evoked potentials [Mai et al 2020].

Retinopathy in *GNB5*-NDD is due to phototransduction recovery deficit in both rod and cone photoreceptors (bradyopsia) and rod ON-bipolar cell dysfunction [Shao et al 2020]. Abnormal findings on fundoscopy are infrequent. Three individuals were reported with optic atrophy or disc pallor [Poke et al 2019, Yazdani et al 2020, Shao et al 2020] and two sibs with reduced retinal pigmentation [De Nittis et al 2021]. The relative contribution of retinopathy and cortical dysfunction to visual impairment is unclear. Visual impairment may affect other aspects of development.

Strabismus is described in six individuals with severe-to-profound ID and one with moderate ID [Malerba et al 2018, Poke et al 2019, Yazdani et al 2020, De Nittis et al 2021].

Myopic refractive errors, described in two children ages two and three years with severe-to-profound ID, measured -1.5 diopters in the younger child [De Nittis et al 2021] and -2.0/-3.0 diopters in the older [Shao et al 2020].

Gastroesophageal Reflux Disease

Pathologic gastric reflux disease (common in children with severe-to-profound ID) may be severe, resulting in hospitalization and/or bleeding [Yazdani et al 2020]. Only two individuals have required long-term gastrostomy tube feeding: one in infancy for failure to thrive, and the other at age five years due to the increased risk of aspiration [Poke et al 2019, Yazdani et al 2020].

Other

Birth weight is usually normal. Postnatal microcephaly or macrocephaly are uncommon. Limited data on other postnatal growth parameters are available.

Brain imaging is usually normal. Occasionally nonspecific changes including prominent cerebrospinal fluid spaces, cerebral or cerebellar atrophy, and/or a thin corpus callosum are noted [Lodder et al 2016, Vernon et al 2018, Poke et al 2019, Tang et al 2020, De Nittis et al 2021].

Mortality

Three individuals with confirmed pathogenic variants in *GNB5* died in childhood [Poke et al 2019, De Nittis et al 2021]. An additional five untested sibs with similar clinical findings also died in childhood [Turkdogan et al 2017, De Nittis et al 2021].

Age at death, reported in 7/8 individuals, ranged from five months to 13 years; all had severe or profound developmental impairment and epilepsy. Circumstances of death were reported in six of the eight:

- In one family [Turkdogan et al 2017]:
  - A girl age five months died during severe acute gastroenteritis.
  - Her brother and sister died at seven and eight months, respectively, during sleep; death was attributed to sudden unexpected death in epilepsy (SUDEP).
  - Another brother presented to hospital with sinus bradycardia and died with multiorgan failure at age seven years.
- A girl age 13 years died in her sleep, possibly from a cardiac arrhythmia or SUDEP [Poke et al 2019].
- In another child, age not specified, death was attributed to cardiac arrest [De Nittis et al 2021].

No publications mentioned coroners' reports.

Genotype-Phenotype Correlations

Existing literature supports a genotype-phenotype correlation.

Variants predicted to cause protein truncation are associated with a severe neurodevelopmental phenotype. Of 31 individuals with severe or profound ID, 26 were homozygous or compound homozygous for nonsense, frameshift, or splice site variants [Lodder et al 2016, Turkdogan et al 2017, Poke et al 2019, Mai et al 2020, Yazdani et al 2020, De Nittis et al 2021]. Two were compound heterozygous for truncating and missense variants [Vernon et al 2018, Tang et al 2020] and three were homozygous for missense variants that were predicted to disrupt protein binding or folding [De Nittis et al 2021].

Missense variants

- Nine individuals from four families who are homozygous for a recurrent missense variant affecting residue 123 (p.Ser123Leu [Lodder et al 2016, Shamseldin et al 2016] or p.Ser123Trp [De Nittis et al 2021]) have either mild ID or language delay without ID.
- Three individuals homozygous for other missense variants have severe ID [De Nittis et al 2021].
- Three individuals who are compound heterozygous for a missense variant and a truncating variant have moderate-to-profound ID at age ≤2 years [Malerba et al 2018, Vernon et al 2018, Tang et al 2020].

Prevalence

GNB5-NDD is rare. It has been reported in 41 individuals and suspected in five deceased sibs with similar phenotypes who did not have molecular genetic testing.

Parental consanguinity is commonly observed.

Of the 25 reported families, nine (36%) are from India or Pakistan and five (20%) are from northern Africa [Lodder et al 2016, Poke et al 2019, Yazdani et al 2020, De Nittis et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GNB5*.

One child was reported with an approximately 193-kb homozygous contiguous gene deletion of chromosome 15q21.2, involving *GNB5*, *BCL2L10*, and *MYO5C* [Sciacca et al 2020]. His features are consistent with biallelic loss of function of *GNB5,* including severe-to-profound neurodevelopmental impairment (he is nonverbal with only head control at age 8 years). Other features include: sinus bradycardia, more pronounced at night; epileptic spasms from age six months; cortical blindness and retinopathy, with erratic eye movements; severe gastroesophageal reflux disease; mild cerebral and cerebellar atrophy; and features of autonomic nervous system impairment on polysomnography, with periodic breathing, desaturations, and episodic bradypnea.

Differential Diagnosis

Because the phenotypic features associated with *GNB5*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

For children with a phenotype consistent with infantile-onset epileptic encephalopathy, all genes known to be associated with early-infantile epileptic encephalopathy (see OMIM Phenotypic Series) should be included in the differential diagnosis.

Management

No clinical practice guidelines for *GNB5*-related neurodevelopmental disorder (*GNB5*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GNB5*-related neurodevelopmental 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 in Individuals with *GNB5*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of length (or height), weight, head circumference	
Neurologic	By pediatric neurologist	• Full neurologic exam • Brain MRI (if not performed at time of initial eval) • EEG if seizures suspected
DD/ID	Developmental assessment by general or developmental pediatrician / SLP eval / psychology eval	• To examine age-appropriate motor, adaptive, cognitive, & speech/language abilities • Eval for early intervention / special education
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To include assessment of: • Gross motor & fine motor skills • Contractures & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Sinus node dysfunction	By pediatric cardiologist	• To incl 12-lead EKG & 24-hr ambulatory (Holter) EKG • Consider implantation of digital EKG loop recorder, or prolonged event monitor recordings to document or exclude assoc of asystole or other arrhythmias w/seizures. • EKG to exclude structural heart disease (not found to date in this condition)
Eyes/Vision	By pediatric ophthalmologist	To incl assessment of vision, fundus exam
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GNB5*-NDD to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy; MOI = mode of inheritance; SLP = speech-language pathology

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists, including a general pediatrician, developmental pediatrician, pediatric neurologist, speech-language pathologist, orthopedist, physical medicine and rehabilitation specialist, physical therapist, occupational therapist, pediatric ophthalmologist, and pediatric cardiologist is recommended.

Table 4. Treatment of Manifestations in Individuals with *GNB5*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Neurologic	Manage hypo- & hypertonia per normal protocols in local area.	
Seizures	Standardized treatment w/ASMs by experienced neurologist	• Treat epileptic encephalopathy per local guidelines specific for seizure type & epilepsy syndrome. • Education of parents/caregivers [1]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Musculoskeletal & ADL	Orthopedics / physical medicine & rehab / PT & OT	• To incl stretching to help avoid contractures & falls • Consider need for positioning & mobility devices, disability parking placard.
Speech/Language	Speech/language therapy	Augmentative communication devices as appropriate [2]
Sinus node dysfunction	Pacing can be considered for symptomatic bradycardia or asystole.	Cardiac pacing only to prevent potentially life-threatening or symptomatic sinus bradycardia, pauses, or asystole; current evidence suggests affected persons have normal chronotropic responses.
Eyes/Vision	Standard treatment(s) per ophthalmologist	Community vision services through early intervention or school district
Poor weight gain / Failure to thrive	• 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
Family support & resources	• 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.

ADL = activities of daily living; ASMs = anti-seizure medications; DD = developmental delay; ID = intellectual disability; 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.

2. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. Augmentative and alternative 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.

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-language pathology (SLP) 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.

Surveillance

Table 5. Recommended Surveillance for Individuals with *GNB5*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Constitutional	Assess linear growth & weight gain.	At each pediatric visit
Neurologic	Assess: • Seizure type & frequency; • ASM side effects.	As required based on seizure frequency & side effects of ASMs
DD/ID	Monitor developmental progress & educational needs.	At each pediatric visit

Table 5. continued from previous page.

System/Concern		Evaluation	Frequency
Speech/Language		Assess effectiveness of current interventions & need for AAC methods.	According to local resource availability
Musculoskeletal & ADL		Physical medicine, OT/PT assessment of mobility, self-help skills	
Sinus node dysfunction	**For those w/known arrhythmic syncope**		Pacing clinic follow up if paced (usually every 6 mos)
	For those w/o known arrhythmic syncope	• Monitor for history suggestive of arrhythmic syncope. • EKG & Holter recordings • Use of event monitors incl implantable loop recorders may help establish whether or not pauses are assoc w/or causative of syncope or seizure activity.	3-6 mo follow up in infancy, ↓ to annual depending on severity of bradycardia
Eyes/Vision		Per treating ophthalmologist / vision specialist	Per treating ophthalmologist / vision specialist
Gastrointestinal/Feeding		Eval of nutritional status & safety of oral intake	At each pediatric visit
Family support & resources		Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

AAC = augmentative and alternative communication; ADL = activities of daily living; ASM = anti-seizure medication

Agents/Circumstances to Avoid

Parasympathomimetics, which should be used with extreme caution because of the potential to cause asystole, are generally only used in the context of general anesthesia or treatment of glaucoma. Access to possible emergent pacing during general anesthesia would be advisable; however, a favorable response to isoprotenerol or epinephrine would be expected [Lodder et al 2016].

Other drugs that can potentiate bradycardia, particularly beta blockers, are best avoided.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk neonates (if prenatal testing was not performed) in order to identify as early as possible those with biallelic *GNB5* pathogenic variants, who should:

- Undergo developmental assessment and monitoring;
- Be referred to a pediatric cardiologist.

Screening in the first days should at least include an EKG and 24-hour Holter recording, repeated periodically thereafter during childhood unless molecular genetic testing demonstrates that the individual has not inherited the biallelic *GNB5* pathogenic variants identified in the proband.

Likewise, it is appropriate to clarify the genetic status of sibs of a proband with mild developmental delay in order to identify as early as possible those with biallelic *GNB5* pathogenic variants who would therefore benefit from cardiac monitoring.

Clarification of genetic status is presumed to be unnecessary for older developmentally normal sibs of a proband with a severe neurodevelopmental phenotype because of phenotypic similarity in affected sibs in all multiplex families reported to date: older developmentally normal sibs of severely affected probands are unlikely to be affected. However, genetic testing for confirmation and reassurance may be offered.

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

GNB5-related neurodevelopmental disorder (*GNB5*-NDD) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *GNB5* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GNB5* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017, Tang et al 2020];
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *GNB5* pathogenic variant, each sib of an affected individual has at conception 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.
- Sibs who inherit biallelic *GNB5* pathogenic variants are expected to have clinical manifestations of *GNB5*-NDD similar to those of the proband (see Genotype-Phenotype Correlations and Management, Evaluation of Relatives at Risk).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has *GNB5*-NDD or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *GNB5*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GNB5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GNB5* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *GNB5* 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.

- **American Heart Association**
  Bradycardia: Slow Heart Rate
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability

- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  www.epilepsy.ca
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **MedlinePlus**
  Intellectual Disability
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page

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. GNB5-Related Neurodevelopmental Disorder : Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
GNB5	15q21.2	Guanine nucleotide-binding protein subunit beta-5	GNB5	GNB5

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 GNB5-Related Neurodevelopmental Disorder (View All in OMIM)

604447	GUANINE NUCLEOTIDE-BINDING PROTEIN, BETA-5; GNB5
617173	LODDER-MERLA SYNDROME, TYPE 1, WITH IMPAIRED INTELLECTUAL DEVELOPMENT AND CARDIAC ARRHYTHMIA; LDMLS1
617182	LODDER-MERLA SYNDROME, TYPE 2, WITH DEVELOPMENTAL DELAY AND WITH OR WITHOUT CARDIAC ARRHYTHMIA; LDMLS2

Molecular Pathogenesis

GNB5 encodes guanine nucleotide-binding protein subunit beta-5 (Gβ5). Although widely expressed, it is predominantly expressed in brain [Jones et al 1998]. Gβ5 dimerizes with proteins in the R7 subfamily of regulators of G-protein signaling, thereby downregulating central nervous system G-protein signaling [Sondek & Siderovski 2001]. Knockout mice exhibit impaired growth, sinoatrial node dysfunction, hyperactivity, and early mortality [Xie et al 2012] (see Mouse Genome Database). Knockout zebrafish have impaired neurologic, cardiac, and retinal function [Lodder et al 2016].

Mechanism of disease causation. Loss of function

Table 6. Notable *GNB5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_016194.4 NP_057278.2	c.348_352delTAAGA	p.Asp116GlufsTer52	Recurrent variant reported in 2 northern European families [Malerba et al 2018, Vernon et al 2018]
	c.262delG	p.(Glu88ArgfsTer8)	Recurrent variant reported in 2 families from Cambodia & China [Poke et al 2019, Mai et al 2020]
	c.368C>T	p.Ser123Leu	Lodder et al [2016], Shamseldin et al [2016], Malerba et al [2018]; see Genotype-Phenotype Correlations.
	c.368C>G	p.Ser123Trp	De Nittis et al [2021]; see Genotype-Phenotype Correlations.
	c.1032C>G	p.(Tyr344Ter)	Recurrent variant reported in 6 families from India & Pakistan [Lodder et al 2016, Poke et al 2019, De Nittis et al 2021]
	c.1032C>A	p.(Tyr344Ter)	Recurrent variant reported in 2 families from Pakistan [Poke et al 2019, Yazdani et al 2020]; *de novo* in 1 family [Tang et al 2020]

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.

Chapter Notes

Author Notes

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Jonathan R Skinner is a paediatric electrophysiologist and genetic cardiologist. His main research interests include a focus on preventing young sudden death through the detection and management of – and translational research into – inherited cardiac conditions. See www.cidg.org.nz.

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Revision History

- 9 September 2021 (gp) Revision: nucleotide variant correction: c.348_352delTAAGA
- 26 August 2021 (bp) Review posted live
- 19 March 2021 (gp) Initial submission

References

Literature Cited

De Nittis P, Efthymiou S, Sarre A, Guex N, Chrast J, Putoux A, Sultan T, Raza Alvi J, Ur Rahman Z, Zafar F, Rana N, Rahman F, Anwar N, Maqbool S, Zaki MS, Gleeson JG, Murphy D, Galehdari H, Shariati G, Mazaheri N, Sedaghat A, Lesca G, Chatron N, Salpietro V, Christoforou M, Houlden H, Simonds WF,

Pedrazzini T, Maroofian R, Reymond A, et al. Inhibition of G-protein signalling in cardiac dysfunction of intellectual developmental disorder with cardiac arrhythmia (IDDCA) syndrome. J Med Genet. 2021;58:815–31. PubMed PMID: 33172956.

Jones PG, Lombardi SJ, Cockett MI. Cloning and tissue distribution of the human G protein β5 cDNA. Biochim Biophys Acta. 1998;1402:288–91. PubMed PMID: 9606987.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Lodder EM, De Nittis P, Koopman CD, Wiszniewski W, Moura de Souza CF, Lahrouchi N, Guex N, Napolioni V, Tessadori F, Beekman L, Nannenberg EA, Boualla L, Blom NA, de Graaff W, Kamermans M, Cocciadiferro D, Malerba N, Mandriani B, Akdemir ZHC, Fish RJ, Eldomery MK, Ratbi I, Wilde AAM, de Boer T, Simonds WF, Neerman-Arbez M, Sutton VR, Kok F, Lupski JR, Reymond A, Bezzina CR, Bakkers J, Merla G. GNB5 mutations cause an autosomal-recessive multisystem syndrome with sinus bradycardia and cognitive disability. Am J Hum Genet. 2016;99:704–10. PubMed PMID: 27523599.

Mai JH, Ou ZH, Chen L, Duan J, Liao JX, Han CX. Intellectual developmental disorder with cardiac arrhythmia syndrome in a family caused by GNB5 variation and literature review. Zhonghua Er Ke Za Zhi. 2020;58:833–7. PubMed PMID: 32987464.

Malerba N, Towner S, Keating K, Squeo GM, Wilson W, Merla G. A NGS-targeted autism/ID panel reveals compound heterozygous GNB5 variants in a novel patient. Front Genet. 2018;9:626. PubMed PMID: 30631341.

Poke G, King C, Muir A, de Valles-Ibanez G, Germano M, Moura de Souza CF, Fung J, Chung B, Fung CW, Mignot C, Ilea A, Keren B, Vermersch AI, Davis S, Stanley T, Moharir M, Kannu P, Shao Z, Malerba N, Merla G, Mefford HC, Scheffer IE, Sadleir LG. The epileptology of GNB5 encephalopathy. Epilepsia. 2019;60:e121–e7. PubMed PMID: 31631344.

Sciacca FL, Ciaccio C, Fontana F, Strano C, Gilardoni F, Pantaleoni C, D'Arrigo S. Severe Phenotype in a patient with homozygous 15q21.2 microdeletion involving BCL2L10, GNB5, and MYO5C genes, resembling infantile developmental disorder with cardiac arrhythmias (IDDCA). Front Genet. 2020;11:399. PubMed PMID: 32477400.

Shamseldin HE, Masuho I, Alenizi A, Alyamani S, Patil DN, Ibrahim N, Martemyanov KA, Alkuraya FS. GNB5 mutation causes a novel neuropsychiatric disorder featuring attention deficit hyperactivity disorder, severely impaired language development and normal cognition. Genome Biol. 2016;17:195. PubMed PMID: 27677260.

Shao Z, Tumber A, Maynes J, Tavares E, Kannu P, Heon E, Vincent A. Unique retinal signaling defect in GNB5-related disease. Doc Ophthalmol. 2020;140:273–7. PubMed PMID: 31720979.

Sondek J, Siderovski DP. Gγ-like (GGL) domains: new frontiers in G-protein signaling and β-propeller scaffolding. Biochem Pharmacol. 2001;61:1329–37. PubMed PMID: 11331068.

Tang M, Wang Y, Xu Y, Tong W, Jin D, Yang XA. IDDCA syndrome in a Chinese infant due to GNB5 biallelic mutations. J Hum Genet. 2020;65:627–31. PubMed PMID: 32203251.

Turkdogan D, Usluer S, Akalin F, Agyuz U, Aslan ES. Familial early infantile epileptic encephalopathy and cardiac conduction disorder: a rare cause of SUDEP in infancy. Seizure. 2017;50:171–2. PubMed PMID: 28697420.

Vernon H, Cohen J, De Nittis P, Fatemi A, McClellan R, Goldstein A, Malerba N, Guex N, Reymond A, Merla G. Intellectual developmental disorder with cardiac arrhythmia syndrome in a child with compound heterozygous GNB5 variants. Clin Genet. 2018;93:1254–6. PubMed PMID: 29368331.

Xie K, Ge S, Collins VE, Haynes CL, Renner KJ, Meisel RL, Lujan R, Martemyanov KA. Gβ5-RGS complexes are gatekeepers of hyperactivity involved in control of multiple neurotransmitter systems. Psychopharmacology. 2012;219:823–34. PubMed PMID: 21766168.

Yazdani S, Badjatiya A, Dorrani N, Lee H, Grody WW, Nelson SF, Dipple KM. Genetic characterization and long-term management of severely affected siblings with intellectual developmental disorder with cardiac arrhythmia syndrome. Mol Genet Metab Rep. 2020;23:100582. PubMed PMID: 32280589.

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