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NLM Citation: Revah-Politi A, Sands TT, Colombo S, et al. *GNB1* Encephalopathy. 2020 Mar 5 [Updated 2021 Apr 15]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

GNB1 Encephalopathy

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Created: March 5, 2020; Revised: April 15, 2021.

Summary

Clinical characteristics

GNB1 encephalopathy (*GNB1*-E) is characterized by moderate-to-severe developmental delay / intellectual disability, structural brain abnormalities, and often infantile hypotonia and seizures. Other less common findings include dystonia, reduced vision, behavior issues, growth delay, gastrointestinal (GI) problems, genitourinary (GU) abnormalities in males, and cutaneous mastocytosis.

Diagnosis/testing

The diagnosis of *GNB1* encephalopathy (*GNB1*-E) is established in a proband by identification of a heterozygous *GNB1* pathogenic variant by molecular genetic testing.

Management

Treatment of manifestations: Developmental delay / intellectual disability, hypotonia, seizures, poor vision, behavior issues, growth delay, GI problems, GU abnormalities in males, and cutaneous mastocytosis are managed as per standard care.

Surveillance: Follow up of the common manifestations at each clinic visit.

Genetic counseling

GNB1-E is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant. If the *GNB1* pathogenic variant identified in the proband is not identified in one of the parents, the risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *GNB1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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Diagnosis

Formal diagnostic criteria for *GNB1* encephalopathy have not been established.

Suggestive Findings

GNB1 encephalopathy (*GNB1*-E) **should be considered** in individuals with the following clinical findings.

Clinical findings

- Moderate to profound developmental delay (DD) or intellectual disability (ID); AND
- One or more of the following features presenting in infancy or childhood:
  - Generalized hypotonia of infancy that can evolve to hypertonia and spasticity
  - Feeding disorder and difficulties with weight gain in infancy
  - Movement disorder (dystonia, tics, ataxia, and chorea)
  - Epilepsy (including generalized, focal, and mixed epilepsy and infantile spasms)
  - Behavior problems (repetitive and stereotypic behaviors, attention-deficit/hyperactivity disorder [ADHD], and/or autism spectrum disorder [ASD])
  - Macrocephaly
  - Slow growth
  - Vision impairment (optic atrophy and cortical visual impairment) and/or abnormal eye movements (strabismus, nystagmus)
  - Gastrointestinal issues (chronic constipation, cyclic vomiting, gastroesophageal reflux disease [GERD], and/or abdominal distention with cramps)
  - Craniofacial anomalies (cleft palate, craniosynostosis)

  Note: When present, dysmorphic features are nonspecific.

Establishing the Diagnosis

The diagnosis of *GNB1* encephalopathy (*GNB1*-E) **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *GNB1* on molecular genetic testing (see Table 1). Note: 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.

Step 1

Molecular genetic testing in any child with DD or an older individual with ID typically begins with chromosomal microarray analysis (CMA), which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications that cannot be detected by sequence analysis.

Step 2

If CMA is not diagnostic, the next step is typically either a multigene panel or comprehensive genomic testing (exome sequencing or genome sequencing). Note: Single-gene testing (sequence analysis of *GNB1,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended, given the difficulty in suspecting the diagnosis of *GNB1*-E based on clinical features alone.

- **An intellectual disability multigene panel** that includes *GNB1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause in a person with a nondiagnostic CMA

while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of *GNB1* encephalopathy, some panels for intellectual disability 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 this disorder an intellectual disability multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not. If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by exome sequencing. Note: To date only one intragenic gene deletion has been reported (see Molecular Genetics).

  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 *GNB1* Encephalopathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
GNB1	Sequence analysis [4]	57/58 [5]
	Gene-targeted deletion/duplication analysis [6]	1/58 [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Individuals with contiguous gene deletions, including 1p36 microdeletion, are not included in these calculations (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. Petrovski et al [2016], Steinrücke et al [2016], Brett et al [2017], Lohmann et al [2017], Hemati et al [2018], Peng et al [2018], Szczałuba et al [2018], Jones et al [2019], Endo et al [2020], Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER - Firth et al [2009])
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.
7. One individual with an intragenic deletion spanning exons 2-5 of *GNB1* is reported in the DECIPHER database [Firth et al 2009]. Limited clinical information is available on this individual. See Molecular Genetics for additional information.

Clinical Characteristics

Clinical Description

GNB1 encephalopathy (*GNB1*-E) is characterized by developmental delay / intellectual disability, structural brain abnormalities, and often infantile hypotonia and seizures. Other less common findings include dystonia, reduced vision, behavior issues, growth delay, gastrointestinal problems, genitourinary abnormalities in males, and cutaneous mastocytosis.

To date, 58 individuals have been identified with *GNB1*-E caused by a heterozygous *GNB1* pathogenic variant [Firth et al 2009, Petrovski et al 2016, Steinrücke et al 2016, Brett et al 2017, Lohmann et al 2017, Hemati et al 2018, Peng et al 2018, Szczałuba et al 2018, Jones et al 2019, Endo et al 2020]. Of note, one individual with a milder phenotype was mosaic for a *GNB1* pathogenic variant [Hemati et al 2018]. The following description of the phenotypic features associated with *GNB1*-E is based on these reports.

Table 2. Selected Clinical Manifestations of *GNB1* Encephalopathy

Manifestation		Frequency (%) [1]
Developmental delay		57/57 (100%)
Intellectual disability		35/47 (74%)
Abnormal muscle tone		41/52 (79%)
Abnormal brain MRI		25/50 (50%)
Epilepsy		27/51 (53%)
Movement disorder	Dystonia	11/50 (22%)
	Other movement disorders	7/50 (14%)
Sensory impairment	Abnormal vision	31/52 (60%)
	Sensorineural hearing loss	3/47 (6%)
Behavior issues		15/36 (42%)
Growth delay (height & weight < −2 SD)		10/49 (20%)
Gastrointestinal problems		12/19 (63%)
Genitourinary anomalies in males		6/17 males (35%)
Macrocephaly (OFC > +2 SD)		9/40 (22%)
Microcephaly (OFC < −2 SD)		3/40 (7%)
Cardiovascular defects		2/18 (11%)
Cutaneous mastocytosis		4/34 (12%)
Craniofacial anomalies	Cleft palate	5/58 (9%)
	Craniosynostosis	3/13 (23%)

OFC = occipital frontal circumference

1. Frequency = # of persons with the manifestation / # of persons examined for this specific manifestation

Developmental delay (DD) and intellectual disability (ID). Moderate-to-severe DD has been reported in almost all individuals with *GNB1* variants. Severe neurodevelopmental deficit, marked by an inability to walk independently, has been reported in about 50% of individuals. Of note, one individual started walking independently at age nine years following intensive physical therapy. Hemiplegia, severe dyskinetic quadriplegia, and spastic diplegia have each been reported in one individual [Petrovski et al 2016, Endo et al 2020].

Speech delay is common; about 40% of individuals are nonverbal. Of note, in two individuals with normal hearing, alternative means of communication (such as sign language) improved communication.

Developmental regression was documented in three individuals. One became visually inattentive, hypotonic, and lethargic at age eight weeks, and had further developmental regression with the onset of infantile spasms at age seven months. Two others had regression of verbal skills by age three years [Petrovski et al 2016].

ID, ranging from mild to severe, has been reported in about 74% of individuals. ID was not reported in two individuals older than age six years [Lohmann et al 2017]. Of note, several individuals with *GNB1* variants were too young at the time of publication to have an informative assessment of cognitive function, and cognitive abilities were not consistently documented in older individuals.

The presence or absence of DD and ID was not documented in one individual in the DECIPHER database [Firth et al 2009] or in the four reported parents with *GNB1* variants [Firth et al 2009, Lohmann et al 2017].

Abnormal brain MRI findings include abnormal or delayed myelination, abnormal corpus callosum, cerebral volume loss, ventriculomegaly, and bilateral polymicrogyria.

Abnormal muscle tone. Generalized hypotonia of infancy can evolve into hypertonia and spasticity over time.

Epilepsy. Seizure types can include tonic, absence, myoclonic, generalized tonic-clonic, and focal seizures, as well as epileptic spasms. Importantly, *GNB1* has been identified as a candidate gene for West syndrome [Peng et al 2018], and several individuals with *GNB1*-E have had West syndrome or infantile spasms [Hemati et al 2018, Endo et al 2020].

EEG may be normal in the first years of life. Hypsarrhythmia, generalized epileptiform discharges or multifocal epileptiform discharges (especially from the temporal regions) may develop and become abundant in sleep.

Movement disorders. Dystonia, the most common movement disorder reported, ranges in severity from mild dystonic positioning of the fingers to generalized dystonia. Myoclonus-dystonia and occasional status dystonicus with dystonic hypertonia have each been reported in one individual [Jones et al 2019, Endo et al 2020]. Tics, ataxia, and chorea have also been seen.

Sensory impairment

- **Vision.** Nystagmus is the most common ophthalmologic finding, reported in 36% of individuals. Nystagmus can be horizontal and vertical, rotatory, and multivectorial; it has been reported to improve with age in two individuals [Hemati et al 2018]. Other eye movement abnormalities include strabismus, upward gaze palsy, gaze deviation, slow ocular pursuit response, continuous reverse ocular dipping, and ophthalmoplegia.

  Abnormal vision due to cortical visual impairment or optic atrophy has been reported in 11% of individuals, including one individual considered to be legally blind. Ocular albinism and possible rod-cone dystrophy were each observed once [Hemati et al 2018]; neither individual was reported to have other genetic variants that could explain these findings.

- **Hearing.** Severe sensorineural hearing loss, both unilateral and bilateral, has been reported. One individual had hypoplasia of the right cochlear nerve in addition to profound sensorineural hearing loss of the right ear; another had both conductive and severe sensorineural hearing loss [Hemati et al 2018].

Behavior issues include repetitive and stereotypic behaviors, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD).

Growth. Poor feeding and poor weight gain in the neonatal period have been reported in about 50% of individuals with *GNB1*-E with a documented neonatal history. Of these, most (8/11) outgrew their feeding difficulties and poor weight gain. Overall, persistent growth delay was reported in 20% of individuals.

Other associated features (inconsistently documented in publications):

- **Gastrointestinal problems.** Recurrent constipation, cyclic vomiting, gastroesophageal reflux disease, hepatic vein anomaly, and distended abdomen with cramps
- **Genitourinary abnormalities in males.** Undescended testes, bifid scrotum, duplicated renal collecting system, and hydronephrosis, each observed in fewer than three individuals.
- **Cardiovascular abnormalities.** Ventricular septal defect, duplicated superior vena cava
- **Craniofacial anomalies.** Cleft palate has been reported in five individuals [Petrovski et al 2016, Brett et al 2017, Hemati et al 2018]. Craniosynostosis was reported in three individuals [Lohmann et al 2017]. Both macrocephaly and microcephaly have been reported. When present, other dysmorphic features are nonspecific.
- **Cutaneous mastocytosis,** a condition in which apparently normal mast cells accumulate in the skin, was reported in four infants, including monozygotic twins [Hemati et al 2018, Szczałuba et al 2018]. Urticaria pigmentosa is the most common presentation of mastocytosis. Cutaneous mastocytosis in children younger than age five years is generally benign, requires no treatment, and can disappear by puberty; however, in rare instances it can progress to systemic mastocytosis which can affect almost all organs [Theoharides et al 2015]. Note: While gain-of-function variants in c-KIT have been observed in cutaneous mastocytosis, exome sequencing on fibroblasts from the monozygotic twins with *GNB1*-E with mastocytosis did not identify any additional potentially causative variants or regions of loss of heterozygosity. No somatic variants in *KIT* or *JAK2* were detected [Hemati et al 2018].
- **Hypothyroidism.** Congenital peripheral hypothyroidism and subclinical hypothyroidism have each been reported once [Petrovski et al 2016, Szczałuba et al 2018]. The true incidence of hypothyroidism is not known.
- **Malignancy.** Acute lymphoblastic leukemia has been reported in one individual with a *de novo* germline *GNB1* pathogenic variant [Brett et al 2017]. Because somatic *GNB1* pathogenic variants affecting the same residues have been detected in individuals with hematologic malignancies [Yoda et al 2015], the possible association of germline *GNB1* pathogenic variants and an increased risk for malignancies has been raised [Petrovski et al 2016].

Prognosis. Regression of skills has been documented in only a few individuals with *GNB1*-E. Life expectancy and common causes of death are not known, as most individuals reported are children or young adults. Of note, the cause of death in a child who died at age four years was unknown [Hemati et al 2018].

Although an increased risk for malignancies has been suggested [Petrovski et al 2016], acute lymphoblastic leukemia has been reported in only one individual with a germline *GNB1* variant [Brett et al 2017].

The absence of congenital anomalies associated with high morbidity and mortality suggests a favorable long-term prognosis with appropriate support and management. The authors are aware of three individuals with *GNB1*-E older than age 18 years reported in the medical literature [Firth et al 2009, Petrovski et al 2016], as well as a 38 year old [unpublished]. In addition, four parents with a *GNB1* variant have been reported [Firth et al 2009, Lohmann et al 2017], 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 under-recognized and under-reported.

Genotype-Phenotype Correlations

Many recurrent *GNB1* variants have been associated with phenotypic variability among individuals with the same variant. Although not conclusive, the following genotype-phenotype correlations have been proposed:

- Fifty-five percent of individuals with dystonia had a p.Ile80 substitution (p.Ile80Thr or p.Ile80Asn). This possible genotype-phenotype correlation was initially suggested by Petrovski et al [2016].
- Three of the four individuals with cutaneous mastocytosis had the p.Ile80Thr variant [Hemati et al 2018].
- A genotype-phenotype correlation between the p.Ile80Thr variant and severe axial hypotonia or hypotonic quadriplegia has been suggested [Endo et al 2020].

Penetrance

Most probands reported to date with *GNB1*-E whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo* *GNB1* pathogenic variant. Penetrance is expected to be 100%.

Prevalence

Fifty-eight individuals with *GNB1*-E caused by a heterozygous pathogenic *GNB1* variant have been reported to date.

No increased prevalence of *GNB1* encephalopathy has been reported in any specific population or ethnic group. No founder variants are known.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GNB1*.

Chromosome 1p36 deletion. *GNB1* can be deleted in individuals with chromosome 1p36 deletion (OMIM 607872), the phenotype of which includes developmental delay / intellectual disability, hypotonia, seizures, structural brain anomalies, congenital heart defects, eye/vision problems, hearing loss, skeletal anomalies, genitourinary anomalies, and typical craniofacial features.

Sporadic malignancies (including hematopoietic, lymphoid, kidney, bladder, skin, and others) occurring as single tumors in the absence of any other findings of *GNB1* encephalopathy frequently harbor somatic variants in *GNB1* that are **not** present in the germline [Yoda et al 2015]. In these circumstances predisposition to these tumors is not heritable. For more information see Cancer and Benign Tumors.

Differential Diagnosis

Because the phenotypic features associated with *GNB1* encephalopathy are not sufficient to diagnose this condition clinically, all disorders with intellectual disability and/or seizures without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series:

- Autosomal Dominant Intellectual Developmental Disorder
- Autosomal Recessive Intellectual Developmental Disorder
- Nonsyndromic X-Linked Intellectual Developmental Disorder
- Syndromic X-Linked Intellectual Developmental Disorder
- Epileptic Encephalopathy, Early Infantile

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GNB1* encephalopathy, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *GNB1* Encephalopathy

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	To incl: • Brain MRI • EEG incl sleep study to characterize any recurrent abnormal episodes & to evaluate for subtle or subclinical seizures & epileptic encephalopathy
Development	Developmental assessment	To incl: • Motor, adaptive, cognitive, & speech/language evaluation • Evaluation for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	In individuals age >12 mos: screen for behavior problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility & activities of daily living & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl evaluation of aspiration risk & nutritional status • Assess for history of recurrent constipation, cyclic vomiting, gastroesophageal reflux disease, & distended abdomen w/cramps. • Consider evaluation for gastric tube placement in those w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	Assess for ↓ vision, abnormal ocular movement, strabismus.
Hearing	Audiologic eval	Assess for hearing loss.
Cardiovascular	Echocardiogram	Assess for congenital heart disease.
Genitourinary	Renal ultrasound exam	Assess for renal anomalies incl duplicated collecting system.
Craniofacial anomalies	Clinical eval	Assess for palatal anomalies & craniosynostosis.
Skin	Skin exam for cutaneous mastocytosis	If lesions are present, referral to dermatologist for: • Confirmation of diagnosis • Recommendations for trigger avoidance • Photographs for serial monitoring • Treatment recommendations
Endocrine/Thyroid	Thyroid panel (incl TSH, T3, &T4 levels)	To evaluate for hypothyroidism

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Hematologic/ Malignancy	CBC	To evaluate for hematologic malignancies
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports/resources	Assess need for: • Community or online resources such as Parent To Parent; • Social work involvement for parental support; • Home nursing referral.

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

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *GNB1* Encephalopathy

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASMs by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
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 if clinical signs/ symptoms of dysphagia
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices; disability parking placard.
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist	Community vision services through early intervention or school district
Cortical visual impairment	No specific treatment; early intervention to help stimulate visual development	
Hearing	Hearing aids may be helpful; per otolaryngologist	Community hearing services through early intervention or school district
Palatal anomalies &/or craniosynostosis	Standardized treatment as recommended by craniofacial team	
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents or laxatives as needed
Dystonia	Standardized treatment per neurologist	Deep brain stimulation was effective in 1 person w/ myoclonus-dystonia. [2]
Cutaneous mastocytosis	Standardized treatment(s) & management per dermatologist	• Avoid substances & environments that may provoke mast cell activation. • Standard treatment, incl non-sedating & longer-acting histamine (H1)-receptor antagonists to treat common symptoms [3]

Table 4. continued from previous page.

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

ASM = anti-seizure medication; 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. Jones et al [2019]

3. Theoharides et al [2015]

Developmental Delay / Intellectual Disability Management Issues

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 and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

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

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

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 by 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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is 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

Table 5. Recommended Surveillance for Individuals with *GNB1* Encephalopathy

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Evaluation of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for recurrent constipation, cyclic vomiting, gastroesophageal reflux, & distended abdomen w/cramps.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Hematologic	• CBC to monitor for hematologic malignancies • Education of family re early clinical signs of hematologic malignancies (e.g., easy bruising due to thrombocytopenia)	Every 6 mos - yr
Skin	Dermatologic evaluation to monitor for development of mastocytosis	At each visit
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing; other local resources) & care coordination.	

CBC = complete blood count; 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

GNB1 encephalopathy (*GNB1*-E) is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *GNB1*-E whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GNB1* pathogenic variant.
- Rarely, individuals diagnosed with *GNB1*-E have inherited a *GNB1* pathogenic variant from a parent. Three unrelated ethnically diverse individuals were reported to have inherited the p.Arg96Leu variant from a parent [Lohmann et al 2017] and one individual inherited the p.Thr243Ala variant from her mother [Firth et al 2009]. Clinical information on parents was not available.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *GNB1* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of parental germline mosaicism have been reported to date.
- Note: A parent with somatic and germline mosaicism for a *GNB1* pathogenic variant may 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 has the *GNB1* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the proband represents a simplex case (i.e., the only affected family member) and the *GNB1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be greater than that of the general population because of the theoretic possibility of parental mosaicism. In a study assessing mosaicism in the apparently asymptomatic parents of children with developmental and epileptic encephalopathy, the frequency of parental somatic and (inferred) germline mosaicism was found to be 10% [Myers et al 2018].

Offspring of a proband. Each child of an individual with *GNB1*-E has a 50% chance of inheriting the *GNB1* pathogenic variant.

Other family members. Given that most probands with *GNB1*-E reported to date have the disorder as a result of a *de novo GNB1* pathogenic variant, 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

If neither parent has a *GNB1* pathogenic variant, the risk to future pregnancies is presumed to be low as the proband most likely has a *de novo GNB1* pathogenic variant. There is, however, a recurrence risk to sibs based on the theoretic possibility of parental germline mosaicism [Myers et al 2018]. Given this risk, prenatal testing and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **GNB1 Foundation**

  www.gnb1.org

- **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

- **MedlinePlus**

  Intellectual Disability

- **VOR: Speaking out for people with intellectual and developmental disabilities**

  Phone: 877-399-4867

  Email: info@vor.net

  www.vor.net

- **Human Disease Genes Website Series - Registry**

  Parents and physicians can submit clinical information on newly diagnosed individuals to the GNB1 Human Disease Genes Website.

  This resource was established to clarify the clinical phenotype associated with pathogenic variants in the complete coding region of GNB1 and to facilitate research into the underlying mechanism of GNB1 encephalopathy.

  GNB1

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. GNB1 Encephalopathy: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
GNB1	1p36.33	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1	GNB1	GNB1

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 GNB1 Encephalopathy (View All in OMIM)

139380	GUANINE NUCLEOTIDE-BINDING PROTEIN, BETA-1; GNB1
616973	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 42; MRD42

Molecular Pathogenesis

Heterotrimeric G protein complexes function as cellular signal transducers for G protein-coupled receptors (GPCRs). They are composed of an alpha (Gα), a beta (Gβ), and a gamma subunit (Gγ). GPCR activation catalyzes a GDP-to-GTP exchange on the Gα subunit, leading to the dissociation of Gα from the obligate dimer Gβγ. Both Gα and Gβγ then bind and regulate a wide variety of downstream effectors.

GNB1 encodes the guanine nucleotide-binding protein subunit beta-1(Gβ1). Effectors of Gβγ include ion channels, phospholipases, adenylyl cyclases, and PI3K and MAPK signaling pathways [Smrcka 2008, Khan et al 2013, Khan et al 2016]. A bioluminescence resonance energy transfer (BRET) assay has been used to test the functional consequence of disease-associated *GNB1* missense variants [Lohmann et al 2017].

Mechanism of disease causation. The mechanism of disease in *GNB1*-E is not fully understood. Most reported variants are missense variants [Firth et al 2009, Petrovski et al 2016, Steinrücke et al 2016, Brett et al 2017, Lohmann et al 2017, Hemati et al 2018, Szczałuba et al 2018, Jones et al 2019, Endo et al 2020] with specific properties:

- Recurrent missense changes
- The vast majority of those tested occurred *de novo.*
- Thirty different missense variants have been reported so far, with 73% of these occurring in exons 6 and 7 (NM_002074.4). The most common variant reported to date is Ile80Thr in exon 6 (seen in 20% of affected individuals).
- Many reported germline missense variants occurred at the same codons and/or were identical to somatic missense variants identified in tumor samples [Yoda et al 2015] (see Cancer and Benign Tumors).
- In functional studies, the abnormal Gβ1 protein impaired function of the G protein heterotrimer [Lohmann et al 2017].

Because most pathogenic variants appear to occur at the surface of interaction between the Gβ1 and Gα subunits or downstream effectors, it is believed that perturbation of this interaction will affect the regulation of the downstream signaling pathways. This may have gain-of-function, dominant-negative, or loss-of-function consequences on the regulation of these pathways.

Research on *GNB1* haploinsufficiency is inconclusive. Although several loss-of-function variants have been associated with disease [Lohmann et al 2017, Endo et al 2020, Schultz-Rogers et al 2020], the pathogenicity of

these variants remains unclear. A functional study of a splice-site variant and a frameshift variant showed reduction/absence of protein expression and, thus, loss of protein function in a BRET assay [Schultz-Rogers et al 2020], suggesting haploinsufficiency as the disease mechanism. In contrast, in one study the phenotype of a heterozygous knockout mouse did not differ from that of the wild type [Okae & Iwakura 2010], whereas the phenotype of a mouse heterozygous for a human pathogenic missense variant was similar to that of human *GNB1*-E [Colombo, personal observation], which is inconsistent with haploinsufficiency. Thus, the pathogenicity of loss-of-function variants remains to be clarified.

Table 6. Notable *GNB1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002074.4 NP_002065.1	c.233A>G	p.Lys78Arg	Recurrent pathogenic variant [Petrovski et al 2016, Hemati et al 2018]
	c.239T>C	p.Ile80Thr	Recurrent pathogenic variant [Petrovski et al 2016, Hemati et al 2018, Endo et al 2020]
	c.239T>A	p.Ile80Asn	Recurrent pathogenic variant [Petrovski et al 2016]
	c.284T>C	p.Leu95Pro	Recurrent pathogenic variant [Petrovski et al 2016, Hemati et al 2018, Endo et al 2020]
	c.287G>T	p.Arg96Leu	Recurrent pathogenic variant, seen in 3 families w/AD inheritance [Lohmann et al 2017]
	c.301A>G	p.Met101Val	Recurrent pathogenic variant [Petrovski et al 2016]
	c.352G>T	p.Asp118Tyr	Identified *de novo* in an affected individual [Jones et al 2019]
	c.353A>G	p.Asp118Gly	Recurrent pathogenic variant [Firth et al 2009, Steinrücke et al 2016, Hemati et al 2018]
	c.727A>G	p.Thr243Ala	Inherited from a mother (See Genetic Counseling.)

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.

Cancer and Benign Tumors

Acute lymphoblastic leukemia has been reported in one individual with a *de novo* germline *GNB1* pathogenic variant [Brett et al 2017].

Recurrent somatic *GNB1* variants have been reported in various cancer types. Because many of the tumor-derived missense variants occurred at the same codons (e.g., p.Lys78Gln, p.Lys78Glu, and p.Arg96His [Yoda et al 2015]) and/or were identical to the missense variants associated with *GNB1-E* (e.g., p.Ile80Thr, p.Ile80Asn, and p.Asp118Tyr [Yoda et al 2015]; Table 6), the possible association of germline *GNB1* pathogenic variants and an increased risk for malignancies has been raised [Petrovski et al 2016].

Chapter Notes

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Acknowledgments

We acknowledge the contribution of the DECIPHER Consortium. The DECIPHER study makes use of data generated by the DECIPHER community. A full list of centers who contributed to the generation of the data is available from decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

Revision History

- 15 April 2021 (aa) Revision: incorporated data from Myers et al [2018], Schultz-Rogers et al [2020]
- 5 March 2020 (bp) Review posted live
- 28 June 2019 (kay) Original submission

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