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GM3 Synthase Deficiency

Synonyms: Amish Infantile Epilepsy Syndrome, Salt and Pepper Developmental Regression Syndrome, ST3GAL5-CDG, ST3GAL5 Deficiency

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Summary

Clinical characteristics

Early clinical features of GM3 synthase deficiency include infantile onset of severe irritability with feeding difficulties, early and intractable seizures, growth failure with acquired microcephaly, sensorineural hearing impairment, hypotonia, and poor visual function. Over time, affected individuals experience severe-to-profound developmental delay and intellectual disability, can develop dystonia with hyperkinetic movements, and may develop pigmentary skin changes of the hands and feet. Affected individuals often have frequent ear infections and pneumonia without evidence of immune dysfunction.

Diagnosis/testing

The diagnosis of GM3 synthase deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *ST3GAL5* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment for new-onset or worsening irritability is based on identification of inciting factors; for example, motility agents for constipation, antibiotic treatment of infections, and standard therapies for GERD, such as proton pump inhibitors. Seizures are treated with anti-seizure medication (ASM), although the majority of electrographic seizures in affected children are clinically silent. No ASM has been demonstrated effective for this condition specifically, ASM treatment may be only partially effective, and multiple ASMs may be required. Feeding therapy may be useful, with consideration of gastrostomy tube placement for persistent poor feeding / growth failure. Hearing aids may be helpful on a case-by-case basis. There is no specific treatment for optic atrophy or cortical blindness, although referral to low vision services is recommended. Dystonia, developmental delay / intellectual disability, sleep disturbances, infectious illnesses, and scoliosis are treated per standard methods.

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Surveillance: At each visit: measure growth parameters, evaluate status and safety of oral intake, monitor for new manifestations (seizures, changes in tone, movement disorders), monitor developmental progress, assess for behavioral changes (new-onset or worsening irritability; aggressive or self-injurious behaviors), monitor for constipation/GERD/emesis, monitor for signs/symptoms of pneumonia, and obtain a non-invasive SpO_2. Annually: physical exam for signs/symptoms of scoliosis. As clinically indicated: Audiologic evaluation, ophthalmologic evaluation, and assessment of mobility, physical medicine, and OT/PT needs.

Therapies under investigation: Oral supplementation with GM3 gangliosides did not alter disease course and demonstrated only modest short-term benefit to affected individuals.

Genetic counseling

GM3 synthase deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ST3GAL5* 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 inheriting neither of the familial pathogenic variants. Once the *ST3GAL5* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for GM3 synthase deficiency have been published.

Suggestive Findings

GM3 synthase deficiency **should be considered** in individuals with the following early and late clinical features, supportive laboratory results, and family history.

Early clinical features

- Severe infantile irritability with feeding difficulties
- Epilepsy, including infantile spasms, tonic-clonic, myoclonic, and/or generalized seizures
- Growth failure
- Sensorineural hearing impairment
- Acquired (e.g., postnatal) progressive microcephaly
- Hypotonia
- Cortical visual impairment or optic atrophy
- Frequent otitis media and pneumonia

Late clinical features

- Severe-to-profound developmental delay and intellectual disability
- Dystonia and hyperkinetic movement disorders, including choreoathetosis and dyskinesia
- Acquired skin hyper- and hypopigmentation anomalies that may change dynamically over time
- Scoliosis

Supportive laboratory results

- The following studies typically are normal or nondiagnostic:
  - Plasma very long-chain fatty acids
  - Plasma amino acids
  - Urine organic acids
  - Plasma total and free carnitine
  - Plasma acylcarnitine profile

- Serum ammonia
- Non-specific abnormalities in serum O-glycan and N-glycan profiles that are not diagnostic of a congenital disorder of glycosylation
- Note: Plasma GM3 ganglioside concentration is extremely low or undetectable. However, this test is not widely clinically available, although it may be available in some specialized academic centers.

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 GM3 synthase deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ST3GAL5* identified by molecular genetic testing (see Table 1).

Note: (1) Affected individuals also have significantly reduced quantification of GM3 ganglioside levels in blood plasma or in cultured skin fibroblasts [Huang et al 2014, Aoki et al 2019]. However, these assays are not readily available clinically. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of biallelic *ST3GAL5* variants of uncertain significance (or of one known *ST3GAL5* pathogenic variant and one *ST3GAL5* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene 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 GM3 synthase deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of GM3 synthase deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ST3GAL5* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications can be considered, although none have been reported to date.

  Note: Targeted analysis for the c.862C>T (p.Arg288Ter) founder pathogenic variant in individuals of Old Order Amish ancestry or the c.740G>A (p.Gly247Asp) founder pathogenic variant in individuals of La Réunion Island ancestry can be performed first [Simpson et al 2004, Heide et al 2022] (see Molecular Genetics and Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the La Réunion Island Population).

- **An epilepsy multigene panel** that includes *ST3GAL5* 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

When the diagnosis of GM3 synthase deficiency has not been considered, comprehensive genomic testing may be performed.

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 GM3 Synthase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ST3GAL5	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, no reported cases of GM3 synthase deficiency were due to either whole- or partial-gene deletions or duplications [Inamori & Inokuchi 2022].

Clinical Characteristics

Clinical Description

GM3 synthase deficiency likely represents a spectrum of disease severity [Inamori & Inokuchi 2022]. Affected individuals were initially described in special populations and consanguineous families, but continue to be identified in more general populations over time. To date, more than 100 individuals from more than a dozen families have been identified with GM3 synthase deficiency in the published literature [Inamori & Inokuchi 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of GM3 Synthase Deficiency

Feature	% of Persons w/Feature [1]	Comment
Irritability	>90%	• Typically severe, beginning in infancy • Caregivers may report sleepless nights.
Epilepsy	>90%	• Typically beginning in infancy • Frequently characterized as epileptic encephalopathy • Seizures are often refractory to medical therapy (see Management).
Growth failure & microcephaly	>90%	Microcephaly is typically acquired (postnatal).
Developmental delay / intellectual disability	>90%	Typically in the profound range
Hypotonia	>90%	Typically mild, beginning in infancy
Dystonia & other movement disorders	>90%	Dystonia & other hyperkinetic movements are later manifestations.
Hearing impairment	>80%	Most fail newborn hearing screening
Frequent otitis media & pneumonia	>80%	If present, typically occurs during infancy & early childhood
Visual impairment	>70%	• Optic atrophy • Cortical blindness • May be underreported without rigorous testing
Gastrointestinal issues	>70%	GERD, constipation, & emesis may be present.
Feeding difficulties	>60%	Often presenting along w/severe irritability during infancy
Skin pigmentation anomalies	~50%	• Not present at birth • Reportedly dynamic, • May be mistaken for freckling
Scoliosis	>30%-99% [1]	Almost universal in late childhood & adolescence

GERD = gastroesophageal reflux disease

1. Some features may develop and/or progress over time, making the estimate of the number of affected individuals who have each feature dependent on age at the time of evaluation.

Irritability and other behavioral issues. In infancy, episodic severe irritability may predominate. Caregivers may report completely sleepless nights accompanied by generalized irritability described as inconsolability and agitation for most of time spent awake. Self-injury may accompany these episodes as the children grow older, with banging, biting, and scratching of limbs described. Increased agitation may be associated with constipation and acute illness, but there has not been a consistent trigger identified for increased agitation. While irritability tends to moderate with age, it can be a source of great duress for caregivers [Bowser et al 2019].

Hypotonia. Mild-to-moderate generalized or axial hypotonia with or without lower extremity spasticity may be noted in the neonatal period and detected as early as the first week of life. Hyoptonia is typically present in all affected individuals before the age of six months, but has also been reported as developing after infancy. Motor delays or poor head control may be the most obvious initial manifestation of the hypotonia [Fragaki et al 2013, Lee et al 2016, Bowser et al 2019, Indellicato et al 2019].

Microcephaly is not typically present at birth. However, postnatal deceleration in head growth leads to age- and sex-adjusted z scores for occipital frontal circumference (OFC) dropping to more than two standard deviations below the mean before the second year of life. After this early deceleration phase, z scores tend to stabilize and typically do not progress through the remainder of life [Authors, personal observations].

Developmental delay and intellectual disability. Affected individuals typically have severe-to-profound developmental delay and intellectual disability after a period of stagnated motor development.

- Children may briefly meet early developmental milestones, despite hypotonia, until onset of seizure activity. However, few affected individuals achieve early developmental milestones, consistent with infantile-onset developmental arrest.
- Ultimately, most affected individuals are nonverbal, lack purposeful movements, and are wheelchair bound with little or no expressive or receptive language skills. However, there are a few cases of ambulatory individuals who may represent a milder form of the disorder.

Epilepsy. Intractable seizures that begin during infancy are a nearly universal finding among individuals with GM3 synthase deficiency; however, a handful of individuals with milder phenotypes have been reported with delayed onset or without clinical evidence of seizures [Lee et al 2016]. Most children are reported to have been started on at least one anti-seizure medication (ASM) by age 3.5 months, and more than half require multiple medications. There is no specific drug or class of ASM that has been reported superior in treating GM3 synthase deficiency-associated epilepsy, and ASMs remain only partially effective (see Management) [Bowser et al 2019].

- Seizures typically begin in infancy around the time of developmental stagnation and with EEG studies consistent with epileptic encephalopathy.
- There is no single seizure type that is typical or pathognomonic for GM3 synthase deficiency. Seizures can range from focal to generalized, with or without motor onset.
- Affected individuals may display multiple types of seizures, including generalized tonic-clonic, myoclonic, tonic, atonic, and behavior arrest [Simpson et al 2004, Yoshikawa et al 2015, Bowser et al 2019]. Convulsive and nonconvulsive status epilepticus have also been reported [Boccuto et al 2014].
    - Generalized tonic-clonic seizures were the most commonly reported by Bowser et al [2019], and EEG studies showed that most seizures (72%) were clinically silent [Bowser et al 2019].
    - Approximately 17% of children will meet criteria for infantile spasms (i.e., West Syndrome) [Bowser et al 2019, Heide et al 2022].

EEG findings. EEG studies are likely to be abnormal in at least 90% of those with GM3 synthase deficiency, even without evidence of clinical seizures [Bowser et al 2019]. Therefore, the majority of electrographic seizures in affected children are clinically silent. EEG findings may include the following:

- Disorganized backgrounds, multifocal discharges, and absent sleep/wake cycles
- Background slow spike-and-wave patterns (found in 75%) and hypsarrhythmia

These EEG findings may fulfill clinical criteria for epilepsy syndromes, including Lennox-Gestaut syndrome or West syndrome.

Dystonia and other hyperkinetic movement disorders. Symptoms of dystonia have been described primarily in affected adolescents and young adults. Movement disorders are also common but typically not present in the newborn or infant period. There is variability in severity and age of onset for both dystonia and movement disorders.

- Bruxism, torticollis, torsion, and various other dystonic findings have been variably reported in individual cases.
- Chorea, ballismus/hemiballsimus, stereotypy, limb/facial dyskinesia, and myoclonus have been described in children and young adults [Simpson et al 2004, Wang & Kilbane 2022].

Neuroimaging. Reported neuroimaging findings are highly variable with most reported as normal.

- Diffuse cerebral atrophy is the most consistent late disease finding. With disease progression, neurodegeneration may be observed.
- Bowser et al [2019] reported thinning of the corpus callosum and subcortical myelination deficits early in the disease, and Fragaki et al [2013] reported hyperintense symmetrical white matter lesions on T_2 sequences in two affected individuals younger than age two years.

- In contrast, serial MRIs were reported as normal until at least age 13 years in one symptomatic affected individual [Indellicato et al 2019].

Growth issues. Prenatal growth, prenatal anatomy scans, and growth parameters at delivery are described as unremarkable in nearly all affected children [Simpson et al 2004, Fragaki et al 2013, Boccuto et al 2014, Wang et al 2016, Indellicato et al 2019]. When compared to unaffected sibs, there is no significant difference in growth parameters at the time of birth [Wang et al 2016]. However, similar to what occurs with head size, postnatal growth deceleration is profound, with most age- and sex-adjusted z scores for length/height and weight dropping to more than two standard deviations below the mean before the second year of life, where they typically remain for the remainder of life [Gordon-Lipkin et al 2018, Bowser et al 2019, Indellicato et al 2019, Heide et al 2022]. There is no intervention that has permanently corrected this severe growth restriction.

Gastrointestinal issues / feeding difficulties. Gastrointestinal issues consistent with dysmotility are reported in the majority of affected individuals. Gastroesophageal reflux disease (GERD), constipation, and recurrent vomiting are reported in more than 70% of affected individuals [Bowser et al 2019].

- Poor feeding in infancy is reported in nearly all affected children. It may be the presenting symptom, as it often precedes the onset of seizures, growth failure, or developmental delay.
- Feeding difficulties are often accompanied by irritability.
- No particular formula or diet has been shown to improve feeding, and assisted feeding may be necessary.
- Improved weight gain and growth improvements with oral ganglioside supplementation and nutritional support with gastrostomy tube (G-tube) placement have both been reported (see Management), but neither has produced lasting changes in growth parameters, suggesting that growth failure may not be driven by poor feeding [Wang et al 2016, Bowser et al 2019, Wang et al 2019].

Hearing impairment. Nearly all affected individuals tested have abnormal hearing screening in the newborn period, with absent distortion-product otoacoustic emissions and absent middle ear muscle reflexes at all frequencies, if evaluated. Auditory brain stem responses are abnormal at this time, and cochlear microphonics are absent [Yoshikawa et al 2015, Bowser et al 2019, Wang et al 2019]. Due to severe-to-profound developmental delay and intellectual disability, the degree of hearing impairment may be hard to determine.

Visual impairment. Early visual impairment is present in most affected individuals beginning in the newborn period, with visual inattentiveness (66%), roving eye movements (30%), or strabismus (30%) as the first symptom of visual concern.

- Visual evoked potentials and ERGs may be normal, indicating retained retinal function as late as the teenage years, and are likely not beneficial in the diagnosis of GM synthase deficiency.
- There are variable reports of optic nerve pallor on standard funduscopic examination.
- Optic atrophy in combination with visual cortical blindness is likely to cause permanent and irreversible vision loss without known treatments [Farukhi et al 2006, Heide et al 2022].

Skin. Abnormal skin pigmentation originally described as "salt and pepper" is found in approximately half of affected individuals by a mean age of six years, but is not present at birth [Wang et al 2013].

- The skin findings are flat macules, typically lentigo-sized, that can be either hypo- or hyperpigmented, found on the dorsal aspect of hands and feet. These lesions are often mistaken for freckles.
- Lesions may be "dynamic" and spontaneously resolve or worsen over time without clear cause.
- Skin findings may be less obvious on individuals with lighter skin tones.
- The presence of typical skin findings may be helpful in the diagnosis of older individuals; however, they are not seen in infancy or early childhood, nor are they constant. Therefore, a lack of skin changes does not preclude the diagnosis.

Other long-term complications

- Frequent otitis media and pneumonia have been reported as common long-term comorbidities of GM3 synthase deficiency, although there has been no evidence of immune dysfunction in affected individuals [Bowser et al 2019].
- Progressive scoliosis has also been reported [Bowser et al 2019].

Prognosis. The median age of death in the literature is 23.5 years, and the most common cause of death is complications of pneumonia [Bowser et al 2019]. In addition, several cases of acute, idiopathic hyperthermia in the second or third decade of life, without evidence of infection, resulting in death within several hours of onset have been observed in a large Old Order Amish cohort [Authors, personal observations].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ST3GAL5* have been identified.

Nomenclature

GM3 synthase deficiency has been referred to as "Amish infantile epilepsy syndrome" and as "salt and pepper developmental regression syndrome" in the published literature, although these designations are considered misleading and somewhat archaic.

- **Amish infantile epilepsy syndrome.** Using the term "Amish" to refer to this condition implies that it is only found in individuals of Amish ancestry, which is untrue. Furthermore, the vast majority of Amish infants with seizures have other genetic or non-genetic causes of epilepsy.
- **Salt and pepper developmental regression syndrome.** Currently there is no objective evidence that individuals with GM3 synthase deficiency experience true "regression."
  - Careful review of the original literature reveals that some publications reference "regression" without specific or concrete definitions or descriptions of the purported developmental skills lost or the timing of the purported regression.
  - In GM3 synthase deficiency, significant, objective developmental milestones are rarely (if ever) met, so they cannot be subsequently lost. Instead, the developmental trajectory is more accurately described as developmental arrest without attainment.
  - With disease progression, neurodegeneration may be observed, but the term "regression" should be reserved for conditions in which there are clearly defined and profound loss of skills.

Prevalence

GM3 synthase deficiency is rare. More than 100 cases have been reported in the literature in several different populations.

The overall prevalence is higher in the Old Order Amish of North America due to the pathogenic founder variant c.862C>T (p.Arg288Ter). The estimated carrier frequency for this population is 1.7% (Anabaptist Variant Server, retrived 8-1-22). Note that this pathogenic variant has also been reported in affected individuals from other populations (French and Pakistani) unrelated to the Old Order Amish, and therefore may represent a recurrent pathogenic variant [Fragaki et al 2013, Gordon-Lipkin et al 2018].

The overall prevalence and carrier frequency is unknown in individuals of La Réunion Island ancestry. All affected individuals with known La Réunion Island ancestry are either homozygous or compound heterozygous for the pathogenic founder variant c.740G>A (p.Gly247Asp) [Heide et al 2022] (see also Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the La Réunion Island Population).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ST3GAL5*.

Differential Diagnosis

Table 3. Selected Genes of Interest in the Differential Diagnosis of GM3 Synthase Deficiency

Gene	Disorder	MOI	Overlapping Features	Distinguishing Features
Multiple genes incl: *ALG1* *ALG3* *ALG6* *MPI* *PMM2* *SRD5A3* *TUSC3*	Other congenital disorders of glycosylation (See Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview.)	AR [1]	Seizures, hypotonia, DD, growth failure, hearing impairment, visual deficits incl optic atrophy (some)	• Most other CDGs are assoc w/ congenital, not acquired, microcephaly. • Skeletal findings (incl enlarged fontanel), liver dysfunction, enteropathy, & hypoglycemia are not seen in GM3 synthase deficiency.
Multiple genes incl: *ARX* *CDKL5* *DCX* *KCNQ2*	Infantile epileptic spasms syndrome (IESS)	AD XL [2]	Seizures (infantile spasms), developmental stagnation/ regression	Hypsarrhythmia, a cardinal feature of IESS, is not consistently reported in GM3 synthase deficiency.
CNTNAP2 (*CASPR2*)	Pitt-Hopkins-like syndrome 1 (PTHSL1) (OMIM 610042)	AR	• Old Order Amish founder variant • Seizures, DD	PTHSL1 is assoc w/focal cortical dysplasia on brain MRI & relative macrocephaly.
FMR1	Fragile X syndrome (FXS) (See *FMR1* Disorders.)	XL	DD, ID	• Relative macrocephaly is seen in FXS, whereas GM3 synthase is assoc w/ relative normal head size at birth followed by acquired microcephaly. • Seizures & irritability are not defining features of FXS. • Note: The physical & behavioral features seen in males w/FXS have been reported in females heterozygous for the *FMR1* full mutation, but w/ lower frequency & milder involvement.
MECP2	Classic & variant Rett syndrome (See *MECP2* Disorders.)	XL	DD, seizures	• Skin dyspigmentation, visual deficits, & hearing impairment are not defining features of Rett syndrome. • Profound regression w/significant loss of acquired developmental skills is not often seen in GM3 synthase deficiency. • *MECP2* classic Rett syndrome & variant Rett syndrome are seen almost exclusively in females. [3]

Table 3. continued from previous page.

Gene	Disorder	MOI	Overlapping Features	Distinguishing Features
SAMHD1	*SAMHD1*-related Aicardi-Goutières syndrome (AGS)	AR	• Old Order Amish founder variant [4] • Microcephaly, seizures, feeding intolerances, neonatal hypotonia, irritability	• *SAMHD1*-related AGS is assoc w/ thrombocytopenia, leukoencephalopathy, & basal ganglia changes on brain MRI. • *SAMHD1*-related AGS is assoc w/dry, scaly skin & chilblains w/o pigmentary changes seen in GM3 synthase deficiency.
ST3GAL3	Developmental & epileptic encephalopathy 15 (DEE15) (OMIM 615006)	AR	Significant overlap, incl seizures, visual impairment, hypotonia, dystonia	• Congenital hearing impairment & acquired microcephaly are not reported in DEE15. • Structural brain malformations noted on imaging in DEE15 may not be present in GM3 synthase deficiency.

AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorder of glycosylation; DD = developmental delay; MOI = mode of inheritance; XL = X-linked

1. Most congenital disorders of N-linked glycosylation and multiple pathways are inherited in an autosomal recessive manner. *MGAT1-*, *ALG13*-CDG, *SLC35A2-*, and *SSR4*-related CDG are inherited in an X-linked manner.

2. ARX-, *CDKL5-*, and *DCX*-related disorders are inherited in an X-linked manner. *KCNQ2*-related disorders are inherited in an autosomal dominant manner. Autosomal recessive inheritance can be seen with other genetic causes of infantile epileptic spasms syndrome.

3. MECP2 classic Rett syndrome and variant Rett syndrome are seen in females; males who are hemizygous for a *MECP2* pathogenic variant most commonly have severe neonatal-onset encephalopathy.

4. A recurrent splice acceptor site pathogenic variant (c.1411-2A>G) in intron 12 is seen in persons of Amish ancestry and represents an ancient founder variant (see Aicardi-Goutières Syndrome).

Management

No clinical practice guidelines for GM3 synthase deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with GM3 synthase deficiency, the evaluations summarized Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. GM3 Synthase Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for growth failure/microcephaly & baseline for growth deceleration
Irritability	Identify source / precipitating factors for new-onset or worsening irritability	Eval should incl assessment for possible: • GERD • Constipation • Seizures • Otitis media • Other infections

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval, incl for hypotonia or movement disorders (in older persons) such as chorea or dystonia	Consider EEG if evidence of new or worsening seizure activity or unexplained irritability, noting that majority of EEGs will be abnormal even in absence of clinical seizures, thus limiting clinical utility of EEG eval.
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Screening for behavior concerns incl: • Irritability • Sleep disturbances • Self-injurious behaviors
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Consider eval for GERD. • Consider swallow eval of aspiration risk & nutritional status. • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Hearing	Audiologic eval	Assess for hearing impairment w/standard DPOAE &/or AEP testing.
Eyes	Ophthalmologic eval	To assess for presence of optic atrophy
Skeletal	Physical exam for signs of scoliosis	If present, consider radiographs of spine & referral to orthopedist
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of GM3 synthase deficiency 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; AEP = auditory evoked potential; DPOAE = distortion-product otoacoustic emission; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for GM3 synthase deficiency.

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

Table 5. GM3 Synthase Deficiency: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Irritability	Treatment depends on underlying source of new-onset or worsening irritability (see Table 4).	• Consider standard therapies such as proton pump inhibitors for GERD, motility agents for constipation, ASM for seizures, & typical antibiotics for infections, as needed. • Off-label use of SSRIs may be considered when precipitating factors are not identified [Authors, personal observations].
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• No ASM has been demonstrated effective specifically for this disorder. • ASM treatment may be only partially effective & multiple ASMs may be required. • Education of parents/caregivers [1] • Anticipatory guidance on proper use of rescue medications for seizure activity & possibility of drug-resistant epilepsy
Dystonia & other hyperkinetic movement disorders	Consider standard therapies for dystonia per neurologist or rehabilitation medicine.	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Sleep disturbance	Consider standard medical therapies for age-appropriate insomnia.	• There is no particular medication that has been proven to be superior for treatment of insomnia. • Antihistamines, melatonin, benzodiazepines, & alpha-adrenergic agonists may be appropriate on case-by-case basis.
Growth failure / Poor feeding	• 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 • Gastrostomy tube placement does not appear to significantly alter growth trajectory. • Oral ganglioside supplementation & nutritional support w/gastrostomy tube has not produced lasting changes in growth parameters [2]; see Therapies Under Investigation.
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Pneumonia	Standard treatment	
Otitis media	Standard treatment per otolaryngologist	Consideration of pressure-equalizing tubes if infections/ effusions are persistent
Hearing	Hearing aids might be helpful on case-by-case basis.	Community hearing services through early intervention or school district
Visual impairment	No specific treatment	Most affected persons w/optic atrophy or evidence of cortical blindness will not benefit from vision correction.
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Scoliosis	Standard treatment per orthopedist	

Table 5. continued from previous page.

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

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy; SSRI = selective serotonin reuptake inhibitor

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. Wang et al [2016], Bowser et al [2019], Wang et al [2019]

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 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 from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies.

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

Surveillance

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

Table 6. GM3 Synthase Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Behavioral assessment for new-onset or worsening irritability, & aggressive or self-injurious behavior	
Gastrointestinal	Monitor for constipation/GERD/emesis.	
Respiratory	• Monitor for signs/symptoms of pneumonia. • Non-invasive SpO_2	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility	As needed
	Physical exam for signs of scoliosis	Annually
Hearing	Audiologic eval	As clinically indicated
Eyes	Ophthalmologic eval	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Recent attempts to ameliorate the effects of the loss of function in GM3 synthase deficiency by oral supplementation with a diet high in the products of the missing enzyme (GM3 gangliosides) showed only modest short-term benefit for affected individuals in a single-arm open label study (NCT02234024). Ultimately, oral supplementation with gangliosides did not alter disease progression [Wang et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GM3 synthase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ST3GAL5* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ST3GAL5* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, 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].
  - 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 an *ST3GAL5* 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 inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Due to the severity of the disorder, affected individuals are unlikely to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ST3GAL5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ST3GAL5* pathogenic variants in the family.

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.
- The carrier frequencies of *ST3GAL5* pathogenic variants are unknown in the general population; however, given that GM3 synthase deficiency is rare, the likelihood that an individual who is a carrier of GM3 synthase deficiency would have a reproductive partner who is also a carrier is low. Exceptions include populations in which a founder pathogenic variant is present, such as the Old Order Amish and individuals of La Réunion Island ancestry (see Prevalence). If both reproductive partners are carriers, offspring have a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ST3GAL5* 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.

- **CDG CARE (Community Alliance and Resource Exchange)**
  Phone: 866-295-7910
  Email: info@cdgcare.com
  cdgcare.org
- **Directory of CDG Patient Advocacy Groups and Local Patient Representatives**
  www.apcdg.com/cdg-patient-groups
- **Foundation Glycosylation (FoG)**
  Canada
  www.thefog.ca
- **Practical Guide to CDG**
  Practical Guide to CDG

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. GM3 Synthase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ST3GAL5	2p11.2	Lactosylceramide alpha-2,3-sialyltransferase	ST3GAL5 database	ST3GAL5	ST3GAL5

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 GM3 Synthase Deficiency (View All in OMIM)

604402	ST3 BETA-GALACTOSIDE ALPHA-2,3-SIALYLTRANSFERASE 5; ST3GAL5
609056	SALT AND PEPPER DEVELOPMENTAL REGRESSION SYNDROME; SPDRS

Molecular Pathogenesis

Broadly speaking, *ST3GAL5* codes for an enzyme critical to the biosynthesis of a class of glycosphingolipids (GSLs) called gangliosides. GM3 is a sialyltransferase, an enzyme that converts lactosylceramide into GM3 ganglioside by adding a sialic acid residue. This is the first and necessary step in the formation of all a- and b-series gangliosides, which are significantly expressed in the normal human brain. Complete loss of function of ST3GAL5 enzymatic activity results in severe reduction or absence of GM3 ganglioside and its downstream derivative gangliosides. The exact functions of these gangliosides are still not known, and the pathogenesis is still not fully understood. Since GSLs straddle the outer cell membrane and extend into the extracellular matrix, they likely participate in cell-to-cell interactions and cell receptor signaling. As such, they are likely integral to brain development, development and maintenance of the organ of Corti (required for hearing), and neural crest cell migration (implicated in pigmentation). For a more in-depth discussion of the general biology of gangliosides, or GM3 in particular, in both human health and disease, see Inokuchi et al [2018] and Schnaar [2019].

Mechanism of disease causation. Loss of function

Table 7. *ST3GAL5* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003896.4 NP_003887.3	c.862C>T	p.Arg288Ter	Founder variant in Old Order Amish [Simpson et al 2004]
	c.740G>A	p.Gly247Asp	Founder variant in persons of La Réunion ancestry [Heide et al 2022]

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

DDC Clinic – Center for Special Needs Children is located in Middlefield, Ohio, USA. In the heart of the world's fourth-largest Amish settlement, DDC Clinic was founded in 1998 by a group of Amish families who were committed to helping special needs children get the care they needed.

Since its humble beginnings, DDC Clinic has grown into a world-class medical facility with cutting-edge research capabilities and an onsite certified molecular diagnostics laboratory serving patients, families, and health professionals worldwide.

Our work encompasses three critical areas of medical services – patient care, research, and education. We provide personalized medical care for special needs children with nearly 200 different rare conditions, and we have served more than 1,500 patient families in 35 US states, Canada, Australia, Europe, and Asia.

For more information, or to contact the authors, go to www.ddcclinic.org.

Acknowledgments

The authors wholeheartedly thank the hundreds of families from the Plain Community affected by GM3 synthase deficiency under the care of DDC Clinic – Center for Special Needs Children. They are the true experts and have graciously allowed us to share their experiences and insights of the disorder with the world. Without their continued support, this chapter would not be possible.

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