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GM2 Activator Deficiency

Synonyms: GM2 Gangliosidosis, AB Variant; Hexosaminidase Activator Deficiency; Tay-Sachs Variant AB

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Summary

Clinical characteristics

Acute infantile GM2 activator deficiency is a neurodegenerative disorder in which infants, who are generally normal at birth, have progressive weakness and slowing of developmental progress between ages four and 12 months. An ensuing developmental plateau is followed by progressively rapid developmental regression. By the second year of life decerebrate posturing, difficulty in swallowing, and worsening seizures lead to an unresponsive vegetative state. Death usually occurs between ages two and three years.

Diagnosis/testing

The diagnosis of GM2 activator deficiency is established in a proband with suggestive findings of GM2 gangliosidosis, normal beta-hexosaminidase A (HEX A) enzyme activity levels, and biallelic pathogenic (or likely pathogenic) variants in *GM2A* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for GM2 activator deficiency. Supportive care to provide adequate nutrition and hydration, manage infectious disease, protect the airway, and control seizures involves multidisciplinary care by specialists in relevant fields.

Surveillance: Periodic multidisciplinary evaluations to monitor existing disease manifestations and identify new manifestations requiring modification of supportive care.

Agents/circumstances to avoid: Positioning that increases aspiration risk during feedings and seizure medication dosages that result in excessive sedation.

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Genetic counseling

GM2 activator deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GM2A* 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 *GM2A* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for GM2 activator deficiency have been published.

Suggestive Findings

GM2 activator deficiency should be suspected in children with the following clinical and imaging findings and family history.

Clinical findings

- **Neurologic**
  - Progressive weakness or loss of motor skills beginning between ages four to 12 months
  - Decreased attentiveness
  - Exaggerated startle response
  - Hypotonia
  - Hyperreflexia
  - Seizures
- **Other.** Cherry-red macula

Brain MRI findings

- Delayed myelination and hyperintense T_2-weighted signal in the subcortical white matter, basal ganglia, and/or thalami [Chen et al 1999, Renaud & Brodsky 2016, Brackmann et al 2017]
- Normal MRI has also been reported [Sakuraba et al 1999].

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 GM2 activator deficiency **is established** in a proband with suggestive findings, normal beta-hexosaminidase A (HEX A) enzyme activity levels, and biallelic pathogenic (or likely pathogenic) variants in *GM2A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *GM2A* variants of uncertain significance (or identification of one known *GM2A* pathogenic variant and one *GM2A* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) (see Option 1) and **comprehensive genomic testing** (exome sequencing, genome sequencing) (see Option 2).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of GM2 activator deficiency overlaps with several biochemically related disorders (GM2 gangliosidoses), most infants with the findings described in Suggestive Findings are likely to be diagnosed using a multigene panel or genomic testing.

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of GM2 activator deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** In rare instances, single-gene testing can be considered for individuals with a high clinical suspicion of a GM2 gangliosidosis and normal HEX A and beta-hexosaminidase B (HEX B) activity. Sequence analysis of *GM2A* 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, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A multigene panel** for GM2 gangliosidoses, lysosomal storage diseases, neurometabolic diseases, or neurodevelopmental diseases would be an appropriate initial test when seeking a molecular diagnosis in most individuals suspected clinically of having GM2 activator deficiency. Such panels include *GM2A* and other genes of interest (see Differential Diagnosis) and are 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 phenotype is indistinguishable from many other inherited disorders characterized by neurodegeneration, epilepsy, and/or hypotonia, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is appropriate. **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 GM2 Activator Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GM2A	Sequence analysis [3]	24/26 [4]
	Gene-targeted deletion/duplication analysis [5]	1 person 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. A homozygous 6-kb deletion of exon 2 (c.82-2668_243+3312del6142) was reported in one individual [Hall et al 2018].

Clinical Characteristics

Clinical Description

Acute infantile GM2 activator deficiency is a neurodegenerative disorder in which infants, who are generally normal at birth, have progressive weakness and slowing of developmental progress between ages four and 12 months. An ensuing developmental plateau is followed by progressively rapid developmental regression. By the second year of life decerebrate posturing, difficulty in swallowing, and worsening seizures lead to an unresponsive vegetative state. Death usually occurs between ages two and three years.

To date, 13 individuals have been reported with acute infantile GM2 activator deficiency [de Baecque et al 1975, Xie et al 1992, Schröder et al 1993, Schepers et al 1996, Chen et al 1999, Sakuraba et al 1999, Kolodny et al 2008, Renaud & Brodsky 2016, Sheth et al 2016, Brackmann et al 2017, Hall et al 2018, İnci et al 2021]. The following description of the phenotypic features associated with acute infantile GM2 activator deficiency is based on these reports.

Table 2. Acute Infantile GM2 Activator Deficiency: Frequency of Select Features

Feature	# of Persons w/Feature	Comment
Developmental delay	13	
Cherry-red macula	13	
Hypotonia	12	Tone not specifically discussed in 13th case & is likely present in all affected persons. While axial tone is universally ↓, limb tone may be ↑ or ↓.
Seizures	9	
Exaggerated startle response	8	
Hyperreflexia	4	Hyperreflexia was present in all reports in which reflexes were specifically discussed.
Hepatomegaly	2	

Acute Infantile GM2 Activator Deficiency

Affected infants are generally normal at birth. Progressive weakness, exaggerated startle, and slowing of developmental progress is typically noted between ages four to 12 months. Decreasing visual attentiveness and unusual eye movements including poor fix-and-follow, typically noted at age three to six months, may be the

first signs prompting parents to seek medical attention; subsequent ophthalmologic evaluation reveals the characteristic cherry-red macula seen in virtually all affected children.

Affected infants reach a developmental plateau followed by developmental regression typically between ages six to ten months. After age eight to ten months, disease progression is rapid. Voluntary movements diminish and the infant becomes progressively less responsive. Vision deteriorates rapidly.

Seizures and myoclonic jerks are common by age 12 months. Partial complex seizures or absence seizures that are initially subtle typically become more severe and more frequent.

Progressive enlargement of the head resulting from reactive cerebral gliosis beginning by age 18 months followed by ventriculomegaly commonly seen in GM2 gangliosidosis has been inconsistently reported in GM2 activator deficiency [Nestrasil et al 2018].

Further deterioration in the second year of life results in decerebrate posturing, difficulty in swallowing, worsening seizures, and finally an unresponsive, vegetative state.

Prognosis. Death from respiratory complications usually occurs between ages two and three years.

Possible Subacute Juvenile GM2 Activator Deficiency

Three members of one family with childhood-onset progressive cognitive decline, hyperkinetic movement disorder, and global cerebral atrophy were homozygous for the *GM2A* missense variant c.164C>T [Salih et al 2015]; this variant, subsequently predicted to be deleterious *in silico,* segregates with the disease in this family.

Another unrelated individual with a childhood-onset progressive movement disorder, cognitive decline, and epilepsy was compound heterozygous for a *GM2A* nonsense variant and the c.164C>T *GM2A* missense variant [Martins et al 2017]. Further studies demonstrated decreased levels of GM2 activator protein and accumulation of GM2 gangliosides in cultured fibroblasts.

The phenotype in these two families likely represents a subacute juvenile form of GM2 activator deficiency similar to that seen in other GM2 gangliosidoses.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

GM2 activator deficiency was one of several disorders, including Tay-Sachs disease (see *HEXA* Disorders) and Sandhoff disease, formerly referred to collectively as "amaurotic idiocy." Once GM2 ganglioside was identified as the major accumulating substrate, the terms "infantile ganglioside lipidosis" and "GM2 gangliosidosis" were introduced. Likewise, when the relationship between the enzymatic activity of beta-hexosaminidase A (HEX A) and GM2 activator protein was identified, the terms "GM2 activator deficiency" and "hexosaminidase activator deficiency" were introduced.

To distinguish GM2 activator deficiency from Tay-Sachs disease and Sandhoff disease – both of which also involve GM2 ganglioside accumulation because of a shared biochemical pathway for the enzymes involved – GM2 activator deficiency is also referred to as "GM2 gangliosidosis, AB variant" or "Tay-Sachs disease variant AB."

Prevalence

To date, 13 individuals have been reported with infantile-onset GM2 activator deficiency [de Baecque et al 1975, Xie et al 1992, Schröder et al 1993, Schepers et al 1996, Chen et al 1999, Sakuraba et al 1999, Kolodny et al 2008, Renaud & Brodsky 2016, Sheth et al 2016, Brackmann et al 2017, Hall et al 2018, İnci et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GM2A*.

Differential Diagnosis

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of Acute Infantile GM2 Activator Deficiency

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comments	Not observed in GM2 activator deficiency
ASPA	Canavan disease		≤6 mos	Macrocephaly, head lag, hypotonia, seizures	Leukoencephalopathy
CLN5 *CLN6* *CLN8* *CTSD* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinoses, infantile & late infantile (OMIM PS256730)		≤6 mos	Visual deficits, seizures	Abnormal ERG
CTSA	Galactosialidosis (OMIM 256540)	+	<6 mos	Seizures	Coarse features, skeletal disease
GALC	Krabbe disease		≤6 mos	Seizures	Leukodystrophy, peripheral neuropathy, irritability
GBA1 (*GBA*)	Gaucher disease type 2		≤6 mos	Seizures in some persons	Oculomotor abnormalities, hypertonia, & opisthotonos; ichthyosiform or collodion skin changes may be seen in persons w/severe involvement.
GFAP	Alexander disease, infantile form		≤6 mos	Macrocephaly, seizures	Leukodystrophy
GLB1	GM1 gangliosidosis type 1 (See *GLB1* Disorders.)	+	≤12 mos	Seizures	Skeletal disease
GNPTAB	Mucolipidosis II (I-cell disease) (See *GNPTAB* Disorders.)		≤12 mos		Coarse facies, hyperplastic gums, skeletal disease; absence of seizures
HEXA	Tay-Sachs disease (See *HEXA* Disorders.)	+	≤6 mos	Clinical course nearly identical to GM2 activator deficiency	
HEXB	Sandhoff disease	+	≤6 mos	Clinical course nearly identical to GM2 activator deficiency	

Table 3. continued from previous page.

Gene	DiffDx Disorder [1]	Clinical Features of DiffDx Disorder			
		Cherry-red macula (≤12 mos)	Onset of neurologic regression	Other features / Comments	Not observed in GM2 activator deficiency
NEU1	Sialidosis type II (OMIM 256550)	+	≤12 mos	Seizures	Coarse facies, skeletal abnormalities
SMPD1	Niemann-Pick disease type A (See Acid Sphingomyelinase Deficiency.)	+	≤12 mos		Poor growth, xanthomas, absence of seizures

ERG = electroretinogram
1. The disorders included in Table 3 are inherited in an autosomal recessive manner, with the exception of Alexander disease, which is inherited in an autosomal dominant manner.

Management

No clinical practice guidelines for acute infantile GM2 activator deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with acute infantile GM2 activator deficiency, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Acute Infantile GM2 Activator Deficiency

System/Concern	Evaluation	Comment
Neurologic	Neurology eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Musculoskeletal system	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Need for adaptive devices • Need for PT (to prevent deformities)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl swallow study for eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk. • Assess for constipation.
Eyes	Ophthalmologic exam	Eval for macular degeneration, cherry-red macula, visual loss
Respiratory	Evaluate for aspiration risk.	Assess need for airway hygiene.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of this disorder 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.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Ethics consultation	Clinical ethics services	• Assess health care decisions in context of best interest of child & values & preferences of family. • For difficult life-prolonging decisions or clarification of treatment options, consider further consultation w/independent clinical teams. [2]

EEG = electroencephalogram; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse
2. Linney et al [2019]

Treatment of Manifestations

There is no cure for GM2 activator deficiency.

Supportive treatment to provide adequate nutrition and hydration, manage infectious disease, protect the airway, and control seizures involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Supportive Treatment of Individuals with Acute Infantile GM2 Activator Deficiency

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist/epileptologist	• Seizures are often progressive & refractory. • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Complete seizure control is seldom achieved & requires balancing w/sedative side effects of ASMs. • Education of parents/caregivers [1]
Abnormal tone / Impaired mobility	PT/OT	For prevention of contractures
Feeding difficulties	Gastrostomy tube	Will ↑ longevity but not preserve developmental function
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Aspiration risks / Excess secretion	Gastrostomy tube, vibrator vest, improved pulmonary toilet, suppression of saliva production	Will ↓ aspiration & improve longevity but not preserve developmental function
Family support	In-home nursing & respite care	Support for health & quality of life of caregivers & sibs
Ethics consultation	Clinical ethics services	• Assess health care decisions in context of best interest of child & values & preferences of family. • For difficult life-prolonging decisions or clarification of treatment options, consider further consultation w/independent clinical teams. [2]

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Linney et al [2019]

Surveillance

There are no formal guidelines for surveillance for individuals with acute infantile GM2 activator deficiency. Table 6 provides suggestions for periodic evaluations to monitor existing disease manifestations and to identify new manifestations requiring modification of supportive care.

Table 6. Recommended Surveillance for Individuals with Acute Infantile GM2 Activator Deficiency

System/Concern	Evaluation	Frequency
Neurologic decline	Eval by pediatric neurologist w/attention to seizure severity & response to ASM	Every 3-6 mos
Abnormal tone / Impaired mobility	• OT/PT assessment of ADL & need for splinting for contractures/scoliosis • Durable medical equipment for mobility	At each visit
Nutrition/feeding	By feeding team re aspiration risk / nutrition needs	
Respiratory	Assess need for airway hygiene.	
Family support & resources	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).	As needed

ADL = activities of daily living; ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid the following:

- Positioning that increases aspiration risk during feedings
- Seizure medication dosages that result in excessive sedation

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

GM2 activator 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 a *GM2A* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GM2A* 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, it is possible that 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]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *GM2A* 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. To date, individuals with GM2 activator deficiency are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GM2A* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GM2A* 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.
- 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 *GM2A* 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.

- **MedlinePlus**
  GM2-gangliosidosis, AB variant

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173

metabolicsupportuk.org

- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  Phone: 617-277-4463
  Email: info@ntsad.org
  www.ntsad.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GM2 Activator Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GM2A	5q33.1	Ganglioside GM2 activator	GM2A database	GM2A	GM2A

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 GM2 Activator Deficiency (View All in OMIM)

272750	GM2-GANGLIOSIDOSIS, AB VARIANT
613109	GM2 ACTIVATOR; GM2A

Molecular Pathogenesis

GM2 activator protein is a substrate-specific cofactor that, together with the enzyme beta-hexosaminidase A (HEX A), catalyzes the degradation of GM2 gangliosides. Gangliosides (normally present in neurons in very small quantities) are progressively stored in neurons, leading to neuronal impairment and loss and causing the characteristic central nervous system and peripheral nervous system neurodegeneration.

HEX A comprises an alpha subunit and a beta subunit encoded by the genes *HEXA* and *HEXB*, respectively. The combination of two beta subunits form the enzyme beta-hexosaminidase B (HEX B).

The forms of GM2 gangliosidosis are Tay-Sachs disease (resulting from biallelic pathogenic variants in *HEXA*), Sandhoff disease (resulting from biallelic pathogenic variants in *HEXB*), and GM2 activator deficiency (resulting from biallelic variants in *GM2A*). For hexosaminidase enzyme findings in these disorders, see Table 7.

A representative diagram of the interaction between these proteins can be found in Figure 1 of Cachon-Gonzalez et al [2018].

Table 7. Hexosaminidase Enzyme Findings in GM2 Gangliosidoses

Disease	HEX A Activity	HEX B Activity	Total HEX Activity	HEX A % Contribution
Tay-Sachs disease	↓	nl	↓	↓
Sandhoff disease	↓	↓	↓	↑
GM2 activator deficiency	Normal	Normal	Normal	Normal

In Tay-Sachs disease total hexosaminidase activity (i.e., HEX A plus HEX B) is decreased, whereas HEX B activity is normal.

In Sandhoff disease both HEX A activity and HEX B activity, as well as total hexosaminidase activity, are decreased; however, the percent contribution from HEX A is increased, because the percent contribution from HEX B is disproportionately decreased by loss of the function of the beta subunit.

In GM2 activator deficiency HEX A and HEX B activity are both normal.

Disease severity in Tay-Sachs and Sandhoff disease is inversely correlated to the residual rate of GM2 ganglioside catabolism. Residual conversion rate of less than 0.5% is thought to correlate with infantile disease, while rates of 2%-4% correlate with juvenile or late-onset forms of Tay-Sachs and Sandhoff disease. Although the pathophysiology of subacute juvenile GM2 activator deficiency is likely also related to residual ganglioside catabolism rates, to date experiments to quantify GM2 conversion rate have not been reported.

Mechanism of disease causation. Loss-of-function *GM2A* variants cause decreased or absent activity of GM2 activator protein.

Table 8. Notable *GM2A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000405.5 NP_000396.2	c.82-2668_243+3312del6142	p.Pro28_Lys81del	Homozygous exon 2 deletion reported in 1 person to date [Hall et al 2018]
	c.164C>T	p.Pro55Leu	Present in 4 persons w/possible subacute-juvenile GM2 activator deficiency, in homozygous state in 1 family w/3 affected sibs [Salih et al 2015] & in compound heterozygous state in 1 affected person in unrelated family [Martins et al 2017]

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

Dr Tifft and Dr Toro are actively involved in clinical research regarding individuals with GM2 activator deficiency. They would be happy to communicate with persons who have any questions regarding diagnosis of GM2 activator deficiency or other considerations.

Dr Tifft, Dr Toro, and Dr Xiao are also interested in hearing from clinicians treating families affected by a GM2 gangliosidosis in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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Revision History

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Note: Pursuant to 17 USC Section 105 of the United States Copyright Act, the *GeneReview* "GM2 Activator Deficiency" is in the public domain in the United States of America.

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