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NLM Citation: Sun A, Wang R. Mucopolysaccharidosis Type VII. 2024 Jan 4. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Mucopolysaccharidosis Type VII

Synonyms: Beta-Glucuronidase Deficiency, MPS7, Sly Syndrome

Angela Sun, MD and Raymond Wang, MD[1,2]

Created: January 4, 2024.

Summary

Clinical characteristics

Individuals with mucopolysaccharidosis type VII (MPS VII) can present perinatally with early demise, nonimmune hydrops fetalis, cholestatic jaundice, and hepatosplenomegaly, or in early childhood with developmental delay and characteristic musculoskeletal features (e.g., short neck, short-trunk short stature, pectus deformity, gibbus, and joint stiffness/contractures) and craniofacial features (e.g., macrocephaly, coarse hair, coarse facies, corneal clouding, and macroglossia). Skeletal survey shows features of dysostosis multiplex including thickened cortical bone, abnormal J-shaped sella turcica, paddle- or oar-shaped ribs, short, thickened clavicles, platyspondyly with anterior beaking of the lower thoracic and lumbar vertebrae, and proximal pointing of the metacarpals and metatarsals. Complications include developmental delay, intellectual disability, hepatosplenomegaly, spinal stenosis, recurrent otitis media, hearing loss, pulmonary disease, obstructive sleep apnea, hernias, feeding difficulties, and heart valve disease.

Diagnosis/testing

The diagnosis of MPS VII is established in a proband with characteristic clinical and radiographic findings, urine glycosaminoglycan (GAG) analysis with elevated concentrations of total GAGs with increased dermatan and chondroitin sulfate, and absent or reduced beta-glucuronidase enzyme activity in leukocytes, fibroblasts, or dried blood spots; and/or biallelic pathogenic variants in *GUSB* identified by molecular genetic testing.

Management

Targeted therapy: Enzyme replacement therapy with vestronidase alfa.

Supportive care: Neonatal intensive care for infants with nonimmune hydrops fetalis; surgical fusion for atlantoaxial instability, surgery as needed for scoliosis, spine monitoring during surgery; anti-inflammatory medications and/or analgesics as needed for pain due to joint stiffness; physical medicine and rehabilitation, physical therapy, and occupational therapy for issues with mobility and activities of daily living; surgical decompression for spinal stenosis, wrist splints and surgery for carpal tunnel syndrome; early intervention

Author Affiliations: 1 Children's Hospital of Orange County, Orange, California; Email: rawang@choc.org. 2 University of California, Irvine, Irvine, California; Email: rawang@choc.org.

services, speech therapy, and school support for developmental issues; tonsillectomy and adenoidectomy for airway obstruction and sleep apnea; positive pressure ventilation as needed; pulmonary toilet for restrictive lung disease; tympanostomy tubes and hearing aids for hearing loss; treatment per ophthalmologist for corneal clouding; thickeners and gastrostomy tube placement as needed for feeding difficulties; surgical repair for hernia; treatment of cardiac disease per cardiologist; hospice care when needed.

Surveillance: Urine dermatan and chondroitin sulfate levels every six to 12 months in individuals on enzyme replacement therapy; assess growth parameters every six to 12 months throughout childhood, then annually; developmental assessment every six to 12 months throughout childhood; orthopedic evaluation annually with radiographs per orthopedist; rehabilitation medicine evaluation as needed; neurologic exam and spine MRI annually throughout childhood and then every two years or per orthopedist in those who have had spinal decompression; ENT and pulmonary evaluations annually with sleep study and pulmonary function tests based on age and clinical manifestations; audiology examination annually throughout childhood and then every two years in adolescents and adults; ophthalmology examination every one to two years; echocardiogram and EKG every one to two years; abdominal MRI every two years or until organomegaly is improved on treatment; nerve conduction study every two years starting in school age or as needed; dental exams every six to 12 months.

Agents/circumstances to avoid: Individuals who have not had cervical fusion should not participate in activities that may result in cervical spine injury such as gymnastics. Cervical spine precautions must be taken during intubation for anesthesia.

Evaluation of relatives at risk: Testing of all at-risk sibs of any age is warranted to identify as early as possible those who would benefit from prompt initiation of enzyme replacement therapy and preventive measures.

Genetic counseling

MPS VII is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GUSB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *GUSB* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for mucopolysaccharidosis type VII (MPS VII) have not been established.

Suggestive Findings

MPS VII **should be suspected** in a proband with any combination of the following clinical, radiographic, laboratory, and family history findings.

Clinical findings

- **Fetal/neonatal presentation**
  - Fetal demise / neonatal mortality
  - Nonimmune hydrops fetalis (Note: Presence of hydrops does not necessarily predict subsequent severity of disease in surviving neonates.)
  - Cholestatic jaundice
  - Hepatosplenomegaly
- **Early childhood presentation**

- Musculoskeletal features (short neck, odontoid hypoplasia, disproportionate short-trunk short stature, pectus carinatum or excavatum, kyphosis, gibbus deformity, scoliosis, contractures, joint stiffness, genu valgum)
- Developmental delay / intellectual disability with variable age of onset and severity that is typically evident by age two years
- Characteristic craniofacial features (macrocephaly, coarse hair, coarse facies, corneal clouding, thick eyebrows, macroglossia, gingival hypertrophy, small and widely spaced teeth) (See Figure 1.)
- Recurrent otitis media or respiratory infections
- Snoring, enlarged tonsils and adenoids, obstructive sleep apnea
- Hearing loss (sensorineural or conductive)
- Prominent abdomen with hepatosplenomegaly
- Hernias (umbilical and/or inguinal)
- Thickening of mitral and/or aortic valve leaflets, valve insufficiency, valve stenosis, left ventricular hypertrophy

Radiographic findings. Skeletal survey shows features of dysostosis multiplex including thickened cortical bone, abnormal J-shaped sella turcica, paddle- or oar-shaped ribs, short, thickened clavicles, platyspondyly and anterior beaking of the lower thoracic and lumbar vertebrae, rounded iliac wings, shallow acetabulae, coxa valga, genu valgum, proximal pointing of the metacarpals and metatarsals, and bullet-shaped phalanges.

Laboratory findings. Urine glycosaminoglycan (GAG) analysis demonstrates elevated concentrations of dermatan and chondroitin sulfate with increased levels of total GAGs.

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 MPS VII **is established** in a proband with increased levels of urinary GAGs, suggestive findings, and:

- Absent or reduced beta-glucuronidase enzyme activity in leukocytes, fibroblasts, or dried blood spots

  AND/OR

- Biallelic pathogenic (or likely pathogenic) variants in *GUSB* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *GUSB* variants of uncertain significance (or of one known *GUSB* pathogenic variant and one *GUSB* 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) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *GUSB* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-

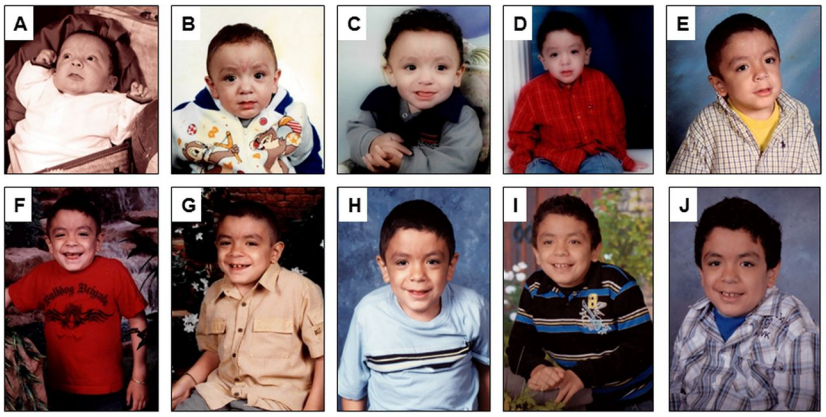

Figure 1. Serial images of a male with mucopolysaccharidosis type VII at ages (A) 2.5 months, (B) six months, (C) one year, (D) three years, (E) five years, (F) six years, (G) seven years, (H) eight years, (I) nine years, and (J) 11 years, showing characteristic craniofacial features (macrocephaly, progressively coarse facies, thick eyebrows, and widely spaced teeth).

Reprinted with permission from Montaño et al [2016]

exon, multiexon, or whole-gene deletions/duplications may not be detected. If 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.

Note: Targeted analysis for pathogenic variants can be performed first in individuals of Mexican, Brazilian, and Japanese ancestry (see Table 7).

A mucopolysaccharidosis multigene panel that includes *GUSB* 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 MPS VII has not been considered because an individual has atypical phenotypic features, **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 Mucopolysaccharidosis Type VII

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GUSB	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	1 reported [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. A homozygous exon 9 deletion was identified in a fetus with nonimmune hydrops [Sparks et al 2020].

Clinical Characteristics

Clinical Description

Individuals with mucopolysaccharidosis type VII (MPS VII) can present perinatally with early demise, nonimmune hydrops fetalis, cholestatic jaundice, and hepatosplenomegaly, or in early childhood with developmental delay and characteristic musculoskeletal and craniofacial features. To date, <200 individuals have been identified with biallelic pathogenic variants in *GUSB*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Mucopolysaccharidosis Type VII: Frequency of Select Features

Feature		% of Persons w/Feature
Growth / constitutional	Disproportionate short stature	100%
	Nonimmune hydrops fetalis	30%-50%
Musculoskeletal features	Dysostosis multiplex	90%
	Pectus carinatum/excavatum	85%
	Joint contractures	85%
	Joint stiffness	75%
	Short-trunk short stature	80%
	Scoliosis	70%
	Kyphosis	70%
	Gibbus	50%-70%
	Genu valgum	60%-70%
	Acetabular dysplasia	50%
	Talipes equinovarus	35%

Table 2. continued from previous page.

Feature		% of Persons w/Feature
Neurologic	Intellectual disability	85%
	Spinal stenosis	25%-50%
	Hydrocephalus	Unknown
	Carpal tunnel syndrome	Unknown
Craniofacial features	Coarse facial features	>80%
	Macrocephaly	>80%
	Corneal clouding	50%-75%
	Small, widely spaced teeth	50%-75%
	Macroglossia	20%-70%
	Gingival hypertrophy	50%-60%
Respiratory/ENT manifestations	Recurrent respiratory infections	50%-70%
	Snoring	60%-70%
	Enlarged tonsils or adenoids	30%-40%
	Obstructive sleep apnea	30%-70%
	Conductive/sensorineural hearing loss	25%-50%
Liver/GI manifestations	Hepatosplenomegaly	75%
	Umbilical/inguinal hernia	60%-80%
	Cholestatic jaundice	5%-10%
Cardiac manifestations	Cardiac valvular disease	30%-50%
	Left ventricular hypertrophy	30%-40%

GI = gastrointestinal
Montaño et al [2016], Zielonka et al [2017], Morrison et al [2019], Poswar et al [2022]

Growth. Disproportionate short-trunk short stature occurs due to vertebral body dysplasia and spinal curvature and is often evident before age two years. Even in individuals with initially normal stature, growth velocity slows prematurely [Montaño et al 2016] so that final adult height is very likely to be two standard deviations below the mean. Those who survive nonimmune hydrops fetalis are generally of shorter stature than those who did not experience hydrops.

As adolescent weight tends to be above the 50th centile, the prevalence of overweight is higher especially for individuals who are not independently ambulatory. A study of intravenous enzyme replacement therapy initiated prior to age five years found improved growth velocity and z scores after 48 weeks of treatment, but long-term effects of therapy on final adult height and weight are not known [Lau et al 2022].

Musculoskeletal features. Dysostosis multiplex may be one of the first noted manifestations of MPS VII. In addition to disproportionate short-trunk short stature, spine manifestations include progressive scoliosis, kyphosis, lumbosacral gibbus, and spinal stenosis most commonly affecting the cervical region. Atlantoaxial instability results from odontoid hypoplasia. Glycosaminoglycan (GAG) storage in joint capsules, ligaments, and other connective tissue make restriction of joint mobility and contractures also very common. This is especially evident in the hip joint, where shallow acetabulae contribute to a high frequency of hip pain, difficulty walking, and osteoarthritis later in childhood and adolescence. Genu valgum and talipes equinovarus can develop. GAG storage can also cause carpal tunnel syndrome.

Neurologic. Spinal stenosis occurs as a result of GAG deposition in the dura and atlantooccipital instability. Spinal cord compression can develop as early as age one to two years and into adolescence. Young individuals or those with cognitive impairment may not report clinical symptoms of myelopathy, but hyperreflexia and ankle clonus can be found on physical exam. Similarly, they may not report symptoms of carpal tunnel syndrome. Hydrocephalus has been reported as a rare complication, but its exact prevalence is not known.

Developmental delay. A high frequency of conductive/mixed hearing loss contributes to speech delay, which is typically not recognized until after age 18 to 24 months. Gross motor and fine motor milestone acquisition is also delayed, a result of skeletal dysplasia compounded with accumulation of GAGs in the central nervous system. This may be evident in the first year of life as infants are delayed in sitting, crawling, standing, and walking. Enzyme replacement therapy may improve motor milestone acquisition, but very few individuals were assessed in the clinical trial [Lau et al 2022].

Intellectual disability. Most children with MPS VII have moderate-to-severe intellectual disability. Additionally, behavioral difficulties such as impulsivity, hyperactivity, insomnia, and hitting/kicking make this one of the most challenging aspects of MPS VII for caregivers [Montaño et al 2016]. As stored central nervous system GAGs are thought to be the etiology of neurocognitive deficits, intravenous enzyme replacement therapy is not expected to impact the intellect.

Craniofacial features. Macrocephaly, coarse hair, and gingival hypertrophy may be present in the neonatal period. Facial features coarsen with age, and affected individuals may develop macroglossia, corneal clouding, thick eyebrows, and thickened lips (see Figure 1). Dental problems include widely spaced teeth and poor enamel.

Respiratory complications. GAG storage in the upper airways and eustachian tubes results in recurrent bacterial acute otitis media as well as upper respiratory tract infections. Individuals often develop acute otitis media before they are able to clear prior middle ear effusions, resulting in chronic otitis and resultant conductive hearing loss. Macroglossia, in conjunction with adenoidal and tonsillar hypertrophy, contribute to upper airway obstructive disease and difficult airway management for anesthesiologists and otolaryngologists. Obstructive sleep apnea, lower respiratory tract infections, and restrictive lung disease also occur. As individuals get older, respiratory complications become one of the leading causes of morbidity and mortality [Montaño et al 2016]. In some instances, families and their care team opt for tracheostomy.

Gastrointestinal manifestations. Hepatosplenomegaly due to GAG storage is a common finding. Umbilical, inguinal, and hiatal hernias are also common. Unlike other MPS types, cholestatic jaundice is a well-known (if infrequent) manifestation of MPS VII and may be a consequence of fetal hepatic sinusoidal congestion and resultant liver dysfunction [Montaño et al 2016]. Feeding difficulties may necessitate thickeners and/or gastrostomy tube placement.

Cardiovascular complications. Accumulation of dermatan and chondroitin sulfate GAGs in heart valves results in progressive thickening of the heart valve leaflets. This is usually observed on echocardiography before age five years. Though initially valve thickening does not interfere with function, progressive disease results in defects of valve coaptation and subsequent valvular insufficiency and/or stenosis. Valvular disease affects all four heart valves but is most clinically significant in the mitral and aortic valves. Rarely, severity of valve dysfunction necessitates surgical valve replacement [Marek et al 2021]. Left ventricular hypertrophy and cardiomyopathy are also common findings. Life-threatening dysrhythmias, likely caused by subendocardial fibrosis, are a recurrent cause of death in individuals with MPS VII [Montaño et al 2016, Lew at al 2018]. Monitoring for abnormal cardiac rhythms should be conducted by experts in MPS during anesthesia.

Genotype-Phenotype Correlations

Genotype-phenotype correlations have been suggested, though sample size is small [Tomatsu et al 2009, Montaño et al 2016]. In general, *GUSB* nonsense variants and deletions tend to be associated with severe

phenotypes. Individuals with residual enzyme activity >1.4% of normal enzyme activity have later disease onset and longer survival [Zielonka et al 2017].

Prevalence

MPS type VII is an ultrarare disorder with a global prevalence estimated to be <200 individuals [Harmatz et al 2018].

GUSB founder variants have been identified in the Mexican population, c.1244C>T (p.Pro415Leu) and c.[1244C>T;1222C>T] (p.[Pro415Leu;Pro408Ser]), the latter being two pathogenic variants occurring in *cis*. The c.1856C>T (p.Ala619Val) allele is a founder variant in the Japanese population [Tomatsu et al 2009]. The pathogenic variant c.526C>T (p.Leu176Phe) accounted for 96% of alleles in a Brazilian cohort, and almost all affected individuals were homozygous [Giugliani et al 2021]. To date, carrier frequency in these populations is unknown.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Lysosomal storage disease. Findings in individuals with mucopolysaccharidosis type VII (MPS VII) overlap those of other lysosomal diseases, particularly other mucopolysaccharide disorders, including those summarized in Table 3. Clinical findings and biochemical testing can distinguish them.

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of Mucopolysaccharidosis Type VII

Gene	Disorder	MOI	Clinical Findings	Laboratory Findings
IDUA	MPS I	AR	Similar to MPS VII	Deficient alpha-L-iduronidase enzyme activity in leukocytes or fibroblasts
IDS	MPS II	XL	Similar to MPS VII but no corneal clouding	Deficient iduronate 2-sulfatase enzyme activity in leukocytes or fibroblasts in the presence of normal activity of at least one other sulfatase
ARSB	MPS VI (OMIM 253200)	AR	Similar to MPS VII	Deficient arylsulfatase B enzyme activity in leukocytes or fibroblasts
GALNS	MPS IVA	AR	Prominent skeletal disease, normal intellect	Deficient N-acetylgalactosamine 6-sulfatase enzyme activity in leukocytes or fibroblasts
GLB1	MPS IVB (See *GLB1*-Related Disorders.)	AR	Prominent skeletal disease, normal intellect	Deficient beta-galactosidase enzyme activity in leukocytes or fibroblasts
GNPTAB	ML II & ML IIIα/β (See *GNPTAB*-Related Disorders.)	AR	Similar to MPS VII but skin is thickened & waxy	Abnormal urine oligosaccharides, increased activity of multiple lysosomal hydrolases in plasma
MAN2B1	Alpha-mannosidosis	AR	Similar to MPS VII but may have psychiatric manifestations in adolescence	Deficient acid alpha-mannosidase enzyme activity in leukocytes or fibroblasts
NEU1	ML I (sialidosis) (OMIM 256550)	AR	Similar to MPS VII but w/vision loss, myoclonic seizures, cherry-red spot	Abnormal urine oligosaccharides, deficient neuraminidase enzyme activity in fibroblasts

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Findings	Laboratory Findings
SUMF1	Multiple sulfatase deficiency	AR	Similar to MPS VII but w/ ichthyosis, retinopathy, seizures	Low activity levels in at least two sulfatase enzymes

AR = autosomal recessive; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked

Management

No clinical practice guidelines for mucopolysaccharidosis type VII (MPS VII) have been published. Due to the clinical disease variability, these recommendations are intended to be a general guide, and management should be tailored to the specific individual.

Evaluations Following Initial Diagnosis

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

Table 4. Mucopolysaccharidosis Type VII: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
General	Consultation w/metabolic physician	Referral to center w/experience in mgmt of lysosomal disorders
Skeletal manifestations	• Assessment of growth incl upper to lower segment ratios • Skeletal survey incl cervical flexion-extension radiographs • Consultation w/orthopedist	Further imaging to be ordered after eval by orthopedist
Neurologic	• Assessment for hyperreflexia & clonus • MRI of whole spine to assess for spinal stenosis	
Development	Developmental assessment	
ENT/Respiratory	Consultation w/ENT specialist & pulmonologist	Imaging & other assessments to be ordered after eval by specialists
Hearing	Audiology eval	
Vision	Ophthalmology exam	
Organomegaly/ Gastrointestinal	• MRI or abdominal ultrasound to assess liver & spleen volume/dimensions • Assessment for hernias	Ultrasound can be done if sedation for MRI is a concern but does not provide volumetric data.
Cardiac	• EKG • Echocardiogram	
Genetic counseling	By genetics professionals [1]	Discuss nature, MOI, & implications of MPS VII to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support

MOI = mode of inheritance; MPS VII = mucopolysaccharidosis type VII
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Enzyme replacement therapy with vestronidase alfa is the only disease-modifying therapy currently available for MPS VII. In a Phase III clinical trial, 12 individuals treated with vestronidase alfa demonstrated a mean 64.8% reduction in urinary dermatan sulfate and 70.6% reduction in chondroitin sulfate excretion after 24 weeks compared to placebo (P <0.0001) [Harmatz et al 2018]. The reduction occurred within the first two weeks of treatment initiation. Ten of 12 participants had clinically meaningful improvements in at least one multi-domain responder index (MDRI) domain (e.g., six-minute walk test, forced vital capacity, and/or shoulder flexion). Regarding safety, the most common adverse events were upper respiratory tract infection, extremity pain, infusion site extravasation, cough, vomiting, rash, and diarrhea. Of 215 total infusions, only two (0.9%) were categorized as hypersensitivity infusion-associated reactions. Seven of 12 participants tested positive for anti-drug antibodies. There was no impact of antibody titers on urine glycosaminoglycan (GAG) reduction. In the long-term extension study, the safety profile was similar, with most adverse events being mild to moderate in severity [Wang et al 2020]. Treated individuals demonstrated sustained reduction of urine GAG levels. In an open-label Phase II study in eight children younger than age five years, similar reduction of urine GAG excretion was observed [Lau et al 2022]. In addition, positive trends were seen in standing height and growth velocity, and hepatomegaly resolved in most.

As with enzyme replacement therapy for other MPS disorders, vestronidase alfa does not cross the blood-brain barrier and thus does not treat central nervous system disease.

Vestronidase alfa is administered at a dose of 4 mg/kg rounded to the next whole vial. Premedication with a non-sedating antihistamine with or without an antipyretic is recommended prior to the infusion. Given the need for long-term treatment, a portacath may be helpful for intravenous access.

Hematopoietic stem cell transplantation (HSCT) was provided to a small number of individuals with variable results. Despite transplant-related complications, if the transplant is performed before the development of irreversible damage (mainly neurologic and skeletal), HSCT can potentially be considered a treatment option for MPS VII [Poswar et al 2022].

Supportive Care

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

Table 5. Mucopolysaccharidosis Type VII: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Nonimmune hydrops fetalis	Neonatal intensive care	
Skeletal manifestations	• Surgical fusion for atlantoaxial instability • Surgical treatment of scoliosis as needed • Spine monitoring during surgeries	Other surgeries such as hip &/or knee surgery per orthopedist
	Anti-inflammatory medications &/or analgesics as needed for pain assoc w/joint stiffness	
	Consultation w/physical medicine & rehab / PT & OT for issues w/ mobility & ADL	Durable medical equipment (e.g., wheelchair, walker)
Neurologic	• Surgical decompression for spinal stenosis • Wrist splints & surgery as needed for carpal tunnel syndrome	
Developmental delay	• Early intervention services • Speech therapy • School support (IEP)	
Airway obstruction / Sleep apnea	• Tonsillectomy & adenoidectomy • Positive pressure ventilation	Tracheal reconstructive or other airway surgery, tracheostomy
Restrictive lung disease	Pulmonary toilet	
Hearing loss	• Tympanostomy tubes • Hearing aids	
Corneal clouding	Treatment per ophthalmologist	
Dysphagia/ Aspiration	• Thickeners as needed • Gastrostomy tube placement	
Hernias	Surgical repair	
Cardiac disease	Treatment per cardiologist	
End-of-life care	Hospice	

ADL = activities of daily living; IEP = individualized education plan; OT = occupational therapy; PT = physical therapy

Surveillance

Due to the broad clinical disease spectrum, surveillance should be tailored to the individual. To monitor existing manifestations, the individual's response to treatment, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Mucopolysaccharidosis Type VII: Recommended Surveillance

System/Concern	Evaluation	Frequency
Biomarkers	Urine dermatan & chondroitin sulfate	Every 6-12 mos in individuals on ERT
Growth/Feeding/Nutrition	Height, weight, & OFC measurement	Every 6-12 mos in infants & children, annually thereafter
Developmental delay / Intellectual disability	Developmental assessment	Every 6-12 mos throughout infancy & childhood
Skeletal manifestations	Orthopedics eval	Annually
	Radiographs	As recommended by orthopedist
	Rehab medicine eval	As needed

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Spinal stenosis	• Neurologic exam • Spine MRI	Annually throughout childhood, then every 2 yrs, or per orthopedist in those who have had spinal decompression
Respiratory	ENT & pulmonary eval	Annually
	• Sleep study • Pulmonary function tests	Based on age & clinical manifestations
Hearing loss	Audiology exam	Annually throughout childhood; every 2 yrs in adolescents/ adults
Corneal clouding / Vision concerns	Ophthalmology exam	Every 1-2 yrs
Cardiac disease	• Echocardiogram • EKG	Every 1-2 yrs
Organomegaly	Abdominal MRI	• Every 2 yrs or until organomegaly is improved on treatment. • Ultrasound can be done if sedation for MRI is a concern but does not provide volumetric data.
Carpal tunnel syndrome	Nerve conduction study	Every 2 yrs or as needed starting at school age
Dental care	Dental exams	Every 6-12 mos

ERT = enzyme replacement therapy; OFC = occipitofrontal circumference

Agents/Circumstances to Avoid

Atlantoaxial instability can cause serious neurologic injury. Individuals who have not had cervical fusion should not participate in activities that may result in cervical spine injury such as gymnastics. Cervical spine precautions must be taken during intubation for anesthesia.

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to identify as early as possible those who would benefit from prompt initiation of enzyme replacement therapy and preventive measures.

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

Mucopolysaccharidosis type VII (MPS VII) 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 *GUSB* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *GUSB* 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 *GUSB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Based on limited case reports, affected sibs appear to manifest similar disease courses [Van Dorpe et al 1996, Montaño et al 2016].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with MPS VII are obligate heterozygotes (carriers) for a pathogenic variant in *GUSB*.

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

Carrier Detection

Molecular genetic testing. Molecular genetic carrier testing for at-risk relatives requires prior identification of the *GUSB* pathogenic variants in the family.

Carriers usually have low-normal or slightly deficient beta-glucuronidase enzyme activity; thus, molecular genetic testing is required to determine carrier status.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with MPS VII, particularly if both partners are of the same ancestral background. Founder variants have been identified in the Mexican, Japanese, and Brazilian populations (see Table 7).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once both *GUSB* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for MPS VII are possible.

Biochemical testing. Beta-glucuronidase enzyme analysis can be performed on cultured chorionic villus cells or amniocytes.

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.

- **Canadian Society for Mucopolysaccharide and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
  mpssociety.ca
- **MedlinePlus**
  Mucopolysaccharidosis type VII
- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
  Email: mps@mpssociety.org.uk
  mpssociety.org.uk
- **National MPS Society**
  Phone: 877-MPS-1001
  mpssociety.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. Mucopolysaccharidosis Type VII: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GUSB	7q11.21	Beta-glucuronidase	GUSB database	GUSB	GUSB

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 Mucopolysaccharidosis Type VII (View All in OMIM)

253220	MUCOPOLYSACCHARIDOSIS, TYPE VII; MPS7
611499	BETA-GLUCURONIDASE; GUSB

Molecular Pathogenesis

Mucopolysaccharidosis type VII is caused by deficiency of the lysosomal enzyme beta-glucuronidase, which is involved in the degradation of chondroitin sulfate, dermatan sulfate, and heparan sulfate. The partially degraded glycosaminoglycans accumulate in the lysosomes of many tissues, leading to cell and organ dysfunction.

Mechanism of disease causation. Loss-of-function variants result in absent or decreased enzyme activity.

***GUSB*-specific laboratory technical considerations.** Pseudodeficiency alleles are non-pathogenic variants that cause decreased enzyme activity in vitro but do not result in clinical disease. At least one pseudodeficiency allele has been reported for *GUSB*, c.454G>A (p.Asp152Asn) [Vervoort et al 1995]. In addition, several pseudogenes exist [Tomatsu et al 2009].

Table 7. *GUSB* Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000181.4 NP_000172.2	c.454G>A	p.Asp152Asn	Pseudodeficiency allele [Vervoort et al 1995]
	c.526C>T	p.Leu176Phe	Founder variant in Brazilian population [Giugliani et al 2021]
	c.1222C>T	p.Pro408Ser	Founder variants in Mexican population [Tomatsu et al 2009]
	c.1244C>T	p.Pro415Leu	
	c.1856C>T	p.Ala619Val	Founder variant in Japanese population [Tomatsu et al 2009]

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

Acknowledgments

The authors wish to thank the individuals with mucopolysaccharidosis type VII (MPS VII) and their families along with international research efforts that continue to improve our understanding of MPS VII.

Revision History

- 4 January 2024 (sw) Review posted live
- 7 July 2023 (as) Original submission

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