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Mucopolysaccharidosis Type III

Synonyms: MPS III, Sanfilippo Syndrome

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Summary

Clinical characteristics

Mucopolysaccharidosis type III (MPS III) is a multisystem lysosomal storage disease characterized by progressive central nervous system degeneration manifest as severe intellectual disability (ID), developmental regression, and other neurologic manifestations including autism spectrum disorder (ASD), behavioral problems, and sleep disturbances. Disease onset is typically before age ten years. Disease course may be rapidly or slowly progressive; some individuals with an extremely attenuated disease course present in mid-to-late adulthood with early-onset dementia with or without a history of ID. Systemic manifestations can include musculoskeletal problems (joint stiffness, contractures, scoliosis, and hip dysplasia), hearing loss, respiratory tract and sinopulmonary infections, and cardiac disease (valvular thickening, defects in the cardiac conduction system). Neurologic decline is seen in all affected individuals; however, clinical severity varies within and among the four MPS III subtypes (defined by the enzyme involved) and even among members of the same family. Death usually occurs in the second or third decade of life secondary to neurologic regression or respiratory tract infections.

Diagnosis/testing

The diagnosis of MPS III is established in a proband with suggestive clinical and laboratory findings in whom either biallelic pathogenic variants in one of four genes (*GNS*, *HGSNAT*, *NAGLU*, and *SGSH*) or deficiency of the respective lysosomal enzyme has been identified.

Management

Treatment of manifestations: Supportive therapies for neurodevelopmental delays, hearing loss, and visual impairment; medications (rather than behavioral therapy) for psychiatric/behavioral issues; physical therapy and/or orthopedic management of musculoskeletal manifestations; and management as prescribed by consulting specialists for seizures, cardiac involvement, sleep disorders, feeding difficulties.

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Surveillance: Routine monitoring of: developmental capabilities and educational needs, destructive or disruptive behaviors; musculoskeletal involvement; hearing; cardiac involvement.

Agents/circumstances to avoid: Procedures requiring anesthesia in centers ill-equipped or inexperienced in caring for patients with complex airway-management issues; hip surgery (due to high risk of osteonecrosis of the femoral head); environments not adapted to minimize risk from unpredictable behaviors.

Therapies under investigation: Despite ongoing research for a variety of therapeutic options, no treatments are currently clinically available for treatment of the primary manifestations of MPS III.

Genetic counseling

MPS III is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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 MPS III-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

Mucopolysaccharidosis Type III: Included Subtypes		
Subtype	**Gene**	**Enzyme** [1]
MPS IIIA	*SGSH*	N-sulphoglucosamine sulphohydrolase
MPS IIIB	*NAGLU*	Alpha-N-acetylglucosaminidase,
MPS IIIC	*HGSNAT*	Heparan-alpha-glucosaminide N-acetyltransferase
MPS IIID	*GNS*	N-acetylglucosamine-6-sulfatase

MPS = mucopolysaccharidosis
1. See Nomenclature for alternate names that may be used to refer to these enzymes.

Diagnosis

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

Suggestive Findings

MPS III **should be suspected** in individuals with the following clinical findings and supportive laboratory or imaging findings.

Clinical findings

- **Age 1-3 years.** Language and motor delays
- **Age 3-10 years**
  - Language and motor delays
  - Behavioral problems including hyperactivity and aggressive or defiant behaviors
  - Sleep disturbances
- **Age ≥10 years**
  - Intellectual disability
  - Progressive developmental regression including loss of toilet training, language (if acquired), and motor skills
  - Seizures
  - Gait disorders

- **General findings**
  - Coarse facies
  - Thick hair and hirsutism
  - Hepatosplenomegaly
  - Joint stiffness
  - Hearing loss
  - Frequent upper-respiratory and ear infections
  - Inguinal and/or umbilical hernias

Note: Clinical findings alone are not diagnostic and may vary by disease severity.

Supportive laboratory findings. Analysis of urinary glycosaminoglycans (GAG) (i.e., heparan sulfate) may be quantitative (measurement of total urinary GAG amount) or qualitative (GAG electrophoresis to analyze specific GAGs present in the urine).

- While quantitative and qualitative analysis of GAGs cannot diagnose specific lysosomal enzyme deficiencies, including MPS III, an abnormality in either quantitative or qualitative GAG analysis is suggestive of an MPS disorder.
- GAG electrophoresis can assist in excluding and including certain MPS disorders; however, definitive diagnosis requires additional testing (see Establishing the Diagnosis).
- Both methods of urinary GAG analysis have reduced sensitivity, especially if urine is dilute. Normal results on urinary GAG analysis cannot rule out an MPS disorder, particularly in the case of MPS III.

Imaging findings

- **Radiographs.** Skeletal survey reveals mild signs of dysostosis multiplex (e.g., thickened "oar-shaped" ribs, scoliosis, kyphosis, misshaped or hypoplastic vertebral bodies, thickened diploic space), particularly in older children with a rapidly progressing form. Hip deformities such as acetabular dysplasia and osteonecrosis of the femoral head are also observed.
- **MRI**
  - Brain MRI demonstrates abnormalities such as white matter alterations (diffuse prolonged T_1 and T_2 relaxation times), enlarged subarachnoid and perivascular spaces, ventriculomegaly, and widening of the cortical sulci consistent with diffuse cerebral atrophy.
  - Spine MRI reveals spinal stenosis or spinal cord compression that can lead to narrowing of the central canal.
- **Echocardiogram** often exhibits valvular anomalies including mitral or aortic valve thickening, mitral or aortic regurgitation, and mitral valve prolapse.

Note: These findings may not be present in early life, may vary by disease severity, and are not specific to MPS III.

Establishing the Diagnosis

The diagnosis of MPS III **is established** in a proband with suggestive clinical and laboratory findings in whom either biallelic pathogenic variants in one of four genes (*GNS*, *HGSNAT*, *NAGLU*, and *SGSH*) (see Table 1) or deficiency of the respective lysosomal enzyme (see scope table) has been identified.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of MPS III is broad and age dependent, individuals with the distinctive

findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas:

- Those with a phenotype indistinguishable from many other inherited disorders with intellectual disability, developmental regression, and/or significant behavioral issues are more likely to be diagnosed using genomic testing (see Option 2).
- Those in whom the diagnosis of MPS III has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When clinical and laboratory findings suggest the diagnosis of MPS III, molecular genetic testing approaches can include use of a **multigene panel**.

An MPS III or mucopolysaccharidosis multigene panel that includes *GNS*, *HGSNAT*, *NAGLU*, *SGSH*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

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

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 III

Gene [1, 2]	Proportion of MPS III Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/duplication analysis [6]
GNS	6%	~84% [7]	~16% [7]
HGSNAT	4%	~98% [8]	Unknown [9]
NAGLU	30%	~90% [10]	Unknown [9]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of MPS III Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/duplication analysis [6]
SGSH	60%	~98% [11]	Unknown [9]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Andrade et al [2015]
4. See Molecular Genetics for information on allelic variants detected in this gene.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Champion et al [2010] and Valstar et al [2010a]) may not be detected by these methods.
7. The detection rate for pathogenic variants in *GNS* by sequence analysis in 16 individuals with MPS IIID was approximately 84%. The other 16% were exon or large intragenic deletions [Valstar et al 2010a].
8. The detection rate for pathogenic variants in *HGSNAT* by sequence analysis in 29 individuals with MPS IIIC was approximately 98% [Ruijter et al 2008].
9. No data on detection rate of gene-targeted deletion/duplication analysis are available.
10. In a study of 24 individuals, the detection rate for pathogenic variants in *NAGLU* was approximately 90% [Valstar et al 2010b].
11. In DNA analysis of 101 individuals with MPS IIIA, the detection rate for pathogenic variants in *SGSH* was approximately 98% [Valstar et al 2010c].

Enzymatic activity of the four enzymes produced by *GNS*, *HGSNAT*, *NAGLU*, and *SGSH* (see scope table) can be measured in multiple tissues; specifically, peripheral blood leukocytes and cultured skin fibroblasts. Blood plasma can also be used to assay activity of alpha-N-acetylglucosaminidase for diagnosis of MPS IIIB.

- The recommended strategy for enzymatic assay is simultaneous enzyme panel testing of all four enzymatic deficiencies associated with MPS IIIA (N-sulphoglucosamine sulphohydrolase), MPS IIIB (alpha-N-acetylglucosaminidase), MPS IIIC (heparan-alpha-glucosaminide N-acetyltransferase), and MPS IIID (N-acetylglucosamine-6-sulfatase). (Note: For alternate enzyme naming systems used by some laboratories, see Nomenclature.) Deficient or very little enzyme activity in any one of these enzymes along with normal activity of the other three enzymes and clinical signs of the disorder is consistent with diagnosis of the corresponding subtype of MPS III.
- Deficiency of both enzymes associated with MPS IIIA and MPS IIID (N-sulphoglucosamine sulphohydrolase and N-acetylglucosamine-6-sulfatase, respectively) – in the context of normal activity of the enzymes associated with MPS IIIB and MPS IIIC – may suggest a diagnosis of multiple sulfatase deficiency rather than MPS III.
- In fluorometric assays for MPS IIIC, endogenous beta-hexosaminidase is used to convert the intermediate substance into the fluorescence-releasing final product. Therefore, individuals with beta-hexosaminidase deficiencies could receive false positive results for MPS IIIC.

Clinical Characteristics

Clinical Description

Mucopolysaccharidosis type III (MPS III), a multisystem lysosomal storage disease that results from glycosaminoglycan (GAG) accumulation, is characterized by extreme clinical variability. Progressive central nervous system degeneration resulting in severe intellectual disability and developmental regression is the most

prominent manifestation. Although often present, the somatic findings characteristic of other mucopolysaccharidoses (MPSs) are generally less clinically striking in individuals with MPS III.

Despite the universal neurologic decline in affected individuals, clinical severity varies within and among the four MPS III subtypes and even among members of the same family. Individuals with MPS III may have rapidly or slowly progressing disease [Valstar et al 2010c]. Some individuals with an extremely attenuated disease course present in mid-to-late adulthood with early-onset dementia with or without history of intellectual disability [Berger-Plantinga et al 2004, Verhoeven et al 2010].

Life span of individuals with MPS III is unpredictable, but shortened. Death usually occurs in the second or third decade of life secondary to neurologic disease or respiratory tract infections [Valstar et al 2010a, Lavery et al 2017]. Although some individuals with more slowly progressive, later-onset, or mild disease can live into their 30s, 40s, or even 50s with excellent medical care, this is atypical. In very rare instances, adults with MPS III have survived into their 60s [Verhoeven et al 2010].

In the following descriptions of clinical involvement in MPS III, it is important to note the potential for bias in the medical literature toward ascertaining/reporting clinical data regarding individuals with the most severe and rapidly progressive disease course.

Craniofacial and physical appearance. Many children have dolichocephaly or macrocephaly. Coarse facies, present in most affected individuals, tend to become more evident over time as GAGs accumulate in soft tissues. Dysmorphisms can include thick alae nasi, lips, and ear helices or lobules and macroglossia. Coarse and thick hair are frequently observed, as are synophrys and hirsutism. Skin is often tough and thick, sometimes causing difficulty with venipuncture.

Hepatosplenomegaly. Abdominal protuberance due to progressive organomegaly can be observed but is not universal. GAG accumulation that results in hepatomegaly and splenomegaly does not lead to dysfunction despite increases in size.

Neurologic. Ventriculomegaly is hypothesized to occur secondary to cerebral atrophy and impaired reabsorption of cerebrospinal fluid. Some individuals may experience symptomatic hydrocephalus.

Seizure disorders, common during later disease stages, are not universal.

Progressive neurodegeneration can result in gait disorders, hyperactive reflexes, or spasticity.

Development and cognition. Early childhood development may be normal; however, it is not uncommon for language or other developmental delays to be present from as early as age one year. Developmental delays are frequently evident in affected children by age two to six years; language development is often more delayed than motor development.

After development plateaus, a progressive loss of motor and cognitive skills begins. In rapidly progressing MPS III, regression may start as early as age three to four years. In those with very mild disease, regression may not become apparent until much later [Shapiro et al 2016, Whitley et al 2018]. If language was acquired, verbal skills are often lost by ages ten to 15 years. Although loss of independent ambulation in most affected individuals occurs between the teen years and the third decade, it can be earlier in those with a more severe disease course. Eventually, neurodegeneration leads to dysphagia, immobility, and unresponsiveness [Ruijter et al 2008].

Psychiatric and behavioral. The behavioral phenotype of MPS III, often a hallmark of the disease, usually begins between ages three and five years. Almost all affected children exhibit hyperactivity often unresponsive to medication. Aggressive and destructive behaviors such as outbursts and tantrums are common and can be difficult to control, particularly in individuals with normal mobility and strength. Behavior becomes less problematic with age due to decreased mobility and initiative resulting from progressive neurodegeneration.

Klüver-Bucy syndrome (a distinct set of neurobehavioral manifestations with psychic blindness, hypersexuality, disinhibition, hyperorality, and hypermetamorphosis) has been reported in individuals with MPS III [Potegal et al 2013, Hu et al 2017].

Early-onset dementia is observed in some individuals, particularly those with later-onset or more slowly progressing disease.

Sleep disturbances, present in 80%-95% of individuals, include difficulties with settling and frequent waking. These sleep disorders are thought to result from irregular sleep/wake patterns; some affected individuals demonstrate complete circadian rhythm reversal [Cross & Hare 2013].

Musculoskeletal. Stature of children is often normal or just below normal.

Joint stiffness or contractures and features of dysostosis multiplex are common, although much less severe than in other MPS disorders. Skeletal manifestations are usually not clinically obvious until after the onset of developmental regression and behavioral concerns.

Scoliosis and hip dysplasia, two of the more common skeletal findings, are usually not severe enough to require surgical correction. Femoral head osteonecrosis is a common cause of hip pain.

Carpal tunnel syndrome and trigger digits can occur [White et al 2011].

Low bone mass and vitamin D insufficiency or deficiency are prevalent and can be observed as early as the teenage years. Patients with decreased mobility or a history of anti-seizure medication use are especially at risk for osteoporosis and fractures [Nur et al 2017].

Hearing loss is common and can be conductive, sensorineural, or mixed due to a combination of dysostosis of the ossicles of the middle ear, inner ear abnormalities, and frequent otitis media.

ENT (otolaryngologic). Chronic and recurrent otitis media and rhinitis accompanied by poor sinus drainage are common as are frequent infections of the adenoids and tonsils, which may be enlarged.

Respiratory. Respiratory tract and sinopulmonary infections are common. Abnormal respiration can also be secondary to neurodegeneration, thick secretions with inefficient drainage, and anatomic airway obstruction. Rarely, the adenoids or tonsils are so enlarged that they cause obstructive sleep apnea. However, sleep apnea may also be due to the significant CNS involvement.

Gastrointestinal. Chronic or recurrent loose stools and/or constipation are common, though the primary cause is unknown. Diarrhea typically is episodic, but can be persistent in some. These concerns may be affected by activity or diet and may be exacerbated by frequent antibiotic treatment of recurrent infections.

Inguinal and umbilical hernias are common. Inguinal hernias may recur after surgical intervention. Umbilical hernias are not usually treated unless they are large or cause other medical concerns.

With progression of neurodegeneration, many affected individuals develop dysphagia and/or problems with chewing and swallowing food, increasing risks for aspiration pneumonia and weight loss secondary to poor feeding in later disease stages.

Cardiovascular. Although GAG storage in the mitral valve, aortic valve, myocardium, and/or cardiac conduction system (causing atrioventricular block) is common, most individuals with MPS III do not require cardiac intervention. Left ventricle ejection fraction is normal in children, but slightly impaired in adults [Nijmeijer et al 2019]. Shortened life span and inactivity of older individuals may explain the paucity of clinical cardiac disease in this population to date.

Ophthalmologic. Corneal opacities, such as corneal clouding, are not usually present in individuals with MPS III. Nonetheless, individuals with MPS III can have atrophy of the optic nerve and retinal degeneration (manifesting as pigmentary retinopathy, poor peripheral vision, and night blindness), particularly in late stages of the disease.

Phenotype Correlations by Gene

The subtypes of MPS III, caused by biallelic pathogenic variants in *SGSH* (MPS IIIA), *NAGLU* (MPS IIIB), *HGSNAT* (MPS IIIC), or *GNS* (MPS IIID), are mainly distinguished by their associated enzymatic deficiencies rather than clear phenotypic differences. While each MPS III subtype exhibits variable expressivity, individuals with MPS IIIA typically have the most severe and rapidly progressing disease course [Valstar et al 2010c].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for pathogenic variants in *GNS* and *HGSNAT* have been identified. Table 2 summarizes genotype-phenotype correlations for *NAGLU* and *SGSH*.

Table 2. Genotype-Phenotype Correlations in Mucopolysaccharidosis Type III

Gene (MPS Subtype)	Genotype-Phenotype Correlation
NAGLU (MPS IIIB)	• Homozygosity for variants causing premature termination of the protein product (nonsense or frameshift pathogenic variants) results in more severe or rapidly progressing phenotypes [Zhao et al 1998, Weber et al 1999]. • Homozygosity for nonsense variant p.Arg297Ter or missense variants p.Val334Phe or p.Pro521Leu is associated with severe disease course [Zhao et al 1998, Weber et al 1999]. • The missense pathogenic variants p.Arg643Cys, p.Ser612Gly, p.Glu634Lys, and p.Leu497Val are only reported in individuals w/attenuated or slowly progressing phenotypes [Valstar et al 2010b].
SGSH (MPS IIIA)	• Homozygotes or compound heterozygotes for variants p.Arg245His, p.Arg74Cys, p.Gln380Arg, p.Ser66Trp, and p.Val361SerfsTer52 (c.1080delC) have rapidly progressing disease course [Meyer et al 2008, Valstar et al 2010c]. • The missense p.Ser298Pro variant is associated with a slowly progressive disease course [Meyer et al 2008, Valstar et al 2010c].

Nomenclature

The four lysosomal enzymes associated with MPS III may be referred to by an alternate naming system (see Table 3).

Table 3. Alternate Naming System for MPS III-Related Enzymes

MPS III Subtype	UniProt Knowledgebase (UniProtKB) Name	Alternative Enzyme Name
MPS IIIA	N-sulphoglucosamine sulphohydrolase	Heparan-N-sulfatase; sulfamidase; sulfamate sulfohydrolase
MPS IIIB	Alpha-N-acetylglucosaminidase	N-acetyl-alpha-D-glucosaminidase
MPS IIIC	Heparan-alpha-glucosaminide N-acetyltransferase	Acetyl CoA: alpha-glucosamine N-acetyltransferase
MPS IIID	N-acetylglucosamine-6-sulfatase	Glucosamine-6-sulfatase

Prevalence

The combined estimated prevalence of MPS III is between 1:50,000 and 1:250,000 depending on the population studied [Khan et al 2017]. This may be an underestimate due to variable expressivity and often mild somatic features of the disease.

Subtypes MPS IIIA and MPS IIIB are the most commonly observed, with estimated incidences of 1:100,000 and 1:200,000, respectively [Zelei et al 2018]. MPS IIIC and MPS IIID are, overall, much less common, with estimated incidences of 1:1,500,000 and 1:1,000,000, respectively [Andrade et al 2015].

Of note, some subtypes of MPS III are more common in certain geographic regions:

- MPS IIIA is globally the most common form of MPS III and the most common type observed in many northern and eastern European nations. It is particularly common in the Cayman Islands, with an incidence estimated as high as 1:400 births, secondary to 1/10 carrier frequency of c.734G>A in *SGSH* [Rady et al 2002].
- MPS IIIB is more common in southern European populations.
- MPS IIID has a higher-than-usual prevalence in Italian and Turkish populations [Valstar et al 2010a].

Genetically Related (Allelic) Disorders

Germline pathogenic variants in *HGSNAT* are also known to be associated with nonsyndromic retinitis pigmentosa (OMIM 616544).

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GNS*, *NAGLU*, or *SGSH*.

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of Mucopolysaccharidosis Type III

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MPS III	Distinguishing from MPS III
GNPTAB	ML II	AR	• Coarse facies • Frequent ear infections • Inguinal & umbilical hernias	• Dysostosis multiplex • Corneal clouding • Significant DD seen in 1st year of life • Death at age ~2 yrs from neurologic decline & multisystem involvement
	ML III alpha/beta		• Coarse facies • Frequent upper-respiratory & ear infections	• Dysostosis multiplex • Slight corneal clouding • Normal to mildly impaired cognitive development
IDUA	MPS I	AR	• Coarse facies • Frequent upper-respiratory & ear infections • Inguinal & umbilical hernias • DD & cognitive decline in severe form of disease • Hepatosplenomegaly	• Dysostosis multiplex • Placid behavior in contrast to aggressive or hyperactive • Abnormal heparan & dermatan sulfate in urine GAG analysis • Corneal clouding • Hydrocephalus
IDS	MPS II	XL	• Coarse facies • Frequent upper-respiratory & ear infections • Inguinal & umbilical hernias • DD & cognitive decline in severe form of disease • Behavioral abnormalities • Hepatosplenomegaly	• Dysostosis multiplex • Observed almost exclusively in males • Abnormal heparan & dermatan sulfate in urine GAG analysis • Hydrocephalus

Table 4. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MPS III	Distinguishing from MPS III
SUMF1	Multiple sulfatase deficiency	AR	• Hepatosplenomegaly • DD & cognitive impairment • Psychomotor regression • Hirsutism • Coarse facies	• Ichthyosis • Abnormal enzymatic activity for multiple sulfatases
RAI1	Smith-Magenis syndrome	See footnote 1	• Speech delay • DD & cognitive impairment • Sleep disturbance • Behavioral outbursts • Hyperactivity	• Infantile hypotonia & failure to thrive • Mild-to-moderate ID w/out regression • Characteristic dysmorphic facies • Stereotypic "lick & flip" & "self-hug" behaviors

AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked
1. Smith-Magenis syndrome is caused either by a 17p11.2 deletion that includes *RAI1* or, less commonly, by a pathogenic variant in *RAI1*. Virtually all occurrences are *de novo.*

Other lysosomal storage diseases (LSDs). Many findings in individuals with MPS III overlap those identified in individuals with other LSDs, particularly other mucopolysaccharide diseases including MPS I and MPS II (see Table 2). Clinical presentation, biochemical testing, and molecular testing can assist in distinguishing other LSDs with findings that overlap with those typically observed in MPS III.

Autism spectrum disorder. Language delay and behavioral concerns can be the most prominent and earliest clinical features of MPS III. Many children with MPS III are suspected of having autism spectrum disorder prior to correct diagnosis.

Attention-deficit/hyperactivity disorder (ADHD). Children with MPS III who have hyperactivity as their most prominent initial clinical feature may be misdiagnosed as having ADHD as their primary diagnosis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with mucopolysaccharidosis type III (MPS III), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Mucopolysaccharidosis Type III

System/Concern	Evaluation	Comment
Constitutional	Abdominal ultrasound	Evaluate for hepatosplenomegaly.
Neurologic	Neurologic examination &/or referral to pediatric neurologist	Consider EEG if seizures are a concern.
	Brain MRI	Evaluate for abnormalities incl hydrocephalus.
Language	Speech & language eval	Delayed to absent acquisition of language
Development	Developmental assessment	To incl motor, adaptive, cognitive, & speech/language eval
		Assess need for early intervention / special education.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Psychiatric/ Behavioral	Referral to psychiatrist	Evaluate for behavioral concerns incl sleep disturbances, hyperactivity, aggressiveness, low frustration tolerance, & ASD-like behaviors.
Musculoskeletal	Skeletal survey & referral to orthopedist	Incl eval for osteonecrosis of femoral head, abnormal vertebra causing ↑ risk for scoliosis, & risk for carpal tunnel syndrome.
	DXA & vitamin D metabolism studies to assess BMD	
	Referral for PT/OT	Evaluate & assess mobility & activities of daily living.
Hearing	Audiogram & referral to otolaryngologist	Evaluate for conductive & sensorineural hearing loss.
Respiratory	Referral to pulmonologist	Evaluate for sleep apnea, wheezing.
Gastrointestinal	Assessment of swallowing, feeding, & nutritional status, particularly in later stages of disease	
Cardiovascular	Echocardiogram	Evaluate for valvular disease & other cardiac anomalies.
Miscellaneous/ Other	Family support/resources	Community or online resources such as Parent to Parent. Social work involvement for parental support.
	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Referral to palliative care specialist	When deemed appropriate by family & care providers

ASD = autism spectrum disorder; BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; OT = occupational therapist; PT = physical therapist

Treatment of Manifestations

It is important to note that developmental advances made by individuals with MPS III secondary to implementation of therapy may be short-lived as a result of the progressive nature of disease.

Table 6. Treatment of Manifestations in Individuals with Mucopolysaccharidosis Type III

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	ASM as determined by neurologist	
Neurodevelopmental delays	Supportive therapies (e.g., speech therapy, PT, OT)	
Psychiatric/ behavioral issues	• Treatment as determined by psychiatrist • Creation of physically safe environment at home	Behavioral therapy is unlikely to be effective, especially since any improvements are often lost w/ disease progression. Risperidone can be considered for treatment of hyperactivity [Kalkan Ucar et al 2010]. Antipsychotic drugs may also be effective.
Sleep disorders	• Consider use of melatonin or other medication [Mahon et al 2014]. • Consider polysomnogram if suspicion of sleep apnea.	Treating sleep disorders is, overall, difficult. Consider referral to pulmonologist if concern for sleep apnea. Home modifications may be helpful for children to avoid falls or injuries at night.

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Musculoskeletal manifestations	• Treatment as determined by orthopedist • PT or hydrotherapy for joint stiffness • Vitamin D therapy in the context of low BMD [Nur et al 2017]	Decisions about surgical intervention should be made in the context of disease course & quality of life. Therapies may be useful, but should not be intensive, especially if they cause pain.
Hearing loss	Ear tube insertion or hearing aid use	
Recurrent ENT/respiratory infections	• Treatment as determined by otolaryngologist • Consider airway clearance therapy, particularly in later disease stages.	• The importance of routine immunizations & annual influenza vaccines should be emphasized. • Pneumococcal vaccine may be considered.
Cardiovascular anomalies	Treatment as determined by cardiologist	Consider bacterial endocarditis prophylaxis for patients w/cardiac abnormalities.
Feeding difficulties w/resulting malnutrition	Gastrostomy tube (G-tube) placement	Difficulty chewing & swallowing, &/or dysphagia are common in later stages of disease. Aspiration may ↑ risk for pulmonary infection.
Visual impairment	Treatment as determined by ophthalmologist	
Palliative care specialist	Per palliative care specialist	See Palliative Care.

ASM = anti-seizure medication; BMD = bone mineral density; OT = occupational therapy; PT = physical therapy

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. In the US, early intervention is a federally funded program available in all states.

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.

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:

- Individualized education plan (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 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.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

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

Palliative Care

As MPS III is a neurodegenerative, progressive, and life-limiting illness, resources for palliative care that are available to help reduce suffering from disease manifestations or improve quality of life should be considered and discussed with family members. Specific support resources desired by families will vary, but options for palliative care include respite care, assistance with symptom management, psychological and other forms of support, assistance with medical decision making, and assistance with creating and updating a care plan.

Surveillance

Due to the progression of MPS III manifestations over time, improvements in symptoms resulting from proper management are not typically long lasting. Consequently, monitoring for deterioration in the affected individual is an appropriate and important part of surveillance.

Table 7. Recommended Surveillance for Individuals with Mucopolysaccharidosis Type III

System/Concern	Evaluation	Frequency
Neurologic	Monitor treatment effectiveness in those w/seizures.	As clinically indicated
Development	Monitor developmental capabilities & educational needs.	Annually
Psychiatric/ Behavioral issues	Assessment of destructive or disruptive behaviors	As clinically indicated
Musculoskeletal	• Monitor joint mobility; assessment by orthopedist. • Monitor BMD w/DXA & vitamin D metabolism studies.	
Hearing	Assessment by audiologist & otolaryngologist	Annually
Cardiovascular	Echocardiogram & EKG to assess for valvular disease & conduction system defects	
Ocular	Ophthalmologic assessment	As clinically indicated

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry

Agents/Circumstances to Avoid

Though airway management during procedures with anesthesia is not typically difficult, anesthesia conducted in ill-equipped medical centers or by personnel with limited experience with patients with difficult airways is not recommended [Clark et al 2018].

Hip surgery is not recommended for individuals with MPS III due to the development of osteonecrosis and collapse of the femoral head [White et al 2011].

To minimize risks posed by unpredictable behavior, children with MPS III should be supervised around or have their environment adapted to avoid the following for their safety:

- Sharp or fragile furniture
- Sharp or fragile toys
- Large electronics
- High structures or surfaces that pose risks of falls and other injuries

Evaluation of Relatives at Risk

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

Pregnancy Management

Very few individuals with MPS III are known to have reproduced. In one case report a woman with slowly progressive MPS IIIB had an unremarkable pregnancy and a healthy child [Verhoeven et al 2010]. Due to the prevalence of valvular disease in MPS III, corresponding evaluation and management is appropriate if a woman with MPS III does achieve pregnancy.

Therapies Under Investigation

Despite ongoing research for a variety of therapeutic options for affected individuals, no treatments are currently clinically available for treatment of primary manifestations of MPS III.

Hematopoietic stem cell transplantation (HSCT) and umbilical cord blood transplantation (UCBT) are not currently considered effective treatment options for MPS III due to the lack of evidence of neurologic benefit.

Enzyme replacement therapy (ERT). Due to the inability of intravenous ERT to permeate the blood-brain barrier sufficiently to prevent neurologic disease progression, intravenous ERT has not been investigated in MPS III as intensively as it has for other lysosomal storage diseases.

Other methods of ERT administration, such as intrathecal injections, are effective in delivering ERT to normalize substrate storage in the CNS of MPS III animal models [King et al 2016]. A clinical trial currently in progress has demonstrated that intrathecal administration of recombinant human heparan-N-sulfatase, which is well tolerated in individuals with MPS IIIA, results in consistent decrease of heparan sulfate in the CSF [Jones et al 2016].

Substrate reduction therapy (SRT) is used successfully to treat other lysosomal storage diseases, such as Gaucher disease. Ongoing research suggests SRT as a future therapeutic option for MPS III.

In vitro studies have shown that siRNA targeting of genes that play a role in synthesis of heparan sulfate leads to decreased heparan sulfate synthesis, decreased GAG storage, and a reversal of the phenotype in fibroblasts of patients with MPS IIIC [Canals et al 2015].

Although genistein inhibits heparan sulfate synthesis and decreases accumulation of heparan sulfate in plasma and urine, it does not improve manifestations of MPS III at doses of 5 mg/kg/day or 10 mg/kg/day [de Ruijter et al 2012]. Future studies regarding genistein use at higher doses may determine whether it has clinical efficacy as a treatment for MPS III.

Chaperone-mediated therapy. The use of pharmacologic chaperones to increase residual lysosomal activity is being explored in MPS III. Certain mutated forms of enzymes implicated in the pathogenesis of MPS III can be rescued by chaperones that restore the natural folding of the enzyme to increase its activity. Chaperones are small enough in size to presumably cross the blood-brain barrier and target the cells with mutant enzyme that are the source of neurologic manifestations of MPS III. It has been proposed that low concentrations of specific chaperone molecules could function as partial enzymatic rescues in MPS IIIB or MPS IIIC.

Gene therapy. Ongoing advances in gene therapy may influence treatment of MPS III.

The use of a variety of MPS III-related gene-encoding viral vectors in mouse and canine models of MPS IIIA, MPS IIIB, and MPS IIID has increased deficient enzyme activity and decreased GAG storage [Scarpa et al 2017].

In children with MPS IIIA or MPS IIIB, intracerebral gene therapy has been well tolerated; findings suggest neurocognitive benefits, including moderate improvements in sleep and behavior. The most remarkable results are observed in the youngest patients, suggesting that earlier therapy may be more beneficial [Tardieu et al 2014, Tardieu et al 2017]. Additional trials regarding gene therapy for MPS III are under way.

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

Mucopolysaccharidosis type III (MPS III) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *GNS*, *HGSNAT*, *NAGLU*, or *SGSH* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with MPS III has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in an MPS III-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier for a pathogenic variant in an MPS III-related gene.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GNS*, *HGSNAT*, *NAGLU*, or *SGSH* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the MPS III-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **Cure Sanfilippo Foundation**
  Email: Contact@CureSanfilippoFoundation.org
  www.curesanfilippofoundation.org
- **Sanfilippo Children's Foundation**
  Australia
  Phone: 1800 664 878
  www.sanfilippo.org.au
- **Team Sanfilippo Foundation**
  Phone: 518-879-6571
  www.teamsanfilippo.org
- **Canadian Society for Mucopolysaccharide and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
  mpssociety.ca
- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
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  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 III: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GNS	12q14.3	N-acetylglucosamine-6-sulfatase	GNS database	GNS	GNS

Table A. continued from previous page.

HGSNAT	8p11.21-p11.1	Heparan-alpha-glucosaminide N-acetyltransferase	Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT) @ LOVD	HGSNAT	HGSNAT
NAGLU	17q21.2	Alpha-N-acetylglucosaminidase	NAGLU database	NAGLU	NAGLU
SGSH	17q25.3	N-sulphoglucosamine sulphohydrolase	SGSH database	SGSH	SGSH

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 III (View All in OMIM)

252900	MUCOPOLYSACCHARIDOSIS, TYPE IIIA; MPS3A
252920	MUCOPOLYSACCHARIDOSIS, TYPE IIIB; MPS3B
252930	MUCOPOLYSACCHARIDOSIS, TYPE IIIC; MPS3C
252940	MUCOPOLYSACCHARIDOSIS, TYPE IIID; MPS3D
605270	N-SULFOGLUCOSAMINE SULFOHYDROLASE; SGSH
607664	N-ACETYLGLUCOSAMINE-6-SULFATASE; GNS
609701	N-ACETYLGLUCOSAMINIDASE, ALPHA-; NAGLU
610453	HEPARAN-ALPHA-GLUCOSAMINIDE N-ACETYLTRANSFERASE; HGSNAT

Molecular Pathogenesis

GNS, *HGSNAT*, *NAGLU*, and *SGSH* encode four distinct lysosomal enzymes that play separate, yet critical, roles in the heparan sulfate degradation pathway. When one of these four enzymes is deficient, heparan sulfate is not fully catabolized and the accumulation of this glycosaminoglycan (GAG) results.

Mechanism of disease causation. Pathogenic variants in *GNS*, *HGSNAT*, *NAGLU*, and *SGSH* causing loss of function are the cause of MPS III.

Table 8. Notable Pathogenic Variants in Genes Causing Mucopolysaccharidosis Type III

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
HGSNAT	NM_152419.3 NP_689632.2	c.1030C>T	p.Arg384Ter	Found in many populations [Ruijter et al 2008]
		c.784G>A	p.Gly262Arg	2 compound heterozygous sisters w/significantly attenuated MPS IIIC [Ruijter et al 2008]
		c.1616C>G	p.Ser539Cys	
		c.518G>A	p.Gly173Asp	2 homozygous sibs w/KBS [2] [Hu et al 2017]

Table 8. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NAGLU	NM_000263.4 NP_000254.2	c.889C>T	p.Arg297Ter	Homozygotes w/severe MPS IIIB [Zhao et al 1998, Weber et al 1999, Valstar et al 2010b]
		c.1000G>T	p.Val334Phe	
		c.1562C>T	p.Pro521Leu	
		c.1927C>T	p.Arg643Cys	Compound heterozygotes or homozygotes w/ attenuated MPS IIIB [Valstar et al 2010b]
		c.1834A>G	p.Ser612Gly	
		c.1900G>A	p.Glu634Lys	
		c.1489C>G	p.Leu497Val	
		c.529C>T	p.Arg117Trp	Compound heterozygous sibs w/extremely attenuated MPS IIIB [Verhoeven et al 2010]
SGSH [3]	NM_000199.5 NP_000190.1	c.220C>T	p.Arg74Cys	Homozygotes w/rapidly progressing MPS IIIA [Valstar et al 2010c]
		c.1139A>G	p.Gln380Arg	
		c.197C>G	p.Ser66Trp	
		c.1080delC	p.Val361SerfsTer52	
		c.734G>A [4]	p.Arg245His	• Homozygotes w/rapidly progressing MPS IIIA • Common in northern European populations & founder variant in the Cayman Islands [Rady et al 2002, Meyer et al 2008]
		c.892T>C	p.Ser298Pro	Homozygotes or compound heterozygotes w/ attenuated MPS IIIA [Meyer et al 2008]

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.
1. Genes are listed alphabetically.
2. Klüver-Bucy syndrome, a neurobehavioral phenotype that can be observed in MPS III
3. See Genotype-Phenotype Correlations.
4. See Prevalence.

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Chapter Notes

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