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Mucolipidosis III Gamma

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Summary

Clinical characteristics

Mucolipidosis III gamma (ML IIIγ) is a slowly progressive inborn error of metabolism mainly affecting skeletal, joint, and connective tissues. Clinical onset is in early childhood; the progressive course results in severe functional impairment and significant morbidity from chronic pain. Cardiorespiratory complications (restrictive lung disease from thoracic involvement, and thickening and insufficiency of the mitral and aortic valves) are rarely clinically significant. A few (probably <10%) affected individuals display mild cognitive impairment.

Diagnosis/testing

The diagnosis of ML IIIγ is established in a proband with suggestive clinical and radiographic findings and biallelic pathogenic variants in *GNPTG* identified on molecular genetic testing.

Management

Treatment of manifestations: No measures are known to be effective in treating the progressive limitation of motion in large and small joints. Low-impact physical therapy is usually well tolerated. In older adolescents and adults joint replacement has been successful in relieving hip pain and knee pain. Carpal tunnel signs, and rarely tarsal tunnel symptoms, may require surgical tendon release procedures for temporary relief. Later in the disease course when bone pain of variable intensity may become frequent, management focuses on pain relief. Bisphosphonate treatment in individuals with significant skeletal disease and markedly decreased bone mineral densitometry can be considered. When significant cardiac valvular dysfunction disrupts ventricular function, valve replacement needs to be considered. Addressing the social and emotional needs of affected individuals and their families is recommended.

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Surveillance: Yearly outpatient clinic visits (unless more frequent pain, cardiac, and/or respiratory monitoring is warranted) to assess pain level, musculoskeletal needs, gross motor and fine motor function, vision, cardiac and respiratory function, development, educational needs, psychological issues, and utilization of community resources. Frequency of DXA scans depends on age and results of prior studies.

Agents/circumstances to avoid: Vigorous stretching exercises because they are ineffective, painful, and may damage the surrounding joint capsule and adjacent tendons.

Genetic counseling

ML IIIγ is inherited in an autosomal recessive manner. If both parents are known to be carriers of one *GNPTG* 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 *GNPTG* pathogenic variants in an affected family member are known, carrier testing for at-risk relatives, prenatal diagnosis for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for mucolipidosis III gamma have not been established.

Suggestive Findings

Mucolipidosis III gamma (ML IIIγ) **should be suspected** in individuals with the following clinical and radiographic findings [Raas-Rothschild et al 2004, Tüysüz et al 2018, Nampoothiri et al 2019].

Clinical findings

- Growth rate deceleration
- Joint stiffness of the fingers, shoulders, and hips
- Gradual mild coarsening of facial features
- Genu valgum
- Spinal deformities including scoliosis and hyperlordosis
- No organomegaly

Radiographic findings. In early childhood, skeletal radiographs reveal mild-to-moderate dysostosis multiplex:

- **Pelvis and hips.** Hypoplastic iliac bones with flared iliac wings and shallow and irregular acetabula and moderate-to-severe dysplasia of the proximal femoral epiphyses – giving rise to coxa valga – are the most striking radiologic abnormalities.
- **Hands and feet.** Diaphyses of metacarpals and phalanges are mildly shortened with "bullet-shaped" distal end of phalanges; carpal bones may be smaller than normal and with osteoporotic changes.
- **Ribs.** Widening especially in the lateral and frontal costochondral junctions
- **Spine.** Generalized platyspondyly; irregularity of the anterior upper and lower vertebral endplates; wedge-shaped and small ovoid vertebral bodies

In late childhood or adolescence, the changes on skeletal radiographs worsen with the development of generalized osteopenia.

Establishing the Diagnosis

The diagnosis of ML IIIγ **is established** in a proband with suggestive clinical and radiographic findings and biallelic pathogenic (or likely pathogenic) variants in *GNPTG* identified on 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 *GNPTG* variants of uncertain significance (or of one known *GNPTG* pathogenic variant and one *GNPTG* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular Genetic Testing

Approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing (see **Option 1**) requires that the clinician determine which gene(s) are likely involved, whereas genomic testing (see **Option 2**) does not.

Option 1. A mucolipidosis or lysosomal storage disorders multigene panel that includes *GNPTG* 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. Comprehensive genomic testing. 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 Mucolipidosis III Gamma

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
GNPTG	Sequence analysis [4]	~99%% [5]
	Gene-targeted deletion/duplication analysis [6]	None detected

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. Data from Nampoothiri et al [2019], Velho et al [2019]
4. 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.
5. Two intronic deletions reported are of a size detectable by sequencing but could be missed due to their location [Persichetti et al 2009].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Supportive Biochemical Findings

Activity of lysosomal hydrolases. In ML IIIγ the activity of nearly all lysosomal hydrolases is up to tenfold higher in serum dried blood and other body fluids (e.g., media from cultured fibroblasts or amniocytes) than in normal controls because mannose-6-phosphate, which is essential to proper targeting of lysosomal acid hydrolases to lysosomes, cannot be added adequately to the hydrolases and they are overexcreted into the extracellular space.

The following lysosomal hydrolases are of most interest as their increased activity in serum and other body fluids is relevant in the differential diagnosis of ML III and lysosomal storage disorders:

- β-D-hexosaminidase (EC 3.2.1.52)
- β-D-glucuronidase (EC 3.2.1.31)
- β-D-galactosidase (EC 3.2.1.23)
- α-D-mannosidase (EC 3.2.1.24)

Note: (1) The intracellular lysosomal hydrolase activity in cultured cells, such as skin fibroblasts, is low compared to control cells and permits support of the diagnosis as well. (2) ML IIIγ cannot be diagnosed by assay of acid hydrolases in leukocytes. (In ML II, specific activity of lysosomal enzymes is elevated in plasma, deficient in fibroblasts, and normal in leukocytes.) (3) Biochemical testing (measurement of lysosomal hydrolase activity) does not distinguish ML III alpha/beta from ML IIIγ. (4) Biochemical testing cannot be used to identify heterozygotes.

UDP-N-acetylglucosamine: lysosomal hydrolase N-acetylglucosamine-1-phosphotransferase enzyme (also known as GlcNAc-phosphotransferase) (EC 2.7.8.17). Demonstration of deficiency of the enzyme GlcNAc-phosphotransferase, encoded by *GNPTAB* (causing *GNPTAB*-related disorders) and *GNPTG* (causing ML IIIγ), confirms the diagnosis of a *GNPTAB*-related disorder and ML IIIγ.

Clinical Characteristics

Clinical Description

Mucolipidosis III gamma (ML IIIγ) is a slowly progressive inborn error of metabolism mainly affecting skeletal, joint, and connective tissues. Clinical onset is in early childhood and the progressive course, including mild cardiac involvement, results in severe functional impairment and significant morbidity. A few (probably <10%) affected individuals may display mild cognitive impairment [Nampoothiri et al 2019], but the majority do not.

The initial manifestation in most affected individuals is joint stiffness in fingers as early as age 18 months [Tüysüz et al 2018].

Growth. Weight and length at birth are within normal limits. Gradual slowing of growth rate begins in early childhood.

Worsening hip and knee contractures add to the poor growth rate. While frank dwarfism does not occur, the height of individuals with ML IIIγ is often below the tenth centile on standard growth curves.

Craniofacial. Dysmorphic facial features are absent or minimal in younger children. Although most individuals with ML IIIγ develop coarsening of the facial features, it often occurs in the first two decades of life, which is more gradual than in ML IIIα/β.

Ophthalmologic. While the corneae are clear by routine clinical inspection, opacities that do not cause ophthalmologic impairment may be appreciated by slit lamp examination in some individuals [Tüysüz et al 2018].

Respiratory. Individuals with ML IIIγ generally do not have pulmonary impairment; however, mild-to-moderate restrictive lung disease may be present in adults due to abnormalities of the spine and ribs that reduce lung capacity [Oussoren et al 2018].

Cardiovascular. Individuals with ML IIIγ are at risk for cardiac involvement. Although gradual thickening and subsequent mitral valve prolapse and insufficiency of the mitral and aortic valves are common from late childhood onward, cardiac function is normal in most affected adults [Oussoren et al 2018, Tüysüz et al 2018].

Gastrointestinal. Hepatomegaly and splenomegaly are absent.

Skeletal / soft connective tissue. Stiffness of finger joints, a cardinal feature, is usually the initial manifestation of the disorder. Moderate-to-severe claw-like flexion deformity of the fingers worsens with time. Limited range of motion of the shoulders is common early in the disease course. Genu valgum deformity occurs in all affected individuals early in the disease.

Hip involvement usually develops during the end of adolescence in ML IIIγ (earlier in ML IIIα/β). Hip involvement progresses over years, finally resulting in destruction of the proximal femoral epiphyses. Limited hip mobility and lower-limb pain can be significant and may result in waddling gait with age.

Carpal tunnel syndrome develops in most affected individuals and may be clinically significant in the second and third decade [Raas-Rothschild et al 2004, Tüysüz et al 2018, Nampoothiri et al 2019].

Spinal deformities develop over time and include scoliosis and hyperlordosis. In one individual atlantoaxial instability required corrective surgery; however, this complication is very uncommon in ML IIIγ [Tüysüz et al 2018, Nampoothiri et al 2019].

Short neck reported in several individuals had no clinical significance [Tüysüz et al 2018].

Chronic pain syndrome significantly impairs the quality of life. It is common and mainly involves the hips, knees, and entire legs and sometimes the hands. Chronic pain syndrome is attributed to skeletal and connective tissue disease. In some affected individuals spinal cord compression due to spinal stenosis (decreased diameter of the spinal canal) and vertebral osteoarthritic changes may also contribute to the chronic pain syndrome.

Osteopenia, confirmed by reduced bone mineral densitometry measured by dual-energy x-ray absorptiometry (DXA), is common.

Neuromotor development and intellect. While motor milestones may be delayed, other aspects of development including language and learning skills are as expected for age. Affected children may require school assistance mostly because of physical limitations. While cognitive function is within the normal range in most affected individuals, a few individuals (probably <10%) have cognitive deficiency. It is still to be determined if this manifestation is related to ML IIIγ given the consanguinity in many reported cases and the possibility of additional genetic causes.

Other. The skin may become mildly thickened with time. Recently, scleroderma-like changes were reported in individuals with Moroccan ancestry [Zrhidri et al 2017].

Genotype-Phenotype Correlations

To date no correlation between severity of disease and type of *GNPTG* pathogenic variant has been reported; however, predicted loss-of-function variants, such as the recurrent variants c.285dupC, c.445delG, and c.499dupC, are associated with a severe phenotype [Tüysüz et al 2018]. See Table 5 for more details.

Nomenclature

UDP-*N*-acetylglucosamine: lysosomal hydrolase *N*-acetylglucosamine 1-phosphotransferasedeficiency disorders. This enzyme is the product of two genes: *GNPTAB*, encoding the alpha and beta subunits, and *GNPTG*, encoding the gamma subunit [Bao et al 1996]. Pathogenic variants in:

- *GNPTAB* cause *GNPTAB*-related disorders, which include the severe phenotype of ML II and the attenuated form of ML IIIα/β;
- *GNPTG* cause ML IIIγ [Cathey et al 2008].

The trivial name of this enzyme is UDPGlcNAc 1-P-transferase; thus, the three ML phenotypes can be considered "UDPGlcNAc 1-P-transferase deficiency disorders" [Leroy 2007].

ML IIIγ was previously referred to as variant pseudo-Hurler polydystrophy* or mucolipidosis IIIC [Cathey et al 2008].

* "Pseudo-Hurler polydystrophy" was the term used from 1966 by Maroteaux and Lamy when they first delineated ML III. They used this term because of the resemblance of ML III to Hurler disease, or mucopolysaccharidosis I (MPS I) [Kornfeld & Sly 2001].

Prevalence

The worldwide estimated incidence of ML II, ML IIIα/β, and ML IIIγ varies between 2.5 and 10 cases per 1,000,000 live births [Velho et al 2019]. The exact prevalence of ML IIIγ is unknown; it is considered an ultra-rare disease.

Most individuals with ML IIIγ known to the authors originated from the Mediterranean region [Raas-Rothschild et al 2004, Persichetti et al 2009, Tüysüz et al 2018]. However, more recent reports include individuals with ML IIIγ from other geographic regions including China, India, South America (Brazil), North America, and North Africa [Persichetti et al 2009, Gao et al 2011, Nampoothiri et al 2019, Velho et al 2019], suggesting that the disorder is pan ethnic.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Mucolipidosis II (ML II), ML IIIα/β, and ML IIIγ are all UDPGlcNAc 1-P-transferase deficiency disorders (see Nomenclature). Whereas the clinical phenotypes of ML IIIα/β and ML IIIγ can be difficult to distinguish, the severe phenotype of ML II is easily differentiated. In general, the ML IIIγ phenotype is less severe than ML IIIα/β.

See Table 2 for inherited disorders to consider in the differential diagnosis of ML IIIγ.

Table 2. Genes to Consider in the Differential Diagnosis of Mucolipidosis III Gamma (ML IIIγ)

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/ML IIIγ	Distinguishing from ML IIIγ
GNPTAB	ML IIIα/β (See *GNPTAB*-Related Disorders.) [1]	AR	Clinical features of ML IIIγ are similar to but milder than those of ML IIIα/β.	No specific ethnic predilection has been reported in ML III α/β. [2]

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/ML IIIγ	Distinguishing from ML IIIγ
CCN6 (WISP3)	Progressive pseudorheumatoid dysplasia	AR	• Joint stiffness & osteoarthritis • Spinal involvement (kyphoscoliosis, platyspondyly) • Claw hands	• Absence of dysostosis multiplex • Disease course less progressive • Normal level of serum hydrolases
COL2A1	Osteoarthritis w/mild chondrodysplasia (See Type II Collagen Disorders Overview.)	AD	• Joint stiffness & osteoarthritis • Mild short stature	• Absence of dysostosis multiplex • Disease course less progressive • Normal level of serum hydrolases
CTSA	Juvenile galactosialidosis (OMIM 256540)	AR	• Joint stiffness • Corneal clouding • Cardiac abnormalities • Facial coarseness • Dysostosis multiplex	• Organomegaly • Normal level of serum hydrolases • ↑ urinary oligosaccharides
GLB1	MPS IV B [3] (See *GLB1*-Related Disorders.)	AR	• Joint stiffness • Corneal clouding • Cardiac abnormalities • Normal intelligence	• Short stature usually more severe (frank dwarfism) • Absence of dysostosis multiplex • Normal level of serum hydrolases
GUSB	MPS VII B [4]	AR	• Dysostosis multiplex • Spinal deformities (kyphoscoliosis) • Coarse facies • Corneal opacities • Cardiac involvement	• Normal level of serum hydrolases
IDS	Slowly progressive MPS II [5]	XL	• Joint stiffness • Corneal clouding • Cardiac abnormalities • Facial coarseness • Dysostosis multiplex	• Organomegaly • Cognitive impairment • Hearing impairment • Normal level of serum hydrolases
IDUA	Slowly progressive MPS I [6]	AR	• Joint stiffness • Corneal clouding • Cardiac abnormalities • Facial coarseness • Dysostosis multiplex	• Organomegaly • Cognitive impairment • Hearing impairment • Normal level of serum hydrolases
MAN2B1	Alpha-mannosidosis	AR	• Facial coarseness • Dysostosis multiplex	• Organomegaly • Cognitive impairment • Hearing impairment • Normal level of serum hydrolases
SLC17A5	Free sialic acid storage disorders	AR	• Facial coarseness • Skeletal abnormalities	• Organomegaly • Cognitive impairment • Neurologic abnormalities • Normal level of serum hydrolases

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/ML IIIγ	Distinguishing from ML IIIγ
SUMF1	Multiple sulfatase deficiency	AR	• Joint stiffness • Corneal clouding • Cardiac abnormalities • Facial coarseness • Dysostosis multiplex	• Organomegaly • Neurologic abnormalities • Cognitive impairment • Normal level of serum hydrolases

AD = autosomal dominant; AR = autosomal recessive; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked
1. Also referred to as pseudo-Hurler polydystrophy
2. Most individuals with ML IIIγ known to the authors originated from the Mediterranean region [Raas-Rothschild et al 2004, Encarnação et al 2009, Persichetti et al 2009].
3. Also referred to as Morquio syndrome type B
4. Also referred to as Sly disease type B
5. Also referred to as Hunter syndrome
6. Also referred to as Hurler-Scheie syndrome or Scheie syndrome

Other disorders to consider

- **Rheumatologic disorders** are often suspected in individuals with ML IIIγ because of slowly decreasing range of motion in large and small joints and increasing pain in the hips [Brik et al 1993].
- **Rheumatoid arthritis** (OMIM 180300) presents with clinical and laboratory signs of inflammation. The activities of the several lysosomal enzymes in serum are normal. Dysostosis multiplex is absent. Family history is not compatible with autosomal recessive inheritance.

Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Mucolipidosis IIIγ

System/Concern	Evaluation	Comment
Constitutional	Height, weight, head circumference	To assess growth rate
Skeletal	Pain assessment	To assess pain scores & involvement
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Incl assessment of: • Lower limb pain (can be significant) • Gross motor & fine motor skills • Hip, knee contractures • Limited range of motion of shoulders • Stiffness of finger joints & Dupuytren-like palmar contractures (starting in late childhood) • Carpal tunnel syndrome • Odontoid dysplasia & risk of atlanto-axial dislocation • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Complete skeletal survey	To better assess skeletal involvement

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Metabolic bone disease	DXA study; biomarkers reflecting bone metabolism	Perform baseline DXA scan: • Children age >5 yrs • Adults at time of diagnosis
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Cardiac	Clinical exam, EKG, echocardiogram	To assess for mitral & aortic valve involvement usually beginning in late childhood
Ophthalmologic	Visual acuity, slit lamp exam	For evidence of corneal opacities
Respiratory	Pulmonary consultation	Lung function studies to evaluate for restrictive lung disease from spine & rib abnormalities
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family support/resources	Assess need for: • Community or online resources (e.g., Parent to Parent); • Social work involvement for parental support.

ADL = activities of daily living; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Supportive and symptomatic management is indicated.

Musculoskeletal

No measures are known to be effective in treating the progressive limitation of motion in large and small joints. Physiotherapy intervention programs need to be adapted to the affected individual's needs. Short sessions of aqua therapy that are "low impact" in regard to joint and tendon strain are usually well tolerated.

Later in the disease course, bone pain of variable intensity may become frequent. Management of pain in the hips is required. In older adolescents and adults, bilateral hip replacement has been successful. In individuals with progressive knee involvement, knee replacement has been successful.

Casts (especially of the hands) during the night hours are usually well tolerated and appear to improve daily functions.

Carpal tunnel signs, and rarely tarsal tunnel symptoms, may require surgical tendon release procedures for temporary relief [Oussoren et al 2018, Tüysüz et al 2018].

In cases with severe spinal deformities with or without spinal cord compression, spinal surgical procedures should be considered.

Routine pain assessment and consultation with a pain specialist should be performed as required.

Of note, in individuals with significant skeletal disease and considerable decrease in bone mineral densitometry (z score<-2.5), bisphosphonates (oral or intravenous) should be highly considered [Tüysüz et al 2018; Tüysüz, personal communication].

Cardiac

When significant valvular dysfunction disrupts ventricular function, valve replacement should be seriously considered. However, such complications are rare in ML IIIγ.

Antibiotic prophylaxis before minor and major surgical procedures (including dental procedures) is appropriate to prevent bacterial endocarditis.

Psychosocial support of affected individuals and their families is recommended.

Anesthesia

As with all storage diseases, anesthesia for individuals with ML IIIγ must be well planned. Because of concerns about airway management, surgical intervention should be undertaken only in tertiary care settings with pediatric anesthesiologists and intensive care physicians.

The anesthetic team should be aware of the following issues:

- Persons with ML IIIγ are small and have a small airway, reduced tracheal suppleness from stiff connective tissue, and progressive narrowing of the airway from mucosal thickening. The use of a smaller endotracheal tube than for age- and size-matched controls is necessary.
- Fiberoptic intubation must be available.
- Persons with ML IIIγ have short necks, and atlanto-axial instability has been reported [Tüysüz et al 2018].
- Jaw and neck movement can be limited.
- Abnormalities of the spine and ribs can limit the individual's capacity to breathe and fully expand the lungs.

Surveillance

Table 4. Recommended Surveillance for Individuals with Mucolipidosis IIIγ

System/Concern	Evaluation	Frequency
Constitutional	Height, weight, head circumference	Yearly
Pain	Assessment of pain level by pain specialist	Yearly
Musculoskeletal	Assessment of range of motion, stiffness & contractures, carpal tunnel syndrome, tarsal tunnel syndrome, ADL	Yearly
Mobility	By PT, physiatrist	Yearly
Fine motor skills	By OT	Yearly
Metabolic bone disease	DXA scan	• Children: 5-yr intervals after baseline study • Adults w/normal studies: 3-yr intervals • Adolescents & adults w/↓ densitometry: 2-yr intervals
Respiratory	Lung function studies	5-yr intervals
Cardiac	Cardiac eval incl echocardiography	Yearly
Ophthalmologic	Monitor visual acuity & corneal opacities.	Yearly
Development/ School issues	General eval	Yearly
Educational resources	General eval	Yearly
Psychological issues	General eval	Yearly

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Community resources	General eval	Yearly

ADL = activities of daily living; DXA = dual-energy x-ray absorptiometry; OT = occupational therapist; PT = physical therapist

Agents/Circumstances to Avoid

Vigorous stretching exercises are not recommended because they are ineffective, painful, and may damage the surrounding joint capsule and adjacent tendons.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

Mucolipidosis III gamma (ML IIIγ) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically heterozygotes (i.e., carriers of one *GNPTG* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GNPTG* pathogenic variant and to allow for reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)

  In one family, only the father of the proband was heterozygous for a *GNPTG* pathogenic variant (a *GNPTG* pathogenic variant was not detected in maternal DNA) and the proband was presumed to have ML IIIγ as the result of one inherited and one *de novo GNPTG* pathogenic variant [Ludwig et al 2017].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be a carrier of one *GNPTG* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with ML IIIγ are obligate heterozygotes (carriers) for a pathogenic variant in *GNPTG*.

Other family members. If both parents are a carrier of one *GNPTG* pathogenic variant, sibs of the proband's parents are at a 50% risk of being carriers of a *GNPTG* pathogenic variant.

Carrier (Heterozygote) Detection

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

Note: Biochemical testing cannot be used to identify heterozygotes.

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.

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 the *GNPTG* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Mucolipidosis III gamma

- **Vaincre les Maladies Lysosomales**
  2 Ter Avenue De France
  Massy 91300

France
Phone: (0033) 1 69 75 40 30
Fax: (0033)1 60 11 15 83
Email: vml@vml-asso.org
Vaincre les Maladies Lysosomales

- **International Advocate for Glycoprotein Storage Diseases (ISMRD)**
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- **National MPS Society**
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  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. Mucolipidosis III Gamma: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GNPTG	16p13.3	N-acetylglucosamine-1-phosphotransferase subunit gamma	GNPTG @ LOVD	GNPTG	GNPTG

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 Mucolipidosis III Gamma (View All in OMIM)

252605	MUCOLIPIDOSIS III GAMMA
607838	N-ACETYLGLUCOSAMINE-1-PHOSPHOTRANSFERASE, GAMMA SUBUNIT; GNPTG

Molecular Pathogenesis

N-acetylglucosamine-1-phosphotransferase is a hexameric enzyme complex composed of two alpha, two beta, and two gamma subunits. The membrane-bound alpha and beta subunits are synthesized as a common alpha/beta precursor encoded by *GNPTAB*, whereas the soluble gamma subunit is encoded by *GNPTG*.

In the Golgi apparatus the gamma subunit directly binds to the alpha subunit and enhances N-acetylglucosamine-1-phosphotransferase activity for mannose-6-phosphate (M6P) modification of specific lysosomal enzymes. Once modified with M6P, the lysosomal hydrolases can attach to the M6P receptor and be targeted to the mature lysosome.

Mechanism of disease causation. ML IIIy occurs by a loss-of-function mechanism. Most disease-associated variants are predicted to be loss-of-function variants. The majority of reported missense variants are located in

the M6P receptor homology (MRH) domain. It is speculated that these variants impair MRH domain function, which plays a major role in binding phosphorylated and non-phosphorylated high-mannose-type N-glycans.

Table 5. Notable *GNPTG* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_032520.3 NP_115909.1	c.196C>T	p.Arg66Ter	Raas-Rothschild et al [2004], Zrhidri et al [2017], Tüysüz et al [2018]
	c.285dupC	p.Phe96LeufsTer32	Genotype-phenotype correlation [Tüysüz et al 2018]
	c.318-1G>C	p.Val107TrpfsTer24	Raas-Rothschild et al [2004], Oussoren et al [2018]
	c.316G>A	p.Gly106Ser	Raas-Rothschild et al [2004], Persichetti et al [2009], Gheldof et al [2019]
	c.333G>A	p.Trp111Ter	Persichetti et al [2009], Cagle [2016]
	c.347_349delACA	p.Asn116del	Tiede et al [2004], Persichetti et al [2009], Tüysüz et al [2018]
	c.445delG	p.Ala149ProfsTer13	Genotype-phenotype correlation [Raas-Rothschild et al 2004, Tüysüz et al 2018]
	c.499dupC	p.Leu167ProfsTer32	Genotype-phenotype correlation [Raas-Rothschild et al 2000, Tüysüz et al 2018]
	c.857C>T	p.Thr286Met	Persichetti et al [2009], Fernández-Marmiesse et al [2014]

Variants listed in the table have been reported in more than one publication and in more than one population, reflecting a possible hot spot.
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

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