

# Mucopolipidosis III Gamma

[*Mucopolipidosis III C, Variant Pseudo Hurler Polydystrophy*]

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## **Annick Raas-Rothschild, MD**

Pediatrician Medical Geneticist  
Department of Human Genetics  
Hadassah Hebrew University Medical Center  
Jerusalem, Israel  
annick@hadassah.org.il

## **Ronen Spiegel, MD**

Pediatrician Medical Geneticist  
Pediatric Department A and Genetic Institute  
Ha'Emek Medical Center  
Afula, Israel  
Rappaport Faculty of Medicine  
Technion – Israel Institute of Technology  
Haifa, Israel  
spiegelr@zahav.net.il

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## Summary

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**Disease characteristics.** Mucopolipidosis III gamma (ML III gamma) is a slowly progressive disorder characterized by childhood-onset of radiographic evidence of mild to moderate dysostosis multiplex; joint stiffness and pain initially in the shoulders, hips, and fingers; and gradual mild coarsening of facial features. Cardiorespiratory complications (restrictive lung disease, thickening and insufficiency of the mitral and aortic valves, left ventricular hypertrophy) can be significant. A few affected individuals have mild cognitive impairment. Because ML III gamma has only recently been distinguished from the more common ML III alpha/beta, previously published descriptions of ML III may have inadvertently included both of these disorders. Thus, much is to yet be learned about the specific manifestations and natural history of ML III gamma.

**Diagnosis/testing.** In ML III gamma the activity of nearly all lysosomal hydrolases is up to tenfold higher in plasma and other body fluids than in normal controls because of inadequate targeting to lysosomes. ML III gamma is caused by mutations in the gene *GNPTG*, which encodes the gamma subunit of the enzyme UDP-*N*-acetylglucosamine: lysosomal hydrolase *N*-acetylglucosamine 1-phosphotransferase. (Of note, the alpha and beta subunits of this enzyme are encoded by the gene *GNPTAB*, mutations in which cause ML III alpha/beta.) Clinically available molecular genetic testing of *GNPTG* detects two disease-causing mutations in more than 95% of individuals with ML III gamma.

**Management.** *Treatment of manifestations:* Low-impact physical therapy is usually well tolerated. Carpal tunnel signs may require tendon release. In late childhood or early adolescence relief of hip pain becomes important; in older adolescents and adults bilateral hip replacement has been successful. Later in the disease course management focuses on relief of general bone pain associated with osteoporosis. *Prevention of secondary complications:* Because of concerns about airway management, surgical intervention should be undertaken only in tertiary care settings with pediatric anesthesiologists and intensivists. *Surveillance:* twice-yearly outpatient clinic visits for young children; annual routine follow-up visits after age six years unless bone pain, deteriorating ambulation, and/or cardiac and respiratory monitoring need more frequent attention. *Agents/circumstances to avoid:* stretching exercises because they are ineffective, painful, and may damage the surrounding joint capsule and adjacent tendons.

**Genetic counseling.** ML III gamma 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. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the disease-causing mutations in the family are known.

## Diagnosis

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### Clinical Diagnosis

The following clinical features, similar to those for mucopolipidosis III alpha/beta, contribute to early diagnosis of mucopolipidosis III gamma (ML III gamma) but are not by themselves diagnostic [Raas-Rothschild et al 2004, Cathey et al 2009]:

- Family history of ML III gamma
- Growth rate deceleration
- Joint stiffness of the fingers, shoulders, and hips
- Gradual mild coarsening of facial features
- Genu valgum
- No organomegaly

In early childhood skeletal radiographs reveal mild to moderate dysostosis multiplex:

- **Pelvis and hips.** Hypoplastic iliac bones with flared iliac wings and shallow acetabula and moderate-to-severe dysplasia of the proximal femoral epiphyses giving rise to coxa valga are the most striking radiologic abnormalities in ML III gamma.
- **Hands and feet.** Diaphyses of metacarpals and phalanges are mildly shortened; carpal bones may be smaller than normal
- **Ribs.** Widening especially in lateral and frontal (costochondral junction) parts
- **Spine.** Mild generalized platyspondyly; anterior inferior hook in lower thoracic and/or higher lumbar vertebrae

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

### Testing

**Activity of lysosomal hydrolases.** In ML III gamma the activity of nearly all lysosomal hydrolases is up to tenfold higher in serum and other body fluids than in normal controls because mannose-6-phosphate (M6P), which is essential to proper targeting of lysosomal acid hydrolases to lysosomes, cannot be added adequately to the hydrolases (see Molecular Genetic Pathogenesis).

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:

- $\beta$ -D-hexosaminidase (EC 3.2.1.52)
- $\beta$ -D-glucuronidase (EC 3.2.1.31)
- $\beta$ -D-galactosidase (EC 3.2.1.23)
- $\alpha$ -D-mannosidase (EC 3.2.1.24)

Note: (1) Lysosomal hydrolase activity in cultured cells, such as skin fibroblasts, is low compared to control cells and permits confirmation of the diagnosis as well. (2) ML III gamma 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 III gamma. (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 ML III alpha/beta) and *GNPTG* (causing

ML III gamma) confirms the diagnosis of ML III alpha/beta and ML III gamma. Note: Such testing is available in only a few research laboratories.

## Molecular Genetic Testing

**Gene.** *GNPTG* is the only gene known to be associated with ML III gamma.

### Research testing

- **Sequence analysis.** Bidirectional sequencing of the entire *GNPTG* coding region and flanking intronic regions detects two disease-causing mutations in more than 95% of individuals with ML III gamma. Types of pathologic variants include missense, splice-site, and nonsense mutations as well as small insertions and deletions that result in a frameshift.

**Table 1. Summary of Molecular Genetic Testing Used in Mucopolipidosis III Gamma**

<b>Gene Symbol</b>	<b>Test Method</b>	<b>Mutations Detected</b>	<b>Mutation Detection Frequency by Test Method <sup>1</sup></b>	<b>Test Availability</b>
<i>GNPTG</i>	<u>Sequence analysis</u>	Sequence variants	>95%	Research only <sup>2</sup>

Test Availability refers to availability in the GeneTests Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene
2. No laboratories offering clinical testing for this gene are listed in the GeneTests Laboratory Directory; clinical confirmation of mutations identified in a research laboratory may be available. See .

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click [here](#).

Carrier status for each parent should be confirmed:

- If the proband appears to be homozygous for a mutation by sequence analysis. Confirming the carrier status of the parents helps determine if the proband either (a) is a compound heterozygote for the identified disease-causing mutation and a deletion or (b) has uniparental disomy (which is theoretically possible but has not been reported to date).
- On rare occasion to identify affected parents who were previously undiagnosed compound heterozygotes or homozygotes [Raas-Rothschild, personal communication].

## Testing Strategy

**To establish the diagnosis in a proband** requires the combination of clinical evaluation and laboratory testing. The following order of evaluation is recommended:

- Family history of other affected members
- Identification of the characteristic clinical and radiographic findings
- Assay of several acid hydrolases in serum (not leukocytes), such as:
  - $\beta$ -D-hexosaminidase (EC 3.2.1.52)
  - $\beta$ -D-glucuronidase (EC 3.2.1.31)
  - $\beta$ -D-galactosidase (EC 3.2.1.23)
  - $\alpha$ -D-mannosidase (EC 3.2.1.24)
  - Arylsulfatase A (EC 3.1.6.1)
- If the clinical findings cannot distinguish between ML III alpha beta and ML III gamma, the options include: sequence analysis of *GNPTG* first if the phenotype is mild and *GNPTAB* second if the phenotype is moderate or severe; alternatively, if the family is large enough and/or if the parents are consanguineous, linkage analysis at 16p13.3 and 12q23.3 can be used to decide whether *GNPTG* or *GNPTAB* should be sequenced.\*

- Sequence analysis of the coding regions and flanking intronic segments of *GNPTG* and/or sequence analysis of the *GNPTG* cDNA if cells are available (lymphoblasts or fibroblasts).\*

\*Note: Because molecular genetic testing is not available on a clinical basis, the above-mentioned clinical uses of molecular genetic testing can only be considered if mutations identified in a research laboratory are confirmed by a clinical laboratory. Clinical confirmation of mutations identified in a research laboratory may be available. See .

**Carrier testing for at-risk relatives** requires prior identification of the disease-causing mutations in the family.

Note: (1) If the affected child cannot be tested, sequence analysis of the *GNPTG* gene in both carrier parents can be performed to identify the two disease-causing alleles. (2) Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

**Prenatal diagnosis and preimplantation genetic diagnosis (PGD)** for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Note: Prenatal diagnosis can be accomplished with assay of lysosomal enzyme activity in cultured chorionic villous cells or cultured amniocytes in pregnancies at increased risk when the disease-causing mutations in the family are not known.

## Genetically Related (Allelic) Disorders

ML III gamma is the only phenotype known to be associated with mutations in *GNPTG*.

## Clinical Description

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### Natural History

Mucopolipidosis III 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 cardiac involvement, results in severe functional impairment and significant morbidity. A few affected individuals may display mild cognitive impairment [Leroy 2007]; the majority do not [Raas-Rothschild, personal communication].

Comprehensive clinical data on ML III alpha/beta have been recently published [Cathey et al 2009]; however, only limited data are available on the natural history of ML III gamma. Therefore, this review discusses the natural history of ML III in general (ML III alpha/beta and ML III gamma) with emphasis on ML III gamma when specifics are known.

**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 III gamma is often below the 10<sup>th</sup> centile on standard growth curves.

**Craniofacial.** Dysmorphic facial features are absent or minimal in younger children. Coarsening of facial features is more gradual in ML III gamma than ML III alpha/beta.

**Ophthalmologic.** The corneae are clear by routine clinical inspection, but opacities that do not cause ophthalmologic impairment may be appreciated by slit-lamp examination in some persons.

**Respiratory.** Mild hoarseness or metallic voice has been reported.

Persons with ML III gamma are small, 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 may be necessary.

Abnormalities of the spine and ribs may limit lung capacity.

**Cardiovascular.** Individuals with ML III are at risk for cardiac involvement. Gradual thickening and subsequent insufficiency of the mitral valve and the aortic valve are common from late childhood onward [Steet et al 2005]. Valve replacement may be required; therefore, careful follow-up is needed.

Rapid progression of cardiac disease is rarely observed in ML III.

**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. 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 III gamma (and earlier in ML III alpha/beta). Hip involvement progresses over years, finally resulting in destruction of the proximal femoral epiphyses. Limited hip mobility and lower limb pain can be significant.

Dupuytren-type palmar contractures may appear from late childhood onward. Moderate to severe claw-like flexion deformity of the fingers worsens with time.

Carpal tunnel syndrome and tarsal tunnel syndrome have been reported [Umehara et al 1997, Tytki-Szymanńska et al 2002, Raas-Rothschild et al 2004, Smuts et al 2009].

Odontoid dysplasia and atlanto-axial dislocation were reported Umehara et al [1997] in one older individual.

**Neuromotor development and intellect.** Neuromotor development may be delayed mainly in reaching motor milestones. Nevertheless, other aspects of development including language and learning skills fit the expected age. Affected children may require school assistance but mostly because of physical limitations.

**Other.** The skin may become thickened with time.

Temporo-mandibular joint dislocation has been reported in one person, leading to difficulties in speech and feeding [Zolkipli et al 2005]. Less severe temporo-mandibular involvement accompanied by feeding inconvenience was also diagnosed in two individuals [Spiegel, unpublished data].

## Genotype-Phenotype Correlations

To date no correlation between severity of disease and type of mutation has been reported.

## Nomenclature

**UDP-N-acetylglucosamine: lysosomal hydrolase N-acetylglucosamine 1-phosphotransferase deficiency 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]. Mutations in:

- *GNPTAB* cause the allelic disorders ML III alpha/beta and ML II
- *GNPTG* cause ML III gamma [Cathey et al 2008]

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

**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].

**Mucolipidosis (ML).** The term mucolipidosis was introduced in 1970 by Spranger & Wiedemann [1970], who provided the first clinical classification of the group of metabolic disorders clinically intermediate between the lipidoses and the mucopolysaccharidoses (storage disorders of glycosaminoglycans).

## Prevalence

Estimates of ML III gamma prevalence are not yet known.

Most individuals with ML III gamma known to the authors originated from the Mediterranean region [Raas-Rothschild et al 2004, Encarnação et al 2009, Persichetti et al 2009]. This is in contrast to ML III alpha/beta which is pan ethnic.

## Differential Diagnosis

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*For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.*

Mucopolipidosis II (ML II) alpha/beta, ML III alpha/beta, and ML III gamma are all UPDGlcNAc 1-P-transferase deficiency disorders (see Nomenclature). Whereas the clinical phenotypes of ML III alpha/beta and ML III gamma can be difficult to distinguish, the severe ML II (I-cell disease) phenotype is easily differentiated.

**ML II alpha/beta.** In ML II, clinical onset is at birth with findings that can include thoracic deformity, kyphosis, clubfeet, deformed long bones, and/or dislocation of the hip(s). The skin is thickened, facial features are coarse, and gingivae are hypertrophic. All children seem to have cardiac involvement, most commonly thickening and insufficiency of the mitral valve and, less frequently, the aortic valve. Progressive mucosal thickening narrows the airways and gradual stiffening of the thoracic cage contributes to respiratory insufficiency, the most common cause of death, usually in early childhood.

**ML III alpha/beta.** No specific ethnic predilection has been reported in ML III alpha/beta [Bargal et al 2006, Cathey et al 2009, Otomo et al 2009, Tappino et al 2009]. If the clinical diagnosis of ML III is strongly suspected and biochemical analysis shows elevated serum concentration of acid hydrolases, GNPTAB molecular genetic testing should be performed to confirm the diagnosis of ML III alpha/beta.

**Rheumatologic disorders** are often suspected in individuals with ML III gamma because of slowly decreasing range of motion in large and small joints and increasing pain in the hips [Brik et al 1993].

**Rheumatoid arthritis** (MIM 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.

**Progressive pseudorheumatoid dysplasia** (PPD) (MIM 208230) is caused by mutations in *WISP3*, the gene encoding the WNT1-inducible signaling pathways protein 3. Initially ML III gamma may be confused with PPD because of the joint stiffness but dysostosis multiplex is not present in PPD and disease course is less progressive.

**Lysosomal storage diseases.** Clinical findings in ML III gamma overlap those observed in nearly all-late onset and/or mild forms of the following **mucopolysaccharidoses** (MPS):

- MPS I (formerly called Hurler-Scheie syndrome or Scheie syndrome) (MIM 607015)
- MPS II (Hunter syndrome) (MIM 309900)
- MPS IV B (Morquio disease type B) (MIM 253010)
- MPS VI B (Maroteaux-Lamy disease type B) (MIM 253200)
- MPS VII B (Sly disease type B) (MIM 253220)

Specific biochemical and molecular genetic testing distinguishes between the mucopolysaccharidoses.

## Management

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### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with ML III gamma, the following evaluations are recommended:

- Basic assessment
  - Growth parameters
  - Pain assessment
  - Orthopedic and functional assessments
  - Psycho-developmental evaluation to follow the individual's developmental progress and program appropriate management
  - Skeletal survey
- Cardiac
  - Clinical examination
  - EKG
  - Echocardiography
- Ophthalmologic evaluation including slit lamp examination
- Metabolic bone disease assessment including evaluation of bone densitometry by DEXA studies and

evaluation of biomarkers reflecting bone metabolism [Robinson et al 2002]

## Treatment of Manifestations

Supportive and symptomatic management is indicated. Psychosocial support of patients and families is recommended.

No known measures are effective in treating the progressive limitation of motion in large and small joints. Physiotherapy intervention programs need to be adapted to the patient'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 a frequent complaint. Management of pain in the hips is required. In older adolescents and adults with milder ML III gamma, bilateral hip replacement has been successful.

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

Carpal tunnel signs and rarely tarsal tunnel symptoms may require surgical tendon release procedures for temporary relief [Smuts et al 2009].

In severe cases, when significant valvular dysfunction disrupts ventricular function, valve replacement should be seriously considered.

## Prevention of Secondary Complications

**Anesthesia.** As with all storage diseases, anesthesia in ML III gamma 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 III gamma 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 III gamma have short necks and atlanto-axial instability has been reported [Umehara et al 1997].
- Jaw and neck movement can be limited
- Abnormalities of the spine and ribs can limit the individual's capacity to breathe and fully expand their lungs.

**Antibiotic prophylaxis.** Persons with valvular involvement should be given antibiotic prophylaxis before minor and major surgical procedures (including dental procedures) to prevent bacterial endocarditis.

## Surveillance

Young children with ML III gamma and their families usually benefit from out-patient clinic visits once a year. Orthopedic and ophthalmologic assessment should be done at least once a year. Follow-up visits are recommended more frequently if any deterioration is observed.

During yearly visits, attention should be paid to pain relief, daily functional abilities, and psychological interventions.

Although cardiac manifestations are usually asymptomatic, monitoring for progressive valvular insufficiency should occur.

Surveillance for metabolic bone disease includes DEXA in five-year intervals.

## 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.

## Testing of Relatives at Risk

Our policy is not to test sibs at risk of being affected with ML III gamma since early diagnosis of affected individuals does not delay or halt disease progression [Author, personal observation].

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

## Therapies Under Investigation

Several individuals with ML III alpha/beta have been treated with monthly intra-venous administration of pamidronate, a bisphosphonate. At present information is insufficient about when in the ML III alpha/beta disease course or at what age such treatment should be initiated [Robinson et al 2002; Sillence, personal communication]. In a recent consensus meeting on the use of bisphosphonate therapy in oligosaccharidoses doubts were raised regarding its usefulness in ML III gamma [MPS Society 2008].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

## Other

**Genetics clinics**, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

**See Consumer Resources** for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

## Genetic Counseling

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*Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.*

## Mode of Inheritance

Mucopolidosis III gamma is inherited in an autosomal recessive manner.

## Risk to Family Members

*This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis.— ED.*

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutant allele).
- Heterozygotes (carriers) are asymptomatic.

### Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected and a 75% chance of being unaffected.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband.** The offspring of an individual with ML III gamma are obligate heterozygotes

(carriers) for the [disease-causing mutation](#).

**Other family members of a proband.** Each sib of the [proband's](#) parents is at a 50% risk of being a [carrier](#).

## Carrier Detection

[Carrier testing](#) of at-risk relatives may be available on a clinical basis from laboratories offering clinical confirmation of [mutations](#) identified in research labs if the [mutations](#) have been identified in the family. See .

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk 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

No laboratories listed in the GeneTests Laboratory Directory offer molecular genetic or biochemical genetic testing for [prenatal diagnosis](#) of ML III gamma. However, prenatal testing may be available for families in which the [disease-causing mutation](#) has been identified [Falik-Zaccai et al 2003]. For laboratories offering [custom prenatal testing](#), see .

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the [disease-causing mutations](#) have been identified. For laboratories offering PGD, see .

## 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. Mucopolipidosis III Gamma: Genes and Databases**

Gene Symbol	Chromosomal Locus	Protein Name	HGMD
GNPTG	16p	N-acetylglucosamine-1-phosphotransferase subunit gamma	GNPTG

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

**Table B. OMIM Entries for Mucopolipidosis III Gamma (View All in OMIM)**

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

## Molecular Genetic Pathogenesis

Newly synthesized lysosomal hydrolases have mannose 6-phosphate (M6P) residues that function as recognition [markers](#) for specific receptors required for lysosomal targeting. The M6P [marker](#) is generated in the Golgi apparatus by the sequential action of two enzymes.

In the first step N-acetylglucosamine-1-phosphotransferase (GlcNAc-phosphotransferase) transfers GlcNAc-1-phosphate to the C6 position mannose residues of acid hydrolases.

In the second step, N-acetylglucosamine-1-phosphodiester  $\alpha$ -N-acetylglucosaminidase (uncovering enzyme) removes N-acetylglucosamine residues thus exposing the M6P residues in order to correctly bind to their lysosomal membrane receptor.

GlcNAc-phosphotransferase is made up of three different subunits: alpha, beta, and gamma in a hexameric  $\alpha 2\beta 2\gamma 2$  subunit complex [Bao et al 1996]. The three subunits are the product of two genes: *GNPTAB* and *GNPTG*.

*GNPTAB*, the gene encoding the alpha and beta subunits, maps to chromosome 12q23 [Tiede et al 2005, Kudo et al 2006]. Mutations in this gene result in mucopolipidosis type III alpha/beta [Bargal et al 2006] and ML II.

*GNPTG*, the gene encoding the gamma subunit of GlcNAc-phosphotransferase located on chromosome 16p13.3 was identified in 2000 [Raas-Rothschild et al 2000]. Mutations in this gene result in mucopolipidosis type III gamma [Raas-Rothschild et al 2004]. The exact role of the  $\gamma$  subunit in the function of GlcNAc-phosphotransferase is not yet understood. Recent studies have proposed that it is important in the proper maintenance of  $\alpha$  and  $\beta$  subunits in the GlcNAc-phosphotransferase complex [Pohl et al 2009].

**Normal allelic variants.** *GNPTG* contains 11 exons that span 11.13 kb of genomic DNA. It encodes a 305-amino acid protein. After cleavage of the 24-amino acid signal peptide, the mature protein ( $\gamma$  subunit) forms disulfide-linked homodimers that become glycosylated at Asn<sup>88</sup> and Asn<sup>115</sup> [Raas-Rothschild et al 2000, Tiede et al 2004].

**Pathologic allelic variants.** A total of 16 disease-causing mutations have been reported (Table 1). They include missense, nonsense, and frameshift mutations as well as small intragenic deletions and insertions. In individuals with ML III gamma, homozygous or compound heterozygous mutations are detected. To date no correlation between severity of the disease and type of mutation has been reported. The list of mutations and their resultant protein changes are described in Table 2.

**Table 2. Selected *GNPTG* Pathologic Allelic Variants**

<b>DNA Nucleotide Change (Alias <sup>1</sup>)</b>	<b>Protein Amino Acid Change</b>	<b>Reference</b>	<b>Reference Sequences</b>
c.318-1G>C (IVS5-1G>C)	( <u>Exon</u> 6 skipping)	Raas-Rothschild et al [2004]	NM_032520.3 NP_115909.1
c.196C>T	p.Arg66X	Raas-Rothschild et al [2004]	
c.316G>A	p.Gly106Ser	Raas-Rothschild et al [2004] Persichetti et al [2009]	
c.333G>A	p.Trp111X	Persichetti et al [2009]	
c.347_349delACA	p.Asn116del	Tiede et al [2004] Persichetti et al [2009]	
c.379_391del13	p.Asp127ProfsX31	Raas-Rothschild et al [2004]	
c.523dupC (522insC)	p.Leu175ProfsX24	Raas-Rothschild et al [2000]	
c.608_609insC (608insC)	p.Gln203HisfsX4	Raas-Rothschild et al [2004]	
c.609+28_610-16del33		Persichetti et al [2009]	
c.610-1C>T (IVS8-1G>T)		Encarnaç�o et al [2009]	
c.610-2A>G		Persichetti et al [2009]	

c.611delG	p.Gly204AlafsX6	Persichetti et al [2009]
c.619_620insT	p.Lys207IlefsX8	Pohl et al [2009]
c.639delT	p.Phe213LeufsX7	Encarnação et al [2009]
c.640_667del28	p.Glu214LysfsX37	Persichetti et al [2009]
c.857C>T	p.Thr286Met	Persichetti et al [2009]

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human [Genome Variation Society](http://www.hgvs.org) ([www.hgvs.org](http://www.hgvs.org)).

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** The exact role of the  $\gamma$  subunit in function of the GlcNAc-phosphotransferase is not entirely understood. Recent studies have proposed that it is important in the proper maintenance of  $\alpha$  and  $\beta$  subunits in the GlcNAc-phosphotransferase complex [Pohl et al 2009].

**Abnormal gene product.** Unknown

## Resources

See *Consumer Resources* for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. *GeneTests* provides information about selected organizations and resources for the benefit of the reader; *GeneTests* is not responsible for information provided by other organizations.—ED.

## References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page

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## Chapter Notes

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