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Sialuria – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Sialuria is characterized by variable and transient signs and symptoms, especially in infancy. These include slightly flat and coarse facies, prolonged neonatal jaundice, equivocal or mild hepatomegaly, microcytic anemia, frequent upper respiratory infections, and episodes of gastroenteritis, dehydration, and transient failure to thrive. Mild developmental delay and hypotonia have been neither consistent nor permanent. Learning difficulty and seizures have been observed later in childhood. Sialuria has been detected retrospectively in an adult without subjective signs or complaints of disease. The long-term outcome of the disorder is unknown to date.

Diagnosis/testing

The diagnosis of sialuria is suggested by highly elevated urinary excretion of free sialic acid using the spectrophotometric or fluorimetric thiobarbituric acid assay or thin-layer chromatography. The diagnosis is formally established by demonstration of significantly raised free sialic acid within the cytoplasm of parenchymal cells or cultured fibroblasts. *GNE* is the only gene in which mutation is known to cause sialuria.

Management

Treatment of manifestations: Persons with sialuria need symptomatic and supportive management, including treatment of anemia, prolonged jaundice, and convulsions. Barbiturates are more effective than other antiepileptic drugs in treating the occasional convulsions in early childhood. Children with sialuria benefit from early developmental intervention and appropriate educational programs.

Surveillance: Follow-up evaluations three to four times in infancy, twice in the second year of life, and once every subsequent year.

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Genetic counseling

Sialuria is inherited in an autosomal dominant manner. If a parent of a proband is affected or has a sialuria-causing variant in *GNE*, the risk to each sib of the proband is 50%. Prenatal testing is possible if the pathogenic variant in a family is known.

Diagnosis

Clinical Diagnosis

The diagnosis of sialuria may be suspected in infants or young children with the following:

- Mild facial coarsening
- Hypotonia
- Equivocal developmental delay
- Frequent upper respiratory infections

Note: The likelihood of sialuria is increased after exclusion of more prevalent disorders that share laboratory results rather than clinical features. See Differential Diagnosis.

Testing

Constitutive overproduction of free sialic acid is the metabolic defect of sialuria [Seppala et al 1999, Huizing 2005]. The sialic acids, a group of negatively charged sugars, are acetyl derivatives of the nine-carbon 3-deoxy-5-amino sugar acid called neuraminic acid. The sialic acid relevant here is N-acetyl-neuraminic acid (NANA).

Free sialic acid levels. Assay of free sialic acid in the urine requires expertise either in the spectrophotometric or the fluorometric thiobarbituric acid assay or in thin-layer chromatography; other methods may fail to detect mild-to-moderate elevation of free sialic acid. The biochemical detection method of Cardo et al [1985] is adequate for assay of free and bound sialic acid in urine and whole-cell homogenates [Leroy et al 2001]. Laboratory methodology for the assay of free sialic acid has been reviewed [Gopaul & Crook 2006].

Provided that the free sialic acid storage disorders can be ruled out, the finding of excessive excretion of free sialic acid (elevated >100-fold) in the urine suggests the diagnosis of sialuria.

Note: (1) In the spectrophotometric method, other substances may either decrease or increase the absorbance and thus lead to spurious results. (2) High-performance liquid chromatography and proton nuclear magnetic resonance spectroscopy (1H-NMR) may be helpful in sorting out relevant differential diagnoses [Seppala et al 1999, Engelke et al 2004, Valianpour et al 2004].

The combination of one- and two-dimensional correlation spectroscopy (COSY):

- Identifies a specific ^{1}H-NMR spectrum for urinary N-acetyl-neuraminic acid in sialuria, which can be distinguished from the spectrum associated with Salla disease [Engelke et al 2004];
- Distinguishes bound sialic acid from free sialic acid and hence distinguishes sialidosis from sialuria.

Cytoplasmic localization of free sialic acid. Establishing that the intracellular distribution of free sialic acid is cytoplasmic instead of lysosomal confirms the diagnosis. In sialuria, subcellular fractionation fails to find evidence of lysosomal accumulation of sialic acid, which is characteristic of free sialic acid storage disorders [Aula & Gahl 2001]. Electron microscopic study of parenchymal cells or cultured fibroblasts shows no damage to the lysosomes, in spite of the high levels of free sialic acid found in the cytoplasm.

Assay of UDP-GlcNAc 2-epimerase activity. Assay of UDP-GlcNAc 2-epimerase enzyme activity in the presence and in the absence of 100-µmol/L cytidine monophosphate-N-acetylneuraminic acid (CMP-Neu5Ac)

confirms the diagnosis. The activity of the wild-type enzyme is inhibited 95% by CMP-Neu5Ac, whereas the enzymatic activity of the mutant protein is barely, if at all, diminished by the natural inhibitor. These studies must be performed in a specialized laboratory.

Oligosaccharides. The urinary excretion of oligosaccharides is normal.

Molecular Genetic Testing

Gene. *GNE* is the only gene in which mutation is known to cause sialuria.

Table 1. Molecular Genetic Testing Used in Sialuria

Gene [1]	Test Method	Variants Detected [2]	Variant Detection Frequency by Test Method [3]
GNE	Sequence analysis [4]	Sequence variants including any in the allosteric domain	6/6 [5, 6]
	Sequence analysis of select exons [7]	Pathogenic missense variants in exons 4 and 5 only [8]	6/6 [5, 6]
	Deletion/duplication analysis [9]	Unknown	Unknown; none reported [10]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
5. Total number of persons known to have been tested to date
6. Six of the seven known persons with sialuria have been tested; all six had identifiable pathogenic variants in *GNE* [Ferreira et al 1999, Seppala et al 1999, Aula & Gahl 2001, Enns et al 2001, Leroy et al 2001, Huizing & Krasnewich 2009]. Variants appear to reside exclusively in the short stretch of consecutive nucleotides that have an important role in the allosteric site (see Molecular Genetics).
7. Exons sequenced may vary by laboratory.
8. Including the allosteric domain (see Molecular Genetics)
9. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosome microarray (CMA) that includes this gene/chromosome segment.
10. No deletions or duplications in *GNE* have been reported to cause sialuria.

Testing Strategy

To confirm/establish the diagnosis in a proband. The following order of diagnostic testing is recommended, especially if more probable differential diagnoses have been ruled out:

1. Assay of free sialic acid in urine
2. Sequence analysis of *GNE* with special attention for pathogenic variants in nucleotides that encode the allosteric site

   Deletion/duplication analysis likely has limited clinical value: such testing is relevant only if no nucleotide change is detectable in or around the allosteric site in a person who fulfills all clinical and biochemical criteria of the diagnosis of sialuria.

Testing at-risk relatives of a proband to identify those who may be mildly affected requires prior identification of the pathogenic variant in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant in the family.

Clinical Characteristics

Clinical Description

A phenotypic definition or natural history of sialuria must remain preliminary as only seven affected persons have been reported [Ferreira et al 1999, Leroy et al 2001]. Signs and symptoms are mild and can be transient.

Pregnancy is usually normal. Affected infants are rather small for gestational age. At birth, the OFC is normal; the facies appear rather flat and slightly coarse. Mild hepatomegaly occurs in the majority of children and prolonged neonatal jaundice can be observed. In early infancy, developmental delay is reported in most children and generalized hypotonia in some. Microcytic anemia in two infants was severe enough to require transfusion. Upper respiratory infections occur frequently into the second year of life, sometimes associated with gastroenteritis, dehydration, and transient failure to thrive. Signs of dysostosis multiplex appear to be transient, but skeletal development is delayed at least in early childhood. There are no signs of any progression of the disorder. Instead clinical expression appears to be limited to infancy or to early childhood at most.

Developmental age or IQ is borderline low. Later in childhood, physical development is normal and intellectual development can be nearly normal. One child had febrile convulsions. In about half of the children who had seizures in childhood, the seizures were controlled with phenobarbital [Leroy et al 2001].

The phenotypic spectrum of sialuria is insufficiently known. Moreover, it may be either equivocally abnormal or indistinguishable from the normal variation in childhood development. It is likely that children with sialuria who have no significant medical problems in infancy and/or early childhood do not come to medical attention at all. The retrospective diagnosis of sialuria in the mother of a proband supports this contention [Leroy et al 2001]. Physically the proband and his affected mother are normal individuals. The mother is the only person in a sibship of six children who did not study beyond elementary school. Her affected son is physically similar to his two older unaffected brothers. He needs special support in regular classes. Hence it is probable, although not proven, that sialuria results in mild intellectual disability. Confirmation of this observation requires the study of more families.

Genotype-Phenotype Correlations

The direct correlation of genotype and phenotype is significant:

- **In sialuria.** In all persons who have been tested, the pathogenic *GNE* missense variant was detected in the putative allosteric site (codons 263 or 266).
- **In hereditary inclusion body myopathy (hIBM).** Homozygous or compound heterozygous *GNE* pathogenic variants are observed outside the allosteric site in the epimerase or the kinase domain [Kayashima et al 2002, Argov et al 2003, Huizing et al 2004, Tomimitsu et al 2004, Huizing 2005] (see Genetically Related Disorders).

Penetrance

Penetrance cannot be estimated clinically as the findings in this disorder are nonspecific and variable between affected persons, as well as transient and limited to early childhood. Moreover, the intellectual disability inconsistently associated with sialuria is neither progressive nor significant.

In contrast, "biochemical" penetrance of the excessive urinary excretion of free sialic acid is probably complete in childhood. Excessive excretion of free sialic acid was also found in the mother of one proband, the only adult reported to have been tested so far. Hence any conclusion about "biochemical" penetrance in adults remains premature.

Anticipation

Anticipation has not been observed. However, no information on possible infantile signs or symptoms is available for the single affected adult known to date.

Nomenclature

Before the simple term "sialuria" was adopted, the disorder was known as French type sialuria, because the first person described with sialuria and those who reported him were French. This descriptive nomenclature was considered useful for differentiation from Finnish type sialuria, the initial designation of the clinically severe free sialic acid storage disorders, infantile free sialic acid storage disorder (ISSD), and Salla disease (see Differential Diagnosis), first described and most frequently observed in Finland.

Prevalence

Sialuria has been reported in only seven persons.

The prevalence of sialuria may be underestimated. Assay of urinary levels of free sialic acid is not a routine laboratory procedure. As a rule, it is performed only in infants or young children with progressive CNS disease for confirmation or exclusion of the free sialic acid storage disorders.

The prevalence of sialuria remains unknown and is probably higher than that estimated from the existing reports of symptomatic persons.

Genetically Related (Allelic) Disorders

In contrast to the dominant gain-of-function effect of heterozygous pathogenic variants in the allosteric site observed in sialuria, homozygous or compound heterozygous *GNE* missense variants are being recognized in adults with an autosomal recessive late-onset type myopathy that is distinct from sialuria (see Inclusion Body Myopathy 2).

The *GNE*-related myopathies have been known by several descriptive terms including hereditary inclusion body myopathy (hIBM), hereditary IBM quadriceps sparing type or h-IBM2 (OMIM 600737), and distal myopathy with rimmed vacuoles (DMRV) or Nonaka myopathy (OMIM 605820). Initially described and delineated as separate myopathies based on muscle pathology, these entities are now known to represent various stages in the natural course of this one disorder [Tomimitsu et al 2004, Huizing 2005, Huizing & Krasnewich 2009]. Initially observed most frequently in various populations in the Middle East [Argov et al 2003], *GNE*-related myopathies more recently have been reported in Japan (Nonaka myopathy) [Kayashima et al 2002, Nishino et al 2002, Tomimitsu et al 2004] and in several groups of European origin [Broccolini et al 2002, Vasconcelos et al 2002].

Hereditary inclusion body myopathy (hIBM) begins in the young adult with gait difficulties resulting from compromised foot dorsiflexion. Muscle weakness, first apparent in the distal limb muscles, progresses in severity. In the early stages of the disorder the proximal limb muscles (quadriceps in the legs and deltoids, biceps, and triceps in the arms) appear to be spared. Weakness in these muscles appears in the later stages of the disorder. There is gradual reduction of muscle bulk in the limbs. Affected persons become wheelchair bound. Intellectual functioning, sensation, and coordination remain intact even when the myopathy becomes more widespread and severe.

Diagnosis is based on the histopathologic findings of red rimmed vacuolar degeneration of muscle fibers; specific MRI T_1-weighted documentation of quadriceps sparing but fatty and fibrous replacement of the surrounding musculature; and molecular genetic testing. Creatine kinase (CK) in plasma may be mildly elevated

in later clinical stages. Urinary excretion of sialic acid is normal [Argov & Mitrani-Rosenbaum 2008, Huizing & Krasnewich 2009].

Differential Diagnosis

Increased Urinary and Intracellular Free Sialic Acid

The free sialic acid storage disorders including Salla disease, intermediate severe Salla disease, and infantile free sialic acid storage disease (ISSD) are neurodegenerative disorders resulting from increased lysosomal storage of free sialic acid [Aula & Gahl 2001]. The mildest phenotype is Salla disease, characterized by normal appearance and normal neurologic findings at birth, followed by slowly progressive neurologic deterioration resulting in mild to moderate motor and developmental delay, truncal ataxia, spasticity, athetosis, intellectual disability, and epileptic seizures [Varho et al 2000, Varho et al 2002]. The most severe phenotype, ISSD, has its onset in early infancy. Affected children have severe delay of development, coarse facial features, generalized hypotonia, hepatosplenomegaly, severe intellectual disability, and cardiomegaly. Death through clinical complications usually occurs before or in early childhood [Lemyre et al 1999]. ISSD is prominent among the metabolic causes of non-immune fatal hydrops fetalis (as a group ~1% of the total) [Bellini et al 2009] that represent a separate phenotypic expression among the free sialic acid storage disorders [Stone & Sidransky 1999].

Free sialic acid storage disorders result from defective transport of free sialic acid out of lysosomes as a consequence of pathogenic variants in *SLC17A5* encoding the lysosomal transport protein sialin [Verheijen et al 1999, Aula et al 2000, Aula et al 2002]. The diagnosis of the free sialic acid storage disorder is suggested by documentation of significantly elevated free (i.e., unconjugated) sialic acid in urine. In Salla disease, urinary excretion of free sialic acid is elevated, but only about one-tenth of that found in sialuria. The diagnosis, suspected by the clinical signs and by lysosomal damage detected by electron microscopic study of skin biopsy specimens, is formally established either by demonstrating lysosomal (rather than cytoplasmic) localization of elevated free sialic acid or identifying pathogenic variants in *SLC17A5*. Homozygosity for the *SLC17A5* pathogenic missense variant p.Arg39Cys results in the typical Finnish Salla disease phenotype of intermediate severity. Compound heterozygotes, who have one copy of this pathogenic variant, have a more severe phenotype that is clinically reminiscent of ISSD. Most individuals homozygous or compound heterozygous for other *SLC17A5* pathogenic variants have either ISSD or more severe forms of Salla disease [Aula et al 2000, Varho et al 2002, Morse et al 2005]. Affected individuals of non-Finnish ancestry usually have clinical features that are more severe than "classic" Salla disease or ISSD [Biancheri et al 2002].

Free sialic acid storage disease caused by homozygosity of the p.Lys136Glu mutated allele in *SLC17A5* has also been reported in two sibs with early clinical onset, mild phenotype, and mild cerebral hypomyelination. The urinary excretion of free sialic acid was within normal limits, but free sialic acid concentration was elevated threefold in the cerebrospinal fluid (CSF) [Mochel et al 2009].

Initial Clinical Features (Coarse Facies, Hypotonia, Hepatomegaly)

Although mild, inconsistent, and transient, the initial clinical features make the differential diagnosis in infants and young children an interesting challenge.

Mucopolysaccharidosis type I (MPS I) is a progressive multisystem disorder with features ranging over a continuum from mild to severe. Affected persons are best described by the terms MPS I with severe, intermediate, or mild disease. Infants with severe MPS I (Hurler disease) have coarse facial features, stiff shoulder joints, and generalized hypotonia at birth. Further coarsening of the facial features occurs within the first two years. Corneal clouding and cardiac involvement, most often not clinically apparent in the first few years, are consistent in MPS I. Cardiac valve dysfunction may soon become apparent on echocardiogram. Progressive skeletal dysplasia (dysostosis multiplex) involving all bones is seen in all persons with severe MPS I

[Spranger 2002]. Linear growth, often excessive between ages six and 18 months, ceases by age three years. Onset of symptoms of intermediate MPS I usually occurs between ages three and eight years and survival to adulthood is common. Persons with mild MPS I are often diagnosed after age 15 years and generally have normal intellect, normal stature, and a near-normal life span [Neufeld & Muenzer 2001, Spranger 2002].

The diagnosis of MPS I relies on the demonstration of deficient activity of the lysosomal enzyme α-L-iduronidase in peripheral blood leukocytes or cultured fibroblasts. Glycosaminoglycan (GAG) (heparan and dermatan sulphate) urinary excretion is a useful preliminary test. *IDUA* is the only gene currently known to be associated with MPS I. Using sequence analysis and/or variant analysis, it is possible to identify both *IDUA* pathogenic variants in 95% of persons with MPS I. MPS I is inherited in an autosomal recessive manner.

Severe types of other, less prevalent mucopolysaccharidoses (MPS). Disorders specifically relevant are MPS VI (Maroteaux-Lamy disease) and MPS VII (Sly disease), which cannot be distinguished clinically from MPS I before age one to two years. In the former, cognitive functioning remains normal or near normal. The diagnosis is made by demonstration in peripheral leukocytes or cultured fibroblasts of significant deficiency of either N-acetylgalactosamine-4-sulphatase or β-D-glucuronidase, respectively. Free sialic acid is normal in urine, which typically has increased amounts of glycosaminoglycans as in MPS I.

Oligosaccharidoses. The more slowly evolving oligosaccharidoses represent an alternate possibility. These disorders are characterized by oligosaccharidurіa and hence excessive excretion of bound sialic acid but no elevation of free sialic acid in the individual's urine. The abnormal features of sialuria are mild compared to those of the oligosaccharidoses:

- **Sialidosis (mucolipidosis I).** Only the initial stages of this rare childhood dysmorphic sialidosis caused by acid sialidase deficiency have features in common with sialuria [Thomas 2001, Leroy 2002a, Leroy 2002b].
- **GM1-gangliosidosis type II.** In this disorder caused by beta-D-galactosidase deficiency, neuromotor regression, skeletal dysostosis multiplex, and organomegaly are less pronounced than in the severe infantile GM1-gangliosidosis type 1, but physical and intellectual morbidity is more pronounced in either than in sialuria [Suzuki et al 2001].
- **Infantile type galactosialidosis.** Associated with the combined deficiency of beta-D-galactosidase and acid sialidase, this disorder is caused by genetic defect of the lysosomal protective protein/cathepsin A (PPCA) [d'Azzo et al 2001]. Like GM1 gangliosidosis, it is a serious CNS and multiorgan disease in which usually only mild dysostosis multiplex and organomegaly are observed.
- **Pseudo-Hurler polydystrophy (mucolipidosis III alpha/beta or mucolipidosis III gamma)** [Cathey et al 2008]. Clinically and etiologically closely related to I-cell disease (mucolipidosis II), pseudo-Hurler polydystrophy has its clinical onset after age two years. It is characterized by joint stiffness and by slowing of physical growth in addition to coarsening of facial features. In this disorder the glycans in lysosomal acid hydrolases are poorly phosphorylated by a mutated UDP-GlcNAc-1-phosphotransferase and, hence, are deficient in mannose-6-phosphate (M6P) markers, which are crucial for binding of the hydrolases to the M6P-receptors (MPRs) and for targeting them to lysosomes.

  Mucolipidosis III alpha/beta is caused by homozygous or compound heterozygous pathogenic variants in *GNPTAB*. Mucolipidosis III gamma is caused by homozygous or compound heterozygous pathogenic variants in *GNPTG* [Kornfeld & Sly 2001, Leroy 2002a, Cathey et al 2010].

Developmental delay. Assay of urinary sialic acid could become part of the metabolic screening in young children with mild hypotonia and developmental delay, sometimes complicated from early childhood by a mild seizure disorder. Sialuria may be considered a cause of borderline intellectual disability, usually considered to have a multifactorial explanation.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in a person diagnosed with sialuria, the following evaluations are recommended, if they have not already been completed. Note: The priority of these recommendations depends on the signs observed in the patient and/or noted by the parents:

- CBC with differential to evaluate for microcytic anemia
- Measurement of serum bilirubin concentration to evaluate for jaundice
- Skeletal survey to evaluate for dysostosis multiplex
- Developmental and neurologic assessment
- EEG when relevant
- Neuroimaging with the purpose of differentiating sialuria from neurodegenerative lysosomal storage disorders

Treatment of Manifestations

Persons with sialuria need symptomatic and supportive management, including treatment of anemia, prolonged but mild jaundice, and convulsions. Barbiturates have been more effective in treating the occasional convulsion in early childhood than other antiepileptic drugs (AEDs).

Affected individuals benefit from early developmental intervention and appropriate educational programs.

Prevention of Secondary Complications

Appropriate antibiotics to prevent secondary bacterial super-infection in the upper/lower airways are indicated.

Surveillance

The following are appropriate:

- Clinical follow up during and after infancy to confirm that CNS disease is not progressive (in contrast to free sialic acid storage disorders) and to document the gradual remission of signs and/or symptoms present in infancy
- Follow-up evaluations three to four times in infancy, twice in the second year of life, and once every subsequent year

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.

Click here (pdf) for information on therapy trials in "knockin" mice yielding preliminary data for future possible therapies in humans.

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

Sialuria is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most persons diagnosed with sialuria do not have a parent known to be affected. However, molecular genetic testing has usually not been performed on both parents; thus, the actual percentage of persons who have inherited the pathogenic variant from a parent is unknown.
- A proband with sialuria most likely has the disorder as the result of a *de novo* pathogenic variant in the allosteric site of *GNE*. Five of the seven persons reported possibly represent simplex cases (i.e., a single affected individual in a family); however, study of urinary excretion of free sialic acid in their close relatives has not been reported.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include study of urinary excretion of free sialic acid of both parents and molecular genetic testing if the pathogenic variant has been identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or has a pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the pathogenic variant found in the proband cannot be detected in the DNA of the either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism. Germline mosaicism has not been reported.

Offspring of a proband. Each child of a person with sialuria has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Interpretation of prenatal diagnosis testing is complicated by the current lack of information about the phenotype, particularly its long-term outcome. Results of prenatal testing cannot predict the age of onset, clinical course, or degree of disability.

Biochemical testing. No prenatal biochemical testing for sialuria has been performed; however, biochemical testing for prenatal diagnosis has been performed in free sialic acid storage disorders.

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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.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. Sialuria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GNE	9p13.3	Bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase	GNE homepage - Leiden Muscular Dystrophy pages	GNE	GNE

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 Sialuria (View All in OMIM)

269921	SIALURIA
603824	UDP-N-ACETYLGLUCOSAMINE 2-EPIMERASE/N-ACETYLMANNOSAMINE KINASE; GNE

Molecular Genetic Pathogenesis

Sialuria. The basic metabolic defect in sialuria is failed allosteric feedback inhibition of the bifunctional UDP-N-acetylglucosamine (UDP-GlcNAc) 2-epimerase (EC 5.1.3.14) / N-acetylmannosamine (ManNAc) kinase (EC

2.7.1.60) (GNE/MNK), rate-limiting enzyme in the biosynthesis of sialic acid (Neu5Ac). The biologic inhibitory substance, CMP-Neu5Ac, the downstream product in this biosynthetic pathway, is formed in the cell nucleus per activation of Neu5Ac by CTP catalyzed by CMP-Neu5Ac synthase. It is subsequently transported into the Golgi apparatus assisted by a specific Golgi membrane protein. It serves in that location as a substrate for different sialyltransferases [Reinke et al 2009]. Feedback inhibition fails when CMP-sialic acid (CMP-neu5Ac) cannot bind to the small mutated allosteric site in GNE/MNK, itself a soluble protein of 722 amino acids found in the cytoplasm, mainly in the Golgi region, and also in the cell nucleus [Krause et al 2005] The allosteric site is still incompletely defined but comprises the consecutive amino acids 263 through 266 in the epimerase functional domain.

In each person with sialuria, the *GNE* pathogenic variant was found to be a missense variant in one of the two nearly adjacent codons in exon 5 (Table 2). In each person, it was found only in the heterozygous state [Ferreira et al 1999, Seppala et al 1999, Aula & Gahl 2001, Enns et al 2001, Leroy et al 2001, Huizing & Krasnewich 2009]. The detection of this molecular defect provided the initial information that identified the allosteric site in the GNE/MNK enzyme and explains the main aspects of the pathogenesis of sialuria. Moreover, the finding that the regulatory pathogenic variant in all persons with sialuria is heterozygous establishes the autosomal dominant mode of inheritance.

The lack of feedback inhibition results in highly excessive production of free sialic acid and in its very elevated concentrations in the cellular cytoplasm, interstitial tissues, and body fluids, such as urine.

Defective allosteric inhibition is not an exceptional cause of human metabolic disease. It has been shown recently also for the glutamate dehydrogenase gene in infants with hyperinsulinism and hyperammonemia (see Familial Hyperinsulinism).

Gene structure. *GNE* consists of 14 exons, 13 of which are located closely together, whereas the recently discovered additional exon of 90 base pairs, named A1, resides 20 kb upstream of exon 1 as outlined in the references in Reinke et al [2009]. Four different mRNA splice variants are transcribed from *GNE*, resulting from alternative splicing of the exons A1, 1, and 2. Exon 1 is a non-coding exon. Hence, two of the splice variants encode a protein of 722 amino acids, hGNE1, as reported for the originally characterized GNE/MNK protein and referred to in most molecular biology studies.

Pathogenic variants. In all persons with sialuria, one of three single missense variants, p.Arg263Leu, p.Arg266Gln, or p.Arg266Trp, was found in only a single *GNE* allele (located in exon 5 and the epimerase domain of GNE/MNK) and associated with highly excessive urinary excretion of free sialic acid. This strongly suggested that the corresponding group of amino acids represents the allosteric site of the enzyme for retroinhibition by CMP-Neu5Ac acid binding [Seppala et al 1999]. In contrast to the sialic acid storage disorders, the clinical consequence has been mild and not associated with lysosomal retention of free sialic acid or by other histologically demonstrable cellular damage. The finding in the symptom-free mother of one of the probands confirms the mild clinical effect and proves the autosomal dominant inheritance of the disorder.

Note: Homozygous or compound heterozygous pathogenic variants in either the epimerase domain or the kinase domain are associated with adult-onset autosomal recessive hereditary inclusion body myopathy (hIBM). See Genetically Related Disorders.

Table 2. Selected *GNE* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.788G>T	p.Arg263Leu	NM_005476.4 [1] NP_005467.1
c.797G>A	p.Arg266Gln	
c. 796C>T	p.Arg266Trp	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. The codon numbers correspond to reference sequence NP_005467.1 (sometimes referred to isoform 2), which contains a different 5' terminal exon compared to transcript variant 1, resulting in translation initiation from an in-frame downstream AUG and an isoform (2) with a shorter N-terminus compared to isoform 1. See Entrez Gene www.ncbi.nlm.nih.gov/gene/10020.

Normal gene product. Uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) 2-epimerase (GNE) (EC 5.1.3.14)/ N-acetylmannosamine (ManNAc) kinase (MNK) (EC 2.7.1.60), a protein of 722 amino acids is a bifunctional enzyme that catalyzes the first rate-limiting step and the second step in the biosynthetic pathway of sialic acid [Seppala et al 1999, Aula & Gahl 2001, Huizing & Krasnewich 2009]. The first of these steps is inhibited by feedback from CMP-neu5Ac. The epimerase activity domain is found in the amino-terminal portion of the protein (amino acids 1 to ~378) and the kinase domain is found in the carboxy-terminal half (amino acids ~410 to 722) [Seppala et al 1999, Huizing 2005]. The allosteric site resides in exon 5 within the epimerase domain. The active site in either enzyme domain is still to be determined. GNE/MNK is a major determinant of cell surface glycoconjugate sialylation and a critical regulator of the function of specific cell-surface adhesion molecules. Bound N-acetyl-neuraminic acid (NANA) is widely distributed in normal tissues and is a constituent of glycoproteins and complex lipids such as gangliosides. In N-linked glycoproteins, NANA is consistently the terminal sugar in the oligosaccharide tree [Huizing & Krasnewich 2009].

Human GNE (GNE/MNK) exists in three different isoforms – hGNE1, hGNE2, and hGNE3 – the latter two possessing extended or deleted N-terminal regions, respectively. The isoform hGNE1 is ubiquitously expressed, most intensively in liver and placenta. Lower concentrations are detectable in muscle, brain, kidney, and pancreas [Reinke et al 2009 and references therein].

It is of interest that as a monomer GNE/MNK has no catalytic activity. It requires di- and even multimerization of the nascent polypeptides in order to become fully active as a bifunctional enzyme [Huizing & Krasnewich 2009, Reinke et al 2009].

Abnormal gene product. Pathogenic variants appear to reside exclusively in the short stretch of consecutive nucleotides in *GNE* that encodes the amino acids 263 to 266, which have an important role in the allosteric site of the gene product, UDP-N-acetylglucosamine 2-epimerase/N-acetyl mannosamine kinase (GNE/MNK). Of note, the borders of the putative allosteric site have not yet been determined [Huizing 2005].

The activity of the bifunctional and rate-limiting GNE enzyme is normal in sialuria fibroblasts, but no longer subject to retro-inhibition by the end-product CMP-sialic acid, when one and only one of the two *GNE* alleles is a pathogenic missense variant in the putative allosteric site in and probably near codons 263 and 266. Hence, there is significant and steady overproduction and vastly excessive urinary excretion of free sialic acid (neu5Ac).

The apparently rare individuals with sialuria have a clinically mild disorder. Nevertheless, a pathogenic variant resulting in an allosteric autosomal dominant metabolic defect is of considerable importance in the study of the various physiologic roles of free sialic acid and of sialylation in tissues. Moreover, the metabolic trait has been shown to be important in the production of biologic molecules with therapeutic potential and in testing the feasibility of silencing mutation effects by RNA interference. Click here for additional information.

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Chapter Notes

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Revision History

- 7 March 2019 (ma) Chapter retired: extremely rare
- 18 October 2012 (me) Comprehensive update posted live
- 2 March 2010 (me) Comprehensive update posted live
- 27 February 2007 (jgl) Revision: clinical testing and prenatal diagnosis no longer available
- 10 March 2006 (me) Comprehensive update posted live
- 14 January 2004 (me) Review posted live
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