Sialuria (French Type): A Comprehensive Disease Characteristics Report

Disease: Sialuria (French type) **Identifiers:** OMIM #269921 · ORPHA:2809 · MONDO:0009359 · Gene: *GNE* (HGNC:23657; 9p13.3) **Category:** Mendelian, autosomal dominant inborn error of metabolism **Report date:** 2026-09-04

Summary

Sialuria is an ultra-rare autosomal dominant inborn error of metabolism in which heterozygous missense mutations at the allosteric (feedback-inhibitor) site of the bifunctional enzyme UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE/MNK) abolish CMP-sialic acid feedback inhibition, causing unregulated cytoplasmic overproduction and gram-quantity urinary excretion of free *N*-acetylneuraminic acid (Neu5Ac, sialic acid). Fewer than a dozen patients have ever been described worldwide, and the reported cases are strikingly homogeneous clinically: infantile onset with developmental delay, mildly coarse facial features, hepatomegaly, and prolonged neonatal jaundice. Unlike its differential diagnoses, sialuria is generally **non-neurodegenerative** and comparatively mild.

The mechanism is now understood at atomic resolution. GNE/MNK catalyzes the first two committed, rate-limiting steps of *de novo* sialic acid biosynthesis, and its epimerase activity is normally braked by binding of the downstream product CMP-Neu5Ac at an allosteric pocket located at the dimer–dimer interface of the enzyme tetramer. All reported sialuria alleles cluster at two arginine residues in this pocket — **Arg263 and Arg266** (current HGVS numbering **Arg294/Arg297**). Crystallography and protein engineering demonstrate that these mutations **retain catalytic activity but destroy feedback inhibition**, producing a gain-of-flux state in which intracellular CMP-sialic acid rises more than 10-fold and free sialic acid overflows into the cytosol and urine.

Sialuria sits at one pole of the *GNE* allelic disorder spectrum. Recessive loss-of-function mutations in the *catalytic* domains of the same gene cause **GNE myopathy** (Nonaka/hereditary inclusion body myopathy), a mechanistically opposite disorder of sialic acid *deficiency*. Sialuria must also be distinguished from the recessive **lysosomal free sialic acid storage disorders**

(FSASD; Salla disease/ISSD) caused by *SLC17A5*/sialin defects, which share elevated urinary free sialic acid but differ in subcellular compartment (lysosomal vs. cytosolic), inheritance (recessive vs. dominant), and clinical course (neurodegenerative vs. relatively benign). No approved disease-specific therapy exists; management is supportive. Allele-specific siRNA silencing of the mutant *GNE* allele has been shown to restore feedback inhibition and normalize free sialic acid in patient fibroblasts, providing proof-of-concept for a future targeted therapy.

1. Disease Information

Overview. Sialuria is a rare autosomal dominant inborn error of metabolism characterized by cytoplasmic accumulation and urinary excretion of gram quantities of free sialic acid, resulting from failure of feedback inhibition of the rate-limiting enzyme of sialic acid synthesis, GNE/MNK (PMID: 29923088). It is sometimes called **sialuria, French type** to distinguish it from the (mechanistically unrelated) free sialic acid storage disorders.

Key identifiers.

Resource	Identifier
OMIM	#269921
Orphanet	ORPHA:2809
MONDO	MONDO:0009359
Gene	*GNE* (HGNC:23657), 9p13.3
Enzyme EC	5.1.3.14 (UDP-GlcNAc 2-epimerase) / 2.7.1.60 (ManNAc kinase)

Synonyms / alternative names. Sialuria French type; GNE-related sialuria; UDP-GlcNAc-2-epimerase feedback-inhibition defect.

Information source. The disease-level knowledge is derived from **aggregated case reports and biochemical/structural studies**, not EHR data. With only ~9 published patients, essentially all information is at the level of individual-patient case reports synthesized into disease-level resources (OMIM, Orphanet).

2. Etiology

Primary cause — genetic. Sialuria is caused by heterozygous (dominant) missense mutations at the **allosteric feedback-inhibitor site** of *GNE*. All nine reported cases carry a heterozygous missense variant at this site, recurrently at **Arg294 (formerly Arg263)** and **Arg297 (formerly Arg266)** (PMID: 29923088). The functional consequence is a **gain-of-function/gain-of-flux** defect: loss of CMP-sialic acid feedback inhibition of GNE-epimerase activity, causing excessive production of free sialic acid.

Genetic risk factors. The causal variants themselves are the sole known risk determinant. No modifier loci or susceptibility SNPs have been reported for this ultra-rare disorder.

Environmental risk factors. None identified. Sialuria is a purely Mendelian, single-gene disorder with no known environmental, toxic, occupational, infectious, dietary, age, or sex contribution to disease occurrence.

Protective factors. None described (genetic or environmental). Given dominant inheritance with the mutant allele driving pathology, allele-specific silencing is being explored as a therapeutic rather than a naturally occurring protective mechanism.

Gene–environment interactions. No gene–environment interaction has been documented. The phenotype tracks directly with the *GNE* allosteric-site genotype.

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3. Phenotypes

The nine published cases share **rather homogeneous clinical features**: developmental delay, mildly coarse features, hepatomegaly, and prolonged neonatal jaundice (PMID: 29923088). The best-documented single case (fifth reported patient, a 7-year-old Portuguese girl) showed developmental delay, hepatomegaly, coarse facies, and urinary excretion of 19 µmol free NeuAc/mg creatinine (PMID: 10356312).

Phenotype	Type	Onset	Severity	Frequency	Suggested HPO
Developmental delay	Neurodevelopmental	Infantile/ childhood	Mild–moderate; often non-progressive	Common (majority)	HP:0001263 (Global developmental delay)
Coarse facial features	Physical/clinical sign	Infantile	Mild	Common	HP:0000280 (Coarse facial features)
Hepatomegaly	Clinical sign	Infantile	Mild–moderate	Common	HP:0002240 (Hepatomegaly)
Prolonged neonatal jaundice	Clinical sign	Neonatal	Mild	Recurrent	HP:0006579 (Prolonged neonatal jaundice)
Elevated urinary free sialic acid	Laboratory abnormality	Congenital/ lifelong	Marked (gram quantities)	Universal (diagnostic hallmark)	HP:0003231 (Sialuria)
Hypotonia	Clinical sign	Infantile	Variable	Reported in some	HP:0001252 (Hypotonia)

Progression. Features are generally **stable/non-progressive**; sialuria is not neurodegenerative, an important distinction from the lysosomal free sialic acid storage disorders. **Age of onset** is neonatal-to-infantile.

Quality of life impact. Mild-to-moderate developmental delay may affect learning and daily functioning; hepatomegaly and coarse facies are generally not disabling. No formal EQ-5D/ SF-36 quality-of-life data exist for this ultra-rare disease. Overall the burden is substantially lower than in FSASD.

4. Genetic / Molecular Information

Causal gene. *GNE* (glucosamine [UDP-*N*-acetyl]-2-epimerase/*N*-acetylmannosamine kinase), 9p13.3, OMIM *603824. Encodes the bifunctional, rate-limiting enzyme of sialic acid biosynthesis (PMID: 23437777).

Pathogenic variants.

Feature	Detail
Affected gene	*GNE* (HGNC:23657)
Variant type	Missense, clustering at the allosteric/feedback site
Recurrent residues	Arg263 and Arg266 (current numbering Arg294/Arg297)
Representative allele	c.797G>A, p.Arg266Gln (p.R266Q)
Classification	Pathogenic (ACMG) — recurrent, functionally validated, segregating with dominant disease
Zygosity	Heterozygous (dominant)
Population allele frequency	Not present at appreciable frequency in gnomAD (ultra-rare; essentially private/de novo or transmitted)
Origin	Germline
Functional consequence	**Gain of function** at the pathway level — retained catalysis with loss of allosteric feedback inhibition

The p.R266Q variant was documented in the Portuguese case, where fibroblast UDP-GlcNAc 2-epimerase was only **26% inhibited by 100 µM CMP-Neu5Ac (normal 79%)**, confirming loss of feedback braking (PMID: 10356312).

Modifier genes. None identified.

Epigenetic information. No DNA-methylation or histone-modification changes have been reported for sialuria; the disorder is a classic single-gene coding-variant condition.

Chromosomal abnormalities. None; sialuria is not associated with aneuploidy, translocations, or copy-number changes.

5. Environmental Information

- **Environmental factors:** None known. Sialuria is not caused or modified by toxins, radiation, pollution, or occupational exposure.
- **Lifestyle factors:** None known. Diet, smoking, alcohol, and exercise are not implicated in onset. (Dietary sialic acid restriction has not been shown to alter the endogenous overproduction that drives the phenotype.)
- **Infectious agents:** Not applicable — sialuria is a Mendelian metabolic disorder. Note that urinary free sialic acid, the diagnostic biomarker, may be **non-specifically elevated in pneumococcal sepsis** (PMID: 36000484), a relevant caveat for interpreting the screening test but not an etiologic factor.

6. Mechanism / Pathophysiology

Ordered causal chain

1. A **heterozygous missense mutation** at the *GNE* allosteric site (Arg263/Arg266 → e.g., R266Q) **alters the CMP-Neu5Ac binding pocket** at the dimer–dimer interface of the GNE/MNK tetramer.
2. This **prevents CMP-sialic acid from locking the epimerase in its closed, inhibited conformation → loss of allosteric feedback inhibition** (demonstrated: crystallography + in vitro inhibition assays).
3. Loss of feedback braking **leaves epimerase catalysis constitutively active** (retained catalytic function; ~94% of wild-type activity in engineered mutants) → **unregulated flux through the de novo pathway** (UDP-GlcNAc → ManNAc → ManNAc-6-P → Neu5Ac-9-P → Neu5Ac).
4. Unregulated flux **raises intracellular CMP-sialic acid >10-fold** and causes **overproduction of free Neu5Ac** (demonstrated in engineered cells).
5. Free Neu5Ac **accumulates in the cytoplasm** (cytosolic, not lysosomal, storage) and **overflows into urine in gram quantities** (demonstrated; the biochemical hallmark).
6. The systemic consequences — **developmental delay, hepatomegaly, coarse facies, prolonged neonatal jaundice** — follow from cellular free–sialic-acid excess and altered

sialylation flux (mechanistic link to specific organ phenotypes remains partly *inferred* rather than fully demonstrated).

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GNE allosteric-site mutation (Arg263/Arg266; R266Q)
        │ alters CMP-Neu5Ac binding pocket at dimer–dimer interface
        ▼
Loss of CMP-sialic acid feedback inhibition of GNE-epimerase
        │ (catalysis retained ~94% WT)
        ▼
Unregulated de novo flux: UDP-GlcNAc → ManNAc → … → Neu5Ac
        ▼
Intracellular CMP-sialic acid ↑ >10×  +  cytosolic free Neu5Ac ↑↑
        ├──► gram-quantity urinary free sialic acid (diagnostic hallmark)
        └──► systemic phenotype (developmental delay, hepatomegaly,
                 coarse facies, neonatal jaundice) [partly inferred]
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Detail by category

Molecular pathways. The de novo **sialic acid biosynthesis / sialylation pathway** (KEGG amino sugar and nucleotide sugar metabolism). Cellular free sialic acids are made via de novo biosynthesis, recycled from lysosomal salvage, and taken up from extracellular sources (PMID: 41352710). GNE/MNK catalyzes the first two committed, rate-limiting steps and is feedback-inhibited by CMP-sialic acid (PMID: 19917666).

Biochemical abnormality (upstream, primary). Failure of allosteric feedback inhibition. "The resultant loss of feedback inhibition of GNE-epimerase activity by CMP-sialic acid causes excessive production of free sialic acid" (PMID: 18653764).

Protein dysfunction. The N-terminal epimerase domain of human GNE forms a **tetramer** in which UDP binds the active site and **CMP-Neu5Ac binds the dimer–dimer interface, locking the enzyme in a tightly closed conformation** (PMID: 26980148). Mutations at Arg263/Arg266 sit in/around this allosteric pocket; the crystallographic binding mode "clearly elucidates why mutations in Arg263 and Arg266 can cause sialuria" (PMID: 26980148). Substrate (UDP-GlcNAc) binding stabilizes the tetramer by increasing dimer–dimer affinity ~98-fold; inhibitors disrupt the assembly (PMID: 41099617).

Metabolic changes (downstream). Cytosolic overaccumulation of free Neu5Ac and >10-fold elevation of the activated donor CMP-sialic acid; free sialic acid is normally degraded to ManNAc and pyruvate in the cytosol (PMID: 41352710). Sialuria represents the

overproduction/accumulation pole of sialic acid disorders — "Sias deficiency and overproduction (accumulation), hyposialylation … and hypersialylation all cause disorders" (PMID: 41352710).

Subcellular localization. Cytoplasm/cytosol (GO:0005829) — critically distinct from the lysosomal accumulation of FSASD. Sialylation itself occurs in the Golgi using CMP-Sia as donor.

Immune / inflammatory involvement. Not a primary feature. Sialuria is not an autoimmune or inflammatory disorder.

Molecular profiling. No sialuria-specific transcriptomic, proteomic, or metabolomic datasets are published beyond direct biochemical measurement of free sialic acid and CMP-sialic acid. Orthogonal in vitro engineering data (below) provide the strongest mechanistic confirmation.

GO / CL term suggestions. GO:0006054 (N-acetylneuraminate metabolic process); GO:0046380 (N-acetylneuraminate biosynthetic process); GO:0008761 (UDP-N-acetylglucosamine 2-epimerase activity); GO:0009384; GO:0005829 (cytosol). No specific cell-type (CL) restriction — the defect is cell-autonomous and broadly expressed (hepatocytes, CL:0000182; fibroblasts, CL:0000057 are documented affected cell types).

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7. Anatomical Structures Affected

Organ level. - **Liver** — hepatomegaly (UBERON:0002107); prolonged neonatal jaundice implicates hepatobiliary handling. - **Brain / CNS** — developmental delay (UBERON:0000955), generally without structural neurodegeneration. - **Craniofacial** — mildly coarse facies (UBERON:0000033, head). - **Kidney / urinary tract** — conduit for gram-quantity urinary sialic acid excretion (not injured).

Body systems. Hepatic/digestive, nervous (developmental), and metabolic systems.

Tissue and cell level. Documented affected cell types include **hepatocytes** (CL:0000182) and **fibroblasts** (CL:0000057, the standard diagnostic cell showing cytosolic free-sialic-acid excess). The defect is fundamentally **cell-autonomous** in any GNE-expressing cell.

Subcellular level. Cytoplasm/cytosol (GO:0005829) is the site of free-sialic-acid overproduction and storage — the defining subcellular contrast with lysosomal (GO:0005764) storage in FSASD.

Localization / lateralization. Systemic/bilateral; no lateralization.

8. Temporal Development

- **Onset:** Congenital/neonatal-to-infantile. Prolonged neonatal jaundice may be the earliest sign; developmental delay and hepatomegaly emerge in infancy/early childhood.
- **Onset pattern:** Chronic/insidious — present from birth as a constitutive metabolic overproduction.
- **Progression:** Generally **stable and non-progressive**; sialuria is not neurodegenerative. This is a key prognostic and differential feature versus FSASD.
- **Disease course:** Chronic, lifelong (the underlying enzymatic dysregulation persists), but with comparatively benign clinical trajectory. Some patients show improvement/ normalization of developmental milestones over time.
- **Remission patterns:** No spontaneous biochemical remission (the genetic defect is constitutive). No approved treatment-induced remission, though allele-specific silencing normalizes biochemistry experimentally.
- **Critical periods:** Infancy/early childhood is the window of clinical recognition; the theoretical window for any future disease-modifying (e.g., allele-silencing) intervention would be early.

9. Inheritance and Population

Epidemiology. Ultra-rare. Only **~9 patients** have been reported worldwide (PMID: 29923088). Prevalence/incidence figures are not formally established (well under 1 per 1,000,000). Orphanet lists it as an ultra-rare condition.

Inheritance. Autosomal dominant — the single most distinctive genetic feature among sialic acid disorders. "Sialuria is a rare autosomal dominant inborn error of metabolism ..." (PMID: 29923088). A single mutant allele suffices because the mutant enzyme escapes feedback and drives overproduction regardless of the normal allele.

- **Penetrance:** Appears complete for the biochemical phenotype (all reported carriers are biochemically affected); clinical severity varies.
- **Expressivity:** Variable but with homogeneous core features.
- **Genetic anticipation:** Not applicable (no repeat expansion).

- **Germline mosaicism / de novo:** Several cases appear sporadic; de novo occurrence is plausible given dominant inheritance, though transmission has been observed.
- **Founder effects / consanguinity:** Not applicable (dominant, not enriched by consanguinity — in contrast to the recessive FSASD, which shows founder/consanguinity effects).
- **Carrier frequency:** Not meaningful for a dominant ultra-rare disorder.

Population demographics. Cases reported across diverse ethnicities (e.g., Portuguese); no ethnic or geographic clustering. No established sex bias. Age distribution centers on pediatric identification.

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10. Diagnostics

Laboratory tests (primary). - **Urine free sialic acid (UFSA)** — the key screening biomarker; markedly (gram-quantity) elevated. "Urine free sialic acid (UFSA) is an important diagnostic biomarker for sialuria" (PMID: 36000484). The Portuguese patient excreted 19 μmol free NeuAc/mg creatinine (PMID: 10356312). - **Fibroblast free sialic acid** — elevated, localized to the **cytosolic** (not lysosomal) fraction on differential centrifugation — the compartment distinction that separates sialuria from FSASD. - **Enzyme feedback-inhibition assay** — fibroblast UDP-GlcNAc 2-epimerase inhibition by 100 μM CMP-Neu5Ac is reduced (26% vs. normal 79%) (PMID: 10356312).

Biomarkers. Free Neu5Ac (CHEBI:45744) in urine, plasma, and cultured cells; elevated intracellular CMP-sialic acid.

Genetic testing. Single-gene *GNE* sequencing targeting the allosteric-site codons (Arg263/Arg266; current Arg294/Arg297) is confirmatory. WES/WGS or a sialic-acid-disorder / metabolic gene panel including both *GNE* and *SLC17A5* is appropriate when the differential is open. CMA, karyotyping, FISH, mtDNA, and repeat-expansion testing are **not** indicated.

Imaging / other modalities. No pathognomonic imaging. Notably, brain MRI in sialuria lacks the hypomyelination/thin corpus callosum seen in FSASD/Salla disease — a useful discriminator.

Differential diagnosis.

Disorder	Gene	Inheritance	Compartment	UFSA elevation	Course
Sialuria (French type)	*GNE* (allosteric)	**AD**	**Cytosolic**	Gram quantities (very high)	Mild, non-neurodegenerative
Free sialic acid storage disorders (Salla/ISSD, FSASD)	*SLC17A5* (sialin)	AR	Lysosomal	10–100×	Neurodegenerative, hypomyelination
GNE myopathy (Nonaka/ HIBM)	*GNE* (catalytic)	AR	— (deficiency)	Not elevated	Adult-onset myopathy
Pneumococcal sepsis (mimic)	—	—	—	Non-specifically elevated	Acute infection

FSASD is caused by biallelic *SLC17A5* defects producing **lysosomal** accumulation with 10–100-fold increased urinary free sialic acid (PMID: 33862140); this contrasts with the cytosolic overproduction of sialuria. UFSA can also be non-specifically raised in pneumococcal sepsis (PMID: 36000484).

Screening. Not part of routine newborn screening. Cascade testing of at-risk relatives (given dominant inheritance) via targeted *GNE* variant testing is reasonable once a proband variant is known.

11. Outcome / Prognosis

- **Survival / mortality:** Sialuria is not associated with early mortality; life expectancy appears largely preserved. This contrasts sharply with infantile FSASD (ISSD), which is often fatal in early childhood.

- **Morbidity / function:** Mild-to-moderate developmental delay is the principal long-term functional concern; hepatomegaly and coarse facies are generally non-disabling. Some patients show developmental improvement over time.
- **Disease course:** Chronic but stable; non-progressive/non-neurodegenerative.
- **Complications:** Few reported; no organ failure or neurodegeneration characteristic of the disorder.
- **Prognostic factors:** Genotype (all reported allosteric-site variants confer the same broad, relatively benign phenotype). No validated prognostic biomarkers beyond the diagnostic free-sialic-acid measurements.
- **Quality-of-life measures:** No formal EQ-5D/SF-36/PROMIS data (ultra-rare disease).

Overall prognosis is **substantially more favorable** than for the lysosomal sialic acid storage disorders.

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12. Treatment

No approved disease-specific therapy exists; management is supportive (developmental support/early intervention, monitoring of hepatomegaly and growth).

Experimental / mechanism-directed. - **Allele-specific RNA interference.** The most compelling proof-of-concept: in sialuria fibroblasts carrying c.797G>A (p.R266Q), synthetic siRNAs specifically targeting the mutant allele produced allele-specific knockdown, "a significant decrease of free sialic acid, to within the normal range" and recovery of CMP-sialic acid feedback inhibition of GNE-epimerase activity after silencing (PMID: 18653764). Because the disorder is dominant and driven by the mutant allele, selectively silencing that allele is a rational therapeutic strategy (NCIT concept: gene-silencing / RNA-interference therapy). - **Small-molecule GNE inhibitors.** GNE oligomerization/assembly can be disrupted pharmacologically; mass-photometry studies show inhibitors (C5, C13, C15) destabilize the tetramer (PMID: 41099617) — a conceptual avenue for dampening overactive flux, though not developed as a sialuria therapy.

Pharmacogenomics, gene/cell/immunotherapy, surgery: Not applicable/none established.

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13. Prevention

- **Primary prevention:** Not applicable for an inherited/de novo dominant single-gene disorder — no lifestyle or environmental modification prevents onset.
- **Secondary prevention:** Early biochemical recognition (urine free sialic acid) enables diagnosis, appropriate developmental support, and avoidance of unnecessary investigations for FSASD/lysosomal storage.
- **Tertiary prevention:** Supportive management of developmental delay.
- **Genetic counseling:** Autosomal dominant transmission implies up to 50% recurrence risk for offspring of an affected parent; counseling and, where a familial variant is known, prenatal/cascade *GNE* testing can be offered. De novo occurrence is common in sporadic cases.
- **Immunization / public health / prophylaxis:** Not applicable.

14. Other Species / Natural Disease

- **Taxonomy / natural disease:** No naturally occurring sialuria has been reported in companion animals or wildlife (NCBI Taxon: *Homo sapiens*, 9606). The disorder is described only in humans.
- **Orthologous genes:** *Gne* is conserved across mammals (mouse *Gne*, NCBI Gene 50798; rat *Gne*). The bifunctional epimerase/kinase and its CMP-sialic acid feedback inhibition are evolutionarily conserved, which underpins the utility of rodent enzyme studies.
- **Comparative biology:** Homologous bacterial hydrolyzing 2-epimerases (e.g., NeuC) and prokaryotic epimerases share the epimerase fold and have informed structural understanding (PMID: 29764940), but bacteria lack the CMP-Neu5Ac allosteric brake that is central to sialuria.
- **Zoonotic potential / transmission:** Not applicable (non-infectious Mendelian disorder).

15. Model Organisms

There is **no dedicated animal model of sialuria** per se, but the mechanism has been decisively validated in **engineered cellular and recombinant systems**:

- **Recombinant rat GNE/MNK "sialuria-like" mutants.** The double mutant **R263L-R266Q retained 93.6% of wild-type catalytic activity but lost CMP-sialic acid feedback inhibition** (PMID: 21436238). Expressing it in EPO-producing **CHO cells increased intracellular CMP-sialic acid >10-fold** and enhanced sialylation of recombinant human erythropoietin (PMID: 21436238). This is orthogonal in vitro confirmation of the gain-of-flux mechanism and, notably, has been exploited as a **biotechnology tool** to boost glycoprotein sialylation.
- **Patient fibroblasts.** Primary sialuria fibroblasts (p.R266Q) reproduce the cytosolic free-sialic-acid accumulation and reduced feedback inhibition and served as the substrate for the allele-specific siRNA rescue (PMID: 18653764, PMID: 10356312).
- **Structural models.** Crystal structures of the human GNE epimerase domain and molecular models map the mutations to the allosteric site (PMID: 26980148, PMID: 19917666).

Phenotype recapitulation: Cellular/recombinant models faithfully reproduce the **biochemical** phenotype (loss of feedback, elevated CMP-Sia/free Sia). **Limitation:** no model captures the intact-organism clinical features (developmental delay, hepatomegaly), leaving the mutation→systemic-phenotype link partly inferred. *(Model organism databases: MGI for mouse* Gne*; recombinant CHO systems for functional assays.)*

Key Findings (with evidence)

F001 — Sialuria is a dominant *GNE* allosteric-site disorder abolishing CMP-sialic acid feedback inhibition

All nine reported cases carry heterozygous missense variants at the *GNE* allosteric (feedback) site, clustering at Arg294 (formerly Arg263) and Arg297 (formerly Arg266). "Sialuria is a rare autosomal dominant inborn error of metabolism characterized by cytoplasmic accumulation and urinary excretion of gram quantities of free sialic acid due to failure of feedback inhibition of the rate-limiting enzyme … UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE/MNK)" (PMID: 29923088). OMIM #269921; gene *GNE* (9p13.3).

F002 — Allele-specific RNAi restores feedback inhibition and normalizes free sialic acid

In p.R266Q sialuria fibroblasts, mutant-allele-specific siRNA "resulted in a significant decrease of free sialic acid, to within the normal range. Feedback inhibition of GNE-epimerase activity by CMP-sialic acid recovered after silencing" (PMID: 18653764). This causally confirms the mechanism and provides therapeutic proof-of-concept.

F003 — Homogeneous clinical phenotype with reduced enzyme inhibitability

The 7-year-old Portuguese patient had "developmental delay, hepatomegaly, coarse facies, and urinary excretion of 19 micromol of free NeuAc/mg creatinine," with epimerase "only 26% inhibited by 100 microM CMP-Neu5Ac (normal, 79%)" (PMID: 10356312). Across cases the features are "developmental delay, mildly coarse features, hepatomegaly and prolonged neonatal jaundice" (PMID: 29923088).

F004 — Must be distinguished from lysosomal FSASD (SLC17A5/sialin)

FSASD is "an extremely rare, autosomal recessive, neurodegenerative, multisystemic disorder caused by defects in the lysosomal sialic acid membrane exporter SLC17A5 (sialin)," causing "10-100-fold increased urinary excretion of free sialic acid" via **lysosomal** accumulation (PMID: 33862140). Sialuria differs by inheritance (dominant), compartment (cytosolic), and course (benign). Urine free sialic acid is the shared biomarker (PMID: 36000484).

F005 — Crystal structure explains the Arg263/Arg266 mutations

"The complex crystal structure of the N-terminal epimerase part of human GNE shows a tetramer in which UDP binds to the active site and CMP-Neu5Ac binds to the dimer-dimer interface. The enzyme is locked in a tightly closed conformation," and "the CMP-Neu5Ac binding mode clearly elucidates why mutations in Arg263 and Arg266 can cause sialuria" (PMID: 26980148).

F006 — A disorder of cytosolic free-sialic-acid overproduction within the biosynthesis/sialylation pathway

"Cellular free Sias are made via de novo biosynthesis, recycled from lysosomal salvage, and even by uptake of extracellular Sias"; "free Sia can be degraded/catabolized into ManNAc and pyruvate in the cytosol"; and "Sias deficiency and overproduction (accumulation), hyposialylation … and hypersialylation all cause disorders" (PMID: 41352710). Sialuria is the overproduction pole.

F007 — Allelic but mechanistically opposite to GNE myopathy

"Mutations in the allosteric region lead to a different disease, sialuria" (PMID: 23437777), whereas "More than 200 homozygous missense or compound heterozygous mutations in GNE … cause a rare neuromuscular disorder, GNE myopathy" (PMID: 35398442) — recessive catalytic loss-of-function producing sialic acid *deficiency*.

F008 — Engineered sialuria-like mutations confirm the gain-of-flux mechanism

"GNE/MNK-R263L-R266Q mutant showed 93.6% relative activity compared with wild type and did not display feedback inhibition," and "CMP-sialic acid concentration of engineered cells was significantly (>10-fold) increased by sialuria-mutated GNE/MNK (R263L-R266Q) expression" (PMID: 21436238).

Mechanistic Model / Interpretation

Sialuria is best understood as a **failure of a metabolic thermostat**. GNE/MNK is the rate-limiting valve of de novo sialic acid synthesis, and CMP-Neu5Ac — the pathway's activated end-product — normally binds an allosteric pocket at the tetramer's dimer–dimer interface to clamp the epimerase shut when sialic acid is abundant. The sialuria mutations (Arg263/Arg266) reshape precisely that pocket. Because catalysis is untouched (~94% of wild-type in engineered enzymes), the valve stays open regardless of downstream sialic acid levels. The result is a **dominant gain-of-flux**: the mutant allele overrides normal regulation, intracellular CMP-sialic acid climbs >10-fold, and free Neu5Ac spills into the cytosol and urine.

This model unifies three independent lines of evidence — **genetics** (all alleles cluster at the allosteric arginines), **structure** (CMP-Neu5Ac binds the interface to lock the closed state; the mutations map to this site), and **function** (engineered mutants and patient cells lose feedback but keep catalysis; allele-specific silencing reverses the biochemistry). It also cleanly explains the two "sister" contrasts: catalytic-domain loss-of-function → deficiency → **GNE myopathy**; lysosomal exporter loss → lysosomal storage → **FSASD**. Sialuria is the mirror image — cytosolic *over*production from a dominant regulatory escape.

Axis	Sialuria	GNE myopathy	FSASD (Salla/ISSD)
Gene / defect	*GNE* allosteric site	*GNE* catalytic domains	*SLC17A5* (sialin)
Molecular effect	Loss of feedback (gain of flux)	Loss of catalysis	Loss of lysosomal export
Sialic acid	Overproduction	Deficiency	Lysosomal accumulation
Compartment	Cytosol	—	Lysosome
Inheritance	AD	AR	AR
Course	Mild, non-progressive	Adult-onset progressive myopathy	Neurodegenerative

Evidence Base

PMID	Title (abbrev.)	Supports
29923088	Sialuria: ninth patient, novel *GNE* mutation	F001, F003 (dominant inheritance, allosteric residues, homogeneous phenotype)
18653764	Allele-specific RNAi in sialuria	F002 (causal proof + therapy)
10356312	Sialuria in a Portuguese girl	F003 (clinical + biochemical characterization)
26980148	Mechanism/inhibition of human GNE epimerase	F005 (structure; Arg263/266 in allosteric pocket)
19917666	Molecular modeling of GNE/MNK	Feedback inhibition; mutation mapping
21436238	Enhanced EPO sialylation via engineered GNE	F008 (retained catalysis, >10× CMP-Sia)
23437777	Novel *GNE* mutations in HIBM	F007 (allosteric → sialuria)
35398442	GNE mutations in Asian GNE myopathy	F007 (>200 recessive catalytic mutations)
33862140	Free sialic acid storage disorder review	F004 (FSASD differential)
36000484	UFSA elevated in pneumococcal sepsis	F004 (biomarker; non-specific mimic)
41352710	Disorders in sialic acid metabolism	F006 (pathway framing)
41099617	Mass photometry of GNE assembly	Tetramer assembly/inhibition (structure)
29764940	Bacterial NeuC epimerase structure	Comparative structural biology

All snippets quoted in this report were verified against stored abstracts during the investigation. Evidence source types: **human clinical** (case reports), **in vitro/recombinant** (engineered GNE, fibroblast assays, RNAi), and **structural/computational** (crystallography, modeling).

Limitations and Knowledge Gaps

1. **Tiny evidence base.** Only ~9 patients have ever been reported; epidemiology (prevalence, incidence, sex ratio, penetrance) is essentially anecdotal.
2. **Mutation → organ-phenotype gap.** The biochemical mechanism is airtight, but *how* cytosolic free-sialic-acid excess produces developmental delay, hepatomegaly, and neonatal jaundice is **inferred, not demonstrated**. No mechanistic tissue-level studies exist.
3. **No dedicated animal model.** Mechanism is validated in cells/recombinant enzymes, not in an intact organism recapitulating clinical disease; natural-history data are lacking.
4. **No omics profiling** (transcriptomic/proteomic/metabolomic beyond direct sialic acid measurement) specific to sialuria patients.
5. **No approved therapy** and no clinical trials; allele-specific silencing remains at the cell-culture proof-of-concept stage.
6. **Numbering ambiguity.** Older literature uses Arg263/Arg266; current HGVS numbering is Arg294/Arg297 — a source of potential confusion in variant curation.

Proposed Follow-up Experiments / Actions

1. **Generate a knock-in mouse** carrying a sialuria allele (e.g., *Gne* R263/R266 equivalent) to test whether cytosolic free-sialic-acid overproduction reproduces hepatomegaly/developmental phenotypes and to define the mutation→organ causal chain.
2. **Patient-derived iPSC models** (hepatocyte and neuronal lineages) to characterize tissue-specific consequences of CMP-sialic acid excess and altered sialylation flux.
3. **Advance allele-specific gene silencing** (siRNA/ASO) toward preclinical development, leveraging the dominant-allele architecture demonstrated in fibroblasts (PMID: 18653764).
4. **Establish an international registry / natural-history study** to quantify prevalence, penetrance, progression, and long-term developmental outcomes.
5. **Multi-omics (metabolomics + glycoproteomics)** on patient cells to map how hypersialylation flux alters specific glycoproteins (e.g., hepatic receptors implicated in glucose homeostasis per PMID: 37777009).

6. **Structure-guided small-molecule "re-braking"** — screen for compounds that restore the closed, inhibited GNE conformation or dampen flux, building on the assembly-modulation data (PMID: 41099617).
7. **Curation harmonization** — standardize variant reporting to current HGVS (Arg294/Arg297) with legacy (Arg263/Arg266) cross-references in ClinVar/OMIM.

Report compiled from 8 confirmed findings and 38 reviewed papers over a 5-iteration autonomous investigation. Evidence classes: human clinical case reports, in vitro/recombinant enzymology, structural biology, and computational modeling.
