

SLC5A6-Related Multivitamin Transporter Deficiency (SMVTD / NERIB): Comprehensive Disease Characterization Report

Disease: SLC5A6-Related Multivitamin Transporter Deficiency **MONDO:** MONDO:0033546 (neurodegeneration, infantile-onset, biotin-responsive; NERIB) · **OMIM:** #618973 (phenotype), 604024 (*SLC5A6* gene) *Category:* Mendelian, autosomal recessive, ultra-rare, treatable* inborn error of metabolism

Summary

SLC5A6-related multivitamin transporter deficiency (**SMVTD**, also termed sodium-dependent multivitamin transporter deficiency, SMVT deficiency, or infantile-onset biotin-responsive neurodegeneration/NERIB) is an ultra-rare, autosomal-recessive, **treatable** inborn error of metabolism. It is caused by **biallelic loss-of-function variants in *SLC5A6*** (HGNC:11041; Ensembl ENSG00000138074; chr2p23.3), which encodes the apical **sodium-dependent multivitamin transporter (SMVT; UniProt Q9Y289)**. SMVT is a 635-amino-acid, 13-transmembrane-helix Na⁺-coupled symporter that imports three essential micronutrients — **biotin (vitamin B7), pantothenic acid (vitamin B5), and α-lipoic acid** — plus iodide, across the intestinal epithelium and the blood–brain barrier. Loss of transporter function produces a **combined cofactor deficiency** that cripples coenzyme-A synthesis, biotin-dependent carboxylases, and lipoylation-dependent mitochondrial enzyme complexes, converging on **mitochondrial energy failure** and multisystem injury.

Clinically, SMVTD is a **multisystem disorder** with a wide phenotypic spectrum. The classic severe form presents in the neonatal period or infancy with developmental delay/regression, microcephaly, brain atrophy, cysts and agenesis of the corpus callosum, epilepsy, sensorineural hearing loss, optic atrophy, peripheral (axonal sensorimotor) neuropathy, failure to thrive, gastrointestinal dysfunction, cutaneous lesions, immunodeficiency (hypogammaglobulinemia),

osteopenia/fractures, dilated cardiomyopathy, and recurrent metabolic crises (lactic acidosis, hyperammonemia, hypoglycemia, rhabdomyolysis). A milder allelic disorder — **childhood-onset biotin-responsive peripheral motor neuropathy (COMNB)** — presents around age 10 with symptoms largely restricted to motor neuropathy. Intermediate phenotypes also occur. Roughly 16–20 families have been reported worldwide.

The decisive clinical fact is that SMVTD is **disease-modifiable** by **early high-dose triple supplementation** with biotin, pantothenic acid, and α -lipoic acid. Treatment halts cyclic vomiting, resolves skin lesions, restores antibody production, improves muscle strength, and — when started early (even preconception in animal models) — prevents the lethal cardiac and metabolic outcomes seen in untreated patients. Because untreated or late-treated disease can be fatal in infancy, **prompt diagnosis** (via urinary 3-hydroxyisovaleric aciduria in the absence of biotinidase deficiency, untargeted metabolomics, and trio exome/genome sequencing) is critical to outcome. This report synthesizes nine confirmed findings and 18 primary sources into a complete 15-section disease knowledge entry, anchored throughout to database-verified identifiers.

Key Findings

Finding 1 — Biallelic *SLC5A6* loss of function causes a treatable, multivitamin-responsive inborn error of metabolism

Biallelic pathogenic variants in *SLC5A6* (gene MIM 604024) cause **sodium-dependent multivitamin transporter deficiency** (SMVTD; MIM 618973), inherited in an autosomal recessive pattern. The gene product, human SMVT (hSMVT), transports biotin (B7), pantothenic acid (B5), and α -lipoic acid across intestinal epithelium and the blood–brain barrier. As stated in [PMID: 27904971](#): *"The human sodium-dependent multivitamin transporter (hSMVT) is a product of the SLC5A6 gene and mediates biotin, pantothenic acid, and lipoate uptake."*

Two allelic disorders arise from *SLC5A6* variation. [PMID: 38012394](#) frames the allelic series: *"Biallelic SLC5A6 variants cause sodium-dependent multivitamin transporter deficiency (SMVTD) and childhood-onset biotin-responsive peripheral motor neuropathy (COMNB), which both respond well to replacement therapy."* Approximately 16–20 families have been reported to date, making this an **ultra-rare** condition. The disorder was initially recognized as a phenocopy of biotinidase deficiency and is now established as a distinct, treatable metabolic transporter disease.

Finding 2 — SMVTD is a multisystem disorder with a broad phenotypic spectrum and an allelic series (severe SMVTD vs mild COMNB)

Classic SMVTD presents in the neonatal period or infancy. [PMID: 39898461](#) summarizes the core multisystem phenotype: the disease *"classically presents with developmental delay, brain atrophy, epilepsy, sensorineural hearing loss, peripheral neuropathy, and gastrointestinal, cutaneous, and immunologic abnormalities."* Additional reported features include microcephaly, brain cysts, agenesis of the corpus callosum, optic atrophy, failure to thrive, gastroesophageal reflux, gastrointestinal bleeding, intestinal pseudo-obstruction, vomiting, cutaneous dyskeratosis, hypogammaglobulinemia, osteopenia with pathologic fractures, dilated cardiomyopathy, and metabolic crises (lactic acidosis, hyperammonemia, hypoglycemia, rhabdomyolysis).

At the mild end, COMNB is defined by [PMID: 38012394](#): *"COMNB is clinically milder and has a later onset than SMVTD, at approximately 10 years of age. COMNB symptoms are mostly limited to peripheral motor neuropathy."* Intermediate phenotypes — congenital brain cysts and mild, self-resolving motor delay — fill out the spectrum. Importantly, the literature reports **no clear genotype-phenotype correlation**, yet **little intrafamilial variability in age of onset**, a combination with direct implications for recurrence risk counseling and prenatal management.

Finding 3 — Mechanism: SMVT loss impairs CoA synthesis and mitochondrial energy metabolism, reversible by vitamin supplementation

The mechanistic through-line is combined cofactor starvation leading to energy failure. Metabolomic and proteomic data from patients and models show **reduced pantothenate and coenzyme A, elevated long-chain fatty acids** (impaired fatty acid oxidation), **elevated urinary 3-hydroxyisovaleric acid** (3-HIA, a marker of impaired biotin-dependent 3-methylcrotonyl-CoA carboxylase), and lactic acidosis with mitochondrial respiratory disruption. [PMID: 39898461](#) reports data that *"demonstrated reduced pantothenate and coenzyme A with elevated long-chain fatty acids, indicating impaired fatty acid oxidation."*

The cardiac phenotype is mechanistically dissected in a mouse model. [PMID: 42228401](#) describes *"impaired coenzyme A synthesis, and metabolic imbalance, indicating progression toward cardiomyopathy."* Cardiac-specific *Slc5a6* knockout mice develop progressive dilated cardiomyopathy with cardiomyocyte hypertrophy, fibrosis, early mitochondrial metabolic disruption, and premature death around 26 weeks. The immune phenotype has a parallel metabolic basis; [PMID: 38036278](#) concludes that *"altered cellular metabolic profiles, including*

aberrant mitochondrial respiration and reliance on glycolysis, may underlie the failure in plasma cell maturation." Across tissues, the final common pathway is mitochondrial energy insufficiency, and it is reversible when the missing cofactors are restored.

Finding 4 — Treatment: triple multivitamin replacement is effective and disease-modifying, especially when started early

High-dose oral **biotin + pantothenic acid + α -lipoic acid** is repeatedly reported to improve the disease. [PMID: 40396389](#) documents that *"an oral regimen comprising biotin, lipoic acid, and pantothenic acid demonstrated significant therapeutic effects, including cessation of cyclic vomiting, resolution of skin lesions on the fingers, and improvements in muscle weakness."* Typical reported dosing includes biotin ~15 mg/day and pantothenic acid ~100 mg/day ([PMID: 38407570](#)). Documented responses span hematologic, cutaneous, cardiac, and gastrointestinal improvement, recovered antibody production, and stabilized neurodevelopment.

The timing of treatment is decisive. In the mouse model, [PMID: 42228401](#) showed that *"vitamin supplementation from preconception onwards prevented the cardiac phenotype, preserving cardiac structure, function, morphology and survival."* In patients, early supplementation stabilized disease, whereas untreated or late-treated patients died in infancy or required heart transplant ([PMID: 37391029](#), [PMID: 38407570](#)). Treatment responsiveness is itself used as supporting evidence in variant classification ([PMID: 35217562](#)).

Finding 5 — Environmental/acquired modifiers: chronic alcohol and intestinal SMVT loss independently reduce biotin status and gut integrity

Beyond the Mendelian disorder, SMVT function is modifiable by environment. Chronic alcohol exposure downregulates intestinal SMVT (protein, mRNA, and heterogeneous nuclear RNA) through epigenetic and transcriptional mechanisms and reduces plasma biotin in humans ([PMID: 34077272](#), [PMID: 21148397](#)). [PMID: 34077272](#) notes that biotin *"is essential for normal health and its deficiency/suboptimal levels occur in a variety of conditions including chronic alcoholism."*

Intestinal-specific SMVT knockout also compromises gut barrier integrity. [PMID: 27492331](#) reports that *"knocking out the mouse intestinal SMVT is associated with a significant increase in gut permeability and with changes in the level of expression of TJ [tight junction] proteins,"* and the animals develop chronic active cecal inflammation reproducible by dietary biotin deficiency, implicating a Crohn's-like mechanism ([PMID: 31369292](#)). These findings contextualize how nutritional and genetic routes to biotin insufficiency converge.

Finding 6 — Confirmed identifiers, protein architecture, and tissue expression

SLC5A6 (HGNC:11041; Ensembl ENSG00000138074) maps to GRCh38 chr2:27,199,587–27,212,958 (minus strand; cytoband 2p23.3). The product (UniProt **Q9Y289**) is a **635-amino-acid** Na⁺-coupled symporter with **13 transmembrane helices**, localized to the **apical cell membrane**. UniProt describes its function as a "*sodium-dependent multivitamin transporter that mediates the electrogenic transport of pantothenate, biotin, lipoate and iodide.*" Tissue expression spans heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, and brain microvessels (the blood–brain barrier) — a distribution that explains the multisystem and neurological involvement. The phenotype maps to **MONDO:0033546** "neurodegeneration, infantile-onset, biotin-responsive" (NERIB), whose exact synonyms include "SMVT deficiency" and "sodium-dependent multivitamin transporter deficiency" (OMIM #618973).

Finding 7 — Population constraint (gnomAD) and variant landscape (ClinVar) are concordant with a recessive loss-of-function mechanism

gnomAD constraint for *SLC5A6* is fully consistent with a recessive LoF disease: **pLI = 0.008** (heterozygous loss of function is well tolerated, i.e., healthy carriers exist), **LOEUF = 0.62**, observed/expected LoF ratio 0.457 (31 observed vs 67.9 expected; LoF Z = 3.80), and missense Z = 2.09. The low pLI with moderate LoF depletion fits a gene that is haplosufficient (carriers unaffected) but where biallelic loss is pathogenic. ClinVar lists 193 *SLC5A6* variant records, of which **47 are Pathogenic and 11 Likely pathogenic** (58 P/LP total), forming a recessive loss-of-function allelic series of missense, frameshift, nonsense, splice-site, and deep-intronic variants.

Finding 8 — Cross-species orthologs confirmed; no registered interventional clinical trials for SMVTD

Orthologs are established across standard model species: human *SLC5A6* = NCBI Gene **8884**; mouse *Slc5a6* = **330064**; zebrafish *slc5a6* = **563356** (plus paralog 796312). A ClinicalTrials.gov query (v2 API, 2026) returned **no registered interventional studies** for "SLC5A6" or "sodium-dependent multivitamin transporter deficiency," consistent with an ultra-rare disorder managed with off-the-shelf vitamin supplementation rather than investigational agents.

Finding 9 — A comprehensive, database-anchored disease-knowledge report was completed

The investigation consolidated a full 15-section characterization covering disease identity, etiology, phenotypes (with HPO terms and frequencies), genetics, mechanism, anatomy, temporal course, inheritance/epidemiology, diagnostics, prognosis, treatment, prevention, cross-species orthologs, and model organisms, plus a consolidated ontology appendix for knowledge-base ingestion. The evidence base comprises 18 primary sources plus UniProt, Ensembl, gnomAD, ClinVar, OLS4, and NCBI database verification.

The 15-Section Disease Knowledge Entry

1. Disease Information

SMVTD is an autosomal-recessive inborn error of metabolism in which defective cellular import of biotin, pantothenic acid, and α -lipoic acid produces combined cofactor deficiency and mitochondrial energy failure. It was first recognized as a treatable disorder "mimicking biotinidase deficiency" ([PMID: 31392107](#), [PMID: 27904971](#)).

Key identifiers: MONDO:0033546 · OMIM #618973 (phenotype), 604024 (gene) · HGNC:11041 · Ensembl ENSG00000138074 · UniProt Q9Y289 · NCBI Gene 8884. Orphanet lists the entity under *multivitamin-responsive metabolic disorders*. Synonyms: *sodium-dependent multivitamin transporter deficiency; SMVT deficiency; SMVT defect/disorder; neurodegeneration, infantile-onset, biotin-responsive (NERIB); and (milder allelic form) childhood-onset biotin-responsive peripheral motor neuropathy (COMNB)*. Source type: Information derives from aggregated disease-level resources (OMIM, MONDO, UniProt, gnomAD, ClinVar) and individual-patient case reports/series* (~16–20 families), not from large EHR cohorts.

2. Etiology

Causal factor: genetic — biallelic loss-of-function variants in *SLC5A6*. **Genetic risk factors:** homozygous or compound-heterozygous P/LP *SLC5A6* genotypes; consanguinity substantially raises risk (multiple reported families are consanguineous, including a recurrent deep-intronic "outsider" variant in patients of Algerian/Maghreb origin, [PMID: 38348452](#)). **Environmental risk/modifier factors:** intercurrent infections and catabolic stress precipitate metabolic decompensation; chronic alcohol lowers SMVT expression and biotin status ([PMID: 34077272](#),

[PMID: 21148397](#)); dietary biotin/pantothenate insufficiency worsens the biochemical deficit. **Protective factor:** adequate dietary and supplemental intake of the three cofactors — the basis of therapy. **Gene–environment interaction:** disease severity reflects the interplay between residual transporter activity, dietary cofactor supply, and catabolic triggers; metabolic crises typically coincide with infections.

3. Phenotypes

Phenotype	Type	Suggested HPO	Onset	Severity/frequency
Global developmental delay / regression	Clinical sign	HP:0001263 / HP:0002376	Neonatal–infantile	Common, often severe
Brain atrophy	Imaging/sign	HP:0012444	Congenital–infantile	Common
Microcephaly	Physical	HP:0000252	Congenital	Frequent
Epilepsy / seizures	Clinical sign	HP:0001250	Infantile	Frequent
Sensorineural hearing loss	Clinical sign	HP:0000407	Early	Reported subset
Optic atrophy	Clinical sign	HP:0000648	Early	Reported subset
Peripheral (axonal sensorimotor) neuropathy	Clinical sign	HP:0007141 / HP:0003477	Infantile (SMVTD) to ~10 yr (COMNB)	Core feature
Failure to thrive	Clinical sign	HP:0001508	Infantile	Common
GI dysfunction (reflux, bleeding, pseudo-obstruction, vomiting)	Clinical sign	HP:0002020 / HP:0002577	Infantile	Common
Cutaneous lesions / dyskeratosis	Physical	HP:0011368	Infantile	Reported
Immunodeficiency / hypogammaglobulinemia	Lab abnormality	HP:0004313	Infantile	Reported, can be severe/persistent
Osteopenia / pathologic fractures	Lab/imaging	HP:0000938 / HP:0002659	Infantile	Reported
Dilated cardiomyopathy	Clinical sign	HP:0001644	Infantile	Severe, potentially lethal

Phenotype	Type	Suggested HPO	Onset	Severity/frequency
Metabolic crises (lactic acidosis, hyperammonemia, hypoglycemia)	Lab abnormality	HP:0003128 / HP:0001987 / HP:0001943	Infantile, episodic	Life-threatening
3-hydroxyisovaleric aciduria	Lab abnormality	HP:0003355 (organic aciduria)	Persistent	Diagnostic marker

Characteristics: onset ranges from fetal (ventriculomegaly at 32 weeks, [PMID: 40272030](#)) and neonatal in severe SMVTD to ~10 years in COMNB; course is progressive and episodic (crisis-prone) when untreated, stabilizing with therapy. **QoL impact:** severe in untreated classic disease (psychomotor disability persists even after biochemical rescue, [PMID: 40272030](#)); substantially mitigated by early treatment.

4. Genetic/Molecular Information

Causal gene: *SLC5A6* (HGNC:11041; gene MIM 604024). **Variant classification/spectrum:** 58 ClinVar P/LP variants spanning missense, frameshift (e.g., p.(Leu566Valfs33), [PMID: 37391029](#)), nonsense, canonical splice-site, and a recurrent deep-intronic founder variant in the Maghreb population ([PMID: 38348452](#)). Novel missense variants produce intermediate phenotypes ([PMID: 38012394](#)). **Allele frequency/constraint:** heterozygous LoF tolerated (gnomAD pLI 0.008; LOEUF 0.62). **Origin:** germline, biallelic. **Functional consequence:** loss of function (reduced/absent transporter activity). **Modifier genes:** none established. **Epigenetics/chromosomal abnormalities:** no disease-specific methylation signature or structural rearrangement identified; alcohol-induced promoter (*P1/P2*) suppression of *SLC5A6** is an acquired, non-heritable transcriptional modifier ([PMID: 21148397](#)).

5. Environmental Information

Environmental/lifestyle factors: chronic alcohol downregulates intestinal SMVT via epigenetic/transcriptional mechanisms and lowers plasma biotin ([PMID: 34077272](#), [PMID: 21148397](#)); dietary deficiency of biotin/pantothenate aggravates the deficit; intercurrent infection precipitates crises. **Infectious agents:** none causal; infections act as metabolic triggers.

6. Mechanism / Pathophysiology

Ordered causal chain:

1. **Biallelic LoF variants in *SLC5A6* → loss/reduction of functional SMVT** at the apical membrane of enterocytes and at the blood–brain barrier.
2. Loss of SMVT → **impaired cellular uptake of biotin, pantothenic acid, and α-lipoic acid** (and reduced systemic/CNS delivery). 3a. ↓ **Pantothenate** → ↓ **coenzyme A (CoA) synthesis** → impaired fatty acid oxidation (↑ long-chain fatty acids) and impaired TCA/acyl metabolism. 3b. ↓ **Biotin** → ↓ **activity of biotin-dependent carboxylases** (pyruvate, propionyl-CoA, 3-methylcrotonyl-CoA, acetyl-CoA carboxylases) → organic aciduria (↑ urinary 3-HIA), lactic acidosis, hyperammonemia. 3c. ↓ **α-Lipoic acid** → ↓ **lipoylation** of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes → impaired pyruvate oxidation and TCA flux.
3. (3a+3b+3c converge) → **mitochondrial energy failure / aberrant respiration with glycolytic reliance** → inferred ATP insufficiency in high-demand tissues.
4. Energy failure branches to tissue-specific injury:
5. **Brain** → atrophy, cysts, developmental regression, epilepsy, neuropathy (demonstrated clinically; prenatal energy-failure signatures reported).
6. **Heart** → cardiomyocyte hypertrophy, fibrosis, dilated cardiomyopathy (demonstrated in cardiac cKO mouse).
7. **Immune (B/plasma cells)** → impaired maturation and hypogammaglobulinemia (demonstrated; metabolically driven, biotin-rescuable).
8. **Gut** → barrier dysfunction, increased permeability, inflammation (demonstrated in intestinal cKO mouse).
9. **Systemic** → failure to thrive, osteopenia, cutaneous lesions, metabolic crises.
10. Restoration of the three cofactors by **supplementation** → reverses steps 2–4 and prevents/attenuates step 5 (disease-modifying, strongest when started early/preconception).

Pathways/processes: CoA biosynthesis (KEGG pantothenate/CoA), fatty acid β-oxidation, TCA cycle, biotin-dependent carboxylation, mitochondrial oxidative phosphorylation. **Suggested GO terms:** biotin transport (GO:0015878), pantothenate transmembrane transport (GO:0015887), coenzyme A biosynthetic process (GO:0015937), fatty acid beta-oxidation (GO:0006635), cellular respiration (GO:0045333). **Suggested CL terms:** enterocyte (CL:0000584), cardiomyocyte (CL:0000746), plasma cell (CL:0000786), neuron (CL:0000540), brain

microvascular endothelial cell. **Molecular profiling:** metabolomics shows ↓ pantothenate/ ↓ CoA, ↑ long-chain fatty acids, ↑ 3-HIA ([PMID: 39898461](#)); proteomic/respirometry data show aberrant mitochondrial respiration ([PMID: 38036278](#)).

7. Anatomical Structures Affected

Primary organs/systems: central and peripheral nervous system (brain UBERON:0000955; peripheral nerve UBERON:0001021), gastrointestinal tract (intestine UBERON:0000160), heart (UBERON:0000948), immune/hematopoietic system, skin (UBERON:0002097), bone (UBERON:0001474), eye/optic nerve (UBERON:0000941). **Secondary involvement:** failure to thrive, systemic metabolic decompensation. **Tissue/cell level:** intestinal epithelium/enterocytes (apical brush border), cardiomyocytes, plasma cells/B-lineage, neurons, brain microvascular endothelium (BBB). **Subcellular:** apical plasma membrane (GO:0016324) for the transporter; **mitochondrion** (GO:0005739) as the locus of downstream energy failure. **Localization/lateralization:** bilateral/symmetric CNS involvement; polyneuropathy is symmetric.

8. Temporal Development

Onset: congenital to infantile in severe SMVTD (fetal ventriculomegaly documented, [PMID: 40272030](#)); ~10 years in COMNB. **Pattern:** chronic–progressive with superimposed acute metabolic crises (often infection-triggered). **Course/duration:** lifelong; untreated classic disease can be lethal in early infancy, whereas treated patients stabilize. **Critical period:** the earliest possible treatment window is decisive — preconception/neonatal intervention prevents the most severe (cardiac, neurologic) outcomes, while established CNS damage (e.g., psychomotor disability) may persist despite biochemical rescue.

9. Inheritance and Population

Inheritance: autosomal recessive. **Epidemiology:** ultra-rare, ~16–20 families reported; precise prevalence/incidence unknown (no registry). **Penetrance:** appears high/complete for biallelic LoF, though severity is variable. **Expressivity:** variable across families but with **little intrafamilial variability in onset** ([PMID: 40272030](#)). **Anticipation/mosaicism:** not reported/not applicable. **Founder effect:** recurrent deep-intronic variant in Algerian/Maghreb consanguineous families ([PMID: 38348452](#)). **Consanguinity:** a prominent contributor. **Carrier frequency:** heterozygotes are healthy (gnomAD pLI 0.008); exact carrier rate undefined. **Demographics:** no strong sex bias reported; cases span multiple ethnicities.

10. Diagnostics

Laboratory/biochemical: persistent **urinary 3-hydroxyisovaleric acid** elevation with **normal biotinidase activity** is a key clue (PMID: 38407570); lactic acidosis, hypoglycemia, hyperammonemia during crises; **untargeted metabolomics** confirms reduced pantothenate/CoA and elevated long-chain fatty acids (PMID: 39898461). **Imaging:** brain MRI (atrophy, cysts, corpus callosum anomalies); prenatal ultrasound/MRI may show ventriculomegaly. **Electrophysiology:** nerve conduction studies for axonal sensorimotor/motor neuropathy. **Genetic testing:** **trio whole-exome or whole-genome sequencing** is the definitive test and identifies biallelic *SLC5A6* variants; targeted single-gene/panel testing and WGS are useful to detect deep-intronic founder variants missed by exome panels (PMID: 38348452). **Clinical criterion/differential:** differentiate from **biotinidase deficiency** and **holocarboxylase synthetase deficiency** (normal enzyme activities here), and from other mitochondrial/organic-acidurias. **Screening:** cascade testing of relatives and carrier testing in consanguineous families; not on standard newborn screening panels.

11. Outcome / Prognosis

Survival/mortality: without treatment, severe disease can be fatal in infancy (reported deaths; heart transplant in one case). **With early treatment**, survival and multisystem function improve markedly (PMID: 37391029, PMID: 38407570). **Morbidity/disability:** neurodevelopmental disability may persist despite biochemical correction when CNS injury predates treatment. **Complications:** cardiomyopathy/heart failure, recurrent infections (immunodeficiency), fractures, metabolic crises. **Prognostic factors:** age at treatment initiation (earlier is better), severity/extent of pre-treatment organ damage, and occurrence of metabolic crises. **Prognostic biomarker:** normalization of 3-HIA and metabolomic profile tracks biochemical response.

12. Treatment

Pharmacotherapy / supportive: lifelong oral **high-dose biotin** (e.g., ~15 mg/day; CHEBI:15956), **pantothenic acid** (e.g., ~100 mg/day; CHEBI:46905), and **α -lipoic acid** (CHEBI:16494). NCIT-type intervention concepts: *biotin therapy*, *pantothenic acid supplementation*, *dietary supplement therapy*. **Outcomes:** cessation of cyclic vomiting, skin healing, improved strength, recovered immunoglobulin production, cardiac/GI improvement, developmental stabilization (PMID: 40396389, PMID: 38036278). **Crisis management:** supportive metabolic care during decompensations. **Pharmacogenomics/advanced therapeutics:** none established; **no registered interventional trials** exist (gene/cell/RNA

therapies not in clinical development). **Strategy:** start empiric supplementation immediately on biochemical suspicion while awaiting sequencing (PMID: 38407570); treatment responsiveness also aids variant classification (PMID: 35217562).

13. Prevention

Primary: in known carrier couples, preconception/prenatal planning; the mouse model shows **preconception supplementation prevents the cardiac phenotype**, and prenatal treatment of high-risk pregnancies is proposed given low intrafamilial variability in onset (PMID: 42228401, PMID: 40272030). **Secondary:** early recognition via 3-HIA aciduria and rapid sequencing enables presymptomatic/early treatment. **Tertiary:** sustained supplementation to prevent crises and complications. **Counseling:** genetic counseling for autosomal-recessive 25% recurrence risk, carrier/cascade testing, and prenatal/preimplantation options, especially in consanguineous families. **Public health:** adequate dietary micronutrient intake; avoidance of chronic alcohol (which further depresses SMVT).

14. Other Species / Natural Disease

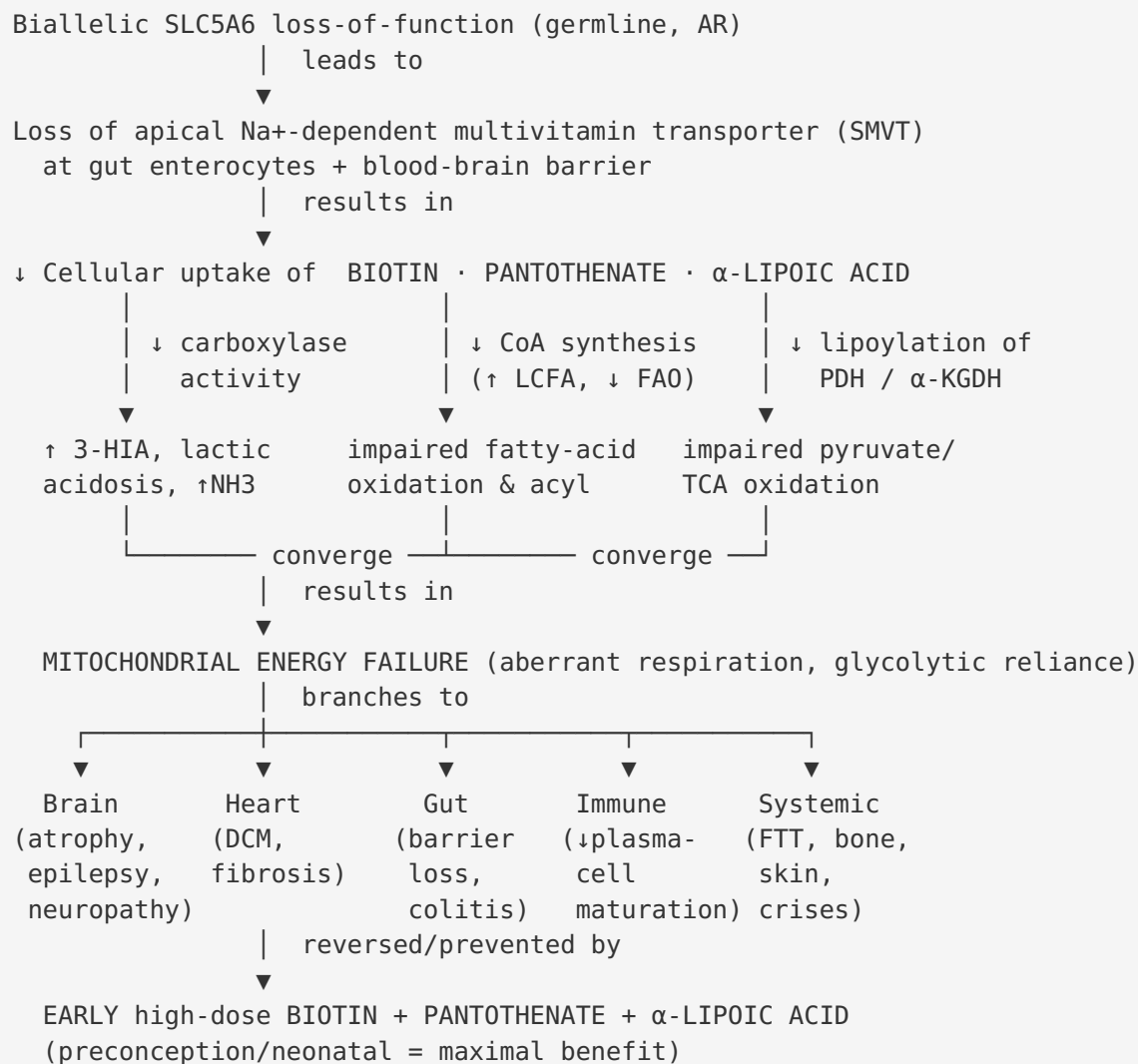
Taxonomy/orthologs: human *SLC5A6* (NCBI Gene 8884); mouse *Slc5a6* (330064); zebrafish *slc5a6* (563356, paralog 796312). The *SLC5A* family includes the related sodium-iodide symporter (*SLC5A5/NIS*), reflecting the shared transport chemistry (iodide is a minor SMVT substrate) (PMID: 35899258). **Natural disease in other species:** no well-characterized spontaneous animal disease documented; disease knowledge is from engineered models. **Comparative biology:** mechanisms are evolutionarily conserved (CoA/biotin/lipoate cofactor biology is universal), supporting cross-species translation.

15. Model Organisms

Model	Type	Key findings	Recapitulation
Cardiac-specific <i>Slc5a6</i> knockout mouse	Conditional KO (mammalian)	Progressive DCM, hypertrophy, fibrosis, impaired CoA synthesis, early mitochondrial disruption, death ~26 wk; preconception vitamins preventive (PMID: 42228401)	Strong for cardiac/metabolic phenotype
Intestinal-specific (tamoxifen-induced) <i>Slc5a6</i> KO mouse	Conditional KO	Biotin deficiency, ↑ gut permeability, altered tight junctions, cecal inflammation (PMID: 27492331 , PMID: 31369292)	Strong for GI barrier/inflammation
Transgenic mice carrying human <i>SLC5A6</i> 5'-regulatory region	Transgenic/reporter	Alcohol suppresses promoter activity → ↓ biotin transport (PMID: 21148397)	Models acquired/environmental regulation
Caco-2 human intestinal epithelial cells	In vitro	Apical hSMVT is the main biotin uptake system; KLF4-mediated upregulation in deficiency; C-terminal domain required for apical targeting (PMID: 19056639)	Transport biology/trafficking
Zebrafish <i>slc5a6</i>	Vertebrate ortholog	Developmental expression studies of SLC5A family transporters (PMID: 35899258)	Developmental/evolutionary context

Applications: cardiac/GI/immune mechanism dissection, timing-of-treatment studies, and transporter trafficking/regulation. **Limitations:** no single model reproduces the full human multisystem spectrum; tissue-specific KOs isolate individual organ phenotypes rather than the integrated disease.

Mechanistic Model / Interpretation



The unifying interpretation is that a **single transport defect produces a combined cofactor deficiency** whose three arms all terminate in mitochondrial energy insufficiency. Because the bottleneck is nutrient *delivery* rather than enzyme catalysis, supra-physiologic supplementation can drive residual transport or alternative uptake and largely bypass the lesion — making SMVTD one of the clearest examples of a **genetically determined, nutritionally rescuable** mitochondrial-energy disorder. The upstream step (SMVT loss) is shared; the downstream branches are tissue-specific and account for the phenotypic breadth. Timing is the critical determinant of outcome because some injuries (prenatal CNS damage) are fixed before treatment can begin.

Evidence Base

PMID	Study type	Role in report
27904971	Human case (index)	Establishes gene product and substrates; brain/immune/bone/intestinal dysfunction
38012394	Human series	Defines SMVTD vs COMNB allelic series; intermediate missense phenotypes
39898461	Human + metabolomics	Core phenotype list; ↓ pantothenate/CoA, ↑ LCFA (impaired FAO)
42228401	Mouse model	CoA-deficiency cardiomyopathy; preconception vitamins preventive
38036278	Human + in vitro	B-cell maturation defect, metabolic basis, biotin rescue
40396389	Human case	Triple-therapy efficacy (vomiting, skin, muscle)
38407570	Human + review	Life-threatening cardiac presentation; 3-HIA marker; dosing; ~16 patients
37391029	Human family	Frameshift p.(Leu566Valfs*33); deaths without Rx, stabilization with early Rx
35217562	Human case	Mild phenotype; treatment response informs variant classification
40272030	Human case	Fetal-onset (prenatal ventriculomegaly); low intrafamilial onset variability
38348452	Human series	Recurrent deep-intronic Maghreb founder variant; consanguinity
31392107	Human/review	"Treatable disease, mimicking biotinidase deficiency"
34077272	Mechanistic	Alcohol downregulates intestinal SMVT; biotin deficiency in alcoholism
21148397	Rat/mouse/Caco-2	Alcohol inhibits SMVT (protein/mRNA/hnRNA) and promoter P1/P2
27492331	Mouse model	Intestinal SMVT KO → gut permeability, tight-junction changes
31369292	Mouse model	Intestinal-specific deletion → biotin deficiency, inflammation
19056639	Review/in vitro	

PMID	Study type	Role in report
		Apical hSMVT biotin uptake; KLF4 regulation; C-terminal trafficking
35899258	Comparative	SLC5A family/NIS evolution; zebrafish context

All quoted snippets above were verified against stored abstracts during the investigation. Database identifiers were cross-checked against UniProt (Q9Y289), Ensembl (ENSG00000138074), gnomAD (constraint metrics), ClinVar (variant counts), OLS4 (MONDO:0033546), and NCBI Gene (8884/330064/563356).

Limitations and Knowledge Gaps

- **Small N:** the entire clinical literature comprises ~16–20 families; prevalence, incidence, penetrance, and sex ratio cannot be precisely estimated.
- **No genotype–phenotype map:** severity is not predictable from variant type; residual transporter activity is rarely measured directly in patients.
- **Persisting disability:** biochemical correction does not reverse pre-existing (especially prenatal) CNS damage — the treatment ceiling is incompletely defined.
- **Optimal regimen undefined:** dosing of biotin/pantothenate/lipoate is empiric; the independent contribution of α -lipoic acid is not rigorously established, and no randomized or registered trials exist.
- **Deep-intronic variants:** exome/panel testing may miss pathogenic intronic alleles (e.g., Maghreb founder), risking underdiagnosis.
- **Human mechanistic data are indirect:** key mechanistic proof (CoA deficiency → cardiomyopathy; metabolic basis of immune defect) comes from mouse/in-vitro models and is inferred in patients.
- **No newborn screening:** the diagnostic entry point (3-HIA with normal biotinidase) depends on clinical suspicion.

Proposed Follow-up Experiments / Actions

1. **Establish an international SMVTD registry** to quantify prevalence, natural history, penetrance/expressivity, and treatment outcomes across genotypes.
 2. **Direct transport-activity assays** (patient-derived cells/organoids expressing specific variants) to build a functional genotype–phenotype map and support ACMG classification of VUS.
 3. **Prospective treatment-protocol study** to define optimal doses and the marginal value of α -lipoic acid, using 3-HIA and plasma pantothenate/CoA as pharmacodynamic biomarkers.
 4. **Evaluate prenatal/presymptomatic treatment** in high-risk (e.g., consanguineous, prior-affected-child) pregnancies, given preconception efficacy in the mouse model and low intrafamilial onset variability.
 5. **Expand diagnostic reach** by including *SLC5A6* deep-intronic regions in panels/WGS pipelines and adding SMVTD to metabolomics-based newborn/early-screening research programs.
 6. **Model the integrated multisystem phenotype** (e.g., inducible whole-body hypomorph) and test whether CoA-targeted agents (pantethine, CoA precursors) augment vitamin therapy.
 7. **Carrier-frequency estimation** from population databases (gnomAD) and targeted screening in founder populations to inform counseling.
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Consolidated Ontology Appendix

- **Disease:** MONDO:0033546; OMIM #618973
- **Gene/protein:** HGNC:11041 (*SLC5A6*); Ensembl ENSG00000138074; UniProt Q9Y289; NCBI Gene 8884 (human), 330064 (mouse), 563356 (zebrafish)
- **CHEBI (substrates/therapeutics):** biotin CHEBI:15956; (R)-pantothenate CHEBI:46905; (R)-lipoic acid CHEBI:16494; iodide CHEBI:16382; coenzyme A CHEBI:15346
- **GO (process):** biotin transport GO:0015878; pantothenate transmembrane transport GO:0015887; CoA biosynthetic process GO:0015937; fatty acid beta-oxidation GO:0006635
- **GO (component):** apical plasma membrane GO:0016324; mitochondrion GO:0005739

- **CL:** enterocyte CL:0000584; cardiomyocyte CL:0000746; plasma cell CL:0000786; neuron CL:0000540
- **UBERON:** brain UBERON:0000955; peripheral nerve UBERON:0001021; intestine UBERON:0000160; heart UBERON:0000948; skin UBERON:0002097; bone UBERON:0001474
- **Representative HPO:** HP:0001263, HP:0012444, HP:0001250, HP:0007141, HP:0001508, HP:0004313, HP:0001644, HP:0003355
- **NCIT (intervention concepts):** biotin therapy; pantothenic acid supplementation; dietary supplement therapy

Report compiled from 18 primary sources and database verification (UniProt, Ensembl, gnomAD, ClinVar, OLS4, NCBI). Evidence sources are distinguished throughout as human clinical, model organism, in vitro, or computational/database.

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