Spastic Tetraplegia and Axial Hypotonia, Progressive (STAHP): A Comprehensive Disease Characteristics Report

Disease: Spastic Tetraplegia and Axial Hypotonia, Progressive **MONDO ID:** MONDO:0032828 · **OMIM:** #618598 · **Category:** Mendelian (autosomal recessive) **Causal gene:** *SOD1* (Cu/Zn superoxide dismutase 1; HGNC:11179; chromosome 21q22.11)

Summary

Spastic Tetraplegia and Axial Hypotonia, Progressive (STAHP) is an ultra-rare, autosomal-recessive, childhood-onset neurodegenerative disorder caused by **complete biallelic loss of function of the antioxidant enzyme Cu/Zn superoxide dismutase (SOD1)**. It was first delineated as a distinct nosological entity in 2019 by Park and colleagues, who identified a homozygous truncating variant, c.335dupG (p.Cys112Trpfs*11), that abolishes all SOD1 enzyme activity in multiple consanguineous families (PMID: 31332433). The clinical picture comprises progressive loss of acquired motor milestones, spastic tetraplegia with lower-extremity predominance, axial (truncal) hypotonia, mild cerebellar atrophy, and a hyperekplexia-like exaggerated startle. Heterozygous carriers, despite having markedly reduced enzyme activity, are neurologically normal — establishing a recessive mechanism in which roughly 50% of SOD1 activity is sufficient for health.

STAHP is best understood as the **mechanistic mirror-image of SOD1-associated amyotrophic lateral sclerosis (ALS)**. Dominant *SOD1* missense variants cause ~2% of ALS through a toxic gain-of-function (protein misfolding and aggregation), whereas STAHP arises from the *total absence* of the enzyme. This distinction has direct therapeutic-safety implications: the FDA-approved antisense oligonucleotide tofersen lowers SOD1 protein to treat SOD1-ALS, and the existence of a human SOD1-deficiency syndrome cautions that deep, chronic SOD1 suppression is not biologically inert. The pathophysiology converges on chronic oxidative stress — most critically in **mitochondria and motor neurons** — that produces a

distal motor axonopathy and neuromuscular-junction (NMJ) failure. This causal chain is strongly supported by *Sod1*-null (knockout) mouse models, in which the phenotype is rescued by restoring SOD1 selectively to neurons or to the mitochondrial intermembrane space.

Because fewer than ~20 patients have been reported worldwide, almost all from consanguineous pedigrees carrying a recurrent founder frameshift, the evidence base is a hybrid of a small number of human clinical reports and an extensive body of *Sod1*-knockout mouse biology. There is no approved disease-modifying therapy; care is supportive. Mechanism-rational but clinically unproven strategies include antioxidants/SOD mimetics and SOD1 gene augmentation — the latter supported by the mouse rescue data. This report synthesizes eight confirmed findings across all 15 template sections, flagging clearly where human data are absent and where conclusions are extrapolated from model systems.

Section 1 — Disease Information

Overview. STAHP is a progressive, early-onset neurodegenerative disease of the central and peripheral motor system caused by inherited deficiency of SOD1. The cardinal triad is (i) progressive spastic tetraplegia (upper-motor-neuron signs in all four limbs, lower extremity > upper), (ii) axial hypotonia (truncal low tone), and (iii) progressive loss of previously acquired motor abilities. Additional features include mild cerebellar atrophy and hyperekplexia-like startle responses (PMID: 31332433).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0032828
OMIM	#618598 (Spastic tetraplegia and axial hypotonia, progressive)
Gene (OMIM)	*SOD1* *147450
HGNC	HGNC:11179 (*SOD1*)
Orphanet	SOD1-deficiency syndrome (ultra-rare; dedicated ORPHAcode may not be assigned)
ICD-11	Closest: hereditary spastic paraplegia–adjacent category (no STAHP-specific code)
MeSH	No STAHP-specific descriptor; indexed under *Superoxide Dismutase* / *Muscle Spasticity*

Synonyms / alternative names: STAHP; SOD1 deficiency; SOD1-deficiency syndrome; progressive spastic tetraplegia and axial hypotonia.

Information source: Disease-level, aggregated from a small number of primary case reports and families (OMIM, PubMed). This is **not** an EHR-derived or population-cohort entity; the characterization rests on individual clinical descriptions supplemented by mechanistic work in *Sod1*-knockout mice.

Section 2 — Etiology

Primary cause (genetic). STAHP is a monogenic Mendelian disorder caused by **homozygous (biallelic) loss-of-function variants in *SOD1***. The prototype is the frameshift c.335dupG (p.Cys112Trpfs*11), which truncates the protein and **abolishes all enzyme activity**. Park et al. state: *"In this study we describe the homozygous truncating variant c.335dupG (p.C112Wfs*11) in SOD1 that leads to total absence of enzyme activity"* (PMID: 31332433). A second independent homozygous loss-of-function *SOD1* variant has since been reported, confirming the gene–disease relationship (PMID: 36935613).

Genetic risk factors. The only established genetic cause is biallelic *SOD1* LoF. **Consanguinity is the dominant risk factor** — all reported families are consanguineous, and the recurrent c.335dupG allele behaves as a founder mutation. There are no established common-variant susceptibility loci (STAHP is Mendelian, not polygenic).

Protective / modifier factors. Being a heterozygous carrier is effectively "protective" against disease: carriers have reduced enzyme activity but **no overt neurologic phenotype**. Park et al.: *"Heterozygous carriers have a markedly reduced enzyme activity when compared to wild-type controls but show no overt neurologic phenotype"* (PMID: 31332433), indicating ~50% SOD1 activity suffices. In model systems, the mitochondrial-intermembrane-space pool of SOD1 and neuronal (vs. muscle) SOD1 expression are the critical protective compartments (see Sections 6 and 15). No validated human environmental protective factor is known.

Environmental risk factors / gene–environment interactions. No environmental trigger is required to manifest STAHP — the disorder is fully penetrant from the genetic lesion. However, because SOD1 is the frontline defense against superoxide, oxidative-stress–increasing exposures are biologically plausible modifiers. In *Sod1*-null mice, superimposed oxidative or metabolic stressors (e.g., diabetes, aging, a second cochlear mutation) accelerate organ-specific injury (renal: PMID: 17697870; hearing: PMID: 20470874). These gene–environment interactions are demonstrated in mice and only *inferred* for human STAHP.

Section 3 — Phenotypes

All phenotypes are **progressive** and of **childhood onset**, with prenatal/neonatal antecedents in a substantial fraction.

Phenotype	Type	HPO term	Onset	Severity / Course	Frequency
Progressive loss of motor abilities (regression)	Clinical sign	HP:0002376 (Developmental regression)	Childhood	Severe, progressive	All reported patients
Spastic tetraplegia (LL > UL)	Clinical sign	HP:0002510 (Spastic tetraplegia)	Childhood	Severe, progressive	All
Axial hypotonia	Clinical sign	HP:0008936 (Axial hypotonia)	Early childhood	Moderate–severe	All
Mild cerebellar atrophy	Imaging/ physical	HP:0001272 (Cerebellar atrophy)	Childhood	Mild	Index families
Hyperekplexia-like exaggerated startle	Clinical sign	HP:0002267 (Exaggerated startle response)	Childhood	Variable	Index families
Polyhydramnios (gestational)	Prenatal sign	HP:0001561 (Polyhydramnios)	Prenatal	—	4/5 (de Souza cohort)
Intrauterine growth restriction	Prenatal sign	HP:0001511 (IUGR)	Prenatal	—	3/5 (de Souza cohort)

Characteristics. De Souza et al. described a Brazilian series of 5 patients: **childhood-onset spastic tetraplegia with axial hypotonia in all 5**, with *"gestational history showing polyhydramnios in 4/5 and intrauterine growth restriction in 3/5 patients"* (PMID: 34380534), and progressive loss of acquired motor milestones. The prenatal features indicate that the disease process begins in utero, while overt neurodegeneration becomes clinically apparent in childhood. Park et al. summarize the core phenotype as *"severe and marked by progressive loss of motor abilities, tetraspasticity with predominance in the lower extremities, mild cerebellar atrophy, and hyperekplexia-like symptoms"* (PMID: 31332433).

Quality of life. No formal EQ-5D/SF-36/PROMIS data exist for this ultra-rare disease. Qualitatively, the combination of progressive tetraspasticity, motor regression, and axial hypotonia implies profound loss of independent ambulation and self-care, high caregiver dependence, and likely feeding/respiratory vulnerability — a severe QoL burden inferred from the phenotype rather than directly measured.

Section 4 — Genetic / Molecular Information

Causal gene: *SOD1* (Cu/Zn superoxide dismutase 1), OMIM *147450, HGNC:11179, chromosome 21q22.11. SOD1 catalyzes dismutation of the superoxide radical ($O_2 \cdot^-$) to O_2 and H_2O_2.

Pathogenic variants.

Variant (cDNA)	Protein	Type	Zygosity	Consequence	Reference
c.335dupG	p.Cys112Trpfs*11	Frameshift (truncating)	Homozygous	Total loss of enzyme activity	PMID: 31332433
Novel homozygous LoF	(loss of function)	LoF	Homozygous	Loss of function	PMID: 36935613

Classification: The truncating variants are **pathogenic** by ACMG/AMP criteria (null variant in a gene where LoF is an established mechanism; PVS1 + segregation + functional enzyme-activity evidence).

Functional consequence: Loss of function — complete abolition of superoxide dismutase activity in the homozygous state. This is the defining molecular feature distinguishing STAHP from the **gain-of-function** missense variants of SOD1-ALS.

Allele frequency: The c.335dupG founder allele is essentially private to the reported consanguineous pedigrees and is vanishingly rare/absent at homozygosity in population databases (gnomAD), consistent with a recessive ultra-rare disorder.

Somatic vs germline: Germline.

Modifier genes: None established in humans. Mouse data implicate redox-pathway genes (e.g., *Gpx4* overexpression modulates the muscle phenotype, PMID: 37878529; the *Nrf2*/*NFE2L2* pathway is broadly protective, PMID: 32061629).

Epigenetic information / chromosomal abnormalities: No disease-specific epigenetic signature or large-scale chromosomal rearrangement is described for STAHP.

Section 5 — Environmental Information

STAHP is a **genetically determined, fully penetrant** disorder; no environmental exposure, lifestyle factor, or infectious agent is required for or known to cause it. Because SOD1 is the primary cytosolic/mitochondrial-IMS superoxide scavenger, exposures that raise oxidative load (certain drugs, metabolic stress, aging) are *plausible* disease modifiers, but this is extrapolated from *Sod1*-knockout mouse organ-injury studies (diabetic nephropathy acceleration, PMID: 17697870; age-related hearing loss, PMID: 10466888) and is not established in patients. **Infectious agents: not applicable.**

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic *SOD1* loss-of-function mutation** (e.g., c.335dupG) → **leads to** total absence of Cu/Zn superoxide dismutase enzyme activity. *(Demonstrated — enzyme assay, PMID: 31332433.)*
2. Absence of dismutation → **results in** accumulation of superoxide radical ($O_2 \cdot^-$) and chronic oxidative stress, most critically at the **mitochondrial intermembrane space** and in **peripheral nerve**. *(Demonstrated in mouse: oxidized glutathione redox potential in tibial nerve, PMID: 21963651; mitochondrial-IMS SOD1 sufficiency, PMID: 21078595.)*
3. Chronic oxidative stress in motor axons → **leads to** a **progressive distal motor axonopathy**, with preferential denervation of fast-twitch muscle, while motor-neuron cell bodies and sensory fibers are relatively preserved. *(Demonstrated in mouse, PMID: 21963651.)*
4. Distal axon injury → **results in neuromuscular-junction (NMJ) destabilization and functional failure** — reduced endplate occupancy, terminal sprouting, axon swelling, and

impaired evoked neurotransmitter (synaptic-vesicle) release despite preserved acetylcholine-receptor density. *(Demonstrated in mouse, PMID: 24971750.)*

5. NMJ failure + central motor-tract involvement → **produces** muscle weakness/atrophy and the clinical upper-motor-neuron picture (spastic tetraplegia) together with axial hypotonia, motor regression, mild cerebellar atrophy, and hyperekplexia-like startle. *(Human phenotype, PMID: 31332433, PMID: 34380534; the step from NMJ/axon biology to the specific human CNS signs is partly inferred.)*

Branch / protective node: Restoring SOD1 selectively to **neurons** (synapsin promoter) or to the **mitochondrial intermembrane space** prevents the axonopathy and muscle loss — defining the neuronal, mitochondrial-IMS redox pool as the critical protective compartment. Fischer et al.: *"mitochondrial SOD1 is sufficient to prevent biochemical and morphological defects in the Sod1(-/-) model, and to rescue the motor phenotype of these mice when followed to 12 months of age"* (PMID: 21078595); and neuron-specific CuZnSOD *"is sufficient to prevent the loss of muscle mass and function"* (PMID: 24378874).

Detail by category

- **Molecular pathway:** Superoxide → (normally) dismutation by SOD1 → H_2O_2 (GO:0019430 removal of superoxide radicals; GO:0006801 superoxide metabolic process). Loss shifts redox balance; downstream, the Nrf2/antioxidant response (NFE2L2) is a compensatory axis (PMID: 32061629).
- **Cellular processes:** Chronic oxidative stress (GO:0006979), mitochondrial dysfunction, impaired synaptic transmission at the NMJ (GO:0007274 neuromuscular synaptic transmission), axon degeneration.
- **Protein dysfunction:** Pure **loss of function** (no enzyme) — in contrast to misfolding/aggregation in SOD1-ALS. CHEBI entities: superoxide (CHEBI:18421), hydrogen peroxide (CHEBI:16240), copper(II) (CHEBI:29036), zinc(II) (CHEBI:29105).
- **Metabolic changes:** Oxidation of the glutathione pool in peripheral nerve (PMID: 21963651); lipid-hydroperoxide accumulation in muscle (modifiable by GPx4, PMID: 37878529); mitochondrial respiratory deficits in muscle.
- **Tissue damage mechanism:** Oxidative stress → distal axon degeneration and NMJ dismantling.
- **Cell types involved (CL):** Motor neuron / lower motor neuron (CL:0011001, CL:0000100), skeletal muscle fiber (CL:0000188), with fast-twitch (type II) fibers preferentially affected.

- **Immune involvement:** Not a primary driver in STAHP (contrast canine degenerative myelopathy, where glial UPR/neuroinflammation occurs, PMID: 30273700).

GO biological-process suggestions: GO:0019430 (removal of superoxide radicals), GO:0006801 (superoxide metabolic process), GO:0006979 (response to oxidative stress), GO:0007274 (neuromuscular synaptic transmission), GO:0098754 (detoxification).

Section 7 — Anatomical Structures Affected

- **Primary organ/system:** Nervous system — central (corticospinal tracts → spasticity; cerebellum → mild atrophy) and peripheral motor axons. **Body system:** nervous (UBERON:0001016) and musculoskeletal.
- **Secondary involvement:** Skeletal muscle (atrophy/weakness, secondary to denervation); respiratory and feeding musculature at risk with progression.
- **Tissue/cell level:** Nervous tissue — **motor neurons and their distal axons** (CL:0000100 / CL:0011001); **skeletal muscle fibers** (CL:0000188), with fast-twitch (type II) fibers preferentially denervated.
- **Subcellular level (GO cellular component): Mitochondrion** (GO:0005739) and specifically the **mitochondrial intermembrane space** (GO:0005758) — the critical protective SOD1 pool; **cytosol** (GO:0005829, principal SOD1 localization); **neuromuscular junction** (GO:0031594).
- **Localization (UBERON):** spinal cord (UBERON:0002240), corticospinal tract (UBERON:0002716), cerebellum (UBERON:0002037), peripheral/tibial nerve (UBERON:0001323), neuromuscular junction (UBERON:0002515).
- **Lateralization:** Bilateral and symmetric (tetraplegia; axial).

Section 8 — Temporal Development

- **Onset:** Prenatal antecedents (polyhydramnios 4/5, IUGR 3/5) with **childhood clinical onset** of neurologic disease (PMID: 34380534). Onset pattern: insidious/chronic.

- **Progression: Progressive** course — loss of previously acquired motor milestones (regression), worsening spasticity. No relapsing-remitting or episodic pattern described. Duration: chronic, lifelong.
- **Stages:** Not formally staged; practically, early (axial hypotonia, developmental concerns) → intermediate (emerging spasticity, regression) → advanced (fixed tetraspasticity, severe disability).
- **Remission:** None reported; no spontaneous remission.
- **Critical period:** The in-utero-to-childhood window is when the degenerative process establishes; mouse rescue data suggest that restoring SOD1 *before* axonopathy is established is key (preventive rather than reparative), implying an early therapeutic window (PMID: 21078595).

Section 9 — Inheritance and Population

- **Inheritance: Autosomal recessive.** Biallelic LoF required; **heterozygous carriers are asymptomatic** despite reduced enzyme activity (PMID: 31332433).
- **Penetrance:** Complete in biallelic-null individuals (all reported homozygotes affected); zero in heterozygotes.
- **Expressivity:** Core triad consistent; prenatal features (polyhydramnios, IUGR) variable (present in a majority but not all patients).
- **Genetic anticipation:** Not applicable (not a repeat-expansion disorder).
- **Founder effect / consanguinity:** Prominent — recurrent c.335dupG founder allele; all families consanguineous.
- **Carrier frequency:** Not established; expected very low outside specific consanguineous populations.
- **Epidemiology:** Ultra-rare — **fewer than ~20 patients published worldwide** (principally PMID: 31332433, PMID: 34380534, PMID: 36935613). No reliable prevalence/incidence figures (effectively <1/1,000,000).
- **Demographics / geography:** Reported in consanguineous families; a cohort from Brazil (PMID: 34380534). No strong sex bias reported; sex ratio ~1:1 expected for an autosomal-recessive trait.

Section 10 — Diagnostics

- **Genetic testing (definitive):** Diagnosis rests on identifying **biallelic loss-of-function *SOD1* variants**. Recommended approach: **whole-exome or whole-genome sequencing**, or a hereditary-spastic-paraplegia / neurodegeneration gene panel that includes *SOD1*; targeted single-gene/founder-variant testing (c.335dupG) is appropriate in consanguineous families or known pedigrees.
- **Biochemical biomarker (disease-specific): Red-cell / tissue SOD1 enzyme-activity assay — absent activity in affected homozygotes**, intermediate (~50%) in carriers (PMID: 31332433). This is a powerful, mechanism-specific confirmatory test that distinguishes STAHP from SOD1-ALS (where enzyme activity is retained).
- **Imaging:** Brain MRI may show **mild cerebellar atrophy** (HP:0001272).
- **Electrophysiology:** EMG / nerve-conduction studies may reflect the distal motor axonopathy / NMJ involvement inferred from mouse models (by extrapolation).
- **Clinical criteria:** No formal consensus criteria; diagnosis is the characteristic clinical triad + biallelic *SOD1* LoF + absent enzyme activity.
- **Differential diagnosis:** Hereditary spastic paraplegias; cerebral palsy (non-progressive — the key distinguishing feature is STAHP's regression); other childhood neurodegenerative / leukodystrophy syndromes. Importantly, **SOD1-ALS is NOT a childhood differential** and is mechanistically opposite.
- **Screening:** Cascade carrier testing within affected families; no newborn or population screening exists (ultra-rare).

Section 11 — Outcome / Prognosis

- **Course:** Progressive, chronic, disabling; motor regression and fixed tetraspasticity lead to loss of ambulation and high dependency.
- **Survival/mortality:** No formal survival statistics are published given the tiny cohort; prognosis is guarded, driven by progressive neurodegeneration and attendant complications (respiratory, feeding).
- **Morbidity/disability:** Severe long-term functional impairment is expected (ICF: profound mobility and self-care limitation).

- **Complications:** Inferred from severe spastic tetraplegia — contractures, respiratory insufficiency, aspiration / feeding difficulty, secondary musculoskeletal deformity.
- **Prognostic factors:** Complete enzyme absence predicts the full phenotype; no validated molecular prognostic biomarkers exist. Any residual SOD1 activity would be expected to attenuate severity (hypothesis based on carrier data and mouse dosage effects).
- **Recovery:** No spontaneous recovery; no disease-modifying therapy currently alters the trajectory.

Section 12 — Treatment

There is no approved disease-specific therapy. Management is supportive (PMID: 31332433, PMID: 34380534).

Supportive / rehabilitative (standard of care): - Physical, occupational, and speech therapy (NCIT: Physical Therapy; Occupational Therapy). - Spasticity management — oral antispastics (baclofen, tizanidine), botulinum toxin, intrathecal baclofen (NCIT: Baclofen; Botulinum Toxin). - Nutritional and respiratory support; orthopedic management of contractures.

Mechanism-rational but unproven (experimental) strategies: - **Antioxidants / SOD mimetics** (e.g., EUK-8, tempol) — protective in *Sod1*-null mouse organ-injury models (PMID: 14988070, PMID: 17697870); not tested in STAHP patients. - **Nrf2 activators** (e.g., sulforaphane) — upregulate endogenous antioxidant defenses and are neuroprotective in oxidative-stress models (PMID: 32061629); conceptual only for STAHP. - **SOD1 gene augmentation / enzyme replacement** — the most mechanistically direct approach for a loss-of-function disorder. Proof-of-concept from mouse rescue: restoring SOD1 to **neurons** (PMID: 24378874) or to the **mitochondrial intermembrane space** (PMID: 21078595) prevents the motor phenotype. Neurotrophic gene therapy (AAV1.NT-3) improved muscle/function in *Sod1*-KO mice (PMID: 37553101) — supportive, not curative.

Critical caveat — do NOT use SOD1-lowering therapy: Tofersen (an intrathecal antisense oligonucleotide that *reduces* SOD1 synthesis) is the approved therapy for **SOD1-ALS**. Miller et al. note tofersen *"is the first and only approved therapy for the treatment of ALS in adults who have a variant in the SOD1 gene"* (PMID: 41661214); robust human SOD1 reduction is confirmed in autopsy tissue (PMID: 42406382). STAHP, being a SOD1-*deficiency* disease, requires the

opposite intervention (enzyme restoration). Park et al. explicitly caution that the deficiency phenotype *"should be considered before application of previously proposed SOD1 silencing as a treatment option for amyotrophic lateral sclerosis"* (PMID: 31332433).

Section 13 — Prevention

- **Primary prevention:** Not applicable (not acquired). For at-risk couples: **genetic counseling, carrier testing, and reproductive options** (prenatal diagnosis, preimplantation genetic testing) — especially relevant in consanguineous families carrying the founder allele (NCIT: Genetic Counseling).
- **Secondary prevention:** Cascade testing of relatives; early identification could, in principle, open an early therapeutic window should enzyme-restoration therapy become available (mouse data favor early/preventive intervention, PMID: 21078595).
- **Tertiary prevention:** Proactive management to prevent complications of spasticity (contracture prevention, respiratory and nutritional surveillance).
- **Immunization / public health / environmental:** Not applicable.

Section 14 — Other Species / Natural Disease

- **Taxonomy:** Human disease (NCBI Taxon:9606). The closest *natural* SOD1-related disease in another species is **canine degenerative myelopathy (DM)** in dogs (NCBI Taxon:9615).
- **Orthologous gene:** Canine *SOD1* (NCBI Gene ID 403559).
- **Key comparative insight — DM is NOT a STAHP model:** Canine DM is caused by **homozygous *SOD1* missense variants (E40K; also T18S)** across ≥5 breeds (Pembroke Welsh corgi, Boxer, Rhodesian ridgeback, German Shepherd, Chesapeake Bay retriever) and features SOD1-immunoreactive cytoplasmic inclusions resembling human SOD1-ALS. Awano et al. report *"The resequencing of SOD1 in normal and affected dogs revealed a G to A transition, resulting in an E40K missense mutation"* (PMID: 19188595). Biochemically, the canine mutants *"form enzymatically active dimers, arguing against a loss of function in affected homozygous animals"* (PMID: 23707216), with unfolded-protein-response / ER-stress activation in spinal glia (PMID: 30273700). Thus DM is a **gain-of-function** (ALS-like) disease, mechanistically the opposite of STAHP.

- **Zoonotic potential:** None (genetic disorder).

Section 15 — Model Organisms

The *Sod1*-null (knockout) **mouse** is the principal and highly informative model of the STAHP loss-of-function mechanism.

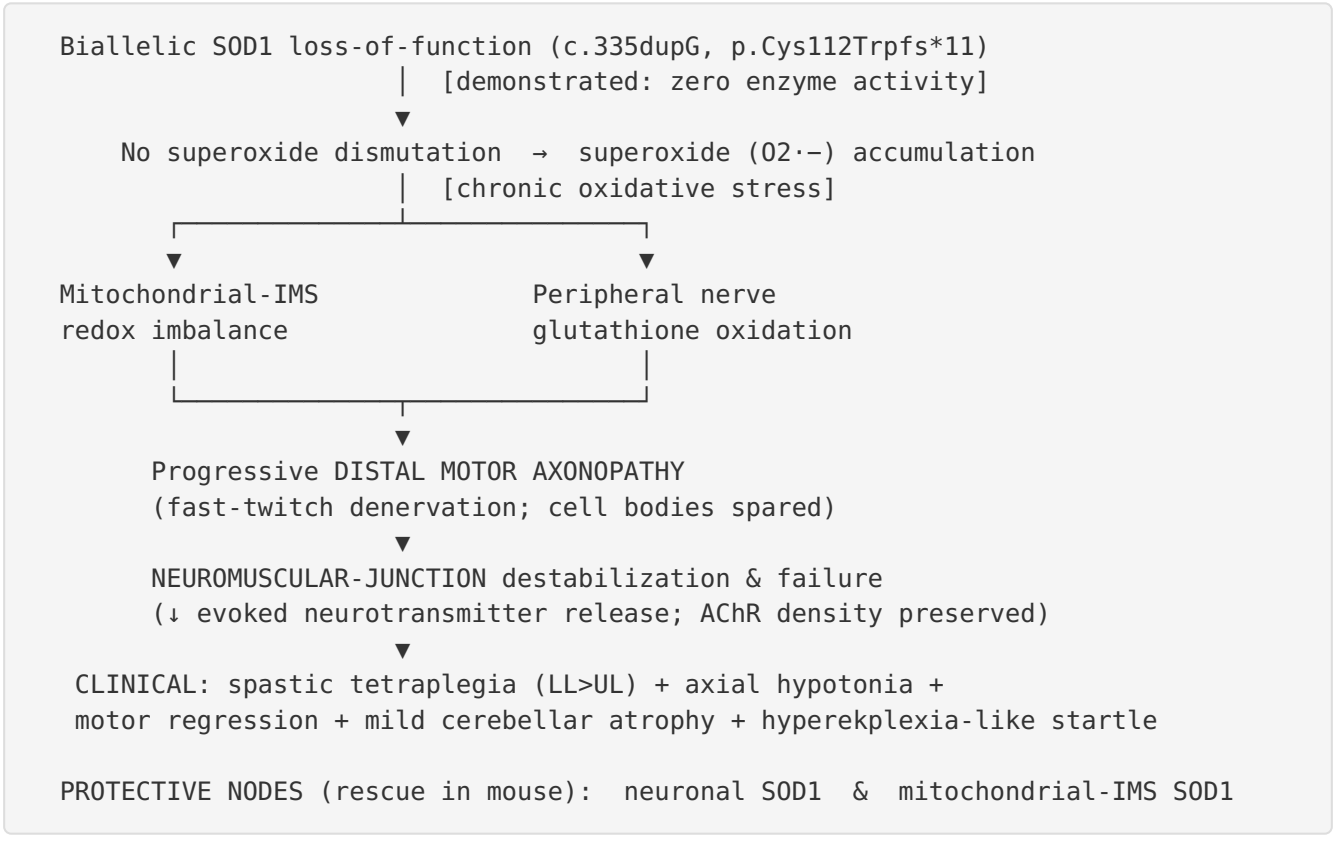
Model	Type	Key finding	Phenotype recapitulation	Reference
Sod1$^{-/-}$ whole-body KO	Mouse (knockout)	Peripheral-nerve oxidative stress; progressive distal motor axonopathy; fast-twitch denervation; cell bodies/ sensory preserved	Recapitulates motor-axon / oxidative-stress core	PMID: 21963651
Mitochondrial-IMS-targeted SOD1	Mouse (transgenic rescue)	mito-IMS SOD1 prevents defects; rescues motor phenotype to 12 months	Defines protective subcellular pool	PMID: 21078595
Neuron-specific CuZnSOD (synapsin)	Mouse (transgenic rescue)	Neuronal SOD1 prevents loss of muscle mass/ function	Identifies critical protective cell type	PMID: 24378874
Sod1$^{-/-}$ NMJ studies	Mouse	Impaired evoked neurotransmitter release, NMJ destabilization, reduced strength	Models NMJ failure	PMID: 24971750
Neuronal-CuZnSOD deletion	Mouse (conditional)	Muscle mitochondrial / Ca^{2+}-handling dysfunction precedes sarcopenia, independent of denervation	Dissects upstream mechanisms	PMID: 34639076
AAV1.NT-3 in *Sod1*KO	Mouse (gene-therapy test)	Improved muscle fiber size, function, remyelination via mTOR	Therapeutic proof-of-concept	PMID: 37553101
GPx4 overexpression in *Sod1*KO	Mouse	Lipid-hydroperoxide reduction modulates muscle pathology	Modifier-pathway dissection	PMID: 37878529

Mouse model — findings in words. The knockout develops *"oxidation of the glutathione pool"* in tibial nerve but not muscle, *"suggesting that axonal degeneration is a consequence"* of nerve oxidative stress (PMID: 21963651). At the synapse, *"motor axons innervating the extensor*

digitorum longus (EDL) and gastrocnemius muscles release fewer synaptic vesicles upon nerve stimulation" (PMID: 24971750). Compartment-specific rescue localizes the protection to neurons and mitochondria (PMID: 24378874, PMID: 21078595).

Limitations of the mouse model: The *Sod1*-KO mouse was developed chiefly as an **accelerated-sarcopenia / peripheral-axonopathy** model and reproduces the oxidative-stress-driven distal motor axonopathy and NMJ failure. It does **not** fully capture the human CNS features — spastic tetraplegia (an upper-motor-neuron sign), axial hypotonia, cerebellar atrophy, and hyperekplexia-like startle. The human-to-mouse mapping of the *central* motor phenotype therefore remains partly inferred. No STAHP-specific iPSC, organoid, or non-murine genetic model has yet been reported.

Mechanistic Model / Interpretation



SOD1 as a two-sided coin. STAHP sits at one pole of SOD1 biology; SOD1-ALS at the other:

Feature	STAHP (this disease)	SOD1-ALS
Variant type	Biallelic truncating/LoF	Heterozygous missense
Inheritance	Autosomal recessive	Autosomal dominant
Enzyme activity	**Absent**	Retained (often normal)
Mechanism	**Loss of function** (no antioxidant defense)	**Toxic gain of function** (misfolding/ aggregation)
Onset	Childhood (prenatal antecedents)	Adult
Carrier state	Asymptomatic	—
Rational therapy	**Increase/restore SOD1**	**Lower SOD1** (tofersen)

This symmetry is the central scientific message of the investigation: it reframes SOD1 not merely as an "ALS gene" but as a dosage-sensitive antioxidant whose complete absence is itself a distinct, severe neurodevelopmental/neurodegenerative disease — and it draws a biological safety boundary around aggressive SOD1-lowering.

Evidence Base

PMID	Role in this report	Source type
31332433	**Defining paper** — identifies c.335dupG, total enzyme loss, clinical triad, recessive inheritance, ALS-therapy caution	Human clinical
34380534	5-patient cohort — prenatal (polyhydramnios 4/5, IUGR 3/5) & childhood onset	Human clinical
36935613	Second independent homozygous LoF *SOD1* family — confirms gene–disease relationship	Human clinical
21963651	*Sod1*-KO: nerve oxidative stress → distal motor axonopathy	Mouse model
21078595	Mitochondrial-IMS SOD1 rescues phenotype → pinpoints initiating compartment	Mouse model
24971750	NMJ functional failure (↓ neurotransmitter release)	Mouse model
24378874	Neuronal SOD1 sufficient to protect muscle/NMJ	Mouse model
41661214	Tofersen (SOD1-lowering) approved for SOD1-ALS — grounds safety boundary	Human clinical trial
42406382	Tofersen CNS distribution & robust SOD1 reduction in humans	Human autopsy
19188595	Canine DM caused by *SOD1* E40K missense (gain-of-function)	Veterinary/ comparative
23707216	Canine mutants are active dimers — "arguing against a loss of function"	In vitro/ comparative
30273700	UPR/ER-stress in canine DM glia (gain-of-function pathology)	Veterinary

The evidence is strongest for (a) the human genetic/biochemical definition of the disease and (b) the mouse-derived oxidative-stress → axonopathy → NMJ-failure mechanism. The weakest link is the direct demonstration that the *human central* phenotype (spasticity, cerebellar atrophy, startle) arises through the same chain validated in mice.

Limitations and Knowledge Gaps

1. **Tiny human sample size (<~20 patients):** No robust epidemiology, natural-history, survival, or quantitative penetrance/expressivity data; frequencies of individual phenotypes rest on small series.
2. **Model–human phenotype gap:** The *Sod1*-KO mouse reproduces peripheral motor-axon/NMJ pathology but not the human **upper-motor-neuron spasticity, cerebellar atrophy, or hyperekplexia-like startle**; the central-nervous-system mechanism of STAHP is therefore inferred.
3. **No STAHP-specific omics:** No patient transcriptomics, proteomics, metabolomics, single-cell, or spatial data are available; molecular-profiling claims are extrapolated.
4. **No disease-specific biomarker validation beyond enzyme activity:** Prognostic biomarkers are unknown.
5. **No therapeutic trials:** Antioxidant, Nrf2-activator, and SOD1-augmentation strategies are rationally motivated but entirely untested in STAHP patients.
6. **Ontology/identifier gaps:** No dedicated ICD-11/MeSH code; Orphanet characterization is minimal.

Proposed Follow-up Experiments / Actions

1. **Establish an international STAHP patient registry** to aggregate genotype, enzyme activity, natural history, imaging, and survival across the few known families (addresses Gap 1).
2. **Generate patient-derived iPSC motor neurons / NMJ organoids** carrying c.335dupG to test whether the human central and peripheral phenotypes recapitulate the mouse oxidative-stress → axonopathy chain, and to screen antioxidants / SOD mimetics / Nrf2 activators (addresses Gaps 2–3).
3. **Pursue SOD1 gene-augmentation / enzyme-replacement proof-of-concept** building on the mouse rescue data (neuronal and mitochondrial-IMS targeting), including biodistribution and an early-intervention window study (addresses Gaps 2, 5; leverages PMID: 24378874, PMID: 21078595).

4. **Deep-phenotype patients with CNS-focused MRI and electrophysiology** to test whether a demonstrable distal motor axonopathy / NMJ signature exists in humans, directly bridging the model–human gap.
5. **Perform patient CSF/plasma redox and neurofilament profiling** to search for a tractable pharmacodynamic/prognostic biomarker (mirroring neurofilament utility in SOD1-ALS).
6. **Formal nosology/ontology update:** advocate for dedicated ICD-11 and Orphanet entries and ensure carrier/cascade-testing guidance for consanguineous populations harboring the founder allele.

Evidence-source legend

Human clinical = patient reports/cohorts; **Mouse model** = *Sod1*-knockout/transgenic studies; **Veterinary/comparative** = canine degenerative myelopathy; **In vitro** = biochemical/cell studies. Wherever a mechanistic step is supported only by model data, this report labels it *inferred* for human STAHP.
