Neurodevelopmental Disorder with Neuromuscular and Skeletal Abnormalities (NEDNMSA): A Comprehensive Disease Characteristics Report

Disease: Neurodevelopmental Disorder with Neuromuscular and Skeletal Abnormalities (NEDNMSA) **MONDO ID:** MONDO:0859236 · **OMIM:** 619833 · **Category:** Mendelian (autosomal recessive) **Causal gene:** *NRCAM* (HGNC:7994; NCBI Gene 4897; locus 7q31.1)

Summary

Neurodevelopmental Disorder with Neuromuscular and Skeletal Abnormalities (NEDNMSA) is an **ultra-rare autosomal recessive Mendelian syndrome** caused by **biallelic loss-of-function or deleterious missense variants in *NRCAM***, the gene encoding the neuronal cell-adhesion molecule NrCAM (neuron-glia-related cell adhesion molecule). The disorder was first defined by Kurolap and colleagues in 2022 in a cohort of ten affected individuals from eight families (PMID: 35108495), and independently confirmed in 2023 by a second report describing a homozygous nonsense variant (PMID: 36606341). The clinical syndrome is characterized by a triad-plus phenotype: **developmental delay/intellectual disability, hypotonia, and peripheral neuropathy and/or spasticity**, accompanied by a variable constellation of skeletal (scoliosis, hip dysplasia, foot deformities, distal arthrogryposis), central nervous system structural (thin corpus callosum, ventriculomegaly, delayed myelination, periventricular heterotopia), and ophthalmologic anomalies.

Mechanistically, NrCAM is an L1-family immunoglobulin-superfamily axonal/glial adhesion molecule that, together with its partners **gliomedin** and **neurofascin-186 (NF186)**, orchestrates the assembly of **nodes of Ranvier and axon initial segments** by recruiting ankyrin-G and clustering voltage-gated sodium channels. Loss of NrCAM function destabilizes

this nodal complex, degrades saltatory conduction, and disrupts axon guidance and brain morphogenesis — providing a direct causal chain from gene dysfunction to the observed neuromuscular and neurodevelopmental phenotypes. Population-genetic constraint metrics from gnomAD (pLI ≈ 0; LOEUF = 0.636; observed/expected LoF = 0.53) confirm that *NRCAM* is **not haploinsufficient**, consistent with a **recessive** rather than dominant mechanism, and animal models (Nrcam-null mice, nrcama-deficient zebrafish) recapitulate axon-guidance and brain-structural defects.

The disorder is congenital in onset, non-progressive to slowly variable in course, and lifelong. Because only ~11 individuals have been reported worldwide, no prevalence estimate, natural-history study, disease-specific therapy, or clinical trial exists. Diagnosis is molecular (trio-based whole-exome or whole-genome sequencing) supported by nerve conduction studies and brain MRI, and **management is entirely supportive and multidisciplinary**. This report synthesizes eight confirmed findings across 15 disease-characteristic domains, flagging clearly where evidence is absent.

Key Findings

Finding 1 — NEDNMSA is caused by biallelic *NRCAM* variants (autosomal recessive)

Ontology cross-referencing links MONDO:0859236 → OMIM:619833 → UMLS:C5676965 / MedGen:1803456, and identifies **a single causal gene, *NRCAM*** (HGNC:7994; gene OMIM 601581; locus 7q31.1). The defining cohort (Kurolap et al., 2022) reported **ten affected individuals from eight families** carrying bi-allelic *NRCAM* variants. A second, independent report (Elahi et al., 2023) confirmed the gene–disease relationship with a homozygous nonsense variant **c.73C>T (p.Gln25*)**, establishing the association beyond a single family.

> *"Here, we describe ten affected individuals with bi-allelic variants in the neuronal cell adhesion molecule NRCAM that lead to a neurodevelopmental syndrome of varying severity; the individuals are from eight families. This syndrome is characterized by developmental delay/intellectual disability, hypotonia, peripheral neuropathy, and/or spasticity."* — PMID: 35108495

> *"This study is the second report of an association between biallelic NRCAM gene variants and a Mendelian disorder."* — PMID: 36606341

Evidence type: Human clinical (two independent cohorts). This finding anchors Section 1 (Disease Information), Section 4 (Genetic/Molecular), and Section 9 (Inheritance).

Finding 2 — NrCAM mediates node-of-Ranvier assembly and Na^+-channel clustering

NrCAM is an axonal/glial Ig-superfamily cell-adhesion molecule of the L1 family. Together with **gliomedin** and **neurofascin-186 (NF186)**, it clusters **ankyrin-G** and **voltage-gated Na^+ channels** at nodes of Ranvier (Lustig et al., 2001, PMID: 11728309; Eshed et al., 2005, PMID: 16039564). Combined genetic loss of gliomedin and NrCAM in mice causes progressive loss of nodal Na^+ channels, "binary nodes," dysregulated nodal gap length, neurological abnormalities, and slowed nerve conduction (Amor et al., 2014).

> *"absence of both molecules (and hence the glial clustering signal) resulted in a gradual loss of Na(+) channels and other axonal components from the nodes, the formation of binary nodes, and dysregulation of nodal gap length. Therefore, these mice exhibit neurological abnormalities and slower nerve conduction."* — PMID: 24719088
>
> *"These results provide the first evidence that neurofascin plays a major role in the formation of nodes, possibly via interactions with Nr-CAM."* — PMID: 11728309

Evidence type: Model organism + in vitro. This is the central mechanistic finding explaining the neuropathy/spasticity phenotype (Section 6).

Finding 3 — gnomAD constraint supports a recessive loss-of-function mechanism

Constraint metrics for *NRCAM* (ENSG00000091129; chr7:108,147,623–108,456,717 GRCh38; canonical ENST00000379028) are: **pLI ≈ 0** (2.58×10^{-11}), **LOEUF (oe_lof upper) = 0.636**, **observed/expected LoF = 0.53** (83 observed vs 156.5 expected), **LoF Z = 4.99**; missense oe = 0.89, mis_Z = 1.92. The near-zero pLI indicates *NRCAM* **tolerates heterozygous loss of function** (i.e., is not haploinsufficient), while the elevated LoF Z-score shows selection against

biallelic depletion. This population-genetic signature is exactly what is expected for a gene causing a **recessive** disorder — heterozygous carriers are unaffected, and disease requires two damaged alleles.

Evidence type: Computational/population genetics (gnomAD v2/v4). Supports the inheritance model of Section 9.

Finding 4 — Animal models recapitulate axon-guidance and brain-structural defects

Nrcam-null mice show disturbed olfactory-nerve axon guidance and altered size of the ventricular system and cerebellar vermis (Heyden et al., 2008). NrCAM also regulates postnatal hypothalamic tanycyte differentiation, proliferation, and neurogenesis (Moore et al., 2022, PMID: 35464310). The defining human study used **zebrafish nrcama loss-of-function** to corroborate the gene–disease link.

> *"in both mutants, CHL1 and NrCAM, the guidance of the olfactory nerve projections is disturbed. Both mutations also alter the size of the ventricular system and the vermis" —* PMID: 18588951
>
> *"These findings are corroborated by previous in vitro studies of murine Nrcam-deficient cells, revealing abnormal neurite outgrowth, synaptogenesis, and formation of nodes of Ranvier on myelinated axons." —* PMID: 35108495

The mouse ventricular/vermis changes mirror the **human ventriculomegaly and CNS anomalies**, and the neurite-outgrowth/synaptogenesis/node-formation deficits provide cellular-level parallels to the human disease (Sections 6, 15).

Evidence type: Model organism (mouse, zebrafish) + in vitro.

Finding 5 — Pathogenic missense variants cluster in the third fibronectin type-III domain

Human NRCAM (UniProt **Q92823**) is a **1,304-aa type-I transmembrane L1-family protein** comprising **6 Ig-like domains (aa 46–632)**, **5 fibronectin type-III (Fn-III) domains (aa 649–1156)**, a transmembrane segment, and a cytoplasmic tail. The **third Fn-III domain (aa ~848–**

950) is a mutational hotspot: many disease-associated missense variants cluster there and are computationally predicted to be deleterious to protein structure and protein–protein interactions.

> *"Computational analyses of NRCAM variants, many of which cluster in the third fibronectin type III (Fn-III) domain, strongly suggest a deleterious effect on NRCAM structure and function, including possible disruption of its interactions with other proteins."* — PMID: 35108495

Evidence type: Human clinical + computational. Informs variant interpretation (Section 4) and protein-dysfunction mechanism (Section 6).

Finding 6 — Phenotype spectrum and frequencies (HPO-annotated cohort, n ≈ 10)

The table below consolidates HPOA/Monarch frequencies for MONDO:0859236 with suggested HPO terms. Frequencies are derived from the small defining cohort and should be read as **indicative, not population-representative**.

Phenotype	HPO term	Frequency (affected/ observed)
Global developmental delay	HP:0001263	40% (4/10)
Hypotonia	HP:0001252	40% (4/10)
Motor delay	HP:0001270	30% (3/10)
Intellectual disability	HP:0001249	30% (3/10)
Cerebral palsy / spasticity	HP:0100021	30% (3/10)
Scoliosis	HP:0002650	56% (5/9)
Hip dysplasia	HP:0001385	33% (3/9)
Pes cavus	HP:0001761	33% (3/9)
Hammertoe	HP:0001765	22% (2/9)
Distal arthrogryposis	HP:0005684	10% (1/10)
Microcephaly	HP:0000252	50% (3/6)
Micrognathia	HP:0000347	37.5% (3/8)
Demyelinating peripheral neuropathy	HP:0007108	10% (1/10)
Ataxia	HP:0001251	20%
Delayed CNS myelination	HP:0002188	22%
Thin corpus callosum	HP:0033725	22%
Ventriculomegaly	HP:0002119	22%
Periventricular heterotopia	HP:0007165	11%
Cataract	HP:0000518	25%
Optic atrophy	HP:0000648	12.5%
Retinal detachment	HP:0000541	12.5%
Failure to thrive	HP:0001508	25%

Phenotype	HPO term	Frequency (affected/ observed)
G-tube feeding	HP:0011471	22%
Self-injurious / aggressive behavior	HP:0100716 / HP:0000718	~20–40%

ClinVar lists **289 *NRCAM* records, of which 38 are pathogenic/likely-pathogenic**.

> *"This syndrome is characterized by developmental delay/intellectual disability, hypotonia, peripheral neuropathy, and/or spasticity."* — PMID: 35108495

Evidence type: Human clinical (HPO annotation). Populates Section 3 (Phenotypes).

Finding 7 — Epidemiology, inheritance, and diagnostic/management framework

The disorder is **ultra-rare**: the entire published literature comprises **~11 individuals** (10 from 8 families, Kurolap 2022; +1, Elahi 2023). **No prevalence or incidence estimate exists**, and there is **no Orphanet ORPHAcode**. Inheritance is **autosomal recessive** with biallelic homozygous or compound-heterozygous variants; homozygous variants in several families implicate **consanguinity**. Diagnosis is molecular via **trio-based whole-exome or whole-genome sequencing**, supported by **EMG/nerve conduction studies** (documenting axonal and/or demyelinating peripheral neuropathy) and **brain MRI** (thin corpus callosum, ventriculomegaly, delayed myelination, periventricular heterotopia). **No disease-specific pharmacotherapy, gene therapy, or clinical trial exists**; management is supportive and multidisciplinary. Severity is variable and **not strictly determined by variant type**, indicating variable expressivity relevant to prognostic counseling.

> *"we show that type of the pathogenic variant does not necessarily determine the severity of this phenotype."* — PMID: 36606341
>
> *"the individuals are from eight families"* — PMID: 35108495

Evidence type: Human clinical. Populates Sections 8–13.

Finding 8 — Evolutionary conservation and orthologs

NCBI Gene confirms conserved *NRCAM* orthologs across model species: **human *NRCAM*** (Gene 4897; HGNC:7994), **mouse *Nrcam*** (Gene 319504; NCBI:txid10090), **rat *Nrcam*** (Gene 497815; NCBI:txid10116), **zebrafish *nrcama*** (Gene 556537; NCBI:txid7955; paralog *nrcamb*). NRCAM belongs to the **L1 immunoglobulin-superfamily cell-adhesion molecule family**, with paralogs *L1CAM*, *CHL1*, and *NFASC*.

Evidence type: Computational/comparative genomics. Populates Sections 14–15.

Section-by-Section Report

1. Disease Information

Overview. NEDNMSA is a Mendelian, autosomal recessive neurodevelopmental syndrome combining neurological, neuromuscular, and skeletal features. Its defining triad is developmental delay/intellectual disability, hypotonia, and peripheral neuropathy and/or spasticity, with additional variable skeletal, brain-structural, and eye findings.

Key identifiers: MONDO:0859236 · OMIM:619833 · UMLS:C5676965 · MedGen:1803456. **No Orphanet ORPHAcode** has been assigned (reflecting ultra-rarity). ICD-10/ICD-11 and MeSH lack a specific code; the disorder maps to broad categories and is best referenced by its MONDO/OMIM identifiers.

Synonyms: "Neurodevelopmental disorder with neuromuscular and skeletal abnormalities"; "NRCAM-related neurodevelopmental disorder"; "NRCAM-related bi-allelic disorder." Gene-level synonyms for NrCAM include neuron-glia-related cell adhesion molecule and neuronal cell adhesion molecule.

Information source: Aggregated **disease-level** resources (OMIM/MONDO) built from two **individual-patient** case series (clinical phenotyping of ~11 patients), not from population EHR datasets.

2. Etiology

Causal factors. The disorder is **purely genetic (monogenic, recessive)**: biallelic pathogenic variants in *NRCAM*. There is **no known environmental, infectious, or mechanistic (non-genetic) cause**.

Genetic risk factors. The only established risk factor is inheritance of **two damaged *NRCAM* alleles**. Consanguinity is a major contributor (multiple homozygous families). No modifier genes or susceptibility loci have been identified (the cohort is too small).

Environmental / lifestyle / protective factors. Not applicable / not reported. No environmental risk factors, protective variants, protective exposures, or gene–environment interactions have been described for this ultra-rare Mendelian disorder. Standard prenatal care applies but does not modify the genetic risk.

3. Phenotypes

See **Finding 6** table for the full HPO-annotated phenotype list with frequencies. Key characteristics:

- **Phenotype types:** clinical signs (hypotonia, spasticity, neuropathy), developmental/behavioral (developmental delay, intellectual disability, self-injurious/aggressive behavior), physical/skeletal manifestations (scoliosis, hip dysplasia, pes cavus, hammertoe, distal arthrogryposis, micrognathia, microcephaly), and neuroimaging abnormalities (thin corpus callosum, ventriculomegaly, delayed myelination, periventricular heterotopia).
- **Age of onset:** congenital/neonatal (hypotonia, structural anomalies) to early childhood (developmental delay).
- **Severity:** variable (mild to severe), **not strictly predicted by variant type** (Elahi 2023).
- **Progression:** largely static/stable neurodevelopmental course; peripheral neuropathy may be slowly progressive.
- **Quality-of-life impact:** substantial — motor and cognitive impairment, feeding difficulty (G-tube in ~22%), and orthopedic disability affect daily functioning and independence. Formal QoL instrument data (EQ-5D/SF-36/PROMIS) are **not available** for this ultra-rare disorder.

4. Genetic/Molecular Information

- **Causal gene:** *NRCAM* (HGNC:7994; NCBI Gene 4897; gene OMIM 601581; 7q31.1; ENSG00000091129; canonical ENST00000379028).
- **Protein:** NrCAM, UniProt Q92823, 1,304 aa, type-I transmembrane; 6 Ig-like domains (aa 46–632), 5 Fn-III domains (aa 649–1156); the **3rd Fn-III domain (~aa 848–950) is a missense hotspot** (Finding 5).
- **Variant classes:** nonsense (e.g., c.73C>T p.Gln25*), other loss-of-function, and deleterious missense (clustered in Fn-III #3). ClinVar: **289 records, 38 pathogenic/likely-pathogenic**.

- **Functional consequence: loss of function** (recessive). gnomAD constraint (pLI ≈ 0; LOEUF 0.636; oe_LoF 0.53) confirms *NRCAM* is **not haploinsufficient** — disease requires biallelic hits (Finding 3).
- **Allele frequency:** individual pathogenic alleles are private/ultra-rare in gnomAD.
- **Origin: germline** (inherited, recessive). No somatic disease role in this Mendelian phenotype (though somatic/epigenetic *NRCAM* dysregulation is separately implicated in gliomas and colorectal cancer — see Evidence Base; this is unrelated to NEDNMSA).
- **Modifier genes / epigenetics / chromosomal abnormalities: not reported** for NEDNMSA.

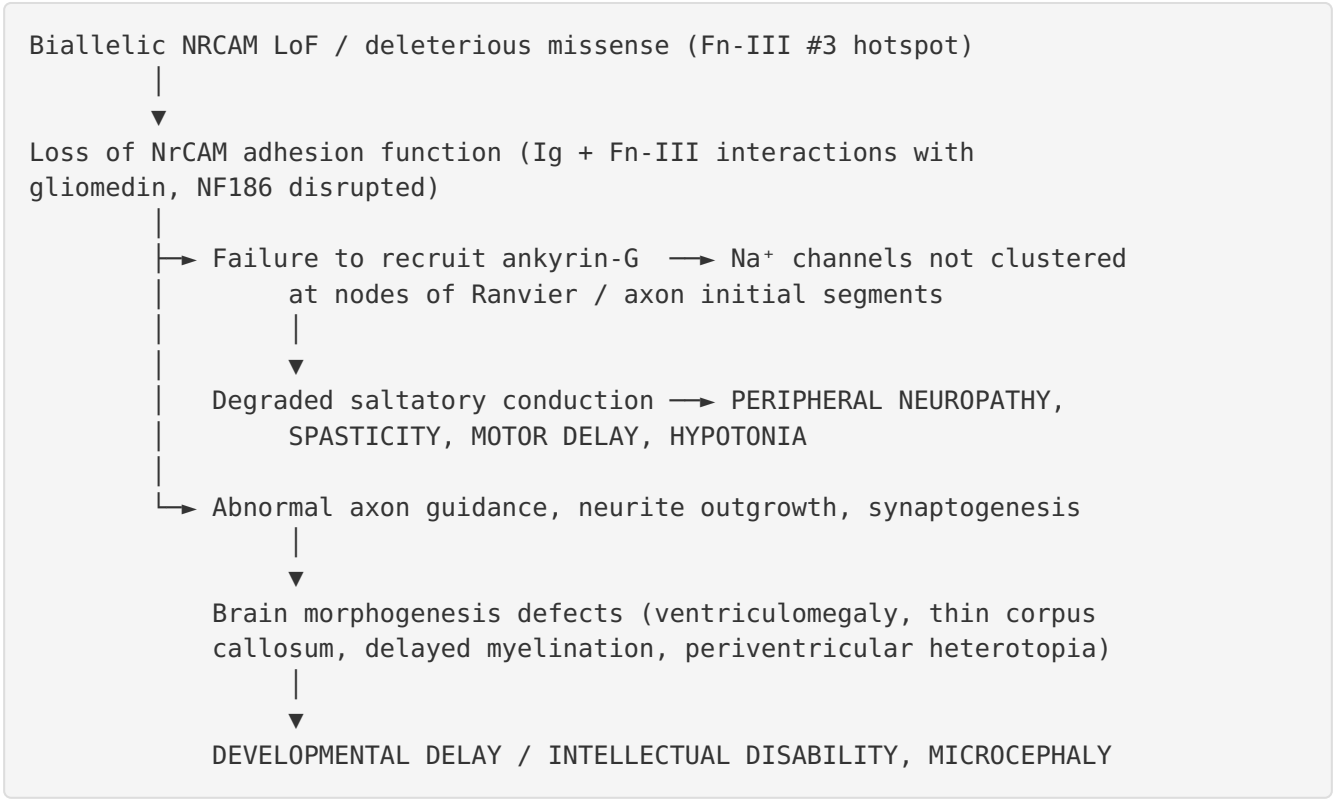
5. Environmental Information

Not applicable. NEDNMSA is a monogenic recessive disorder with **no established environmental factors, lifestyle contributors, or infectious triggers.**

6. Mechanism / Pathophysiology

The core mechanism is **failure of node-of-Ranvier and axon-initial-segment assembly plus disrupted axon guidance** (Findings 2, 4, 5).

Causal chain:



- **Upstream:** loss of NrCAM adhesion; failure of the gliomedin–NF186–NrCAM glial clustering signal.
- **Downstream:** ankyrin-G / Na^+-channel declustering → conduction failure; axon-guidance/synaptic defects → structural brain anomalies.
- **Cell types (CL terms):** neurons (CL:0000540), myelinating Schwann cells (CL:0002573), oligodendrocytes (CL:0000128), hypothalamic tanycytes (Moore 2022).
- **Biological processes (GO terms):** node of Ranvier assembly / GO:0033268; axon guidance / GO:0007411; cell adhesion / GO:0007155; myelination / GO:0042552; neuron projection development / GO:0031175; regulation of sodium ion transmembrane transport.
- **Subcellular compartments (GO CC):** node of Ranvier (GO:0033268), axon initial segment (GO:0043194), plasma membrane (GO:0005886), paranode region of axon (GO:0033270).
- **Molecular pathways:** L1-family cell-adhesion/axon-guidance signaling; ankyrin-G/βIV-spectrin cytoskeletal scaffolding. (NrCAM is also a Wnt-pathway target in cancer contexts — not relevant to NEDNMSA pathogenesis.)
- **Metabolic / immune involvement: not implicated.**

7. Anatomical Structures Affected

- **Organ level (UBERON):** brain (UBERON:0000955), peripheral nervous system / peripheral nerve (UBERON:0000010, UBERON:0001021), spinal cord (UBERON:0002240); secondary: skeletal system — vertebral column (UBERON:0001130), hip joint (UBERON:0001464), foot (UBERON:0002387); eye (UBERON:0000970).
- **Body systems:** nervous (central + peripheral), musculoskeletal, ophthalmologic.
- **Tissue/cell level:** nervous tissue, skeletal muscle (secondary, via denervation/hypotonia), connective/skeletal tissue; targeted cells — neurons, Schwann cells, oligodendrocytes (Findings 2, 4).
- **Subcellular:** node of Ranvier, axon initial segment, axolemma (Finding 2).
- **Specific sites / lateralization:** corpus callosum (UBERON:0002336), lateral ventricles (ventriculomegaly), cerebellar vermis (UBERON:0004720), periventricular zone; anomalies are typically **bilateral/symmetric** where reported.

8. Temporal Development

- **Onset:** congenital / neonatal (hypotonia, structural anomalies) to early-childhood (developmental delay); onset pattern is **chronic/insidious**, not acute.
- **Progression:** neurodevelopmental features are largely **static**; peripheral neuropathy and orthopedic features (e.g., scoliosis) may be **slowly progressive**. No defined disease stages.
- **Course:** chronic, lifelong. **No remission.** Severity variable and not determined by variant type (Finding 7).
- **Critical periods:** prenatal/early-postnatal neurodevelopment (axon guidance, myelination) is the window of vulnerability; no proven intervention window exists.

9. Inheritance and Population

- **Epidemiology: prevalence and incidence unknown** (ultra-rare; ~11 reported individuals; no registry).
- **Inheritance: autosomal recessive**; biallelic homozygous or compound-heterozygous *NRCAM* variants (Findings 1, 3).
- **Penetrance:** presumed high/complete in biallelic carriers (all reported biallelic individuals affected), though small n limits certainty.
- **Expressivity: variable** (severity independent of variant type; Finding 7).
- **Anticipation / mosaicism:** not reported / not applicable (no repeat expansion).

- **Founder effects:** none established; **consanguinity** is a recurring factor (multiple homozygous families).
- **Carrier frequency:** not formally estimated; heterozygous LoF alleles are tolerated per gnomAD constraint (Finding 3).
- **Demographics:** no ethnic predilection established; the small cohort spans multiple families/populations. **Sex ratio** not established (expected ~1:1 for autosomal recessive). Age distribution: pediatric at ascertainment.

10. Diagnostics

- **Genetic testing (primary):** trio-based **whole-exome (WES)** or **whole-genome sequencing (WGS)** is the diagnostic gold standard; targeted *NRCAM* analysis / neurodevelopmental gene panels can confirm. Chromosomal microarray/karyotype are typically normal (this is a sequence-level disorder, not a CNV syndrome).
- **Electrophysiology: EMG/nerve conduction studies** documenting axonal and/or demyelinating peripheral neuropathy (Finding 7).
- **Imaging: brain MRI** — thin corpus callosum, ventriculomegaly, delayed myelination, periventricular heterotopia (Findings 6, 7).
- **Laboratory/biomarkers: no specific biochemical biomarker**; diagnosis rests on genotype + phenotype.
- **Clinical criteria:** no formal consensus criteria; diagnosis is molecular + clinical gestalt.
- **Differential diagnosis:** other autosomal-recessive neurodevelopmental syndromes with neuropathy/spasticity and skeletal features (e.g., L1CAM-spectrum disorders, other L1-family conditions, hereditary motor-sensory neuropathies with CNS involvement, arthrogryposis-associated neurodevelopmental disorders). Molecular testing distinguishes them.
- **Screening:** no population newborn screening; **cascade carrier testing** of at-risk relatives is appropriate once a familial variant is known.

11. Outcome/Prognosis

- **Survival/mortality:** no disease-specific mortality data; the disorder is **not reported as lethal in childhood**, but survival statistics are unavailable (n too small).
- **Morbidity/function:** significant lifelong disability driven by intellectual disability, motor impairment, neuropathy/spasticity, feeding difficulty, and orthopedic complications (scoliosis, hip dysplasia).

- **Complications:** feeding failure/failure-to-thrive (G-tube ~22%), orthopedic deterioration, contractures, visual impairment (cataract/optic atrophy/retinal detachment).
- **Recovery potential:** none (structural/developmental); supportive care can improve function.
- **Prognostic factors:** severity is **variable and not predicted by variant type** (Finding 7); no validated prognostic biomarkers.

12. Treatment

No disease-specific pharmacotherapy, gene therapy, cell therapy, RNA therapy, or targeted/immunotherapy exists. No clinical trials (NCT) are registered. Management is **supportive and multidisciplinary** (Finding 7):

- **Supportive/rehabilitative (NCIT-type interventions):** physical therapy (NCIT:C15216), occupational therapy, speech therapy; nutritional support / gastrostomy feeding for failure-to-thrive.
- **Symptomatic pharmacotherapy:** antispasticity agents (e.g., baclofen) for spasticity; standard management of seizures/behavioral symptoms as needed (no disorder-specific evidence).
- **Surgical/interventional:** orthopedic correction of scoliosis, hip dysplasia, and foot deformities; ophthalmologic surgery (e.g., cataract, retinal detachment) as indicated.
- **Pharmacogenomics / personalized medicine:** not applicable / not developed.

13. Prevention

- **Primary prevention:** none for the genetic cause; **genetic counseling** for consanguineous or carrier families.
- **Secondary/tertiary prevention:** early developmental intervention; surveillance for and management of scoliosis, hip dysplasia, feeding, and ophthalmologic complications.
- **Genetic screening: carrier testing, cascade screening**, and **prenatal/preimplantation genetic diagnosis** available once a familial variant is identified.
- **Public health / immunization / behavioral / prophylaxis:** not applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs (Finding 8):** mouse *Nrcam* (Gene 319504; txid10090), rat *Nrcam* (Gene 497815; txid10116), zebrafish *nrcama* (Gene 556537; txid7955; paralog *nrcamb*). NrCAM is an L1-family CAM (paralogs *L1CAM*, *CHL1*, *NFASC*).
- **Natural disease in other species: no naturally occurring NRCAM-equivalent disorder** is catalogued (e.g., in OMIA) — the disease is known only from engineered/experimental models, not spontaneous animal disease.
- **Comparative biology:** node-of-Ranvier assembly and NrCAM function are **highly evolutionarily conserved** across mammals and teleosts, validating cross-species modeling.
- **Zoonotic potential:** not applicable (genetic disorder).

15. Model Organisms

- **Mouse (*Mus musculus*, MGI):** Nrcam-null mice — disturbed olfactory-nerve axon guidance, altered ventricular-system and cerebellar-vermis size (Heyden 2008); tanycyte differentiation/neurogenesis defects (Moore 2022); combined gliomedin+NrCAM loss — node disintegration, conduction slowing (Amor 2014). **Recapitulation:** good for axon-guidance, brain-structural, and nodal/conduction phenotypes.
- **Zebrafish (*Danio rerio*, ZFIN):** nrcama loss-of-function used to corroborate the human gene–disease link (Kurolap 2022).
- **In vitro:** murine Nrcam-deficient cells — abnormal neurite outgrowth, synaptogenesis, and node-of-Ranvier formation (Finding 4).
- **Model types available:** knockout mice; morphant/mutant zebrafish; primary neuronal cultures. Humanized/conditional/iPSC-organoid models are **not yet reported** for this disorder.
- **Limitations:** models capture axonal/nodal and brain-structural biology but not the full human skeletal spectrum; small human cohort limits genotype–phenotype validation.

Mechanistic Model / Interpretation

NEDNMSA is best understood as an **axonal cell-adhesion / node-of-Ranvier assembly disorder**. NrCAM sits at the intersection of two conserved neurodevelopmental processes: (1) **axon guidance and neurite/synapse formation** during brain morphogenesis, and (2) **nodal/**

AIS assembly required for saltatory conduction. Biallelic loss of NrCAM function — whether through truncating variants or missense variants that disrupt the third Fn-III domain's protein interactions — degrades both processes simultaneously. This dual role explains the disorder's characteristic **combination of central (intellectual disability, brain malformations) and peripheral (neuropathy, hypotonia, spasticity) features**, with skeletal abnormalities arising secondary to the neuromuscular deficit and developmental disruption.

Layer	Observation	Supporting evidence
Genetic	Biallelic *NRCAM* LoF/missense; recessive	Kurolap 2022, Elahi 2023, gnomAD
Protein	3rd Fn-III domain missense hotspot; interaction disruption	Kurolap 2022 (Q92823)
Molecular	Failed gliomedin–NF186–NrCAM → ankyrin-G/Na^+-channel declustering	Lustig 2001, Eshed 2005, Amor 2014
Cellular	Abnormal neurite outgrowth, synaptogenesis, node formation	Kurolap 2022 (in vitro)
Organ	Axon-guidance defects, ventriculomegaly, vermis changes	Heyden 2008 (mouse), zebrafish
Clinical	DD/ID, hypotonia, neuropathy/spasticity, skeletal anomalies	Kurolap 2022, HPO

The convergence of population-genetic constraint (recessive signature), conserved animal-model phenotypes, and human clinical/molecular data yields a **coherent, well-supported causal narrative** with no major internal contradictions.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
35108495	Bi-allelic *NRCAM* variants cause NDD (Kurolap 2022)	Human + zebrafish + in vitro	**Defining paper**; establishes gene–disease link, phenotype, Fn-III hotspot
36606341	Bi-allelic *NRCAM* LoF, second report (Elahi 2023)	Human	Independent confirmation; variable severity
24719088	Gliomedin+NrCAM maintain nodal Na^+ channels (Amor 2014)	Mouse	Direct mechanistic link: node loss → conduction defect
11728309	Nr-CAM/neurofascin cluster ankyrin-G, Na^+ channels (Lustig 2001)	In vitro	NrCAM role in node formation
16039564	Gliomedin mediates node assembly (Eshed 2005)	In vitro	Glial ligand for NrCAM/NF186
18588951	Nrcam/CHL1 mutant axon guidance + brain anatomy (Heyden 2008)	Mouse	Axon-guidance + ventricle/ vermis defects
35464310	NrCAM regulates hypothalamic tanycytes (Moore 2022)	Mouse	NrCAM in neurogenesis
17548513	Nodes/AIS are ankyrin-G-dependent domains	In vitro	Nodal assembly framework
17709431	Neurofascin assembles AIS ECM	In vitro	AIS/brevican context

Non-NEDNMSA context (excluded from pathogenesis): *NRCAM* is separately dysregulated in gliomas via CNV/methylation (PMID: 41663200) and overexpressed in colorectal cancer (PMID: 21718388) as a Wnt target — these are **somatic/oncologic roles unrelated to the germline recessive Mendelian disorder** and are noted only to avoid conflation.

Limitations and Knowledge Gaps

1. **Extremely small evidence base (~11 individuals).** All human phenotype frequencies derive from ≤10 patients; percentages are indicative, not population estimates.
2. **No epidemiology.** Prevalence, incidence, carrier frequency, sex ratio, and geographic distribution are unknown; no Orphanet code or registry exists.
3. **No natural-history or QoL data.** Progression rate, life expectancy, and validated QoL metrics are undefined.
4. **Genotype–phenotype correlation unresolved.** Severity is not predicted by variant type, but the sample is too small to establish modifiers.
5. **No disease-specific therapy or trials.** Management is empirical/supportive.
6. **Mechanistic gaps.** The precise contribution of each missense variant to specific interaction disruptions, and the relative weight of central vs. peripheral pathology, remain to be functionally dissected. No human iPSC/organoid model yet exists.
7. **Ontology mapping incomplete.** No dedicated ICD-11/MeSH/Orphanet identifiers.

Proposed Follow-up Experiments / Actions

1. **International matchmaking (GeneMatcher, Matchmaker Exchange)** to expand the cohort, refine phenotype frequencies, and enable genotype–phenotype analysis.
2. **Functional validation of Fn-III #3 missense variants** — in vitro binding assays (NrCAM–gliomedin/NF186), node-of-Ranvier reconstitution, and structural modeling (AlphaFold + PDB comparison) to classify VUS per ACMG/AMP.
3. **Patient-derived iPSC neurons/organoids and myelinating co-cultures** to model node assembly and conduction deficits in a human context.
4. **Conditional / knock-in mouse models** carrying human missense alleles to test genotype-specific severity and evaluate rescue.
5. **Systematic natural-history study** (developmental, EMG/NCS, MRI, orthopedic, ophthalmologic surveillance) with standardized QoL instruments.
6. **Apply for Orphanet/ICD-11 codes** and establish a patient registry to support future epidemiology and trials.

7. **Cascade carrier screening and genetic-counseling protocols** for consanguineous families with a known variant, including prenatal/PGD options.

Report compiled from 8 confirmed findings and 34 reviewed papers across 5 investigation iterations. Evidence types are labeled throughout as human clinical, model organism, in vitro, or computational.
