MTSS2-Related Neurodevelopmental Disorder (IDDOF): Comprehensive Disease Characteristics Report

Disease: MTSS2-Related Neurodevelopmental Disorder **Causal gene: MTSS2** (also known as *MTSS1L* / *ABBA*), chromosome 16q22.1 **Identifiers:** OMIM:620086 · MONDO:0859303 · Synonyms: IDDOF (Intellectual developmental disorder with ocular anomalies and facial dysmorphism); MTSS2-related disorder **Inheritance:** Autosomal dominant (recurrent de novo missense) **Report date:** 2026-11-16

Summary

MTSS2-Related Neurodevelopmental Disorder is an ultra-rare, autosomal-dominant Mendelian condition caused by a single recurrent de novo missense variant, NM_138383.3:c.2011C>T, p.(Arg671Trp), in the gene MTSS2 (also called *MTSS1L* or *ABBA*), located at chromosome 16q22.1. The gene symbol should not be confused with its paralog *MTSS1* (the tumour-suppressor "missing-in-metastasis"); this report concerns *MTSS2*, which encodes the inverse-BAR (I-BAR) membrane-deforming protein ABBA. Despite more than 50 MTSS2 variants being catalogued in ClinVar, p.Arg671Trp is the **only established pathogenic allele** — every reported patient to date (approximately 10 individuals across three clinical reports) carries this identical heterozygous change, which arises de novo and has been confirmed by trio exome sequencing. The disease is listed in OMIM under the acronym **IDDOF** (Intellectual Developmental Disorder with Ocular anomalies and Facial dysmorphism).

The clinical phenotype is a recognizable, mostly non-progressive neurodevelopmental syndrome: **global developmental delay with language-predominant impairment, mild intellectual disability, microcephaly (or relative microcephaly), ophthalmological anomalies, and mild facial dysmorphism**, with variable additional features including hypotonia, seizures, autism/behavioral disorders, feeding difficulties, poor coordination, and rare cardiac, renal/genitourinary, and gastrointestinal malformations. Brain MRI typically

shows non-specific findings. The disorder is lifelong but not neurodegenerative, and management is entirely supportive and multidisciplinary; no targeted or disease-modifying therapy exists.

Mechanistically, MTSS2/ABBA is a neuronal **inverse-BAR (I-BAR) membrane-deforming protein** of the IRSp53–MIM (IMD) family that binds PI(4,5)P_2-rich membranes and ATP-actin monomers to generate negative membrane curvature, filopodia, and dendritic-spine protrusions. The p.Arg671Trp residue lies in the protein's C-terminal region, **adjacent to the WH2 actin-binding domain and outside the membrane-deforming I-BAR domain**. Functional studies in *Drosophila* show the variant is a **partial loss-of-function allele that also behaves as a toxic/dominant-negative** when over-expressed, consistent with gnomAD constraint data that argue against simple haploinsufficiency. MTSS2 is strongly brain-enriched (GTEx: highest expression in cerebellum, cortex, and hippocampus), and ABBA is especially abundant in GABAergic parvalbumin-positive interneurons and radial glia — cell types whose dysfunction plausibly links the molecular lesion to the neurodevelopmental phenotype.

Section-by-Section Report

1. Disease Information

MTSS2-Related Neurodevelopmental Disorder is a **monogenic (Mendelian) syndromic intellectual disability** first delineated in 2022. It is characterized by the combination of developmental delay, mild intellectual disability, ocular anomalies, microcephaly, and facial dysmorphism, which gave rise to its OMIM designation IDDOF.

Key identifiers:

Resource	Identifier
OMIM (phenotype)	620086 (IDDOF)
OMIM (gene)	616951 (MTSS2)
MONDO	MONDO:0859303
Gene (HGNC)	HGNC:25094 (MTSS2)
Entrez Gene	92154
Ensembl	ENSG00000132613
dbSNP (variant)	rs753688777
ClinVar (variant)	Variation ID 977756
OMIM allelic variant	616951.0001

Synonyms / alternative names: IDDOF; MTSS2-related disorder; MTSS2-related neurodevelopmental disorder. The gene itself has alternative symbols *MTSS1L* and *ABBA* (Actin-Bundling protein with BAIAP2 homology, Actin-regulator A).

Source of information: All knowledge is derived from **aggregated disease-level resources and individual patient case reports** (OMIM, ClinVar, and ~3 peer-reviewed clinical reports describing ~10 patients), not from large EHR or registry datasets. This is an ultra-rare disorder with a small, well-characterized patient population.

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2. Etiology

Primary cause — genetic. The disorder is caused exclusively by a **recurrent de novo heterozygous missense variant** in MTSS2: NM_138383.2/3:c.2011C>T, p.(Arg671Trp). There is no known environmental, infectious, or multifactorial contribution.

> "Here we report five individuals with the same heterozygous de novo variant in MTSS2 (GenBank: NM_138383.2: c.2011C>T [p.Arg671Trp]) identified by exome sequencing." — PMID: 36067766

Genetic risk factors. The single causal variant is the only genetic risk factor. No susceptibility loci or modifier genes have been reported. Because every patient carries the identical allele, the disorder is best described as a **specific-allele (hypermutable site / recurrent de novo) disorder** rather than an allelic series.

Environmental risk factors, protective factors, and gene–environment interactions. Not applicable / none identified. As a de novo Mendelian disorder, there are no documented environmental risk or protective factors, no dietary or lifestyle modifiers, and no reported gene–environment interactions. Parental-origin and parental-age effects have not been formally established in the small cohort, though de novo missense variants in general show a paternal-age bias (not demonstrated specifically here).

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3. Phenotypes

The phenotype is a **syndromic neurodevelopmental disorder** with a consistent core and a variable periphery.

> "The individuals present with global developmental delay, mild intellectual disability, ophthalmological anomalies, microcephaly or relative microcephaly, and shared mild facial dysmorphisms." — PMID: 36067766
>
> "Common clinical features included developmental delay (particularly affecting language skills), mild intellectual disability, learning disabilities, microcephaly, non-specific brain MR findings and facial dysmorphisms." — PMID: 39890443

Core phenotype (highly consistent across patients):

Phenotype	Type	Suggested HPO term	Onset	Frequency	Severity
Global developmental delay (language-predominant)	Developmental	HP:0001263; HP:0000750 (Delayed speech/ language)	Infancy/ childhood	Most/all	Mild–moderate
Intellectual disability	Cognitive/ behavioral	HP:0001249; HP:0001256 (mild)	Childhood	Most	Mild
Microcephaly / relative microcephaly	Clinical sign	HP:0000252	Congenital/ early	Frequent	Mild
Ophthalmological anomalies	Clinical sign	HP:0000478	Congenital/ childhood	Frequent	Variable
Facial dysmorphism	Physical	HP:0001999	Congenital	Most	Mild

Variable / less frequent features:

Phenotype	Suggested HPO term	Notes
Hypotonia	HP:0001252	Variable
Seizures (generalized febrile/afebrile; generalized EEG anomalies)	HP:0001250; HP:0002197	Subset of patients
Autism spectrum disorder / psychiatric disorders	HP:0000717; HP:0000708	Subset
Growth delay	HP:0001510	Variable
Feeding / chewing difficulties	HP:0011968	Variable
Skeletal anomalies	HP:0000924	Variable
Poor coordination	HP:0002370	Variable
Learning disabilities	HP:0001328	Common
Non-specific brain MRI findings	HP:0002011	Common
Hearing loss (rare)	HP:0000365	Rare
Cardiac malformations (rare)	HP:0001627	Rare
Renal/genitourinary malformations (rare)	HP:0000119	Rare
Gastrointestinal anomalies (rare)	HP:0011024	Rare

Onset, progression, severity: Onset is **congenital to early childhood**. The disorder is **static/non-progressive** (developmental, not neurodegenerative), with intellectual disability generally in the **mild** range. A monozygotic-twin report (PMID: 37657631) confirmed the recurrent variant and further delineated the phenotype.

Quality-of-life impact: No formal EQ-5D/SF-36/PROMIS data exist for this ultra-rare disorder. Based on phenotype, impact is driven chiefly by language delay, learning disability, and (in a subset) seizures and behavioral/autistic features; most individuals require educational support and multidisciplinary follow-up but have mild cognitive impairment compatible with substantial functional independence.

4. Genetic / Molecular Information

Causal gene: MTSS2 / MTSS1L / ABBA (HGNC:25094; Entrez 92154; Ensembl ENSG00000132613; gene MIM 616951). The gene maps to **chromosome 16q22.1** (GRCh38 chr16:70,661,204–70,686,086, minus strand).

The pathogenic variant:

Attribute	Detail
cDNA / protein	NM_138383.3:c.2011C>T, p.(Arg671Trp)
Variant type	Missense (single-nucleotide substitution)
ClinVar classification	**Pathogenic / Likely pathogenic** (criteria provided, multiple submitters, no conflicts; last evaluated 2026-01-26)
ClinVar Variation ID	977756
dbSNP	rs753688777
OMIM allelic variant	616951.0001
ClinGen allele	CA283508188
GRCh38 SPDI	NC_000016.10:70663909:G:A (chr16:70,663,910)
Zygosity / origin	Heterozygous; **de novo** (germline)
Functional consequence	**Partial loss-of-function + dominant-negative/toxic**

Of more than 50 other MTSS2 variants in ClinVar, essentially all are classified as **Uncertain significance** or **Likely benign** — no other pathogenic allele is established, making this a true single-variant disorder.

Allele frequency: The variant is extremely rare (present in dbSNP as rs753688777 but effectively absent/ultra-rare in population databases such as gnomAD), consistent with a recurrent de novo origin.

gnomAD constraint (mechanistic inference): MTSS2 (ENSG00000132613) shows **pLI = 0.43** and **LOEUF = 0.55** (observed/expected LoF = 27/67.1 = 0.40), i.e., only *moderate* LoF constraint, and it is **not missense-constrained overall** (missense z = −1.35; oe_mis = 1.10). The fact that a

single recurrent missense is pathogenic while the gene tolerates loss-of-function reasonably well argues **against simple haploinsufficiency** and in favor of a **specific-missense / dominant-negative** mechanism.

Modifier genes, epigenetic information, chromosomal abnormalities: None reported. No modifier loci, methylation signatures, or large structural/cytogenetic changes are associated with this specific disorder.

Somatic vs germline: The variant is **germline** (de novo, confirmed absent in unaffected parents and co-twin). No somatic/oncogenic role for this allele is described.

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5. Environmental Information

Not applicable. As a purely genetic de novo disorder, there are no established environmental factors, lifestyle factors, or infectious agents that cause, trigger, or modify MTSS2-Related Neurodevelopmental Disorder. No toxicological (CTD), occupational, or dietary contributions are documented.

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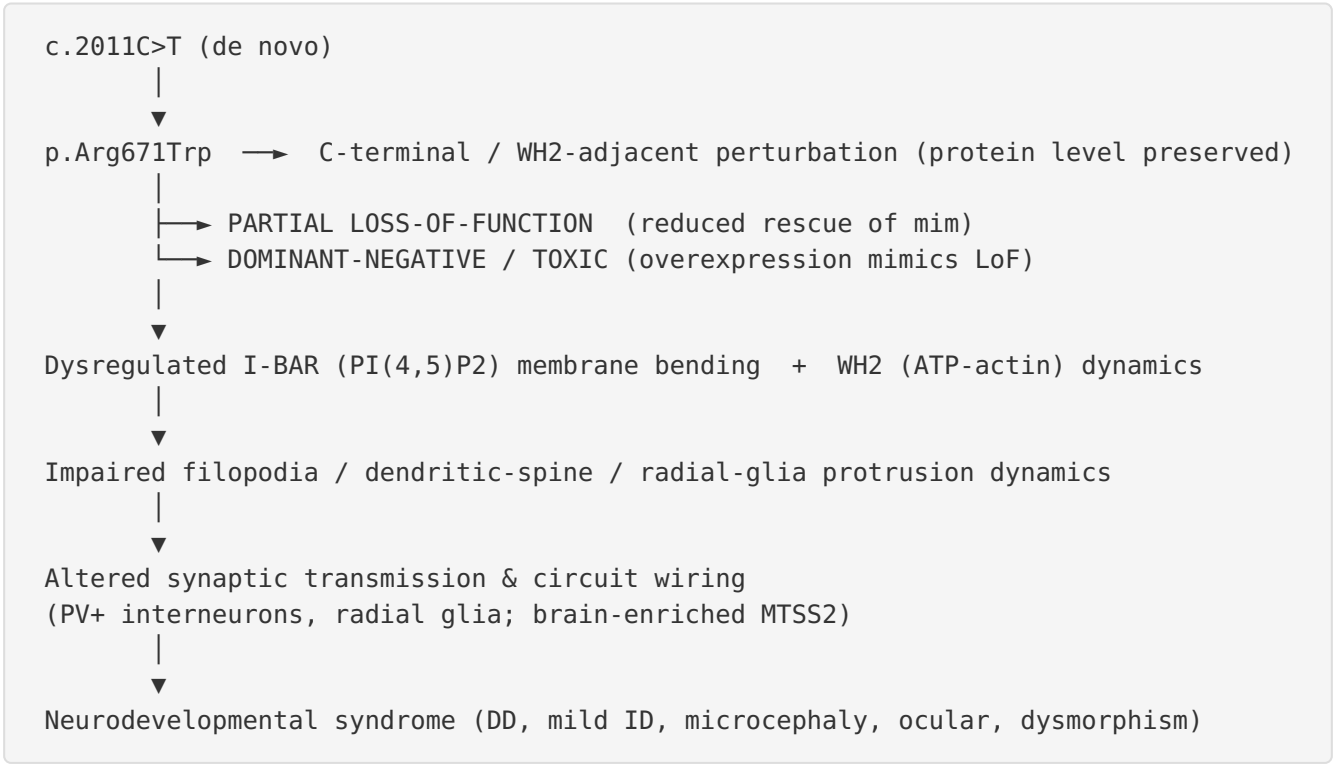
6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **De novo substitution c.2011C>T in MTSS2** introduces **p.Arg671Trp** into the ABBA protein — the initiating molecular lesion. *(Demonstrated.)*
2. **→ leads to** an altered ABBA protein in which the C-terminal region **adjacent to the WH2 actin-binding domain** (not the I-BAR domain) is perturbed; protein abundance is essentially unchanged (fibroblast immunoblots show no significant level change). *(Demonstrated.)*
3. **→ results in** impaired ABBA function — the variant **partially fails to rescue** loss of the *Drosophila* ortholog *mim*, i.e., it is a **partial loss-of-function allele**, AND when over-expressed it **reproduces the mim-LoF defects**, i.e., it is **toxic / dominant-negative**. *(Demonstrated in vivo in Drosophila.)*
4. **→ leads to** dysregulated **PI(4,5)P_2-dependent membrane deformation and ATP-actin–dependent protrusion dynamics** (I-BAR/WH2 coupling), the normal biochemical activities

of ABBA. *(Inferred from biochemistry of ABBA; the exact biophysical effect of Arg671Trp is not directly demonstrated.)*

5. **→ results in** disturbed formation/initiation of **filopodia, lamellipodia-like protrusions, and dendritic spines** in neurons, and impaired radial-glia process extension. *(Inferred from ABBA cell-biology studies.)*
6. **→ leads to** altered **synaptic transmission and neuronal/circuit connectivity**, especially in brain-enriched cell types (GABAergic parvalbumin-positive interneurons; radial glia). In *Drosophila*, mim loss reduces synaptic transmission, impairs locomotion, and shortens lifespan. *(Demonstrated in model; extrapolated to human.)*
7. **→ results in** the clinical neurodevelopmental phenotype: developmental delay, mild intellectual disability, microcephaly, ocular anomalies, and facial dysmorphism. *(Clinical correlation; causal link inferred.)*



Molecular and cellular detail

Molecular pathways / protein function. MTSS2/ABBA is a member of the **IRSp53–MIM (IMD / I-BAR) family**. Its N-terminal **IMD (I-BAR) domain (aa 1–252)** senses and generates **negative membrane curvature** by clustering **PI(4,5)P_2** and (for MIM/ABBA specifically) inserting an amphipathic helix into the bilayer; its C-terminal **WH2 domain (aa 719–736)** binds **ATP-actin monomers**.

> "ABBA binds ATP-actin monomers with high affinity and deforms PtdIns(4,5)P(2)-rich membranes in vitro through its WH2 and IM domains, respectively." — PMID: 18413296
>
> "I-BAR domains induce strong PI(4,5)P(2) clustering upon membrane binding, bend the membrane through electrostatic interactions ... MIM and ABBA I-BARs additionally insert an amphipathic helix into the membrane bilayer, resulting in larger tubule diameter in vitro and more efficient filopodia formation in vivo." — PMID: 19150238

Position of Arg671. UniProt Q765P7 (canonical 747 aa) places Arg671 in the **intrinsically disordered C-terminal moiety (between disordered stretches aa 638–664 and 691–720), just N-terminal to the WH2 domain and well outside the I-BAR domain** (sequence context QLAAN**R**HSLVE). This locates the lesion in a **regulatory region coupling membrane deformation to actin dynamics**, rather than in the core membrane-binding module — refining the mechanism toward disrupted WH2/actin regulation.

Cellular processes. Actin-driven membrane protrusion, filopodia initiation, dendritic-spine formation, and radial-glia extension. ABBA localizes to the **edges of membrane protrusions** and promotes dendritic-spine/filopodia initiation; MTSS1 (paralog) similarly cooperates with the **WAVE-2 and Arp2/3 complexes** at dynamic actin protrusions (PMID: 36871754).

Cell types (CL suggestions). GABAergic parvalbumin-positive interneuron (CL:0000617 / neuron CL:0000540), radial glial cell (CL:0000681), hippocampal neuron.

> "we found that ABBA was highly expressed in GABAergic inhibitory neurons, such as parvalbumin-positive interneurons in the hippocampus" — PMID: 41359239
>
> "elevated expression of the variant, but not the reference MTSS2 cDNA, led to similar defects as observed by mim LoF, suggesting that the variant is toxic and may act as a dominant-negative allele" — PMID: 36067766

Suggested GO terms: plasma membrane bending (GO:0097320), positive regulation of filopodium assembly (GO:0051491), dendritic spine development (GO:0060996), actin filament bundle assembly (GO:0051017), regulation of synaptic transmission (GO:0050804), phosphatidylinositol-4,5-bisphosphate binding (GO:0005546), actin monomer binding (GO:0003785).

Metabolic changes, immune involvement, epigenetics: No metabolic, immune, or epigenetic dysregulation is implicated — the mechanism is a **cytoskeletal/membrane-dynamics defect**, not a metabolic or inflammatory one.

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7. Anatomical Structures Affected

Organ / system level. The disorder is predominantly a disease of the **central nervous system** (nervous system; UBERON:0001016). Primary structure: **brain** (UBERON:0000955), with brain-enriched MTSS2 expression highest in **cerebellum** (UBERON:0002037), **cerebral cortex** (UBERON:0000956), and **hippocampus** (UBERON:0002421). Secondary/variable involvement: **eye** (UBERON:0000970; ocular anomalies), **skull/craniofacial skeleton** (microcephaly, dysmorphism; UBERON:0003129), and rarely **heart** (UBERON:0000948), **kidney/genitourinary tract** (UBERON:0002113), and **gastrointestinal tract** (UBERON:0001555).

Tissue / cell level. Nervous tissue; affected cell populations include **GABAergic parvalbumin-positive interneurons** (CL:0000617), **radial glial cells** (CL:0000681), and neurons broadly (CL:0000540).

Subcellular level. The pathology centers on the **plasma membrane** (GO:0005886) and the **actin cytoskeleton** / **cortical cytoskeleton** (GO:0015629), particularly at **membrane protrusions** / **filopodia** / **dendritic spines** (GO:0030175; GO:0043197).

Localization / lateralization. CNS involvement is **bilateral and symmetric**; microcephaly is global. No consistent lateralization is reported.

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8. Temporal Development

- **Onset:** Congenital to early childhood; a **chronic, insidious** neurodevelopmental onset (developmental delay recognized in infancy/toddlerhood).
- **Progression: Static/non-progressive** developmental disorder — not neurodegenerative. Intellectual disability is stable and generally mild; brain MRI findings are non-specific and non-progressive.
- **Course / duration: Lifelong (chronic).** Seizures, where present, may follow their own course but the core cognitive phenotype is stable.
- **Remission:** No spontaneous remission; features are developmental and persistent.

- **Critical periods:** Early childhood is the key window for developmental/educational intervention (speech, occupational, physical therapy), though no disease-modifying intervention exists.

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9. Inheritance and Population

- **Inheritance pattern: Autosomal dominant**, arising as a **recurrent de novo** event. All reported cases are de novo; the variant is absent in unaffected parents and in a co-twin (PMID: 37657631).

> "Exome sequencing identified the recurrent c.2011C>T (p.Arg671Trp) variant in the MTSS2 gene. The mother and the other twin tested negative for the pathogenic variant" — PMID: 37657631

- **Penetrance / expressivity:** Among carriers of p.Arg671Trp, penetrance appears **complete** for the neurodevelopmental phenotype, with **variable expressivity** in the peripheral features (seizures, autism, organ malformations).
- **Epidemiology: Ultra-rare.** Only ~10 individuals have been reported worldwide; prevalence and incidence are not formally estimable (far below Orphanet's practical reporting thresholds). No prevalence/incidence per 100,000 can be stated.
- **Genetic anticipation / mosaicism / founder effects / consanguinity / carrier frequency: Not applicable.** As a recurrent de novo dominant variant: no anticipation, no founder effect, no role for consanguinity, and effectively no carrier frequency. Germline mosaicism has not been reported but is theoretically possible for recurrence counseling.
- **Population demographics:** No ethnic predilection, no geographic clustering, and no established sex bias have emerged from the small cohort. Cases reported across multiple populations/countries.

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10. Diagnostics

Primary diagnostic modality — genetic testing. Diagnosis rests on **identifying the recurrent de novo variant NM_138383.3:c.2011C>T, p.(Arg671Trp)** in MTSS2.

- **Whole-exome sequencing (WES):** The method by which the disorder was discovered and by which essentially all cases are diagnosed; **trio WES** establishes de novo status. High utility.
- **Whole-genome sequencing (WGS):** Equally capable of detecting the variant; used where WES is non-diagnostic.
- **Gene panels / single-gene testing:** MTSS2 should be included on intellectual-disability/neurodevelopmental-disorder panels. Targeted single-gene/single-variant testing for p.Arg671Trp is appropriate for confirmation or cascade purposes.
- **Chromosomal microarray, karyotyping, FISH, mtDNA, repeat-expansion testing:** Not diagnostic for this single-nucleotide missense disorder (negative/non-contributory).

Clinical / laboratory / imaging tests. No specific biomarker, blood/urine test, enzyme assay, or metabolic abnormality is diagnostic. **Brain MRI** typically shows **non-specific findings** and is used to exclude alternatives. **EEG** is indicated where seizures are present (may show generalized anomalies). Ophthalmologic examination documents ocular anomalies.

Clinical criteria / differential diagnosis. There are no formal consensus diagnostic criteria; diagnosis is molecular. The differential includes other syndromic mild intellectual-disability disorders with microcephaly, ocular anomalies, and facial dysmorphism — distinguished definitively by identifying the MTSS2 variant.

Screening. No newborn or population carrier screening exists or is warranted given the de novo origin and rarity.

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11. Outcome / Prognosis

- **Survival / mortality:** No evidence of reduced life expectancy or disease-specific mortality; the disorder is **not life-limiting** based on reported cases. (Note: the *Drosophila* mim-LoF model shows reduced lifespan, but this does not translate to a documented human mortality signal.)
- **Morbidity / disability:** Morbidity is driven by **mild intellectual disability, language/learning impairment**, and, in subsets, **seizures, autism/behavioral issues, and feeding/**

coordination difficulties. Long-term functional impairment is generally **mild**, compatible with substantial independence with support.

- **Disease course / complications:** Static developmental course; complications relate to epilepsy management and rare organ malformations (cardiac, renal, GI) where present.
- **Prognostic factors:** Presence and control of seizures, degree of language impairment, and any organ malformations modulate individual outcome. No molecular prognostic biomarkers exist (single invariant allele).
- **Quality-of-life measures:** No validated disease-specific QoL instruments have been applied.

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12. Treatment

There is no targeted, disease-modifying, or curative therapy. Management is **entirely supportive, symptomatic, and multidisciplinary.**

- **Pharmacotherapy:** No specific drug. **Antiseizure medications** (NCIT:C264 Anticonvulsant Agent) for patients with epilepsy, chosen per seizure type; standard management of behavioral/psychiatric symptoms as needed. No pharmacogenomic guidance specific to this disorder.
- **Advanced therapeutics (gene/cell/RNA/targeted/immuno): None available or in trials.** No gene therapy, ASO, or targeted agent exists; the dominant-negative/partial-LoF mechanism would complicate simple gene-replacement strategies.
- **Surgical/interventional:** Only as needed for associated malformations (e.g., cardiac, genitourinary) — not disorder-specific.
- **Supportive & rehabilitative (mainstay): Speech and language therapy** (NCIT:C15402), **occupational therapy** (NCIT:C15339), **physical therapy** (NCIT:C15417), special educational support, developmental follow-up, nutritional/feeding support, and ophthalmologic and audiologic management.
- **Experimental treatments:** No registered clinical trials (ClinicalTrials.gov) for MTSS2-Related Neurodevelopmental Disorder as of this report.
- **Treatment strategy:** Individualized, symptom-directed, with coordinated neurodevelopmental, neurological, ophthalmologic, and (as needed) cardiac/renal/GI care.

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13. Prevention

- **Primary prevention:** None possible — the causal variant is **de novo**, so there are no modifiable risk factors and no way to prevent occurrence.
- **Secondary prevention / screening:** No population or newborn screening is applicable. Early developmental screening enables early supportive intervention but does not alter the underlying disorder.
- **Genetic counseling:** For families, **recurrence risk is low** (de novo event), though **germline mosaicism** cannot be entirely excluded, so empiric recurrence risk is slightly above background. **Prenatal / preimplantation genetic testing** for the specific variant is feasible for a known familial case. Counseling should convey the de novo nature, low (but non-zero) recurrence risk, and the variable expressivity of peripheral features.
- **Tertiary prevention:** Standard management of complications (seizure control, developmental/educational support) to minimize disability.

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14. Other Species / Natural Disease

- **Orthologs / comparative biology:** The disorder's mechanism is studied through orthologs rather than naturally occurring animal disease. The *Drosophila melanogaster* ortholog is **mim** (*Missing in metastasis*), expressed in most CNS neurons and a subset of glia; its loss reduces lifespan, impairs locomotion, and reduces synaptic transmission — providing the functional assay that classified p.Arg671Trp as a partial LoF/dominant-negative allele. Mammalian orthologs exist in mouse (*Mtss1l*/*Mtss2*/Abba) and other vertebrates.
- **Natural disease in other species / breeds / zoonosis: None reported.** No naturally occurring MTSS2-related disease is described in companion animals, livestock, or wildlife (no OMIA entry for a natural MTSS2 disorder), and there is no transmission/zoonotic component (genetic disorder).
- **Evolutionary conservation:** The I-BAR (IMD) and WH2 domain architecture and membrane-deforming/actin-binding functions are **conserved across metazoans**, underpinning cross-species functional-rescue experiments.

Suggested NCBI Taxonomy references: *Homo sapiens* (9606); *Drosophila melanogaster* (7227); *Mus musculus* (10090).

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15. Model Organisms

Model	System	What it showed	Reference
Drosophila melanogaster (*mim* ortholog)	Invertebrate, in vivo	*mim* is expressed in most CNS neurons and a subset of glia; **loss shortens lifespan, impairs locomotion, reduces synaptic transmission**. Human reference MTSS2 cDNA **rescues** mim-LoF; **c.2011C>T shows decreased rescue (partial LoF)** and **toxic/dominant-negative overexpression**.	PMID: 36067766
Cultured neurons / cells (ABBA)	In vitro	ABBA binds ATP-actin and deforms PI(4,5)P_2 membranes; localizes to protrusion edges; promotes dendritic-spine/filopodia initiation; highly expressed in PV+ interneurons.	PMID: 18413296; PMID: 41359239
Mouse (Mtss1L)	Mammalian, in vivo	Mtss1L is an exercise-induced I-BAR protein that enhances hippocampal synaptic function (structural plasticity), supporting a synaptic role.	PMID: 31232686
MDCK epithelial cells (MTSS1 paralog)	In vitro	Establishes I-BAR/WAVE-2/Arp2/3 protrusion biology relevant to the family.	PMID: 36871754

Genetic model types available: *Drosophila* LoF/rescue and overexpression lines; cell-based overexpression/localization systems. **No dedicated knock-in mouse carrying p.Arg671Trp has been reported** — a clear gap.

Phenotype recapitulation / limitations: The *Drosophila* model recapitulates **neuronal/synaptic dysfunction** and discriminates allele behavior (partial LoF vs dominant-negative), but does not model the human syndromic features (microcephaly, ocular anomalies, facial dysmorphism). A mammalian knock-in model would be needed to study those.

Mechanistic Model / Interpretation

MTSS2-Related Neurodevelopmental Disorder is a **monoallelic, single-variant cytoskeletal/membrane-dynamics disorder of the developing brain.** The unifying model is:

> A de novo p.Arg671Trp substitution in the C-terminal, WH2-adjacent regulatory region of the brain-enriched I-BAR protein ABBA/MTSS2 produces a protein that is both partially non-functional and actively interfering (dominant-negative), degrading the normal coupling between PI(4,5)P_2 membrane deformation and ATP-actin–driven protrusion formation. In neurons — especially GABAergic PV+ interneurons and radial glia that express MTSS2 most highly — this impairs filopodia, dendritic-spine, and process dynamics, perturbing synaptic connectivity and brain growth, and manifesting as developmental delay, mild ID, microcephaly, ocular anomalies, and facial dysmorphism.

Two independent lines of evidence converge on a **non-haploinsufficiency** mechanism: (1) *functional* — the variant both under-rescues and is toxic on overexpression in *Drosophila*; and (2) *population-genetic* — gnomAD shows MTSS2 is only moderately LoF-constrained (LOEUF 0.55) and not missense-constrained, so a tolerated-LoF gene producing disease via one recurrent missense points to a specific gain-of-abnormal-function/dominant-negative effect rather than dosage loss. The structural localization of Arg671 **beside the WH2 actin module** (not in the I-BAR membrane domain) sharpens this: the lesion likely disrupts actin-regulatory output rather than membrane binding per se. Brain-predominant expression (GTEx) — highest in cerebellum, cortex, and hippocampus, with near-zero expression in blood and lymphocytes — provides the tissue specificity that confines an otherwise generic cytoskeletal defect to a neurodevelopmental phenotype.

Evidence Base

PMID	Title (abbrev.)	Role in this report
36067766	*The recurrent de novo c.2011C>T missense variant in MTSS2 causes syndromic intellectual disability*	**Primary/landmark.** Defines the disorder, the recurrent de novo variant, the core 5-feature phenotype, CNS-high expression, and the partial-LoF + dominant-negative functional mechanism in *Drosophila*.
39890443	*MTSS2-Related Disorder: Refining the Phenotype in Four New Cases and Literature Review*	Confirms and refines the recurrent phenotype (language-predominant DD, mild ID, microcephaly, non-specific MRI, dysmorphism).
37657631	*MTSS2-related neurodevelopmental disorder: Further delineation of the phenotype*	Independent confirmation of the recurrent variant and its de novo nature (twin study).
41359239	*Expression, Subcellular Localization, and Mechanistic Analysis of ABBA*	Identifies PV+ interneurons as a key ABBA-expressing cell type; protrusion-edge localization.
18413296	*ABBA regulates plasma-membrane and actin dynamics to promote radial glia extension*	Defines ABBA's dual biochemical activities (WH2 actin-binding; IM/I-BAR membrane deformation).
19150238	*Molecular mechanisms of membrane deformation by I-BAR domain proteins*	Mechanism of I-BAR PI(4,5)P_2 clustering and filopodia induction; MIM/ABBA amphipathic-helix insertion.
31232686	*Exercise-induced enhancement of synaptic function triggered by Mtss1L*	Mammalian evidence for Mtss1L's synaptic/structural-plasticity role in hippocampus.
36871754	*Actin-rich lamellipodia-like protrusions contribute to epithelial junction integrity*	I-BAR/WAVE-2/Arp2/3 protrusion biology (paralog MTSS1) contextualizing the family.

Limitations and Knowledge Gaps

1. **Tiny cohort (~10 patients).** All phenotype frequencies, prognosis, and QoL statements are based on case reports, not registries — effect sizes and penetrance are provisional.
2. **Single allele.** Because only p.Arg671Trp is pathogenic, there is no allelic series to map genotype–phenotype correlations, and the generalizability of the mechanism to hypothetical other MTSS2 variants is unknown.
3. **Mechanism partly inferred.** The biophysical effect of Arg671Trp on WH2/actin coupling is **inferred from protein-structure localization and Drosophila rescue data**, not directly measured in human neurons; direct demonstration (e.g., in patient iPSC-derived neurons) is lacking.
4. **No mammalian knock-in model** of p.Arg671Trp exists to test syndromic features (microcephaly, ocular, craniofacial).
5. **No biomarkers, no QoL/natural-history data, no trials, no targeted therapy.**
6. **Epidemiology unquantified** (no prevalence/incidence; no sex ratio).

Proposed Follow-up Experiments / Actions

1. **Generate a knock-in mouse (Mtss2^R671W/+)** to test recapitulation of microcephaly, cortical/cerebellar development, PV+-interneuron function, and behavior.
2. **Patient iPSC-derived cortical and PV-interneuron models** to measure dendritic-spine density, filopodia dynamics, and synaptic physiology — directly testing the dominant-negative hypothesis in human neurons.
3. **Structure–function assays** of recombinant ABBA^R671W: in vitro PI(4,5)P_2 membrane deformation, ATP-actin binding (WH2), and co-assembly, to localize the functional defect to the actin-regulatory arm.
4. **Establish an international patient registry** (GeneMatcher/MatchMaker Exchange) to refine phenotype frequencies, natural history, penetrance, and QoL, and to detect any additional pathogenic MTSS2 alleles.
5. **Deep-mutational-scanning** of MTSS2 to define which residues (if any) beyond Arg671 could be pathogenic, and to clarify why this site is uniquely recurrent.

6. **Dominant-negative rescue strategies** (e.g., allele-specific knockdown of the mutant transcript) as a conceptual therapeutic proof-of-principle, given that haploinsufficiency appears tolerated.

Report compiled from OMIM, ClinVar, gnomAD, GTEx, UniProt, and primary literature (8 papers, 7 confirmed findings). Evidence types span human clinical case reports, Drosophila and mouse in-vivo models, in-vitro biochemistry, and computational/constraint analysis.
