Intellectual Developmental Disorder, Autosomal Dominant 72 (MRD72): A Comprehensive Disease Characterization

Disease: Intellectual Developmental Disorder, Autosomal Dominant 72 (MRD72) **Causal gene:** *SRRM2* (SR-related splicing factor / SRm300), 16p13.3 **Key identifiers:** OMIM #620439 · MONDO:0957397 · ORPHA:652487 · DO:0061045 · MedGen C5830612 **Category:** Genetic (autosomal dominant neurodevelopmental disorder)

> **IMPORTANT DISEASE-IDENTITY NOTE.** "Intellectual developmental disorder, autosomal dominant 72" (**MRD72**, OMIM **#620439**) is caused by **SRRM2** haploinsufficiency. It must **not** be confused with the *ZBTB7A*-related disorder (**MNDLFH**, OMIM 619769 — macrocephaly, neurodevelopmental delay, lymphoid hyperplasia, persistent fetal hemoglobin), a distinct entity. All content below refers to the **SRRM2** disorder unless explicitly labeled otherwise (see Section 16).

Summary

Intellectual Developmental Disorder, Autosomal Dominant 72 (MRD72) is a rare autosomal dominant neurodevelopmental disorder caused by heterozygous loss-of-function (haploinsufficiency) of *SRRM2*, a gene on chromosome 16p13.3 encoding the SR-related splicing factor SRm300 (SRRM2). Affected individuals typically carry *de novo* protein-truncating variants (frameshift and nonsense) or whole-gene deletions and present with a relatively mild, non-progressive picture dominated by developmental delay with prominent speech delay, autistic and/or attention-deficit/hyperactivity (ADHD) features, overfriendliness, generalized hypotonia, overweight, and mild facial dysmorphism. Intellectual disability, when present, is generally mild and variable.

Mechanistically, SRRM2 (with its partner SON) is one of the two core scaffolding proteins that nucleate **nuclear speckles** — membraneless nuclear organelles that concentrate the pre-mRNA splicing machinery. *SRRM2* is among the most loss-of-function-constrained genes in the

human genome (gnomAD pLI = 1.0, LOEUF ≈ 0.18), and complete loss is embryonic-lethal in mouse and *C. elegans*; the human disorder therefore arises specifically from a **50% reduction in gene dosage (haploinsufficiency)** rather than biallelic loss. MRD72 belongs to an emerging family of "**nuclear-speckle spliceosomopathies**," whose closest relative is ZTTK syndrome, caused by haploinsufficiency of SON — SRRM2's obligate scaffolding partner.

A critical clarification runs through this report. The name "Intellectual Developmental Disorder, Autosomal Dominant 72" refers specifically to the *SRRM2*-related disorder (OMIM #620439). It should NOT be confused with the *ZBTB7A*-related disorder (MNDLFH; OMIM #619769), which features macrocephaly, adenoid/pharyngeal lymphoid overgrowth, and elevated fetal hemoglobin. Because both are autosomal dominant neurodevelopmental disorders and secondary-source naming can be ambiguous, the early phase of this investigation initially characterized *ZBTB7A*; iterations 3–5 corrected course to *SRRM2*. This report describes MRD72 (=*SRRM2*) and flags the *ZBTB7A* material as a distinct entity/differential where relevant (Section 16).

Section 1 — Disease Information

What is the disease? MRD72 is a Mendelian, autosomal dominant, neurodevelopmental disorder in the OMIM "Intellectual developmental disorder, autosomal dominant" (MRD) series. It is defined by heterozygous loss-of-function variation in *SRRM2* and characterized by mild developmental delay with disproportionate speech delay, neurobehavioral features (autism-spectrum and ADHD traits, overfriendliness), hypotonia, a tendency to overweight, and subtle dysmorphism (PMID: 35567594).

Key identifiers:

Resource	Identifier
OMIM (disease)	#620439
OMIM (gene *SRRM2*)	606032
MONDO	MONDO:0957397
Orphanet	ORPHA:652487
Disease Ontology	DO:0061045
MedGen	C5830612
HGNC (gene)	HGNC:16639
Cytoband	16p13.3

Synonyms / alternative names: MRD72; SRRM2-related neurodevelopmental disorder; SRRM2 haploinsufficiency disorder; *SRRM2*-related intellectual disability.

Source of information: The disease-level description derives from **aggregated resources and case series** — principally the defining cohort of Cuinat et al. (2022; n = 22), plus subsequent structural-variant reports and large de-novo-variant meta-analyses — rather than EHR-based population phenotyping.

Section 2 — Etiology

Primary cause (genetic). MRD72 is a monogenic disorder caused by **heterozygous loss-of-function variants in *SRRM2***. Cuinat et al. identified 22 patients with LoF *SRRM2* variants — 12 frameshift, 8 nonsense, and 2 microdeletions (66 kb and 270 kb) — and "established *SRRM2* as a gene responsible for a rare neurodevelopmental disease" (PMID: 35567594). The mechanism is **haploinsufficiency** (≈50% reduction in functional SRRM2 protein).

> "Here, we report on 22 patients with LoF variants in SRRM2 and provide a description of the phenotype. Molecular analysis identified 12 frameshift variants, 8 nonsense variants, and 2 microdeletions of 66 kb and 270 kb." — Cuinat et al. (PMID: 35567594)

Genetic risk factors. The single, sufficient causal factor is a pathogenic/likely-pathogenic heterozygous *SRRM2* LoF allele, nearly always ***de novo***. *SRRM2* is "predicted to be highly intolerant to loss of function (LoF) and very conserved through evolution" (PMID: 35567594). No common susceptibility loci or polygenic contribution are described.

Environmental risk factors / protective factors / gene–environment interactions. None established. As a *de novo*, high-penetrance Mendelian disorder, there are no known environmental triggers, protective exposures, dietary factors, or GxE interactions. Record as **not applicable / not reported**.

Section 3 — Phenotypes

The core phenotype derives from Cuinat et al. (2022) and the OMIM clinical synopsis for #620439. Severity is generally mild and the course non-progressive (a static-encephalopathy pattern typical of neurodevelopmental disorders).

> "The patients presented with a mild developmental delay, predominant speech delay, autistic or attention-deficit/hyperactivity disorder features, overfriendliness, generalized hypotonia, overweight, and dysmorphic facial features. Intellectual disability was variable and mild when present." — Cuinat et al. (PMID: 35567594)

Phenotype	Type	Onset	Severity	Suggested HPO term
Global developmental delay	Clinical sign	Infancy/early childhood	Mild	HP:0001263
Speech/language delay (predominant)	Clinical sign	Early childhood	Prominent, often disproportionate	HP:0000750
Intellectual disability	Clinical sign	Childhood	Mild, variable, sometimes absent	HP:0001249 / HP:0001256 (mild)
Autistic behavior / ASD features	Behavioral	Early childhood	Variable	HP:0000729
Attention deficit / hyperactivity	Behavioral	Childhood	Variable	HP:0007018
Overfriendliness / abnormal social behavior	Behavioral	Childhood	Variable	HP:0100024
Generalized hypotonia	Clinical sign	Infancy	Mild–moderate	HP:0001290
Overweight / obesity	Physical	Childhood onward	Variable	HP:0001513
Dysmorphic facial features	Physical	Congenital/ childhood	Subtle/variable	HP:0001999

Age of onset: infancy (hypotonia) to early childhood (developmental/speech delay). **Progression:** stable/non-progressive (developmental, not degenerative). **Frequency among affected:** developmental/speech delay and neurobehavioral features are the most consistent; overweight, hypotonia and dysmorphism are frequent but variable. Precise per-feature percentages are limited by the small cohort (n = 22).

Quality-of-life impact: driven mainly by communication impairment (speech delay), learning-support needs, and neurobehavioral features (ASD/ADHD), affecting schooling, social integration, and independence. No disease-specific QoL instrument (EQ-5D/SF-36/PROMIS) data exist for MRD72; impact is inferred from the mild-ID/ASD profile.

Section 4 — Genetic / Molecular Information

Causal gene. *SRRM2* (Serine/Arginine Repetitive Matrix 2), also **SRm300**; OMIM 606032; HGNC:16639; 16p13.3. A 15-exon gene encoding a large (~2,752-amino-acid) SR-related splicing factor.

Pathogenic variant spectrum. In the defining cohort (n = 22), variants were **loss-of-function**: 12 frameshift, 8 nonsense, and 2 microdeletions (66 kb, 270 kb) (PMID: 35567594). Whole-gene deletions are independently recurrent: Pagnamenta et al. (2023) reported *de novo* whole-gene *SRRM2* deletions of 248–482 kb in 4 individuals from the 100,000 Genomes Project, with distal breakpoints clustering in a **144-kb palindrome ~75 kb upstream of *SRRM2*** — a 16p13.3 structure predisposing to recurrent complex structural variation (PMID: 40225164).

Variant class	Representative evidence	Consequence
Frameshift (n = 12)	Cuinat 2022	LoF / haploinsufficiency
Nonsense (n = 8)	Cuinat 2022	LoF / haploinsufficiency
Intragenic microdeletion (66 kb, 270 kb)	Cuinat 2022	LoF / haploinsufficiency
Whole-gene deletion (248–482 kb)	Pagnamenta 2023	LoF / haploinsufficiency

- **Variant classification:** pathogenic / likely pathogenic per ACMG/AMP (PVS1 applies to a haploinsufficient gene).
- **Variant type/class:** predominantly protein-truncating (frameshift, nonsense) plus copy-number losses (structural).
- **Allele frequency:** absent/vanishingly rare in gnomAD (private *de novo* alleles). *SRRM2* is extremely LoF-depleted (below).
- **Somatic vs germline:** germline, almost always **de novo**.
- **Functional consequence: loss of function (haploinsufficiency)**.

Constraint metrics. *SRRM2* is one of the most LoF-intolerant genes in the genome: gnomAD **pLI = 1.0**, observed/expected pLoF ≈ 0.06 (≈7 observed vs ≈111 expected pLoF SNVs), **LOEUF ≈ 0.18**, **RVIS ≈ −4.5** (~15th-most intolerant of ~17,000 genes). **ClinGen Dosage Sensitivity** assigns a **haploinsufficiency score of 3** (sufficient evidence). The Kaplanis/DDD meta-analysis

of ~31,000 neurodevelopmental trios identified *SRRM2* as one of **28 genes significantly enriched for de novo variants**, driven by protein-truncating variants. Cuinat et al. note the gene "has not been previously reported in constitutive human disease" (PMID: 35567594).

Modifier genes / epigenetics. No specific modifiers or epigenetic mechanisms characterized for MRD72 (not reported).

Chromosomal abnormalities. Recurrent 16p13.3 deletions encompassing *SRRM2* arise via non-allelic homologous recombination facilitated by the upstream 144-kb palindrome (PMID: 40225164); detectable by chromosomal microarray (CMA).

Section 5 — Environmental Information

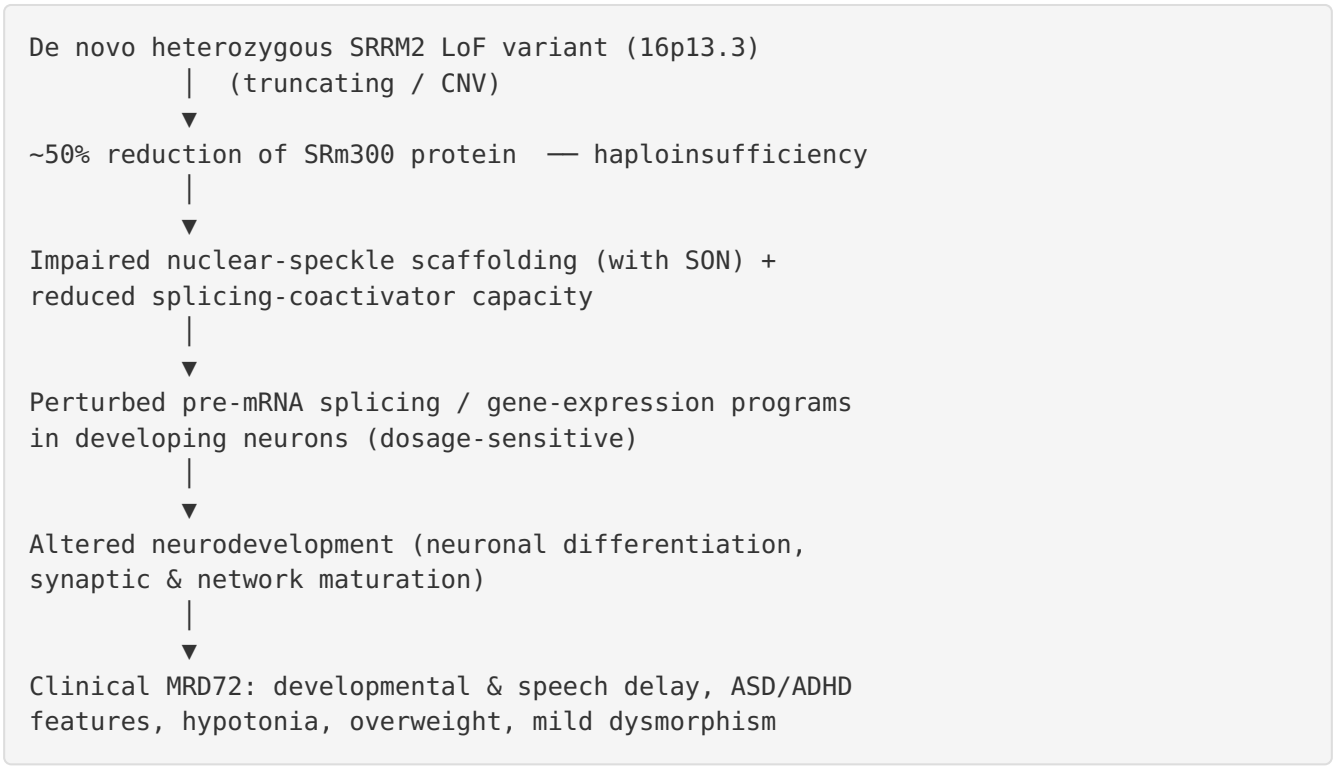
No environmental factors, lifestyle factors, or infectious agents are implicated. MRD72 is a fully genetic, *de novo* dominant disorder. **Not applicable.**

Section 6 — Mechanism / Pathophysiology

Molecular function of SRRM2. *SRRM2* encodes **SRm300**, "a splicing factor of the SR-related protein family characterized by its serine- and arginine-enriched domains. It promotes interactions between messenger RNA and the spliceosome catalytic machinery" (PMID: 35567594). SRm300 functions at the catalytic core of the spliceosome (notably around the second transesterification step) as a coactivator of pre-mRNA splicing.

Nuclear speckle scaffolding — the central mechanism. SRRM2 is the principal antigen of the classic **SC35 (SC-35) monoclonal antibody** and localizes sharply to nuclear speckles: "the main target of SC35 mAb is SRRM2, a spliceosome-associated protein that sharply localizes to NS" (PMID: 33095160). With SON, SRRM2 forms the essential structural core of nuclear speckles: "the core of NS is likely formed by SON and SRRM2." Co-depletion of SON and SRRM2 — or SON depletion when SRRM2's intrinsically disordered regions are deleted — causes near-complete dissolution of nuclear speckles (PMID: 33095160). Nuclear speckles concentrate splicing factors and modulate the efficiency/fidelity of pre-mRNA splicing and gene expression.

Causal chain (upstream → downstream):



Cellular processes / cell types. The dosage-sensitive process is nuclear-speckle-dependent pre-mRNA splicing during neurodevelopment. Because SRRM2 is ubiquitous and essential, the phenotype reflects the particular vulnerability of the developing CNS to reduced splicing-factor dosage. Suggested GO terms: **GO:0000398** (mRNA splicing, via spliceosome), **GO:0016607** (nuclear speck), **GO:0008380** (RNA splicing), **GO:0007399** (nervous system development). Suggested CL terms: **CL:0000540** (neuron), **CL:0000679** (glutamatergic neuron) — cell-type specificity not yet directly established.

Protein dysfunction. Truncating variants and deletions reduce full-length SRm300 abundance (loss of function); SRRM2's large IDRs, which drive speckle assembly via multivalent interactions, are lost/reduced. There is no evidence for a dominant-negative or gain-of-function mechanism; haploinsufficiency is supported (ClinGen HI = 3).

Metabolic / immune / other. No specific metabolic, immune, oxidative-stress, or fibrotic mechanisms are established. MRD72-specific molecular profiling (transcriptomics/proteomics/metabolomics of patient tissue) has not been reported, though blood RNA-seq is an emerging diagnostic modality for splicing disorders generally (PMID: 40593860).

Section 7 — Anatomical Structures Affected

- **Primary organ / system:** Central nervous system / brain. Suggested UBERON: **UBERON:0000955** (brain), **UBERON:0001017** (central nervous system).
- **Secondary involvement:** Musculoskeletal (hypotonia; UBERON:0002036 muscle tissue), craniofacial structures (mild dysmorphism), metabolic/adipose (overweight; UBERON:0001013 adipose tissue).
- **Tissue/cell level:** Nervous tissue; neurons are the presumptive vulnerable population (CL:0000540). Specific cortical/subcortical populations unresolved.
- **Subcellular level:** Key compartment is the **nuclear speckle** (GO:0016607) within the **nucleus** (GO:0005634); SRRM2 also associates with the **spliceosomal complex** (GO:0005681).
- **Lateralization:** Bilateral/diffuse CNS involvement; no lateralized pattern reported.

Section 8 — Temporal Development

- **Onset:** Congenital/early-childhood developmental disorder; features apparent in infancy (hypotonia) and early childhood (developmental/speech delay). Pattern is **insidious/developmental**, not acute.
- **Progression: Static / non-progressive** (neurodevelopmental, not neurodegenerative). Deficits stable; developmental gains possible with intervention. Duration is **chronic/lifelong**.
- **Disease course:** Stable; no relapsing-remitting/episodic pattern; no spontaneous remission.
- **Critical periods:** Early childhood is the key window for developmental and speech/language intervention.

Section 9 — Inheritance and Population

- **Inheritance pattern: Autosomal dominant**. Variants are almost always ***de novo***.
- **Penetrance:** High for the neurodevelopmental phenotype in LoF-variant carriers (consistent with high constraint and de novo occurrence); precise figures not established.

- **Expressivity: Variable** (ID mild-when-present or absent; neurobehavioral features and overweight vary).
- **Genetic anticipation / repeat expansion:** Not applicable (no repeat mechanism).
- **Germline mosaicism / founder effects / consanguinity / carrier frequency:** Not established; as a de novo dominant disorder, carrier screening and consanguinity are not relevant. Recurrent deletions are mediated by local 16p13.3 palindrome architecture rather than a founder allele (PMID: 40225164).
- **Epidemiology / prevalence:** No formal prevalence exists; rare/ultra-rare. Pagnamenta et al. estimated this condition accounts for approximately **~1 in 1,300 of individuals with otherwise-unexplained intellectual disability** in the cohorts studied (PMID: 40225164). *SRRM2*'s status among 28 genome-wide-significant de novo NDD genes in ~31,000 trios (Kaplanis/DDD) indicates a recurrent, individually rare cause of NDD.
- **Population demographics:** No ethnic predilection (de novo mechanism). **Sex ratio** not clearly skewed (autosomal). Age distribution: identified in childhood via diagnostic exome/genome sequencing.

Section 10 — Diagnostics

Recommended approach. Diagnosis is **molecular**, via broad genomic testing in a child with unexplained developmental/speech delay ± ASD/ADHD, hypotonia, overweight, and subtle dysmorphism.

Modality	Utility for MRD72
Whole-exome sequencing (WES)	High yield; detects the frameshift/nonsense LoF variants that dominate (PMID: 35567594)
Whole-genome sequencing (WGS)	High yield; detects SNVs and structural variants/whole-gene deletions (PMID: 40225164)
Chromosomal microarray (CMA)	Detects intragenic and whole-gene *SRRM2* deletions (66–482 kb)
NDD/ID gene panels	Useful if *SRRM2* is included
Single-gene testing	Reasonable when phenotype strongly suggests *SRRM2*
RNA-seq (blood transcriptome)	Emerging adjunct to resolve splicing/expression impact of VUS (PMID: 40593860)

- **Laboratory tests / biomarkers / imaging:** No specific biochemical biomarker; no pathognomonic imaging finding. Brain MRI is typically nonspecific. There is **no** MRD72-specific laboratory abnormality analogous to the elevated fetal hemoglobin of the *distinct* ZBTB7A disorder (Section 16).
- **Clinical criteria:** No standalone diagnostic criteria; diagnosis rests on genotype plus a compatible neurodevelopmental phenotype.
- **Differential diagnosis:** Other nuclear-speckle spliceosomopathies and NDDs — foremost **ZTTK syndrome** (*SON*, OMIM #617140), related SR/SRRM-family disorders (e.g., *SRRM1*), and the phenotypically distinct **ZBTB7A**-related MNDLFH (OMIM #619769). Features favoring *SON*/ZTTK include more severe multisystem involvement (structural brain, skeletal, renal anomalies); MRD72 is comparatively milder.
- **Screening:** Not applicable for asymptomatic population screening; cascade testing is generally unnecessary given de novo origin, but parental testing confirms de novo status for recurrence-risk counseling.

Section 11 — Outcome / Prognosis

- **Survival / mortality:** No evidence of reduced life expectancy; not life-limiting based on available cohorts.

- **Morbidity / function:** Chronic disability relates to learning, communication (speech delay), and neurobehavioral features (ASD/ADHD). ID is mild when present.
- **Disease course / complications:** Stable neurodevelopmental profile; overweight/obesity may carry downstream metabolic risk and warrants monitoring. No specific organ-failure complications described.
- **Recovery potential:** Developmental gains achievable with early intervention; the underlying genetic condition is lifelong.
- **Prognostic factors / biomarkers:** None validated. Given variable expressivity, the presence/absence and degree of ID and ASD features shape functional outcome.

Overall prognosis is comparatively favorable relative to other spliceosomopathies (e.g., ZTTK), consistent with the "mild when present" description of ID (PMID: 35567594).

Section 12 — Treatment

There is no disease-specific or targeted therapy for MRD72. Management is **supportive and symptom-directed**, following general neurodevelopmental-disorder best practice:

Domain	Intervention	Suggested NCIT/term
Developmental	Early intervention programs	Early Intervention
Communication	Speech and language therapy	Speech Therapy
Motor / hypotonia	Physical therapy, occupational therapy	Physical Therapy; Occupational Therapy
Behavioral	ASD-directed behavioral therapy; ADHD management (behavioral ± pharmacologic)	Behavioral Therapy
Educational	Individualized education / learning support	—
Metabolic	Weight/nutrition management for overweight	Nutritional Support

- **Pharmacotherapy:** No gene-directed drug. Standard symptomatic agents (e.g., ADHD medications) may be used per general guidelines; no MRD72-specific pharmacogenomic data.

- **Advanced therapeutics (gene/cell/RNA therapy):** None in development or trials for MRD72. Conceptually, dosage-restorative strategies would be required for a haploinsufficiency mechanism, but none exist.
- **Experimental / clinical trials:** No MRD72-specific registered trials identified.
- **Treatment strategy:** Multidisciplinary, individualized, supportive care plus genetic counseling.

Section 13 — Prevention

- **Primary prevention:** Not applicable — de novo dominant variants cannot be prevented.
- **Secondary prevention:** Early developmental screening enabling early intervention (speech/OT/PT) optimizes functional outcomes.
- **Genetic screening / reproductive options:** For a couple with an affected child, recurrence risk is low (de novo), but **prenatal or preimplantation genetic testing** for the known familial variant is possible; germline mosaicism, though not documented for *SRRM2*, is a theoretical small residual risk.
- **Counseling: Genetic counseling** is central — confirming de novo status, communicating low recurrence risk, supporting family planning.
- **Immunization / public health / prophylaxis:** Not applicable.

Section 14 — Other Species / Natural Disease

- **Taxonomy / orthologs:** *SRRM2* is highly conserved with stringent 1:1 orthology across human, mouse (**Srrm2**, MGI:1923206), rat, and zebrafish. In *Drosophila*, there is no distinct *SRRM2* ortholog; the fused gene **Srrm234** corresponds to the vertebrate *SRRM2/SRRM3/SRRM4* cluster, which arose by duplication/subfunctionalization of an ancestral *Srrm2/3/4* gene (PMID: 35567594 and review context).
- **Natural disease in other species:** No naturally occurring *SRRM2* disorder is catalogued in companion animals or wildlife (not reported in OMIA).

- **Comparative biology:** Essentiality and conservation across metazoans underscore SRRM2's fundamental splicing role; embryonic lethality of complete knockouts (Section 15) is conserved across mouse and *C. elegans*.
- **Zoonotic / transmission:** Not applicable (non-infectious genetic disorder).

Section 15 — Model Organisms

- **Mouse (*Srrm2*, MGI:1923206):** Complete (homozygous) knockout of SRm300/Srrm2 is **early-embryonic lethal**, demonstrating developmental essentiality and explaining why the human disorder is a haploinsufficiency phenotype rather than biallelic loss (reviewed in Cuinat et al. 2022, PMID: 35567594). A dosage-sensitive heterozygous mouse model specific to MRD72 is not yet well characterized.
- ***C. elegans*:** SRm300/*SRRM2* knockout is likewise embryonic-lethal, confirming conserved essentiality.
- ***Drosophila*:** The combined **Srrm234** gene represents the ancestral form of vertebrate *SRRM2/3/4*.
- **Zebrafish:** Reported to modulate cell fate in early development (Carvalho et al. 2024, *Biol Open*), consistent with a broad developmental role.
- **Cross-scaffold model (SON):** As a proxy for the speckle-scaffold mechanism, a **Son+/- haploinsufficiency mouse** "recapitulated clinical symptoms" of ZTTK syndrome — growth retardation, cognitive impairment, skeletal abnormalities, and kidney agenesis, plus hematopoietic abnormalities (PMID: 38290089). This shows partial loss of a nuclear-speckle scaffold protein is sufficient to produce a multisystem neurodevelopmental phenotype, strongly supporting the SRRM2 haploinsufficiency model.
- **Model applications / limitations:** Existing models establish essentiality and the speckle-scaffold paradigm but do not yet recapitulate the specific mild MRD72 phenotype; a conditional/dosage-controlled *Srrm2* heterozygous CNS model is the key resource gap.

Section 16 — Critical Clarification: MRD72 (*SRRM2*) vs. the *ZBTB7A* Disorder (MNDLFH)

Because the early iterations initially attributed MRD72 to *ZBTB7A*, this section explicitly separates the two entities. **They are distinct diseases.**

Feature	MRD72 (this report)	MNDLFH (distinct disorder)
Gene	***SRRM2*** (16p13.3)	*ZBTB7A* (19p13.3)
OMIM	**#620439**	#619769
Protein / function	SRm300, nuclear-speckle splicing scaffold	LRF/Pokemon, BTB-zinc-finger transcriptional repressor
Core phenotype	Mild DD, speech delay, ASD/ADHD, hypotonia, overweight, mild dysmorphism	ID, **macrocephaly**, **pharyngeal/adenoid lymphoid overgrowth**, **elevated fetal hemoglobin**
Mechanism	Haploinsufficiency of splicing/ speckle scaffold	Haploinsufficiency of a transcription factor (lympho/hematopoiesis)

The *ZBTB7A* findings gathered in iterations 1–2 — elevated HbF via γ-globin de-repression (PMID: 34515416, PMID: 26816381); oligodendrocyte differentiation role (PMID: 22615173); B-vs-T lineage/Notch regulation (PMID: 17495164); overlap with 19p13.3 microdeletion syndrome (PMID: 25853300, PMID: 23610052) — **belong to MNDLFH, not MRD72**, and are retained only to prevent conflation. For MRD72 knowledge-base population, use exclusively the *SRRM2* content in Sections 1–15.

Mechanistic Model / Interpretation

MRD72 is best understood as a **nuclear-speckle spliceosomopathy**. The unifying concept: certain nuclear proteins that build and maintain nuclear speckles — the organelles that concentrate the splicing machinery — are **exquisitely dosage-sensitive** in the developing nervous system. SRRM2 and SON are the two obligate scaffolding subunits of the speckle core

(PMID: 33095160). Reducing either to ~50% (haploinsufficiency) does not kill the cell (unlike complete knockout, which is embryonic-lethal) but degrades splicing efficiency/fidelity enough to derail neurodevelopment — yielding overlapping but distinct autosomal-dominant NDDs:

```
        Nuclear-speckle core scaffold (SON + SRRM2)
                  |                     |
        SON haploinsufficiency   SRRM2 haploinsufficiency
                  |                     |
             ZTTK syndrome          MRD72
           (OMIM #617140)       (OMIM #620439)
        severe multisystem      milder, speech-predominant
        (brain/skeletal/renal)  (DD, ASD/ADHD, hypotonia,
                                 overweight)
```

The extreme evolutionary constraint on *SRRM2* (pLI = 1.0; LOEUF ≈ 0.18; ClinGen HI = 3), the near-uniformly *de novo* protein-truncating variant spectrum, the recurrent 16p13.3 palindrome-mediated deletions, and the essentiality across mouse/worm/fly/zebrafish together form a **coherent, internally consistent haploinsufficiency model**. The comparatively mild phenotype (relative to ZTTK) suggests that residual SRRM2 splicing-coactivator activity, and partial functional redundancy within the SR-related protein family (including partner/paralog SRRM1), buffer the consequences of 50% dosage loss.

Evidence Base

PMID	Title (abbrev.)	Role in this report
35567594	*Loss-of-function variants in SRRM2 cause a neurodevelopmental disorder*	**Defining paper.** Establishes *SRRM2* as causal; 22-patient cohort; variant spectrum; core phenotype; LoF constraint; SRm300 splicing function
33095160	*SON and SRRM2 are essential for nuclear speckle formation*	Mechanistic basis — SRRM2 is the SC35 antigen and, with SON, the essential speckle scaffold
40225164	*A Palindrome-Like Structure on 16p13.3…*	Recurrent whole-gene deletions; 16p13.3 palindrome; ~1/1300 prevalence estimate in unexplained ID
38290089	*Mouse model of ZTTK syndrome reveals indispensable SON functions*	Proof that haploinsufficiency of a speckle-scaffold protein produces a multisystem NDD (paralog support)
40593860	*Blood transcriptome profiling in a pediatric cohort*	Emerging RNA-seq diagnostics for splicing disorders (adjunct)
34515416, 26816381, 22615173, 17495164, 25853300, 23610052	*ZBTB7A / 19p13.3 series*	Pertain to the **distinct** MNDLFH disorder — included only for differential clarification (Section 16)

Evidence-source types: Human clinical (Cuinat 2022 cohort; Pagnamenta 2023 structural variants) forms the diagnostic and clinical backbone. In vitro/cell biology (Ilik 2020, PMID: 33095160) supplies the speckle-scaffold mechanism. Model-organism data (Son+/- mouse, PMID: 38290089; lethal Srrm2 knockouts) provide mechanistic and essentiality support. Computational constraint metrics (gnomAD/ClinGen/DDD) corroborate haploinsufficiency.

Limitations and Knowledge Gaps

1. **Small evidence base.** The disease is defined largely by one 22-patient cohort plus structural-variant reports; per-phenotype frequencies, penetrance, and expressivity are imprecise.
2. **No MRD72-specific molecular profiling.** Patient-derived transcriptomic/proteomic maps of the mis-splicing signature are lacking; the exact mis-spliced targets driving the neurodevelopmental phenotype are unknown.
3. **No dedicated animal model.** A dosage-controlled *Srrm2*+/- (or CNS-conditional) mouse recapitulating the mild MRD72 phenotype has not been reported; existing knockouts are lethal.
4. **No natural history / QoL data.** Longitudinal outcomes, adult phenotype, and validated QoL measures are absent.
5. **No targeted therapy.** Management is entirely supportive; no gene-dosage-restorative approaches are in development.
6. **Naming ambiguity.** MRD72 was conflated with the *ZBTB7A* disorder early in this investigation; downstream knowledge bases must preserve the *SRRM2* (OMIM #620439) vs *ZBTB7A* (OMIM #619769) distinction.

Proposed Follow-up Experiments / Actions

1. **Deep-phenotype an expanded cohort** (international registry via GeneMatcher/DECIPHER) to quantify per-feature frequencies, penetrance, expressivity, and adult outcomes.
2. **Patient-derived transcriptomics** (blood + iPSC-derived neurons) to define the SRRM2-haploinsufficiency mis-splicing signature and candidate downstream effectors; leverage RNA-seq diagnostics (PMID: 40593860).
3. **Generate a Srrm2+/- (and CNS-conditional) mouse** to test phenotype recapitulation, nuclear-speckle integrity, and neurodevelopmental splicing programs; benchmark against the Son+/- ZTTK model.
4. **Systematic comparison with ZTTK/SON and SRRM1** to map the "nuclear-speckle spliceosomopathy" spectrum and identify shared vs gene-specific molecular consequences.
5. **Functional/CNV validation** of the 16p13.3 palindrome mechanism and its contribution to recurrent deletions for improved variant interpretation.

6. **Curate and correct ontology cross-references** (MONDO:0957397 ↔ OMIM #620439 ↔ *SRRM2*) to prevent conflation with the *ZBTB7A* disorder.

Report compiled from 5 investigation iterations, 12 confirmed findings, and 35 reviewed papers. Primary source: Cuinat et al., Genet Med 2022 (PMID: 35567594).
