ZMYND11-Related Intellectual Disability, Autosomal Dominant 30 (MRD30): A Comprehensive Disease Characterization

Disease: ZMYND11-related intellectual disability, autosomal dominant 30 (MRD30) **OMIM:** #616083 · **MONDO:** MONDO:0014486 · **Gene:** *ZMYND11* (10p15.3) · **Category:** Mendelian, autosomal dominant

Summary

MRD30 is an ultra-rare, autosomal dominant neurodevelopmental disorder caused by heterozygous loss-of-function (haploinsufficiency) of *ZMYND11* at chromosome 10p15.3. *ZMYND11* is the critical gene of the contiguous 10p15.3 microdeletion syndrome: patients with 10p15.3 deletions and patients with intragenic *ZMYND11* truncating variants share an overlapping core phenotype of hypotonia, intellectual disability/global developmental delay, facial dysmorphism, speech and motor delay, seizures, and significant behavioral problems. An intragenic deletion affecting only the 5′UTR and first two exons confirms that a single functional copy of the gene is insufficient — the mechanism is haploinsufficiency, not a dominant-negative or gain-of-function effect (PMID: 34818214; PMID: 34216016).

Mechanistically, ZMYND11 (also called **BS69** or **BRAM1**) is a **chromatin reader** that specifically recognizes the trimethylated histone variant **H3.3 at lysine 36 (H3.3K36me3)** through its tandem PHD–Bromo–PWWP domains, and additionally carries a C-terminal MYND zinc-finger domain. Reading this histone mark, ZMYND11 fine-tunes RNA polymerase II transcription (elongation control, promoter/initiation occupancy, Pol II pausing) and couples chromatin state to pre-mRNA splicing, mainly regulating intron retention by antagonizing the U5 snRNP component EFTUD2. In the developing human cortex, ZMYND11 loss de-represses latent developmental gene programs, releases restraint on the histone methyltransferase KMT2A, and disrupts a brain-specific RNA isoform switch mediated by the splicing regulator RBFOX2 — collectively impairing cortical progenitor and neuron production (PMID: 25263594; PMID: 41068108; PMID: 41279818).

Clinically, MRD30 is a lifelong, largely **static (non-neurodegenerative)** disorder with congenital-to-early-childhood onset. Neurodevelopmental deficits are essentially fully penetrant; dysmorphic features and epilepsy are variable, with seizure prognosis ranging from spontaneous remission to drug resistance. Most pathogenic variants arise **de novo**, but rare inherited cases from mildly affected parents demonstrate variable expressivity and incomplete penetrance. There is **no curative or gene-specific therapy**; management is symptomatic and multidisciplinary. This report synthesizes 14 confirmed findings from 28 reviewed papers into a complete disease knowledge-base entry across all 15 requested domains.

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1. Disease Information

MRD30 is a Mendelian, monogenic neurodevelopmental disorder in the intellectual-disability spectrum. It is defined molecularly by haploinsufficiency of *ZMYND11* and represents the "pure gene" counterpart of the 10p15.3 microdeletion syndrome, in which *ZMYND11* is the critical dosage-sensitive gene (PMID: 34216016).

Key identifiers (F014):

Resource	Identifier
OMIM	#616083 (Intellectual developmental disorder, autosomal dominant 30; MRD30)
MONDO	MONDO:0014486
Gene (HGNC)	*ZMYND11*, HGNC:29316
NCBI Gene	10778
UniProt	Q15326
Locus	10p15.3
Gene aliases	BS69, BRAM1

Synonyms / alternative names (F014): ZMYND11-related intellectual disability; ZMYND11-related neurodevelopmental disorder; ZMYND11-related syndromic intellectual disability; MRD30; and — for the deletion form — 10p15.3 microdeletion syndrome (of which *ZMYND11* is the critical gene).

Information source type: The knowledge base for MRD30 is derived from **aggregated case reports and small cohorts** plus functional/mechanistic studies (patient-derived iPSC/cortical organoid, mouse ESC/MEF, and zebrafish models), **not** from population-scale EHR datasets (PMID: 34216016). Suggested ontology mapping: **MONDO:0014486**.

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2. Etiology

Disease causal factors (F014): MRD30 etiology is **exclusively genetic**. It is caused by heterozygous loss-of-function or deleterious variants in *ZMYND11* (nonsense, frameshift, canonical splice-site, missense, whole-gene or intragenic deletions) or by 10p15.3 deletions that remove *ZMYND11*. There are **no established environmental, lifestyle, toxic, occupational, or infectious causal or risk factors**, and no known protective factors or gene–environment interactions.

Genetic risk factors: The only risk factor is carriage of a pathogenic *ZMYND11* variant. *ZMYND11* is a highly loss-of-function–intolerant, dosage-sensitive gene; heterozygous LoF is sufficient to cause disease, and pathogenic LoF alleles are essentially absent from population controls (gnomAD) (F013). Variants are distributed across the gene with no precise genotype–phenotype correlation, though missense and LoF classes show partially distinct phenotypic emphases (see Section 4) (PMID: 34216016; PMID: 41820311).

Environmental / lifestyle / infectious factors: None identified or applicable (F014). No CTD/toxicogenomic, NHANES-type lifestyle, or infectious-agent associations are established for this monogenic disorder.

Gene–environment interactions: None reported.

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3. Phenotypes

The MRD30 core phenotype is a syndromic neurodevelopmental disorder. Across cohorts, affected individuals show **hypotonia, intellectual disability/global developmental delay, facial dysmorphism, speech and motor delay, seizures, and significant behavioral problems** (including autism spectrum disorder, ADHD, and aggression) (PMID: 34818214; F003).

> *"patients harboring 10p15.3 microdeletions or pathogenic ZMYND11 truncating variants share similar clinical features including hypotonia, intellectual disability, facial dysmorphisms, speech and motor delays, seizures, and significant behavioral problems"* (PMID: 34818214)

Epilepsy subtypes (F003). In a cohort of ~20 individuals, ZMYND11-associated epilepsy fell into three groups:

Epilepsy group	n	Notes
(i) Atypical benign partial epilepsy (ABPE) / idiopathic focal epilepsy	8	Centrotemporal features
(ii) Generalised epilepsies / infantile epileptic encephalopathy	4	More severe end
(iii) Unclassified	8	—

> *"Individuals with ZMYND11 associated epilepsy fell into three groups: (i) atypical benign partial epilepsy or idiopathic focal epilepsy (n = 8); (ii) generalised epilepsies/infantile epileptic encephalopathy (n = 4); (iii) unclassified (n = 8)"* (PMID: 34216016)

Phenotype characteristics. Onset is congenital to early childhood. **"Neurodevelopmental deficits were invariable. Dysmorphic features were variable."** (PMID: 34216016) — i.e., near-complete penetrance for the neurodevelopmental core, with variable expressivity of dysmorphism and epilepsy. Seizure progression ranges from spontaneous remission to drug-resistant. Individual reports additionally document **sensorineural hearing loss, ataxic gait, a happy disposition (Angelman-like), and rarer features** such as eosinophilic esophagitis and severe allergies.

> *"seizures, global developmental delay, sensorineural hearing loss, hypotonia, dysmorphic features, and other features including a happy disposition and ataxic gait similar to Angelman syndrome"* (PMID: 27626064)

Suggested HPO terms:

Phenotype	HPO term	Frequency / severity
Intellectual disability / global developmental delay	HP:0001249 / HP:0001263	Invariable (near-100%); mild–severe
Hypotonia	HP:0001252	Common
Seizures	HP:0001250	Variable subset; remission to drug-resistant
Delayed speech and language development	HP:0000750	Common
Motor delay	HP:0001270	Common
Autism spectrum disorder / behavioral abnormality	HP:0000729 / HP:0000708	Common
Facial dysmorphism	HP:0001999	Variable
Sensorineural hearing impairment	HP:0000407	Reported (subset)
Strabismus	HP:0000486	Enriched in missense variants
Ataxic gait	HP:0002066	Reported
Aggressive behavior	HP:0000718	Reported

Quality-of-life impact. Disease-specific EQ-5D/SF-36 data are **not available** for this ultra-rare disorder. By clinical extrapolation, lifelong intellectual disability, communication impairment, behavioral difficulties, and (in a subset) epilepsy substantially affect daily functioning, independence, and caregiver burden.

4. Genetic / Molecular Information

Causal gene (F001, F014): *ZMYND11* (zinc finger MYND-type containing 11; alias BS69/BRAM1), 10p15.3; HGNC:29316; NCBI Gene 10778; UniProt Q15326; OMIM disease #616083.

Variant spectrum and classification (F006, F008, F013). Most reported MRD30 patients carry **loss-of-function** variants — nonsense, frameshift, canonical splice-site, and whole/partial-gene deletions. **Missense variants are rarer** (~13 reported) and their mechanistic characteristics are less defined. Variants are classified per ACMG/AMP criteria and are distributed across the gene with no precise genotype–phenotype correlation.

> *"Most previously reported patients harbor loss-of-function (LoF) variants, whereas missense variants are rare and their clinical and mechanistic characteristics remain insufficiently defined"* (PMID: 41820311)

Missense vs. LoF genotype–phenotype (F006). Aggregate analysis of the 13 reported missense variants (including recurrent **c.1798C>T, p.Arg600Trp**) suggests higher frequencies of **strabismus, hypotonia, and severe intellectual disability** than LoF variants, plus associations with microcephaly, broad nasal alae, short stature, cryptorchidism, and nipple anomalies.

> *"Aggregate analysis of reported 13 missense variants suggested higher frequencies of strabismus, hypotonia and severe intellectual disability compared with LoF variants"* (PMID: 41820311)

Allele frequency / origin. Pathogenic *ZMYND11* LoF alleles are essentially **absent from population databases (gnomAD)**, consistent with strong LoF constraint. Variants are **germline** (not somatic in the disease context) and mostly **de novo**, with rare inherited cases (F013).

Functional consequences (F001). The unifying mechanism is **loss of function / haploinsufficiency**. An intragenic deletion removing only the 5′UTR + first two exons produced the same phenotype, confirming that reduced dosage — rather than a dominant-negative product — drives disease.

> *"our report contributes to expand the clinical and mutational spectrum of ZMYND11 and confirms haploinsufficiency as the underlying disease mechanism"* (PMID: 34818214)

Dosage sensitivity / chromatinopathy overlap (F006). ZMYND11 is dosage-sensitive; its perturbation has also been linked to **Cornelia de Lange Syndrome (CdLS)-like** phenotypes, placing MRD30 within the broader family of chromatinopathies. Adult presentations may include movement disorders. Independently, *ZMYND11* LoF is an FDR-significant **schizophrenia** risk gene (PMID: 40753099).

> *"ZMYND11, a dosage-sensitive gene, has been associated with Cornelia de Lange Syndrome (CdLS)-like phenotypes, and its haploinsufficiency is linked to 10p15.3 microdeletion syndrome"* (PMID: 42003802)

Modifier genes. None specifically established for pure MRD30. In the contiguous-deletion form, co-deleted neighbors (*DIP2C*, *GATA3*) modify the phenotype (Section 10).

Epigenetic information. ZMYND11's own function is epigenetic (H3.3K36me3 reading); no disease-specific DNA-methylation episignature has been definitively established, though its role in chromatin regulation makes an episignature plausible (a knowledge gap).

Chromosomal abnormalities (F008, F010). 10p15.3 deletions (detected by CMA/karyotype/FISH), ring chromosome 10, inv dup del(10p), and complex rearrangements involving 10p can remove *ZMYND11* and cause the deletion form of the disorder.

Suggested ontology terms: Gene product — **UniProt Q15326**; molecular function — **GO:0035064** (methylated histone binding), **GO:0003682** (chromatin binding).

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5. Environmental Information

Not applicable. MRD30 is a monogenic disorder with no established environmental, lifestyle, or infectious contributors (F014). No toxin, radiation, pollution, occupational-exposure, dietary, or pathogen association is documented. This section is included for completeness and is explicitly negative.

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6. Mechanism / Pathophysiology

Domain architecture and histone-reader function (F002, F004)

ZMYND11/BS69 contains tandemly arranged **PHD, Bromo, and PWWP** chromatin-recognition modules plus a C-terminal **MYND** zinc-finger domain. Together these read the histone variant mark **H3.3K36me3**.

> *"BS69 (also called ZMYND11) contains tandemly arranged PHD, BROMO, and PWWP domains, which are chromatin recognition modalities. Here, we show that BS69 selectively recognizes histone variant H3.3 lysine 36 trimethylation (H3.3K36me3) via its chromatin-binding domains."* (PMID: 25263594)

ZMYND11 was originally identified as a specific reader for H3.3K36me3 and a candidate tumor suppressor; some oncogenic H3.3 mutations abrogate the H3.3K36me3/BS69 interaction, underscoring its functional importance.

> *"two recent studies identified BS69/ZMYND11, which was proposed to be a candidate tumor suppressor, as a specific reader for a modified form of H3.3 (H3.3K36me3)"* (PMID: 25453099)

The chromatin-reader function connects directly to epilepsy pathogenesis: *"ZMYND11 is one of a small group of chromatin reader genes associated in the pathogenesis of epilepsy, and specifically ABPE"* (PMID: 34216016).

Coupling chromatin to transcription and splicing (F004)

Beyond elongation control, ZMYND11 couples the H3K36me3 chromatin state to **pre-mRNA processing**, mainly regulating **intron retention (IR)** by antagonizing the U5 snRNP spliceosome component **EFTUD2**; this depends on binding H3K36me3-decorated chromatin.

> *"BS69 mainly regulates intron retention (IR)... BS69 promotes IR by antagonizing EFTUD2 through physical interactions. We further show that regulation of IR by BS69 also depends on its binding to H3K36me3-decorated chromatin."* (PMID: 25263594)

More recent data show ZMYND11 also localizes to **gene promoters** and regulates **transcription initiation**:

> *"ZMYND11 deficiency reduces the pausing index of Pol II, H3.3, and H3K36me3, indicating impaired transcription initiation"* (PMID: 42262664)

Neurodevelopmental convergence (F005, F007)

In human cortical models, **ZMYND11 mutations impair cortical progenitor and neuron production**; ZMYND11-deficient neural stem cells **upregulate inappropriate developmental pathways**, disrupting neurogenesis, and ZMYND11 controls a **brain-specific RNA isoform switch involving RBFOX2**.

> *"mutations in ZMYND11, a newly implicated risk gene, impair human cortical progenitor and neuron production"* (PMID: 41068108) *"ZMYND11-deficient cortical neural stem cells upregulate inappropriate developmental pathways, leading to disrupted neurogenesis"* (PMID: 41068108) *"ZMYND11 regulates a brain-specific RNA isoform switch involving the splicing regulator RBFOX2"* (PMID: 41068108)

A complementary mechanistic axis: **ZMYND11 restrains the histone methyltransferase KMT2A (MLL1)** to enable a neuronal developmental program (PMID: 41279818), linking MRD30 to the KMT2A/COMPASS chromatin-modifier network implicated in neurodevelopmental disorders.

Causal chain (upstream → downstream)

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ZMYND11 haploinsufficiency (heterozygous LoF / 10p15.3 deletion)
        │
        ▼
Reduced reading of H3.3K36me3 on gene bodies & promoters
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        ├─► Impaired Pol II elongation control + reduced Pol II pausing (initiation)
        ├─► Loss of EFTUD2 antagonism → aberrant intron retention / mis-splicing
        ├─► Disrupted RBFOX2-dependent brain-specific isoform switch
        └─► Loss of restraint on KMT2A → de-repression of latent developmental genes
        │
        ▼
Cortical neural stem cells activate inappropriate developmental programs
        │
        ▼
Impaired cortical progenitor & neuron production (disrupted corticogenesis)
        │
        ▼
Intellectual disability, developmental delay, seizures, behavioral problems
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Cell types & compartments: neural stem/progenitor cells and cortical neurons (**CL:0000047** neural stem cell; **CL:0000679** glutamatergic neuron); subcellular localization is the **nucleus**/**chromatin** (**GO:0005634** nucleus; **GO:0000785** chromatin).

Suggested GO biological processes: GO:0006357 (regulation of transcription by RNA Pol II), GO:0008380 (RNA splicing), GO:0006397 (mRNA processing), GO:0021987 (cerebral cortex development), GO:0022008 (neurogenesis).

Immune, metabolic, oxidative-stress mechanisms: Not central to MRD30 pathophysiology. (Co-deleted *DIP2C* perturbs sphingolipid metabolism/myelination in the deletion syndrome — Section 10 — but this is not ZMYND11-intrinsic.)

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7. Anatomical Structures Affected

Primary organ / system (F005, F010): the **brain / central nervous system** (nervous system) — specifically the developing **cerebral cortex** (**UBERON:0000955** brain; **UBERON:0000956** cerebral cortex).

Tissue and cell level: nervous tissue; neural stem/progenitor cells and cortical neurons (**CL:0000047**, **CL:0000679**).

Subcellular level: nucleus and chromatin (**GO:0005634**, **GO:0000785**).

Secondary / contiguous-deletion involvement (F010): In larger 10p15.3 deletions, additional organs are affected because neighboring genes are co-deleted — **heart** (congenital heart defects, via *DIP2C*), **kidney**, **parathyroid** (hypoparathyroidism, via *GATA3*/DGS2), **skeleton** (short stature, hand/foot malformation, butterfly vertebrae, scoliosis), **inner ear** (sensorineural deafness), and rarely the **GI tract** (refractory gastroparesis). Some patients show cerebellar/posterior-fossa malformations (ring chromosome 10 cases).

> *"Recurrent 10p15.3 microdeletion syndrome is a rare multisystem disorder characterized by abnormal facial features, global developmental delay (DD)/intellectual disability (ID), short stature, hand/foot malformation, and congenital heart defects (CHDs)"* (PMID: 40915331)

Lateralization: CNS involvement is bilateral/diffuse (a developmental, not focal-lesion, disorder), though focal epileptiform (e.g., centrotemporal) EEG features occur.

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8. Temporal Development

Onset (F011): Congenital to early childhood — neonatal hypotonia and infantile developmental delay are typical; onset pattern is **chronic/insidious**, not acute.

Progression (F011): The disorder is **chronic and lifelong** and the neurodevelopmental deficit is **largely static (non-neurodegenerative)** rather than progressive. Neurodevelopmental deficits are essentially invariable (fully penetrant).

> *"Seizure prognosis ranged from spontaneous remission to drug resistant. Neurodevelopmental deficits were invariable."* (PMID: 34216016)

Course patterns / adult evolution (F011): Epilepsy course is variable (episodic/remitting to drug-resistant). A distinct subset develops or worsens a **movement disorder (dystonia/ataxia/tremor) in adulthood**, prompting adult neurological referral and underscoring the need for lifelong surveillance.

> *"displayed a movement disorder (dystonia/ataxia/tremor) which manifested for the first time, or worsened, in the adulthood"* (PMID: 35172867)

Critical periods: Cortical neurogenesis (fetal/early-postnatal) is the key vulnerable window, consistent with the corticogenesis defect and congenital onset (F005). Prenatal presentations are nonspecific (Section 10).

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9. Inheritance and Population

Epidemiology (F013): MRD30 is **ultra-rare**; only on the order of dozens of individuals are reported worldwide (e.g., a 2021 study assembled 20 individuals with epilepsy). **No population prevalence or incidence estimate is established.**

Inheritance (F008, F013): Autosomal dominant. Pathogenic variants mostly arise **de novo**; rare inherited cases from mildly/variably affected parents demonstrate **incomplete penetrance and variable expressivity**.

> *"Variants were distributed across the gene and mostly de novo with no precise genotype-phenotype correlation."* (PMID: 34216016) *"Parental CMA analysis revealed that the 10p15.3 microdeletion was inherited from the father, who displayed mild language impairment"* (PMID: 39696561)

Penetrance / expressivity: Neurodevelopmental deficits are near-fully penetrant; dysmorphism, epilepsy, and additional features are variably expressed. Germline mosaicism is plausible for de novo cases but not specifically quantified.

Founder effects / consanguinity / carrier frequency: No founder effect described; consanguinity is not relevant (dominant, mostly de novo). Carrier frequency in the healthy population is effectively negligible given strong LoF constraint (gnomAD).

Demographics (F013): Reported in **both sexes with no clear sex predilection** and across diverse populations; no ethnic or geographic clustering is established.

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10. Diagnostics

Recommended approach (F008). Diagnosis is **molecular**. Point/truncating *ZMYND11* variants are detected by **whole-exome or whole-genome sequencing** or by **epilepsy/intellectual-disability gene panels**, with variants classified per **ACMG/AMP** criteria. 10p15.3 deletions are detected by **chromosomal microarray analysis (CMA)**, **karyotyping**, and **FISH**; prenatally by amniocentesis + CMA.

> *"Genetic evaluation was performed using gene panels or exome sequencing; variants were classified using American College of Medical Genetics (ACMG) criteria"* (PMID: 34216016)

Test	Utility in MRD30
WES / WGS	High — detects intragenic point/truncating variants (first-line for ID/epilepsy)
Epilepsy/ID gene panels	High — targeted detection of *ZMYND11* variants
Chromosomal microarray (CMA)	Detects 10p15.3 deletions and contiguous-gene involvement
Karyotype / FISH	Detects ring chr10, inv dup del(10p), translocations involving 10p
Prenatal (amniocentesis + CMA)	Detects deletions; correlate with ultrasound

Prenatal / fetal features (F008). Nonspecific: increased **nuchal translucency** (first trimester), **fetal growth restriction** (third trimester), and skeletal anomalies (butterfly vertebrae, scoliosis).

> *"Two cases were diagnosed in the first trimester because of increased nuchal translucency (NT). Three had normal routine first-trimester and second-trimester ultrasound scans, and were diagnosed because of fetal growth restriction (FGR)"* (PMID: 42362275)

Ancillary tests. EEG (for epilepsy classification, including centrotemporal/ABPE patterns), brain MRI (may show cerebellar/posterior-fossa anomalies in some deletion/ring-chromosome cases), and audiology/ophthalmology assessments for hearing loss and strabismus. No specific blood/urine biomarker or enzyme assay exists.

Differential diagnosis. Angelman syndrome (happy disposition, ataxic gait, hypotonia — overlap noted in individual reports; PMID: 27626064), other chromatinopathies including Cornelia de Lange-like presentations (PMID: 42003802), and — for contiguous deletions — HDR/Barakat syndrome (via *GATA3*) and DiGeorge-region disorders.

Distinguishing pure MRD30 from the contiguous-deletion syndrome (F010). Pure *ZMYND11* disruption (point variants or small intragenic deletions) causes the **core neurodevelopmental phenotype only**. Larger deletions add features from co-deleted neighbors: *DIP2C* (congenital heart defects, short stature, hand/foot malformation, abnormal myelination/sphingolipid metabolism) and, for larger terminal deletions, *GATA3* + DiGeorge critical region 2 (DGS2) → **hypoparathyroidism, sensorineural deafness, renal abnormalities** (HDR/Barakat-like).

> *"We identified Disco Interacting Protein 2 Homolog C (DIP2C) as a putative candidate gene underlying CHDs"* (PMID: 40915331) *"includes the ZMYND11 and GATA3 genes and a partial critical region of the DiGeorge syndrome 2 gene (DGS2)"* (PMID: 34049562)

Screening / cascade testing. Once a familial variant is identified, targeted cascade testing of at-risk relatives is appropriate given documented inherited/variably expressed cases. No population newborn screening exists.

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11. Outcome / Prognosis

Survival / mortality (F011). MRD30 is **not associated with reduced life expectancy** in the reported literature; it is a static neurodevelopmental disorder rather than a lethal or neurodegenerative one. No disease-specific mortality rate is established.

Morbidity / function. The principal burden is **lifelong intellectual disability and developmental disability**, with communication impairment, behavioral difficulties (ASD/ADHD/aggression), and — in a subset — epilepsy and adult movement disorders contributing to functional impairment and caregiver dependence. Formal disability/QoL metrics (ICF, EQ-5D, PROMIS) have not been reported for this rare disorder.

Disease course / complications. Complications include drug-resistant epilepsy (subset), adult-onset/worsening movement disorder, sensorineural hearing loss, and — in contiguous deletions — cardiac, renal, endocrine, and GI complications. Recovery to normal cognition does not occur; developmental gains are achievable with early intervention.

Prognostic factors (F006, F011). Variant class appears prognostically relevant: missense variants (e.g., p.Arg600Trp) associate with **more severe intellectual disability, strabismus, and hypotonia**. Seizure severity/drug-resistance and the presence of contiguous-gene deletions also influence prognosis. No validated molecular prognostic biomarker exists.

12. Treatment

No disease-specific or curative therapy exists (F012). Management is **symptomatic and multidisciplinary**, following general neurodevelopmental-disorder care:

Domain	Intervention	Suggested NCIT concept
Epilepsy	Antiseizure medications (ASMs); recognize drug-resistant subset	NCIT:C264 (Anticonvulsant Agent)
Development	Early developmental intervention	NCIT:C15275 (Rehabilitation Therapy)
Motor / hypotonia	Physical & occupational therapy	NCIT:C15242 / NCIT:C15226
Speech / language	Speech-language therapy	NCIT:C15275
Behavior (ASD/ADHD/ aggression)	Behavioral & educational support	NCIT:C15319 (Behavioral Therapy)
Sensory	Vision (strabismus) & hearing surveillance/ treatment	—
Contiguous deletions	Cardiac, renal, parathyroid/endocrine, skeletal evaluation & management	—

> *"Seizure prognosis ranged from spontaneous remission to drug resistant."* (PMID: 34216016) — justifies individualized antiseizure management including recognition of drug-resistant epilepsy.

Emerging / experimental directions (F012). Cellular studies indicate that defects seen in ZMYND11-deficient and related chromatin-ASD-gene models can be **partially rescued by enhancing ZMYND11 function**, hinting at future targeted approaches — but nothing is clinically available.

> *"Similar defects are observed in other chromatin-related ASD risk genes, some of which are partially rescued by enhancing ZMYND11 function"* (PMID: 41068108)

Pharmacogenomics / gene / cell / RNA therapy: No approved targeted, gene-, cell-, or RNA-based therapy; no MRD30-specific pharmacogenomic guidance. There are no registered disease-specific interventional trials at the time of this review.

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13. Prevention

Because MRD30 is a monogenic disorder with no environmental component, prevention is limited to **genetic risk management** (F013, F014):

- **Primary prevention:** Not applicable in the classical sense (no modifiable environmental risk). For families with a known variant, **genetic counseling, prenatal diagnosis, and preimplantation genetic testing (PGT)** can inform reproductive decisions.
- **Secondary prevention:** Early molecular diagnosis (WES/WGS/CMA) enables early developmental intervention and surveillance for epilepsy, hearing, and vision problems.
- **Tertiary prevention:** Proactive management of complications — antiseizure therapy, adult neurological surveillance for movement disorders, and organ-specific monitoring in contiguous-deletion cases.
- **Genetic counseling:** Given that most variants are de novo but inherited/variably expressed cases occur, recurrence-risk counseling should account for **variable expressivity, incomplete penetrance, and possible parental mosaicism**; cascade testing follows identification of a familial variant.

No immunization, behavioral, or public-health/environmental prevention is applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs (F009):** *ZMYND11* is evolutionarily conserved; functional orthologs are studied in **mouse** (*Zmynd11*) and **zebrafish** (*bs69*/*zmynd11*). Human gene NCBI Gene 10778.
- **Natural disease in animals:** No naturally occurring companion-animal or wildlife disease is described (OMIA has no established entry for a natural ZMYND11 disorder). This is a research-modeled, not a naturally recognized veterinary, condition.
- **Comparative biology:** Disease mechanisms (H3.3K36me3 reading, transcription/splicing control, developmental-signaling regulation) are conserved. In zebrafish, **Mga modulates Bmpr1a activity by antagonizing Bs69**, providing an in-vivo developmental-signaling (BMP) context (PMID: 30324105).
- **Transmission / zoonosis:** Not applicable (genetic disorder).

15. Model Organisms

Available models (F009):

System	Model	Key finding	PMID
Human iPSC / cortical organoid	*ZMYND11*-deficient cortical NSCs	Impaired progenitor/neuron production; de-repressed latent genes; RBFOX2 splicing switch	41068108
Mouse ESC / MEF	*Zmynd11* deficiency	Impaired transcription initiation; reduced Pol II pausing index	42262664
Zebrafish	*bs69* (Mga–Bmpr1a axis)	In-vivo BMP developmental-signaling model	30324105
Mouse (neighboring *Dip2c*)	Het/hom *Dip2c* mutants	Dosage-sensitive cognitive impairment, hyperlocomotion, abnormal sphingolipid metabolism/myelination	41054236
Zebrafish (neighboring *dip2ca*)	*dip2ca* knockdown	Craniofacial and cardiac defects	40915331

> *"heterozygous mutant mice displayed only mild cognitive impairment, recapitulating the dosage-sensitive phenotype observed in human 10p15.3 microdeletion syndrome"* (PMID: 41054236) — dosage-sensitive model for the neighboring 10p15.3 gene *DIP2C*.

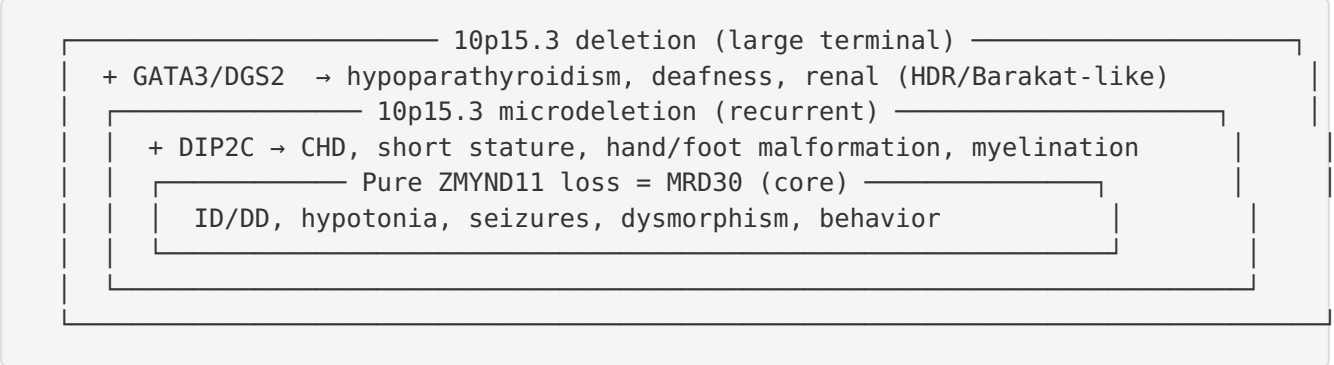
Phenotype recapitulation & limitations. Human iPSC/cortical-organoid models faithfully reproduce the **corticogenesis defect** and molecular signatures (latent-gene de-repression, RBFOX2 splicing) and are the most disease-relevant system. Mouse ESC/MEF models capture the transcription/chromatin mechanism. **Limitations:** no published constitutive *Zmynd11* knockout mouse fully modeling the MRD30 behavioral/seizure phenotype was identified; zebrafish/mouse *Dip2c* models inform the contiguous-deletion (not pure-*ZMYND11*) phenotype. **Genetic-model types available:** cellular knockout/deficiency and organoid systems; a humanized or conditional neuronal knockout mouse would be a valuable addition.

Applications & resources: Cortical organoids for mechanism and drug-rescue screening; ESC/MEF for chromatin/transcription assays; zebrafish for developmental signaling. Resources: MGI (*Zmynd11*), ZFIN (*bs69*/*zmynd11*), Cellosaurus (patient iPSC lines).

Mechanistic Model / Interpretation

MRD30 is best understood as a **chromatinopathy of transcriptional–splicing coupling in the developing cortex**. A single functional dose of *ZMYND11* is insufficient for normal reading of the H3.3K36me3 mark deposited on active gene bodies. The immediate consequence is dysregulated RNA Pol II behavior (elongation control plus initiation/pausing) and loss of the ZMYND11–EFTUD2 balance that governs intron retention. Layered on top, ZMYND11 normally **restrains KMT2A** and enforces a **brain-specific RBFOX2 isoform switch**. When ZMYND11 is halved, latent developmental gene programs are inappropriately activated, cortical neural stem cells fail to execute proper neurogenesis, and the mature cortex is built from too few, mis-specified neurons — producing intellectual disability, developmental delay, epilepsy, and behavioral phenotypes. Because the insult is developmental and completed early, the clinical disorder is **static rather than degenerative**, explaining its lifelong-but-stable natural history (with a distinct adult movement-disorder subset).

Two "concentric" clinical entities emerge from the same locus:



This nested model is the single most clinically actionable synthesis: the **size and gene content of the lesion predict which additional organ systems require evaluation**, while the ZMYND11 core drives the neurodevelopmental phenotype in every case.

Evidence Base

PMID	Title (abbrev.)	Role
34818214	Intragenic *ZMYND11* deletion / DD	**Confirms haploinsufficiency mechanism**; deletion–truncating phenotypic equivalence
34216016	*ZMYND11* epilepsies + NDD (cohort ~20)	Critical-gene status; epilepsy subtypes; de novo predominance; diagnostic methods; penetrance
25263594	BS69/ZMYND11 reads H3.3K36me3, regulates splicing	Domain architecture; H3.3K36me3 reader; EFTUD2/intron-retention
25453099	Histone H3.3 and cancer reader connection	Reader specificity; tumor-suppressor context
42262664	ZMYND11 at promoters / initiation	Transcription initiation & Pol II pausing role
41068108	ZMYND11 safeguards corticogenesis	Corticogenesis defect; latent-gene de-repression; RBFOX2; partial rescue
41279818	ZMYND11 restrains KMT2A	KMT2A restraint enabling neuronal program
41820311	p.Arg600Trp / missense phenotype	Missense-vs-LoF genotype–phenotype
42003802	7p dup + 10p del chromatinopathy	Dosage sensitivity; CdLS-like overlap
27626064	De novo missense; DD/seizures/ hypotonia	Individual multisystem phenotype; Angelman-like features
35172867	NDD in adulthood — movement disorder	Adult-onset/worsening movement disorder
39696561	Prenatal pure 10p15.3 deletion	Inherited case, variable expressivity
42362275	Prenatal 10p15.3 (5 cases)	Nonspecific prenatal features (NT, FGR)
40915331	DIP2C and CHD in 10p15.3	Attributes CHD to co-deleted *DIP2C*
41054236	*Dip2c* deficiency / sphingolipids in mice	Dosage-sensitive mouse model (neighboring gene)
34049562	Large 10p15.3p13 deletion	*GATA3*/DGS2 co-deletion adds endocrine/renal/ hearing features

PMID	Title (abbrev.)	Role
30324105	Mga–Bmpr1a–Bs69 in zebrafish	Zebrafish developmental-signaling model
40753099	Schizophrenia exome risk genes	*ZMYND11* LoF as FDR-significant SCZ risk gene

Evidence source types: human clinical (case reports/small cohorts), in vitro/iPSC (human cortical organoids), model organism (mouse ESC/MEF, zebrafish), and computational/genetic (exome burden). No population EHR or randomized-trial evidence exists for this ultra-rare disorder.

Limitations and Knowledge Gaps

1. **Small evidence base.** All clinical knowledge derives from case reports and small cohorts (dozens of patients). No prevalence/incidence estimate, no natural-history registry, and no controlled trials exist.
2. **No population-scale or QoL data.** Formal disability, EQ-5D/SF-36/PROMIS, and long-term functional-outcome metrics are unreported.
3. **Genotype–phenotype resolution is coarse.** Missense-vs-LoF differences are suggested from aggregate analysis of only ~13 missense variants; larger, systematically phenotyped cohorts are needed.
4. **No definitive disease-specific episignature** or biomarker has been validated, despite ZMYND11's chromatin role.
5. **Model gap.** No published constitutive/conditional *Zmynd11*-knockout mouse fully recapitulating the MRD30 behavioral/seizure phenotype was identified; much mouse evidence pertains to the neighboring gene *DIP2C*.
6. **Contiguous-gene confounding.** Deletion-based literature mixes *ZMYND11* effects with those of *DIP2C*, *GATA3*, and DGS2, complicating attribution — mitigated only by pure-variant/intragenic-deletion cases.
7. **No therapeutics.** Rescue-by-enhancement is a cellular observation only, with no translational pathway yet.

Proposed Follow-up Experiments / Actions

1. **Assemble an international MRD30 registry** with standardized deep phenotyping (HPO-coded), variant-class stratification, and longitudinal follow-up to establish penetrance, expressivity, and prognostic factors quantitatively.
2. **Systematic genotype–phenotype study** contrasting LoF vs. missense (especially recurrent p.Arg600Trp) with functional assays of reader capacity, EFTUD2 antagonism, and KMT2A restraint.
3. **Test for a DNA-methylation episignature** in patient blood to enable a diagnostic biomarker and VUS reclassification.
4. **Generate a conditional neuronal *Zmynd11* mouse** (and validate against patient cortical organoids) to model behavior, seizures, and to serve as a preclinical rescue platform.
5. **Mechanistic dissection of the RBFOX2 splicing switch and KMT2A axis** in patient neurons, with multi-omics (RNA-seq intron-retention analysis, CUT&RUN for H3.3K36me3/ZMYND11, Pol II ChIP).
6. **Pursue "enhance-ZMYND11-function" or downstream-node therapeutic screens** (e.g., modulating KMT2A/COMPASS activity or splicing) in cortical organoids to identify actionable targets.
7. **Standardize clinical care pathways** distinguishing pure MRD30 from contiguous-deletion syndrome, specifying which patients need cardiac (*DIP2C*), renal/parathyroid/audiologic (*GATA3*/DGS2) evaluation, and lifelong adult neurological surveillance for movement disorders.

Report compiled from 14 confirmed findings across 5 investigation iterations and 28 reviewed publications. Ontology suggestions provided for MONDO, HPO, GO, CL, UBERON, and NCIT to support knowledge-base ingestion.
