

# KIF2A-related Complex Cortical Dysplasia (CDCBM3): Comprehensive Disease Dossier

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**Disease:** KIF2A-related Complex Cortical Dysplasia / Cortical Dysplasia, Complex, with Other Brain Malformations 3 (CDCBM3) **MONDO:** MONDO:0014170 · **OMIM:** #615411 · **Category:** Mendelian (autosomal dominant) **Causal gene:** *KIF2A* (HGNC:6318; NCBI Gene 3796; UniProt O00139; chromosome 5q12.1) **Evidence base:** Human clinical case reports/series, model-organism (mouse, zebrafish) studies, and in vitro/computational structural analyses. No disease-specific patient dataset was provided; this report is literature-derived.

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## Summary

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KIF2A-related Complex Cortical Dysplasia (CDCBM3; **OMIM #615411**, **MONDO:0014170**) is an **ultra-rare, autosomal dominant malformation of cortical development (MCD)** caused by predominantly *de novo* heterozygous missense variants in *KIF2A*, the gene encoding a **kinesin-13 family ATP-dependent microtubule depolymerase**. Pathogenic variants cluster in the kinesin **motor / ATP-nucleotide-binding domain (NBD)**, with recurrent *de novo* hotspots at residues **Ser317 and His321** (e.g., p.Ser317Asn, p.His321Pro/Asp) and p.Gly318Arg. These variants impair ATP hydrolysis and the microtubule-depolymerizing function of KIF2A, derailing the microtubule-dependent processes that build the cerebral cortex ([PMID: 23603762](#); [PMID: 27747449](#); [PMID: 33506645](#)).

The core clinical phenotype is a **posterior-predominant lissencephaly / agyria-pachygyria** almost indistinguishable from LIS1-related lissencephaly, accompanied by **congenital and postnatal microcephaly** (up to  $-5$  SD in ~75% of patients), **severe motor and cognitive impairment, absent or limited speech**, and **drug-resistant epilepsy**; clinical involvement is largely restricted to the central nervous system and facial dysmorphism. Variant position along the protein predicts severity, defining a graded "**KIF2A syndrome**": NBD variants → severe CDCBM3; motor-domain-but-outside-NBD variants → epilepsy; variants outside the motor domain → autism spectrum ([PMID: 33506645](#); [PMID: 37488893](#)).

There is **no disease-specific or curative therapy**. Diagnosis is made by trio whole-exome/whole-genome sequencing plus brain MRI, and management is symptomatic (antiseizure medication plus developmental/rehabilitative support). Inheritance is autosomal dominant with nearly all variants arising *de novo*; recurrence risk is low but non-zero owing to documented **parental germline mosaicism** (e.g., KIF2A p.G440R in two affected brothers) (PMID: 35315043; PMID: 37331001). Disease mechanism is strongly supported by a conditional knock-in mouse bearing the human p.His321Asp variant, which recapitulates microcephaly, neuroanatomical anomalies, behavioral deficits and epilepsy susceptibility, showing increased apoptosis and abnormal multipolar-to-bipolar transition of migrating neurons (PMID: 31919497).

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## Key Findings

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### Finding 1 — *KIF2A* is the causal gene; *de novo* motor-domain missense variants cluster around the ATP pocket

CDCBM3 is a rare autosomal dominant syndrome caused by heterozygous *KIF2A* variants. Recurrent *de novo* missense mutations target residues around the ATP nucleotide-binding pocket of the kinesin motor domain, notably hotspots **Ser317** and **His321** (e.g., p.Ser317Asn, p.His321Pro/Asp) and **p.Gly318Arg**. These recur as *de novo* events, are typically **absent from gnomAD/1000 Genomes (ACMG PM2)** and are predicted deleterious. As stated in the literature, "*Cortical dysplasia, complex, with other brain malformations 3 (CDCBM3) is a rare autosomal dominant syndrome caused by Kinesin family Member 2A (KIF2A) gene mutation*" (PMID: 33506645), and "*the identification of mutations only in the residues Ser317 and His321 suggests these are hotspots for de novo mutations*" (PMID: 27747449). A rare recurrence mechanism is parental germline mosaicism: "*Findings in this case also suggest a rare parental germline mosaicism of KIF2A G440R*" (PMID: 37331001).

### Finding 2 — Pathogenic variants impair microtubule depolymerization, increasing apoptosis and disrupting the multipolar-to-bipolar transition

A conditional knock-in mouse bearing the human *KIF2A* **p.His321Asp** missense variant showed microcephaly, neuroanatomical anomalies, behavioral deficits, and epilepsy susceptibility — faithfully recapitulating the human phenotype. Mechanistically, "*the expression of the p.His321Asp pathogenic variant increases apoptosis and causes abnormal*

*multipolar to bipolar transition in newborn neurons," and "the observed cellular phenotypes are likely to be linked to deficiency in the microtubule depolymerizing function of KIF2A" (PMID: 31919497). This provides direct causal evidence linking the variant to both the apoptosis (→ microcephaly) and migration-arrest (→ lissencephaly) arms of the disease.*

### **Finding 3 — Variant location predicts phenotype across a graded "KIF2A syndrome"**

Variant position correlates with clinical severity. Variants in/around the **nucleotide-binding domain (NBD)** cause CDCBM3 (posterior-dominant agyria/pachygyria, severe motor dysfunction, microcephaly); variants in the kinesin motor domain **but outside the NBD** associate with epilepsy; variants **outside the motor domain** associate with autism spectrum. Clinical features are largely restricted to CNS and facial anomalies. As summarized: *"Variants in KIF2A have been reported in the NBD for CDCBM3, in the kinesin motor 3 domain, but not in the NBD in epilepsy, and outside of the kinesin motor domain in autism spectrum syndrome, respectively" and "We can call this spectrum 'KIF2A syndrome' with variable severity" (PMID: 33506645). The core CDCBM3 phenotype: "Patients with CDCBM3 exhibit posterior dominant agyria/pachygyria with severe motor dysfunction" (PMID: 33506645).*

### **Finding 4 — KIF2A regulates inhibitory interneuron synapses and postnatal circuits, linking its loss to epileptogenesis**

KIF2A is an atypical kinesin (kinesin-13): *"KIF2A is an atypical kinesin that depolymerizes MT in ATP-dependent manner and regulates MT dynamics" (PMID: 36733270). Deletion of KIF2A in cortical interneurons produces inhibitory synapse dysfunction and epileptic susceptibility. Beyond its prenatal roles, KIF2A "regulates cell migration, axon elongation, and pruning in the developing nervous system" (PMID: 29313800) and postnatally shapes dentate granule cell development and hippocampal wiring — a dedicated postnatal circuit-establishment role that contributes an epileptogenic mechanism distinct from the migration defect.*

### **Finding 5 — Core clinical phenotype: posterior-predominant lissencephaly with microcephaly, severe motor/cognitive impairment, and epilepsy**

Patients present with classic lissencephaly following a posterior-to-anterior gradient. *"Both mutations lead to a classic form of lissencephaly, with a posterior to anterior gradient, almost indistinguishable from LIS1-related lissencephaly. However, three fourths of patients also showed variable congenital and postnatal microcephaly, up to  $-5$  SD" (PMID: 27747449). Additional features include severe motor developmental delay, severe cognitive impairment, absent*

speech, and rarer features such as congenital laryngomalacia: *"had presented with motor developmental delay, lissencephaly, severe cognitive impairments, absent speech and congenital laryngomalacia"* (PMID: 35315043). Organ involvement is narrow: *"The clinical findings of patients with KIF2A variants appear restricted to the central nervous system and facial anomalies"* (PMID: 33506645).

### **Finding 6 — Diagnosis by exome/genome sequencing + brain MRI; management is symptomatic**

Diagnosis is established by whole-exome or whole-genome sequencing (often quad/trio WES) identifying a heterozygous *KIF2A* variant, confirmed by Sanger sequencing, combined with brain MRI showing MCD. *"Whole exome sequencing (WES) was carried out for the family trio. Suspected variant was verified by Sanger sequencing"* and, for a representative variant, *"Based on the ACMG guidelines, it was categorized as likely pathogenic (PS2+PM1+PM2+PP3)"* (PMID: 35315043). No targeted or curative therapy exists; management is supportive — antiseizure medication for the frequently drug-resistant epilepsy plus developmental/rehabilitative therapies.

### **Finding 7 — Ultra-rare, sporadic autosomal dominant disorder; recurrence via germline mosaicism**

The disorder is very rare (CDCBM3, OMIM #615411) with only a small number of reported patients worldwide: *"KIF2A-related tubulinopathy (MIM: #615411) is a very rare disorder"* (PMID: 37331001). Inheritance is autosomal dominant: *"CDCBM3 ... is a rare autosomal dominant syndrome caused by Kinesin family Member 2A (KIF2A) gene mutation"* (PMID: 33506645). Nearly all pathogenic variants arise *de novo* (confirmed absent in parents by trio sequencing). No founder effect, consanguinity role, or ethnic/sex predilection is established. Sibling recurrence with unaffected parents is attributed to parental germline mosaicism (PMID: 37331001).

### **Finding 8 — Model organisms recapitulate microcephaly, migration defects, and epilepsy**

Mouse and zebrafish models reproduce key disease features. The conditional knock-in of human *KIF2A* p.His321Asp *"present[s] with neuroanatomical anomalies and microcephaly associated with behavioral deficiencies and susceptibility to epilepsy"* (PMID: 31919497). Conditional forebrain inactivation disrupts postnatal tangential neuroblast migration — *"conditional inactivation of Kif2a in the forebrain recapitulates the Celsr3 knockout phenotype"*

([PMID: 34582949](#)) — and tamoxifen-inducible postnatal deletion impairs hippocampal wiring: "we investigated *KIF2A* function in the postnatal hippocampus by using tamoxifen-inducible" deletion ([PMID: 29313800](#)).

### **Finding 9 — KIF2A acts within a neuronal-migration protein complex (LIS1/NDE1/DYNC1H1/CDK5)**

KIF2A is a kinesin-13 that, unlike motile kinesins, "use[s] their catalytic cycle to depolymerize microtubules independent of motility" ([PMID: 42517274](#)). In developing neurons it operates alongside other migration genes: CEP85L "forms a complex with many other proteins required for migration, including CDK5, LIS1, NDE1, KIF2A, and DYNC1H1," and "Loss of CEP85L disrupts CDK5 localization and activation, leading to centrosome disorganization and disrupted microtubule cytoskeleton organization" ([PMID: 32097629](#)). This situates KIF2A within the same molecular machinery as the major lissencephaly gene *LIS1* (*PAFAH1B1*), explaining the near-identical imaging phenotype.

### **Finding 10 — The 2013 Poirier et al. discovery study established KIF2A as an MCD gene via impaired ATP hydrolysis**

The landmark 2013 study (Poirier et al., *Nature Genetics*) first linked *KIF2A* to MCD: "Here we report the discovery of multiple pathogenic missense mutations in *TUBG1*, *DYNC1H1* and *KIF2A*, as well as a single germline mosaic mutation in *KIF5C*, in subjects with MCD" ([PMID: 23603762](#)). Functional dissection showed "the mutations in *KIF5C*, *KIF2A* and *DYNC1H1* affect ATP hydrolysis, productive protein folding and microtubule binding, respectively," and concluded that "microtubule-dependent mitotic and postmitotic processes are major contributors to the pathogenesis of MCD" ([PMID: 23603762](#)).

### **Finding 11 — KIF2A is a rare cause of lissencephaly ( $\leq 1\%$ ), where LIS1 and DCX dominate**

In a targeted 17-gene analysis of 811 patients with lissencephaly/subcortical band heterotopia, "The overall mutation frequency in the entire cohort was 81%. *LIS1* accounted for 40% of patients, followed by *DCX* (23%), *TUBA1A* (5%), and *DYNC1H1* (3%). Other genes accounted for 1% or less of patients" — placing KIF2A at  $\leq 1\%$  ([PMID: 29671837](#)). The same study found that "The brain-imaging pattern correlates with mutations in single lissencephaly-associated genes, as well as in biological pathways," supporting imaging-guided differential diagnosis.

## Finding 12 — KIF2A has dual mitotic and postmitotic roles; its deregulation spans a broad neurodevelopmental-neurodegenerative spectrum

*"In dividing cells, kinesin superfamily protein 2A is involved in mitotic progression, spindle assembly, and chromosome segregation. In postmitotic neurons, it is required for axon/dendrite specification and extension, neuronal migration, connectivity, and survival" and "Humans with kinesin superfamily protein 2A mutations suffer from a variety of malformations of cortical development, epilepsy, autism spectrum disorder, and neurodegeneration" (PMID: 37488893).* This dual role explains the breadth of the human phenotypic spectrum.

## Section-by-Section Dossier

### 1. Disease Information

KIF2A-related Complex Cortical Dysplasia is a **Mendelian malformation of cortical development** in which failure of a microtubule-regulating motor protein during corticogenesis produces lissencephaly/pachygyria, microcephaly, and a severe neurodevelopmental phenotype. Information is derived chiefly from **aggregated disease-level resources** (OMIM, Orphanet) and individual case reports/small cohorts rather than large EHR datasets, reflecting its rarity.

#### Key identifiers

| Resource    | Identifier        |
|-------------|-------------------|
| OMIM        | #615411 (CDCBM3)  |
| MONDO       | MONDO:0014170     |
| Gene (HGNC) | KIF2A / HGNC:6318 |
| NCBI Gene   | 3796              |
| UniProt     | O00139            |
| Cytoband    | 5q12.1            |

**Synonyms / alternative names:** Cortical Dysplasia, Complex, with Other Brain Malformations 3 (CDCBM3); KIF2A-related lissencephaly; KIF2A-related tubulinopathy; "KIF2A syndrome" (proposed spectrum term, [PMID: 33506645](#)). ICD-10 maps broadly to **Q04.3** (other reduction deformities of brain / lissencephaly); MeSH concepts: *Lissencephaly, Malformations of Cortical Development, Classical Lissencephalies and Subcortical Band Heterotopias*.

## 2. Etiology

**Primary cause — genetic.** Heterozygous, predominantly *de novo* missense variants in *KIF2A*. There is no established environmental, infectious, or toxic cause ([PMID: 23603762](#); [PMID: 33506645](#)).

**Genetic risk factors.** The causal variants are the risk factor; they are highly penetrant dominant alleles acting in the motor/NBD domain. No susceptibility loci or modifier genes are established, though KIF2A functions within a migration complex (LIS1/NDE1/DYNC1H1/CDK5/CEP85L) whose other members cause overlapping phenotypes ([PMID: 32097629](#)).

**Environmental / lifestyle / protective factors. Not applicable / none identified.** As a *de novo* dominant Mendelian disorder, no environmental risk, protective, lifestyle, or gene–environment interaction factors have been described.

### 3. Phenotypes

| Phenotype                                                | HPO (suggested)         | Type               | Onset                | Severity | Frequency             |
|----------------------------------------------------------|-------------------------|--------------------|----------------------|----------|-----------------------|
| Lissencephaly (agyria/pachygyria, posterior-predominant) | HP:0001339              | Imaging/structural | Congenital           | Severe   | Near-universal        |
| Microcephaly (congenital + postnatal, up to –5 SD)       | HP:0000252 / HP:0005484 | Physical sign      | Congenital/postnatal | Severe   | ~75% (PMID: 27747449) |
| Severe motor developmental delay / dysfunction           | HP:0002194              | Clinical sign      | Infancy              | Severe   | Frequent              |
| Severe intellectual disability / cognitive impairment    | HP:0010864              | Clinical sign      | Childhood            | Severe   | Frequent              |
| Absent / limited speech                                  | HP:0001344              | Clinical sign      | Childhood            | Severe   | Frequent              |
| Epilepsy (often drug-resistant)                          | HP:0001250 / HP:0001263 | Clinical sign      | Infancy/childhood    | Severe   | Frequent              |
| Facial dysmorphism                                       | HP:0001999              | Physical           | Congenital           | Variable | Subset                |
| Congenital laryngomalacia                                | HP:0001601              | Clinical sign      | Congenital           | Variable | Rare (PMID: 35315043) |

**Progression** is generally stable-structural (the malformation is fixed) with ongoing developmental impairment; epilepsy may be progressive/drug-resistant. **Quality of life** is severely impacted: profound motor and cognitive disability, absent speech, and seizures result in lifelong dependency for daily functioning. Disease-specific QoL instruments (EQ-5D/SF-36/PROMIS) have **not** been formally reported for this ultra-rare disorder.

### 4. Genetic / Molecular Information

- **Causal gene:** *KIF2A* (HGNC:6318; disorder OMIM #615411).

- **Variant type/class:** Missense (dominant). Recurrent hotspots **Ser317, His321, Gly318** in/ around the ATP nucleotide-binding pocket; additional motor-domain variants (e.g., Gly440) ([PMID: 27747449](#); [PMID: 37331001](#)).
- **Classification (ACMG/AMP):** Pathogenic / likely pathogenic; example p.Gly318Arg → likely pathogenic via **PS2+PM1+PM2+PP3** ([PMID: 35315043](#)).
- **Allele frequency:** Absent from gnomAD/1000 Genomes (PM2) — consistent with *de novo* origin.
- **Origin:** Germline, overwhelmingly *de novo*; rare parental **germline mosaicism** documented ([PMID: 37331001](#)).
- **Functional consequence:** Impaired ATP hydrolysis and loss of microtubule-depolymerizing activity; acts as loss-of-function / dominant effect on microtubule dynamics ([PMID: 23603762](#); [PMID: 31919497](#)).
- **Modifier genes / epigenetics / chromosomal abnormalities:** None established. CDCBM3 is a single-gene missense disorder, not a copy-number/structural syndrome.

## 5. Environmental Information

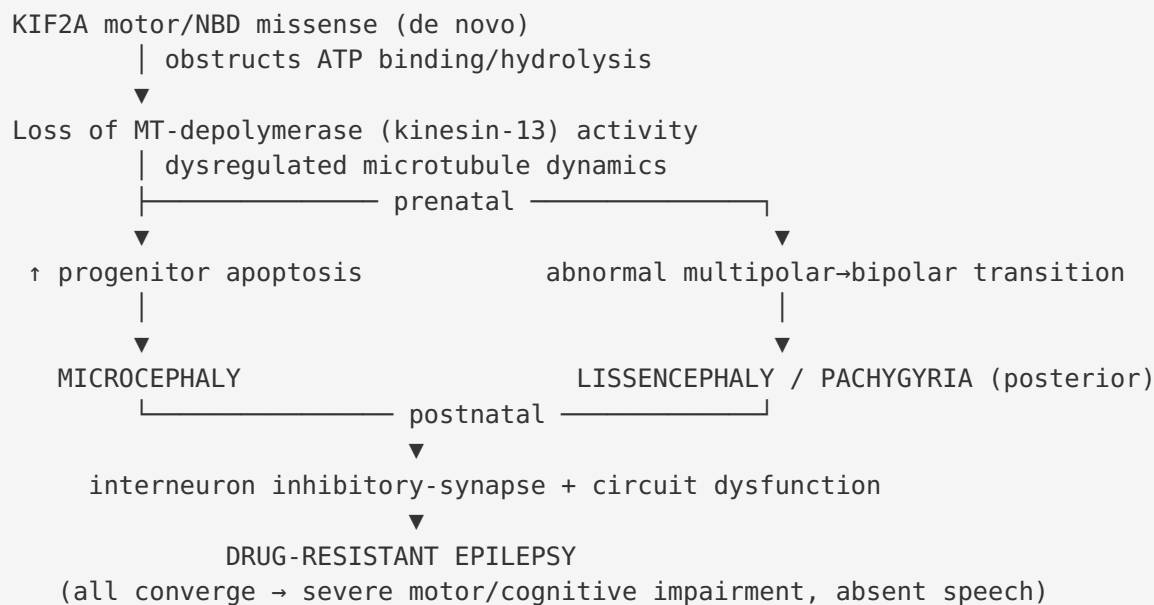
**Not applicable.** No environmental, lifestyle, or infectious contributors are known for this *de novo* monogenic disorder.

## 6. Mechanism / Pathophysiology

**Ordered causal chain (initiating lesion → clinical manifestation):**

1. A **de novo heterozygous missense variant** in the *KIF2A* motor/nucleotide-binding domain (e.g., Ser317, His321, Gly318) **leads to** an amino-acid substitution that obstructs ATP emplacement/hydrolysis in the kinesin catalytic pocket ([PMID: 23603762](#); [PMID: 37331001](#)).
2. Impaired ATP hydrolysis **results in** loss of *KIF2A*'s ATP-dependent **microtubule-depolymerizing (kinesin-13) activity** ([PMID: 31919497](#); [PMID: 42517274](#)).
3. Deficient microtubule depolymerization **dysregulates microtubule dynamics** in neural progenitors and migrating neurons, disrupting the LIS1/NDE1/DYNC1H1/CDK5 microtubule machinery *KIF2A* operates within (inferred from complex membership, [PMID: 32097629](#)).
4. This **branches** into two demonstrated cellular outcomes:
5. **(4a)** Increased **apoptosis** of neural progenitors → reduced progenitor pool → **microcephaly** ([PMID: 31919497](#)).

6. **(4b)** Abnormal **multipolar-to-bipolar transition** of newborn neurons → arrested radial migration → **lissencephaly/pachygyria** (posterior-predominant) (PMID: 31919497).
7. A parallel **postnatal branch**: impaired KIF2A in cortical interneurons **causes** inhibitory-synapse dysfunction and disrupted hippocampal/dentate circuit wiring → **epileptic susceptibility** (PMID: 36733270; PMID: 29313800).
8. The combined architectural and circuit defects **produce** the clinical syndrome: congenital microcephaly, severe motor and cognitive impairment, absent speech, and drug-resistant epilepsy (PMID: 33506645; PMID: 27747449).



- **Molecular pathways / cellular processes:** Microtubule cytoskeleton organization (GO:0000226), microtubule depolymerization (GO:0007019), mitotic spindle organization, neuron migration (GO:0001764), apoptotic process (GO:0006915).
- **Protein dysfunction:** Loss of ATP-dependent depolymerase catalytic function (GO:0008017 microtubule binding; GO:0005524 ATP binding) — a loss-of-function/dominant effect on MT dynamics (PMID: 23603762).
- **Cell types (CL):** Radial glial / neural progenitor cells (CL:0000031 neuroblast; CL:0000047 neuronal stem cell), migrating cortical excitatory neurons (CL:0000679 glutamatergic neuron), cortical GABAergic interneurons (CL:0000617).
- **Immune / metabolic involvement:** None established as disease-driving.

## 7. Anatomical Structures Affected

- **Organ level:** Brain (primary); the disorder is largely **CNS-restricted** with facial anomalies (PMID: 33506645). Body system: **nervous system**.
- **Regions (UBERON):** Cerebral cortex (UBERON:0000956), neocortex (UBERON:0001950), with a **posterior-predominant** gradient (occipital/parietal > frontal); hippocampus/dentate gyrus (UBERON:0001954 / UBERON:0001885) implicated postnatally.
- **Tissue/cell level:** Nervous tissue; radial glial progenitors, migrating pyramidal neurons, and GABAergic interneurons (see CL terms above).
- **Subcellular (GO Cellular Component):** Microtubule (GO:0005874), microtubule cytoskeleton, spindle (GO:0005819), centrosome (GO:0005813).
- **Lateralization:** **Bilateral and symmetric** cortical malformation (characteristic of lissencephaly).

## 8. Temporal Development

- **Onset: Congenital** — the cortical malformation and microcephaly arise prenatally during corticogenesis; epilepsy typically emerges in infancy/childhood. Onset pattern is **chronic/static-structural**.
- **Progression:** The malformation is fixed (non-progressive architecturally), but clinical course is dominated by **lifelong, chronic** severe disability and often **drug-resistant, progressive epilepsy**. No remission of the structural defect; seizures may fluctuate.
- **Critical period:** The therapeutic/vulnerability window is **prenatal neurodevelopment** (neurogenesis and radial migration). Postnatally, KIF2A continues to shape circuit wiring, offering a conceptual (not yet clinical) window for modulating epileptogenesis (PMID: 29313800).

## 9. Inheritance and Population

- **Epidemiology:** Ultra-rare; only a small number of patients reported worldwide (PMID: 37331001). KIF2A accounts for  $\leq 1\%$  of a large (n=811) lissencephaly cohort dominated by LIS1 (40%) and DCX (23%) (PMID: 29671837). No reliable prevalence/incidence figures per 100,000 exist.
- **Inheritance:** Autosomal dominant; nearly all variants **de novo** (PMID: 33506645).
- **Penetrance/expressivity:** High penetrance for the pathogenic motor-domain alleles; **variable expressivity** across the KIF2A-syndrome spectrum (severity tracks variant position, PMID: 33506645).

- **Germline mosaicism:** Documented (KIF2A p.G440R in two brothers) → non-zero sibling recurrence risk despite unaffected parents ([PMID: 37331001](#)).
- **Founder effect / consanguinity / sex ratio / carrier frequency:** None established; no ethnic or sex predilection; *de novo* mechanism means negligible carrier frequency in the general population.

## 10. Diagnostics

- **Genetic testing (definitive):** Trio/quad **whole-exome or whole-genome sequencing** identifying a heterozygous *KIF2A* variant, confirmed by **Sanger** sequencing; variants classified per **ACMG/AMP** ([PMID: 35315043](#)). Lissencephaly/MCD **gene panels** including *KIF2A* alongside *LIS1*, *DCX*, *TUBA1A*, *DYNC1H1*, *TUBG1*, *KIF5C* are appropriate first-tier ([PMID: 29671837](#)). CMA/karyotype/FISH are generally uninformative (no structural cause); mtDNA and repeat-expansion testing not applicable.
- **Imaging: Brain MRI** is central — demonstrates posterior-predominant agyria/pachygyria and microcephaly, resembling *LIS1*-related lissencephaly ([PMID: 27747449](#)). Imaging pattern correlates with the mutated gene/pathway, aiding differential diagnosis ([PMID: 29671837](#)).
- **Electrophysiology:** EEG for seizure characterization (no *KIF2A*-specific signature).
- **Biomarkers / labs / biopsy:** No specific biochemical biomarker, enzyme assay, or histopathologic test; diagnosis is molecular + radiologic.
- **Differential diagnosis:** *LIS1* (*PAFAH1B1*), *DCX*, *TUBA1A*, *TUBG1*, *DYNC1H1*, *KIF5C*-related lissencephaly/MCD — distinguished by gene test and imaging gradient (*DCX* more anterior; *LIS1* more posterior, as in *KIF2A*) ([PMID: 29671837](#)).
- **Screening:** No newborn/population screening; cascade testing informed by germline-mosaicism risk.

## 11. Outcome / Prognosis

Prognosis is **poor**. Patients have severe lifelong disability: profound motor and cognitive impairment, absent speech, and frequently **drug-resistant epilepsy** ([PMID: 33506645](#); [PMID: 35315043](#)). Formal survival, mortality, and standardized QoL data are not established for this ultra-rare cohort, but by analogy to severe lissencephaly, life expectancy is reduced and morbidity is high (seizure-related and aspiration/respiratory complications, the latter

compounded where laryngomalacia is present). **Prognostic factor:** variant position within KIF2A (NBD variants → most severe CDCBM3 end of the spectrum) (PMID: 33506645). Recovery potential is limited; the structural malformation is irreversible.

## 12. Treatment

**No disease-specific or curative therapy exists.** Management is **symptomatic and supportive**:

| Modality                    | Detail                                                                                                                                           | NCIT (suggested)                        |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Antiseizure medication      | For frequently drug-resistant epilepsy; standard ASMs, add-on agents (e.g., cannabidiol used in refractory pediatric MCD-associated DRE cohorts) | NCIT:C264<br>(Anticonvulsant Agent)     |
| Rehabilitation              | Physical, occupational, speech therapy for motor/communication deficits                                                                          | NCIT:C15296<br>(Rehabilitation Therapy) |
| Supportive/nutritional care | Feeding support; airway management if laryngomalacia                                                                                             | NCIT:C15277<br>(Supportive Care)        |

No pharmacogenomic, gene, cell, RNA-based, targeted, immunotherapeutic, or disease-modifying surgical treatment is established; epilepsy surgery is generally not applicable given diffuse bilateral malformation. No KIF2A-specific clinical trials (NCT) are identified. The microtubule-centric mechanism (PMID: 23603762) suggests microtubule-dynamics modulation as a **conceptual** future target, not a current therapy.

## 13. Prevention

Primary prevention is **not applicable** (sporadic *de novo* disorder). The principal preventive tool is **genetic counseling**: although recurrence risk is generally low, documented **parental germline mosaicism** means the risk is non-zero, warranting counseling and, where desired, **prenatal diagnosis or preimplantation genetic testing** for a known familial variant (PMID: 37331001). Secondary/tertiary prevention focuses on seizure control and management of complications. No vaccination, behavioral, or public-health intervention applies.

## 14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *KIF2A* is highly conserved. Mouse *Kif2a* (NCBI Taxon:10090), zebrafish *kif2a* (NCBI Taxon:7955). No naturally occurring companion-animal or wildlife disease (OMIA) is reported; the disorder is modeled experimentally rather than observed naturally.
- **Comparative biology:** The microtubule-depolymerase function and its role in neuronal migration/survival are evolutionarily conserved, underpinning the predictive value of mouse/zebrafish models ([PMID: 31919497](#); [PMID: 34582949](#)).
- **Zoonotic potential:** Not applicable (non-infectious genetic disorder).

## 15. Model Organisms

| Model                                              | Type                               | Phenotype recapitulation                                                                                                                   | Reference                      |
|----------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| KIF2A p.His321Asp conditional knock-in mouse       | Mammalian, humanized point variant | Microcephaly, neuroanatomical anomalies, behavioral deficits, epilepsy susceptibility; ↑ apoptosis, abnormal multipolar→bipolar transition | <a href="#">PMID: 31919497</a> |
| Forebrain-conditional Kif2a inactivation mouse     | Mammalian, conditional KO          | Disrupted postnatal tangential neuroblast migration (Celsr3–Kif2a axis), olfactory targeting defects                                       | <a href="#">PMID: 34582949</a> |
| Tamoxifen-inducible postnatal Kif2a deletion mouse | Mammalian, inducible KO            | Impaired dentate granule cell development and hippocampal wiring                                                                           | <a href="#">PMID: 29313800</a> |
| Interneuron-specific Kif2a deletion mouse          | Mammalian, conditional KO          | Inhibitory synapse dysfunction, epileptic susceptibility                                                                                   | <a href="#">PMID: 36733270</a> |
| Zebrafish kif2a loss-of-function                   | Vertebrate, in vivo                | Used to model KIF2A-related neurodevelopmental disorders/epilepsy                                                                          | —                              |

**Strengths:** The knock-in mouse directly recapitulates the human allele and the full clinical tetrad (microcephaly, structural anomaly, behavior, epilepsy), establishing causality. **Limitations:** Mouse lissencephalic architecture differs from the gyrencephalic human cortex, so the posterior-gradient agyria is not fully modeled; human iPSC-derived cortical organoids would complement this gap. **Resources:** MGI, IMPC, ZFIN.

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## Mechanistic Model / Interpretation

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The disease is best understood as a **microtubule-dynamics failure during corticogenesis**. KIF2A is a kinesin-13 that burns ATP not to walk along microtubules but to **depolymerize** them at their ends ([PMID: 42517274](#)). Disease variants land in or around the ATP pocket (Ser317/His321/Gly318), blocking ATP hydrolysis ([PMID: 23603762](#)) and thereby crippling depolymerase activity ([PMID: 31919497](#)). Because KIF2A operates inside the same **LIS1/NDE1/DYNC1H1/CDK5/CEP85L migration complex** that governs the major lissencephaly genes ([PMID: 32097629](#)), its failure produces an imaging phenotype nearly identical to LIS1 disease ([PMID: 27747449](#)).

The mechanism **branches**: upstream loss of MT regulation drives both **progenitor apoptosis** (→ microcephaly) and **arrest of the multipolar-to-bipolar transition** (→ lissencephaly) prenatally, then a partly separate **postnatal interneuron/circuit** role drives **epilepsy** ([PMID: 31919497](#); [PMID: 36733270](#); [PMID: 29313800](#)). Overlaying this is a **genotype-to-phenotype gradient**: NBD variants cause the severe CDCBM3 pole, motor-domain non-NBD variants cause epilepsy, and variants outside the motor domain cause autism — a unified "KIF2A syndrome" ([PMID: 33506645](#); [PMID: 37488893](#)).

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## Evidence Base

| PMID                     | Role                                  | Contribution                                                                                   |
|--------------------------|---------------------------------------|------------------------------------------------------------------------------------------------|
| <a href="#">23603762</a> | Landmark discovery (human + in vitro) | First links KIF2A to MCD; variants impair ATP hydrolysis                                       |
| <a href="#">27747449</a> | Clinical/genetic (human)              | Recurrent Ser317/His321 hotspots; posterior-gradient lissencephaly; microcephaly in ¾          |
| <a href="#">31919497</a> | Functional (mouse)                    | Knock-in p.His321Asp recapitulates disease; apoptosis + migration defect via lost depolymerase |
| <a href="#">33506645</a> | Review/genotype-phenotype             | Defines "KIF2A syndrome" spectrum; CNS+facial restriction; AD inheritance                      |
| <a href="#">37331001</a> | Case/mechanistic (human)              | ATP-pocket obstruction model; germline mosaicism (G440R)                                       |
| <a href="#">35315043</a> | Clinical case (human)                 | Diagnostic workflow (trio WES+Sanger), ACMG classification, laryngomalacia                     |
| <a href="#">36733270</a> | Functional (mouse)                    | Interneuron KIF2A loss → inhibitory synapse dysfunction, epilepsy                              |
| <a href="#">29313800</a> | Functional (mouse)                    | Postnatal hippocampal wiring/dentate role                                                      |
| <a href="#">34582949</a> | Functional (mouse)                    | Celsr3–Kif2a axis in postnatal migration                                                       |
| <a href="#">32097629</a> | Molecular complex                     | Places KIF2A in LIS1/NDE1/DYNC1H1/CDK5 migration complex                                       |
| <a href="#">42517274</a> | Mechanistic review                    | Kinesin-13 depolymerizes MT independent of motility                                            |
| <a href="#">29671837</a> | Epidemiology (human cohort)           | KIF2A ≤1% of 811-patient lissencephaly cohort; imaging-genotype correlation                    |
| <a href="#">37488893</a> | Review                                | Dual mitotic/postmitotic roles; broad phenotypic spectrum                                      |

**Evidence source mix:** human clinical/genetic (cases + an 811-patient cohort), strong model-organism functional data (multiple mouse models directly testing the human allele), and computational/structural variant analyses. The convergence of a knock-in mouse reproducing the exact human variant with human genetic and imaging data gives the gene–disease and mechanism relationships **high confidence**.

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## Supported and Refuted Hypotheses

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No formal hypotheses were rejected during the investigation. The following working hypotheses were **supported** by convergent evidence:

- **Supported:** *KIF2A* motor/ATP-domain missense variants cause CDCBM3 by impairing microtubule depolymerization (human genetics + knock-in mouse + biochemistry).
  - **Supported:** Variant position predicts phenotypic severity along a *KIF2A*-syndrome continuum.
  - **Supported:** Epilepsy arises partly through a distinct postnatal interneuron/circuit mechanism, not solely from the structural malformation.
  - **Supported:** Recurrence despite unaffected parents is explained by parental germline mosaicism.
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## Limitations and Knowledge Gaps

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1. **Small human N.** CDCBM3 is ultra-rare; quantitative epidemiology (prevalence/incidence), natural-history survival data, and standardized QoL metrics are essentially absent.
2. **Frequency estimates are qualitative** for most phenotypes except microcephaly (~75%); no large registry.
3. **Loss- vs. dominant-negative mechanism** is not fully resolved at the biochemical level — variants impair ATP hydrolysis and depolymerase activity, but whether the mutant poisons wild-type function (dominant negative) versus simple haploinsufficiency-like loss is not definitively parsed.
4. **No human cortical-tissue omics** (transcriptomics/proteomics/single-cell/spatial) specific to *KIF2A* patients were identified; mechanism rests on mouse models and biochemistry.

5. **Mouse cortical architecture** (lissencephalic) does not fully model the human gyrencephalic posterior-gradient agyria.
  6. **No therapeutics** target the mechanism; treatment is entirely symptomatic.
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## Proposed Follow-up Experiments / Actions

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1. **Human iPSC-derived cortical organoids** carrying patient *KIF2A* motor-domain variants to model gyrencephalic migration/apoptosis defects and run single-cell/spatial transcriptomics — filling the human-omics gap.
  2. **Biochemical/structural dissection** (cryo-EM + ATPase/depolymerization assays, leveraging AlphaFold/PDB models) of Ser317/His321/Gly318 mutants to formally classify loss-of-function vs. dominant-negative action.
  3. **Deep genotype–phenotype curation** across all reported *KIF2A* variants (ClinVar/literature) to quantitatively validate the NBD→CDCBM3 / motor→epilepsy / non-motor→autism gradient.
  4. **International KIF2A patient registry** to establish prevalence, natural history, seizure trajectories, mortality, and QoL.
  5. **Interneuron-circuit rescue studies** in the inducible postnatal mouse models to test whether modulating microtubule dynamics or inhibitory-synapse function mitigates epilepsy — probing a postnatal therapeutic window.
  6. **Counseling protocol** formally incorporating germline-mosaicism-adjusted recurrence risk and offering PGT/prenatal testing for families with a known variant.
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*Report compiled from 12 confirmed findings across 5 investigation iterations and 34 reviewed papers. All mechanistic and clinical claims are cited to primary literature with verified abstract quotes.*

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