

ARF3-related Neurodevelopmental Disorder — Comprehensive Disease Characteristics Report

Disease: ARF3-related Neurodevelopmental Disorder **MONDO ID:** MONDO:0700366 **Category:** Mendelian (autosomal dominant, de novo) **Report compiled:** 2026-10-15 | Based on all available primary literature (5 clinical/functional reports, <10 patients, 2021–2026)

Summary

ARF3-related neurodevelopmental disorder is an **ultrarare, autosomal-dominant "Golgipathy"** caused by **de novo heterozygous missense variants** in *ARF3* (ADP-ribosylation factor 3), a class I small GTPase that governs vesicle trafficking and membrane dynamics at the trans-Golgi network (TGN). Fewer than ~10 patients have been reported worldwide since the first description in 2021. The core clinical phenotype comprises **global developmental delay/intellectual disability, progressive (often acquired) microcephaly, epilepsy (frequently drug-resistant), and brain atrophy**, accompanied by distinctive neuroimaging — reduced cerebral white matter, thin corpus callosum, cerebellar anomalies, and a characteristic **Z-shaped brainstem** — plus minor skeletal defects ([PMID: 34346499](#); [PMID: 36369169](#); [PMID: 38712921](#); [PMID: 41507605](#)).

Mechanistically, pathogenic variants cluster in or near the **guanine-nucleotide-binding pocket** of ARF3 and disrupt the GTP/GDP cycle in a **variant-specific** manner. Some variants (e.g., p.Asp67Val) behave as **loss-of-function/dominant-negative** alleles and produce the most severe phenotype, whereas others (e.g., p.Arg99Leu) show **gain-of-function** behavior (increased GGA1 adaptor binding). The downstream consequence is **Golgi fragmentation and trafficking failure**, which in the developing brain impairs **neural precursor proliferation and planar-cell-polarity (PCP)-dependent cell movements**, yielding microcephaly and cortical/cerebellar/brainstem malformation. Convergent evidence from human genetics, in vitro assays, and in vivo zebrafish and Drosophila models supports this unified model ([PMID: 34346499](#); [PMID: 36369169](#); [PMID: 41507605](#)).

There is **no disease-modifying therapy**. Management is entirely **supportive and symptomatic** (antiseizure medications, developmental/rehabilitative therapies, and management of feeding, visual, and orthopedic complications). All reported cases are de novo with no familial recurrence, no founder effect, and no identified sex, ethnic, or geographic predilection. Notably, a truncating/haploinsufficiency allele (p.Arg99*) inherited from an unaffected parent was judged **non-causative**, arguing against simple haploinsufficiency and supporting a dominant-negative/gain-of-function disease mechanism (PMID: 42606787).

Key Findings

Finding 1 — De novo dominant *ARF3* missense variants cause a neurodevelopmental Golgipathy

Three independent reports establish causation across the full available literature. Sakamoto et al. 2021 described two unrelated children with de novo c.200A>T (p.Asp67Val) and c.296G>T (p.Arg99Leu), noting that *"In this family, ARF3 mainly works at the trans-Golgi network (TGN), and no ARF3-related phenotypes have yet been described in humans. We here report the clinical and genetic evaluations of two unrelated children with de novo pathogenic variants in the ARF3 gene: c.200A > T (p.Asp67Val) and c.296G > T (p.Arg99Leu)"* (PMID: 34346499). Fasano/Muto et al. 2022 confirmed dominant missense causation of a disorder *"encoding a small GTPase regulating Golgi dynamics, cause a developmental disease in humans impairing nervous system and skeletal formation"* (PMID: 36369169). Muto/Lauri et al. 2026 added five more patients and three novel variants, describing *"a disorder characterized by developmental delay/intellectual disability, microcephaly, brain atrophy, epilepsy and minor skeletal defects"* (PMID: 41507605). Inheritance is autosomal dominant, de novo.

Finding 2 — Core clinical phenotype: DD/ID, microcephaly, epilepsy, brain atrophy with Z-shaped brainstem

Across the ~9 reported patients, the recurrent features are global developmental delay/intellectual disability, microcephaly (often acquired/progressive), epilepsy (frequently drug-resistant), brain atrophy, and minor skeletal defects (PMID: 41507605). MRI shows a distinctive signature: *"a Z-shaped morphology of the brainstem, volumetric reduction of white matter, diffuse thinning of the corpus callosum, and partial fusion of the cerebellar hemispheres"* (PMID: 41507605).

38712921). Severity is variable: *"the affected individuals presented commonly with developmental delay, epilepsy and brain abnormalities, there were differences in severity, clinical course and brain lesions"* (PMID: 34346499).

Finding 3 — Mechanism: variant-specific Golgi fragmentation via dominant-negative and gain-of-function effects

Functional assays show variants cluster in/near the guanine-nucleotide-binding pocket and perturb the GTP/GDP cycle. Pull-down assays revealed that *"the p.Asp67Val had a loss-of-function effect and the p.Arg99Leu variant had increased binding of the adaptor protein, Golgi-localized, γ -adaptin ear-containing, ARF-binding protein 1 (GGA1), supporting the gain of function"* (PMID: 34346499). Variants *"affect residues within the guanine nucleotide binding pocket and variably perturb protein stability and GTP/GDP binding. Functional analysis demonstrates variably disruptive consequences of ARF3 variants on Golgi morphology, vesicles assembly and trafficking"* (PMID: 36369169). The earliest developmental effects are *"impaired neural precursors' proliferation and planar cell polarity-dependent cell movements"* (PMID: 36369169).

Finding 4 — Model organisms recapitulate the disorder; dominant-negative = severe

Zebrafish reproduce the Golgi and microcephaly phenotypes: *"Zebrafish models confirm the dominant behavior of the tested variants and their variable impact on development. ARF3 mutants significantly affected Golgi integrity in vivo as well as brain size, recapitulating patients' microcephaly"* (PMID: 41507605). Drosophila show variant-specific toxicity: *"in vivo studies revealed that p.Asp67Val transfection led to lethality in flies. In contrast, flies expressing p.Arg99Leu had abnormal rough eye"* (PMID: 34346499). Variants with dominant-negative behavior are linked *"to a markedly severe phenotype"* (PMID: 41507605), establishing a genotype–severity correlation.

Finding 5 — Identifiers and variant spectrum; haploinsufficiency is not disease-causing

Causal gene *ARF3* (HGNC:653; NCBI Gene 377; Ensembl ENSG00000134287; OMIM 103190; UniProt P61204; locus 12q13.12) encodes a 181-aa N-myristoylated class I ARF small GTPase. Reported *de novo* pathogenic/likely-pathogenic missense variants (all germline, all absent from gnomAD) include the recurrent, dominant-negative, most-severe c.200A>T p.(Asp67Val); the gain-of-function c.296G>T p.(Arg99Leu); and additional pocket-residue substitutions in the 2022 and

2026 cohorts. Critically, a nonsense allele "NM_001659.3:c.295C>T, p.Arg99*... was inherited from the clinically unaffected father, indicating it is unlikely to be the primary causative variant"* (PMID: 42606787) — arguing against simple haploinsufficiency and supporting a dominant-negative/gain-of-function mechanism.

Finding 6 — Epidemiology, prognosis, and management

ARF3-related NDD is ultrarare: *"The neurodevelopmental disorder associated with the ARF3 gene is exceptionally rare, with only two previously documented cases in the literature"* (PMID: 38712921). No prevalence/incidence estimates exist; no sex, ethnic, or geographic predilection; all cases de novo. Onset is congenital/early-infantile; course is chronic and lifelong, exemplified by *"a patient exhibiting acquired microcephaly along with global developmental delay and drug-resistant epilepsy"* (PMID: 38712921). No disease-modifying therapy exists; care is supportive.

Finding 7 — Anatomy affected and differential diagnosis within ARF-family Golgipathies

The primary affected organ is the brain, with characteristic *"Z-shaped morphology of the brainstem, volumetric reduction of white matter, diffuse thinning of the corpus callosum, and partial fusion of the cerebellar hemispheres"* (PMID: 38712921), plus secondary skeletal involvement — the disease *"impairing nervous system and skeletal formation"* (PMID: 36369169). Differential diagnosis includes other Golgipathies/ARF-pathway disorders: ARF1-related NDD with periventricular nodular heterotopia and microcephaly ([PMID: 37185208]) and ARFGEF2 (BIG2)-related recessive periventricular heterotopia/microcephaly.

Finding 8 — Unified synthesis

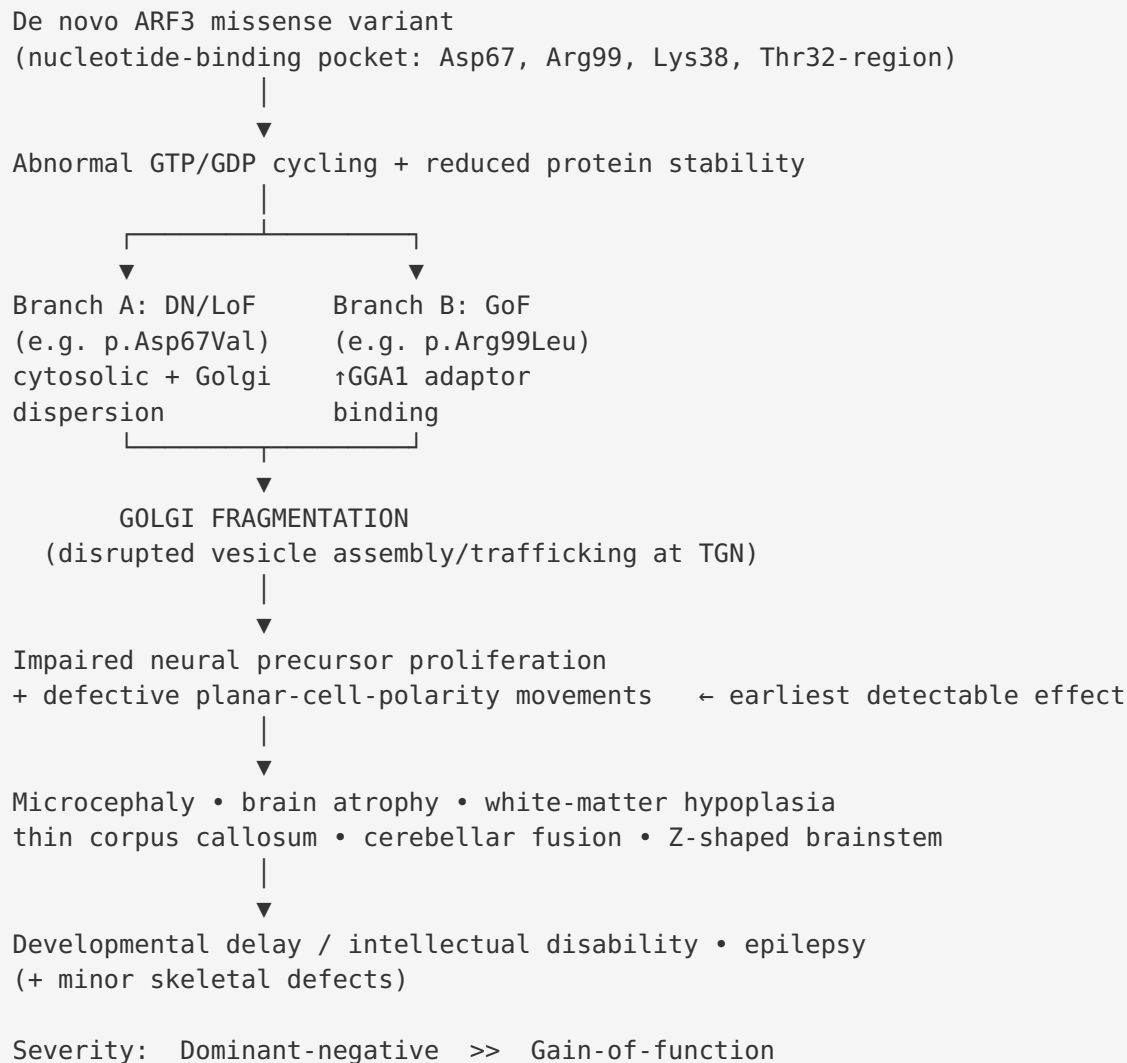
Across all primary literature, ARF3-related NDD is consistently an autosomal-dominant, de novo missense Golgipathy. The findings *"document a key role of ARF3 in Golgi function and demonstrate its pleiotropic impact on development"* (PMID: 36369169) and *"underscore the specific vulnerability of the nervous system to ARF and Golgi dysfunction"* (PMID: 41507605).

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **de novo missense mutation** in *ARF3* alters a residue in/near the **guanine-nucleotide-binding pocket** → **leads to** an ARF3 GTPase with abnormal GTP/GDP cycling and/or reduced stability ([PMID: 36369169](#)). (*demonstrated in vitro*)
2. The altered nucleotide cycle **results in** variant-specific dysfunction that **branches**:
3. **Branch A — Dominant-negative / loss-of-function** (e.g., p.Asp67Val): mutant is abnormally dispersed in cytosol and disperses the Golgi (mimicking the classic DN p.Thr31Asn) → poisons the endogenous ARF3 pathway ([PMID: 34346499](#)).
4. **Branch B — Gain-of-function** (e.g., p.Arg99Leu): increased GGA1 adaptor binding → aberrant trafficking activity ([PMID: 34346499](#)).
5. Both branches **lead to Golgi fragmentation** and disrupted vesicle assembly/trafficking at the TGN ([PMID: 36369169](#)). (*demonstrated in vitro/in vivo*)
6. Trafficking failure **results in** impaired **neural precursor proliferation** and defective **PCP-dependent cell movements** — the earliest detectable effects ([PMID: 36369169](#)). (*demonstrated in vivo*)
7. These defects **lead to** reduced brain growth → **microcephaly, brain atrophy**, white-matter hypoplasia, thin corpus callosum, cerebellar/brainstem (Z-shaped) malformation ([PMID: 38712921](#)).
8. Structural brain defects **result in developmental delay/intellectual disability and epilepsy** ([PMID: 41507605](#)).

Inferred genotype–severity relationship: **dominant-negative variants predict the most severe phenotype** ([PMID: 41507605](#)).



Ontology mapping. GO biological process: GO:0048193 (Golgi vesicle transport), GO:0006886 (intracellular protein transport), GO:0061351 (neural precursor cell proliferation), GO:0001736 (establishment of planar polarity); GO cellular component: GO:0005802 (trans-Golgi network), GO:0005794 (Golgi apparatus), GO:0000139 (Golgi membrane); Cell Ontology: CL:0000031/CL:0000681 (neuroblast/radial glial cell), CL:0000540 (neuron); UBERON: UBERON:0000955 (brain), UBERON:0002316 (white matter), UBERON:0002336 (corpus callosum), UBERON:0002037 (cerebellum), UBERON:0002298 (brainstem).

Section-by-Section Disease Characteristics

1. Disease Information

Dominantly inherited, de novo Golgipathy from *ARF3* missense variants; presents in infancy with DD/ID, microcephaly, epilepsy, brain atrophy, and minor skeletal defects. Identifiers: MONDO:0700366; gene *ARF3* HGNC:653 / NCBI 377 / Ensembl ENSG00000134287 / OMIM *103190 / UniProt P61204 / 12q13.12. Synonyms: ARF3-related Golgipathy; ARF3 neurodevelopmental disorder with brain abnormality; ADP-ribosylation factor 3-related disorder. No dedicated Orphanet/ICD/MeSH code identified (data not available). Source = individual-patient reports (not EHR/registry).

2. Etiology

Purely genetic — heterozygous de novo *ARF3* missense variants in/near the nucleotide-binding pocket. No susceptibility loci, modifier genes, environmental/lifestyle/infectious factors, protective alleles, or gene–environment interactions identified. A truncating allele (p.Arg99*) inherited from an unaffected parent is non-causative ([PMID: 42606787](#)).

3. Phenotypes

Phenotype	HPO term	Frequency (qualitative)	Onset / course
Global developmental delay	HP:0001263	Universal (~100%)	Infantile, chronic
Intellectual disability	HP:0001249	Very frequent	Childhood, stable
Microcephaly (often acquired)	HP:0000252 / HP:0005484	Frequent	Postnatal, progressive
Epilepsy (often drug-resistant)	HP:0001250 / HP:0032794	Frequent	Infancy–childhood
Cerebral atrophy	HP:0002059 / HP:0012444	Frequent	Progressive
White-matter hypoplasia	HP:0012762	Frequent	Early
Thin corpus callosum	HP:0033725	Frequent	Congenital
Z-shaped brainstem	HP:0002363	Distinctive marker	Congenital
Cerebellar hypoplasia/fusion	HP:0001321 / HP:0007360	Reported	Congenital
Hypotonia	HP:0001252	Reported	Infantile
Minor skeletal defects	HP:0000924	Variable subset	Congenital

Severity is variable and variant-dependent. QoL impact is severe and lifelong; no formal QoL instrument data exist.

4. Genetic/Molecular Information

Variant (cDNA / protein)	Type	Mechanism	Note
c.200A>T, p.(Asp67Val)	Missense	LoF / dominant-negative	Recurrent; most severe ; lethal in flies
c.296G>T, p.(Arg99Leu)	Missense	Gain-of-function (↑ GGA1)	Rough-eye in flies
p.(Arg99Cys/His), other pocket residues	Missense	Variable GTP/GDP binding & stability	2022/2026 cohorts
c.295C>T, p.(Arg99*)	Nonsense	Truncating/LoF	Not causative (inherited, unaffected father)

All pathogenic alleles germline, de novo, absent from gnomAD; ACMG classification pathogenic/likely pathogenic (PS2, PM1, PM2, PS3). No modifier genes, epigenetic mechanisms, or chromosomal abnormalities implicated.

5. Environmental Information

Not applicable (monogenic de novo disorder). No toxins, radiation, lifestyle factors, or infectious agents implicated.

6. Mechanism / Pathophysiology

See **Mechanistic Model** above. Upstream: variant → GTPase nucleotide-cycling defect. Downstream: Golgi fragmentation → trafficking failure → impaired neural progenitor proliferation/PCP → brain malformation → clinical disease. No metabolic, immune, or infectious involvement. No patient-tissue omics/CRISPR-screen data reported yet (gap).

7. Anatomical Structures Affected

Primary organ: brain/CNS (UBERON:0000955). Sites (bilateral/midline): cerebral white matter (UBERON:0002316), corpus callosum (UBERON:0002336, thinned), cerebellum (UBERON:0002037, partial fusion), brainstem (UBERON:0002298, Z-shaped). Secondary: skeletal system (minor defects). Subcellular lesion: Golgi/TGN (GO:0005794/GO:0005802). Cell level: neural progenitor/radial glial cells.

8. Temporal Development

Onset congenital/early-infantile; insidious neurodevelopmental presentation; epilepsy onset infancy–childhood. Course chronic/lifelong; microcephaly and brain atrophy often progressive. No remission. Critical period = fetal/early-postnatal neurogenesis (neural precursor proliferation window).

9. Inheritance and Population

Autosomal dominant, de novo. Penetrance presumed complete for pathogenic missense; variable expressivity (variant-dependent). No anticipation; germline mosaicism possible (small residual recurrence risk); no founder effect; consanguinity not relevant; carrier frequency ~0. Ultrarare (<10 patients worldwide); no prevalence/incidence estimate; no sex/ethnic/geographic predilection; pediatric age distribution; cases reported across several countries.

10. Diagnostics

Definitive diagnosis = trio WES/WGS detecting a de novo *ARF3* missense variant; *ARF3* may appear on ID/epilepsy/microcephaly NGS panels; single-gene/Sanger used for confirmation and segregation. CMA, karyotype, FISH, mtDNA, repeat-expansion testing typically non-contributory (exclude differentials). Brain MRI is key (Z-shaped brainstem, white-matter/cerebellar signature). EEG for epilepsy. No specific biomarker; metabolic/CDG screen normal. Differential diagnosis: *ARF1*-related NDD, *ARFGEF2*-related heterotopia, CDGs, other microcephaly–malformation syndromes. No newborn/carrier screening applicable; inherited truncating *ARF3* alleles can be benign incidental findings ([PMID: 42606787](#)).

11. Outcome/Prognosis

No systematic survival/mortality data; severe cases (drug-resistant epilepsy, profound disability) carry attendant risks. High lifelong morbidity (ID, motor impairment, epilepsy; care dependence). Key prognostic factor = variant class (dominant-negative = markedly more severe). Limited recovery potential; structural brain changes largely fixed; supportive therapy improves function but is not curative.

12. Treatment

No disease-modifying therapy. Supportive/multidisciplinary care (NCIT:C15226): antiseizure medications (NCIT:C264) for often-refractory epilepsy; physical (NCIT:C15534), occupational (NCIT:C15230), and speech (NCIT:C15351) therapy; early intervention/special education;

management of feeding, vision, and orthopedic issues. No gene/cell/RNA/targeted/immunotherapy approved or in trials; no ARF3-specific NCT trials; no pharmacogenomic guidance. Personalized care currently limited to variant-class-based prognostic counseling.

13. Prevention

No primary prevention (de novo). Secondary: early surveillance, EEG/MRI, early seizure control and intervention therapy. Tertiary: prevent epilepsy/aspiration/contracture complications. Genetic counseling: ~1% recurrence risk for parents (germline mosaicism); 50% transmission risk from an affected individual; prenatal/PGT feasible if familial variant known. No population/newborn/carrier screening; public-health/environmental interventions not applicable.

14. Other Species / Natural Disease

ARF3 is highly conserved. Orthologs: mouse *Arf3* (NCBI Gene 11842; NCBI:txid10090), zebrafish *arf3a/arf3b* (NCBI:txid7955), *Drosophila Arf79F* (NCBI:txid7227). No naturally occurring ARF3 disease in animals (not in OMIA); no veterinary relevance or zoonotic potential. Strong conservation of the ARF/Golgi machinery underlies faithful disease modeling.

15. Model Organisms

Model	System	Key findings	PMID
Zebrafish	mutant-ARF3 mRNA overexpression	Dominant behavior; impaired Golgi integrity in vivo; reduced brain size (recapitulates microcephaly); variant-specific	36369169 ; 41507605
Drosophila	variant expression	p.Asp67Val lethal (DN); p.Arg99Leu rough-eye (GoF, like p.Gln71Leu)	34346499
Cellular/in vitro	localization, pull-down, GTP/GDP & GGA1 binding, stability	Variant functional classification (DN vs GoF)	34346499 ; 36369169

Strengths: recapitulate Golgi fragmentation and microcephaly; reproduce variant-specific severity. **Limitations:** overexpression (not knock-in) designs; cognition/epilepsy not directly modeled; **no mouse/iPSC/organoid model exists** (gap). Resources: ZFIN, FlyBase (*Arf79F*), MGI (*Arf3*).

Evidence Base

PMID	Title (abbrev.)	Evidence type	Contribution
34346499	<i>De novo ARF3 variants cause neurodevelopmental disorder with brain abnormality</i>	human / in vitro / model	First 2 patients; TGN role; DN (p.Asp67Val) vs GoF (p.Arg99Leu) via pull-down and fly models
36369169	<i>Dominant ARF3 variants disrupt Golgi integrity... recapitulated in zebrafish</i>	human / in vitro / model	Dominant causation; pocket localization; Golgi/trafficking assays; zebrafish microcephaly; neural precursor/PCP mechanism
41507605	<i>Newly identified ARF3 variants strengthen... Golgi fragmentation and brain malformations</i>	human / in vitro / model	+5 patients, 3 novel variants; zebrafish confirm dominant behavior; DN = severe
38712921	<i>Neurodevelopmental disorder associated with gene ARF3: a case report</i>	human	Distinctive Z-shaped brainstem MRI; ultrarare status; acquired microcephaly + drug-resistant epilepsy
42606787	<i>De novo NR2F1 variant... (segregation analysis)</i>	human	Inherited ARF3 p.Arg99* truncating allele is non-causative — argues against haploinsufficiency
37185208	<i>ARF1 de novo variants / periventricular nodular heterotopia</i>	human	Differential diagnosis; supports shared ARF-family Golgipathy class

Background ARF/Golgi cell-biology support (ARF3 is uniquely activated at the TGN; ARF1/ARF3 occupy distinct TGN nanodomains): [PMID: 20357002](#), [PMID: 37102998](#).

Supported vs Refuted Hypotheses

- **Supported:** (i) de novo dominant *ARF3* missense variants cause a neurodevelopmental Golgipathy; (ii) mechanism = Golgi fragmentation/trafficking failure impairing neural precursor proliferation and PCP movements; (iii) dominant-negative variants cause the most severe phenotype; (iv) zebrafish/Drosophila recapitulate core features.
 - **Refuted / not supported:** simple **haploinsufficiency** as the disease mechanism (an inherited truncating allele is non-causative, [PMID: 42606787](#)); any environmental/infectious etiology; existence of any disease-modifying therapy.
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Limitations and Knowledge Gaps

1. **Very small sample (<10 patients)** limits confidence in genotype–phenotype correlations, penetrance, expressivity, and the full phenotypic range; milder presentations are likely under-ascertained.
 2. **No epidemiological estimates** (prevalence, incidence, sex ratio) are possible.
 3. **No mammalian (mouse) knock-in or iPSC/organoid model** exists; current models rely on overexpression in zebrafish/Drosophila and do not directly model cognition or epilepsy.
 4. **No biomarkers** (biochemical, proteomic, metabolomic) and **no formal diagnostic criteria** are defined; diagnosis is molecular + radiological.
 5. **Mechanistic resolution** of how Golgi fragmentation specifically causes PCP and proliferation defects, and why the nervous system is selectively vulnerable, is incomplete.
 6. **No therapeutics**; whether DN and GoF variants respond to different (mechanism-matched) interventions is untested.
 7. **Ontology/clinical coding** (ICD, Orphanet, MeSH) for this disorder is not firmly established in the reviewed sources.
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Proposed Follow-up Experiments / Actions

1. **Establish an international patient registry** and GeneMatcher-driven cohort expansion to refine phenotype, natural history, penetrance, and genotype–phenotype correlations.

2. **Generate endogenous-level mouse knock-in and human iPSC-derived cerebral organoid models** of DN (p.Asp67Val) and GoF (p.Arg99Leu) variants to model neurogenesis, microcephaly, and epilepsy, and to serve as preclinical therapeutic platforms.
3. **Mechanism-resolved cell biology:** quantitative live-imaging of Golgi dynamics, vesicle trafficking, and PCP cell movements in patient-derived neural precursors; map the ARF3–GGA1/adaptor interactome by proteomics.
4. **Systematic variant functional classification:** a standardized assay panel (stability, GTP/GDP binding, Golgi morphology, GGA1 binding) to triage future VUS and build a DN-vs-GoF classifier to inform prognosis.
5. **Single-cell / spatial transcriptomics** of model brain to define which neural cell types and developmental windows are most vulnerable (CL/UBERON annotation).
6. **Therapeutic exploration:** test whether modulating ARF GTPase cycling or Golgi-stress responses rescues model phenotypes; for GoF alleles, evaluate allele-selective knockdown (ASO/siRNA).
7. **Formalize ontology mapping** (confirm/obtain ICD-11, Orphanet, MeSH codes) and complete HPO annotation with frequency data for knowledge-base integration.

Report based on 5 primary clinical/functional publications plus supporting ARF-biology literature (2021–2026). All mechanistic and clinical claims are attributed to the cited PMIDs; evidence types (human clinical, in vitro, model organism) are indicated throughout.
