Periventricular Nodular Heterotopia 8 (PVNH8 / ARF1-related neurodevelopmental disorder): A Comprehensive Disease Characterization

Disease: Periventricular Nodular Heterotopia 8 (PVNH8) **Causal gene: ARF1** (ADP-ribosylation factor 1), HGNC:652, NCBI Gene 375, locus 1q42.13 **OMIM:** 618185 • **MONDO:** MONDO:0032588 **Synonyms:** PVNH8; ARF1-related periventricular nodular heterotopia; ARF1-related neurodevelopmental disorder **Category:** Mendelian, autosomal dominant

Summary

Periventricular Nodular Heterotopia 8 (PVNH8; OMIM 618185, MONDO:0032588) is a rare **autosomal dominant neurodevelopmental disorder caused by heterozygous variants in *ARF1***, the gene encoding ADP-ribosylation factor 1, a small Ras-superfamily GTPase that governs vesicular membrane traffic at the Golgi apparatus and endosomes. Despite the disease name emphasizing periventricular nodular heterotopia (PVNH), the defining clinical feature of the disorder is **near-universal neurodevelopmental impairment** — intellectual disability and speech delay are present in essentially all patients, whereas PVNH itself occurs in only about 30% of individuals. The disorder is therefore better understood as an "ARF1-related neurodevelopmental disorder" with PVNH as a non-obligate imaging feature, a point reinforced by the largest cohort assembled to date (de Sainte Agathe et al., 2023, n=17). This report concerns the ARF1 gene specifically and should not be confused with other PVNH subtypes (e.g., PVNH1/*FLNA* at Xq28, PVNH2/*ARFGEF2*), which involve different genes.

Mechanistically, pathogenic ARF1 variants converge on **impaired cortical neuronal migration** but reach it by two distinct molecular routes. Recurrent missense variants that cluster in the GTPase nucleotide-binding and switch regions (notably the p.Arg99His hotspot) act by **gain of function / constitutive activation**, mimicking the classic Q71L constitutively active mutant: they cause Golgi swelling, increased recruitment of vesicle coat machinery

(COPI, AP-1, GGA3), and resistance to brefeldin A. In parallel, truncating/loss-of-function variants and 1q42 copy-number losses cause disease through **haploinsufficiency**. Both routes disrupt the Golgi-dependent membrane trafficking that migrating neurons require, producing a neuronal migration disorder. ARF1 is among the most constraint-intolerant genes in the human genome (gnomAD pLI = 0.999; LoF o/e = 0.056; missense Z = 4.73), consistent with strong dosage sensitivity.

Clinically, diagnosis rests on **brain MRI** (showing nodular gray-matter signal lining the lateral ventricles and other migration-disorder features) combined with **exome/genome sequencing** or targeted malformation-of-cortical-development gene panels; chromosomal microarray detects 1q42 CNVs. There is **no disease-modifying therapy**: management is entirely symptomatic — anti-seizure medication for epilepsy (which may be drug-resistant), stereo-EEG-guided surgery/thermocoagulation for refractory focal seizures arising from heterotopic nodules, and developmental, physical, occupational, and speech therapy for intellectual disability and motor delay.

Key Findings

Finding 1 — PVNH8 is caused by heterozygous *ARF1* variants, usually de novo, inherited rarely (autosomal dominant)

PVNH8 is a Mendelian, autosomal dominant condition. The pivotal cohort study — de Sainte Agathe et al. 2023 (*J Med Genet*), assembled internationally through GeneMatcher — identified causal variants in 17 unrelated individuals, more than tripling the handful of previously reported cases: *"De novo variants (10 missense, 1 frameshift, 1 splice altering resulting in 9 residues insertion) in ARF1 were identified among 17 unrelated individuals."* Most variants arise **de novo**, but the disorder is transmissible: Gana et al. 2022 reported the **first inherited** (paternally transmitted) ARF1 variant in a girl with intellectual disability and PVNH, establishing that affected individuals can pass the allele to offspring and that expressivity is variable (the transmitting father was more mildly affected). The causal gene is **ARF1** (HGNC:652, NCBI Gene 375) at **1q42.13**; the disease is catalogued as OMIM 618185 and MONDO:0032588.

- PMID: 37185208: *"De novo variants (10 missense, 1 frameshift, 1 splice altering resulting in 9 residues insertion) in ARF1 were identified among 17 unrelated individuals."*

- PMID: 34353862: *"We report the first inherited variant of ARF1 in a girl with intellectual disability and periventricular nodular heterotopia who inherited the variant from the father."*

Finding 2 — Core phenotype: intellectual disability, microcephaly, seizures, and periventricular nodular heterotopia

The clinical core of PVNH8 is a neurodevelopmental tetrad. de Sainte Agathe et al. 2023 summarized the phenotype as *"intellectual disability (ID), microcephaly, seizures and PVNH... microretrognathia was common. Various hearing and visual defects were recurrent, and interestingly, some inflammatory features were reported. MRI of the brain frequently showed abnormalities consistent with a neuronal migration disorder,"* concluding that this is *"an autosomal dominant syndrome with a phenotypic spectrum including severe ID, microcephaly, seizures and PVNH due to impaired neuronal migration."* An independent 2025 Chinese report (Lian et al.) confirmed the recurring feature set of *"intellectual disability, microcephaly, epilepsy, and periventricular nodular heterotopia (PVNH)."* Expressivity is variable: several carriers (the transmitting father in Gana 2022; the p.R99H patient in Ishida 2023; the p.L170Pro patient in Lian 2025) lacked PVNH despite full neurodevelopmental involvement.

- PMID: 37185208: *"Detailed phenotypes included intellectual disability (ID), microcephaly, seizures and PVNH."*
- PMID: 40689678: *"individuals harbouring variants in the ARF1 gene display a consistent set of phenotypic features, including intellectual disability, microcephaly, epilepsy, and periventricular nodular heterotopia (PVNH)."*

Finding 3 — Per-phenotype frequencies: developmental disability is universal, PVNH is a minority feature (~30%)

A crucial, counter-intuitive result from the detailed phenotyping (de Sainte Agathe et al. 2023, Table 1, n=17) is that **the eponymous PVNH is not the most frequent feature**. The quantified frequencies are:

Phenotype	Frequency	HPO term
Intellectual disability	100% (14/14)	HP:0001249
Speech delay (first words ~19 mo)	100% (17/17)	HP:0000750
Ability to form sentences	only 30% (5/16)	HP:0002463 (impaired)
Delayed walking (mean 27 mo)	majority	HP:0002540
Hypotonia	68% (12/17)	HP:0001252
Thin corpus callosum	55% (9/17)	HP:0033725
Microcephaly (<−3 SD)	50% (10/17; mean HC −1.3 SD)	HP:0000252
ADHD / autism	50% (6/11)	HP:0007018 / HP:0000717
Seizures	48% (8/17)	HP:0001250
Periventricular nodular heterotopia	**30% (4/17)**	**HP:0032388**
Spasticity	25% (4/17)	HP:0001257
Growth delay	25% (4/16)	HP:0001510
Ataxia	21% (4/17)	HP:0001251

The authors explicitly noted that a previously reported R99H individual (Ge et al.) *"was incorrectly described with PVNH,"* reinforcing that PVNH is non-obligate. This has direct knowledge-base implications: **ID and speech delay should be annotated as near-100% features, while PVNH should carry a ~30% frequency.**

- PMID: 37185208: *"Detailed phenotypes included intellectual disability (ID), microcephaly, seizures and PVNH."* (Per-feature percentages from Table 1 of the same paper.)

Finding 4 — Dual mechanism: disrupted Golgi/vesicle trafficking impairs cortical neuronal migration via gain-of-function OR haploinsufficiency

ARF1 is a small GTPase that regulates membrane traffic at the Golgi and endosomes by recruiting coat proteins (COPI, AP-1, GGA3) and lipid-modifying enzymes. Pathogenic variants converge on impaired neuronal migration by two mechanistically distinct allele classes:

Gain of function / constitutive activation. The recurrent p.R99H variant behaves like the constitutively active Q71L mutant. Ishida et al. 2023 showed the variant *"caused swelling of the Golgi apparatus, increased the recruitment of coat proteins such as coat protein complex I, adaptor protein complex 1 and GGA3... R99H-ARF1 bound more tightly to the ARF1-effector GGA3,"* concluding *"the pathogenetic mechanism of the R99H-ARF1 variant involves constitutive activation with resultant Golgi and endosomal alterations."* Ishiguro et al. 2024 (*J Biochem*) extended this: multiple variants (R19C, F51L, R99C, R99H) show increased GDP/GTP exchange, several are GAP-insensitive, and *"transient expression of p.R99C, p.R99H and p.K127E... resulted in the disruption of the Golgi apparatus."* Critically, in utero electroporation showed that *"p.R99C, p.R99H and p.K127E cause a migration defect,"* with Golgi expansion in migrating cortical neurons — directly linking the molecular lesion to the migration phenotype.

Haploinsufficiency / loss of function. Gana et al. 2022 concluded that *"haploinsufficiency of this gene causes a recognisable neurological disorder with abnormal neuronal migration,"* a route also supported by the LoF variants (frameshift, splice) in the de Sainte Agathe cohort and by pathogenic 1q42 deletions.

- PMID: 36345169: *"the pathogenetic mechanism of the R99H-ARF1 variant involves constitutive activation with resultant Golgi and endosomal alterations."*
- PMID: 39052890: *"In utero electroporation-mediated gene transfer into the cortical neurons of embryonic mice demonstrated that p.R99C, p.R99H and p.K127E cause a migration defect."*
- PMID: 34353862: *"haploinsufficiency of this gene causes a recognisable neurological disorder with abnormal neuronal migration and variable clinical expressivity."*

Finding 5 — ARF1 is extremely intolerant to loss-of-function and missense variation (gnomAD), supporting dosage sensitivity

gnomAD v2 constraint metrics for ARF1 (ENSG00000143761; GRCh38 chr1:228,082,660–228,099,212) place it among the most constrained genes in the genome: **pLI = 0.999**; **LoF observed/expected = 0.056** (obs 1 / exp 18.0; 90% CI 0.020–0.264); **missense o/e = 0.295** (obs 73 / exp 247; missense Z = 4.73); LoF Z = 3.40. This extreme intolerance is mechanistically

coherent with a haploinsufficiency route (loss of one allele is barely tolerated in the population) and with the severe, near-fully-penetrant neurodevelopmental phenotype observed in patients.

Finding 6 — Pathogenic variant catalog: recurrent missense hotspots plus 1q42 CNVs

ClinVar (reference transcript NM_001658.4) lists roughly **24 Pathogenic** + **7 Likely-pathogenic** + **2 P/LP** ARF1 entries. Recurrent pathogenic/likely-pathogenic missense variants cluster in the GTPase core/switch regions:

Variant (protein)	cDNA	Region / note
p.Arg19Cys	c.55C>T	N-terminal region
p.Tyr35His / p.Tyr35Asp	c.103T>C / c.103T>G	switch I
p.Thr48Ile	c.143C>T	interswitch
p.Phe51Leu	c.151T>C / c.153C>A	interswitch
p.Val68Met	c.202G>A	switch II
p.Gly70Ser	c.208G>A	switch II/catalytic
p.Asp93Gly	c.278A>G	conflicting
p.Arg99His	**c.296G>A**	**switch II hotspot (GoF)**
p.Arg99Cys	c.295C>T	switch II hotspot
p.Lys127Glu	c.379A>G	nucleotide-binding loop
p.Pro131Arg / p.Pro131Leu	c.392C>G / c.392C>T	131; Leu conflicting
p.Leu170Pro	c.509T>C	C-terminal (Lian 2025)

Loss-of-function de novo variants (1 frameshift, 1 splice) were reported by de Sainte Agathe 2023. Large **1q42.13 deletions** and **1q41–q44 duplications/triplications** involving ARF1 are also classified pathogenic (contiguous-gene/CNV events). All reported point variants are **germline**, de novo or rarely inherited; **no somatic** ARF1 variants are implicated in this disorder.

- PMID: 40689678: *"A de novo variant, c.509T > C (p.Leu170Pro), was detected in the ARF1 gene."*
- PMID: 37185208: *"De novo variants (10 missense, 1 frameshift, 1 splice altering resulting in 9 residues insertion) in ARF1."*

Finding 7 — Protein architecture explains the clustering of pathogenic residues

UniProt P84077 (human ARF1, 181 aa) annotates: **N-myristoylation on Gly2** ("N-myristoyl glycine"); an **N-terminal amphipathic region** (residues 3–16) *"important for the stable binding to the membranes"*; and guanine-nucleotide/phosphate binding sites at residues ~24–32 (P-loop / switch I), 126–129, and 160. Pathogenic missense residues map directly onto these functional elements: R19 (N-terminal region), Y35/T48/F51 (switch I / interswitch), V68/G70/R99 (switch II / catalytic region, R99 hotspot), K127/P131 (126–129 nucleotide-binding loop), and L170 (C-terminal). ARF1 is a Ras-superfamily small GTPase (InterPro IPR006689 / Pfam PF00025 'Arf'). This structural mapping rationalizes why switch-region substitutions lock ARF1 in the active (GTP-bound) state and produce a gain-of-function phenotype.

Finding 8 — Diagnosis and management are MRI- and genetics-based, with symptomatic (non-curative) treatment

Diagnosis: Brain MRI is the key imaging modality, showing nodules of gray-matter signal lining the lateral ventricles and features of a neuronal migration disorder (de Sainte Agathe 2023: *"MRI of the brain frequently showed abnormalities consistent with a neuronal migration disorder"*). Molecular diagnosis is by exome/genome sequencing or multigene malformation-of-cortical-development panels and single-gene ARF1 testing; chromosomal microarray detects 1q42 CNVs.

Management: Entirely symptomatic. Anti-seizure medications treat epilepsy, which can be drug-resistant (Lian 2025 described *"focal seizures... that were resistant to various anti-seizure medications"*). Developmental, physical, occupational, and speech therapy address intellectual disability and motor delay. For drug-resistant focal epilepsy arising from heterotopic nodules,

stereo-EEG-guided surgery is used: Dannhoff et al. 2024 reported SEEG-guided radiofrequency thermocoagulation *"in periventricular nodular heterotopia where 81% of patients are responders."* **No disease-modifying or ARF1-targeted therapy exists.**

- PMID: 38957431: *"periventricular nodular heterotopia where 81% of patients are responders."*
- PMID: 40689678: *"focal seizures on a fixed side that were resistant to various anti-seizure medications."*

Finding 9 — Model organisms: mouse in utero electroporation and Drosophila neuroblast studies

Mouse. Ishiguro et al. 2024 used in utero electroporation of ARF1 variants into embryonic mouse cortical neurons, reproducing a radial migration defect with Golgi expansion. Matsuki et al. 2024 showed ARF1-3 expression rises from E13 to P30 in telencephalon, consistent with a developmental role. Ito et al. 2026 showed Arf1 knockdown confines dentate granule cells to the GCL/hilus region, implicating Arf1 (downstream of the GEF IQSEC2) in neuronal positioning and dendritic development.

Drosophila. Gujar et al. 2025 (*PNAS*) showed Arf1 and ARFGEF2/Sec71 control neuroblast (neural stem cell) asymmetric division and polarity by anchoring nonmuscle myosin II and regulating PI(4)P pools, noting that *"dysregulation in the balance between self-renewal and differentiation can lead to tumor formation or neurodevelopmental disorders."*

- PMID: 39052890: *"In utero electroporation-mediated gene transfer into the cortical neurons of embryonic mice demonstrated that p.R99C, p.R99H and p.K127E cause a migration defect."*
- PMID: 40208939: *"Arf1 and ARFGEF2/Sec71 control asymmetric division of Drosophila NSCs by facilitating the localization of myosin II regulatory light chain."*

Finding 10 — ARF1 biology links to N-myristoylation and a candidate gene–environment axis

ARF1 function requires **N-myristoylation** of its N-terminal glycine, enabling its myristoyl-switch membrane insertion upon GTP loading. Wei et al. 2025 (*J Hazard Mater*) showed, in a rat model, that prenatal amoxicillin exposure reduced gut *Lachnospiraceae* and the metabolite **myristic acid**, which *"hindered the N-myristoylation of ADP-ribosylation factor 1 (ARF1), impaired the normal degradation of the stimulator of interferon genes protein, inhibited autophagic processes, and promoted M1 polarization of microglia, ultimately leading to depressive-like behaviors"*; myristic acid supplementation reversed the abnormalities. This is a

model-organism result on ARF1 regulation and a candidate gene–environment axis — **not** direct evidence in PVNH8 patients — but it flags N-myristoylation and the gut microbiome–myristic acid axis as a mechanistically plausible modifier worth future study.

- PMID: 39672059: *"hindered the N-myristoylation of ADP-ribosylation factor 1 (ARF1), impaired the normal degradation of the stimulator of interferon genes protein, inhibited autophagic processes, and promoted M1 polarization of microglia."*

Mechanistic Model / Interpretation

Ordered causal chain (mutation → clinical manifestation)

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1. Heterozygous ARF1 variant arises (de novo, rarely inherited; germline)
        │
        ├── BRANCH A — Gain-of-function missense (switch I/II, e.g. R99H, R99C, K127E)
        │      2A. Variant protein locks ARF1 in GTP-bound "active" state (mimics Q71L)
        │      3A. leads to constitutive recruitment of coat machinery (COPI, AP-1, GGA3)
        │      4A. results in Golgi swelling / disruption + endosomal alterations
        │
        └── BRANCH B — Loss-of-function (frameshift/splice/CNV) → haploinsufficiency
               2B. Reduced ARF1 dosage (gene is ~fully LoF-intolerant: o/e 0.056)
               3B. leads to insufficient Golgi/vesicle trafficking capacity
        │
        ▼  (both branches converge)
5. Disrupted Golgi-dependent membrane trafficking in developing neurons
        │
        ▼
6. Impaired radial migration of cortical neurons (shown by in utero electroporation;
   Golgi expansion seen in migrating neurons) — INFERRED to also underlie nodule
   formation when neurons fail to complete migration
        │
        ├──▼ 7a. Subset: neurons arrested near ventricle → periventricular nodular
        │         heterotopia (PVNH, ~30% of patients) [HP:0032388]
        │
        └──▼ 7b. Disordered cortical architecture / connectivity →
                 universal intellectual disability + speech delay,
                 variable microcephaly, epilepsy, hypotonia, thin corpus callosum
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The key interpretive insight is that **PVNH is a downstream, partially penetrant readout** of a more fundamental and universal defect in neuronal migration/cortical development. The disease name over-weights an imaging feature seen in a minority of patients. "ARF1-related neurodevelopmental disorder" better captures the biology.

Upstream vs downstream

- **Upstream:** the ARF1 variant and its effect on the GTPase cycle (nucleotide state, GAP sensitivity, effector binding).
- **Midstream:** Golgi/endosomal trafficking disruption (coat recruitment, Golgi morphology).
- **Downstream:** cortical neuron migration failure → cortical malformation → clinical neurodevelopmental phenotype.

Cell types and biological processes (ontology suggestions)

- **Cell types (CL):** migrating cortical projection neurons / radial-migrating neuroblasts (CL:0000679 glutamatergic neuron; CL:0000099 interneuron), neural stem/progenitor cells (CL:0000047), dentate granule cells.
- **Biological processes (GO):** neuron migration (GO:0001764), Golgi vesicle transport (GO:0048193), COPI coating of Golgi vesicle (GO:0048205), intracellular protein transport (GO:0006886), regulation of ARF protein signal transduction (GO:0032012), protein N-myristoylation (GO:0051697).
- **Cellular components (GO CC):** Golgi apparatus (GO:0005794), Golgi membrane (GO:0000139), endosome (GO:0005768), COPI vesicle coat (GO:0030126).
- **Anatomy (UBERON):** cerebral cortex (UBERON:0000956), lateral ventricle (UBERON:0002285), periventricular zone, corpus callosum (UBERON:0002336).
- **Chemical (CHEBI):** GTP (CHEBI:15996), GDP (CHEBI:17552), myristic acid (CHEBI:28875).

Evidence Base

PMID	Study (type)	Contribution	Supports / Challenges
37185208	de Sainte Agathe et al. 2023, *J Med Genet* (human cohort, n=17)	Largest cohort; de novo variant spectrum; per-feature frequencies; defines syndrome	Supports F001, F002, F003, F006
34353862	Gana et al. 2022 (human; first inherited case)	Autosomal dominant transmission; haploinsufficiency route; variable expressivity	Supports F001, F004 (LoF branch)
36345169	Ishida et al. 2023 (in vitro functional)	R99H = constitutive activation (GoF); Golgi/endosomal alterations; patient lacked PVNH	Supports F004 (GoF branch), F003
39052890	Ishiguro et al. 2024, *J Biochem* (in vitro + mouse IUE)	Variant GEF/GAP kinetics; Golgi disruption; direct migration defect in mouse cortex	Supports F004, F009
40689678	Lian et al. 2025 (human case, China)	p.L170Pro; drug-resistant focal epilepsy; patient lacked PVNH	Supports F002, F006, F008
38957431	Dannhoff et al. 2024 (clinical series)	SEEG-guided thermocoagulation for PVNH epilepsy; 81% responders	Supports F008 (management)
40208939	Gujar et al. 2025, *PNAS* (Drosophila)	Arf1/Sec71 control NSC asymmetric division via myosin II / PI(4)P	Supports F009 (model organism)
39672059	Wei et al. 2025, *J Hazard Mater* (rat)	N-myristoylation of ARF1 modulated by gut microbiota/ myristic acid	Supports F010 (GxE candidate; indirect)

Non-literature evidence: gnomAD v2 constraint (F005), ClinVar variant catalog (F006), UniProt P84077 / InterPro / Pfam protein architecture (F007).

Section-by-Section Disease Characterization

1. Disease information. PVNH8 is a rare Mendelian autosomal dominant neurodevelopmental disorder (OMIM 618185; MONDO:0032588; Orphanet classifies it within the periventricular nodular heterotopia spectrum). MeSH lacks a PVNH8-specific term; the closest is "Periventricular Nodular Heterotopia." Information is derived from **aggregated disease-level cohorts and individual case reports** (de Sainte Agathe n=17; Gana; Ishida; Lian), not EHR-scale registries.

2. Etiology. The sole cause is a heterozygous **germline ARF1 variant** — predominantly de novo, rarely inherited. No environmental or infectious cause is established. Genetic risk = carrying a pathogenic ARF1 allele; advanced paternal age is a general (not disorder-specific) risk factor for de novo mutations. No protective alleles are known. A candidate gene–environment axis (myristic acid/gut microbiota affecting ARF1 N-myristoylation) exists only in rodent data (F010).

3. Phenotypes. See Finding 3 table (HPO terms provided). Onset is congenital/neonatal to early childhood; course is largely stable (developmental, non-degenerative) though epilepsy may be progressive/drug-resistant. Severity is variable but ID is typically moderate-to-severe, with major quality-of-life impact on communication, independence, and (where epilepsy is present) seizure burden.

4. Genetic/molecular. Causal gene **ARF1** (HGNC:652; OMIM gene 103180). Variant classes: missense (GoF hotspots R99H/R99C), frameshift, splice, and CNV (1q42 deletion). ACMG classification for recurrent variants: Pathogenic/Likely pathogenic. Allele frequency in gnomAD ≈ absent (ultra-constrained gene). Functional consequence is **allele-dependent** — gain-of-function (constitutive activation) or loss-of-function/haploinsufficiency. No established modifier genes or disease-specific epigenetic signatures.

5. Environmental. None established as causal. Rodent data implicate gut microbiota/myristic acid in ARF1 regulation (indirect).

6. Mechanism. See causal chain above.

7. Anatomical structures. Primary organ: **brain** (cerebral cortex, periventricular region lining the lateral ventricles, corpus callosum). Body system: central **nervous** system. Tissue: neural/gray matter. Cells: migrating cortical neurons, neural progenitors. Subcellular: **Golgi apparatus** and endosomes (GO:0005794, GO:0005768). Lateralization: PVNH nodules are typically **bilateral** but can be asymmetric/unilateral.

8. Temporal development. Congenital origin (the prenatal neuronal-migration window is the critical period); developmental delay is apparent in infancy/early childhood; course is chronic and lifelong, generally non-progressive except for epilepsy.

9. Inheritance and population. Autosomal dominant; mostly de novo. Penetrance for the neurodevelopmental phenotype appears high/near-complete, with **variable expressivity** (especially for PVNH, ~30%). Prevalence is unknown (ultra-rare; <50 reported individuals worldwide). No founder effect, consanguinity requirement, or strong sex bias is established. Germline mosaicism is plausible for apparently de novo cases but not formally quantified.

10. Diagnostics. Brain MRI + exome/genome sequencing or malformation-of-cortical-development gene panels; single-gene ARF1 testing; chromosomal microarray for 1q42 CNVs. EEG for seizure characterization. No biomarker or biochemical assay is diagnostic. Differential diagnosis includes other PVNH genes — **FLNA** (X-linked PVNH1, the most common cause), **ARFGEF2** (autosomal recessive PVNH2), and other migration-disorder genes; ARF1 is distinguished by its de novo autosomal dominant pattern and the dominant neurodevelopmental (rather than isolated PVNH) picture.

11. Outcome/prognosis. Non-lethal in general; life expectancy is not established to be markedly reduced but may be affected by severe epilepsy/comorbidities. Chronic disability is expected, driven by universal ID and speech impairment; prognosis for refractory epilepsy is guarded, though SEEG-guided surgery helps a majority of PVNH epilepsy cases (81% responders).

12. Treatment. No disease-modifying therapy. Anti-seizure medications; SEEG-guided radiofrequency thermocoagulation / resective surgery for refractory focal seizures (NCIT: surgical procedure); developmental, physical, occupational, speech therapy (NCIT: rehabilitation therapy). No gene/cell/RNA therapy exists. Personalized approaches would, in principle, differ for GoF vs LoF alleles (e.g., activation-lowering vs dosage-restoring strategies) but none are clinical.

13. Prevention. No primary prevention (de novo mutations). Secondary/tertiary prevention = early developmental intervention and epilepsy management. **Genetic counseling** is central: recurrence risk is low for de novo cases (but non-zero due to possible gonadal mosaicism), and 50% for a transmitting carrier (as in Gana 2022). Prenatal/preimplantation testing is feasible once a familial variant is known.

14. Other species / natural disease. ARF1 is highly conserved; orthologs exist in mouse (*Arf1*, NCBI Gene 11840), rat, zebrafish, and *Drosophila* (*Arf79F*). No naturally occurring companion-animal disease is catalogued in OMIA for ARF1; relevance is via experimental models.

15. Model organisms. Mouse in utero electroporation (recapitulates the migration defect and Golgi expansion — strong face validity for the cortical phenotype); *Drosophila* neuroblast polarity models (mechanistic insight into asymmetric division). Limitations: current models demonstrate the cellular migration defect but do not fully recapitulate the composite human syndrome (ID, microcephaly, epilepsy, PVNH together), and no constitutive knock-in mouse of a recurrent hotspot allele with full phenotyping has been reported.

Limitations and Knowledge Gaps

1. **Small sample size.** Fewer than ~50 individuals are reported worldwide; frequency estimates (e.g., PVNH 30%) derive mainly from a single n=17 cohort and are subject to ascertainment bias.
2. **Genotype–phenotype correlation is incomplete.** Whether GoF vs LoF alleles predict PVNH presence, epilepsy severity, or ID degree remains unresolved; both classes produce overlapping phenotypes.
3. **Penetrance/expressivity not formally quantified**, especially for inherited alleles — only one inherited pedigree is documented.
4. **No epidemiological prevalence/incidence** figures exist; the disorder is too rare for registry-based estimates.
5. **Mechanism of PVNH specifically** (why only ~30% develop nodules) is not understood — it may depend on allele type, modifier genes, or stochastic developmental factors.
6. **The N-myristoylation / gut-microbiota axis** is rodent-only and not validated as a human disease modifier.
7. **No disease-modifying therapy or clinical trial** exists; treatment evidence is extrapolated from general PVNH/epilepsy management.

Proposed Follow-up Experiments / Actions

1. **Generate knock-in mouse models** of recurrent hotspot alleles (e.g., Arf1 R99H) and LoF alleles for side-by-side phenotyping of cortical migration, PVNH formation, seizures, and behavior — to test whether allele class drives PVNH penetrance.
2. **Patient-derived iPSC cortical organoids** comparing GoF vs LoF variants to model human-specific neuronal migration and nodule formation, with live-imaging of Golgi dynamics.
3. **Systematic genotype–phenotype meta-analysis** across all reported cases to statistically test whether GoF alleles associate with specific features (PVNH, epilepsy type, microcephaly severity).
4. **Functional classification of all VUS** in ARF1 (nucleotide exchange, GAP sensitivity, effector binding, Golgi morphology assays) to build a variant-effect map that distinguishes GoF from LoF for clinical reporting.
5. **Deep natural-history study / patient registry** to capture prevalence, developmental trajectories, epilepsy course, and quality-of-life outcomes.
6. **Test the N-myristoylation axis** (myristic acid supplementation, NMT activity) in ARF1 neuronal models to evaluate a candidate modifiable pathway.
7. **Evaluate allele-specific therapeutic strategies** — dosage restoration (for LoF) vs activity dampening/allele-specific knockdown (for GoF) — in preclinical models.

Evidence source types are indicated throughout: human clinical (cohorts/case reports), in vitro functional (biochemistry/cell biology), model organism (mouse IUE, Drosophila, rat), and computational/database (gnomAD, ClinVar, UniProt). All mechanistic and clinical claims are anchored to the PMIDs cited above.
