Periventricular Nodular Heterotopia 7 (PVNH7, NEDD4L): Comprehensive Disease Report

Disease: Periventricular Nodular Heterotopia 7 (PVNH7) **Causal gene: NEDD4L** (NEDD4-2; HECT-type E3 ubiquitin–protein ligase; chromosome 18q21; HGNC:7728; NCBI Gene 23327; UniProt Q96PU5) **OMIM:** 617201 | **MONDO:** MONDO:0014966 **Category:** Mendelian, autosomal dominant malformation of cortical development

Summary

Periventricular Nodular Heterotopia 7 (PVNH7) is an ultra-rare, autosomal-dominant malformation of cortical development caused by **mostly de novo heterozygous missense variants in NEDD4L**, the gene encoding the HECT-type E3 ubiquitin–protein ligase **NEDD4-2** on chromosome 18q21. The disease was defined by Broix et al. in 2016, who showed that missense mutations clustering in the catalytic **HECT domain** of NEDD4L cause periventricular nodular heterotopia (PNH) accompanied by a distinctive syndromic constellation. The causal gene is NEDD4L — this is important to state up front because "periventricular nodular heterotopia" is a genetically heterogeneous radiological entity, and the far more common classic form is X-linked and caused by *FLNA*, a different gene with a different clinical and inheritance profile.

Mechanistically, PVNH7 arises when mutant NEDD4-2 protein — which is sensitive to proteasomal degradation — deregulates **AKT–mTORC1 signaling** and the **Dab1/Reelin** pathway, impairing neurogenesis, neuronal positioning, and the terminal translocation of migrating neurons. Neurons that fail to migrate are retained as **bilateral periventricular nodules** lining the lateral ventricles. The condition is not a simple loss-of-function/haploinsufficiency disorder: both mutant protein and excess wild-type NEDD4L perturb cortical development, pointing to dosage/activity sensitivity. Clinically, PVNH7 presents as a recognizable syndrome of bilateral PNH, perisylvian polymicrogyria, cleft palate, 2–3 toe syndactyly, seizures (including infantile spasms), hypotonia, and variable global developmental delay/intellectual disability.

As of 2023, only **eight pathogenic NEDD4L variants across ~15 cases worldwide** had been reported, so population-level epidemiology, penetrance estimates, and natural-history data remain largely undefined. Inheritance is autosomal dominant with documented parental mosaicism and marked intra-familial variability. There is **no disease-specific or curative therapy**; management is symptomatic and multidisciplinary (antiseizure medication, cleft-palate repair, developmental/rehabilitative therapy, and genetic counseling). Because the disorder deregulates mTORC1/AKT, **mTOR inhibition (rapamycin/sirolimus) is a mechanistic/theoretical target**, supported by rescue experiments in other mTORopathy models, but no clinical trials exist for PVNH7.

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1. Disease Information

Overview. PVNH7 is a Mendelian malformation of cortical development (MCD) in the periventricular nodular heterotopia family. On brain MRI it is defined by nodules of gray-matter-isointense neurons that are ectopically retained along the walls of the lateral ventricles. PVNH7 specifically denotes the form caused by NEDD4L and is distinguished by a syndromic pattern that includes cortical malformation beyond the nodules themselves (typically perisylvian polymicrogyria), orofacial clefting, and distal limb anomalies.

Key identifiers.

Resource	Identifier
OMIM	617201
MONDO	MONDO:0014966
Gene (HGNC)	NEDD4L / HGNC:7728
NCBI Gene / UniProt	23327 / Q96PU5
Chromosomal locus	18q21
Inheritance	Autosomal dominant (mostly de novo)

ICD-10/ICD-11, Orphanet, and MeSH do not maintain a dedicated code that cleanly separates PVNH7 from the broader "periventricular nodular heterotopia" grouping; PNH overall maps to the malformations-of-cortical-development/neuronal-migration-disorder categories (ICD-10 Q04.8 "other congenital malformations of brain" is used pragmatically).

Synonyms: periventricular nodular heterotopia 7; PVNH7; periventricular nodular heterotopia type 7; NEDD4L periventricular nodular heterotopia; periventricular nodular heterotopia caused by mutation in NEDD4L.

Source of information. The knowledge base here is derived from **aggregated disease-level resources** (OMIM, MONDO) plus **individual patient case reports and small case series** in the primary literature — not from a large EHR cohort, because the disease is ultra-rare.

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2. Etiology

Primary cause — genetic. PVNH7 is caused by heterozygous pathogenic missense variants in **NEDD4L**. The overwhelming majority are **de novo**, though inherited/familial transmission and parental somatic/germline mosaicism are documented. There is no known infectious or primary environmental cause.

Genetic risk factors. The causal variants themselves are the risk factor; they cluster in the catalytic HECT domain (with at least one recurrent WW-domain variant, p.Arg208Gln). No susceptibility loci or modifier genes have been formally established for PVNH7, given the tiny case count.

Environmental risk factors / protective factors. None established. No toxin, lifestyle, occupational exposure, dietary, or protective allele has been linked to PVNH7. Because the disorder is caused by highly penetrant de novo dominant variants, environmental contribution is expected to be minimal.

Gene–environment interactions. None described. This is a monogenic developmental malformation; GxE data are not available.

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3. Phenotypes

Across the reported cases, PVNH7 produces a recurrent multi-system constellation. The table below summarizes the core phenotypes with suggested HPO terms and qualitative frequency.

Phenotype	Type	HPO suggestion	Onset	Frequency (qualitative)
Bilateral periventricular nodular heterotopia	Imaging/ structural sign	HP:0032388 (periventricular nodular heterotopia)	Congenital	~All cases
Perisylvian polymicrogyria	Imaging/ structural sign	HP:0002126 (polymicrogyria)	Congenital	Frequent
Seizures / infantile spasms	Clinical sign	HP:0001250 (seizure); HP:0012469 (infantile spasms)	Infancy–childhood	Most cases
Global developmental delay / intellectual disability	Clinical sign	HP:0001263; HP:0001249	Infancy onward	Frequent, variable
Cleft palate	Physical malformation	HP:0000175 (cleft palate)	Congenital	Frequent
2–3 toe syndactyly	Physical malformation	HP:0001770 (toe syndactyly)	Congenital	Frequent
Hypotonia	Clinical sign	HP:0001252	Infancy	Common
Absent/delayed speech & walking	Developmental	HP:0001344; HP:0002540	Childhood	Common
Microretrognathia	Physical malformation	HP:0000308	Congenital	Reported
Strabismus	Clinical sign	HP:0000486	Childhood	Reported
Hypospadias	Physical malformation	HP:0000047	Congenital	Reported (males)

"All patients reported with NEDD4L HECT domain mutations showed periventricular nodular heterotopia, and most had seizures, cortex anomalies, cleft palate and syndactyly" (P 28515470).

Severity and progression. The structural brain malformation is static (non-progressive), but its clinical consequences — epilepsy and developmental impairment — evolve over time. Severity is **highly variable**, even within a single family: a familial case carrying p.Arg208Gln spanned the range from **isolated bilateral PNH** to **severe neurodevelopmental delay with refractory seizures** — "Phenotypic features in the proband consisted of severe neurodevelopmental delay, refractory seizures, bilateral PNH, and perisylvian polymicrogyria" (P 32117442).

A mosaic-carrier father had an affected prior fetus with hypokinesia and flexion contractures, suggesting the prenatal spectrum extends to a severe fetal akinesia-like presentation (P 30393983).

Quality-of-life impact. No formal EQ-5D/SF-36/PROMIS data exist for PVNH7. Qualitatively, QoL is driven by seizure burden (which may be drug-resistant) and by intellectual disability/motor impairment that affect speech, ambulation, and independence. Cleft palate adds feeding/speech burden early in life.

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4. Genetic / Molecular Information

Causal gene. NEDD4L (neural precursor cell expressed, developmentally down-regulated 4-like), encoding **NEDD4-2**, a HECT-type E3 ubiquitin–protein ligase (HGNC:7728; NCBI Gene 23327; UniProt Q96PU5; chromosome 18q21). "Missense mutations in NEDD4L mapping to the HECT domain of the encoded E3 ubiquitin ligase lead to PNH associated with toe syndactyly, cleft palate and neurodevelopmental delay" (P 27694961).

Protein architecture. NEDD4-2 contains an N-terminal **C2 domain** (membrane/calcium binding), **four WW domains** that bind PY/L-PxY motifs in substrates, and a C-terminal catalytic **HECT domain** that transfers ubiquitin (P 12698368 ; P 18498246).

Pathogenic variants. PVNH7 variants are predominantly **missense** and cluster in the **HECT domain**, with a recurrent WW-domain variant also reported:

Variant (protein)	cDNA / notes	Domain	Classification
p.Glu893Lys (= p.Glu873Lys)	NM_001144967.2 c.2677G>A (= NM_015277 c.2617G>A) — recurrent	HECT	Pathogenic
p.Leu706Pro	c.2117T>C — de novo	HECT	Likely pathogenic (ACMG)
p.Tyr679His	—	HECT	Pathogenic
p.Gln900Arg	—	HECT	Pathogenic
p.Arg208Gln	familial, variable expressivity	WW domain	Pathogenic

A de novo heterozygous missense mechanism is documented: "de novo heterozygous missense mutation in the NEDD4L gene (NM_015277: c.2617G>A; p.Glu873Lys)" (P 28515470).

Note the nomenclature caveat: the variant initially described as "novel" p.Glu873Lys (NM_015277) is **identical** to p.Glu893Lys (NM_001144967) reported by Broix et al.; a published Author Correction clarified it is **recurrent, not novel** (P 31028281).

The p.Leu706Pro variant was reported as "a heterozygous c.2117T>C (p.Leu706Pro) variant... a de novo variant... predicted to be likely pathogenic according to the American College of Medical Genetics Guidelines" (P 31922594).

Allele frequency. These are private/de novo disease alleles essentially absent from population databases (gnomAD); no appreciable population allele frequency.

Somatic vs germline. Germline (constitutional) in affected individuals; **parental mosaicism** (somatic/germline) has been documented — "Molecular testing from peripheral blood identified the healthy father to carry the NEDD4L variant in mosaic state" (P 30393983).

Functional consequences. PVNH7 is **not a simple loss-of-function disorder.** PNH-associated mutants are **sensitive to proteasomal degradation** — "Cellular and expression data showed sensitivity of PNH-associated mutants to proteasome degradation"

(P 27694961) — and both mutant protein and **excess wild-type NEDD4L** disrupt neurodevelopment, indicating dosage/activity sensitivity rather than haploinsufficiency. A functional case study of p.Gln900Arg found the variant "did not affect mRNA expression, whereas WB and IF results indicated that the level of muta[nt protein]..." was altered, consistent with protein-level destabilization (P 36934385). The net downstream effect is **deregulation of mTORC1 and AKT activities**.

Modifier genes / epigenetics / chromosomal abnormalities. No specific modifier genes or epigenetic marks are established for PVNH7. In the broader PNH population, array-CGH detects causative copy-number variants in a substantial subset (~35.7% of PNH vs 9.1% of polymicrogyria), underscoring extreme genetic heterogeneity of the PNH phenotype generally (P 30683929) — but PVNH7 proper is defined by the point mutations in NEDD4L, not CNVs.

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5. Environmental Information

No environmental factors, lifestyle factors, toxins, radiation exposures, or infectious agents have been implicated in PVNH7. It is a monogenic developmental disorder. This section is **not applicable** beyond noting the absence of evidence.

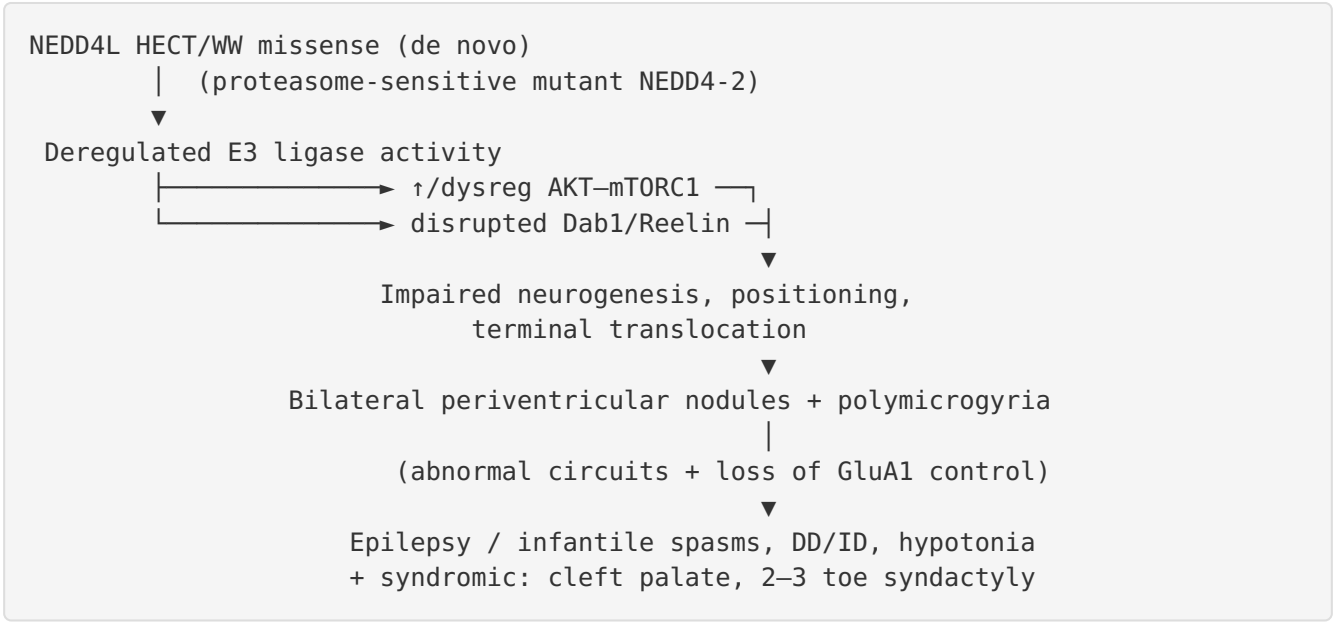
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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **de novo (or mosaic-inherited) heterozygous missense mutation in NEDD4L**, clustering in the catalytic HECT domain (or a WW domain), arises in the germline → produces a **structurally altered, proteasome-sensitive NEDD4-2 protein** (demonstrated: proteasome sensitivity; P 27694961).

2. The altered NEDD4-2 **deregulates its E3 ubiquitin-ligase activity and substrate handling → abnormal signaling output**, specifically "deregulation of mTORC1 and AKT activities" (demonstrated in overexpression systems; P 27694961).
3. In parallel, excess/dysregulated NEDD4L activity **disrupts Dab1**, a key node of the **Reelin pathway** that guides neuronal migration — "Excess wild-type NEDD4L leads to disruption of Dab1 and mTORC1 pathways" (P 27694961).
4. Deregulated AKT–mTORC1 and Dab1/Reelin signaling **impairs neurogenesis, neuronal positioning, and terminal translocation** of migrating cortical neurons — "PNH-related mutants and excess wild-type NEDD4L affect neurogenesis, neuronal positioning and terminal translocation" (demonstrated by in utero electroporation; P 27694961).
5. Neurons that fail to complete radial migration **are retained ectopically along the lateral ventricles → bilateral periventricular nodular heterotopia**; cortical organization is further disturbed → **perisylvian polymicrogyria** (inferred from imaging + migration defect).
6. The abnormal cortical circuitry, combined with NEDD4-2's physiological role in down-regulating the **AMPA receptor GluA1 subunit** (loss of this regulation elevates neuronal activity), **lowers seizure threshold → epilepsy/infantile spasms** — "Nedd4-2 mediates neuronal activity and seizure susceptibility through ubiquitination of GluA1 subunit of the… AMPA receptor" (demonstrated in Nedd4-2-deficient mice; P 28212375; mechanistic bridge to PVNH7 inferred).
7. Disrupted cortical development and NEDD4-2's broader developmental roles **manifest systemically as developmental delay/intellectual disability, hypotonia, and non-CNS malformations (cleft palate, toe syndactyly)** (inferred from consistent clinical co-occurrence).



Supporting detail

Molecular pathways. PI3K–AKT–**mTORC1** is the central deregulated axis (P 27694961). NEDD4-family ligases act **downstream** of PI3K/PTEN–mTORC1 signaling and promote neurite/axonal growth; PTEN controls Nedd4-1 expression by modulating mTORC1 activity — "PTEN controls neurite growth by regulating Nedd4-1 expression" (P 25157163). The **Reelin–Dab1** migration pathway is the second affected arm (P 27694961).

Cellular processes. Neurogenesis, radial neuronal migration, neuronal positioning, and terminal translocation are the core affected processes. Suggested GO terms: **GO:0001764** (neuron migration), **GO:0022008** (neurogenesis), **GO:0021799** (cerebral cortex radially oriented cell migration), **GO:0016567** (protein ubiquitination), **GO:0032008** (positive regulation of TOR signaling).

Protein dysfunction. Mutant NEDD4-2 is destabilized/proteasome-sensitive with altered catalytic/substrate behavior — a complex, non-simple loss-of-function effect with evidence of dosage sensitivity (P 27694961 ;

). P 36934385

Nedd4-2 stability is itself regulated by an intramolecular WW–HECT PY-motif interaction and by SGK1/PKA phosphorylation with 14-3-3 binding (; P 18498246). P 16716084

Cell types involved. Cortical neural progenitors and migrating projection (pyramidal) neurons. Suggested CL terms: **CL:0000047** (neural stem cell / neural progenitor), **CL:0000679** (glutamatergic neuron), **CL:0000598** (pyramidal neuron).

Ion channel / receptor links. NEDD4-2's canonical substrate is the epithelial Na^+ channel ENaC — "The epithelial Na(+) channel ENaC is the best studied example of a Nedd4/Nedd4-like substrate" ( ) P 12698368 — whose dysregulation causes the unrelated **Liddle syndrome** hypertension phenotype ( ). P 20675381

In brain, NEDD4-2 ubiquitinates the **AMPA receptor GluA1 subunit**; Nedd4-2-deficient mice show elevated neuronal activity and increased kainic-acid seizure susceptibility, normalized by genetically reducing GluA1 ( ). P 28212375

Context-dependence caveat. Not all systems show the same magnitude of signaling change: Kato et al. (2017) found only **subtle AKT–mTOR deregulation in patient lymphoblastoid cell lines**, versus the robust effects in forced-overexpression/in-utero electroporation systems — a reminder that the quantitative mechanism is context-dependent.

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7. Anatomical Structures Affected

Organ / system level. Primary organ: the **brain** (central nervous system). The disorder also affects **craniofacial** structures (palate → cleft palate; jaw → microretrognathia) and **distal limbs** (toes → 2–3 syndactyly), with occasional genitourinary involvement (hypospadias) and reported strabismus (ocular motility).

Tissue and cell level. Nervous tissue — specifically the developing cerebral cortex. Affected cell populations: neural progenitors and migrating cortical neurons (CL:0000047; CL:0000598).

Subcellular level. The pathology centers on the **ubiquitin–proteasome system** (cytoplasmic; mutant protein degraded by the proteasome) and on **mTORC1 signaling at the lysosomal surface/cytoplasm**. Suggested GO cellular component terms: **GO:0005737** (cytoplasm), **GO:0000502** (proteasome complex).

Localization. Nodules line the walls of the **lateral ventricles** (UBERON:0002285, lateral ventricle of the brain; periventricular region). Associated polymicrogyria is **perisylvian** (around the Sylvian fissure / insular cortex). Lateralization is characteristically **bilateral** in PVNH7 — a feature of diagnostic and prognostic importance. Suggested UBERON terms: **UBERON:0002285** (lateral ventricle), **UBERON:0000956** (cerebral cortex).

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8. Temporal Development

Onset. The structural malformation is **congenital** (established during fetal corticogenesis). Clinical onset: seizures typically emerge in **infancy to childhood** (infantile spasms can be an early manifestation); developmental delay becomes apparent across infancy and early childhood. In the broader PNH-epilepsy population, "Mean seizure onset age was 7.9 years" (P 37119372), though PVNH7's syndromic, bilateral pattern tends toward earlier and more severe presentations.

Progression. The brain malformation itself is **static/non-progressive**. The clinical course is dominated by epilepsy, which may be **self-limited, pharmacoresponsive, or drug-resistant** depending on malformation pattern, and by a **chronic, lifelong** developmental disability. Disease duration is lifelong.

Patterns / critical periods. The critical period is **fetal cortical neurogenesis and migration** (second trimester), when the malformation is laid down — the only true window for primary prevention would be preconception/prenatal. Post-natally there is no remission of the structural lesion; "remission" applies only to seizure control achieved with medication or, in selected drug-resistant focal cases, surgery.

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9. Inheritance and Population

Epidemiology. PVNH7 is **ultra-rare**: "only eight NEDD4L pathogenic variants have been identified across 15 cases of PVNH7 worldwide" as of 2023 (36934385).

No reliable prevalence or incidence figures exist, and no separate Orphanet prevalence class is defined for PVNH7.

Inheritance. Autosomal dominant. The majority of cases are **de novo heterozygous missense** variants, but familial transmission occurs, and **parental somatic/germline mosaicism** is documented (30393983).

Penetrance and expressivity. Penetrance appears high for carriers of a constitutional pathogenic variant, but **expressivity is strikingly variable** — the familial p.Arg208Gln pedigree ranged from isolated bilateral PNH to severe neurodevelopmental delay (32117442).

Formal penetrance estimates are not possible with so few cases.

Anticipation / founder effects / consanguinity / carrier frequency. No genetic anticipation (not a repeat-expansion disorder). No founder effect, ethnic clustering, or consanguinity role established. Carrier frequency is effectively nil in the general population (de novo dominant disease).

Population demographics. No sex predilection established. No geographic/ethnic clustering of the disease or of specific variants. The recurrent p.Glu893Lys/p.Glu873Lys variant is the most frequently reported allele but reflects a mutational hotspot rather than a population founder.

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10. Diagnostics

Imaging (first-line). Brain MRI is the primary diagnostic modality: it demonstrates nodules of gray-matter-isointense neurons lining the lateral ventricles; in PVNH7 the nodules are **bilateral**, frequently with **perisylvian polymicrogyria**.

Molecular confirmation. Diagnosis is confirmed by **trio whole-exome sequencing** (proband + parents) with **Sanger confirmation** of a de novo NEDD4L variant — the standard approach "verified the genetic etiology using Trio-whole-exome and Sanger sequencing" (P 36934385). WES is high-yield because it establishes de novo status and distinguishes PVNH7 from other genetic PNH forms. Gene panels for malformations of cortical development / neuronal migration disorders should include NEDD4L alongside FLNA, ARFGEF2, and others. **Chromosomal microarray (array-CGH)** is recommended as a first-line test in PNH generally (especially sporadic, non-classical cases) because CNVs are a cumulatively frequent cause (~35.7% in one PNH series; P 30683929) — though PVNH7 itself is a point-mutation disorder.

Differential diagnosis. The principal genetic differentials are:

Gene	Inheritance	Distinguishing features
FLNA (classic PNH)	X-linked dominant	Predominantly females; male prenatal lethality; cardiovascular, pulmonary (childhood interstitial lung disease), skeletal, GI involvement; no cleft palate + toe syndactyly constellation (P 37422633 ; P 30547349)
ARFGEF2	Autosomal recessive	Microcephaly, severe DD
NEDD4L (PVNH7)	Autosomal dominant (de novo)	Bilateral PNH + polymicrogyria + **cleft palate** + **2–3 toe syndactyly** — a unique constellation

"The unique constellation of clinical features in patients with NEDD4L mutations might help clinically distinguish them from patients with other genetic mutations including FLNA" (P 28515470).

Laboratory / biomarkers / electrophysiology. No specific blood/urine biomarker exists. **EEG** is used to characterize seizures (and may show hypsarrhythmia in infantile spasms). No omics-based or liquid-biopsy diagnostic is established.

Screening. Because most cases are de novo, there is no population carrier-screening program. For families with an identified variant (including mosaic parents), **cascade testing and prenatal/preimplantation genetic testing** are feasible.

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11. Outcome / Prognosis

Survival/mortality. PVNH7 is not primarily a lethal disorder postnatally; no specific survival or mortality statistics are published. The severe end of the prenatal spectrum (fetal hypokinesia/flexion contractures in an affected fetus; P 30393983) indicates the possibility of a severe/lethal fetal presentation in some pregnancies.

Morbidity and function. The dominant morbidity is **epilepsy** (potentially drug-resistant) and **neurodevelopmental disability** (intellectual disability, motor delay, speech impairment). Epilepsy prognosis is stratified by nodule distribution:

PNH pattern	Drug-resistance
Isolated single-nodule PNH	No drug-resistant seizures
PVNH-Plus, bilateral nodules (the PVNH7 pattern)	**Highest drug resistance (39%)**

In a retrospective cohort of 100 PVNH patients with seizures, mean onset was 7.9 years; 10 had self-limited epilepsy, 35 more were pharmacoresponsive, 55 had ongoing seizures, and 23 met drug-resistance criteria; "PVNH-Plus with bilateral nodules demonstrated the highest proportion of drug resistance (39%)" (P 37119372). Because PVNH7 characteristically presents as bilateral PNH plus an additional malformation (polymicrogyria), affected individuals fall into this **higher-severity stratum**.

Complications and recovery. Complications include refractory seizures, feeding/speech difficulty from cleft palate, and functional impairment. The structural brain lesion does not resolve; recovery is limited to seizure control and developmental gains with therapy.

Prognostic factors. Bilateral + syndromic malformation pattern (worse epilepsy prognosis), seizure burden, and degree of developmental delay are the main prognostic indicators. No molecular prognostic biomarker is validated; intra-familial variability (P 32117442) limits genotype-based prediction.

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12. Treatment

No disease-modifying or NEDD4L-specific therapy exists. Management is **symptomatic and multidisciplinary** (NCIT suggestions in parentheses):

- **Antiseizure medication** for epilepsy — e.g., **valproate** (Convulex): "The patient was treated with Convulex 300 mg/mL for the successful seizure control" (P 34087865). (NCIT: Anticonvulsant Agent; Valproic Acid.)
- **Surgical repair of cleft palate** (NCIT: Cleft Palate Repair / Palatoplasty).
- **Treatment of associated anomalies**, e.g., levothyroxine for thyroid dysfunction where present (NCIT: Levothyroxine).
- **Developmental / rehabilitative therapy** — physical, occupational, and speech therapy (NCIT: Physical Therapy; Occupational Therapy; Speech Therapy).
- **Epilepsy surgery** may be considered for selected drug-resistant focal cases (NCIT: Epilepsy Surgery).

Mechanistic/experimental target. Because PVNH7 deregulates mTORC1/AKT, **mTOR inhibitors (rapamycin/sirolimus)** are a **theoretical** disease-mechanism target. This rationale is supported by rescue of mTORopathy phenotypes by rapamycin in animal models — "prenatal treatment with mTORC1 inhibitor rapamycin rescued the phenotype" in a Depdc5 mTORopathy model (P 26873552)

— and rapamycin reversed mTOR-dependent morphological/localization defects from GATOR1-subunit knockdown in neurons (P 29481864).

No clinical trials of mTOR inhibition exist for PVNH7, and the structural malformation is established prenatally, limiting postnatal disease modification.

Pharmacogenomics / advanced therapeutics. No PVNH7-specific pharmacogenomic guidance. No gene, cell, RNA-based, targeted, or immunotherapy is available or in trial for this indication.

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13. Prevention

- **Primary prevention:** Not possible postnatally (malformation is congenital). For families with a known variant, options are preconception counseling, **preimplantation genetic testing (PGT)**, and **prenatal diagnosis**.
- **Secondary prevention:** Early MRI and genetic diagnosis enable early seizure management and developmental intervention.
- **Tertiary prevention:** Optimizing antiseizure therapy to prevent status epilepticus and developmental regression; multidisciplinary care to manage complications.
- **Genetic counseling:** Essential. Counseling must address the predominantly **de novo** origin, the documented **parental mosaicism** (which affects recurrence risk for apparently de novo cases; P 30393983), and the **variable expressivity** that complicates prognostic prediction within families (P 32117442).
- **Immunization / public health / environmental interventions:** Not applicable.

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14. Other Species / Natural Disease

No naturally occurring animal disease equivalent to PVNH7 is cataloged (e.g., in OMIA). The gene is evolutionarily conserved: **Nedd4l/Nedd4-2 orthologs** exist in mouse (NCBI Gene: *Nedd4l*; *Mus musculus*, NCBI Taxon txid10090), rat (*Rattus norvegicus*, txid10116), and other vertebrates. Comparative mechanistic conservation is strong — mouse studies of Nedd4-2 (AMPA/GluA1 regulation and seizure susceptibility; ENaC regulation) directly inform the human mechanism. No zoonotic potential or cross-species transmission (not applicable — genetic developmental disorder).

15. Model Organisms

- **Mouse models [model organism].** The most informative is the **Nedd4-2-deficient mouse** (e.g., *Nedd4-2^andi^*), which shows elevated neuronal activity and increased kainic-acid seizure susceptibility, normalized by genetically reducing GluA1 — modeling the epilepsy arm of NEDD4L dysfunction
  (P 28212375).
  Conditional Nedd4-1/Nedd4-2 knockout mice demonstrate that these ligases are required for axonal growth/branching in CNS neurons
  (P 25157163).
- **In utero electroporation (mouse) [model organism].** The landmark functional system for PVNH7: expression of PNH-related mutants or excess wild-type NEDD4L in the developing mouse cortex reproduced defective neurogenesis, neuronal positioning, and terminal translocation, and revealed the AKT–mTORC1 and Dab1 mechanisms
  (P 27694961).
  This is the best recapitulation of the **migration defect** underlying the nodules.
- **In vitro / cellular models [in vitro].** Patient-derived **lymphoblastoid cell lines** (showed only subtle AKT–mTOR changes — a model limitation highlighting context-dependence; Kato 2017) and expression constructs demonstrating proteasome sensitivity of mutants
  (P 27694961)
  and protein-level destabilization

( ). P 36934385

Neuroblastoma (N2a) and neural progenitor cell systems are used to study mTORC1-dependent morphology in related mTORopathies

( ). P 29481864

- **Related mTORopathy models [model organism].** The **Depdc5 knockout rat** ( ) P 26873552 and **DEPDC5/NPRL3 knockdown** neuronal models ( ) P 29481864 are not NEDD4L models but validate the mTORC1-rescue-by-rapamycin logic relevant to PVNH7's pathway.

Recapitulation and limitations. In utero electroporation recapitulates the core neuronal migration/heterotopia phenotype and the signaling deregulation well. Limitations: no single published model reproduces the **full human syndrome** (bilateral PNH + polymicrogyria + cleft palate + toe syndactyly) simultaneously; lymphoblastoid cells underrepresent the signaling phenotype; and dosage-sensitivity effects are hard to model precisely.

Resources: MGI (*Nedd4l*), IMPC/KOMP for knockout alleles, and standard mouse repositories.

Mechanistic Model / Interpretation

PVNH7 is best understood as a **ubiquitin-ligase/mTOR-pathway "corticogenesis" disorder with dosage sensitivity.** The unifying model: a destabilizing, proteasome-sensitive HECT-domain missense change in NEDD4-2 perturbs the ligase's normal control over the AKT–mTORC1 growth-signaling axis and over Dab1/Reelin migration signaling. Because both mutant protein and excess wild-type protein are deleterious, the system is exquisitely sensitive to the **level and activity** of NEDD4-2 during a narrow fetal window of neurogenesis and radial migration. The consequence is twofold: (1) a **structural** failure of neurons to reach the cortex, producing bilateral periventricular nodules and polymicrogyria; and (2) an **excitability** liability, because NEDD4-2 normally throttles the AMPA-receptor GluA1 subunit, and its dysfunction lowers seizure threshold. The syndromic non-CNS features (cleft palate, toe syndactyly) reflect NEDD4-2's broader developmental roles. This model explains the clinical

stratification — bilateral "PVNH-Plus" portends the worst epilepsy — and identifies **mTOR inhibition** as the only rational, if currently unproven and likely prenatal-window-limited, disease-mechanism target.

Evidence Base

PMID	Title (abbrev.)	Role
PMID: 27694961	*Mutations in the HECT domain of NEDD4L lead to AKT-mTOR pathway deregulation and cause PNH*	**Landmark**: defines gene, HECT clustering, proteasome sensitivity, AKT-mTORC1/Dab1 mechanism, migration defect
PMID: 28515470	*Missense mutation in HECT domain of NEDD4L… PNH, polymicrogyria, cleft palate*	De novo heterozygous inheritance; core phenotype; FLNA differential
PMID: 31028281	*Author Correction*	Clarifies p.Glu873Lys = p.Glu893Lys is recurrent, not novel
PMID: 32117442	*Recurrent NEDD4L Variant in PNH, Polymicrogyria and Syndactyly*	Familial p.Arg208Gln; variable expressivity; bilateral PNH + polymicrogyria
PMID: 30393983	*Familial NEDD4L variant… and a fetus with hypokinesia*	Parental mosaicism; severe fetal spectrum
PMID: 36934385	*Genetic analysis of PVNH7… Case and literature summary*	Trio-WES diagnosis; 8 variants/15 cases; protein (not mRNA) destabilization
PMID: 34087865	*Admixed phenotype of NEDD4L-associated PNH*	Symptomatic valproate seizure control
PMID: 31922594	*PVNH7 caused by NEDD4L variant*	p.Leu706Pro de novo, likely pathogenic (ACMG)
PMID: 28212375	*Nedd4-2 mediates neuronal activity and seizure susceptibility through AMPA receptors*	Links NEDD4L to seizures via GluA1 (mouse)
PMID: 12698368	*Nedd4/Nedd4-like ubiquitylation in epithelial transport*	Domain architecture; ENaC substrate
PMID: 18498246	*Regulation of Nedd4-2 self-ubiquitination via HECT PY motif*	Protein stability regulation
PMID: 16716084	*14-3-3 / SGK1 phosphorylation regulation of Nedd4-2*	Regulatory control of the ligase
PMID: 20675381	*Hrs controls ENaC sorting (Nedd4-2)*	Canonical trafficking substrate biology; Liddle syndrome

PMID	Title (abbrev.)	Role
PMID: 25157163	*Nedd4-1 downstream of PI3K/PTEN-mTORC1 to promote neurite growth*	Places NEDD4 in mTOR network; axon growth
PMID: 30683929	*Genomic CNVs in PNH — extreme heterogeneity*	Array-CGH as first-line test in PNH
PMID: 37119372	*Phenotypic spectrum of epilepsy with PNH*	Epilepsy prognosis stratification; onset 7.9 y; 39% drug resistance in bilateral PVNH-Plus
PMID: 37422633	*PNH associated with FLNA*	FLNA differential diagnosis
PMID: 30547349	*FLNA mutations and interstitial lung disease*	FLNA phenotype distinction
PMID: 26873552	*Depdc5 knockout rat: mTORopathy model*	Rapamycin rescue rationale
PMID: 29481864	*DEPDC5/NPRL3 modulate mTOR in neurons*	Rapamycin-reversible mTOR phenotype

Limitations and Knowledge Gaps

1. **Ultra-rarity.** With only ~15 reported cases and 8 variants, all frequency estimates are qualitative; prevalence, incidence, penetrance, and sex ratio are unquantified.
2. **Mechanism context-dependence.** Robust AKT–mTORC1 deregulation is seen in overexpression/in-utero electroporation systems but is only subtle in patient lymphoblastoid cells (Kato 2017) — the quantitative in vivo mechanism remains uncertain, and whether gain-of-function, loss-of-function, or dominant-negative best describes individual variants is unresolved.
3. **No full-syndrome animal model.** Existing models capture either the migration defect or the seizure phenotype, not the complete human syndrome including cleft palate and syndactyly.
4. **No therapeutic evidence.** mTOR inhibition is purely theoretical for PVNH7; the structural lesion is prenatal, so postnatal disease modification may be inherently limited.

5. **Weak genotype–phenotype correlation**, confounded by marked intra-familial variability (p.Arg208Gln pedigree).
6. **No natural-history, QoL, or long-term outcome data** specific to PVNH7.

Proposed Follow-up Experiments / Actions

1. **Establish an international PVNH7 registry** (GeneMatcher-based) to aggregate cases, variants, imaging, and outcomes — the single highest-value action given rarity.
2. **Variant-specific functional dissection** using isogenic human iPSC-derived cortical organoids/neurons carrying each recurrent variant (p.Glu893Lys, p.Leu706Pro, p.Tyr679His, p.Gln900Arg, p.Arg208Gln) to quantify effects on NEDD4-2 stability, ubiquitin-ligase activity, AKT–mTORC1 output, and Dab1/Reelin signaling in a human, non-overexpression context.
3. **Humanized/knock-in mouse models** of recurrent HECT variants to test whether the full syndrome is recapitulated and to perform **prenatal rapamycin rescue** experiments.
4. **GluA1/AMPA-receptor characterization** in patient-derived neurons to determine whether seizure susceptibility maps to the same GluA1 mechanism shown in Nedd4-2-deficient mice, which could nominate AMPA-receptor modulators (e.g., perampanel) as a mechanism-matched antiseizure choice.
5. **Systematic parental mosaicism screening** (deep sequencing of multiple tissues) in apparently de novo cases to refine recurrence-risk counseling.
6. **Prospective natural-history and QoL study** capturing seizure trajectory, developmental outcomes, and drug-resistance predictors across nodule distribution patterns.
