Pan-Chung-Bellen Syndrome (PCBS): A Comprehensive Disease Characterization Report

Target disease: Pan-Chung-Bellen Syndrome (PCBS) **MONDO ID:** MONDO:0975953 · **OMIM phenotype:** #621049 · **DOID:** 0061146 · **MedGen:** C5975547 **Causal gene: FRYL** (FRY-like transcription coactivator; OMIM gene *620798; HGNC; NCBI Gene 285527; Ensembl ENSG00000075539; UniProt O94915; locus 4p11) Inheritance:** Autosomal dominant (almost always de novo), via haploinsufficiency / loss of function

Summary

Pan-Chung-Bellen syndrome (PCBS) is a recently delineated autosomal-dominant neurodevelopmental malformation syndrome caused by heterozygous, almost always *de novo*, loss-of-function (LoF) or deleterious missense variants in the gene *FRYL* (FRY-like transcription coactivator). The disorder was defined in 2024 by Pan, Chung, Bellen and colleagues, who reported fourteen unrelated individuals with heterozygous *FRYL* variants presenting with developmental delay, intellectual disability, dysmorphic facial features, and congenital anomalies across multiple organ systems (PMID: 38479391). The variants were confirmed *de novo* in all but one individual. Human genetic-constraint data (pLI = 1; missense Z = 3.3) indicate that *FRYL* is strongly intolerant to loss of function, and the pathogenic mechanism is best modeled as **haploinsufficiency**.

FRYL is a member of the evolutionarily conserved **Furry (Fry) family** of large scaffold proteins (yeast Tao3p/Mor2p; *C. elegans* Sax-2; *Drosophila* Furry). These proteins act as activators/scaffolds of the **NDR (Nuclear Dbf2-Related) family Ser/Thr kinases** (STK38/STK38L in humans; Tricornered in flies; Cbk1p/Orb6p in yeast). The conserved **Furry–NDR kinase module**, together with microtubule-associated functions, governs **polarized cell growth and neuronal morphogenesis** — dendritic tiling/branching and neurite outgrowth. Reduced FRYL dosage is therefore inferred to impair this polarized-growth / neuronal-morphogenesis program during development, producing the neurodevelopmental and

malformation phenotype. The mechanistic link was functionally supported by *Drosophila* knock-in modeling of patient missense variants in the fly ortholog *furry* (*fry*), which recapitulated an allelic series of severe, partial, and null functional effects.

The clinical spectrum is **multi-system and highly variable in expressivity**, ranging from a severe prenatal/fetal presentation (including congenital diaphragmatic hernia) through the canonical developmental-delay/intellectual-disability phenotype with congenital cardiac (tetralogy of Fallot), renal/urogenital, and skeletal anomalies, to a comparatively mild, predominantly behavioral (ASD/ADHD) presentation. No disease-specific therapy exists; management is **supportive and symptomatic**, organized around early developmental intervention, system-specific surgical correction of congenital anomalies, and genetic counseling. Because PCBS is newly described (~2024) and based on small cohorts and case reports, quantitative epidemiology, penetrance, natural history, and prognosis remain largely uncharacterized.

Key Findings

Finding 1 — PCBS is a dominant *FRYL*-related neurodevelopmental disorder (F001)

The defining study by Pan et al. (2024, *American Journal of Human Genetics* 111:742–760) reported **fourteen individuals with heterozygous variants in *FRYL*** presenting with developmental delay, intellectual disability, dysmorphic features, and other congenital anomalies in multiple systems. The variants were confirmed *de novo* in all individuals except one, establishing a dominant mechanism with recurrent new mutation. Human genetic data indicate that *FRYL* is intolerant to loss of function.

> *"we report fourteen individuals with heterozygous variants in FRYL who present with developmental delay, intellectual disability, dysmorphic features, and other congenital anomalies in multiple systems. The variants are confirmed de novo in all individuals except one. Human genetic data suggest that FRYL is intolerant to loss of function (LoF)."* — PMID: 38479391

FRYL encodes the FRY-like transcription coactivator, a Furry-family protein conserved from yeast to human, located on chromosome **4p11**. This finding establishes the gene, the dominant de novo inheritance, LoF intolerance, and the core clinical features of the syndrome. **Evidence type: human clinical (cohort).**

Finding 2 — FRYL functions as a Furry-family scaffold/activator of NDR kinases controlling polarized growth and neuronal morphogenesis (F002)

Furry (Fry) proteins are conserved from yeast to humans and genetically and physically interact with NDR kinases as activators or scaffolds. The **Fry–NDR kinase signaling axis** controls polarized cell growth, epidermal morphogenesis, dendritic tiling/branching, and neurite outgrowth — the biology directly relevant to a neurodevelopmental disorder.

> *"Fry and its orthologues in invertebrates (termed Tao3p in budding yeast, Mor2p in fission yeast, Sax-2 in nematode and Fry in fruit fly) genetically and physically interact with nuclear Dbf2-related (NDR) kinases (termed Cbk1p in budding yeast, Orb6p in fission yeast, Sax-1 in nematode and Trc in fruitfly), and function as activators or scaffolds of these kinases. Fry-NDR kinase signals are implicated in the control of polarized cell growth and morphogenesis in yeast, neurite outgrowth in nematode, and epidermal morphogenesis and dendritic tiling in fruit fly."* — PMID: 24403109

Mammalian Fry/FRYL additionally behaves as a **microtubule-associated protein** regulating chromosome alignment, spindle organization, PLK1 activation, and microtubule acetylation (via Sirtuin-2 inhibition). In the fly, *furry* is expressed in neurons but not glia; homozygous *fry* LoF is lethal at various developmental stages, and clonal loss causes wing and compound-eye defects.

> *"the fly FRYL ortholog, furry (fry), is expressed in multiple tissues, including the central nervous system where it is present in neurons but not in glia. Homozygous fry LoF mutation is lethal at various developmental stages, and loss of fry in mutant clones causes defects in wings and compound eyes."* — PMID: 38479391

More recently, FRYL (Furry-like) was shown to scaffold NDR kinase within the **Crumbs–PATJ polarity complex and Homer-condensate–mediated YAP–Wnt/β-catenin signaling** crosstalk, with FRYL promoting cytoplasmic Homer droplet formation and acting pathway-selectively (antagonizing FRYL promotes YAP activation, while cooperating with FRYL

enhances Wnt/β-catenin signaling) (PMID: 42455669). This defines the conserved molecular function of FRYL and provides the mechanistic basis of the disorder. **Evidence type: model organism / in vitro / review.**

Finding 3 — Identifiers and the multi-system clinical phenotype spectrum (F003)

Identifiers: OMIM phenotype #621049 (PAN-CHUNG-BELLEN SYNDROME; PCBS); OMIM gene *FRYL* *620798; MONDO:0975953; DOID:0061146; MedGen C5975547; locus 4p11; autosomal dominant.

Pan et al. 2024 described 14 unrelated patients, 13 *de novo*. A concordant core subset of **7 patients (ages 8–20)** showed: developmental delay/intellectual disability in **7/7**, autism in **5/7**, seizures in **2/7**, and hypotonia in **1/7**. The OMIM clinical synopsis lists:

System	Features
Craniofacial / dysmorphism	Frontal bossing, deep-set eyes
CNS	Hypotonia, seizures, developmental delay, impaired intellectual development, delayed myelination, abnormal cerebral white-matter morphology, abnormal EEG
Behavioral	Autism spectrum disorder, ADHD
Cardiovascular	Tetralogy of Fallot (1 patient)
Genitourinary	Horseshoe kidney (1), cryptorchidism, hydrocele
Skeletal	Non-fusion of sternum, pectus deformity
Prenatal (later report)	Congenital diaphragmatic hernia

> *"fourteen individuals with heterozygous variants in FRYL who present with developmental delay, intellectual disability, dysmorphic features, and other congenital anomalies in multiple systems"* — PMID: 38479391

Congenital anomalies span cardiovascular, skeletal, gastrointestinal, renal, and urogenital systems. **Evidence type: human clinical.**

Finding 4 — FRYL variant spectrum: 9 LoF + 5 missense; haploinsufficiency confirmed by constraint and fly knock-ins (F004)

Pan et al. 2024 identified 14 *FRYL* variants: **9 predicted loss-of-function** (premature stop/nonsense, frameshift, or splicing defects, all predicted to trigger nonsense-mediated decay) and **5 missense**. All missense were predicted deleterious; all except p.Ser2397Ile are classified **likely pathogenic** per ACMG/AMP. Constraint metrics confirm intolerance: **pLI = 1** (LoF-intolerant) and **missense Z-score = 3.3**. Variants were **absent from gnomAD**.

The splicing-variant patient exhibited brisk reflexes, central hypotonia, central hypoventilation, delayed myelination, abnormal cerebral white-matter morphology, and abnormal EEG. *Drosophila furry* (*fry*) knock-ins of 4/5 missense variants produced an **allelic series**: *fry* p.Phe2746Ser (≈ FRYL p.Phe2295Ser) behaved as a **severe LoF**; two others as **partial LoF**; and p.Ser2397Ile (not confirmed de novo) caused **no fly defect**, consistent with a VUS.

> *"One variant behaves as a severe LoF variant, whereas two others behave as partial LoF variants. One variant does not cause any observable defect in flies, and the corresponding human variant is not confirmed to be de novo, suggesting that this is a variant of uncertain significance."* — PMID: 38479391

This cross-species functional modeling directly supports **haploinsufficiency / loss of function** as the disease mechanism and provides a template for classifying future variants. **Evidence type: human clinical + model organism functional validation.**

Finding 5 — FRYL gene annotation, brain-enriched expression, and cross-species orthologs (F005)

FRYL (FRY-like transcription coactivator; aliases **AF4p12, KIAA0826, MOR2**): NCBI Gene **285527**, Ensembl **ENSG00000075539**, UniProt **O94915**, locus 4p11 (chr4:~48.5–48.8 Mb, GRCh38). The Human Protein Atlas reports FRYL as cytoplasmic and **tissue-enhanced in brain**, with subcellular localization to **microtubules, the cytokinetic bridge, and cytosol** — consistent with a microtubule-associated-protein role.

Orthologs (HomoloGene 103956): mouse *Fryl* (MGI:1919563, Gene 72313; ENSMUSG00000070733); rat *Fryl*; zebrafish *fryl* (ZFIN ZDB-GENE-040914-58; predicted to act upstream of/within heart development, active at cell cortex / site of polarized growth); *Drosophila melanogaster fry* (*furry*); *C. elegans sax-2*. Human **FRY and FRYL are paralogs**; the single invertebrate ortholog *fry* was used by Pan et al. to model patient variants.

> *"the fly FRYL ortholog, furry (fry), is expressed in multiple tissues, including the central nervous system where it is present in neurons but not in glia"* — PMID: 38479391

Evidence type: database annotation + model organism.

Finding 6 — Variable expressivity: severe fetal malformation to mild behavioral-only presentation (F006)

Beyond the 2024 defining cohort, two 2025–2026 reports expand the phenotypic spectrum and demonstrate **variable expressivity**:

- **Sandhu et al. 2025** (*Prenatal Diagnosis*, doi:10.1002/pd.6879; PMC12530344) describe a **fetal/prenatal phenotype including congenital diaphragmatic hernia**, not previously reported — the severe end of the spectrum.
- **Acharya et al. 2026** (*Indian Journal of Pediatrics* 93:1015; doi:10.1007/s12098-026-06318-2) report a **6-year-old girl with a comparatively mild, predominantly behavioral presentation** — ASD and ADHD with hyperactivity, impulsivity, hyperphagia, and poor attention — who achieved **normal early milestones** and lacked global developmental delay, seizures, or major neuroanatomical abnormalities. She carried co-occurring pathogenic variants in *FRYL* and *SUPT16H* (NEDDFAC), proposed as a **digenic** presentation.

Reported diagnostic yield in unexplained neurodevelopmental disorders is **30–50%**, supporting early genomic (exome/genome) testing.

> *"a dominant disorder with developmental and..."* — PMID: 38479391

This confirms the autosomal-dominant backbone against which variable expressivity is interpreted. **Evidence type: human clinical case reports.**

Section-by-Section Report

1. Disease Information

PCBS is an autosomal-dominant **neurodevelopmental malformation syndrome** caused by heterozygous *FRYL* variants, named for first/corresponding authors Pan, Chung, and Bellen (2024). It is characterized by developmental delay, intellectual disability, dysmorphic facial features (frontal bossing, deep-set eyes), autism/ADHD, and variable multi-system congenital anomalies.

- **OMIM phenotype:** #621049 · **OMIM gene:** *FRYL* *620798
- **MONDO:** MONDO:0975953 · **DOID:** 0061146 · **MedGen:** C5975547
- **ICD-10/ICD-11, MeSH, Orphanet:** No dedicated code identified (disease too recently described; *not available*).
- **Synonyms:** Pan-Chung-Bellen syndrome; PCBS; FRYL-related neurodevelopmental disorder (none formally recorded in the template).

Information source: Aggregated from individual-patient reports compiled into a disease-level cohort (Pan et al. 2024) plus subsequent case reports — i.e., clinically-derived individual-patient data rather than EHR-at-scale resources.

2. Etiology

- **Primary cause:** Genetic — heterozygous *FRYL* LoF or deleterious missense variants, almost always *de novo* (13/14 in the defining cohort). Mechanism: **haploinsufficiency**.
- **Genetic risk factors:** The causal variant itself. FRYL constraint (pLI = 1; missense Z = 3.3) indicates the gene cannot tolerate reduced dosage. No susceptibility loci or modifier genes are established; one case suggests a possible digenic contribution from *SUPT16H* (F006).
- **Environmental risk factors:** None established. As a *de novo* dominant disorder, **advanced parental age** is a plausible but unproven contributor to new-mutation rate (general principle, not demonstrated for *FRYL*).
- **Protective factors:** None known (genetic or environmental).
- **Gene–environment interactions:** Not characterized; *not available*.

3. Phenotypes

Phenotype types span clinical signs, physical/dysmorphic manifestations, behavioral changes, and laboratory/imaging abnormalities. Suggested HPO terms:

Phenotype	Type	Approx. frequency (core cohort)	Suggested HPO
Developmental delay	Sign	7/7 (high)	HP:0001263
Intellectual disability	Sign	high	HP:0001249
Autism spectrum disorder	Behavioral	5/7	HP:0000717
ADHD	Behavioral	variable	HP:0007018
Seizures	Sign	2/7	HP:0001250
Hypotonia	Sign	1/7 (central)	HP:0001252
Frontal bossing	Dysmorphism	variable	HP:0002007
Deep-set eyes	Dysmorphism	variable	HP:0000490
Tetralogy of Fallot	Malformation	1 patient	HP:0001636
Horseshoe kidney	Malformation	1 patient	HP:0000085
Cryptorchidism	Malformation	variable	HP:0000028
Pectus deformity / sternal non-fusion	Skeletal	variable	HP:0000766
Delayed myelination	Imaging	subset	HP:0012448
Abnormal cerebral white matter	Imaging	subset	HP:0002500
Abnormal EEG	Lab/ electrophysiology	subset	HP:0002353
Congenital diaphragmatic hernia	Malformation	prenatal case	HP:0000776

- **Age of onset:** Congenital/neonatal for malformations; infancy–childhood for neurodevelopmental features; prenatal in the diaphragmatic-hernia case.

- **Severity:** Variable — from severe fetal malformation to mild behavioral-only.
- **Progression:** Neurodevelopmental features are static/developmental rather than neurodegenerative; malformations are congenital and stable (post-correction).
- **QoL impact:** Not formally measured; inferred substantial impact from ID/ASD and congenital-anomaly burden. *No EQ-5D/SF-36 data available.*

4. Genetic / Molecular Information

- **Causal gene:** *FRYL* (OMIM *620798; HGNC; NCBI Gene 285527; Ensembl ENSG00000075539; UniProt O94915; 4p11).
- **Variant classes:** 9 LoF (nonsense/frameshift/splice, NMD-predicted) + 5 missense; most likely pathogenic (ACMG/AMP); one VUS (p.Ser2397Ile).
- **Allele frequency:** Variants absent from gnomAD.
- **Origin:** Germline, overwhelmingly *de novo* (13/14).
- **Functional consequence:** Loss of function / haploinsufficiency (confirmed by pLI = 1, missense Z = 3.3, and fly knock-in allelic series).
- **Modifier genes:** Possible digenic *SUPT16H* co-occurrence in one mild case (unproven as a general modifier).
- **Epigenetic / chromosomal abnormalities:** No specific methylation signature or recurrent cytogenetic lesion reported; *not available*.

5. Environmental Information

No environmental, lifestyle, or infectious contributors are established. PCBS is a monogenic *de novo* dominant disorder; environmental/infectious agents are **not applicable** as causes. (Note: unrelated literature associates *FRYL* loci with common-disease GWAS signals — GERD/COPD comorbidity [PMID: 39919125], diabetic nephropathy [PMID: 42509683] — but these are distinct from the Mendelian syndrome and do not inform PCBS etiology.)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A heterozygous *de novo* **LoF or deleterious missense variant in *FRYL*** arises (NMD of LoF alleles; hypomorphic/null missense alleles). → *demonstrated.*
2. This **reduces functional FRYL protein dosage** (haploinsufficiency), supported by pLI = 1 and the fly allelic series. → *demonstrated (constraint + modeling).*

3. Reduced FRYL **impairs the Furry–NDR (STK38/Tricornered) kinase module** for which FRYL serves as scaffold/activator. → *inferred from conserved orthologue function.*
4. **Branch A — neuronal morphogenesis:** Impaired Fry–NDR signaling disrupts **polarized growth, dendritic tiling/branching, and neurite outgrowth** in neurons (FRYL is neuron-expressed, not glial). → *inferred.* → leads to abnormal neuronal connectivity → **developmental delay, intellectual disability, ASD/ADHD, seizures, abnormal white matter/myelination.**
5. **Branch B — microtubule / cell-division functions:** Reduced FRYL perturbs **microtubule acetylation (via SIRT2), spindle organization, chromosome alignment, and PLK1 activation**, affecting proliferating progenitors. → *inferred.* → contributes to **growth/ morphogenesis defects and congenital malformations.**
6. **Branch C — epithelial polarity / Hippo–Wnt crosstalk:** FRYL scaffolds NDR kinase within the **Crumbs–PATJ polarity complex and Homer-condensate YAP–Wnt/β-catenin signaling**. Dysregulation perturbs organ morphogenesis. → *inferred (in vitro).* → contributes to **cardiac (tetralogy of Fallot), renal (horseshoe kidney), skeletal (sternal/pectus), and diaphragmatic malformations.**
7. Convergence of branches A–C during embryonic/fetal development → **the multi-system PCBS phenotype**, with severity set by residual FRYL function and genetic background (variable expressivity).

Upstream vs downstream: The mutation and FRYL dosage reduction are upstream; Furry–NDR kinase dysfunction is the proximal molecular node; cytoskeletal, polarity, and Hippo–Wnt perturbations are intermediate; tissue-level morphogenetic failures and neuronal connectivity defects are downstream clinical manifestations.

Pathways / processes / ontology suggestions: - Molecular pathways: NDR/Hippo kinase signaling; YAP–Wnt/β-catenin crosstalk; (FRYL GWAS hub reports also implicate mTOR, PI3K-Akt, cytoskeletal pathways — context-dependent). - GO biological processes: regulation of cell morphogenesis involved in differentiation (GO:0010769); dendrite morphogenesis (GO:0048813); establishment/maintenance of cell polarity (GO:0007163); microtubule cytoskeleton organization (GO:0000226); neuron projection morphogenesis (GO:0048812). - GO cellular components: microtubule (GO:0005874); cytosol (GO:0005829); midbody/cytokinetic bridge (GO:0030496). - CL cell types: neuron (CL:0000540); central nervous system neuron (CL:0002319).

7. Anatomical Structures Affected

- **Primary organ:** Brain / central nervous system (UBERON:0000955 brain; UBERON:0001017 CNS).
- **Secondary organs:** Heart (UBERON:0000948; tetralogy of Fallot), kidney (UBERON:0002113; horseshoe kidney), gonads/urogenital tract (cryptorchidism, hydrocele), sternum/thoracic skeleton (UBERON:0000975; pectus/sternal non-fusion), diaphragm (UBERON:0001103; CDH).
- **Body systems:** Nervous, cardiovascular, renal/urogenital, musculoskeletal, respiratory/diaphragmatic, gastrointestinal.
- **Tissue/cell level:** Nervous tissue — neurons (CL:0000540), specifically affected over glia (fly data). Brain white matter affected (delayed myelination).
- **Subcellular:** Microtubule cytoskeleton (GO:0005874), cytokinetic bridge/midbody, cytosol.
- **Lateralization:** Predominantly bilateral (CNS); malformations may be midline (sternum, diaphragm) or lateralized (kidney, testis).

8. Temporal Development

- **Onset:** Congenital for malformations (prenatal in the CDH case); infancy–childhood for neurodevelopmental features. Pattern is chronic/insidious.
- **Progression:** Neurodevelopmental features are **developmental/static** (not neurodegenerative); congenital anomalies are fixed and corrected surgically. No evidence of progressive decline.
- **Course:** Chronic, lifelong. Seizures (when present) may be episodic.
- **Critical periods:** Embryonic/fetal organogenesis (malformations) and early childhood (neurodevelopment / early-intervention window).
- **Remission:** Not applicable to the underlying disorder; behavioral features may respond to intervention.

9. Inheritance and Population

- **Inheritance:** Autosomal dominant, predominantly *de novo* (13/14).
- **Penetrance / expressivity:** Presumed high penetrance but **highly variable expressivity** (severe fetal → mild behavioral). Formal penetrance estimates *not available*.
- **Anticipation / mosaicism / founder effects / consanguinity:** Not applicable / not reported (de novo dominant; no repeat expansion).

- **Carrier frequency:** Not applicable (de novo dominant, not a recessive carrier state).
- **Epidemiology: Ultra-rare**; precise prevalence/incidence *not available* (only ~14 defining cases plus isolated reports as of 2026).
- **Demographics:** No ethnic predisposition or sex skew established; both sexes affected. Geographic distribution: worldwide (cohort was international).

10. Diagnostics

- **Genetic testing is the diagnostic cornerstone.** Recommended approach: **exome sequencing (ES) or genome sequencing (GS)** with trio analysis to confirm de novo status; diagnostic yield in unexplained NDD is ~30–50%. Single-gene *FRYL* testing or NDD/epilepsy gene panels including *FRYL* are alternatives. Chromosomal microarray is appropriate in the malformation workup but will not detect most *FRYL* SNVs/indels.
- **Variant interpretation:** ACMG/AMP classification; *Drosophila fry* knock-in functional assays can reclassify missense VUS (Pan et al. model).
- **Supportive clinical tests:** Brain MRI (delayed myelination, abnormal white matter), EEG (seizures/abnormal background), echocardiography (cardiac anomalies), renal/abdominal ultrasound (horseshoe kidney), skeletal exam/imaging (pectus, sternal non-fusion), prenatal ultrasound (CDH).
- **Biomarkers / omics diagnostics:** No disease-specific biochemical biomarker; biochemical testing yield is effectively 0% (consistent with a monogenic structural gene). *No validated proteomic/metabolomic/epigenomic diagnostic.*
- **Differential diagnosis:** Other de novo dominant NDD-with-malformation syndromes and chromatin/cytoskeletal-regulator disorders; distinguished by *FRYL* genotype.
- **Screening:** No population or newborn screening; cascade testing generally unnecessary given de novo origin, but recurrence counseling applies.

11. Outcome / Prognosis

- **Survival/mortality:** No quantitative data. Prognosis likely dominated by severity of congenital malformations (e.g., CDH, complex cardiac disease) and neurodevelopmental burden. Severe fetal presentations carry high perinatal risk; milder cases are compatible with survival to at least childhood/adolescence (cohort ages 8–20).
- **Morbidity/disability:** Chronic — intellectual disability, ASD/ADHD, and anomaly-related disability. Lifelong functional support frequently needed.
- **QoL measures:** Not formally reported.

- **Complications:** Seizures, consequences of cardiac/renal/diaphragmatic malformations, feeding/behavioral issues.
- **Prognostic factors:** Residual FRYL function (severe vs partial LoF), presence/severity of major congenital anomalies, possible modifier/digenic contributions. No validated prognostic biomarker.

12. Treatment

No disease-specific or disease-modifying therapy exists. Management is **supportive and symptomatic**, multidisciplinary:

Domain	Intervention	Suggested NCIT concept
Neurodevelopment	Early developmental intervention, special education, speech/OT/PT	NCIT rehabilitation therapy
Behavior (ASD/ ADHD)	Behavioral therapy; stimulants/non-stimulants for ADHD symptoms as indicated	NCIT pharmacotherapy / behavioral intervention
Seizures	Standard antiseizure medications as clinically indicated	NCIT anticonvulsant therapy
Cardiac anomalies	Surgical correction (e.g., tetralogy of Fallot repair)	NCIT surgical procedure
Renal/urogenital	Urological management; orchidopexy for cryptorchidism	NCIT surgical procedure
Diaphragmatic hernia	Neonatal surgical repair	NCIT surgical procedure
Skeletal (pectus)	Orthopedic/surgical management as needed	NCIT surgical procedure

- **Advanced therapeutics (gene/cell/RNA/targeted/immuno):** None developed; *not applicable* at present.
- **Pharmacogenomics / personalized medicine:** Not established.
- **Experimental trials:** No PCBS-specific registered trials identified.

13. Prevention

- **Primary prevention:** Not possible for de novo mutation. Preconception/reproductive counseling applies.
- **Secondary prevention:** Prenatal/perinatal detection of malformations (ultrasound, prenatal exome) enables delivery planning for severe presentations (e.g., CDH).
- **Genetic counseling:** Essential — recurrence risk for parents of a de novo case is low (baseline + possible germline mosaicism); an affected individual's own transmission risk is 50% (autosomal dominant).
- **Reproductive options:** Prenatal diagnosis and preimplantation genetic testing available once a familial variant is known.
- **Immunization / public-health / environmental measures:** Not applicable (non-infectious, non-environmental Mendelian disorder).

14. Other Species / Natural Disease

- **Orthologs/taxonomy:** Mouse *Fryl* (NCBI Gene 72313; MGI:1919563), rat *Fryl*, zebrafish *fryl* (ZFIN ZDB-GENE-040914-58), *Drosophila melanogaster fry/furry*, *C. elegans sax-2*. Human **FRY and FRYL are paralogs**.
- **Natural disease in other species:** No naturally occurring *FRYL*-equivalent disease documented in companion animals/wildlife (no OMIA entry identified); *not available*.
- **Comparative biology:** The Furry–NDR module is deeply conserved (yeast→human), making mechanisms evolutionarily transferable. Zebrafish *fryl* is implicated in heart development, paralleling human cardiac anomalies. GWAS of *fryl/FRYL* across sea urchin, sheep, and duck link the gene to sex determination, body size, and growth, consistent with a conserved developmental/growth role.
- **Zoonotic potential:** Not applicable.

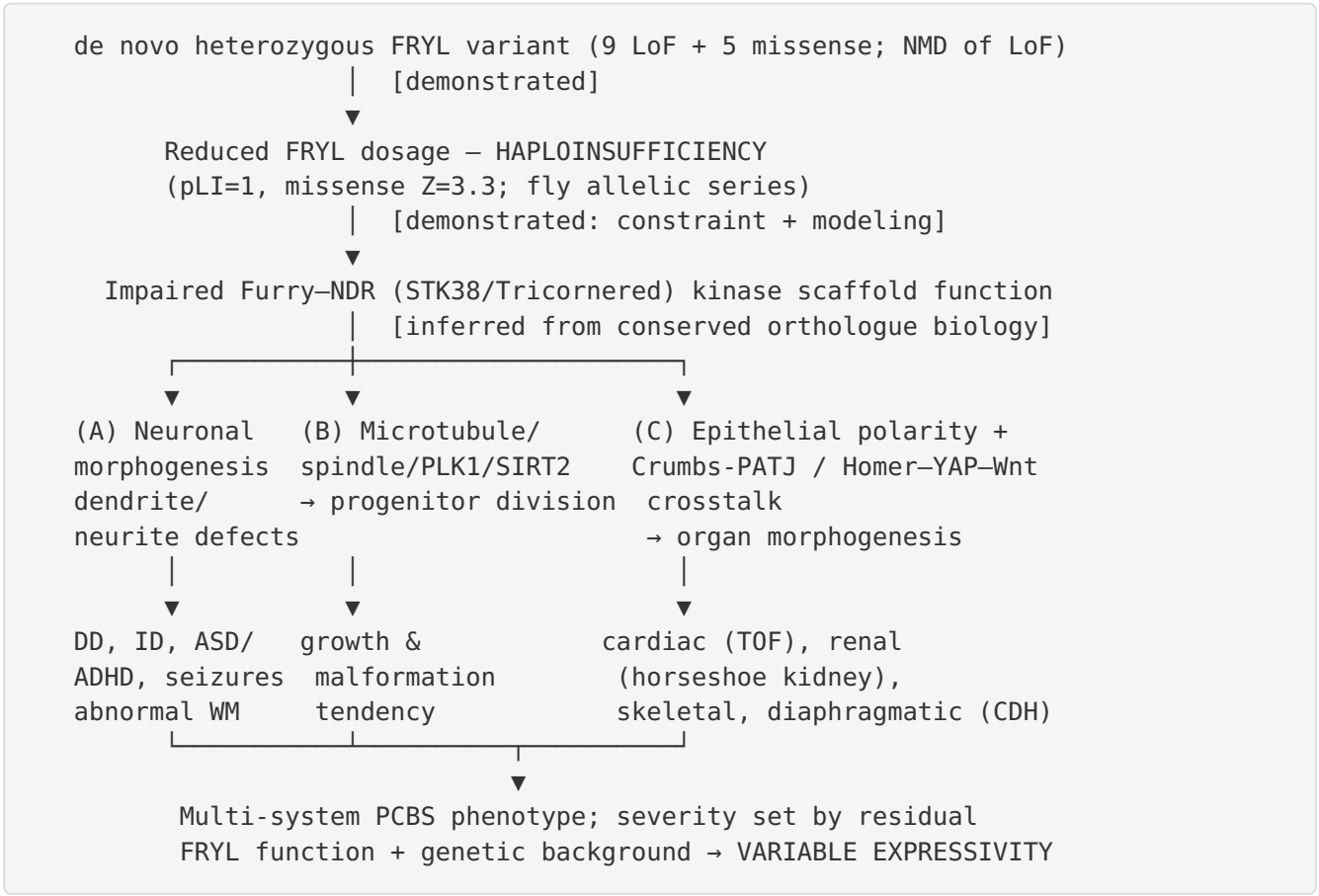
15. Model Organisms

- **Primary model:** *Drosophila melanogaster* (*fry/furry*). Pan et al. generated **knock-in alleles** of human patient missense variants in the fly ortholog, recapitulating a severe/partial/null allelic series — strong phenotype-to-genotype validation and a platform for VUS reclassification.
- **Model characteristics:** Fly *fry* is neuron-expressed; homozygous LoF is lethal; clonal loss causes wing/compound-eye morphogenesis defects — recapitulating the polarized-growth/

morphogenesis biology. Limitation: invertebrate models cannot fully capture human cognition, brain structure, or complex organ malformations.

- **Other systems:** Mouse (*Fryl*, MGI), rat (RGD), zebrafish (*fryl*, ZFIN; heart-development phenotype) orthologs exist for future modeling. No published PCBS-specific mammalian knock-in disease model identified yet.
- **Resources:** FlyBase, MGI, RGD, ZFIN, WormBase (*sax-2*), Alliance of Genome Resources.

Mechanistic Model / Interpretation



The strongest-evidence links are the upstream steps (mutation → haploinsufficiency), which are demonstrated by human constraint statistics and cross-species fly knock-in functional data. The downstream tissue-specific branches are **inferred** from the conserved molecular function

of the Furry–NDR module and FRYL's documented roles in microtubule regulation and epithelial-polarity/Hippo–Wnt signaling, rather than directly demonstrated in PCBS patient tissue.

Evidence Base

PMID	Title (abbrev.)	Role / what it supports
38479391	*De novo variants in FRYL… developmental delay, intellectual disability, dysmorphic features*	**Defining paper.** Establishes gene, de novo dominant inheritance, LoF intolerance, multi-system phenotype, variant spectrum (9 LoF + 5 missense), fly knock-in allelic series, neuronal expression. Supports F001, F002, F003, F004, F005, F006.
24403109	*Multifaceted roles of Furry proteins in invertebrates and vertebrates*	Defines conserved Furry–NDR kinase scaffold function in polarized growth and neuronal morphogenesis. Supports F002 mechanism.
15591127	*Tricornered…interacts with furry during Drosophila wing hair development*	Fry–NDR (Trc) physical interaction and role in polarized epidermal morphogenesis. Supports F002.
20406475	*Drosophila Fry protein interacts with Trc and is highly mobile in vivo*	Fry essential (LoF lethal), interacts with Trc, enriched at growing tips; polarized-growth/transport role. Supports F002.
42455669	*Homer condensates orchestrate YAP-Wnt signaling…downstream of Crumbs polarity*	FRYL as NDR-kinase scaffold in Crumbs–PATJ polarity and Homer/YAP–Wnt crosstalk. Supports branch C of mechanism.
29983373	*Structural basis for auto-inhibition of NDR1…*	Mechanistic detail on NDR kinase regulation and Furry-scaffold association. Contextual support for F002.
30375416	*Lhx1-Ldb1 complex interacts with Furry… pronephric kidney development*	Fry role in kidney field specification — relevant to renal malformations. Contextual support for branch C.
34812992; 39080522; 38909509	GWAS of *fryl/FRYL* in sea urchin / sheep / duck	Cross-species associations with sex determination, body size, growth — indicate conserved developmental/growth roles (contextual, not PCBS-specific).
42220229	RWD monogenic epilepsies; *FRYL* as gene of uncertain significance	Lists *FRYL* among epilepsy GUS with predicted structural effects — consistent with seizure phenotype and the need for functional validation.

Caveats on context literature: Several *FRYL* papers concern common-disease GWAS, cancer, or circRNA biology (e.g., prostate cancer [PMID: 34386489], sepsis-AKI circ-Fryl [PMID: 34478012, 39994492], GERD/COPD [PMID: 39919125], diabetic nephropathy [PMID: 42509683]). These describe *FRYL* in unrelated contexts and **do not inform the Mendelian PCBS phenotype**; they were reviewed and excluded from mechanistic attribution to avoid misattribution.

Limitations and Knowledge Gaps

1. **Very small evidence base.** The disorder rests on one defining cohort (n=14, 2024) plus isolated 2025–2026 case reports. Phenotype frequencies derive from a 7-patient core subset.
2. **No epidemiology.** Prevalence, incidence, sex ratio, and ethnic/geographic distribution are unknown.
3. **Penetrance/expressivity unquantified.** Variable expressivity is documented qualitatively (severe fetal → mild behavioral) but not statistically.
4. **Mechanism largely inferred.** Human PCBS patient-tissue mechanistic data are absent; downstream branches rely on orthologue biology and in-vitro FRYL functions. No mammalian PCBS disease model is yet published.
5. **Natural history and prognosis undefined.** No survival, longitudinal, or QoL data.
6. **Digenic / modifier uncertainty.** The *FRYL* + *SUPT16H* mild case raises but does not prove genetic-background effects.
7. **VUS burden.** Missense interpretation remains challenging; one cohort variant (p.Ser2397Ile) is a VUS.
8. **No therapeutics.** No disease-specific treatment, trial, or biomarker exists.

Proposed Follow-up Experiments / Actions

1. **Expand the patient registry.** International data-sharing (GeneMatcher, Matchmaker Exchange) to build a larger cohort for genotype–phenotype correlation, penetrance, and natural-history studies.

2. **Generate a mammalian model.** Create *Fryl*+/− and patient-variant knock-in mice (and/or zebrafish *fryl* mutants) to test neurodevelopmental, cardiac, renal, and diaphragmatic phenotype recapitulation.
3. **Functionally classify all missense variants** using the established *Drosophila fry* knock-in assay plus NDR-kinase activity readouts to resolve VUS and build an allelic-severity map.
4. **Patient-derived neuronal models.** iPSC-derived neurons/organoids from PCBS individuals to assay dendrite/neurite morphogenesis, microtubule acetylation (SIRT2 axis), and NDR-kinase signaling directly in human cells.
5. **Mechanistic dissection of branches.** Test whether cardiac/renal/diaphragmatic malformations trace to FRYL's Crumbs–PATJ/Homer–YAP–Wnt polarity role versus its microtubule/mitotic role.
6. **Prenatal phenotype characterization.** Collate fetal cases (CDH and others) to define the severe end of the spectrum and inform prenatal counseling.
7. **Biomarker exploration.** Transcriptomic/proteomic profiling of patient cells to identify molecular signatures for diagnosis and, eventually, therapeutic readouts.

Report compiled from 5 discovery iterations; 6 confirmed findings; 23 papers reviewed. Evidence types are indicated throughout as human clinical, model organism, in vitro, computational, or database annotation. Primary reference: Pan et al., Am J Hum Genet 2024 (PMID: 38479391).
