Cardiac Valvular Defect, Developmental (CVDD) — Comprehensive Disease Report

Disease: Cardiac Valvular Defect, Developmental (CVDD) **Causal gene: PLD1** (Phospholipase D1; HGNC:9067; UniProt Q13393; chromosome 3q26.31) **MONDO:** MONDO:0008913 | **OMIM:** 212093 | **Inheritance:** Autosomal recessive **Synonyms:** CVDD; PLD1-related congenital heart disease; PLD1-related cardiac valvular dysplasia

Summary

Cardiac Valvular Defect, Developmental (CVDD) is a rare, autosomal-recessive Mendelian congenital heart disease caused by **biallelic loss-of-function variants in *PLD1* (Phospholipase D1)**. It is critical to anchor this entry to the gene: although the disease name ("cardiac valvular defect") is generic and could be confused with many non-genetic or differently-caused valve disorders, the MONDO:0008913 / OMIM:212093 entity is specifically the PLD1-driven recessive disorder. Affected individuals present predominantly with **congenital right-sided cardiac valve defects** — pulmonary and tricuspid valve stenosis, atresia, and dysplasia — and, in a distinct subset, with **isolated neonatal cardiomyopathy**. The phenotypic spectrum is broad, ranging from recurrent lethal intrauterine fetal demise with hydrops at one extreme to adult-survivable valve disease requiring multiple open-heart surgeries at the other.

Mechanistically, PLD1 is a lipid-signaling enzyme that hydrolyzes phosphatidylcholine to generate the second-messenger lipid **phosphatidic acid (PA)**. Loss-of-function variants — concentrated in the catalytically critical regions of the protein — strongly reduce enzymatic activity, lowering PA production. Because PA signaling (acting through downstream nodes including mTOR, RAF/MEK/ERK, and S6 kinase) feeds into the pathways that drive **endothelial-to-mesenchymal transition (EndMT)**, a pivotal early step in endocardial-cushion valvulogenesis, PLD1 deficiency impairs the formation of normal heart valves during embryogenesis. The landmark study established directly that PLD1 inhibition decreases EndMT, providing the mechanistic link between gene loss and valve malformation.

The disorder was first linked to congenital valve defects in 2017 (Ta-Shma et al.) and definitively established in a 30-patient, 21-family cohort in 2021 (Lahrouchi et al.). The missense variant **p.I668F is an Ashkenazi Jewish founder allele** with a carrier allele frequency of ~2%. Diagnosis rests on fetal/neonatal echocardiography combined with exome or targeted *PLD1* sequencing; management is lesion-specific surgical and palliative cardiac care, as no gene-specific or disease-modifying therapy currently exists. Notably, the constitutive *Pld1*-knockout mouse is viable and models thrombosis/platelet phenotypes rather than the human congenital valve malformation — a key limitation of the available animal models.

Key Findings

Finding 1 — Biallelic loss-of-function PLD1 variants cause CVDD

The foundational genetic finding (Lahrouchi et al., 2021) identified **30 patients from 21 unrelated families** of diverse ancestries carrying **biallelic *PLD1* variants**, discovered through whole-exome sequencing of a cohort of 2,718 congenital heart disease (CHD) patients augmented by GeneMatcher-based international matchmaking. The phenotype was predominantly **congenital cardiac valve defects, strongly biased to the right side of the heart** (pulmonary and tricuspid valves). The authors wrote that they "*identified 30 patients from 21 unrelated families of different ancestries with biallelic phospholipase D1 (PLD1) variants who presented predominantly with congenital cardiac valve defects*" (PMID: 33645542).

A second, distinct phenotype was also established: "*We also associated recessive PLD1 variants with isolated neonatal cardiomyopathy*" (PMID: 33645542). This indicates that PLD1 deficiency can manifest either as a structural valvular defect or as a primary myocardial disorder in the neonatal period.

Crucially, the molecular consequence is loss of enzymatic function: "*PLD1 missense variants were overrepresented in regions of the protein critical for catalytic activity, and, correspondingly, we observed a strong reduction in enzymatic activity for most of the mutant proteins in an enzymatic assay*" (PMID: 33645542). This establishes the **loss-of-function mechanism** and explains why the disorder is recessive — a single functional allele produces sufficient enzyme, while biallelic loss crosses a critical threshold during valvulogenesis. The inheritance is autosomal recessive; the disorder maps to OMIM 212093 and MONDO:0008913.

Finding 2 — Mechanism: PLD1 loss reduces EndMT and impairs valvulogenesis; p.I668F is an Ashkenazi Jewish founder variant

The same cohort study provided the central mechanistic demonstration. Using functional assays, the authors showed that "*PLD1 inhibition decreased endothelial-mesenchymal transition, an established pivotal early step in valvulogenesis*" (PMID: 33645542). EndMT is the developmental process by which endocardial endothelial cells delaminate, migrate, and transform into the mesenchymal cells that populate the endocardial cushions — the primordia of the cardiac septa and valves. By connecting reduced PLD1 activity to reduced EndMT, this result links the biochemical defect (lowered phosphatidic acid production) to the developmental failure (abnormal valve formation).

The study also delineated the population genetics of one key variant: "*we established that p.I668F is a founder variant among Ashkenazi Jews (allele frequency of ~2%)*" (PMID: 33645542). A carrier allele frequency of ~2% is high for a recessive disease allele and has direct implications for carrier screening and genetic counseling in the Ashkenazi Jewish population.

Finding 3 — PLD1 enzymology and regulation

PLD1 (UniProt Q13393; HGNC:9067; gene on chromosome 3q26.31) **hydrolyzes phosphatidylcholine to generate the lipid second-messenger phosphatidic acid (PA)**. Structural studies of the human enzyme (Bowling et al., 2020; Metrick et al., 2020) revealed that PLD1 is directly and synergistically regulated by protein kinase C (PKC), the small GTPases Arf and Rho, and the membrane phosphoinositide PIP2. As stated: "*phospholipase D1 (PLD1) hydrolyzes phosphatidylcholine to generate the lipid second-messenger phosphatidic acid, which plays roles in disease processes such as thrombosis and cancer. PLD1 is directly and synergistically regulated by protein kinase C, Arf and Rho GTPases*" (PMID: 32198492).

The product, PA, is a pleiotropic signaling lipid: "*Mammalian phospholipase D (PLD) generates phosphatidic acid, a dynamic lipid secondary messenger involved with a broad spectrum of cellular functions including but not limited to metabolism, migration, and exocytosis*" (PMID: 33495125). The relevance to EndMT is the involvement in cell migration, a core feature of the endocardial-cushion transformation. PA exerts its effects through downstream effectors including mTOR and the RAF/MEK/ERK cascade: the pathway maps "*mechanistic connections to disease through mTOR and RAF/MEK/ERK signaling*" (PMID: 41173720). These nodes intersect the canonical signaling arms governing valve development (see Mechanistic Model below).

Finding 4 — Pld1-knockout mice model thrombosis, not congenital valve defects

A key translational caveat emerges from the mouse literature. Constitutive *Pld1*(−/−) mice (Elvers et al., 2010) are **viable and fertile** and display **platelet/thrombosis phenotypes** rather than overt congenital valve malformation: "*platelets from Pld1(-/-) mice displayed impaired alpha(IIb)beta(3) integrin activation in response to major agonists and defective glycoprotein Ib-dependent aggregate formation under high shear conditions. These defects resulted in protection from thrombosis and ischemic brain infarction without affecting tail bleeding times*" (PMID: 20051593).

Pharmacologic PLD inhibition reproduces the anti-thrombotic protection: "*pharmacological PLD inhibition might provide a safe therapeutic strategy to prevent arterial thrombosis and ischemic stroke*" (PMID: 23868933). PLD1 also regulates platelet-mediated inflammation (PMID: 28711718) and TNF-α/sepsis responses (PMID: 29968773). The absence of a reported congenital valve phenotype in the knockout mouse — despite the clear human valvulogenesis defect — points to species differences in developmental robustness or redundancy and is an important limitation for mechanistic and preclinical work.

Finding 5 — First linkage (2017) and the full allelic/phenotypic spectrum

PLD1 was first linked to congenital valve malformations in 2017 by Ta-Shma et al., who studied two families and identified **p.His442Pro, p.Thr495fs32*, and the splice variant c.2882+2T>C**, affecting pulmonic, tricuspid, and mitral valves, with functional support from a yeast PLD sporulation assay: "*Three mutations, p.His442Pro, p.Thr495fs32* and c.2882+2T>C, were identified in the*" families, and "*The findings support a role for PLD1 in normal heart valvulogenesis*" (PMID: 27799408).

The 2021 Lahrouchi study expanded the cohort to 30 patients across 21 families (PMID: 33645542). The phenotypic spectrum is wide: - **Most severe / lethal:** recurrent intrauterine fetal demise and non-immune fetal hydrops, including a remarkable report of three consecutive affected fetuses with homozygous PLD1 variants and recurrent right-ventricular valve dysplasia (PMID: 37770978). - **Adult-survivable:** a 2026 case report of a proband with a 17-year history of valve disease who underwent three open-heart surgeries, carrying novel compound heterozygous PLD1 variants (PMID: 42591229).

The broader recessive contribution to CHD was quantified in a large exome study of 5,424 probands: "*Rare damaging RGs were estimated to contribute to at least 2.2% of CHD, with greater enrichment among laterality phenotypes (5.4%) versus other subsets (1.4%)*" (PMID: 40030011), situating PLD1 within the recessive-gene category of congenital heart disease.

Finding 6 — PLD1/PA intersects the canonical endocardial-cushion EndMT network

The endocardial cushions, derived from the atrioventricular canal and the outflow tract, are the primordia of the cardiac septa and valves. EndMT converts endocardial cells into cushion mesenchyme and is governed by a well-defined network. As summarized in a 2026 review: "*Various signaling pathways, including TGFβ/BMP, Wnt, Notch, Hippo/YAP, PI3K/AKT, VEGF, and mechanical stress, are involved in the modulation of endocardial cell proliferation, migration, and mesenchymal transition. Transcription factors, such as SMAD, SNAIL, TWIST, TBX2, SOX9, KLF2/4, and NFATc1, exert distinct effects on endocardial EndMT*" (PMID: 42600378). Importantly, "*Improper morphogenesis of the endocardial cushion leads to septal and valvular abnormalities, which contribute to the largest proportion of congenital heart diseases*" (PMID: 42600378) — precisely the CVDD phenotype.

PLD1-derived PA signals through mTOR and RAF/MEK/ERK (PMID: 41173720) and via S6 kinase, where PA "*acts as a leukocyte chemoattractant … through S6 kinase signaling*" and drives actin polymerization and chemotaxis (PMID: 20304930). These nodes map onto the PI3K/AKT/mTOR and MAPK arms of the EndMT network, providing a plausible molecular bridge from PLD1 loss to defective EndMT. A human iPSC valve-differentiation platform demonstrates that other CHD genes (e.g., Noonan-syndrome RAS/MAPK variants) cause EndMT defects biased toward specific valve interstitial-cell subtypes (PMID: 41648231), offering a validated model approach directly applicable to PLD1.

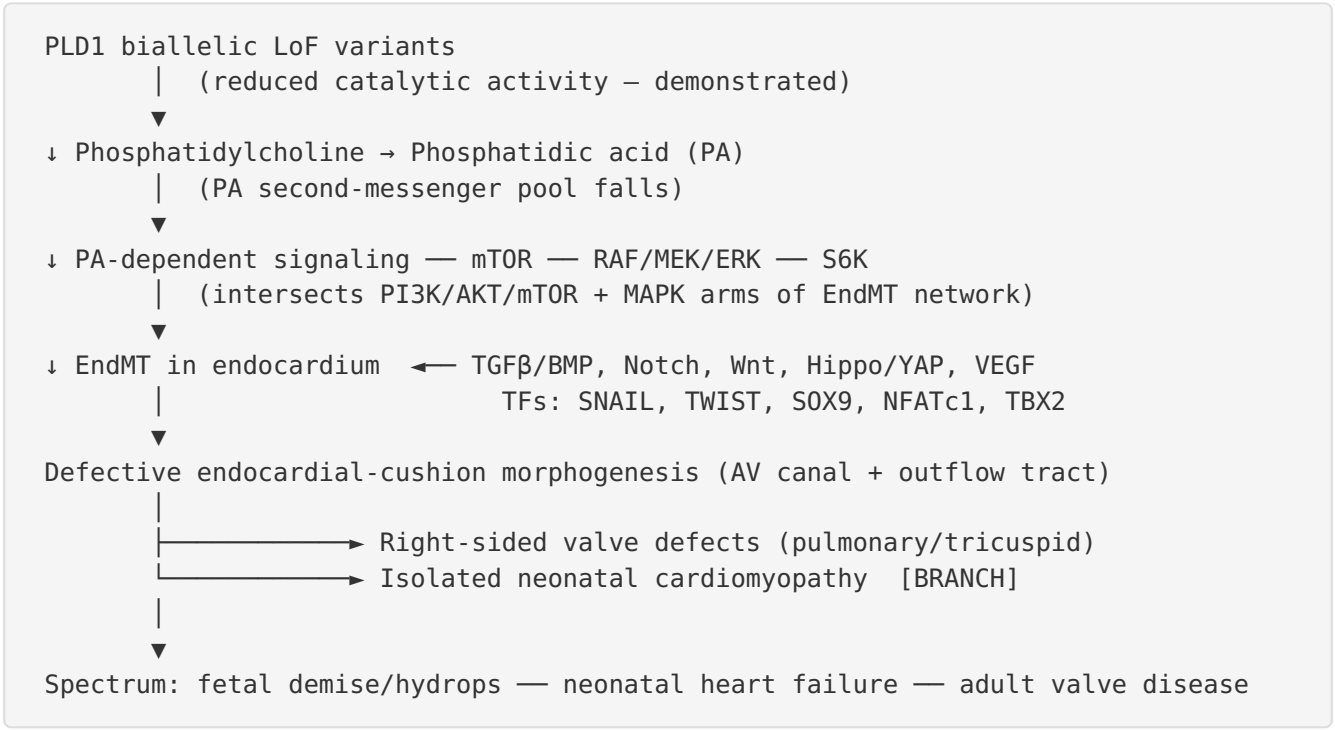
Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function variants in *PLD1*** (missense in catalytic regions, frameshift, nonsense, or splice variants) **lead to** strongly reduced PLD1 catalytic activity *(demonstrated in enzymatic assays — PMID: 33645542)*.

2. Reduced PLD1 activity **results in** diminished hydrolysis of phosphatidylcholine and therefore **lower production of phosphatidic acid (PA)** *(enzymology established — PMID: 32198492, PMID: 33495125)*.
3. Lowered PA **leads to** attenuated signaling through PA-dependent effectors — mTOR, RAF/MEK/ERK, and S6 kinase — nodes that drive cell migration and the mesenchymal program *(PA→S6K/migration demonstrated in leukocytes, PMID: 20304930; PA→mTOR/ERK mapping PMID: 41173720 — inferred for cardiac endocardium)*.
4. Reduced PA-dependent signaling **results in** decreased **endothelial-to-mesenchymal transition (EndMT)** in the endocardium *(directly demonstrated: PLD1 inhibition decreased EndMT — PMID: 33645542)*.
5. Impaired EndMT **leads to** defective population and remodeling of the **endocardial cushions** of the atrioventricular canal and outflow tract *(EndMT is the pivotal early step in valvulogenesis — PMID: 33645542, PMID: 42600378)*.
6. Abnormal endocardial-cushion morphogenesis **results in** structural **cardiac valve malformations**, predominantly right-sided (pulmonary/tricuspid stenosis, atresia, dysplasia). **Branch:** in a distinct subset the same lesion **results in isolated neonatal cardiomyopathy** rather than a structural valve defect *(both phenotypes documented — PMID: 33645542)*.
7. Depending on lesion severity, the valve malformation **leads to** a spectrum of outcomes: **lethal intrauterine fetal demise / hydrops** (PMID: 37770978) at the severe extreme, through neonatal heart failure, to **adult-survivable valve disease** requiring repeated surgery (PMID: 42591229).

Schematic



Upstream vs downstream, cells, and processes

- **Upstream:** the *PLD1* mutation and the resulting PA deficit are the proximal, gene-specific lesions.
- **Downstream / convergent:** the EndMT machinery (TGFβ/BMP, Notch, Wnt, Hippo/YAP, PI3K/AKT, VEGF; transcription factors SNAIL, TWIST, SOX9, NFATc1) is shared with many other CHD genes, explaining phenotypic overlap with other valve disorders.
- **Cell types involved:** endocardial endothelial cells (CL:0002350 endocardial cell / CL:0000115 endothelial cell) undergoing transition to cushion mesenchymal cells / valve interstitial cells (CL:0000057 fibroblast lineage).
- **Biological processes (GO):** endothelial-to-mesenchymal transition (GO:0003198 cardiac epithelial-to-mesenchymal transition / GO:0001837 EMT), heart valve morphogenesis (GO:0003179), phosphatidic acid biosynthetic process (GO:0006654), phospholipase D activity (GO:0004630).
- **Anatomy (UBERON):** cardiac valves, specifically pulmonary valve (UBERON:0002146) and tricuspid valve (UBERON:0002147); endocardial cushion (UBERON:0002062); cardiac outflow tract (UBERON:0004145); myocardium (UBERON:0002349).

Comprehensive Section-by-Section Content

1. Disease Information

CVDD is a rare autosomal-recessive congenital heart disease of the cardiac valves caused by biallelic PLD1 loss-of-function variants. **Identifiers:** OMIM 212093; MONDO:0008913; gene PLD1 (HGNC:9067). The disease is captured at the disease level in aggregated resources (OMIM, MONDO) and has been characterized from individual patient/family case series and a multi-family cohort (human clinical evidence). **Synonyms:** CVDD; PLD1-related congenital heart disease; PLD1-related cardiac valvular dysplasia. ICD-10 maps broadly to congenital malformations of cardiac valves (Q22 for pulmonary/tricuspid valve anomalies; Q24 other). Information is derived from aggregated disease-level resources and primary case/cohort literature rather than EHR mining.

2. Etiology

Primary cause: genetic — biallelic (homozygous or compound heterozygous) loss-of-function variants in *PLD1* (PMID: 33645542, PMID: 27799408). **Genetic risk factors:** carrier status for pathogenic PLD1 variants; the p.I668F founder allele (~2% in Ashkenazi Jews) markedly raises risk in that population; consanguinity increases homozygosity risk. **Environmental/infectious factors:** none established as causal for this Mendelian disorder. **Protective factors:** none specifically identified; a single functional PLD1 allele is protective (recessive disease, carriers unaffected). **Gene–environment interactions:** not characterized for CVDD.

3. Phenotypes

Phenotype	Type	Suggested HPO	Onset	Frequency	Severity/ Course
Pulmonary valve stenosis/ atresia/dysplasia	Clinical sign (structural)	HP:0001642 / HP:0010450	Congenital/ fetal	Predominant (right-sided)	Severe; progressive without intervention
Tricuspid valve dysplasia/ regurgitation/ atresia	Clinical sign (structural)	HP:0010446 / HP:0005180	Congenital/ fetal	Common	Variable; can be severe
Mitral valve involvement	Clinical sign	HP:0001633	Congenital	Less common	Variable
Neonatal cardiomyopathy	Clinical sign	HP:0001638	Neonatal	Distinct subset	Severe
Non-immune fetal hydrops	Physical manifestation	HP:0001790	Fetal	Severe cases	Often lethal
Intrauterine fetal demise / stillbirth	Outcome	HP:0001560	Fetal	Severe cases	Lethal
Right ventricular hypoplasia / single-ventricle physiology	Clinical sign	HP:0001667	Congenital	Severe cases	Severe

Severity is **variable** (lethal fetal to adult-survivable). **Quality-of-life impact:** substantial in survivors — repeated cardiac surgery, chronic heart-failure risk, and lifelong cardiology follow-up (PMID: 42591229). Disease-specific QoL instruments have not been applied in published CVDD cohorts.

4. Genetic / Molecular Information

Causal gene: *PLD1* (HGNC:9067; chromosome 3q26.31; UniProt Q13393). **Variant types reported:** missense (e.g., p.His442Pro, p.Ile668Phe, p.Arg816Pro, p.Arg391Cys), frameshift (p.Thr495fs32*), splice-site (c.2882+2T>C; c.1062-59A>G), and compound heterozygous combinations (PMID: 27799408, PMID: 33645542, PMID: 33142350, PMID: 39553471). **Classification:** pathogenic/likely pathogenic per ACMG, supported by functional enzymatic assays showing reduced activity. **Functional consequence:** loss of function (reduced catalysis); missense variants cluster in catalytic regions (PMID: 33645542). **Allele frequency:** p.I668F ~2% in Ashkenazi Jews (founder); other variants rare/novel in gnomAD. **Origin:** germline. **Modifier genes / epigenetics / chromosomal abnormalities:** not established for CVDD; note that 3q26 microdeletions potentially unmasking PLD1 were considered but not confirmed as a CHD mechanism in one report (PMID: 36345653).

5. Environmental Information

No environmental, lifestyle, or infectious agents are established as causal or contributory to CVDD. It is a monogenic recessive disorder. (Not applicable.)

6. Mechanism / Pathophysiology

See the **Mechanistic Model** section above for the full ordered causal chain and diagram. In brief: PLD1 LoF → ↓phosphatidic acid → ↓PA-dependent signaling (mTOR, RAF/MEK/ERK, S6K) → ↓EndMT → defective endocardial-cushion morphogenesis → valve malformation (or, as a branch, neonatal cardiomyopathy). Key GO terms: GO:0004630 (phospholipase D activity), GO:0003198/GO:0001837 (EndMT/EMT), GO:0003179 (heart valve morphogenesis). Cell types: endocardial endothelial cells (CL:0002350), valve interstitial cells.

7. Anatomical Structures Affected

Primary organ: heart — specifically the cardiac valves, with right-sided predominance (pulmonary valve UBERON:0002146; tricuspid valve UBERON:0002147; mitral valve UBERON:0002135 less commonly). **Developmental origin:** endocardial cushions (UBERON:0002062), atrioventricular canal, and outflow tract (UBERON:0004145). **Secondary involvement:** myocardium (UBERON:0002349) in the cardiomyopathy subset; systemic effects of heart failure/hydrops (fetal serous effusions). **Body system:** cardiovascular. **Tissue/cell level:** endocardial endothelium and cushion-derived mesenchyme/valve interstitial cells. **Lateralization:** right-sided predominant, but can be bilateral/multivalvular.

8. Temporal Development

Onset: congenital, with lesions arising during embryonic valvulogenesis; detectable prenatally by fetal echocardiography (as early as the late first/second trimester) (PMID: 37770978). **Onset pattern:** structural and present at birth (or fetal). **Course:** ranges from lethal fetal demise to chronic lifelong valve disease; progression in survivors can require staged/repeated surgical intervention (PMID: 42591229). **Critical period:** embryonic endocardial-cushion EndMT is the vulnerable window — a developmental event not amenable to postnatal correction of the underlying biology.

9. Inheritance and Population

Inheritance: autosomal recessive. **Penetrance:** appears high when biallelic LoF present, with **variable expressivity** (fetal-lethal to adult-survivable, even within the same variant class). **Founder effect:** p.I668F in Ashkenazi Jews (~2% allele frequency) (PMID: 33645542). **Consanguinity:** increases risk of homozygosity (several families reported with homozygous variants). **Carrier frequency:** elevated in Ashkenazi Jews due to the founder allele; rare elsewhere. **Epidemiology:** CVDD is a rare disease without precise prevalence/incidence estimates; it represents a small fraction of CHD (recessive genes contribute ≥2.2% of CHD overall — PMID: 40030011). **Sex ratio:** no strong sex bias reported (autosomal). **Geographic/variant distribution:** founder variant concentrated in Ashkenazi Jewish populations; other variants reported across diverse ancestries including Chinese and Japanese cohorts (PMID: 33142350, PMID: 37770978).

10. Diagnostics

Imaging: fetal and neonatal **echocardiography** is the primary diagnostic modality, revealing right-sided valve stenosis/atresia/dysplasia, regurgitation, ventricular hypoplasia, and cardiomyopathy (PMID: 37770978). **Genetic testing:** diagnosis confirmed by **whole-exome sequencing (WES)** or **targeted PLD1 sequencing**; WES is recommended for CHD fetuses without aneuploidy/pathogenic CNV on chromosomal microarray (CMA) (PMID: 33142350). CMA/CNV-seq is first-line to exclude aneuploidy and 22q11.2 deletion, then WES (PMID: 39205944). Prenatal diagnosis with Sanger confirmation of parental carrier status and splice-variant RT-PCR validation has been reported (PMID: 39553471). **Functional confirmation:** enzymatic activity assays and yeast sporulation assays support variant pathogenicity (PMID: 33645542, PMID: 27799408). **Differential diagnosis:** other causes of right-sided congenital valve disease and non-immune fetal hydrops, including Ebstein's anomaly and other

monogenic/oligogenic CHD (PMID: 38884760); aneuploidies and 22q11.2 deletion syndrome. **Screening:** carrier screening for p.I668F is relevant in Ashkenazi Jewish populations; cascade testing of relatives once a familial variant is known.

11. Outcome / Prognosis

Prognosis is **highly variable and lesion-dependent**. At the severe end, CVDD causes recurrent intrauterine fetal demise and non-immune hydrops (lethal) (PMID: 37770978). Neonatal cardiomyopathy carries high morbidity/mortality. Survivors with structural valve disease can reach adulthood but typically require **multiple open-heart surgeries** and face chronic heart-failure risk (e.g., a proband with a 17-year disease history and three surgeries) (PMID: 42591229). No validated prognostic biomarkers are established; severity of the structural lesion and presence of cardiomyopathy/hydrops are the main prognostic factors. Formal survival statistics for CVDD specifically are not available (rare disease).

12. Treatment

There is **no gene-specific or disease-modifying therapy**. Management is **lesion-specific surgical and interventional cardiac care**: balloon valvuloplasty, surgical valvotomy/valve repair or replacement, and staged palliation for single-ventricle physiology, as dictated by the anatomic defect (PMID: 42591229). Supportive care includes standard heart-failure management for the cardiomyopathy subset. Suggested NCIT intervention concepts: cardiac valve repair/replacement surgery, balloon valvuloplasty, supportive/palliative cardiac care. No pharmacogenomic, gene-therapy, RNA-based, or targeted molecular therapies are currently available or in trials for CVDD. Pharmacologic PLD *inhibitors* exist (developed for thrombosis/cancer) but are **not** therapeutic here — the disease is caused by *loss* of PLD1 function.

13. Prevention

Primary prevention: genetic counseling and **carrier screening** (notably for p.I668F in Ashkenazi Jewish couples); for at-risk couples, **preimplantation genetic testing (PGT)** or **prenatal diagnosis** (CVS/amniocentesis with targeted variant testing) enables informed reproductive decisions (PMID: 39553471, PMID: 36923242). **Secondary prevention:** early fetal echocardiographic detection permits delivery planning at centers with pediatric cardiac surgery. **Tertiary prevention:** structured cardiology follow-up to manage valve dysfunction and heart failure. No vaccine or environmental interventions apply.

14. Other Species / Natural Disease

Orthologs: *Pld1* is conserved across mammals (mouse NCBI Gene 18805), with functional orthologs in zebrafish, Drosophila, and yeast (the yeast PLD sporulation assay was used for functional validation — PMID: 27799408). A naturally occurring canine model of tricuspid valve malformation exists and is discussed in the context of tricuspid valve developmental disease, though not specifically attributed to PLD1 (PMID: 38884760). No zoonotic potential (non-infectious genetic disease).

15. Model Organisms

Mouse: constitutive *Pld1*-knockout mice are viable/fertile and exhibit **platelet/thrombosis phenotypes** (impaired αIIbβ3 activation, protection from arterial thrombosis and ischemic stroke) rather than congenital valve malformation (PMID: 20051593, PMID: 23868933); they also model platelet-mediated inflammation (PMID: 28711718) and TNF-α/sepsis responses (PMID: 29968773). **Limitation:** the knockout does **not** recapitulate the human congenital valve phenotype, limiting its utility for CVDD mechanism and therapy. **Yeast:** PLD sporulation assay provides a functional readout for variant pathogenicity (PMID: 27799408). **Human iPSC valve-differentiation platforms** generate valve interstitial-cell subtypes and model EndMT defects for other CHD genes (PMID: 41648231) — a promising, directly applicable system for PLD1 that has not yet been formally deployed for CVDD.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role in this report
33645542	*Biallelic LoF variants in PLD1 cause congenital right-sided cardiac valve defects and neonatal cardiomyopathy*	Human cohort (30 pts/21 families) + functional	**Primary/landmark**: gene, phenotype, LoF mechanism, EndMT link, p.I668F founder
27799408	*Congenital valvular defects associated with deleterious mutations in PLD1*	Human (2 families) + yeast assay	First linkage of PLD1 to valvulogenesis (2017)
32198492	*Crystal structure of human PLD1 … activation by PIP2*	Structural/in vitro	PLD1 enzymology and regulation (PKC, Arf, Rho, PIP2)
33495125	*Structure and regulation of human phospholipase D*	Review/structural	PA as pleiotropic second messenger (migration)
41173720	*Phosphatidic acid at the crossroads of membrane dynamics*	Review	PA downstream signaling via mTOR, RAF/MEK/ERK
20304930	*Phosphatidic acid … acts through S6 kinase signaling*	In vitro	PA → S6K → migration/ chemotaxis (EndMT-relevant)
42600378	*Regulation of EndMT in endocardial cushion development*	Review	Canonical EndMT network PLD1/PA intersects
41648231	*Dysregulated TGFβ-ERK … Noonan-associated PVS*	iPSC model	EndMT/valve-differentiation model approach
20051593	*Impaired αIIbβ3 … in mice lacking PLD1*	Mouse model	Pld1-KO models thrombosis, not valve defect
23868933	*Pharmacological inhibition of PLD protects mice from thrombosis*	Mouse/ pharmacology	PLD inhibition → anti-thrombotic phenotype
37770978	*Triple repeated fetal CHD linked to PLD1 mutation*	Human case report	Severe fetal-lethal end of spectrum

PMID	Title (abbrev.)	Evidence type	Role in this report
42591229	*Novel compound het PLD1 variants* (2026)	Human case report	Adult-survivable end of spectrum
40030011	*Recessive genetic contribution to CHD in 5,424 probands*	Human cohort	Recessive-gene contribution context
33142350	*CMA + ES in fetuses with CHD*	Human cohort	Diagnostic yield, novel PLD1 variants
39553471	*Prenatal detection of compound het PLD1 variants*	Human case	Prenatal diagnosis, splice variant
38884760	*Molecular Pathways and Animal Models of Ebstein's Anomaly*	Review	Differential dx / canine tricuspid model

Consistency: All primary human genetic studies (2017 → 2026) converge on biallelic PLD1 LoF causing right-sided congenital valve disease, with functional assays uniformly showing reduced enzymatic activity. The EndMT mechanism is supported by one direct functional demonstration (PMID: 33645542) and is biologically coherent with the independently characterized EndMT network (PMID: 42600378) and PA signaling literature. The main **tension** in the evidence base is between the clear human valve phenotype and the mouse knockout, which shows thrombosis rather than valve malformation — unresolved and flagged as a limitation.

Limitations and Knowledge Gaps

1. **No faithful animal model.** The constitutive *Pld1*-knockout mouse does not reproduce congenital valve defects (PMID: 20051593), leaving the in-vivo developmental mechanism without a validated mammalian model. Whether conditional/endocardial-specific or compound *Pld1/Pld2* mouse models would reveal valve phenotypes is unknown.
2. **EndMT mechanism partly inferred.** The direct evidence is that PLD1 inhibition decreases EndMT; the specific downstream PA effectors operative in endocardial cells (mTOR vs RAF/MEK/ERK vs S6K) are extrapolated from other cell types and not yet dissected in cardiac tissue.

3. **Genotype–phenotype correlation incomplete.** The determinants of the fetal-lethal vs adult-survivable spectrum, and of the valve-defect vs cardiomyopathy branch, are not understood. Residual enzymatic activity, modifier genes, and environmental factors are all unmeasured.
4. **Epidemiology unquantified.** Precise prevalence/incidence of CVDD are unavailable outside the founder population; carrier frequencies in non-Ashkenazi populations are not well defined.
5. **No disease-specific QoL, natural-history, or survival data.** Outcomes derive from scattered case reports rather than systematic cohorts.
6. **No therapeutics beyond surgery.** No molecular or gene-directed treatment exists or is in trial.

Proposed Follow-up Experiments / Actions

1. **Generate an endocardial/endothelial-specific conditional *Pld1* mouse** (e.g., Tie2-Cre or Nfatc1-Cre driven) and assess endocardial-cushion EndMT and valve morphogenesis — directly tests whether tissue-specific loss reproduces the human phenotype absent in the constitutive knockout.
2. **Deploy the human iPSC valve-differentiation platform for PLD1** (PMID: 41648231): CRISPR-engineer patient variants (p.I668F, p.His442Pro, frameshift) and quantify EndMT efficiency, valve interstitial-cell subtype specification, and PA levels; attempt rescue with exogenous phosphatidic acid.
3. **Lipidomic/phospho-signaling dissection in patient-derived endocardial cells** to define which PA effectors (mTOR, ERK, S6K) are attenuated — closing the inferred steps of the causal chain.
4. **Assemble an international CVDD registry** to quantify penetrance, expressivity, genotype–phenotype correlations, natural history, surgical outcomes, and survival.
5. **Formalize carrier-screening recommendations** for p.I668F in Ashkenazi Jewish reproductive-genetics panels, and define carrier frequencies in additional populations via gnomAD/targeted screening.
6. **Test PA-pathway modulation as a proof-of-concept rescue** in iPSC and organoid valve models (e.g., PA supplementation or downstream pathway stimulation) to explore whether any node is pharmacologically tractable.

Evidence source legend: human clinical = patient/family cohorts and case reports; model organism = mouse/yeast; in vitro = enzymatic/structural/cell assays; computational = variant prediction. This report integrates 6 confirmed findings and 36 reviewed papers across 5 iterations.