

Cytosolic Phospholipase A2 Alpha (cPLA2 α) Deficiency — Comprehensive Disease Report

Disease: Cytosolic Phospholipase A2 Alpha Deficiency **MONDO ID:** MONDO:0018794 **Gene:** *PLA2G4A* (cytosolic phospholipase A2 group IVA; HGNC:9035) **Category:** Mendelian (ultra-rare autosomal recessive inborn error of eicosanoid biosynthesis)

Summary

Cytosolic phospholipase A2 alpha (cPLA2 α) deficiency is an **ultra-rare autosomal-recessive inborn error of lipid-mediator metabolism** caused by biallelic loss-of-function variants in *PLA2G4A*. cPLA2 α is the rate-limiting enzyme that selectively liberates **arachidonic acid (AA)** from the *sn*-2 position of membrane glycerophospholipids; the released AA is the obligate substrate for cyclooxygenases (COX-1/COX-2) and lipoxygenases (5-LOX, 12-LOX) that make **prostaglandins, thromboxanes, prostacyclin, and leukotrienes**. When both alleles of *PLA2G4A* are inactivated, the cell can no longer provide AA on demand, and the entire downstream eicosanoid cascade is starved of substrate. The clinical consequence is a distinctive **two-part phenotype**: (1) a prostaglandin-deficiency "NSAID-like" **ulcerating, stenosing, and fistulating small-intestinal enteropathy** with iron-deficiency anemia, recurrent GI bleeding, and protein-losing enteropathy; and (2) a thromboxane-dependent **platelet-function bleeding diathesis**.

The disease has been described in only a handful of unrelated families worldwide (fewer than ~5 published probands as of this review), making it one of the rarest known Mendelian eicosanoid disorders. The molecular diagnosis is anchored by a biochemical signature — **markedly reduced platelet thromboxane B2 (TxB2) and 12-HETE, reduced calcium-ionophore-induced leukotriene B4, and depressed urinary prostanoid metabolites** — followed by confirmatory *PLA2G4A* sequencing. The defect is upstream of COX: platelet aggregation to ADP and collagen is blunted but is **restored by exogenous arachidonic acid**, localizing the lesion to AA release rather than to the COX/synthase machinery itself.

There is **no approved disease-specific therapy**. Management is supportive and mechanism-based: strict NSAID avoidance, **prostaglandin replacement (misoprostol, a PGE1 analog)**, mucosal protection, iron and nutritional support, and bleeding management. Importantly, the inherited human deficiency essentially recapitulates the **predicted on-target toxicity** of pharmacologic cPLA2 α inhibition — a drug class long pursued for asthma, rheumatoid arthritis, inflammatory bowel disease, and psoriasis — and the mouse and human data together serve as a cautionary natural experiment about the consequences of complete cPLA2 α blockade.

1. Disease Information

Overview. cPLA2 α deficiency is a monogenic disorder of eicosanoid biosynthesis. Loss of the group IVA cytosolic phospholipase A2 abolishes the regulated, stimulus-coupled release of arachidonic acid, producing a systemic shortage of prostaglandins, thromboxanes, prostacyclin, and leukotrienes. The two cardinal clinical domains are chronic small-bowel ulceration/stenosis and a platelet-type bleeding tendency.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0018794
Gene	<i>PLA2G4A</i> , HGNC:9035, NCBI Gene 5321, UniProt P47712
Chromosomal locus	1q31.1
Protein	85-kDa cytosolic phospholipase A2, group IVA (cPLA2 α)

Synonyms / alternative names. cPLA2-alpha deficiency; cytosolic phospholipase A2 group IVA deficiency; PLA2G4A deficiency; "enteropathy of prostaglandin deficiency"; inherited human cPLA2 α deficiency. Clinically overlapping descriptive term: a "prostaglandin-related enteropathy."

Information source. Evidence is derived almost entirely from **individual-patient reports and small kindreds** (human clinical case studies) complemented by **mouse knockout models** and **in vitro enzymology**, rather than from aggregated EHR or population-disease registries. This reflects the extreme rarity of the condition.

2. Etiology

Primary cause — genetic. The disease is caused by **biallelic (homozygous or compound-heterozygous) loss-of-function variants in *PLA2G4A***. No environmental or infectious cause is implicated as the primary driver.

Genetic risk / causal variants. - Compound heterozygous **p.Ser111Pro + [p.Arg485His; p.Lys651Arg]** (Adler et al., 2008; [PMID: 18451993](#)). - Homozygous **c.1723G>C, p.Asp575His** (Faioni et al., 2014; [PMID: 25102815](#)). - p.Lys651Arg is a common polymorphism, essentially neutral for catalysis (functional data below).

Modifier genes. Co-inherited **mild factor XI deficiency** was observed in one family (proband, sister, mother) and is a plausible modifier of the bleeding phenotype (Faioni et al., 2014; [PMID: 25102815](#)).

Environmental risk factors / triggers. NSAIDs (COX inhibitors) are expected to **aggravate** the enteropathy because they act downstream of the already-starved pathway; occult NSAID use is a key confounder in differential diagnosis.

Protective factors. None established genetically. Mechanistically, **prostaglandin replacement** (misoprostol, PGE2/prostacyclin analogs) is protective in models (see §6, §12).

Gene–environment interactions. The defining interaction is **NSAID exposure on a prostaglandin-deficient background** — pharmacologic COX inhibition in a patient who already cannot supply AA would be expected to compound mucosal injury. Urinary prostanoid-metabolite screening can distinguish inherited deficiency from occult NSAID enteropathy.

3. Phenotypes

Phenotype	Type	Onset	Severity / course	Frequency	Suggested HPO
Recurrent small-intestinal ulcers	Clinical sign / structural	Childhood–young adult	Severe, recurrent/progressive	Core feature (all probands)	HP:0005263 (gastrointestinal ulceration)
Intestinal strictures / stenosis / subocclusion	Structural	Young adult	Moderate–severe, progressive	Frequent	HP:0005214 (intestinal stricture)
Intestinal fistula / perforation	Structural	Variable	Severe	Reported	HP:0005208 (enteric fistula) / intestinal perforation
Iron-deficiency anemia	Lab abnormality	Childhood–adult	Moderate, chronic	Frequent	HP:0001891
GI blood loss / occult bleeding	Clinical sign	Childhood–adult	Chronic	Frequent	HP:0002239 (GI hemorrhage)
Protein-losing enteropathy / edema	Lab + sign	Adult	Moderate	Reported	HP:0000969 (edema) / protein-losing enteropathy
Platelet-type bleeding diathesis	Clinical sign / lab	Early (childhood)	Mild–moderate	In recessive homozygotes	HP:0011869 (abnormal platelet function); HP:0001892 (abnormal bleeding)
Recurrent abdominal pain	Symptom	Childhood–adult	Moderate, episodic	Frequent	HP:0002027

Onset and progression. Symptoms typically begin in **childhood to young adulthood**; the course is **chronic, recurrent, and progressive** for the enteropathy (ulcers → strictures → subocclusion/fistula), while the bleeding tendency is lifelong but generally **mild-to-moderate**.

Quality-of-life impact. Recurrent ulceration, strictures, chronic anemia, and protein-losing enteropathy impose substantial GI morbidity, risk of repeated surgery, nutritional compromise, and transfusion dependence. No disease-specific EQ-5D/SF-36 data exist given rarity.

Supporting evidence: Adler et al., 2008/2009 ([PMID: 18451993](#); [PMID: 19148786](#)); Faioni et al., 2014 ([PMID: 25102815](#)); Guisado Vasco et al., 2014 ([PMID: 24035666](#)); McAlindon, 2022 ([PMID: 35275899](#)).

4. Genetic / Molecular Information

Causal gene. *PLA2G4A* (HGNC:9035; NCBI Gene 5321; UniProt P47712), 1q31.1, encoding the 85-kDa group IVA cytosolic phospholipase A2 (cPLA2 α).

Protein architecture. cPLA2 α comprises an **N-terminal Ca²⁺-dependent C2 domain** (membrane targeting/translocation) and a **catalytic domain with an unusual Ser-Asp catalytic dyad** located in a hydrophobic funnel with a flexible lid governing interfacial activation; it **selectively cleaves arachidonyl phospholipids** (Dessen et al., 1999; [PMID: 10319815](#)).

"An unusual Ser-Asp dyad located in a deep cleft at the center of a predominantly hydrophobic funnel selectively cleaves arachidonyl phospholipids." — Dessen et al., 1999 ([PMID: 10319815](#))

Pathogenic variants and functional consequences.

Variant (protein)	Nucleotide	Type	Functional effect	Evidence
p.Ser111Pro	—	Missense	Impairs Ca²⁺ binding & Golgi/membrane translocation ; catalysis intact	Reed et al., 2011 (PMID: 21247147)
p.Arg485His	—	Missense	Nearly devoid of catalytic activity	Reed et al., 2011 (PMID: 21247147)
p.Lys651Arg	—	Missense	Common polymorphism; activity slightly > wild type (neutral)	Reed et al., 2011 (PMID: 21247147)
p.Asp575His	c.1723G>C	Missense	Protein instability — transcribed but not stably translated; undetectable protein	Faioni 2014 (PMID: 25102815); Zulueta 2015 (PMID: 25904158)

"the R485H mutant was nearly devoid of any catalytic activity, that the S111P mutation did not affect the enzyme activity" — Reed et al., 2011 (PMID: 21247147)

The **compound-heterozygous** Adler patient thus carries one allele that cannot catalyze (R485H) and one allele that cannot translocate to membranes (S111P) — a two-hit convergence that abolishes effective enzyme function. The **homozygous** Faioni/Zulueta mechanism is **protein instability**: the mRNA is present but protein is undetectable on Western blot.

"suggesting that the variant is transcribed, but not translated or translated into an unstable protein" — Faioni et al., 2014 (PMID: 25102815)

Variant classification. All reported disease alleles behave as **loss-of-function** (ACMG: pathogenic/likely pathogenic on functional + segregation grounds). **Allele frequency:** disease alleles are private/ultra-rare; p.Lys651Arg is a common benign polymorphism.

Somatic vs germline. All reported disease variants are **germline**. (Of note, somatic/expression-level *PLA2G4A* changes appear in cancer contexts — e.g., colorectal cancer ferroptosis regulation, PMID: 41400081 — but these are unrelated to the Mendelian deficiency.)

Modifier genes / epigenetics / chromosomal abnormalities. Co-inherited factor XI deficiency modifies bleeding (above). No disease-specific epigenetic signature or chromosomal abnormality is described.

5. Environmental Information

- **Environmental factors:** No environmental agent causes the disease. **NSAIDs/COX inhibitors** are expected to exacerbate the enteropathy and should be avoided.
 - **Lifestyle factors:** None established.
 - **Infectious agents:** Not applicable; the disorder is not infectious. (Secondary bacterial complications of ulceration/perforation are possible, as with any severe enteropathy.)
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6. Mechanism / Pathophysiology

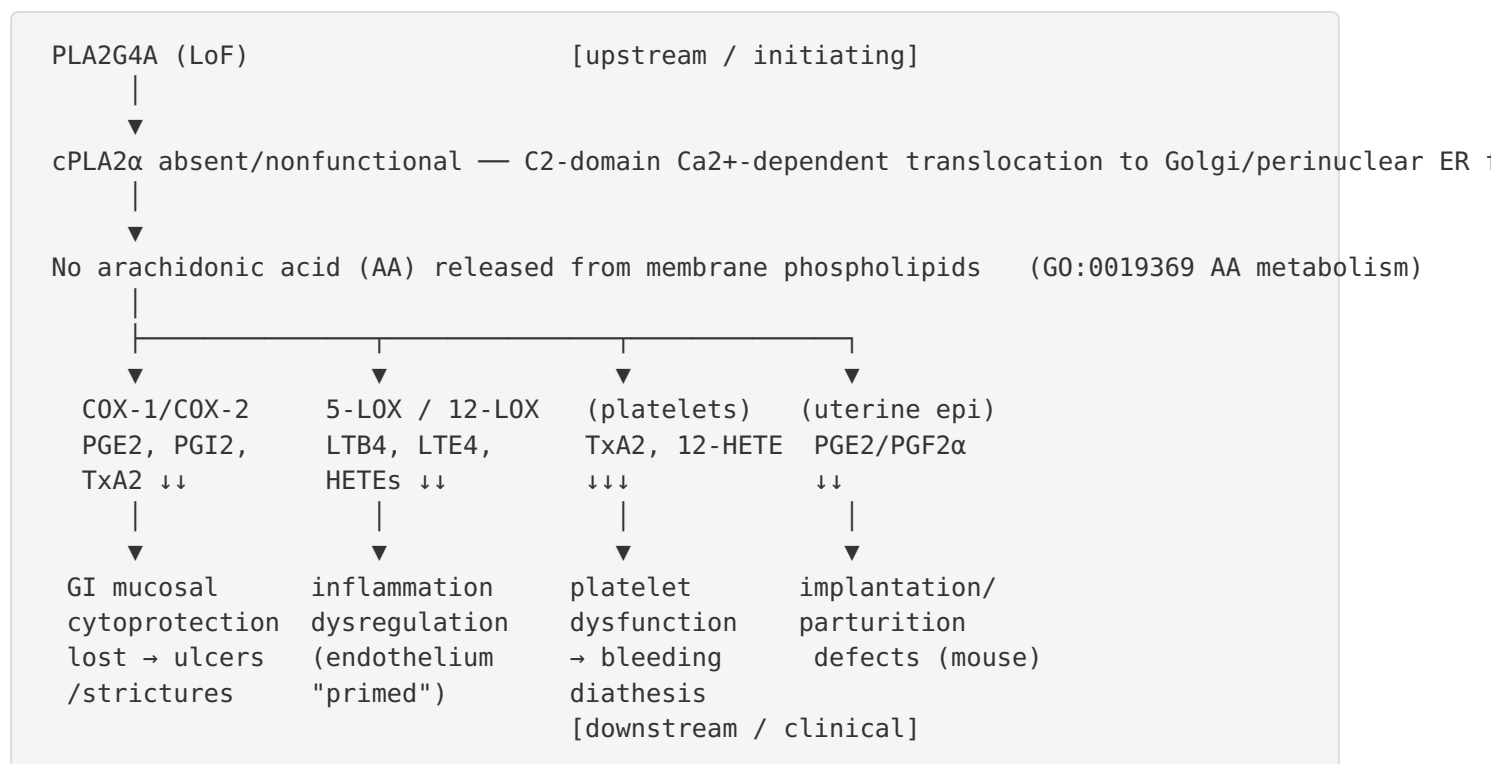
Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic LoF variants in *PLA2G4A*** (catalytic-dead p.Arg485His, translocation-dead p.Ser111Pro, or unstable p.Asp575His) **lead to** absent or non-functional cPLA2 α protein.
2. Loss of functional cPLA2 α **results in** failure to release **arachidonic acid** from the *sn*-2 position of membrane phospholipids upon cell stimulation (the rate-limiting step).
3. AA substrate starvation **leads to** collapse of downstream **COX** (prostaglandins, thromboxane, prostacyclin) and **LOX** (leukotrienes, HETEs) product formation across cell types.
4. **Branch A — Platelets:** Near-absent **thromboxane A2/B2 and 12-HETE results in** defective platelet activation/aggregation and degranulation to ADP and collagen → **bleeding diathesis**. (The defect is upstream of COX — exogenous AA restores aggregation.)
5. **Branch B — GI mucosa:** Deficient **cytoprotective prostaglandins (PGE2, prostacyclin)** in the small-bowel mucosa **results in** loss of mucosal defense → recurrent **ulceration → stenosis/strictures → fistula/perforation**, with **GI bleeding, iron-deficiency anemia, and protein-losing enteropathy** (an "endogenous NSAID-enteropathy" phenotype). *Inferred* from the mechanistic parallel to NSAID enteropathy plus depressed urinary prostanoids.

6. **Branch C — Endothelium/leukocytes:** Reduced (but not absent) endothelial **prostacyclin** and near-absent leukocyte **PGE2/LTB4** lead to a pro-inflammatory, "primed" endothelial/leukocyte state.
7. **Branch D — Reproduction (model-demonstrated):** Loss of uterine epithelial cPLA2 α -derived prostaglandins **results in** deferred implantation, delayed parturition, and small litters (mouse).

"These findings suggested deficient AA release from membrane phospholipids by cytosolic phospholipase A2-alpha (cPLA2-alpha), which regulates cyclooxygenase- and lipoxygenase-mediated eicosanoid production by catalyzing the release of their substrate, AA." — Adler et al., 2009 (PMID: 19148786)

Pathway, cell, and compartment diagram



Molecular pathways: arachidonic acid metabolism; eicosanoid (prostaglandin/thromboxane/leukotriene) biosynthesis (KEGG hsa00590; Reactome AA metabolism). **Cellular processes:** inflammation, platelet activation/degranulation, mucosal cytoprotection. **Subcellular compartments:** cytosol → **Golgi/perinuclear ER/nuclear envelope** (site of Ca²⁺-triggered cPLA2 α translocation and AA release). GO CC: GO:0005829 (cytosol), GO:0005794 (Golgi

apparatus), GO:0005635 (nuclear envelope). **Suggested GO BP:** GO:0019369 (arachidonic acid metabolic process), GO:0001516 (prostaglandin biosynthetic process), GO:0006954 (inflammatory response), GO:0030168 (platelet activation). **Suggested CL:** CL:0000233 (platelet/thrombocyte), CL:0000235 (macrophage), CL:0000066 (epithelial cell; intestinal/uterine luminal epithelium), CL:0002139 (endothelial cell). **CHEBI:** CHEBI:15843 (arachidonic acid), CHEBI:26333 (prostaglandin), CHEBI:26347 (prostanoid/thromboxane), CHEBI:25029 (leukotriene).

Quantitative biochemical signature (human)

Analyte	Control	Patient	Source
Serum TxB2 production	100%	4.6% (P<0.006)	PMID: 19148786
Serum 12-HETE	100%	1.3% (P<0.005)	PMID: 19148786
Leukocyte LTB4 biosynthesis	100%	~3%	PMID: 19148786
Platelet TxA2	20.5 ± 1.4 ng/ml	0.1 ng/ml	PMID: 26183771
Leukocyte PGE2	21.9 ± 7.4 ng/ml	1.9 ng/ml	PMID: 26183771
Endothelial prostacyclin (PGI2)	956 ± 422 pg/ml	196 pg/ml (reduced, not absent)	PMID: 26183771
Urinary prostacyclin metabolites	100%	18.4%	PMID: 26183771
Urinary PGE2 metabolites	100%	~77.8%	PMID: 26183771

A key nuance: the deficiency is **near-complete in platelets and leukocytes** but only **partial in endothelium** (residual prostacyclin), implying cell-type-specific compensation by other phospholipases, and leaving the endothelium "primed for inflammation."

"cPLA2 α -deficient endothelial cells showed reduced, but not absent, formation of prostaglandin I₂ (prostacyclin; control 956 $\pm$ 422 pg/ml vs. patient 196 pg/ml) and were primed for inflammation." — Kirkby et al., 2015 ([PMID: 26183771](#))

7. Anatomical Structures Affected

- **Primary organ: Small intestine** (UBERON:0002108) — recurrent ulceration, stenosis, fistula. Body system: **digestive system** (UBERON:0001007).
- **Hematologic involvement: Platelets/blood** (platelet dysfunction, bleeding diathesis).
- **Secondary/complication organs:** systemic effects of chronic GI blood loss (anemia) and protein loss (edema). Endothelium/vasculature shows a pro-inflammatory state.
- **Model-demonstrated additional organs (mouse): uterus** (UBERON:0000995, reproductive failure), **kidney** (UBERON:0002113, concentration defect), **heart** (exaggerated ischemia–reperfusion injury), **lung/airway** (reduced bronchial reactivity), **brain** (altered injury susceptibility).
- **Tissue/cell level:** intestinal **luminal epithelium** (CL:0000066), **platelets** (CL:0000233), **macrophages/leukocytes** (CL:0000235), **endothelial cells** (CL:0002139); uterine luminal epithelium in mouse.
- **Subcellular:** cytosol, Golgi apparatus, nuclear envelope/perinuclear ER (site of AA release).
- **Lateralization:** Not applicable (systemic/bilateral by nature).

8. Temporal Development

- **Onset:** childhood to young adulthood; **chronic/insidious** onset of GI symptoms; bleeding tendency apparent early.
- **Progression:** the enteropathy is **progressive** (ulcers $\rightarrow$ strictures/stenosis $\rightarrow$ subocclusion $\rightarrow$ fistula/perforation), punctuated by **episodic** flares of pain and bleeding.
- **Disease course / duration: chronic, lifelong.** No spontaneous remission is described; remission of mucosal injury is treatment-related (prostaglandin replacement, NSAID avoidance).

- **Critical periods / windows for intervention:** prevention of NSAID exposure throughout life; early prostaglandin replacement to protect mucosa and manage bleeding.

9. Inheritance and Population

- **Inheritance: autosomal recessive.** Homozygous (p.Asp575His) and compound-heterozygous (p.Ser111Pro/p.Arg485His) genotypes described.
- **Penetrance/expressivity:** The severe recessive phenotype requires biallelic LoF. **Heterozygotes show partial penetrance for the GI phenotype:** in the Faioni kindred, **GI ulcers affected 5/14 heterozygous members under 40 years vs 1/16 wild-type members over 60 years;** crucially, **no heterozygote had a bleeding diathesis** (bleeding is strictly recessive).

"Platelet aggregation and degranulation induced by adenosine diphosphate or collagen were diminished but were normal in response to arachidonic acid." — Adler et al., 2008 ([PMID: 18451993](#))

- **Epidemiology: Ultra-rare** — fewer than ~5 published probands across 2–3 unrelated families; no reliable prevalence/incidence figures exist. Orphanet/OMIM-level aggregation is limited by rarity.
- **Founder effects / consanguinity / carrier frequency:** The homozygous p.Asp575His family is consistent with identity-by-descent; no established founder population or carrier-frequency estimate. Disease alleles are private/ultra-rare in gnomAD.
- **Sex ratio / demographics:** Both sexes affected (reported male proband + twin sister; siblings). No sex predilection established. No defined geographic/ethnic clustering.

10. Diagnostics

Biochemical (first-line, disease-defining): - Platelet TxB2 / 12-HETE — markedly reduced. - Calcium-ionophore-induced leukocyte LTB4 — markedly reduced; urinary LTE4 may be undetectable. - Urinary prostanoid metabolites (e.g., 11-dehydro-TxB2, PGE2/PGI2 metabolites) — depressed. Also useful to **exclude occult NSAID use.** - Platelet aggregometry:

blunted response to ADP/collagen that is **normalized by exogenous arachidonic acid** — the pathognomonic "upstream of COX" signature. - **Western blot: platelet cPLA2 α undetectable** (p.Asp575His homozygotes).

"platelet cPLA2 α was undetectable by Western Blotting in the proband and his sister" — Faioni et al., 2014 ([PMID: 25102815](#))

Genetic testing: Single-gene *PLA2G4A* sequencing confirms the diagnosis; WES/WGS or a GI/platelet-disorder gene panel is reasonable in undiagnosed cases. Functional confirmation (enzyme assay, translocation, protein stability) supports VUS interpretation.

Imaging/endoscopy: capsule endoscopy, enterography (CT/MR), and small-bowel studies reveal multifocal ulcers, short strictures, and subocclusion; biopsy shows superficial submucosal ulceration with edema.

Clinical criteria / differential diagnosis: There are no formal consensus criteria. Diagnosis rests on the **tetrad of small-bowel ulcerating/stenosing disease + platelet-type bleeding + global eicosanoid deficiency + biallelic *PLA2G4A* variants**. Key differentials: - **SLCO2A1-related chronic enteropathy (CEAS/CMUSE)** — prostaglandin **transporter** defect, phenotypically overlapping. - **NSAID enteropathy** — excluded by urinary metabolite screen (occult NSAID use). - Crohn's disease, cryptogenic multifocal ulcerating stenosing enteritis (CMUSE), other platelet secretion/aggregation disorders.

"Mutations in the *PLA2G4A* gene result in cytosolic phospholipase A2 α deficiency and reduced arachidonic acid for prostaglandin synthesis leading to a severe ulcerating, stenosing and fistulating small bowel disease." — McAlindon, 2022 ([PMID: 35275899](#))

Screening: No population or newborn screening exists. Cascade genetic testing of relatives is appropriate once a family variant is known.

11. Outcome / Prognosis

- **Survival/mortality:** No formal survival data; the disorder is not typically rapidly lethal but carries morbidity from recurrent surgery, perforation risk, chronic anemia, and protein loss. Life expectancy data are unavailable given rarity.

- **Morbidity/function:** Substantial — recurrent small-bowel obstruction/strictures, fistula/perforation, iron-deficiency anemia, protein-losing enteropathy with edema, and a lifelong bleeding tendency.
 - **Complications:** bowel stenosis/subocclusion, fistulae, perforation, chronic GI hemorrhage, transfusion dependence, nutritional deficiency.
 - **Prognostic factors:** degree of residual eicosanoid production (cell-type dependent), NSAID avoidance, access to prostaglandin replacement, surgical burden.
 - **Recovery:** chronic disease; mucosal protection and NSAID avoidance can reduce flares, but the underlying enzymatic defect is permanent.
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12. Treatment

No approved disease-specific (curative) therapy exists. Management is **supportive and mechanism-based**:

Intervention	Rationale / evidence	Suggested NCIT
Misoprostol (PGE1 analog) — prostaglandin replacement	Replaces deficient cytoprotective prostaglandin; misoprostol ameliorated eicosanoid-deficiency injury in cPLA2 α -null hearts (PMID: 21884509)	NCIT:C62042 (Misoprostol)
NSAID avoidance	Patients cannot buffer further COX inhibition	—
Iron supplementation / transfusion	Chronic GI blood loss, iron-deficiency anemia	NCIT:C29059 (Iron)
Nutritional support (protein-losing enteropathy)	Edema, hypoproteinemia	—
Mucosal protection / ulcer management	Symptomatic ulcer/stricture control	—
Surgical resection / stricturoplasty	Obstructing strictures, fistula, perforation	NCIT (bowel resection)
Bleeding management (platelet support, antifibrinolytics)	Platelet-function defect	—

"the enhanced injury is ameliorated by treatment with the PGE analog, misoprostol" — Kerkelä et al., 2011 ([PMID: 21884509](#))

Preclinical proof-of-concept for **prostaglandin replacement** also comes from the reproductive rescue in Pla2g4a-null mice:

"Pla2g4a-null females that received PGE2 + carbaprostacyclin at the time of implantation delivered earlier (20.5 +/- 0.2 days vs. 21.6 +/- 0.2 days, P < 0.01)" — Brown et al., 2009 ([PMID: 19684335](#))

Advanced/experimental therapeutics: No gene therapy, RNA therapy, or targeted therapy is in clinical use for this indication. Conceptually, **enzyme/gene replacement** of *PLA2G4A* or **downstream eicosanoid-analog supplementation** are rational future directions. No registered NCT trials are specific to this ultra-rare disease.

Personalized medicine: Treatment is inherently genotype-driven (confirmed biallelic LoF); cell-type-specific residual activity may influence response.

13. Prevention

- **Primary prevention:** Not applicable to disease occurrence (Mendelian). **Preconception/ prenatal genetic counseling and carrier testing** in affected families; options include prenatal diagnosis and preimplantation genetic testing for known family variants.
 - **Secondary prevention:** Cascade genetic testing of at-risk relatives; early biochemical screening (eicosanoid profiling) in symptomatic kin.
 - **Tertiary prevention (preventing complications): strict NSAID avoidance**, prostaglandin replacement (misoprostol), iron repletion, and surveillance for strictures/bleeding to prevent perforation and obstruction.
 - **Counseling:** Autosomal-recessive recurrence risk (25% for carrier couples); heterozygotes may have a milder GI predisposition but no bleeding risk — relevant genetic-counseling nuance.
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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *Pla2g4a* is conserved; mouse *Pla2g4a* (NCBI Gene 18783) is the principal model ortholog. Human NCBI Gene 5321.
 - **Natural disease in other species:** No well-characterized naturally occurring companion-animal or wildlife disease is documented; knowledge derives from engineered mouse knockouts.
 - **Comparative biology:** The mouse knockout **recapitulates core human features** (intestinal ulceration; near-absent eicosanoid production) while revealing **additional organ roles** (renal concentration defect, reproductive failure, context-dependent cardioprotection/neuroprotection) — demonstrating strong evolutionary conservation of the AA-release → eicosanoid axis.
 - **Zoonotic potential:** None (non-infectious genetic disease).
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15. Model Organisms

Mouse (*Mus musculus*) *Pla2g4a* knockout is the definitive model.

Model / study	Key phenotypes	Relevance
Uozumi et al., 1997, <i>Nature</i> (PMID: 9403692)	↓ eicosanoids & PAF in peritoneal macrophages; reduced ovalbumin anaphylaxis and bronchial reactivity; females fail to deliver (rescuable by progesterone-receptor antagonist)	First KO; non-redundant role in allergy & reproduction
Uozumi & Shimizu, 2002 (review) (PMID: 12432909)	Normal growth but renal concentration defect + intestinal ulcerative lesions ; small litters; milder anaphylaxis, lung injury, I/R, MPTP, polyposis	Recapitulates hallmark intestinal ulceration
Brown et al., 2009 (PMID: 19684335)	↓ uterine PGE2/PGF2α/6-keto-PGF1α/TxB2; delayed implantation/parturition; rescued by PGE2 + carbaprostacyclin	Pharmacologic prostaglandin rescue
Kerkelä et al., 2011 (PMID: 21884509)	Exaggerated cardiac ischemia–reperfusion injury ; ↓ PGE2; ameliorated by misoprostol	cPLA2α is cardioprotective ; caution for inhibition
Sapirstein & Bonventre, 2000 (PMID: 10905638)	Protected against neuronal injury in ischemia/reperfusion & MPTP	Context-dependent (protective in brain)

"Their ovalbumin-induced anaphylactic responses were significantly reduced, as was their bronchial reactivity to methacholine." — Uozumi et al., 1997 (PMID: 9403692)

"Close examinations have revealed a renal concentration defect and intestinal ulcerative lesions." — Uozumi & Shimizu, 2002 (PMID: 12432909)

"In each model cPLA2 deficient mice are protected against neuronal injury when compared to their wild type littermate controls." — Sapirstein & Bonventre, 2000 (PMID: 10905638)

Model limitations: Mouse knockouts reveal additional organ phenotypes (renal, reproductive, cardiac) that are not prominent clinical features in the few described human patients — partly reflecting the small human sample and possible species-specific phospholipase redundancy. The **direction of effect is context-dependent** (protective in brain, deleterious in heart/intestine), complicating extrapolation.

In vitro / structural models: Recombinant cPLA2 α enzymology (Reed et al., 2011, [PMID: 21247147](#)); crystal structure (Dessen et al., 1999, [PMID: 10319815](#)); cellular expression/stability assays (Zulueta et al., 2015, [PMID: 25904158](#)).

Key Findings (with statistical evidence)

F001 — cPLA2 α deficiency is an autosomal-recessive *PLA2G4A* disorder causing eicosanoid-deficiency enteropathy with platelet dysfunction. Two unrelated families anchor the entity. The Adler proband (compound heterozygous p.Ser111Pro + [p.Arg485His; p.Lys651Arg]) had multiple small-intestinal ulcers, markedly reduced platelet TxB2/12-HETE and ionophore-induced LTB4, and diminished aggregation/degranulation to ADP/collagen that **normalized with arachidonic acid** — proving the lesion is upstream of COX ([PMID: 18451993](#)). The Faioni family (homozygous p.Asp575His, a 27-year-old man and his twin sister) showed early bleeding diathesis, recurrent GI ulcers, undetectable platelet cPLA2 α on Western blot, and extremely low serum TxB2/12-HETE and urinary 11-dehydro-TxB2 ([PMID: 25102815](#)).

F002 — Prostaglandin deficiency mechanistically links cPLA2 α loss to an NSAID-like enteropathy. Adler's "enteropathy of prostaglandin deficiency" patient had chronic recurrent small-intestinal ulcers, small-bowel perforations, and GI blood loss **despite no COX-inhibitor use**, with serum TxB2 at 4.6% ($P < 0.006$) and 12-HETE at 1.3% ($P < 0.005$) of controls, leukocyte LTB4 at ~3%, and undetectable urinary LTE4 ([PMID: 19148786](#)).

F003 / F006 / F009 — Mouse knockouts validate causality and reveal multi-organ roles. Pla2g4a-null mice show significantly decreased uterine PGE2/PGF2 α /6-keto-PGF1 α /TxB2 with delayed implantation and parturition, pharmacologically rescued by PGE2 + carbaprostacyclin (20.5 ± 0.2 vs 21.6 ± 0.2 days, $P < 0.01$) ([PMID: 19684335](#)). Broader knockout data show intestinal ulceration plus a renal concentration defect ([PMID: 12432909](#)) and the landmark non-redundant role in allergy and reproduction ([PMID: 9403692](#)). Context-dependence is notable — protective in brain injury ([PMID: 10905638](#)) but deleterious in cardiac I/R ([PMID: 21884509](#)).

F004 — Structure–function maps each variant to a distinct defect. cPLA2 α uses a Ser-Asp catalytic dyad selective for arachidonyl phospholipids ([PMID: 10319815](#)); p.Arg485His abolishes catalysis, p.Ser111Pro abolishes Ca²⁺-dependent membrane translocation without affecting catalysis, and p.Lys651Arg is neutral ([PMID: 21247147](#)). Compound heterozygosity therefore combines two separable loss-of-function mechanisms.

F005 — Cell-type-specific eicosanoid loss. Platelet TxA2 (20.5 $\pm$ 1.4 $\rightarrow$ 0.1 ng/ml) and leukocyte PGE2 (21.9 $\pm$ 7.4 $\rightarrow$ 1.9 ng/ml) are nearly abolished, whereas endothelial prostacyclin is reduced but not absent (956 $\pm$ 422 $\rightarrow$ 196 pg/ml), leaving endothelium "primed for inflammation"; urinary prostacyclin metabolites fell to 18.4% while PGE2 metabolites remained $\sim$ 77.8% of control ([PMID: 26183771](#)).

F007 — A prostaglandin-related ulcerating/stenosing/fistulating small-bowel disease. The full phenotype (ulcers, strictures, fistulae, iron-deficiency anemia, protein-losing enteropathy) sits in a differential with SLCO2A1-CMUSE and NSAID enteropathy; a urinary-metabolite screen reveals occult NSAID use ([PMID: 35275899](#); [PMID: 24035666](#)).

F008 — p.Asp575His acts via protein instability; heterozygotes show partial GI penetrance. The variant is transcribed but yields unstable/undetectable protein ([PMID: 25102815](#); [PMID: 25904158](#)); GI ulcers affected 5/14 heterozygotes (<40 y) vs 1/16 wild-type (>60 y), while bleeding was strictly recessive, and co-inherited mild factor XI deficiency may modify bleeding.

F010 — Management is supportive prostaglandin replacement; the human deficiency is the on-target toxicity of cPLA2 α inhibition. cPLA2 α is a long-standing anti-inflammatory/anti-asthma drug target ([PMID: 16712837](#)); the inherited human deficiency therefore defines the predicted toxicity (GI ulceration + bleeding) of complete pharmacologic blockade, with misoprostol-based replacement supported by model rescue ([PMID: 21884509](#); [PMID: 19684335](#)).

Mechanistic Model / Interpretation

The disease is best understood as a **single enzymatic "choke point" failure** with pleiotropic downstream consequences. cPLA2 α sits at the apex of eicosanoid signaling as the only PLA2 that selectively and efficiently releases arachidonate on cell activation. Because every prostaglandin, thromboxane, prostacyclin, and leukotriene depends on this released AA, a complete loss collapses the whole lipid-mediator network simultaneously — but **not uniformly across cell types**. Platelets and leukocytes, which rely heavily on cPLA2 α -derived

AA, lose ~99% of their thromboxane/HETE/leukotriene output, explaining the bleeding and inflammatory-regulation defects. The small-intestinal mucosa loses cytoprotective prostaglandins, producing an "endogenous NSAID enteropathy." The endothelium retains partial prostacyclin production (residual/compensatory phospholipases), yet is pushed toward a pro-inflammatory state.

Supported hypotheses:

- AR LoF of PLA2G4A is causal ✓
- Global eicosanoid deficiency ✓
- Upstream-of-COX platelet lesion ✓
- Prostaglandin-deficiency enteropathy ✓
- Misoprostol/PG-analog rescue (model) ✓

Refuted / excluded:

- Primary environmental/infectious cause ✕
- COX/synthase-level defect (AA rescues) ✕
- Dominant bleeding in heterozygotes ✕

This mechanistic model also unifies the **human deficiency and the pharmacology**: cPLA2 α has been pursued as an anti-inflammatory drug target, and the inherited human loss-of-function phenotype is effectively the toxicology readout of maximal target engagement — a point reinforced by mouse data showing cPLA2 α is cardioprotective and its loss worsens cardiac ischemia–reperfusion injury.

Evidence Base

PMID	Study	Source type	Contribution
18451993	Adler 2008	Human clinical	First human case; compound-het genotype; platelet/eicosanoid defect upstream of AA
19148786	Adler 2009	Human clinical	"Enteropathy of prostaglandin deficiency"; quantified global eicosanoid loss
25102815	Faioni 2014	Human clinical	Homozygous p.Asp575His; undetectable protein; heterozygote penetrance; factor XI
25904158	Zulueta 2015	In vitro	Protein instability mechanism for p.Asp575His
21247147	Reed 2011	In vitro	Functional mapping of patient variants (catalysis vs translocation)
10319815	Dessen 1999	Structural	Crystal structure; Ser-Asp dyad; arachidonyl selectivity
26183771	Kirkby 2015	Human clinical	Cell-type-specific eicosanoid loss; endothelium primed for inflammation
19684335	Brown 2009	Model organism	KO reproductive phenotype; prostaglandin rescue
12432909	Uozumi 2002	Model organism	KO review; intestinal ulceration + renal defect
9403692	Uozumi 1997	Model organism	First KO; allergy + parturition roles
21884509	Kerkelä 2011	Model organism	Cardioprotective role; misoprostol rescue; inhibition caution
10905638	Sapirstein 2000	Model organism	Neuroprotection from cPLA2 α loss (context dependence)
35275899	McAlindon 2022	Review	Prostaglandin-related enteropathy framework; differentials
24035666	Guisado Vasco 2014	Human clinical	CMUSE-type presentation; anemia, protein-losing enteropathy
16712837	Malaviya 2006	Model organism	cPLA2 α as anti-inflammatory drug target (toxicity context)

Limitations and Knowledge Gaps

1. **Extremely small human sample.** Fewer than ~5 published probands; no prevalence, incidence, survival, or validated quality-of-life data. Phenotype spectrum and natural history are incompletely defined.
 2. **No formal diagnostic criteria or guidelines.** Diagnosis is ad hoc (biochemical + genetic).
 3. **Variant-level data are sparse.** Only a few alleles are characterized; no comprehensive ClinVar landscape or founder analysis.
 4. **Mouse–human discordance.** Knockouts show renal, reproductive, cardiac, and neurologic phenotypes not clearly prominent in patients, and the effect direction is context-dependent — complicating extrapolation.
 5. **Therapy is unproven in humans.** Misoprostol/prostaglandin replacement is supported only by model rescue and mechanistic reasoning, not controlled human trials.
 6. **Modifier biology underexplored.** Cell-type-specific residual eicosanoid production (e.g., endothelial prostacyclin) and modifiers like factor XI are only beginning to be understood.
 7. **No epigenetic, single-cell, or multi-omic patient datasets** exist for this disease.
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Proposed Follow-up Experiments / Actions

1. **Establish an international patient registry / GeneMatcher outreach** to aggregate additional probands and define natural history, penetrance, and genotype–phenotype correlations.
2. **Standardize a diagnostic biochemical panel** (platelet TxB2/12-HETE, ionophore-induced LTB4, urinary 11-dehydro-TxB2 and PGI2/PGE2 metabolites, AA-rescue aggregometry) as a reproducible workup, with urinary-metabolite screening to exclude occult NSAID use.
3. **Functionally characterize all reported and novel variants** (catalysis, Ca²⁺ binding/translocation, protein stability) to build an ACMG-grade functional-evidence database.
4. **Conduct n-of-1 or small controlled studies of misoprostol/prostaglandin-analog replacement** for enteropathy and bleeding, with eicosanoid-metabolite and mucosal-healing endpoints.

5. **Develop patient iPSC-derived intestinal organoids and megakaryocytes/platelets** to model mucosal cytoprotection and platelet dysfunction and to test eicosanoid-replacement and gene-correction strategies.
 6. **Build conditional, tissue-specific mouse models** (intestinal epithelium, platelet) to dissect the enteropathy and bleeding mechanisms separately and test prostaglandin rescue.
 7. **Formalize a differential-diagnosis protocol** distinguishing cPLA2 α deficiency from SLCO2A1-CEAS/CMUSE and occult NSAID enteropathy using urinary metabolite screening plus targeted gene panels.
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Report compiled from 10 confirmed findings across 5 investigation iterations and 46 reviewed papers. Evidence integrates human clinical case series, in vitro enzymology and structural biology, and mouse genetic models.

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