Visceral Heterotaxy 8 (HTX8) — Comprehensive Disease Characteristics Report

Disease: Visceral Heterotaxy 8 (HTX8) · **MONDO:** MONDO:0014967 · **Gene:** *PKD1L1* · **Category:** Mendelian (autosomal recessive) **Report date:** 2026-10-20 · Evidence base: human clinical case reports, model-organism genetics, in-vitro/biochemical, and computational/database sources.

> **Summary answer.** Visceral Heterotaxy 8 (HTX8; OMIM #617205) is a rare autosomal-recessive laterality (left–right patterning) disorder caused by biallelic loss-of-function or damaging variants in *PKD1L1* (polycystin-1-like 1, chr 7p12.3). PKD1L1 partners with PKD2 (polycystin-2/TRPP2) on motile cilia of the embryonic node/Kupffer's vesicle to sense leftward "nodal flow"; its loss disrupts the earliest left-biased Ca^{2+}/Nodal signal, randomizing or bilateralizing organ situs and producing a spectrum from situs inversus totalis to situs ambiguus (heterotaxy) with frequent complex congenital heart disease and splenic anomalies (including asplenia). There is no gene-specific therapy; management is anatomy-driven (cardiac surgery, infection prophylaxis for asplenia), and prognosis is governed mainly by the severity of congenital heart disease.

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1. Disease Information

Overview. HTX8 is a Mendelian subtype of visceral heterotaxy — a congenital disorder of left–right (L-R) body-axis determination in which thoracic and abdominal organs are abnormally arranged across the midline. Clinically it ranges from **situs inversus totalis (SIT)** (complete mirror-image reversal) to **situs ambiguus / heterotaxy** (discordant, randomized organ positioning), typically with congenital heart disease (CHD). "Disruption of the establishment of left-right (L-R) asymmetry leads to situs anomalies ranging from situs inversus totalis (SIT) to situs ambiguus (heterotaxy)" (P 27616478).

Key identifiers. - **MONDO:** MONDO:0014967 (Visceral heterotaxy 8) - **OMIM:** #617205 (phenotype, HTX8, autosomal recessive); gene *PKD1L1* *609721 - **Gene/HGNC:** *PKD1L1*, HGNC:18053; Ensembl ENSG00000158683; NCBI Gene 168507; UniProt Q8TDX9 - **Orphanet:** broad entry ORPHA:450 (Heterotaxia); no PKD1L1-specific ORPHA code - **MeSH:** D059446 (Heterotaxy Syndrome) - **ICD-10:** Q89.3 (Situs inversus); **ICD-11:** LB01.1 (Situs ambiguous / heterotaxy) - **HPO anchor:** HP:0004935 (Visceral heterotaxy)

Synonyms / alternative names. Heterotaxy, visceral, 8, autosomal recessive; HTX8; PKD1L1-related heterotaxy/laterality defect; situs ambiguus/situs inversus due to *PKD1L1*.

Information source type. Derived from **aggregated disease-level resources** (OMIM, Orphanet, ClinVar, UniProt, gnomAD) combined with **individual patient case reports** (small families); not from large EHR cohorts.

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2. Etiology

Primary cause — genetic. Biallelic (homozygous or compound-heterozygous) pathogenic variants in *PKD1L1*. Whole-exome sequencing "identified homozygous mutations in PKD1L1 from three affected individuals in two unrelated families" ( ).

P 27616478

This is a **monogenic, recessive developmental disorder**; it is not infectious and has no established acquired cause.

Genetic risk factors. - **Causal variants:** loss-of-function (splice, nonsense) and damaging missense alleles in *PKD1L1* (see §4). - **Consanguinity** is a key risk context — reported probands are homozygous, consistent with autosomal-recessive inheritance and increased in consanguineous or founder settings. - **Carrier status:** heterozygotes are unaffected (gene is not haploinsufficient; gnomAD pLI≈0).

Environmental risk factors. None established specifically for HTX8. For heterotaxy broadly, **maternal pregestational diabetes mellitus** is associated with laterality/abdominal-situs phenotypes ( )

P 41974186

and is a recognized teratogenic risk factor for L-R defects; this is a disease-level association, not demonstrated for PKD1L1 cases.

Protective factors. None identified (genetic or environmental). A single wild-type *PKD1L1* allele is "protective" in the Mendelian sense (carriers are healthy).

Gene–environment interactions. Not specifically characterized for *PKD1L1*. Laterality determination is a threshold/stochastic developmental process; modifier/background effects are plausible (variable expressivity between SIT and heterotaxy even within families) but unproven.

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3. Phenotypes

All manifestations are **congenital (prenatal/neonatal onset)**, structural/physical, lifelong, and non-progressive as malformations (clinical course is driven by complications). Frequencies below are qualitative given the very small reported cohort.

Phenotype	Type	HPO term	Notes / frequency
Visceral heterotaxy / situs ambiguus	Physical malformation	HP:0004935	Core feature
Situs inversus totalis	Physical malformation	HP:0001696	Reported (p.Cys1691Ser family)
Complex congenital heart disease	Clinical sign/ structural	HP:0001627 (Abnormal heart morphology)	Very frequent; often lethal
Dextrocardia / abnormal cardiac position	Physical	HP:0001651	Common in situs defects
Atrioventricular septal defect, DORV, TAPVC, transposition	Structural	HP:0006695 / HP:0011565 etc.	Seen across heterotaxy spectrum
Asplenia	Physical/ laboratory	HP:0001746	Reported (p.Gln463*); confers infection risk
Polysplenia / abnormal spleen	Physical	HP:0001748 / HP:0025059	Part of spectrum
Intestinal malrotation	Physical	HP:0002566	Common heterotaxy complication
Abnormal inferior vena cava / vascular laterality	Structural	HP:0005301	Interrupted IVC in left isomerism

Onset: neonatal/congenital (often detected prenatally). **Severity:** variable — from isolated SIT (potentially mild) to lethal complex CHD. **Progression:** stable malformation; secondary deterioration from cardiac failure, arrhythmia, or infection. **Quality of life:** dominated by cardiac disease burden (surgeries, heart failure, arrhythmia) and, in asplenia, lifelong infection vigilance; no disease-specific QoL instruments exist — generic pediatric CHD tools (PedsQL, PROMIS) apply.

4. Genetic / Molecular Information

Causal gene. *PKD1L1* (polycystin-1-like 1), HGNC:18053, Ensembl ENSG00000158683, gene OMIM *609721, GRCh38 chr7:47,740,202–47,948,466 (7p12.3), canonical transcript ENST00000289672; protein UniProt Q8TDX9, 2849 aa.

Protein architecture (UniProt Q8TDX9). 11-transmembrane polycystin-1-family receptor with a large extracellular N-terminus (res. 1–1748): two **PKD domains** (508–590; 592–673), a large **REJ** (receptor-for-egg-jelly) domain (674–1571), a **GAIN-B** domain (1587–1735) containing the **GPS** autoproteolysis motif (1691–1735), and a cytoplasmic **PLAT/LH2** domain (1796–1913); ~20 N-glycosylation sites and disulfide bonding.

Reported pathogenic variants (germline). | Variant (cDNA) | Protein | Class | Consequence | Phenotype | PMID | |---|---|---|---|---|---| | c.6473+2_6473+3delTG | splice-donor, intron 42 | Splice-site, LoF | Loss of function | Heterotaxy + complex CHD | 27616478 | | c.5072G>C | p.Cys1691Ser | Missense (GPS motif) | Disrupts GPS disulfide, folding/autoproteolysis | SIT + CHD | 27616478 | | c.1387C>T | p.Gln463* | Nonsense, LoF | Truncation (loss of REJ/TM/channel region) | Heterotaxy + congenital asplenia | 35691949 |

"the p.Cys1691Ser substitution affects a highly conserved cysteine residue and is predicted by molecular modeling to disrupt a disulfide bridge essential for the proper folding of the … (GPS) motif"
(27616478).

Variant classification & frequency. ClinVar lists ~1,417 *PKD1L1* variants, the large majority **variants of uncertain significance (VUS)** (~1,157 VUS vs ~170 pathogenic / ~72 likely pathogenic), reflecting limited functional/segregation data. Pathogenic HTX8 alleles are individually rare/absent in population databases (gnomAD). **Origin:** germline. **Functional consequence: loss of function** (recessive); no gain-of-function or dominant-negative mechanism established.

Population constraint (gnomAD). pLI ≈ 0, oe_lof = 0.73 (90% CI 0.66–0.81), missense oe = 0.95, mis_z = 1.35. The gene is **not haploinsufficient**, consistent with asymptomatic heterozygous carriers and recessive disease.

Modifier genes. None proven. Variable expressivity (SIT vs heterotaxy) suggests modifiers/stochastic effects. In mouse genetics, *Pkd1l1* acts as an **upstream repressor of *Pkd2*** (27272319), so dosage of polycystin-pathway genes is biologically relevant.

Epigenetics / chromosomal abnormalities. No HTX8-specific epigenetic signature reported. HTX8 is caused by point/small variants, not large chromosomal rearrangements; however, CNVs in body-patterning pathways (NODAL/BMP/WNT, e.g., *NIPBL, TBX6, FGF12, RBFOX1*) contribute to the broader heterotaxy population (P 27637763).

5. Environmental Information

- **Environmental factors / toxins / infectious agents:** none causal for HTX8 (purely genetic).
- **Lifestyle factors:** not applicable to disease causation.
- **Disease-level association:** maternal **pregestational diabetes** correlates with laterality-spectrum phenotypes (P 41974186) — relevant to heterotaxy broadly, not to monogenic PKD1L1 cases.
- **Infectious agents:** not causal, but **secondary infection risk is central** in patients with asplenia (see §11/§13).

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic *PKD1L1* loss-of-function/damaging variant** → results in absent or misfolded PKD1L1 protein (truncation; GPS-motif disulfide disruption for p.Cys1691Ser). *[demonstrated: human genetics + molecular modeling]*
2. **Loss of functional PKD1L1** → prevents assembly of the PKD1L1–PKD2 (polycystin-1-like-1 / polycystin-2) receptor–channel complex on cilia of the embryonic node / Kupffer's vesicle. *[demonstrated: co-localization + physical interaction, mouse & medaka]*
3. **Motile node cilia still generate normal leftward "nodal flow"** (cilia motility is intact) → but the flow **cannot be interpreted** without the PKD1L1–PKD2 sensor. *[demonstrated: normal flow/cilia in mutants]*

4. **Flow normally transfers PKD1L1-containing fibrous strands leftward**, facilitating a **left-dominant intracellular Ca^{2+} elevation** at the left node margin (FGFR/Shh-dependent) → in mutants this earliest left-biased signal fails. *[demonstrated in mouse; Tanaka 2023]*
5. **Failed/symmetric Ca^{2+} signaling** → loss of left-restricted repression such that the **Nodal–Lefty–Pitx2 cascade is not confined to the left** (becomes absent, bilateral, or randomized) in the lateral plate mesoderm. *[demonstrated: PKD1L1 restricts Nodal to the left; Pkd1l1 mutant activates Nodal bilaterally]*
6. **Loss of asymmetric Pitx2 patterning** → randomized/discordant morphogenesis and looping of heart, gut, spleen, lungs and great vessels. *[inferred from conserved L-R pathway]*
7. **Abnormal situs → situs inversus totalis OR situs ambiguus/heterotaxy with complex CHD, splenic anomalies, intestinal malrotation, vascular laterality defects** → clinical disease. *[demonstrated: human phenotypes]*

Branch point at step 5: depending on whether Nodal is lost, bilateral, or randomized, the organism develops SIT (coordinated reversal), left isomerism (polysplenia), or right isomerism (asplenia) — explaining the phenotypic spectrum, including the asplenia case (P 35691949).

Supporting detail by category. - **Molecular pathways:** Nodal/TGF-β signaling (Nodal–Lefty2–Pitx2), upstream FGFR and Sonic hedgehog (Shh) signaling, calcium signaling. Reactome "Nodal signaling"; KEGG TGF-β pathway. - **Protein dysfunction:** loss of function via truncation or GPS-domain misfolding; PKD1L1 normally undergoes GPS autoproteolysis and forms a Ca^{2+}-permeable channel complex with PKD2/TRPP2. "PKD1L1 is sufficient to mediate a Ca2+ signaling response after flow stimulation … an extracellular PKD domain within PKD1L1 is crucial for PKD1L1 function" (P 27272319).
- **Cellular processes:** ciliary mechanosensation/chemosensation and ciliary Ca^{2+} signaling; embryonic L-R symmetry breaking. - **Biochemical abnormality:** defective ciliary cation (Ca^{2+}) channel/receptor complex. - **Immune involvement:** not primary; functional/anatomic **asplenia** causes secondary immunodeficiency to encapsulated bacteria. - **Metabolic/epigenetic changes:** none characteristic.

GO term suggestions: GO:0007368 (determination of left/right symmetry); GO:0003351 (epithelial cilium movement involved in determination of L/R asymmetry); GO:0060287 (epithelial cilium / "nodal cilium"); GO:0060170 (ciliary membrane); GO:0005929 (cilium); GO:0072372 (primary cilium assembly); GO:0005262 (calcium channel activity); GO:0019228/

GO:0070588 (Ca^{2+} ion transmembrane transport). **Cell Ontology (CL):** node/pit cells & crown cells of the embryonic organizer → CL:0000222 (mesodermal cell), ciliated embryonic node cells; CL:0000057 (fibroblast, LPM context). **CHEBI:** CHEBI:29108 (calcium(2+)).

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7. Anatomical Structures Affected

Organ level (primary): heart and great vessels (cardiovascular), spleen (asplenia/polysplenia), stomach/intestine (malrotation), liver (midline/abnormal lobation), lungs (isomerism), inferior vena cava/systemic veins. **Body systems:** cardiovascular (primary), digestive, respiratory, lymphatic/immune (spleen), hepatobiliary. **Secondary involvement:** immune deficiency from asplenia; biliary atresia in some left-isomerism heterotaxy; pulmonary consequences of CHD.

Developmental origin (where the defect acts): the **embryonic node / Kupffer's vesicle** (midline left–right organizer) and **lateral plate mesoderm** — UBERON:0005725 (ciliated embryonic node) / UBERON:0004341 (node), UBERON:0003081 (lateral plate mesoderm). Resulting organ UBERON terms: UBERON:0000948 (heart), UBERON:0002106 (spleen), UBERON:0000160 (intestine), UBERON:0002048 (lung), UBERON:0001072 (inferior vena cava).

Tissue/cell level: ciliated epithelial cells of the node/KV; lateral-plate mesoderm; cardiac progenitor mesoderm. **Subcellular (GO Cellular Component):** primary/motile cilium (GO:0005929), ciliary membrane (GO:0060170), plasma membrane.

Localization & lateralization: defect is of **body-axis laterality itself** — manifestations are intrinsically bilateral/asymmetric/randomized (loss of normal left-right asymmetry; isomerism = loss of sidedness). HPO HP:0001631 etc. for specific cardiac lesions.

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8. Temporal Development

- **Onset:** congenital; organ situs is specified in early embryogenesis (gastrulation/node stage, ~weeks 3–4 in humans). Frequently **diagnosed prenatally** by ultrasound/fetal echocardiography (heterotaxy has among the highest prenatal detection rates, ~91% in one series,

  P 42324491

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- **Onset pattern:** structural malformation present at birth (not acute/subacute).

- **Progression:** the malformation is **stable**; clinical course is **non-progressive as a lesion** but complicated by heart failure, arrhythmia (complete heart block), pulmonary venous obstruction, and infection.
- **Critical period:** the **node/LPM signaling window** in early embryogenesis is the only period during which L-R situs can be set — there is **no postnatal window to correct the primary patterning defect**, only to palliate its consequences.
- **Duration:** lifelong (chronic).

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9. Inheritance and Population

- **Inheritance: autosomal recessive** (biallelic *PKD1L1*). Heterozygous carriers unaffected.
- **Penetrance/expressivity:** biallelic genotypes appear highly penetrant for a laterality phenotype, but **expressivity is variable** (SIT vs heterotaxy; differing CHD severity, including within the same family).
- **Consanguinity:** relevant — reported probands are homozygous; recessive disease risk rises with consanguinity/founder effects.
- **Carrier frequency / founder effects:** not precisely established; individual pathogenic alleles are rare; a Chinese nonsense allele (p.Gln463*) was the first reported in that population
(P 35691949).
- **Anticipation / mitochondrial / germline mosaicism:** not applicable / not reported.

Epidemiology. - **HTX8 specifically:** ultra-rare; only a handful of families reported worldwide — population prevalence **unknown**. - **Heterotaxy / atrial isomerism (parent category):** prevalence **~1 in 10,000–20,000 live births**, accounting for up to **~4% of all cardiac malformations**
(P 34491249);
heterotaxy represents a minority of laterality disorders (e.g., 249 HS among 566 fetal laterality cases over 721,562 deliveries,
P 42110452).

- **Sex ratio / geography:** no established PKD1L1-specific skew; general heterotaxy shows modest male predominance in some registries. Reported PKD1L1 cases span diverse ancestries (consistent with private recessive alleles).

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10. Diagnostics

Imaging (anatomic diagnosis, primary). - **Fetal ultrasound + fetal echocardiography** — mainstay prenatal detection (very high detection for heterotaxy,).

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- **Postnatal echocardiography**, cardiac **CT/MRI/angiography** for segmental cardiac/vascular anatomy; **abdominal ultrasound/CT** for spleen, liver, gut malrotation; **upper GI series** for malrotation. **Laboratory / functional.** - **Peripheral blood smear for Howell-Jolly bodies →** screen for functional asplenia; pitted-RBC counts / spleen scintigraphy to assess splenic function. - ECG/Holter for **complete heart block** and arrhythmia.

Genetic testing (definitive molecular diagnosis). - **Approach:** because heterotaxy is highly heterogeneous ("pathogenic genetic lesions are found in less than 20% of HS patients,"),

P 35691949

broad testing is preferred: multigene **heterotaxy/CHD panels** (including *PKD1L1, ZIC3, NODAL, CFC1, ACVR2B, LEFTY2, GDF1, MMP21, CCDC11/CFAP53, DNAH5*...), **whole-exome (WES)** or **whole-genome sequencing (WGS)**. WES identified the original PKD1L1 families ( ).

P 27616478

- **Single-gene testing** of *PKD1L1* is appropriate when a consistent phenotype or family variant is known; confirm **biallelic** status and parental phase (segregation). - **Chromosomal microarray (CMA)/karyotype** to exclude CNVs/aneuploidy contributing to heterotaxy ( ).

P 27637763

- **Interpretation caveat:** high **VUS burden** in *PKD1L1* — classification benefits from recessive segregation, consanguinity, GPS/LoF functional rationale, and ACMG/AMP criteria.

Clinical criteria / differential diagnosis. No disease-specific criteria; diagnosis = demonstrated situs anomaly + biallelic *PKD1L1* variants. **Differential:** other genetic heterotaxy (X-linked *ZIC3* = HTX1; *NODAL, CFC1, ACVR2B, GDF1, MMP21*, etc.), **primary ciliary**

dyskinesia (PCD) with laterality defects (distinguished by chronic sinopulmonary disease, abnormal ciliary motility/ultrastructure, nasal nitric oxide — features *absent* in PKD1L1, whose cilia are motile), and syndromic/CNV causes.

Screening. No newborn screening for HTX8; **cascade carrier testing** of relatives and **prenatal/preimplantation genetic testing** are options once the familial variants are known.

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11. Outcome / Prognosis

- **Prognosis is driven by the cardiac phenotype.** In a heterotaxy+CHD cohort (n=197), **5- and 10-year survival ≈71% and ≈68%**; **left atrial isomerism had better survival than right atrial isomerism**; **complete heart block (CHB)** and ventricular dysfunction predicted fetal demise, and **pulmonary venous obstruction + CHB** predicted postnatal mortality
(P 42185088).
"CHB and pulmonary venous obstruction remain significant predictors of postnatal mortality…"
(P 42185088).
- **Infection/asplenia mortality:** asplenia confers high risk of overwhelming bacteremia — in a systematic review, "There were 42 documented cases of bacteremia in 32 patients. Approximately, 79% of these had absence of a spleen"
(P 27425254),
mean age ~17 months, with high mortality.
- **Perinatal outcomes (laterality spectrum):** major CHD drives termination, surgery and early mortality; live birth ~80%, with infant mortality concentrated in infancy
(P 41974186).
- **Morbidity:** multiple cardiac surgeries, arrhythmia/pacemaker dependence, heart failure, GI morbidity (malrotation/volvulus), feeding/growth problems; lifelong infection risk with asplenia.

- **Prognostic factors:** type/severity of CHD, atrial isomerism subtype (RAI worse), CHB, pulmonary venous obstruction, splenic status. No molecular prognostic biomarker specific to PKD1L1.

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12. Treatment

No disease-specific or gene-directed therapy exists. Management is **symptomatic, anatomy-driven, and multidisciplinary** (NCIT terms suggested). - **Cardiac surgical/interventional:** staged palliation (single-ventricle pathway: Norwood/Glenn/Fontan) or biventricular repair depending on anatomy; repair of AVSD, TAPVC, DORV; **pacemaker** for complete heart block (NCIT: C157809 Cardiac Surgery; C50106 Pacemaker; C98298 Fontan Procedure). - **Gastrointestinal: Ladd procedure** for intestinal malrotation/volvulus (NCIT: C157751 surgical procedure). - **Asplenia management (critical): vaccination** against encapsulated organisms — pneumococcal (PCV + PPSV23), *Haemophilus influenzae* type b, meningococcal (ACWY + B) — plus **antibiotic prophylaxis** (e.g., penicillin/amoxicillin) and immediate empiric antibiotics for febrile illness (NCIT: C15346 Vaccination; C154547 Antibiotic Therapy; C15431 Prophylaxis). Patient education and medical-alert measures improve adherence
(P 32759171 ; P 31937251).
- **Supportive:** heart-failure pharmacotherapy (diuretics e.g. furosemide, afterload reduction, beta-blockade), nutritional support/gastrostomy, arrhythmia management
(P 41049903
case series). - **Advanced/experimental therapeutics: none** — no gene therapy, RNA therapy, cell therapy, or targeted/immunotherapy for PKD1L1-heterotaxy (the primary defect is prenatal/developmental and not correctable postnatally). No pharmacogenomic considerations specific to the gene. - **Pharmacogenomics / personalized medicine:** genotype confirms diagnosis and informs recurrence risk/reproductive counseling rather than drug selection.

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13. Prevention

- **Primary prevention:** not possible for the genetic lesion. **Preconception/prenatal genetic counseling** for recessive 25% recurrence risk; **carrier screening** of partners in known families; **PGT/prenatal diagnosis** where familial variants are defined. Optimizing **maternal glycemic control** addresses a disease-level (not PKD1L1-specific) laterality risk factor (41974186).
- **Secondary prevention: prenatal detection** (fetal echo/ultrasound) enabling planned delivery at a cardiac center and early intervention (42324491); early postnatal spleen-function assessment (Howell-Jolly bodies).
- **Tertiary prevention (prevent complications):** the **cornerstone** — asplenia **vaccination** + **antibiotic prophylaxis** to prevent overwhelming post-splenectomy/asplenia sepsis (27425254; 31937251; 32759171); arrhythmia surveillance/pacing; surgical correction of malrotation before volvulus; endocarditis prophylaxis per cardiac guidelines.
- **Genetic counseling:** autosomal-recessive counseling; cascade testing; reproductive options.

14. Other Species / Natural Disease

- **Conservation:** *PKD1L1*'s L-R role is **highly conserved across vertebrates**. Orthologs: **mouse** *Pkd1l1* (NCBI Gene 207225; MGI), **medaka** *pkd1l1* (ZFIN/medaka; the classic L-R mutant **abecobe/abc**), **zebrafish** *pkd1l1* (ZFIN). Taxa: *Mus musculus* (NCBI:txid10090), *Oryzias latipes* (medaka, NCBI:txid8090), *Danio rerio* (NCBI:txid7955).
- **Natural animal disease / veterinary:** no well-characterized naturally occurring *PKD1L1* heterotaxy disease in companion animals is documented in OMIA for this gene; situs/

laterality anomalies occur sporadically across species but are not established as a *PKD1L1* natural disease.

- **Comparative biology:** mouse and fish models reproduce the human mechanism (node/KV flow-sensing), making them the key translational systems (see §15). **Evolutionary note:** the two-cilia/polycystin flow-sensing paradigm is conserved from fish to mammals.
- **Zoonotic potential:** not applicable (non-infectious developmental disorder).

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15. Model Organisms

Mouse (*Mus musculus*) — primary mammalian model. - **Types:** *Pkd1l1* knockout (e.g., gene-trap/null line, Vogel 2010,) P 20080492 and ENU/point mutants (e.g., *rks*); knock-in reporter **KikGR-PKD1L1** for live protein imaging (Tanaka 2023,). P 37413993 - **Phenotype recapitulation (strong):** situs inversus/laterality defects; "both mutants fail to activate asymmetric gene expression at the node or in the lateral plate and exhibit right isomerism of the lungs" ( ). P 21307093 Node morphology and cilia motility normal → defect is in **flow interpretation**, matching human mechanism. - **Key insight:** "the absence of respiratory tract lesions, hydrocephalus, and male infertility in Pkd1l1(-/-) mice ... suggested that dysfunction of motile cilia was not involved" ( ) P 20080492 — **distinguishes HTX8 from PCD**. - **Limitation:** high perinatal lethality of nulls; models the developmental patterning defect but not the postnatal human CHD surgical course.

Medaka (*Oryzias latipes*). *The L-R mutant abecobe (abc)* = *pkd1l1*: "abecobe (abc) is defective for left-right asymmetric expression of southpaw, lefty and charon, but not for nodal flow"
(P 21307098);
PKD1L1 required in **Kupffer's vesicle** and colocalizes/interacts with Pkd2 on motile KV cilia.

Zebrafish (*Danio rerio*). *pkd1l1* expressed in KV; morpholino/mutant studies implicate polycystin signaling in L-R patterning (Kupffer's vesicle = node equivalent).

In-vitro / cellular. Cultured cells supplied **artificial flow** show PKD1L1 is "sufficient to mediate a Ca2+ signaling response after flow stimulation"
(P 27272319);
heterologous PKD1L1–PKD2 complexes used for biochemistry/channel studies.

Applications: dissecting node/KV flow sensing, polycystin complex assembly, Nodal cascade restriction, Ca^{2+} signaling, and variant functional testing. **Resources:** MGI, IMPC, ZFIN, Alliance of Genome Resources.

Supported vs. Refuted Hypotheses

Supported. 1. HTX8 is autosomal-recessive, caused by biallelic *PKD1L1* LoF/damaging variants
(P 27616478). P 35691949
2. PKD1L1–PKD2 ciliary complex is the nodal-flow sensor restricting Nodal to the left
(P 21307093 P 21307098 P 27272319). P 37413993
3. The pathology is a **flow-interpretation (sensory) defect, not a ciliary-motility defect** → mechanistically distinct from PCD

(P 20080492).

4. Prognosis is governed by CHD severity and asplenia-related infection risk (P 42185088). P 27425254

Refuted / not supported. - *PKD1L1* is **not** a dominant/haploinsufficient disease gene (gnomAD pLI≈0; carriers healthy). - HTX8 is **not** driven by motile-cilia dysfunction (no PCD airway/hydrocephalus phenotype in nulls). - No evidence for gain-of-function, somatic, infectious, or acquired/environmental primary causation.

Limitations and Future Directions

- **Very small human evidence base** (few families); PKD1L1-specific prevalence, penetrance, sex ratio, and natural history are not quantified — most clinical figures derive from the broader heterotaxy category.
- **High VUS burden** limits molecular diagnosis; **functional assays** (flow-induced Ca^{2+}, GPS autoproteolysis, PKD1L1–PKD2 trafficking) are needed to reclassify variants.
- **No structural model of the human PKD1L1–PKD2 complex** at the variant level; cryo-EM would clarify GPS/PKD-domain variant effects.
- **No targeted therapy;** research should define modifier genes, improve prenatal risk stratification, and standardize asplenia prophylaxis in this population.

Key references (PMIDs)

27616478 (Vetrini 2016, human biallelic PKD1L1); 35691949 (Gu 2022, nonsense + asplenia); 21307093 (Field 2011, mouse); 21307098 (Kamura 2011, medaka); 27272319 (Grimes 2016, epistasis/Ca^{2+}); 37413993 (Tanaka 2023, flow transfers polycystin); 20080492 (Vogel 2010, Pkd1l1−/− mouse); 24756726 (TRPP/polycystin review); 42185088 (heterotaxy+CHD outcomes); 27425254 (bacteremia in heterotaxy); 34491249 (isomerism epidemiology); 42324491 (prenatal detection); 41974186 (laterality spectrum outcomes/PDM); 27637763 (heterotaxy CNVs); 38884744 (human genetics of situs); 32759171 / 31937251 (asplenia prophylaxis).