Neurooculocardiogenitourinary Syndrome (NOCGUS) — Comprehensive Disease Report

Disease: Neurooculocardiogenitourinary Syndrome (NOCGUS) **Causal gene: WDR37** (WD repeat–containing protein 37; HGNC:31406; NCBIGene:22884; Ensembl ENSG00000047056; UniProt Q9Y2I8) **OMIM:** #618652 · **MONDO:** 0032850 · **Orphanet:** 684305 · **DOID:** 0111675 · **GARD:** 0027365 · **UMLS:** C5231443 · **MedGen:** 1684841

Summary

Neurooculocardiogenitourinary syndrome (NOCGUS) is a rare, severe, autosomal-dominant multisystem developmental disorder caused by de novo missense variants (and rare splice variants) that cluster in the conserved N-terminal region upstream of the WD40 repeat domain of the *WDR37* gene (chromosome 10p13; protein UniProt Q9Y2I8, 494 amino acids with seven WD40 repeats). The disorder was defined simultaneously in 2019 by two independent cohorts — Reis et al. (*American Journal of Human Genetics*) and Kanca et al. — who reported unrelated probands with de novo variants in a narrow N-terminal mutational hotspot. The name "neurooculocardiogenitourinary" is an acronym for the four organ systems most consistently involved: the **nervous system** (epilepsy, intellectual disability, absent speech, cerebellar hypoplasia), the **eye** (coloboma, microphthalmia, Peters/anterior-segment anomalies), the **heart** (septal defects), and the **genitourinary tract** (cryptorchidism, renal dysplasia).

The clinical picture is defined by near-universal epilepsy, global developmental delay/intellectual disability with absent speech, a recognizable facial gestalt reminiscent of CHARGE syndrome, and the hallmark ocular feature of **coloboma**. Severity is highly variable, ranging from infantile lethality with complex multisystem malformation at one extreme to milder developmental delay at the other. Mechanistically, WDR37 is a binding partner of the phosphofurin acidic cluster sorting proteins **PACS1** and **PACS2**; the WDR37–PACS1–PACS2 axis governs intracellular protein trafficking and endoplasmic-reticulum (ER) calcium handling.

NOCGUS, PACS1 (Schuurs-Hoeijmakers) syndrome, and PACS2 syndrome form an overlapping clinical-molecular spectrum sharing epilepsy, intellectual disability, cerebellar atrophy, distinctive facies, and coloboma.

Importantly, population constraint data and model-organism genetics argue that NOCGUS does **not** arise from simple haploinsufficiency. *WDR37* is constrained against loss-of-function (gnomAD LOEUF 0.412, pLI 0.57), all pathogenic alleles are clustered de novo missense (not truncating), and a Drosophila *wdr37* null is homozygous viable. Mutant WDR37 protein is correctly localized but expressed at reduced levels, favoring a gain-of-function or dominant-negative mechanism. There is currently no disease-modifying therapy; management is entirely supportive and multidisciplinary.

Section 1 — Disease Information

Overview. NOCGUS is a congenital, autosomal-dominant, multisystemic malformation/neurodevelopmental syndrome. The acronym reflects the organ systems named in the disorder: **neuro** (brain/seizures/cognition), **oculo** (eye), **cardio** (heart), and **genitourinary** (kidneys, genitalia). Kanca et al. summarized the neurodevelopmental core as "epilepsy, colobomas, facial dysmorphology reminiscent of CHARGE syndrome, developmental delay and intellectual disability, and cerebellar hypoplasia" (PMID: 31327508).

Key identifiers.

Resource	Identifier
OMIM	#618652
MONDO	MONDO:0032850
Orphanet	684305
Disease Ontology (DOID)	0111675
GARD	0027365
UMLS	C5231443
MedGen	1684841
Causal gene	WDR37 (HGNC:31406; NCBIGene:22884; Ensembl ENSG00000047056; UniProt Q9Y2I8)

Synonyms / alternative names. Official abbreviation **NOCGUS**; "WDR37 syndrome"; "WDR37-related disorder"; "WDR37-associated neurooculocardiogenitourinary syndrome." No synonyms were originally recorded in the source template; the above are established in the literature and MONDO cross-references.

Source of information. Information is derived from **aggregated disease-level resources** (OMIM, Orphanet, MONDO, HPO) and from **individual-patient case reports/case series** published in the primary literature (Reis 2019, Kanca 2019, Hay 2020, and subsequent single-case reports). This is an ultra-rare disorder with an estimated <60 published patients; all knowledge is case-based rather than from EHR-scale or registry cohorts.

Section 2 — Etiology

Disease causal factors. NOCGUS is a **monogenic (Mendelian) disorder**. The primary cause is a heterozygous, almost always **de novo**, pathogenic variant in *WDR37*. There is no known environmental, infectious, or multifactorial contribution. Reis et al. reported "four de novo missense variants predicted to affect the N-terminal region of WDR37—p.Ser119Phe, p.Thr125Ile, p.Ser129Cys, and p.Thr130Ile—in unrelated individuals with a previously unrecognized syndrome" (PMID: 31327510). Kanca et al. "identified five pediatric probands with de novo variants in WDR37" (PMID: 31327508).

Genetic risk factors. The sole known genetic cause is a de novo pathogenic *WDR37* variant in the N-terminal mutational hotspot. No susceptibility loci or modifier genes have been formally established. Because variants are de novo, there are effectively no inherited risk alleles in the general population.

Environmental risk factors. None identified. Advanced paternal age is a theoretical contributor to de novo mutation burden generally, but has not been specifically studied in NOCGUS.

Protective factors. None identified (genetic or environmental). *WDR37* is constrained against loss-of-function (see Section 4), but this reflects gene essentiality rather than a protective allele.

Gene–environment interactions. None described. As a fully penetrant de novo Mendelian malformation syndrome, NOCGUS has no documented GxE component.

Section 3 — Phenotypes

Phenotype frequencies below come from the official HPO annotation set for OMIM:618652 (frequencies derived primarily from the Kanca et al. cohort, PMID: 31327508), supplemented by Reis et al. and later case reports.

Neurological phenotypes (near-universal)

Phenotype	HPO term	Frequency	Notes
Seizure / epilepsy	HP:0001250	5/5	Often early infantile onset
Intellectual disability	HP:0001249	4/4	Typically moderate–severe
Global developmental delay	HP:0001263	4/4	
Absent speech	HP:0001344	4/4	
Cerebellar hypoplasia / vermian anomaly	HP:0001321	Frequent	Structural brain malformation

Ocular phenotypes (hallmark)

Phenotype	HPO term	Frequency	Notes
Coloboma	HP:0000589	4/5	Iris, retinal, choroidal; **the hallmark feature**
Microphthalmia	HP:0000568	3/5	
Peters anomaly / anterior-segment dysgenesis	HP:0000659	1/5	Corneal opacity
Microcornea	HP:0000482	Variable	

Craniofacial / dysmorphic (CHARGE-like)

Phenotype	HPO term	Frequency
Abnormal palmar crease	HP:0010490	5/5
Prominent nasal bridge	HP:0000426	5/5
Downturned corners of mouth	HP:0002714	5/5
Smooth philtrum	HP:0000319	4/4

Cardiac

Phenotype	HPO term	Frequency
Ventricular septal defect (most common CHD)	HP:0001629	3/5
Atrial septal defect	HP:0001631	2/5
Patent ductus arteriosus	HP:0001643	2/5

Genitourinary

Phenotype	HPO term	Frequency
Bilateral cryptorchidism	HP:0008689	2/2 (males)
Renal dysplasia / polycystic kidney	HP:0000110 / HP:0000113	Reported in severe cases

Other

- **Sensorineural hearing impairment** (HP:0000407) — 2/4
- **Poor feeding** and **poor postnatal growth** — frequent (Reis 2019)
- **Anal atresia** — reported in a splice-variant case (Samejima 2024, PMID: 38044197)

Phenotype characteristics. Onset is **congenital/neonatal** for malformations (coloboma, CHD, cerebellar anomaly) and **infantile** for epilepsy. Severity is **highly variable** — Reis et al. reported "death in infancy in one individual," whereas Hay et al. (2020) expanded the spectrum "to include those with milder developmental delay" (PMID: 32530092). The course is generally **stable/non-progressive** developmentally; a systematic review found that regression/skill loss is uncommon and the syndromes should not be classified as primarily regressive (PMID: 42794636).

Quality-of-life impact. Severe, lifelong. Combined intellectual disability, absent speech, epilepsy, and visual impairment produce profound dependence for daily functioning. No disease-specific QoL instrument data (EQ-5D/SF-36/PROMIS) exist for this ultra-rare disorder.

Section 4 — Genetic / Molecular Information

Causal gene. *WDR37* (HGNC:31406; NCBIGene:22884; Ensembl ENSG00000047056; canonical transcript ENST00000358220). Genomic location chr10:1,095,478–1,178,237 (GRCh37), 10p13. Protein UniProt **Q9Y2I8** (WDR37_HUMAN), **494 amino acids**, with **seven WD40 repeats** and predominantly cytoplasmic localization.

Pathogenic variants. The founding variants were all **de novo missense** changes in a tight N-terminal cluster upstream of the WD40 domain:

Variant (protein)	Source
p.Ser119Phe	Reis 2019 (PMID: 31327510)
p.Thr125Ile	Reis 2019
p.Ser129Cys	Reis 2019
p.Thr130Ile	Reis 2019
p.Thr115Ile	Hay 2020 (PMID: 32530092)
p.Ser119Tyr	Hay 2020
c.727-27_727-24del (intronic, aberrant splicing → p.S242_I243ins21aa)	Samejima 2024 (PMID: 38044197)

Hay et al. noted the variants "fall within a highly conserved region upstream of the WD-repeat domains, within an apparent mutation cluster." Sorokina et al. (2021) identified a **distinct new cluster** of disease-associated variants and performed functional analyses of mutant proteins (PMID: 34642815).

- **Variant classification (ACMG/AMP):** Pathogenic / Likely pathogenic (de novo occurrence + hotspot clustering + absence from population databases). ClinVar (queried Nov 2026) contains ~228 *WDR37* records, dozens classified Pathogenic/Likely pathogenic.
- **Variant type/class:** predominantly **missense**; one **intronic splice** variant.
- **Allele frequency:** pathogenic alleles are **absent from gnomAD** (de novo).
- **Somatic vs germline: germline de novo**.
- **Functional consequence:** mutant protein is correctly localized but expressed at reduced levels — consistent with **gain-of-function or dominant-negative** rather than haploinsufficiency.

Non-haploinsufficiency mechanism (Finding F004). *WDR37* is constrained against loss-of-function: gnomAD v2.1.1 reports observed/expected LoF = 0.209 (90% CI 0.113–0.412; LOEUF 0.412), LoF Z = 3.93, pLI = 0.57; missense o/e = 0.637 (Z = 2.31). Critically, **all known pathogenic alleles are de novo missense (or one splice) clustered in the N-terminal/WD40 region, not truncating**. Kanca et al. showed a Drosophila *wdr37* null "are homozygous viable but display severe bang sensitivity, a phenotype associated with seizures in flies" (PMID: 31327508) — a homozygous-viable null supports that loss-of-function alone is not the human disease mechanism.

Modifier genes. None established. Given the WDR37–PACS1–PACS2 interaction, *PACS1*/*PACS2* are candidate biological modulators but have not been shown to modify NOCGUS severity.

Epigenetic information. No disease-specific methylation/histone signature has been reported for NOCGUS.

Chromosomal abnormalities. None; NOCGUS is caused by point/small variants, not by large CNVs.

Section 5 — Environmental Information

No environmental, lifestyle, or infectious factors contribute to NOCGUS. It is a fully penetrant monogenic de novo disorder. This section is **not applicable**.

Section 6 — Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation)

1. A **de novo missense variant** arises in the conserved N-terminal region (hotspot ~aa 115–130) of *WDR37* → **leads to** an amino-acid substitution in the WDR37 protein near its WD40 β-propeller platform.
2. The variant protein is **correctly localized to the cytoplasm but expressed at reduced levels → results in** altered WDR37 dosage/activity (not complete loss). *[Inferred from functional studies; Sorokina 2021]*
3. Because WDR37 **binds PACS1 and PACS2 and the two proteins are mutually required for stable expression**, perturbed WDR37 → **destabilizes the WDR37–PACS1–PACS2 complex** that recognizes cargo and controls sorting. *[Demonstrated: co-IP, cryo-EM]*
4. Disruption of this complex → **impairs intracellular protein trafficking and ER calcium flux** normally controlled by Pacs1–Wdr37. *[Demonstrated in mouse: Nair-Gill 2021]*
5. **Branch A (development):** dysregulated trafficking/calcium signaling during organogenesis → **impairs development of neural crest– and neuroectoderm-derived structures** → coloboma, anterior-segment dysgenesis, cerebellar hypoplasia, CHARGE-like facies, cardiac

septal and genitourinary malformations. *[Inferred from phenotype convergence across the WDR37–PACS1–PACS2 axis]*

6. **Branch B (neuronal excitability):** altered ER calcium handling and neuronal function → **lowers seizure threshold** → epilepsy (paralleled by bang-sensitivity in the Drosophila null). *[Model-organism supported]*
7. Combined developmental and functional CNS disruption → **intellectual disability, developmental delay, absent speech** — the clinical endpoint.

Molecular detail

- **Molecular pathways / protein interactions.** Sorokina et al. showed "the ability of WDR37 to form homodimers and to strongly bind PACS1 and PACS2 phosphofurin acidic cluster sorting proteins; immunocytochemistry confirmed colocalization of WDR37 with PACS1 and PACS2 in human cells" (PMID: 34642815). Xiao et al. solved the cryo-EM structure: "Pacs1 binds Wdr37 through a conserved interface within its furin-binding region (FBR)… This interaction stabilizes Wdr37 and is critical for the expression of both proteins" (PMID: 41279321).
- **Cellular processes.** ER calcium homeostasis; protein cargo sorting/trafficking; lymphocyte quiescence. Nair-Gill et al. demonstrated "Calcium flux control by Pacs1-Wdr37 promotes lymphocyte quiescence" (PMID: 33630350).
- **Protein dysfunction.** WD40 β-propeller scaffold protein; variant substitutions in the N-terminal FBR-interacting region reduce stability and likely perturb complex assembly (dominant-negative/gain-of-function).
- **Shared axis.** Yamamoto et al. proposed that "dysregulation of the WDR37-PACS1-PACS2 axis results in a spectrum that is recognizable by intellectual disability, distinctive facial features, and coloboma," and that "this group of genes may be involved in ocular development" (PMID: 33369122).

Suggested ontology terms

- **GO biological process:** protein targeting (GO:0006605); intracellular protein transport (GO:0006886); regulation of ER calcium ion concentration (GO:0032469); calcium ion transport (GO:0006816).
- **GO cellular component:** cytoplasm (GO:0005737); endoplasmic reticulum (GO:0005783).
- **CL cell types:** neuron (CL:0000540); neural crest cell (CL:0000333); cerebellar Purkinje cell (CL:0000121); lymphocyte (CL:0000542).

Section 7 — Anatomical Structures Affected

Organ level (primary). - **Brain** (UBERON:0000955) — cerebellum (UBERON:0002037), especially vermis; cerebral cortex. - **Eye** (UBERON:0000970) — iris, retina, choroid (coloboma), cornea/anterior segment, globe (microphthalmia). - **Heart** (UBERON:0000948) — interventricular/interatrial septa. - **Kidney** (UBERON:0002113) and **male genitalia** (testis, UBERON:0000473).

Secondary / body-system involvement. Nervous (CNS), visual, cardiovascular, genitourinary/renal, musculoskeletal (skeletal anomalies; Hay 2020), auditory (sensorineural hearing loss), and gastrointestinal (anal atresia in one case).

Tissue / cell level. Neuroectoderm- and neural crest–derived tissues are prominently affected, consistent with the coloboma + craniofacial + cardiac-outflow + enteric pattern (a "neurocristopathy-like" distribution). Cerebellar Purkinje/granule neurons implicated by cerebellar hypoplasia.

Subcellular level. Cytoplasm (GO:0005737); endoplasmic reticulum (GO:0005783) — site of PACS1–WDR37 calcium-flux control.

Localization / lateralization. Ocular and genitourinary findings are typically **bilateral** (e.g., bilateral microphthalmia/coloboma, bilateral cryptorchidism), though severity can be asymmetric.

Section 8 — Temporal Development

- **Onset: Congenital** (structural malformations present at birth; a neonatal case showed severe bilateral ocular abnormalities identified at birth — PMID: 42546896). Epilepsy is typically **early infantile**.
- **Onset pattern:** congenital/insidious for developmental features; seizures may present acutely.
- **Progression:** Developmentally **stable/non-progressive** in most patients; regression is uncommon and does not define the disorder (PMID: 42794636).
- **Disease course:** chronic, lifelong. Severity spans infantile lethality (Reis 2019) to milder delay (Hay 2020).

- **Critical periods:** organogenesis (first trimester) is the window during which the malformations (eye, heart, cerebellum, kidney) are established — making prenatal/early mechanisms the key vulnerability window.

Section 9 — Inheritance and Population

- **Inheritance: Autosomal dominant** (HP:0000006), essentially always via **de novo** variants. Recurrence risk for unaffected parents is low (germline mosaicism not formally documented but theoretically possible).
- **Penetrance:** Complete for the molecular/malformation phenotype among reported probands.
- **Expressivity: Highly variable** (infantile lethal → mild DD).
- **Epidemiology:** No prevalence/incidence estimate exists; **ultra-rare**, with <60 published patients worldwide as of 2026. Orphanet lists it without a prevalence class.
- **Founder effects / consanguinity:** Not applicable (de novo).
- **Carrier frequency:** Not applicable (de novo; constrained gene, no common pathogenic alleles).
- **Population demographics:** Reported across diverse populations (Caucasian — Hay 2020; Mexican patients — PMID: 37064331; Japanese — Samejima 2024). No ethnic predilection.
- **Sex ratio:** No established skew; genitourinary features (cryptorchidism) are male-specific.

Section 10 — Diagnostics

Genetic testing (definitive). Diagnosis rests on identifying a de novo pathogenic *WDR37* variant. Recommended approaches: - **Whole-exome sequencing (WES)** — the primary diagnostic modality; most reported cases were ascertained by trio exome (e.g., "Clinical exome sequencing identified a de novo pathogenic variant in the WDR37 gene, confirming the diagnosis," PMID: 42546896). - **Whole-genome sequencing (WGS)** — useful to detect deep intronic/splice variants (as in the c.727-27_727-24del splice case, PMID: 38044197); RT-PCR confirmed aberrant splicing in that patient. - **Multigene panels** — *WDR37* should be included on panels for intellectual disability, epilepsy, and structural eye disorders; Hay et al. explicitly "promote the inclusion of WDR37 on gene panels for intellectual disability, epilepsy and

structural eye disorders." - **Trio analysis** confirms de novo status, strongly supporting pathogenicity (ACMG PS2). - CMA/karyotype/FISH are generally unrevealing (no CNV mechanism).

Clinical / imaging workup. Brain MRI (cerebellar hypoplasia/vermian anomaly); detailed ophthalmologic exam (coloboma, microphthalmia, anterior-segment dysgenesis); echocardiography (septal defects); renal ultrasound; hearing evaluation. "Early ophthalmologic evaluation in neonates with multisystem congenital anomalies may provide important diagnostic clues to rare genetic syndromes" (PMID: 42546896).

Biomarkers / omics. No validated biochemical biomarker or clinical omics test for NOCGUS.

Differential diagnosis. CHARGE syndrome (facial overlap), PACS1 (Schuurs-Hoeijmakers) syndrome, PACS2 syndrome, and other coloboma/anterior-segment-dysgenesis disorders. Coloboma is a shared feature across the WDR37–PACS1–PACS2 axis (PMID: 33369122).

Screening. No newborn or carrier screening (de novo, ultra-rare).

Section 11 — Outcome / Prognosis

- **Survival/mortality:** Variable. At least one infant died in infancy (Reis 2019); severe neonatal presentations with complex CHD, renal dysplasia, and cerebellar malformation carry high early mortality. Milder cases survive into childhood/adulthood (an affected adult is reported in the axis-overlap literature).
- **Morbidity/function:** Profound — lifelong intellectual disability, absent speech, refractory epilepsy risk, and visual impairment produce severe disability and full-care dependence.
- **Complications:** Seizure-related morbidity, feeding difficulties/failure to thrive, visual loss, cardiac and renal complications.
- **Recovery:** No recovery of the underlying developmental deficits; developmentally stable with supportive care.
- **Prognostic factors:** Degree of structural malformation (especially CHD severity, renal involvement, cerebellar malformation) and seizure control drive outcome. No molecular prognostic biomarker beyond the general severity-by-variant correlations suggested within the hotspot.

Section 12 — Treatment

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

- **Pharmacotherapy:** Antiseizure medications for epilepsy (agent choice per seizure semiology; no NOCGUS-specific regimen). NCIT: Anticonvulsant Agent (C264).
- **Surgical/interventional:** Repair of congenital heart defects (VSD/ASD/PDA); orchidopexy for cryptorchidism; management of anal atresia/urological anomalies; ophthalmologic surgery as indicated.
- **Supportive/rehabilitative:** Early developmental intervention, physical/occupational/speech therapy (AAC given absent speech), feeding support (NG/gastrostomy for poor feeding), low-vision services, hearing aids/audiologic support.
- **Advanced therapeutics / pharmacogenomics / experimental trials:** None reported; no NCT-registered trials specific to NOCGUS. Antisense-oligonucleotide and client-protein-targeting strategies have been proposed conceptually for the related PACS1 disorder (given its gain-of-function/dominant-negative mechanism, PMID: 36077045) and are a plausible future direction for WDR37, but remain theoretical.

NCIT suggestions: Supportive Care (C133453); Anticonvulsant Agent (C264); Physical Therapy (C15321); Occupational Therapy (C15317); Speech Therapy (C15349); Surgical Procedure (C15329).

Section 13 — Prevention

- **Primary prevention:** Not possible (de novo mutation).
- **Secondary prevention:** Early multisystem surveillance (cardiac, renal, ophthalmologic, audiologic, developmental) after diagnosis to detect and treat complications.
- **Tertiary prevention:** Seizure control, feeding/nutrition optimization, vision/hearing support, and developmental therapies to limit secondary disability.
- **Genetic counseling:** Essential. Recurrence risk for parents of an affected de novo child is low but non-zero (germline mosaicism cannot be excluded); affected individuals rarely reproduce. Prenatal/preimplantation testing is feasible once a familial variant is known.
- **Immunization / public-health / behavioral / environmental prevention:** Not applicable.

Section 14 — Other Species / Natural Disease

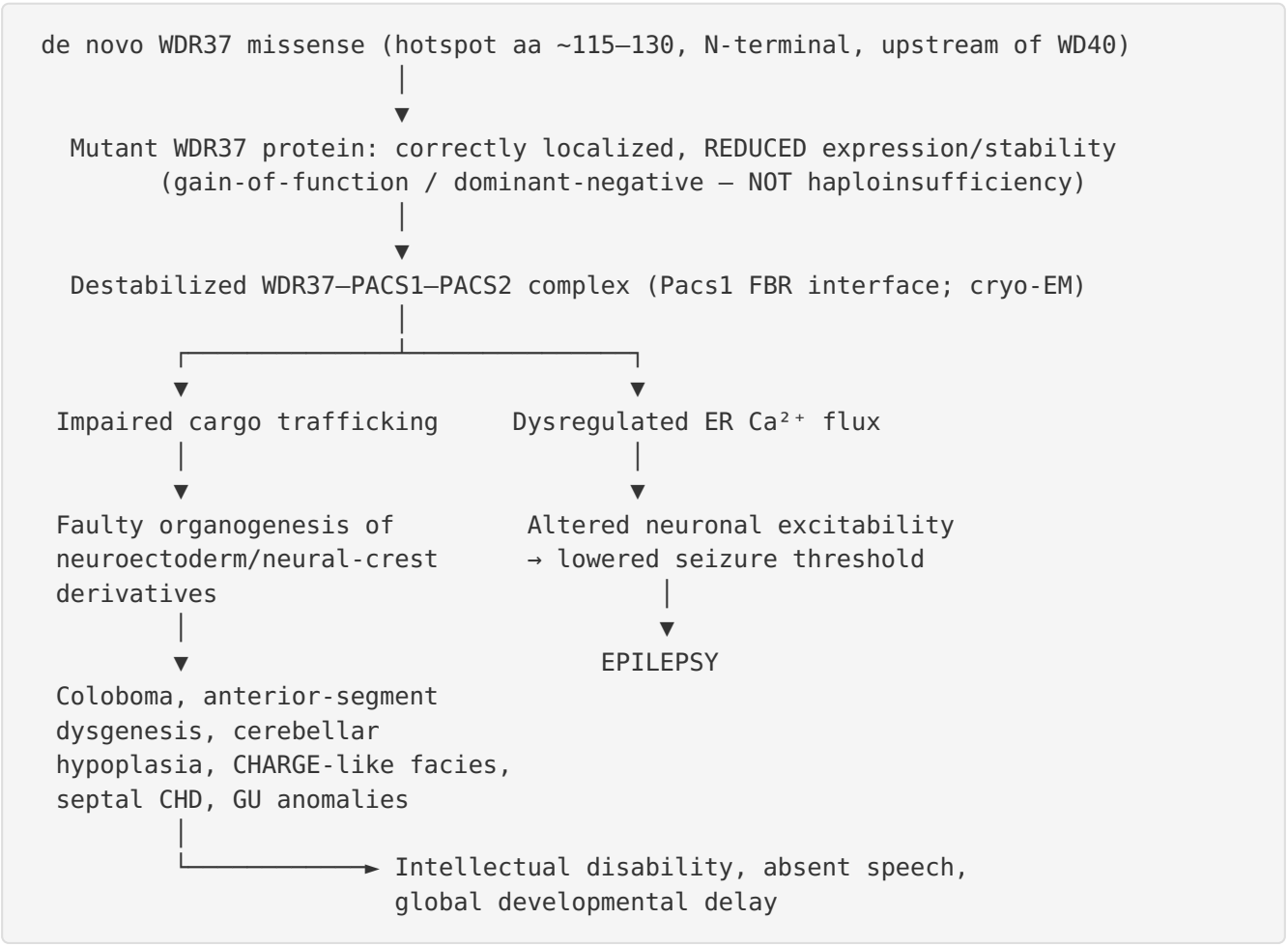
- **Orthologous genes.** *Wdr37* exists in mouse (*Mus musculus*, NCBI Taxon 10090), fly (*Drosophila melanogaster*, Taxon 7227), and *C. elegans* (Taxon 6239, ortholog *wdr-37*). The PACS–WDR37 interaction is evolutionarily conserved: in *C. elegans*, "cePACS-1 and ceWDR-37 colocalize to somatic cytoplasm… and are mutually required for expression, supporting a conclusion that the intermolecular dependence… is evolutionarily conserved" (PMID: 39031646).
- **Natural disease / veterinary relevance.** No naturally occurring NOCGUS-equivalent disease has been reported in companion animals or wildlife (not in OMIA). *WDR37* appears as a candidate gene in livestock growth-trait GWAS (Korean native chickens PMID: 34440344; Dongliao black pigs PMID: 40665728), but these are unrelated QTL associations, not the human syndrome.
- **Zoonotic potential:** None (genetic disorder).

Section 15 — Model Organisms

Model	System	Key finding	Reference
Drosophila melanogaster	*wdr37* null	Homozygous viable but severe **bang sensitivity** (seizure-associated phenotype) — supports non-haploinsufficiency and links WDR37 to neuronal excitability	Kanca 2019 PMID: 31327508
Mus musculus	Pacs1–Wdr37	Controls **ER calcium flux** to promote **lymphocyte quiescence**; loss predisposes to lymphoproliferative disease	Nair-Gill 2021 PMID: 33630350
C. elegans	*wdr-37* / *pacs-1*	Conserved colocalization and **mutual requirement for expression**; human PACS1 complements worm PACS-1 in neurons; variant editing alters neuronal localization	PMID: 39031646
In vitro (human cells)	Overexpression / co-IP / ICC	WDR37 homodimerizes, binds PACS1/PACS2, colocalizes; variant proteins analyzed functionally	Sorokina 2021 PMID: 34642815
Cryo-EM (recombinant)	Pacs1–Wdr37 complex	Structural basis of assembly; Pacs1 FBR interface stabilizes Wdr37	Xiao 2025 PMID: 41279321

Phenotype recapitulation. No mouse knock-in of the human N-terminal hotspot variants has been reported; existing models capture molecular (complex assembly, calcium flux) and partial neuronal (seizure-like bang sensitivity) aspects rather than the full multisystem malformation syndrome. **Model limitation:** the developmental malformation spectrum (coloboma, CHD, cerebellar hypoplasia) has not been fully reproduced in a vertebrate genetic model of the specific human variants.

Mechanistic Model (synthesis)



The upstream, demonstrated steps are the physical WDR37–PACS1/2 interaction and the calcium-flux/lymphocyte function (in vitro and mouse). The downstream developmental branch (how trafficking/calcium dysregulation produces coloboma and the organ malformations) is **inferred from phenotypic convergence** across the WDR37–PACS1–PACS2 axis rather than directly demonstrated.

Evidence Base

PMID	Title (abbrev.)	Contribution
31327510	*De Novo Missense Variants in WDR37 Cause a Severe Multisystemic Syndrome*	Founding cohort; 4 de novo N-terminal missense variants; defines multisystem phenotype incl. infantile lethality
31327508	*De Novo Variants in WDR37… Epilepsy, Colobomas… Cerebellar Hypoplasia*	Independent cohort (5 probands); Drosophila null (homozygous viable, bang-sensitive); HPO frequency source
34642815	*WDR37 syndrome… functional analyses of mutant proteins*	Homodimerization; strong PACS1/PACS2 binding; new variant cluster
41279321	*Structural Basis for Pacs1-Wdr37 Complex Assembly and Stability*	Cryo-EM; Pacs1 FBR interface stabilizes Wdr37; mutual expression dependence
33630350	*Calcium flux control by Pacs1-Wdr37…*	Functional role in ER Ca^{2+} flux and lymphocyte quiescence (mouse)
33369122	*Coloboma… WDR37-PACS1-PACS2 axis*	Establishes the shared clinical-molecular axis; coloboma as unifying feature
32530092	*Expanding the phenotypic spectrum… de novo WDR37*	Milder cases; p.Thr115Ile, p.Ser119Tyr; panel-inclusion recommendation
38044197	*Splicing variant of WDR37…*	First splice variant; novel phenotypes (anal atresia, polycystic kidney)
42546896	*Severe bilateral coloboma/ microphthalmia in a neonate…*	Severe neonatal ocular/multisystem presentation; exome-confirmed
39031646	*PACS-1 variant… C. elegans model*	Evolutionary conservation of PACS–WDR37 interaction
42794636	*Loss of acquired skills in PACS1/ PACS2/WDR37…*	Regression uncommon; not a primarily regressive disorder
36077045	*Molecular basis of Schuurs-Hoeijmakers (PACS1)…*	Proposes gain-of-function/dominant-negative and ASO therapeutic concepts for the axis

Limitations and Knowledge Gaps

1. **Small N.** All clinical knowledge derives from <60 published patients; frequency estimates (e.g., 5/5, 4/5) are from tiny cohorts and are statistically fragile.
2. **No prevalence/incidence data.** Epidemiology is unquantified.
3. **Mechanism partly inferred.** The link from WDR37–PACS1/2 complex disruption to the specific developmental malformations (coloboma, CHD) is based on phenotypic convergence, not direct experimental demonstration in a vertebrate model of the human variants.
4. **No knock-in animal model** of the human N-terminal hotspot variants recapitulating the full syndrome.
5. **Genotype–phenotype correlations** within the hotspot (why some variants are lethal and others mild) are unresolved.
6. **No biomarkers, no QoL data, no natural-history study, no therapy.**

Proposed Follow-up Experiments / Actions

1. **Generate a knock-in mouse (or zebrafish)** carrying a human hotspot variant (e.g., p.Ser119Phe) to test whether it reproduces coloboma, cerebellar hypoplasia, CHD, and seizures — directly testing the developmental branch of the model.
2. **Quantify the variant's effect on the WDR37–PACS1–PACS2 complex** using the cryo-EM framework (Xiao 2025): measure complex stability, stoichiometry, and ER Ca^{2+} flux for each pathogenic variant to establish gain-of-function vs dominant-negative.
3. **Single-cell/spatial transcriptomics of developing eye and cerebellum** in the model to define cell-type-specific consequences (Purkinje, neural crest, optic-fissure cells).
4. **Establish an international NOCGUS registry/natural-history study** to obtain robust phenotype frequencies, survival, and genotype–phenotype correlations.
5. **Explore ASO / allele-selective knockdown** of the mutant *WDR37* allele (by analogy with PACS1 strategies, PMID: 36077045) as a proof-of-concept precision therapy if a dominant-negative/gain-of-function mechanism is confirmed.

Report compiled from OMIM, MONDO, HPO, gnomAD, UniProt, ClinVar, and primary literature. Evidence source types: human clinical case series/reports (Reis, Kanca, Hay, Samejima, neonate report, Mexican cohort); model organism (Drosophila, mouse, C. elegans); in vitro and structural (Sorokina, Xiao).
