SEC61A1 Deficiency (MONDO:0100337): A Comprehensive Disease Characterization

Summary

SEC61A1 deficiency is a rare autosomal-dominant multisystem disorder caused by heterozygous pathogenic variants in **SEC61A1** (HGNC:18276; OMIM gene 609213; chr3q21.3; ENSG00000058262), the gene encoding the pore-forming **α-subunit of the Sec61 protein-translocation channel (translocon)** in the endoplasmic reticulum (ER). Sec61α is a dual-function membrane protein: it forms the central aqueous conduit through which secretory and membrane proteins are co-translationally translocated across/into the ER membrane (GO:0008320 transmembrane protein transporter activity), and it simultaneously functions as a passive ER calcium-leak channel (GO:0005262 calcium channel activity). Because the protein sits at the hub of the secretory pathway, dominant mutations produce a pleiotropic "translocopathy" that strikes the most highly secretory and proliferative cell lineages — renal tubular/juxtaglomerular cells, antibody-secreting plasma cells, and maturing granulocytes.

Under the umbrella concept MONDO:0100337 ("SEC61A1 deficiency"), the disease resolves into **three distinct dominant OMIM phenotypes**: (1) **ADTKD-SEC61A1 / familial juvenile hyperuricemic nephropathy 4 (HNFJ4, OMIM 617056)** — early-onset progressive chronic kidney disease (CKD) with hyperuricemia, congenital anemia, growth retardation and renal cysts; (2) **common variable immunodeficiency 15 (CVID15, OMIM 620670)** — a plasma-cell differentiation block producing hypogammaglobulinemia; and (3) **severe congenital neutropenia 11 (SCN11, OMIM 620674)** — a granulocytic maturation arrest. Additional reported features expand the spectrum to hypomagnesemia, hypoaldosteronism with salt-wasting, cognitive impairment, microcephaly and epilepsy.

The unifying mechanism is impaired co-translational protein translocation combined with dysregulated ER calcium homeostasis, which together trigger a terminal (apoptotic) unfolded-protein response (UPR) in secretory lineages. SEC61A1's extreme population-genetic constraint (gnomAD pLI = 0.9998; missense Z = 5.53) confirms strong dosage sensitivity and supports a haploinsufficiency/dominant-negative model. There is currently no curative therapy; management is organ-specific and supportive (dialysis/transplant, immunoglobulin

replacement, G-CSF, fludrocortisone). The chemical chaperone **4-phenylbutyrate**, which rescues the mutant translocon's renin-transport defect in vitro, is the leading mechanism-based experimental avenue.

Key Findings

Finding 1 — SEC61A1 is the causal gene; heterozygous loss-of-function causes ADTKD

The founding disease association was established by Bolar et al. 2016 (PMID: 27392076), who identified heterozygous missense variants **c.553A>G (p.Thr185Ala)** and **c.200T>G (p.Val67Gly)** in two families with autosomal-dominant tubulointerstitial kidney disease (ADTKD) plus congenital anemia. Both variants affect *"functionally important and conserved residues in SEC61."* Critically, the study provided direct tissue-level mechanistic evidence: *"Both transiently expressed SEC6A1A variants are delocalized to the Golgi, a finding confirmed in a renal biopsy from an affected individual."* Functional confirmation came from a zebrafish model: suppression or CRISPR deletion of the ortholog *sec61al2* induced pronephric tubule convolution defects that were rescued by wild-type human mRNA but **not** by the patient/mutant mRNA — establishing loss of function as the disease mechanism. This finding anchors the causal gene and the two founding ADTKD-SEC61A1 variants.

Finding 2 — SEC61A1 mutations also cause primary antibody deficiency (CVID) via a plasma-cell differentiation block

Schubert et al. 2018 (PMID: 28782633) extended the phenotype to humoral immunodeficiency. They *"identified novel heterozygous missense (c.254T>A, p.V85D) and nonsense (c.1325G>T, p.E381*) mutations in SEC61A1, segregating with the disease phenotype" *across 11 patients from two families presenting with hypogammaglobulinemia and recurrent respiratory infections. B cells from patients failed to differentiate into plasma cells in vitro. Mechanistically,* "SEC61A1-V85D was deficient in cotranslational protein translocation, and it disturbed the cellular calcium homeostasis in HeLa cells,"* and triggered the terminal unfolded-protein response. This connects the translocation defect and calcium dysregulation directly to the failure of the most secretory immune lineage (the plasma cell), and defines the immune arm later catalogued as CVID15.

Finding 3 — A druggable molecular defect: phenylbutyrate rescues mutant renin transport

Sicking et al. 2022 (PMID: 35064074) dissected the biochemical consequence of the ADTKD mutations. The V67G and T185A Sec61α mutants impair translocation/transport of **preprorenin** into the ER lumen, offering a plausible explanation for the renal/juxtaglomerular phenotype. Importantly, *"Phenylbutyrate rescues the transport defect of the Sec61α mutations V67G and T185A for renin,"* establishing a pharmacological rescue of the molecular lesion and a concrete therapeutic hypothesis. The study also reinforced the channel's dual role, moving both protein substrates and calcium ions across the ER membrane.

Finding 4 — An expanding multisystem phenotype beyond the kidney

Across the ~15 reported patients (reviewed by Zhong et al. 2026, PMID: 41850665), the renal presentation comprises early-onset CKD with hyperuricemia, bland urinary sediment, absence of significant proteinuria, and renal cysts. Extrarenal features are prominent: *"The extrarenal features included growth retardation, hematological abnormalities, cognitive impairment, and immunological abnormalities."* Hematological abnormalities span normocytic normochromic anemia and neutropenia/agranulocytosis. Newer case reports continue to broaden the spectrum: a pediatric case from Oman (p.Thr185Ser, c.554C>G) presented with **hypomagnesemia, epilepsy, and microcephaly** — epilepsy being a previously unreported ADTKD-SEC61A1 feature (PMID: 42730770) — and Karpman et al. 2024 documented **hypoaldosteronism with salt-wasting** that was *"successfully treated with fludrocortisone"* (PMID: 39135939).

Finding 5 — Extreme intolerance to variation supports dominant haploinsufficiency

Population-genetic constraint data from gnomAD v2.1.1 strongly support a dosage-sensitive mechanism. For SEC61A1 (ENSG00000058262; HGNC:18276; chr3:128,051,641–128,071,683 GRCh38; 3q21.3):

Metric	Value	Interpretation
pLI	0.9998	Near-certain intolerance to loss of function
LOEUF (oe_lof upper)	0.418	Constrained
observed/expected LoF	0.272 (obs 15 / exp 55.2)	~73% depletion of LoF alleles
LoF Z	4.59	Strong LoF constraint
missense Z	5.53 (oe_mis 0.471)	Strong missense constraint

This profile is characteristic of a haploinsufficient, dominant-acting gene, consistent with the autosomal-dominant inheritance observed clinically.

Finding 6 — The severe congenital neutropenia arm (SCN11) unifies three phenotypes

The official disease concept MONDO:0100337 ("SEC61A1 deficiency") is defined as any Mendelian disease caused by SEC61A1 mutation, *"characterized by variable presentation of phenotypes... including autosomal dominant tubulointerstitial kidney disease, primary antibody deficiency, and severe congenital neutropenia."* Van Nieuwenhove et al. 2020 (PMID: 32325141) established the myeloid arm: *"We identified a novel de novo missense mutation in SEC61A1 (c.A275G;p.Q92R) in a patient with SCN"* (designated SCN11). The shared mechanism was confirmed — *"The mutation results in diminished protein expression, disturbed protein translocation, and an increase in calcium leakage from the endoplasmic reticulum"* — along with UPR dysregulation. Wang et al. 2026 (PMID: 42056350) reported a second SCN variant, c.1135T>C (p.Trp379Arg), noting *"This is the second reported SEC61A1 variant associated with SCN11, expanding the genetic and phenotypic spectrum of SCN."* ClinVar (Oct 2025) lists 393 SEC61A1 records, including 25 pathogenic and 6 likely pathogenic, with the large majority (~360) classified as variants of uncertain significance.

Finding 7 — Three resolved OMIM entities under one MONDO umbrella

Gene–disease association resolution (Monarch/OLS/MONDO) catalogues three distinct entities caused by SEC61A1:

Arm	Disease	OMIM	MONDO	Other IDs
Kidney	Hyperuricemic nephropathy, familial juvenile, 4 (HNFJ4) / ADTKD-SEC61A1	617056	MONDO:0014891	DOID:0061120
Immune	Immunodeficiency, common variable, 15 (CVID15)	620670	MONDO:0958013	Orphanet:697417
Myeloid	Neutropenia, severe congenital, 11, autosomal dominant (SCN11)	620674	MONDO:0958017	—

All three are umbrella'd by **MONDO:0100337** ("SEC61A1 deficiency"). GO molecular-function annotation confirms the dual activity: **GO:0008320** (transmembrane protein transporter activity) and **GO:0005262** (calcium channel activity), with cellular component **GO:0005784** (Sec61 translocon complex). Note: an earlier label "CVID13" was corrected to **CVID15** during the investigation.

Finding 8 — Deep evolutionary conservation supports model-organism transferability

SEC61A1 is deeply conserved (HomoloGene:55537), with verified orthologs: human SEC61A1 (NCBIGene:29927), mouse *Sec61a1* (NCBIGene:53421), rat *Sec61a1* (NCBIGene:80843), zebrafish *sec61al1* (NCBIGene:192298) and *sec61al2* (NCBIGene:266796), and yeast *SEC61* (NCBIGene:851095), plus orthologs across Xenopus, chicken, dog, cow, and primates. Complete loss of translocon function is expected to be lethal, consistent with the dominant, heterozygous nature of human disease. Disease-relevant modeling has succeeded in zebrafish for the renal phenotype (*"Suppression or CRISPR-mediated deletions of sec61al2 in zebrafish embryos induced convolution defects of the pronephric tubules but not the pronephric ducts"*; PMID: 27392076) and via CD34+ granulocytic differentiation assays for the SCN arm (PMID: 32325141).

Report by Template Section

1. Disease Information

SEC61A1 deficiency is a rare autosomal-dominant Mendelian translocopathy caused by heterozygous variants in **SEC61A1**, the Sec61 translocon α-subunit gene. **Key identifiers:** MONDO:0100337 (umbrella); constituent entities HNFJ4/ADTKD-SEC61A1 (OMIM 617056, MONDO:0014891, DOID:0061120), CVID15 (OMIM 620670, MONDO:0958013, Orphanet:697417), SCN11 (OMIM 620674, MONDO:0958017); gene OMIM 609213; HGNC:18276. **Synonyms/ alternative names:** ADTKD-SEC61A1; familial juvenile hyperuricemic nephropathy type 4; Sec61-alphopathy/translocopathy. Information is derived from **aggregated disease-level resources** (OMIM, MONDO, Orphanet, ClinVar, gnomAD) combined with **individual-patient reports/case series** (the primary literature cited throughout).

2. Etiology

Causal factor: monogenic — heterozygous pathogenic variants in SEC61A1. **Genetic risk:** the causal variant itself is sufficient; no susceptibility loci or modifier genes are established. The extreme gnomAD constraint (pLI 0.9998, missense Z 5.53) indicates strong purifying selection. **Environmental risk/protective factors and gene–environment interactions:** none established; this is a Mendelian disorder with no documented environmental contribution. A single founding de novo variant (p.Q92R, SCN11) indicates that disease can arise sporadically.

3. Phenotypes

Representative phenotypes with suggested HPO terms:

Phenotype	Type	HPO suggestion	Characteristics
Chronic kidney disease / tubulointerstitial nephropathy	Clinical sign	HP:0012622 / HP:0000112	Early-onset, progressive to ESRD in adulthood
Hyperuricemia / gout	Lab abnormality	HP:0002149	Juvenile onset
Bland urinary sediment / absent proteinuria	Lab abnormality (negative finding)	—	Characteristic for ADTKD
Renal cysts / glomerulocystic disease	Physical manifestation	HP:0000107	Variable
Congenital/normocytic anemia	Lab abnormality	HP:0001903	Neonatal/congenital
Neutropenia / agranulocytosis	Lab abnormality	HP:0001875	SCN11 arm; severe
Hypogammaglobulinemia / recurrent infections	Lab abnormality / symptom	HP:0004313 / HP:0002719	CVID15 arm; plasma-cell block
Growth retardation	Physical	HP:0001510	Variable
Cognitive impairment	Behavioral/neuro	HP:0100543	Reported subset
Hypomagnesemia	Lab abnormality	HP:0002917	Newer feature
Hypoaldosteronism / salt-wasting	Lab abnormality	HP:0000846	Fludrocortisone-responsive
Epilepsy, microcephaly	Clinical sign	HP:0001250 / HP:0000252	Rare, pediatric (p.Thr185Ser)

Onset ranges from congenital/neonatal (anemia, neutropenia) to childhood/adolescence (CKD). Severity is variable; the renal course is progressive. Quality-of-life impact is substantial owing to lifelong CKD/dialysis dependence, infection susceptibility, and transfusion/growth issues; no disease-specific QoL instruments have been applied.

4. Genetic / Molecular Information

Causal gene: SEC61A1 (OMIM 609213; HGNC:18276; 3q21.3). **Pathogenic variants** (all germline, mostly heterozygous dominant): missense p.Thr185Ala (c.553A>G), p.Val67Gly (c.200T>G), p.Thr185Ser (c.554C>G) — ADTKD; p.Val85Asp (c.254T>A) and nonsense p.Glu381

*(c.1325G>T) — CVID; p.Gln92Arg (c.A275G, de novo) and p.Trp379Arg (c.1135T>C) — SCN11. Variant classes: predominantly missense, with a disease-relevant nonsense allele. ClinVar (Oct 2025): 393 records (25 pathogenic, 6 likely pathogenic, ~360 VUS). Allele frequency: pathogenic alleles are absent/ultra-rare in gnomAD; the gene is strongly LoF- and missense-constrained. Functional consequence: loss of function with likely dominant-negative contribution (mutant subunit incorporated into the heterotrimeric channel). Modifier genes/epigenetics/chromosomal abnormalities:** none established.

5. Environmental Information

Not applicable — no environmental, lifestyle, or infectious contributors are known. Recurrent infections are a *consequence* of the immunodeficiency/neutropenia arms, not a cause.

6. Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation): 1. A heterozygous SEC61A1 variant (missense or nonsense) **leads to** a defective or reduced Sec61α subunit incorporated into the ER translocon. 2. This **results in** impaired co-translational translocation of secretory/membrane precursor proteins into the ER (demonstrated for preprorenin) **and**, in parallel (branch), increased passive Ca^{2+} leak from the ER lumen through the defective channel (demonstrated in HeLa cells and CD34+ cells). 3. Reduced protein import **leads to** mislocalization of Sec61α to the Golgi (shown in patient renal biopsy) and accumulation of untranslocated/misfolded client proteins. 4. Protein-folding stress plus disturbed ER Ca^{2+} homeostasis **results in** activation of ER stress and the **terminal (apoptotic) unfolded-protein response**. 5. In the most secretory/proliferative lineages this **results in** cell dysfunction/death — branching into: (a) renal tubular + juxtaglomerular cells → tubulointerstitial fibrosis, impaired renin/renal function → CKD, hyperuricemia, anemia, hypoaldosteronism; (b) plasma cells → differentiation block → hypogammaglobulinemia (CVID15); (c) granulocyte precursors → maturation arrest → severe congenital neutropenia (SCN11).

Upstream: the translocation defect and Ca^{2+} dysregulation. **Downstream:** UPR-driven apoptosis and lineage-specific functional failure. **Molecular pathways/processes:** protein targeting to ER (GO:0045047), SRP-dependent co-translational translocation (GO:0006614), response to ER stress/UPR (GO:0030968), ER calcium ion homeostasis (GO:0032469), apoptotic process (GO:0006915). **Cell types (CL):** kidney tubule epithelial cell, juxtaglomerular cell, plasma cell (CL:0000786), neutrophil/granulocyte precursor (CL:0000775). **Subcellular compartment:** ER membrane / Sec61 translocon complex (GO:0005784), ER (GO:0005783).

Protein dysfunction: loss of channel conductance for protein substrates + aberrant Ca^{2+} leak; mislocalization to Golgi; likely dominant-negative assembly into the heterotrimeric Sec61 complex (structural context from cryo-EM studies PMID: 33398175, PMID: 21499241).

7. Anatomical Structures Affected

Primary organs: kidney (UBERON:0002113) — tubulointerstitium, juxtaglomerular apparatus; bone marrow (UBERON:0002371) — myeloid compartment; secondary lymphoid organs / plasma-cell niches. **Secondary involvement:** systemic (anemia, growth retardation), adrenal/renin-angiotensin-aldosterone axis (hypoaldosteronism), CNS (cognitive impairment, epilepsy, microcephaly). **Body systems:** urinary, hematopoietic/immune, endocrine, nervous. **Tissues/cells:** renal epithelial cells, plasma cells (CL:0000786), neutrophils (CL:0000775). **Subcellular:** ER membrane (GO:0005789), Sec61 translocon (GO:0005784). **Localization:** bilateral kidney involvement; systemic hematologic/immune involvement.

8. Temporal Development

Onset: congenital/neonatal for anemia and neutropenia; childhood-to-adolescent for CKD/hyperuricemia; insidious and chronic. **Progression:** renal disease is slowly progressive, advancing to end-stage kidney disease in adulthood (ESRD present at diagnosis in a substantial fraction of ADTKD cohorts). **Course:** chronic, lifelong, progressive; no spontaneous remission. **Critical windows:** early diagnosis enables renal-protective management, infection prophylaxis, and G-CSF initiation for neutropenia.

9. Inheritance and Population

Inheritance: autosomal dominant; de novo occurrence documented (SCN11 p.Q92R). **Penetrance/expressivity:** appears high-penetrance but with highly variable expressivity (which organ arm predominates differs among families/variants). **Epidemiology:** ultra-rare; SEC61A1 accounts for a very small minority of ADTKD cases (ADTKD overall ~5% of monogenic CKD; SEC61A1 is among the rarest subtypes, with single-family yields in large cohorts such as the Japanese cohort of PMID: 39976632). No formal prevalence/incidence estimates exist. **Founder effects/consanguinity:** none established; gnomAD shows pathogenic alleles are essentially absent. **Carrier frequency:** not applicable (dominant, de novo or inherited heterozygous). **Sex ratio/geographic distribution:** no established skew; cases reported across multiple populations (Europe, Japan, Middle East).

10. Diagnostics

Genetic testing is the diagnostic cornerstone. ADTKD is defined by identification of a pathogenic variant in one of UMOD, MUC1, REN, HNF1B, or SEC61A1. Recommended approaches: targeted single-gene/panel testing (ADTKD gene panels), whole-exome or whole-genome sequencing for unexplained CKD; long-read sequencing is especially useful to resolve MUC1 but exome/genome suffices for SEC61A1. **Supportive clinical/lab findings:** elevated creatinine with **bland urinary sediment and minimal proteinuria**, hyperuricemia/gout, normocytic anemia, neutropenia, hypogammaglobulinemia, hypomagnesemia, low aldosterone. **Imaging:** normal-to-small kidneys ± cysts. **Biopsy:** nonspecific tubulointerstitial fibrosis/tubular atrophy; immunostaining can show Sec61α Golgi mislocalization (research setting). **Differential diagnosis:** other ADTKD subtypes (UMOD, MUC1, REN, HNF1B), and newly described ADTKD-JAG1 (PMID: 41061854); for the immune/myeloid arms, other causes of CVID and congenital neutropenia (e.g., ELANE). **Screening:** cascade genetic testing of at-risk relatives.

11. Outcome / Prognosis

The renal arm carries a guarded prognosis, progressing to ESRD requiring dialysis or transplantation in adulthood; transplantation is effective as the defect is intrinsic to kidney tissue but systemic. The immune arm risks recurrent/chronic infection and bronchiectasis if untreated; the myeloid arm risks severe bacterial infection and, as with other SCN, potential long-term leukemia surveillance considerations. Overall morbidity is high (lifelong CKD, infection susceptibility, growth impairment). No formal survival statistics exist given rarity. **Prognostic factors:** specific variant/predominant organ arm, age at CKD onset, and severity of cytopenias.

12. Treatment

No curative, mechanism-targeted therapy is approved; management is **organ-specific and supportive**: - **Renal:** CKD management, uric-acid lowering (e.g., allopurinol), renal replacement therapy — dialysis and kidney transplantation (NCIT:C157763 kidney transplantation). - **Immune (CVID15):** immunoglobulin replacement therapy (IVIG/SCIG; NCIT:C29071 immunoglobulin therapy), infection prophylaxis. - **Myeloid (SCN11):** granulocyte colony-stimulating factor / G-CSF (filgrastim; NCIT:C1583). - **Endocrine:** fludrocortisone for hypoaldosteronism/salt-wasting (demonstrated effective, PMID: 39135939). - **Hematologic:** transfusion support for anemia; magnesium supplementation for hypomagnesemia. - **Experimental / mechanism-based:** the chemical chaperone **4-phenylbutyrate** rescues the

mutant translocon's renin-transport defect in vitro (PMID: 35064074) and is the leading candidate for molecular correction; not yet trialed clinically for this disease. **Pharmacogenomics, gene/cell/RNA therapies:** none established.

13. Prevention

No primary prevention (Mendelian). **Secondary prevention:** early genetic diagnosis enables renal-protective care, infection prophylaxis/immunoglobulin, and timely G-CSF. **Genetic counseling** is central: 50% transmission risk for an affected heterozygous parent; de novo cases possible. Prenatal/preimplantation genetic testing is feasible when a familial variant is known. Cascade testing identifies at-risk relatives for surveillance.

14. Other Species / Natural Disease

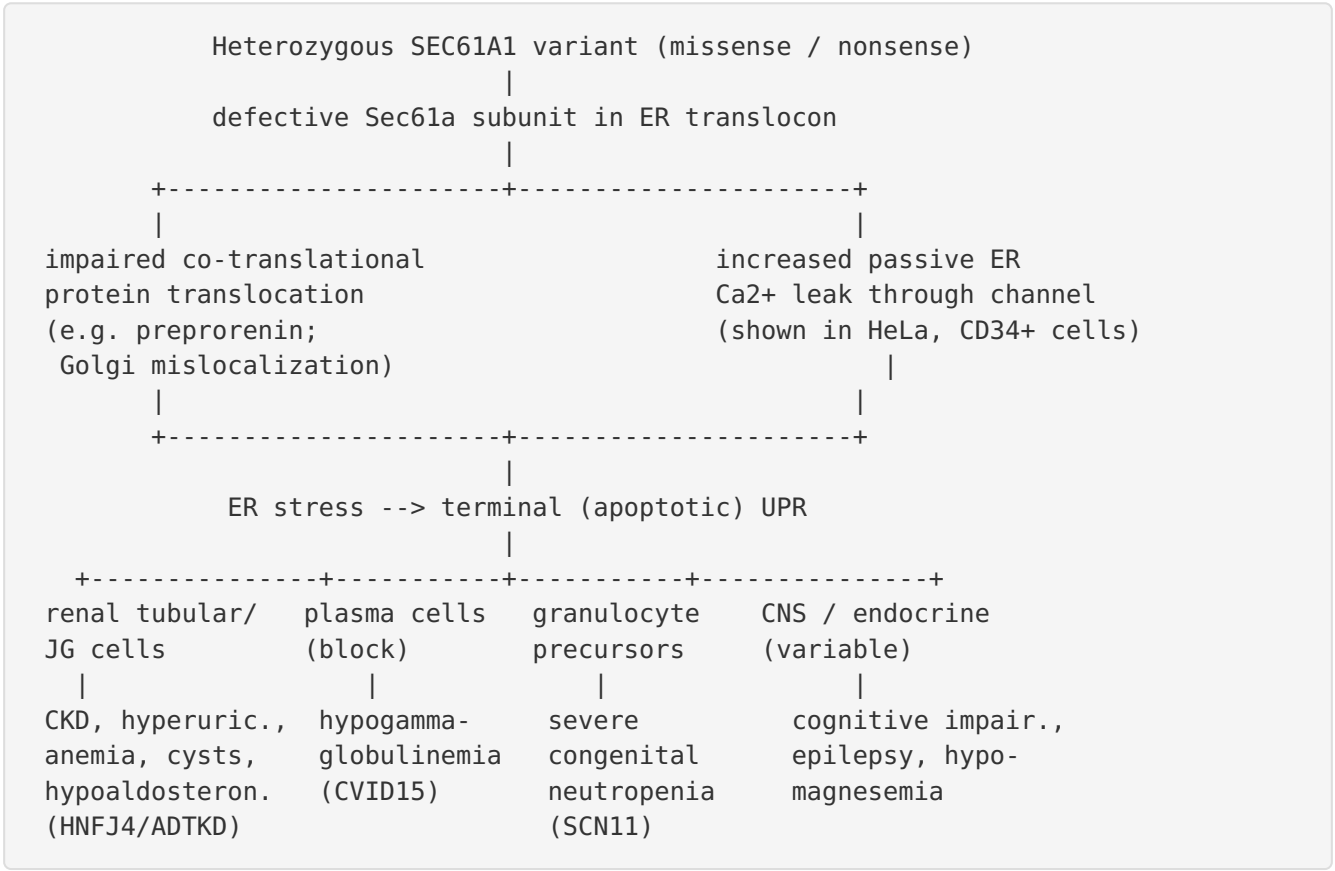
SEC61A1 is deeply conserved across eukaryotes (HomoloGene:55537), with orthologs in mouse, rat, zebrafish, Xenopus, chicken, dog, cow, primates, and yeast (see Finding 8 for NCBI Gene IDs; NCBI Taxon IDs: human 9606, mouse 10090, rat 10116, zebrafish 7955, *S. cerevisiae* 559292). No naturally occurring SEC61A1 disease has been catalogued in companion animals or wildlife (no OMIA entry identified); complete translocon loss is presumed embryonic-lethal. No zoonotic relevance (non-infectious disease).

15. Model Organisms

- **Zebrafish (*Danio rerio*):** morpholino knockdown and CRISPR deletion of *sec61al2* reproduce pronephric tubule convolution defects; human wild-type mRNA rescues but mutant mRNA does not — a validated model of the renal phenotype (PMID: 27392076). Resource: ZFIN.
- **Cellular/in vitro:** HeLa cells expressing SEC61A1-V85D show translocation and calcium-homeostasis defects and UPR induction (PMID: 28782633); patient CD34+ cells modeling granulocytic differentiation recapitulate the SCN maturation arrest (PMID: 32325141). Biochemical reconstitution of preprorenin transport assessed the renin defect and phenylbutyrate rescue (PMID: 35064074).
- **Yeast and structural systems:** *S. cerevisiae* and thermophilic fungal Sec61–Sec62–Sec63 complexes provided the cryo-EM structural framework for channel gating (PMID: 33398175).
- **Mammalian knockout:** no published mouse model specific to the human disease variants was identified; complete Sec61a1 knockout is expected lethal. Resources: MGI, RGD, ZFIN, IMPC. **Phenotype recapitulation:** strong for the renal (zebrafish) and cellular/immune/

myeloid (in vitro) arms. **Limitation:** no whole-mammal model captures the full multisystem human phenotype.

Mechanistic Model / Interpretation



The central insight is **lineage selectivity through shared biochemistry**: a single ubiquitously expressed translocon defect manifests preferentially in cells with the heaviest secretory/folding load and highest proliferative demand, where the combined protein-translocation deficit and ER-calcium dysregulation most readily tip cells into apoptotic UPR. The same molecular lesion thus produces three nosologically distinct dominant diseases that share one mechanism — a paradigm of a monogenic "translocopathy."

Evidence Base

PMID	Title (abbrev.)	Role	Evidence type
27392076	*Heterozygous LoF SEC61A1 mutations cause ADTKD with anemia*	Founding ADTKD variants; Golgi mislocalization in biopsy; zebrafish rescue	Human clinical + model organism
28782633	*Plasma cell deficiency with heterozygous SEC61A1 mutations*	CVID arm; V85D translocation + Ca^{2+} defect; terminal UPR	Human clinical + in vitro
35064074	*Phenylbutyrate rescues Sec61α V67G/T185A renin transport*	Druggable mechanism; preprorenin defect	In vitro / biochemical
41850665	*De novo SEC61A1 in congenital anemia + early kidney disease*	Multisystem phenotype review	Human clinical review
39135939	*Hypoaldosteronism from novel SEC61A1 variant*	Hypoaldosteronism; fludrocortisone treatment	Human clinical
32325141	*Defective Sec61α1 underlies autosomal dominant SCN*	SCN11 arm; Q92R; translocation + Ca^{2+} leak + UPR	Human clinical + in vitro
42056350	*Novel de novo SEC61A1 variant in SCN*	Second SCN11 variant (W379R)	Human clinical
42730770	*Rare ADTKD in children (Oman)*	p.Thr185Ser; epilepsy, microcephaly, hypomagnesemia	Human clinical
33398175	*Stepwise gating of Sec61 by Sec63/Sec62*	Structural basis of channel gating	Structural/cryo-EM
21499241	*Cryo-EM of ribosome–SecYE in membrane*	Translocon architecture	Structural/cryo-EM
34519781	*Clinical and genetic spectra of ADTKD*	Places SEC61A1 among ADTKD genes	Review
36531871	*ADTKD: emerging cause of genetic CKD*	Gene-based ADTKD classification	Review
39976632	*ADTKD phenotype/genotype in a Japanese cohort*	Rarity of SEC61A1 (1 of 40 families)	Human clinical cohort

PMID	Title (abbrev.)	Role	Evidence type
41061854	*ADTKD-JAG1*	Differential diagnosis; haploinsufficiency parallel	Human clinical

All three mechanistic studies ([27392076], [28782633], [32325141]) converge on the same molecular defect (impaired translocation + ER Ca^{2+} dysregulation + UPR), lending strong internal consistency. The constraint data (gnomAD) and conservation data (HomoloGene) are independent, non-literature lines of support for the dosage-sensitive dominant model.

Limitations and Knowledge Gaps

1. **Small evidence base.** Fewer than ~20 patients are reported across all three arms; prevalence/incidence, penetrance, expressivity, and sex/geographic distribution remain poorly quantified.
2. **Genotype–phenotype correlation unresolved.** It is unclear why some variants predominantly cause renal disease, others immunodeficiency, and others neutropenia; no systematic structure–function map of variant position vs. organ arm exists.
3. **Dominant-negative vs. haploinsufficiency.** The relative contributions are inferred; the nonsense allele (E381*) suggests haploinsufficiency, while missense Golgi-mislocalization suggests a dominant-negative/toxic component — these may differ by variant.
4. **No whole-mammal disease model** captures the full multisystem phenotype; mechanistic work relies on zebrafish (renal) and cell lines.
5. **Therapeutics unproven in vivo.** Phenylbutyrate rescue is purely in vitro; no clinical trial data exist for any mechanism-targeted therapy.
6. **VUS burden.** ~360 of 393 ClinVar entries are VUS, complicating clinical interpretation of novel variants.
7. **Rare features** (epilepsy, microcephaly, cognitive impairment) are reported in single cases and their causal link to SEC61A1 requires replication.

Proposed Follow-up Experiments / Actions

1. **Build an international SEC61A1 patient registry** to quantify prevalence, penetrance, organ-arm frequencies, and natural history across all three OMIM entities.
2. **Systematic variant functional mapping:** assay a panel of patient and ClinVar VUS variants in parallel for (a) protein translocation, (b) ER Ca^{2+} leak, (c) UPR induction, and (d) lineage-specific differentiation (plasma-cell and granulocyte in vitro assays), to resolve genotype–phenotype correlation and reclassify VUS.
3. **Generate a conditional/knock-in mouse** carrying a recurrent human variant (e.g., p.Thr185Ala) to test multisystem recapitulation and serve as a preclinical therapeutic platform.
4. **Preclinical test of 4-phenylbutyrate and other chemical chaperones / UPR modulators** (e.g., ISRIB, TUDCA) in zebrafish and patient-derived cells/organoids across renal, plasma-cell, and myeloid readouts.
5. **iPSC-derived organoid models** (kidney organoids, plasma-cell differentiation, granulopoiesis) from patient cells to dissect lineage selectivity and screen candidate drugs.
6. **Structural studies** of mutant Sec61α within the heterotrimeric channel (cryo-EM) to clarify dominant-negative assembly and channel gating/Ca^{2+}-leak defects.
7. **Prospective surveillance protocols** combining renal, immune, and hematologic monitoring for genetically diagnosed individuals, and evaluation of early G-CSF/immunoglobulin/renal-protective intervention outcomes.

Evidence source legend: human clinical, model organism (zebrafish), in vitro/biochemical, structural (cryo-EM), computational (gnomAD constraint, HomoloGene conservation).
