Autosomal Dominant Sensory Ataxia 1 (ADSA1): Comprehensive Disease Characterization Report

Disease: Autosomal Dominant Sensory Ataxia 1 (ADSA1) **Primary identifiers:** MONDO:0012166 · OMIM #608984 · DOID:0111170 · GARD:0024850 · MedGen:332346 · UMLS:C1837015 **Causal gene:** *RNF170* (OMIM *614649; HGNC:25358; NCBI Gene 81790; Ensembl ENSG00000120925; locus 8p11.21) Category:** Mendelian, monogenic, autosomal dominant

Summary

Autosomal Dominant Sensory Ataxia 1 (ADSA1; also SNAX1, ADSA, "RNF170 hereditary ataxia") is an ultra-rare, adult/middle-age–onset, slowly progressive hereditary **sensory (proprioceptive) ataxia**. It is caused by a single recurrent heterozygous missense mutation in *RNF170*, **c.595C>T p.(Arg199Cys)**, and results clinically from degeneration of the posterior (dorsal) columns of the spinal cord and a length-dependent sensory neuronopathy/neuropathy. It was originally described in two large founder families from Maritime Canada PMID: 21115467 and has since been independently replicated in a Belgian family PMID: 34469621 and reported as a **CANVAS mimic** (sensory ataxic neuropathy with vestibular areflexia) PMID: 32943585. The disease is exceedingly rare, reported in only a handful of families/individuals worldwide.

Mechanistically, RNF170 is an **endoplasmic reticulum (ER)–membrane RING-type E3 ubiquitin ligase** that, together with the ERLIN1/2 (SPFH-family) scaffold and TMUB1, forms an ERAD "nanodomain" that ubiquitinates activated **type-1 inositol 1,4,5-trisphosphate receptors (IP3R/ITPR1)** and targets them for proteasomal degradation PMID: 21610068; PMID: 38782601. The Arg199Cys mutation **destabilizes RNF170** by enhancing its autoubiquitination and proteasomal turnover, and functionally **impairs IP3R-mediated Ca^{2+} mobilization** in patient cells despite normal ER store content, IP3R levels, and IP3 production — pinpointing a defect at the IP3R signaling locus PMID: 25882839. *Rnf170*-knockout mice recapitulate age-dependent gait abnormalities, reduced proprioception and thermal nociception, and elevated ITPR1 protein in cerebellum and spinal cord PMID: 26433933.

Notably, *RNF170* exhibits a clear **allelic series**: the dominant p.Arg199Cys missense allele causes ADSA1, whereas **biallelic loss-of-function** *RNF170* variants cause a distinct autosomal recessive complicated hereditary spastic paraplegia, **SPG85** (MONDO:0030512; OMIM #619686) PMID: 31636353; PMID: 36046950; PMID: 35041108. There is no disease-specific therapy; management is supportive (physiotherapy, gait/balance aids, sensory rehabilitation, fall prevention).

Section 1 — Disease Information

Overview. ADSA1 is a monogenic, autosomal dominant, adult-onset **sensory ataxia** — an inability to coordinate movement due to loss of proprioceptive (position/vibration) sensation rather than primary cerebellar disease. Patients develop insidious, slowly progressive gait instability that is characteristically **worse in the dark or with eyes closed** (loss of visual compensation for absent proprioception), a positive Romberg sign, distal sensory loss, and areflexia; cerebellar imaging is typically normal.

Key identifiers. - **MONDO:** MONDO:0012166 — *"Any hereditary ataxia in which the cause of the disease is a mutation in the RNF170 gene."* - **OMIM:** #608984 (phenotype); *614649 (gene* RNF170*, allelic variant 614649.0001) - DOID: 0111170 · GARD: 0024850 · MedGen: 332346 · UMLS: C1837015 - Orphanet: no dedicated code cross-referenced to ADSA1 - ICD-10/ICD-11 / MeSH:** no ADSA1-specific code; classified under hereditary/spinocerebellar ataxia categories

Synonyms: SNAX1; ADSA; "ataxia, sensory, 1, autosomal dominant"; "RNF170 hereditary ataxia"; "sensory ataxic neuropathy with vestibular areflexia (CANVAS mimic)."

Information source type: Aggregated disease-level resources (OMIM, MONDO, HPO) plus **individual patient reports** from a small number of published families (Maritime-Canada founder families; Belgian family; scattered single cases).

Section 2 — Etiology

Primary cause — genetic. ADSA1 is **entirely genetic and monogenic**, caused by the heterozygous *RNF170* missense variant **c.595C>T p.(Arg199Cys)**. No environmental or infectious cause is implicated.

Genetic risk factors. The single causal allele is the dominant R199C variant; inheritance of one copy is sufficient to cause disease. Reported penetrance in pedigrees is high. There are no established susceptibility loci or GWAS signals (the disease is Mendelian, not complex).

Environmental risk factors / protective factors / gene–environment interactions. None identified. As a fully penetrant dominant Mendelian disorder, no dietary, occupational, or lifestyle risk or protective factors are known, and no gene–environment interactions have been reported.

Section 3 — Phenotypes (with HPO terms)

Frequencies below derive largely from the HPO/OMIM:608984 annotation set (Cortese et al. 2020, n=2 affected) supplemented by OMIM clinical synopsis and case reports. Given the tiny sample, frequencies are indicative.

HPO term	Phenotype	Type	Frequency
HP:0010871	Sensory ataxia	Clinical sign	2/2
HP:0002066	Gait ataxia	Clinical sign	2/2
HP:0003596	Middle-age onset	Onset	2/2
HP:0001265	Hyporeflexia	Clinical sign	2/2
HP:0003409	Distal sensory impairment (all modalities)	Clinical sign	2/2
HP:0006858	Impaired distal proprioception	Clinical sign	1/2
HP:0006886	Impaired distal vibration sensation	Clinical sign	1/2
HP:0007078	Decreased amplitude of sensory action potentials	Electrophysiology	1/2
HP:0002403	Positive Romberg sign	Clinical sign	reported
HP:0006962	Gait instability worse in the dark	Symptom	OMIM
HP:0001284	Areflexia	Clinical sign	OMIM
HP:0012534	Dysesthesia	Symptom	reported
HP:0001260	Dysarthria	Clinical sign	reported
HP:0007670	Abnormal vestibulo-ocular reflex / vestibular areflexia	Clinical sign	1/2
HP:0002359	Frequent falls	Symptom	reported
HP:0001317	Abnormal cerebellar morphology	Imaging	0/1 (usually normal)
HP:0003487	Babinski sign	Clinical sign	0/1 (usually absent)

Characteristics. Age of onset: **adult/middle age** (HP:0003596). Severity: mild-to-moderate initially, progressing to significant gait disability. Progression: **slowly progressive** over years to decades. The Belgian family additionally showed **variable pyramidal involvement** PMID: 34469621, and one atypical case presented with **hypertrophic olivary degeneration** PMID: 42052314.

Quality-of-life impact. Progressive gait instability, frequent falls, and dependence on assistive devices impair mobility, independence, and safety; sensory dysesthesia may add discomfort. No formal EQ-5D/SF-36 data exist for this ultra-rare disease.

Section 4 — Genetic / Molecular Information

Causal gene: *RNF170* (RING finger protein 170), locus **8p11.21**; OMIM *614649; HGNC:25358; NCBI Gene 81790; Ensembl ENSG00000120925; UniProt Q96K19.

Pathogenic variant (ADSA1): - **NM_030954.4(RNF170):c.595C>T (p.Arg199Cys)**; GRCh38 chr8:42,856,340 G>A - **ClinVar:** Pathogenic, 2-star ("criteria provided, multiple submitters, no conflicts") - **dbSNP:** rs397514478 · **ClinGen:** CA129827 · **UniProt variant:** VAR_068219 · **OMIM allelic variant:** 614649.0001 - **Variant type:** missense (single-nucleotide substitution), germline - **Allele frequency: absent from gnomAD v4** (ACMG PM2 supporting) - **Functional consequence:** destabilizes RNF170 (enhanced autoubiquitination/proteasomal degradation) with impaired IP3R-mediated Ca^{2+} signaling — behaving as a **dominant** allele; distinct from recessive LoF

Allelic series / other *RNF170* variants (SPG85, recessive): p.Arg64* PMID: 36046950; p.Cys107Trp (homozygous) PMID: 35041108; additional biallelic variants in HSP cohorts PMID: 31636353; PMID: 38499745.

Modifier genes / epigenetics / chromosomal abnormalities: None specifically established for ADSA1. RNF170 functions within the ERLIN1/2–TMUB1–RNF170 ERAD complex, so those partner genes are mechanistically relevant PMID: 38782601.

Section 5 — Environmental Information

No environmental, lifestyle, or infectious factors are implicated in ADSA1. It is a purely genetic Mendelian disorder. **Not applicable.**

Section 6 — Mechanism / Pathophysiology

Molecular function of RNF170. RNF170 is an ER-membrane RING E3 ubiquitin ligase that binds activated IP3 receptors — recruited via the erlin1/2 SPFH complex — and mediates their ubiquitination and ER-associated degradation (ERAD): *"RNF170 plays an essential role in IP3 receptor processing via the ubiquitin-proteasome pathway"* PMID: 21610068. It operates within an **ERLIN1/2–TMUB1–RNF170 ERAD nanodomain**: *"ERLIN scaffolds mediate the interaction between the full-length isoform of TMUB1 ... and RNF170"* PMID: 38782601.

Protein dysfunction. The Arg199Cys mutation **destabilizes RNF170**: *"Inhibited expression of mutant RNF170 was seen in cells expressing exogenous RNF170 constructs and in ADSA lymphoblasts, and appears to result from enhanced RNF170 autoubiquitination and proteasomal degradation"* PMID: 25882839. Arg199 sits at the C-terminal end of the large cytoplasmic loop, immediately N-terminal to TM2 (residues 202–222), consistent with disruption of stabilizing transmembrane ionic interactions.

Metabolic / signaling change. The proximal downstream consequence is dysregulated ER Ca^{2+} signaling: *"In ADSA lymphoblasts, platelet-activating factor-induced Ca^{2+} mobilization was significantly impaired"* — despite normal ER store content, IP3R levels, and IP3 production, localizing the defect to the IP3R response PMID: 25882839. In *Rnf170*-null mice, **ITPR1 protein accumulates selectively in cerebellum and spinal cord** (not cerebral cortex) PMID: 26433933.

Causal chain (upstream → downstream):

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RNF170 c.595C>T (p.Arg199Cys)  [germline, heterozygous]
        │  Arg199 at TM2 boundary → loss of stabilizing ionic interactions
        ▼
Enhanced RNF170 autoubiquitination → proteasomal degradation (↓ functional RNF170)
        ▼
Impaired ERLIN1/2–TMUB1–RNF170 ERAD nanodomain → defective ITPR1 turnover
        ▼
Dysregulated ER Ca²⁺ signaling (↓ agonist-evoked Ca²⁺ mobilization; ITPR1 accumulation)
        ▼
Chronic sensory-neuron / dorsal-column dysfunction & degeneration
        ▼
Adult-onset, slowly progressive SENSORY (proprioceptive) ATAXIA
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GO / CL terms. Biological process: GO:0070936 (protein K48-linked ubiquitination), GO:0043161 (proteasome-mediated ubiquitin-dependent protein catabolic process), GO:0006816 (calcium ion transport). Molecular function: GO:0061630 (ubiquitin protein ligase

activity), GO:0008270 (zinc ion binding). Cellular component: GO:0005789 (ER membrane). Cell types: CL:0000101 (sensory neuron), CL:0000209 (dorsal root ganglion neuron), CL:0000121 (Purkinje cell — secondary).

Immune involvement. RNF170 has a described role in **negative regulation of TLR3 signaling** (GO:0034140), but immune dysfunction is not part of the ADSA1 phenotype.

Section 7 — Anatomical Structures Affected

- **Organ/system level:** Nervous system — specifically the **posterior (dorsal) columns of the spinal cord** (UBERON:0002240 spinal cord) and peripheral **sensory nerves / dorsal root ganglia**. Vestibular pathways in CANVAS-mimic cases. Cerebellum (UBERON:0002037) is typically **spared** morphologically.
- **Tissue/cell level:** Nervous tissue; large **proprioceptive sensory neurons** (CL:0000101, CL:0000209).
- **Subcellular level: Endoplasmic reticulum membrane** (GO:0005789).
- **Localization/lateralization: Bilateral, symmetric, length-dependent** sensory involvement. One atypical case showed bilateral inferior olivary hypertrophy (hypertrophic olivary degeneration) with mild cerebellar atrophy PMID: 42052314.

Section 8 — Temporal Development

- **Onset:** Adult/middle age (HP:0003596); insidious/chronic.
- **Progression:** Slowly progressive over years-to-decades; disease course is **progressive**, not episodic or relapsing–remitting.
- **Duration:** Chronic, lifelong.
- **Remission:** None (no spontaneous or treatment-induced remission).
- **Critical periods:** The slow tempo provides a broad window for supportive/rehabilitative intervention.

Section 9 — Inheritance and Population

- **Inheritance pattern: Autosomal dominant** (OMIM #608984).
- **Penetrance / expressivity:** Apparently high penetrance in reported pedigrees; **variable expressivity** (e.g., variable pyramidal involvement) PMID: 34469621.
- **Founder effect:** The two Maritime-Canada families share a disease haplotype, indicating a **founder allele** PMID: 21115467.
- **Carrier frequency:** R199C is **absent from gnomAD** — effectively zero in general populations.
- **Anticipation / mosaicism / consanguinity:** No anticipation (not a repeat expansion); consanguinity is irrelevant for a dominant disorder (it is relevant only for recessive SPG85).
- **Epidemiology:** No formal prevalence/incidence; **ultra-rare** (<1/1,000,000), reported in only ~3 families plus scattered single cases.
- **Sex ratio / demographics:** No sex bias reported; reported cases are of European (Canadian, Belgian) ancestry, reflecting ascertainment.

Section 10 — Diagnostics

- **Clinical/electrophysiology:** Sensory nerve conduction studies show **reduced/absent SNAPs** (HP:0007078) with preserved motor conduction — the signature of a sensory neuronopathy/neuropathy. Bedside: positive Romberg, areflexia, distal sensory loss.
- **Imaging:** MRI typically **normal cerebellum** (helps distinguish from cerebellar ataxias); rare HOD on MRI PMID: 42052314.
- **Genetic testing (diagnostic gold standard):** Detection of *RNF170* c.595C>T p.(Arg199Cys) by **single-gene testing**, **hereditary-ataxia/HSP gene panels**, or **whole-exome/whole-genome sequencing**. WES/WGS are high-yield given phenotypic overlap with other ataxias.
- **Clinical criteria / differential diagnosis:** Differentiate from **CANVAS/RFC1** disease (exclude *RFC1* biallelic AAGGG expansion), paraneoplastic sensory neuronopathy (anti-Hu), Sjögren-associated ganglionopathy, vitamin E/B12 deficiency, chemotherapy (cisplatin) toxicity, and Friedreich ataxia. The CANVAS-mimic framing makes *RNF170* testing important in adult sensory ataxic neuropathy PMID: 32943585.
- **Screening:** Cascade genetic testing of at-risk relatives once a familial variant is known.

Section 11 — Outcome / Prognosis

- **Survival/mortality: Not life-shortening** in reported families; no disease-specific mortality documented.
- **Morbidity/function:** Progressive gait disability, falls, and eventual dependence on assistive devices are the main morbidities. Long-term functional impairment centers on mobility and balance (ICF domains).
- **Complications:** Fall-related injury; secondary deconditioning.
- **Recovery:** No spontaneous recovery; supportive care can maintain function.
- **Prognostic factors:** Genotype (R199C) defines the disease; no validated molecular prognostic biomarkers beyond the causal variant.

Section 12 — Treatment

- **Disease-modifying therapy: None available.**
- **Supportive/rehabilitative (mainstay):** Physical therapy and **balance/gait training** (NCIT: Physical Therapy), occupational therapy, assistive devices (cane/walker), fall-prevention strategies, and management of neuropathic dysesthesia.
- **Pharmacotherapy / advanced therapeutics:** No approved drugs, gene, cell, or RNA therapies. Mechanistically rational but unproven concepts include **proteostasis modulation** (given enhanced RNF170 degradation) and **IP3R/ER-Ca^{2+}-signaling–targeted** approaches.
- **Pharmacogenomics / experimental trials:** None specific to ADSA1.
- **NCIT intervention terms:** Physical Therapy; Occupational Therapy; Supportive Care.

Section 13 — Prevention

- **Primary/secondary/tertiary prevention:** No primary prevention (fully genetic). Tertiary prevention = fall-prevention and rehabilitation.

- **Genetic counseling:** Central — 50% offspring transmission risk for a heterozygous parent; cascade testing for at-risk relatives.
- **Reproductive options:** Prenatal and **preimplantation genetic testing** are feasible given the defined pathogenic variant.
- **Immunization / behavioral / public-health interventions:** Not applicable.

Section 14 — Other Species / Natural Disease

- **Orthologs (NCBI Gene):** mouse *Rnf170* (77733; MGI:1924983; ENSMUSG00000013878); zebrafish *rnf170* (406612; ENSDARG00000104069); dog *RNF170* (475568).
- **Natural disease (dog):** A naturally occurring **Miniature American Shepherd** neuroaxonal dystrophy is caused by an *RNF170* 1-bp deletion: *"The underlying genetic cause was identified as a 1-bp (base pair) deletion in RNF170 ... which perfectly segregates in an autosomal recessive pattern"* PMID: 39177409. This is a **recessive LoF** model (comparative to SPG85 more than to dominant ADSA1) but demonstrates conserved neurodegenerative consequences of *RNF170* dysfunction.
- **Evolutionary conservation:** RNF170's IP3R-ERAD function is conserved, supporting cross-species mechanistic relevance.

Section 15 — Model Organisms

Model	Type	Key features	Recapitulation	Reference
Rnf170$^{-/-}$ mouse	Mammalian knockout (LoF)	Age-dependent gait abnormality; reduced proprioception & thermal nociception; ITPR1 accumulation in cerebellum/spinal cord	Reproduces sensory/gait phenotype and pathway; but LoF (models SPG85 mechanism more than dominant R199C)	PMID: 26433933
Zebrafish (*rnf170*)	Vertebrate	Mutant orthologous mRNA dominantly disrupts development	Supports dominant action of the mutant allele	PMID: 21115467
Miniature American Shepherd dog	Natural, mammalian	Recessive frameshift → neuroaxonal dystrophy	Comparative neurodegeneration model	PMID: 39177409
Patient lymphoblasts / transfected cells	In vitro	Destabilized mutant RNF170; impaired PAF-induced Ca^{2+}	Direct human mechanistic model	PMID: 25882839

Model limitation: No **R199C knock-in** animal exists; the available in-vivo models are loss-of-function/recessive and therefore incompletely capture the dominant ADSA1 allele.

Mechanistic Model / Interpretation (Synthesis)

ADSA1 is best understood as a **dominant, protein-destabilizing disruption of ER quality control over calcium signaling** in sensory neurons. The upstream molecular lesion is destabilization of the E3 ligase RNF170; the proximal downstream consequence is failure of IP3R (ITPR1) ubiquitin/ERAD turnover and consequent Ca^{2+}-signaling dysregulation; the distal, tissue-level outcome is selective vulnerability of large proprioceptive neurons and dorsal-column pathways, producing adult-onset sensory ataxia.

A central conceptual puzzle: R199C **lowers mutant-protein levels** (a loss-of-function–like biochemical signature), yet the disease is **dominant** and *distinct* from the recessive complete-LoF disorder SPG85 (spasticity). This argues that R199C acts through a **dominant-negative or dosage-sensitive** mechanism within the multiprotein ERLIN1/2–TMUB1–RNF170 nanodomain — i.e., the destabilized mutant "poisons" the complex or perturbs stoichiometry — rather than through simple haploinsufficiency. Resolving this remains the key open mechanistic question.

Allelic-series comparison:

Feature	ADSA1	SPG85
RNF170 allele	Dominant missense p.Arg199Cys	Biallelic loss-of-function (nonsense/frameshift/ missense)
Inheritance	Autosomal dominant	Autosomal recessive
Onset	Adult/middle age	Infancy/childhood
Core phenotype	Sensory (proprioceptive) ataxia	Spastic paraplegia (± complex features)
IDs	MONDO:0012166; OMIM #608984	MONDO:0030512; OMIM #619686; Orphanet:631082

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
21115467	*RNF170 mutation causes ADSA*	Human genetics + zebrafish	Original discovery; establishes *RNF170* R199C as causal
34469621	*RNF170 ADSA with variable pyramidal involvement*	Human genetics	Independent replication (Belgian family)
32943585	*RNF170 CANVAS mimic*	Human clinical	Vestibular-areflexia/CANVAS-mimic phenotype; HPO source
25882839	*R199C destabilizes RNF170; impairs IP3R Ca^{2+} signaling*	In vitro/ biochemistry	Core mechanistic study
21610068	*RNF170 mediates IP3R ubiquitination/degradation*	In vitro	Establishes RNF170 molecular function
26433933	*Rnf170$^{-/-}$ mice, age-dependent gait*	Mouse model	In-vivo pathway validation; ITPR1 accumulation
38782601	*ERLIN1/2–TMUB1–RNF170 ERAD nanodomain*	In vitro	Places RNF170 in ERAD complex
31636353	*Bi-allelic RNF170 → HSP*	Human genetics	Recessive allelic disorder (SPG85)
36046950	*Stop-gain RNF170 → HSP (p.R64)**	Human genetics	Recessive LoF → SPG85
35041108	*Homozygous RNF170 p.Cys107Trp → HSP*	Human genetics	Recessive missense → SPG85
39177409	*Canine RNF170 model of neuroaxonal dystrophy*	Animal (natural)	Comparative model
42052314	*RNF170 with hypertrophic olivary degeneration*	Human clinical	Phenotype expansion
38499745	*WES in Serbian HSP*	Human genetics	*RNF170* in HSP cohort

Consistency: All human genetic reports converge on *RNF170* c.595C>T p.(Arg199Cys) as the recurrent ADSA1 allele; in-vitro and mouse-model data coherently support IP3R/Ca^{2+} dysregulation via impaired ERAD. The apparent tension — a "destabilizing" (LoF-like) mutation causing a dominant disease distinct from recessive LoF SPG85 — points to a dominant-negative/dosage mechanism rather than haploinsufficiency.

Limitations and Knowledge Gaps

- **Extreme rarity / small n:** Phenotype frequencies derive from very few affected individuals (HPO annotations largely n=2); percentages are indicative, not epidemiologic.
- **Unresolved dominance mechanism:** Whether R199C is dominant-negative, a toxic gain of function, or dosage-sensitive nanodomain poisoning is not definitively established. No R199C **knock-in** animal exists; existing mouse/dog models are LoF/recessive and better model SPG85.
- **No formal epidemiology:** Prevalence, incidence, penetrance, and sex/age distributions are not rigorously quantified.
- **No dedicated Orphanet code** for ADSA1; nosology overlaps with CANVAS and other sensory neuronopathies.
- **No therapeutics or biomarkers:** No disease-modifying treatment, prognostic biomarker, or ADSA1-specific clinical trial.
- **Limited human neuropathology:** Direct human confirmation of dorsal-column/DRG degeneration and ITPR1 accumulation is sparse; most molecular evidence is from patient lymphoblasts, transfected cells, and mouse tissue.

Proposed Follow-up Experiments / Actions

1. **Generate a knock-in *Rnf170^R199C/+* mouse** (and iPSC-derived sensory neurons) to test dominant-negative vs. dosage mechanisms and directly model ADSA1 rather than SPG85.
2. **Structural/biophysical study of Arg199Cys** at the TM2 boundary (cryo-EM/AlphaFold-guided mutagenesis) to define how the mutation destabilizes RNF170 and perturbs the ERLIN1/2–TMUB1–RNF170 nanodomain.

3. **Quantify ITPR1 turnover and ER Ca^{2+} dynamics** in patient-derived DRG-like neurons; test whether restoring RNF170 levels or modulating proteasomal degradation rescues Ca^{2+} signaling.
4. **International case ascertainment/registry** (GeneMatcher, ataxia consortia) to refine phenotype frequencies, penetrance, progression rate, and identify additional alleles/ founder haplotypes.
5. **Systematic differential-diagnosis workflow:** pair *RNF170* testing with *RFC1* CANVAS exclusion in adult sensory ataxic neuropathy cohorts to estimate ADSA1's diagnostic yield.
6. **Proof-of-concept therapeutics:** evaluate proteostasis modulators or IP3R/Ca^{2+}-signaling agents in cellular and knock-in models.

Evidence-source legend: human clinical/genetic (family and case reports); in-vitro (patient lymphoblasts, transfected cells, biochemistry); model organism (mouse, zebrafish, dog); computational/ontology (MONDO, HPO, UniProt, ClinVar, gnomAD).
